Attachment 3

Repatriation Medical Authority

Investigation into

Anxiety disorder & Panic disorder – focussed mefloquine & definition - Substance/medication-induced anxiety disorder

For the **Repatriation Medical Authority**
For the **October 2016** RMA Meeting

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Glossary/abbreviations

ACE	angiotensin-converting enzyme
AChE	acetylcholinesterase
AD	anxiety disorder
ADR	adverse drug reaction
AEDs	antiepileptic drugs
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
AUS	alcohol use disorder
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BDI	Beck's Depression Inventory
BK-MDMA	Methylone(beta-keto-MDMA)
BMI	body mass index
BoP	balance of probabilities
BPH	benign prostatic hyperplasia
BPI	Brief Pain Inventory
BSI	Brief Symptom Inventory
C&P	proguanil in combination
CABG	coronary artery bypass graft
CAD	coronary artery disease
CBC	complete blood cell count
CHF	congestive heart failure
CI	confidence interval
CIPD	corticosteroid-induced neuropsychiatric disorders
CL/F	clearance
CNS	central nervous system
CO	carbon monoxide
CO_2	carbon dioxide
COCs	combined oral contraceptives
CRP	C-reactive protein
CS	corticosteroid
CSE	chronic solvent-induced encephalopathy
DAAC	Drug Abuse Advisory
DAT	dopamine transporter
DHA-PPQ	dihydroartemisinin-piperaquine
DSM	Diagnostic and Statistical Manual of Mental Health
DSSI	Delusions-Symptoms-States Inventory
ECA	Epidemiology Catchment Area
ED	erectile dysfunction
EEG	electroencephalograph
ER	endoplasmic reticulum
ESEMeD	European Study of the Epidemiology of Mental Disorders, NESDA Netherlands Study of Depression and Anxiety
ESR	erythrocyte sedimentation rate
FDA	Food & Drug Administration
FSS	Fatigue Severity Scale

GAD	generalised anxiety disorder
GADI	Generalized Anxiety Disorder Inventory
GPRD	UK-based General Practice Research Database
HAART	highly active antiretroviral therapy
HADS	Hospital Anxiety and Depression scale
HADS-D	Hospital Anxiety and Depression scale - depression
HAM-A	Hamilton Rating Scale for Anxiety
HAS	Hamilton Anxiety Scale
HCV	hepatitis C virus
HE	hygienic effect
HPA	hypothalamic-pituitary-adrenal
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
IFN	interferon alpha
IFX	infliximab
INC	intranasal corticosteroid
ISC	independent steering committee
IT	insulin treatment
Ka	absorption rate constant
LUTS	lower urinary tract symptoms
MA	methamphetamine
MAC	minimum alveolar concentration
MAS-3	mefloquine-artesunate
MDD	major depressive disorder
MDMA	3, 4- methylenedioxymethamphetamine - Ecstasy, E or XTC
MDPV	3,4-Methylenedioxypyrovalerone
MH	medium/high
MI	myocardial infarction
MMPI	Minnesota Multiphasic Personality Inventory
MMSE	Mini-Mental State Examination
MPA	Methiopropamine
NAB	Neuropsychological Assessment Battery
NCS	National Comorbidity Survey
NCTB	neurobehavioural core test battery
ND	nicotine dependence
NESARC	National Epidemiologic Survey in Alcohol and Related Conditions
NET	norepinephrine transporter
NIT	non-insulin treatment
NL	non-/low
NP	neuropsychiatric
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSMHWB	Australian National Survey of Mental Health and Wellbeing of Adults
OCD	obsessive-compulsive disorder
OCP	oral contraceptive pill
OEL	Occupational Exposure Limits

OEL-years	OEL-weighted exposure years
OP	organophosphate
OR	odds ratio
PD	panic disorder
PET	positron emission tomography
POMS	Profile of Mood States
RCTs	randomised control trials
RE	role emotional
RH	reasonable hypothesis
RMA	Repatriation Medical Authority
RR	relative risk
SCID	Structured Clinical Interview
SCL-35	Symptom Checklist-35
SCL-90-R	Symptom Checklist-90-Revised
SCs	synthetic cannabinoids
SF-36	Short Form Health Survey
SLE	systemic lupus erythematosus
SoP	statement of principles
SRQ	Self-Report Questionnaire
SST	psychosocial stress test
STAI	State-Trait Anxiety Inventory
SUDs	substance use disorders
THC	delta-9-tetrahydrocannabinol
TURP	transurethral resection of the prostate
TWA	time weighted average
UAE	embolization of the uterine arteries
Ultram	tramadol hydrochloride
VA	Veterans' Affairs
VEP	visual evoked potential
V/F	volume of distribution
VT	vitality
WHO	World Health Organisation
ZCSYA	Zurich Cohorts Study of Young Adults

Current Statements of Principles

Substance/Medication-induced anxiety disorder is not currently covered by a SoP.
Anxiety disorder – 102 & 103/2014
Panic disorder – 68 & 69/2009

Background

A request dated 30 April 2015 was received from Rear Admiral Walker AM, Surgeon General, Australian Defence Force. The request identified new information concerning adverse health effects from the use of the anti-malarial medication mefloquine, and requested that a focussed review of Statements of Principles concerning a number of conditions be undertaken.

After consideration of the request, supporting documentation and a discussion paper prepared by the Principal Medical Officer, the Authority decided to notify an investigation of some of the contents of the Statements of Principles concerning anxiety disorder and panic disorder, restricted to the definition of the condition and “mefloquine” as a causal factor. Two Investigation Notices were published in the Government Notices of Gazette on 30 June 2015.

Submissions/correspondence

An email dated 4 January 2015 was received concerning adverse effects of mefloquine from Dr JCQ which included an unpublished paper entitled "mefloquine toxicity syndrome, exposure, diagnosis and treatment." All relevant cited references were obtained for further scrutiny.

A further email dated 2 March was received from Mr NR checking the progress of "investigation into the use of the anti malarial drug MEFLOQUINE which has emotional/behavioural side effects." No attachments or citations were provided.

A further letter and request for review was received dated 12 April 2016 from the Vice Chief of the Defence Force, Joint Health Command. The request stated:

This application is only seeking to have the contents of relevant Statements of Principles reviewed in terms of the use of tafenoquine as a causal or aggravating factor.

Tafenoquine is an experimental anti-malarial drug from the 8-aminoquinolines group and an analogue of another anti-malarial drug, primaquine that has been extensively used by Defence.

As tafenoquine has not been registered by any drug regulatory agency there is no post marketing information. The most significant side-effects identified during clinical trials appear to vortex be keratopathy and methaemoglobinaemia. The potential for haemolytic anaemia in G6PD enzyme deficient individuals is also identified. It would appear that tafenoquine, as an 'anti-malarial' would be accepted as a causal factor in epileptic seizure and as a drug that causes oxidation of haemoglobin as causal factor for methaemoglobinaemia. It is not clear whether it would be accepted for tinnitus and sensorineral hearing loss as a "quinine derivative".

It may meet the reasonable hypothesis standard that tafenoquine would share similar side-effects as primaquine and chloroquine given their drug class relationship and the observed side-effects of tafenoquine. It is therefore requested that consideration be given to adding

tafenoquine to Sop's that currently include either primaquine or chloroquine as a causative or aggravating factor.

Enclosures:

- TGA approved product information for Primacin (primaquine)
- TGA approved product information for PIaquenil (chloroquine) **- Under central nervous system adverse effects – nervousness is listed as a very rare side effect.**
- Summary of published literature on tafenoquine **Extracted from PubMed on-line 10 April 2016** (see below)

I. Cochrane Database Syst Rev. 2015 Apr 29;4. Tafenoquine for preventing relapse in people with Plasmodium vivax malaria. Rajapakse S, Rodrigo C, Fernando SD. ***No mention of anxiety or panic as an adverse event***

2.Occup Med (Lond). 2015 Apr;65(3):256-8. Occupational asthma from tafenoquine in the pharmaceutical industry implications for QSAR. Cannon J, Fitzgerald B, Seed M, Agius R, Jiwany A, Cullinan P. ***No mention of anxiety or panic as an adverse event***

3. J Clin Pharmacol.2014 Sep;54(9):995-1005. Tafenoquine at therapeutic concentrations does not prolong Fridericia-corrected QT interval in healthy subjects. Green JA, Patel AK, Patel BR, Hussaini A, Harrell EJ, McDonald MJ, Carter N, Mohamed K, Duparc S, Miller AK. ***No mention of anxiety or panic as an adverse event***

4. Lancet. 2014 Mar 22;383(9922):, 049-58. Tafenoquine plus chloroquine for the treatment and relapse prevention of Plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, Krudsood S, Gupta SK, Kochar SK, Arthur P, Chuenchom N, M6hrle JJ, Duparc S, Ugwuegbulam C, Kleim JP, Carter N, Green JA, Kellam L. ***No mention of anxiety or panic as an adverse event***

5. Antimicrob Agents Chemother. 2010 Feb;54(2):792-8. Randomized, double-blind study of the safety, toIerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team. **

6. Am J Trop Med Hyg. 2009 Aug;81(2):356-62. A randomized, double-blind, safety and tolerability study to assess the ophthalmic and renal effects of tafenoquine 200 mg weekly versus placebo for 6 months in healthy volunteers. Leary KJ, Riel MA, Roy MJ, Cantilena LR, Bi D, Brater DC, van de Pol C, Pruett K, Kerr C, Veazey JM Jr, Beboso R, Ohrt C. ***No mention of anxiety or panic as an adverse event***

7. Trans R Soc Trop Med Hyg. 2008 Nov;102(11):, 095-, 01 The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of Plasmodium vivax malaria in the Southwest Pacific. Elmes NJ, Nasveld PE, Kitchener SJ, Kocisko DA, Edstein MD. ***No mention of anxiety or panic as an adverse event***

8. Am J Trop Med Hyg. 2007 Mar;76(3):494-6. Tafenoquine for the treatment of recurrent Plasmodium vivax malaria. Kitchener S, Nasveld P, Edstein MD. ***No mention of anxiety or panic as an adverse event***

9. J Infect Dis. 2004 Oct I5; 90(8):1456-63 Efficacy of monthly tafenoquine for prophylaxis of Plasmodium vivax and multidrug-resistant P. falciparum malaria. Walsh DS, Earnsila C, Sasiprapha T, Sangkharomya S, Khaewsathien P, Supakalin P, Tang DB, Jarasrumgsichol P, Cherdchu C, Edstein MD, Rieckmann KH, Brewer TG. ***No mention of anxiety or panic as an adverse event***

I0. Trans R SOC Trop Med Hyg. 2002 Nov-Dec;96(6):683-4. Comparison of tafenoquine MIR238605) and primaquine in the postexposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. Nasveld P, Kitchener S, Edstein M, Rieckmann K. ***No mention of anxiety or panic as an adverse event***

11. Clin Infect Dis. 2003 Mar I;36(5):541-9. A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against Plasmodium falciparum. Hale BR, Owusu-Agyei S, Fryauff DJ, Koram A, Adjuik M, Oduro AR, Prescott WR, Baird JK, Nkrumah F, Ritchie TL, Franke ED, Binka FN, Horton J, Hoffman SL. ***No mention of anxiety or panic as an adverse event***

12. Lancet. 2000 Jun 10;355(9220):2041-5. Malaria chemoprophylaxis with tafenoquine: a randomised study. Lell B', Faucher JF, Missinou MA, Borrmann S, Dangelmaier O, Horton J, Kremsner PG. ***No mention of anxiety or panic as an adverse event***

13. J Infect Dis. 1999 Oct;, 80(4):, 282-7. Randomized dose-ranging study of the safety and efficacy of WR 238605 (Tafenoquine) in the prevention of relapse of PIasmodiumn vivax malaria in Thailand. Walsh DS, Looareesuwan S, Wilairatana P, Heppner DG Jr, Tang DB, Brewer TG, Chokejindachai W, Viriyavejakul P, Kyle DE, Milhous WK, Schuster BG, Horton J, Braitman DJ, Brueckner RP. ***No mention of anxiety or panic as an adverse event***

14. Am J Trop Med Hyg. I 998 May;58(5):645-9. First-time-in-humans safety and pharmacokinetics of WR 238605, a new antimalarial. Brueckner RP Lasseter KC, Lin ET, Schuster BG. ***No mention of anxiety or panic as an adverse event***

**** Only 1 study mentions anxiety and/or panic attacks as an adverse event.**

Literature Search

Literature searches were conducted using the Ovid search engine from 1996 to October week 3 2015, limited to English language. The search terms were:

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1 *Anxiety Disorders/ci [Chemically Induced] (67)

2 limit 1 to (english language and "review articles" and humans) (3)

3 *Anxiety Disorders/ci [Chemically Induced] (67)

4 limit 3 to (english language and humans) (41)

5 exp Anxiety Disorders/ci, ep, et [Chemically Induced, Epidemiology, Etiology] (18219)

6 limit 5 to (english language and humans) (16700)

7 mefloquine.mp. or Mefloquine/ (1756)

8 6 and 7 (3)

3 articles were retrieved of which 3 articles were selected for further study. Articles were selected based on relevance, study quality, reliability and journal authority. The above search was supplemented by specific searches for **anxiety disorders/symptoms** and **panic attacks** and other substances/medications which induce these symptoms, internet searches, manual searches of reference lists and extracts from relevant sections of textbooks.

In addition to the above literature search, the report entitled "Health Risks and Occupation as a Firefighter" by Professor T Guidotti[1] was consulted to identify any additional sound medical-scientific evidence relevant to the risks associated with being a firefighter. No data related to anxiety or panic disorder as an outcome was identified.

The search identified a number of potential risk factors. At the direction of the RMA, the following list of putative risk factors was not explored in any further detail:

Definition

Current definition

There is no current definition, as the anxiety disorder SoPs and panic disorder, exclude symptoms which are the direct result of a substance or medication

In the anxiety disorder Statements of Principles, Nos 102 & 103 of 2014, the generalised anxiety disorder (GAD) definition excludes the presence of anxiety symptomatology which are the direct result of a substance or medication. The disturbance may not be attributable to the physiological effects of a substance (for example, a drug of abuse, a medication) or another medical condition (for example, hyperthyroidism). The anxiety disorder Statements of Principles also specifically exclude substance/medication-induced anxiety disorder from the definition of anxiety disorder.

In the panic disorder Statements of Principles, Nos 68 & 69 of 2009, the definition excludes the presence of panic attacks which are the direct result of a substance or medication. The panic attacks may not be due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).

The Diagnostic and statistical manual of mental disorders (DSM-5) [2] categorise the presence of anxiety symptoms and panic attacks which are the direct effect of a drug or a substance under the ***substance/medication-induced anxiety disorder*** category. The diagnostic criteria appears below:

Diagnostic Criteria

1. Panic attacks or anxiety is predominant in the clinical picture.
2. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):
    1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
    2. The involved substance/medication is capable of producing the symptoms in Criterion A.

[1] Guidotti TL (2014), Health Risks and Occupation as a Firefighter. Consultant's report prepared for the Department of Veterans' Affairs. 072440

[2] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783

3. The disturbance is not better explained by an anxiety disorder that is not substance/medication-induced. Such evidence of an independent anxiety disorder could include the following:
    - The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced anxiety disorder (e.g., a history of recurrent non-substance/medication-related episodes).
4. The disturbance does not occur exclusively during the course of a delirium.
5. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and they are sufficiently severe to warrant clinical attention.

Synonyms

Nil

ICD codes

Nil

Introduction

Should the RMA consider that mefloquine-induced anxiety disorder is a disease, injury or death as defined under the *Veterans' Entitlements Act 1986*, the most logical approach would be to determine Statements of Principles concerning substance/medication-induced anxiety disorder including the use of mefloquine as a factor in the Statements of Principles. This approach has been utilised in the depressive disorder Statements of Principles which include substance/medication-induced depressive disorder as a sub-category in these Statements of Principles.

Substance/medication-induced anxiety disorder

The DSM-5[3] discusses the development and course of substance/medication-induced anxiety disorder and other features of the condition as outlined below.

DSM-5 Diagnostic Features

The essential features of substance/medication-induced anxiety disorder are prominent symptoms of panic or anxiety (Criterion A) that are judged to be due to the effects of a substance (e.g., a drug of abuse, a medication, or a toxin exposure). The panic or anxiety symptoms must have developed during or soon after substance intoxication or withdrawal or after exposure to a medication, and the substances or medications must be capable of producing the symptoms (Criterion B2). Substance/medication-induced anxiety disorder due to a prescribed treatment for a mental disorder or another medical condition must have its onset while the individual is receiving the medication (or during withdrawal, if a withdrawal is associated with the medication). Once the treatment is discontinued, the panic or anxiety symptoms will usually improve or remit within days to several weeks to a month (depending on the half-life of the substance/medication and the presence of withdrawal). The diagnosis of substance/medication-induced anxiety disorder should not be given if the onset of the panic or

[3] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783 pp.226, 228-229.

anxiety symptoms precedes the substance/medication intoxication or withdrawal, or if the symptoms persist for a substantial period of time (i.e., usually longer than 1 month) from the time of severe intoxication or withdrawal. If the panic or anxiety symptoms persist for substantial periods of time, other causes for the symptoms should be considered.

The substance/medication-induced anxiety disorder diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A are predominant in the clinical picture and are sufficiently severe to warrant independent clinical attention.

Associated Features Supporting Diagnosis

Panic or anxiety can occur in association with intoxication with the following classes of substances: alcohol, caffeine, cannabis, phencyclidine, other hallucinogens, inhalants, stimulants (including cocaine), and other (or unknown) substances. Panic or anxiety can occur in association with withdrawal from the following classes of substances: alcohol; opioids; sedatives, hypnotics, and anxiolytics; stimulants (including cocaine); and other (or unknown) substances. Some medications that evoke anxiety symptoms include anesthetics and analgesics, sympathomimetics or other bronchodilators, anticholinergics, insulin, thyroid preparations, oral contraceptives, antihistamines, antiparkinsonian medications, corticosteroids, antihypertensive and cardiovascular medications, anticonvulsants, lithium carbonate, antipsychotic medications, and antidepressant medications. Heavy metals and toxins (e.g., organophosphate insecticide, nerve gases, carbon monoxide, carbon dioxide, volatile substances such as gasoline and paint) may also cause panic or anxiety symptoms.

Prevalence

The prevalence of substance/medication-induced anxiety disorder is not clear. General population data suggest that it may be rare, with a 12-month prevalence of approximately 0.002%(Grant et al. 2004). However, in clinical populations, the prevalence is likely to be higher.

Diagnostic Markers

Laboratory assessments (e.g., urine toxicology) may be useful to measure substance intoxication as part of an assessment for substance/medication-induced anxiety disorder.

Substance/Medication-Induced Mental Disorders

The DSM-5[4] provides advice about substance/medication induced mental disorders in general which provides pertinent information when assessing the evidence related to these disorders.

The substance/medication-induced mental disorders are potentially severe, usually temporary, **but sometimes persisting central nervous system (CNS) syndromes that develop in the context of the effects of substances of abuse, medications, or several toxins.** They are distinguished from the substance use disorders, in which a cluster of cognitive, behavioral, and physiological symptoms contribute to the continued use of a substance despite significant substance-related problems. The substance/medication-induced mental disorders may be induced by the 10 classes of substances that produce substance use disorders, or by a great

[4] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783 pp. 486-90.

variety of other medications used in medical treatment. Each substance-induced mental disorder is described in the relevant chapter (e.g., “Depressive Disorders,” “Neurocognitive Disorders”), and therefore, only a brief description is offered here. All substance/medication-induced disorders share common characteristics. It is important to recognize these common features to aid in the detection of these disorders. These features are described as follows:

A.The disorder represents a clinically significant symptomatic presentation of a relevant mental disorder.

B.There is evidence from the history, physical examination, or laboratory findings of both of the following:

1.The disorder developed during or within 1 month of a substance intoxication or withdrawal or taking a medication; and

2.The involved substance/medication is capable of producing the mental disorder.

C.The disorder is not better explained by an independent mental disorder (i.e., one that is not substance- or medication-induced). Such evidence of an independent mental disorder could include the following:

1.The disorder preceded the onset of severe intoxication or withdrawal or exposure to the medication; or

2.The full mental disorder persisted for a substantial period of time (e.g., at least 1 month) after the cessation of acute withdrawal or severe intoxication or taking the medication. This criterion does not apply to substance-induced neurocognitive disorders or hallucinogen persisting perception disorder, which persist beyond the cessation of acute intoxication or withdrawal.

D.The disorder does not occur exclusively during the course of a delirium.

E.The disorder causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Features

Some generalizations can be made regarding the categories of substances capable of producing clinically relevant substance-induced mental disorders. In general, the more sedating drugs (sedative, hypnotics, or anxiolytics, and alcohol) can produce prominent and clinically significant depressive disorders during intoxication, while anxiety conditions are likely to be observed during withdrawal syndromes from these substances (Schuckit 2006a). Also, during intoxication, the more stimulating substances (e.g., amphetamines and cocaine) are likely to be associated with substance-induced psychotic disorders and substance-induced anxiety disorders (McLellan et al. 1979), with substance-induced major depressive episodes observed during withdrawal. Both the more sedating and more stimulating drugs are likely to produce significant but temporary sleep and sexual disturbances (Van Reen et al. 2006). An overview of the relationship between specific categories of substances and specific psychiatric syndromes is presented in Table.

The medication-induced conditions include what are often idiosyncratic CNS reactions or relatively extreme examples of side effects for a wide range of medications taken for a variety of medical concerns. These include neurocognitive complications of anesthetics, antihistamines, antihypertensives, and a variety of other medications and toxins (e.g.,

organophosphates, insecticides, carbon monoxide), as described in the chapter on neurocognitive disorders. Psychotic syndromes may be temporarily experienced in the context of anticholinergic, cardiovascular, and steroid drugs, as well as during use of stimulant-like and depressant-like prescription or over-the-counter drugs. Temporary but severe mood disturbances can be observed with a wide range of medications, including steroids, antihypertensives, disulfiram, and any prescription or over-the-counter depressant or stimulant-like substances. A similar range of medications can be associated with temporary anxiety syndromes, sexual dysfunctions, and conditions of disturbed sleep.

In general, to be considered a substance/medication-induced mental disorder, there must be evidence that the disorder being observed is not likely to be better explained by an independent mental condition. The latter are most likely to be seen if the mental disorder was present before the severe intoxication or withdrawal or medication administration, or, with the exception of several substance-induced persisting disorders listed in Table, continued more than 1 month after cessation of acute withdrawal, severe intoxication, or use of the medications(Caton et al. 2005; Hasin et al. 2002; Schuckit 2006a). When symptoms are only observed during a delirium (e.g., alcohol withdrawal delirium), the mental disorder should be diagnosed as a delirium, and the psychiatric syndrome occurring during the delirium should not also be diagnosed separately, as many symptoms (including disturbances in mood, anxiety, and reality testing) are commonly seen during agitated, confused states. The features associated with each relevant major mental disorder are similar whether observed with independent or substance/medication-induced mental disorders. However, individuals with substance/medication-induced mental disorders are likely to also demonstrate the associated features seen with the specific category of substance or medication, as listed in other subsections of this chapter.

Development and Course

Substance-induced mental disorders develop in the context of intoxication or withdrawal from substances of abuse, and medication-induced mental disorders are seen with prescribed or over-the-counter medications that are taken at the suggested doses. Both conditions are usually temporary and likely to disappear within 1 month or so of cessation of acute withdrawal, severe intoxication, or use of the medication. Exceptions to these generalizations occur for certain long-duration substance-induced disorders: substance-associated neurocognitive disorders that relate to conditions such as alcohol-induced neurocognitive disorder, inhalant-induced neurocognitive disorder, and sedative-, hypnotic-, or anxiolytic-induced neurocognitive disorder; and hallucinogen persisting perception disorder (“flashbacks”; see the section “Hallucinogen-Related Disorders” later in this chapter). However, most other substance/medication-induced mental disorders, regardless of the severity of the symptoms, are likely to improve relatively quickly with abstinence and unlikely to remain clinically relevant for more than 1 month after complete cessation of use.

As is true of many consequences of heavy substance use, some individuals are more and others less prone toward specific substance-induced disorders(Alia-Klein et al. 2011; Fu et al. 2002; Nunes et al. 2006; Nurnberger et al. 2004). Similar types of predispositions may make some individuals more likely to develop psychiatric side effects of some types of medications, but not others. However, it is unclear whether individuals with family histories or personal prior histories with independent psychiatric syndromes are more likely to develop the induced

syndrome once the consideration is made as to whether the quantity and frequency of the substance was sufficient to lead to the development of a substance-induced syndrome.

There are indications that the intake of substances of abuse or some medications with psychiatric side effects in the context of a preexisting mental disorder is likely to result in an intensification of the preexisting independent syndrome (Fu et al. 2002; Swendsen et al. 2010). The risk for substance/medication-induced mental disorders is likely to increase with both the quantity and the frequency of consumption of the relevant substance.

The symptom profiles for the substance/medication-induced mental disorders resemble independent mental disorders (Caton et al. 2005; Hasin et al. 2006; Regier et al. 1990; Schuckit et al. 1997). While the symptoms of substance/medication-induced mental disorders can be identical to those of independent mental disorders (e.g., delusions, hallucinations, psychoses, major depressive episodes, anxiety syndromes), and although they can have the same severe consequences (e.g., suicide) (Aharonovich et al. 2002), most induced mental disorders are likely to improve in a matter of days to weeks of abstinence (Brown et al. 1995; Gilder et al. 2004; Nunes and Rounsaville 2006; Schuckit et al. 2007).

The substance/medication-induced mental disorders are an important part of the differential diagnoses for the independent psychiatric conditions. The importance of recognizing an induced mental disorder is similar to the relevance of identifying the possible role of some medical conditions and medication reactions before diagnosing an independent mental disorder. Symptoms of substance- and medication-induced mental disorders may be identical cross-sectionally to those of independent mental disorders but have different treatments and prognoses from the independent condition.

Functional Consequences of Substance/Medication-Induced Mental Disorders

The same consequences related to the relevant independent mental disorder (e.g., suicide attempts) are likely to apply to the substance/medication-induced mental disorders, but these are likely to disappear within 1 month after abstinence. Similarly, the same functional consequences associated with the relevant substance use disorder are likely to be seen for the substance-induced mental disorders.

Findings

Mefloquine

Summary of important issues

This exposure was the subject of a request for review. The identified articles in the request for review were identified and scrutinised and further articles were also obtained.

Reviews

Quinn (2015)[5] suggests an hypothesis to explain the prodromal and acute neuropsychiatric sequelae resulting from exposure to mefloquine.

The alkaloid toxin quinine and its derivative compounds have been used for many centuries as effective medications for the prevention and treatment of malaria. More recently, synthetic derivatives, such as the quinoline derivative mefloquine (bis(trifluoromethyl)-(2-piperidyl)-4-quinolinemethanol), have been widely used to combat disease caused by chloroquine resistant strains of the malaria parasite, Plasmodium falciparum. However, the parent compound quinine, as well as its more recent counterparts, suffers from an incidence of adverse neuropsychiatric side effects ranging from mild mood disturbances and anxiety to hallucinations, seizures, and psychosis. This review considers how the pharmacology, cellular neurobiology, and membrane channel kinetics of mefloquine could lead to the significant and sometimes life-threatening neurotoxicity associated with mefloquine exposure. A key role for mefloquine blockade of ATP-sensitive potassium channels and connexins in the substantia nigra is considered as a unifying hypothesis for the pathogenesis of severe neuropsychiatric events after mefloquine exposure in humans.

According to **McCarthy (2015)**[6],

"The manufacturer currently cites a randomized control trial (RCT) in which treatment-related neuropsychiatric adverse events occurred in 28.8% of the mefloquine recipients, with the affected percentages including strange or vivid dreams, 13.7%; insomnia, 13.5%; dizziness or vertigo, 8.9%; visual difficulties, 3.3%; anxiety, 3.7%; and depression, 3.5% [Roche Products, 2014]. Post-marketing data is also cited by the manufacturer to report the incidence of neuropsychiatric adverse effects. Psychiatric disorders include very common (>1/10), abnormal dreams and insomnia; common (≥1/100 to <1/10), anxiety and depression; and uncommon (≥1/1,000 to <1/100), agitation, restlessness, mood swings, panic attacks, confusional state, hallucinations, aggression, bipolar disorder, psychotic disorder including delusional disorder, depersonalisation and mania, paranoia, and suicidal ideation.

Neurological disorders include common (≥1/100 to <1/10), dizziness, headache, and vertigo; uncommon (≥1/1,000 to <1/100), balance disorder, somnolence, syncope, convulsions, memory impairment, peripheral sensory neuropathy and peripheral motor neuropathy

[5] Quinn JC (2015). Complex membrane channel blockade: a unifying hypothesis for the prodromal and acute neuropsychiatric sequelae resulting from exposure to the antimalarial drug mefloquine. Journal of Parasitology Research, ID 368064: 12 pages. 076939

[6] McCarthy S (2015). Malaria prevention, mefloquine neurotoxicity, neuropsychiatric illness, and risk-benefit analysis in the Australian Defence Force. Journal of Parasitology Research, ID287651: 23 pages. 069474

(including paraesthesia, tremor, and ataxia), encephalopathy, and vestibular disorders (long-term) including tinnitus and hearing impaired [Roche products, 2014]" (p. 5).

According to the **US Food and Drug Administration (FDA; 2013)**[7]

"The mefloquine drug label already states that mefloquine should not be prescribed to prevent malaria in patients with major psychiatric disorders or with a history of seizures. The changes to the mefloquine drug label better describe the possibility of persistent neurologic (vestibular) adverse effects after mefloquine is discontinued and the possibility of permanent vestibular damage.

In conducting its assessment of vestibular adverse reactions associated with mefloquine use, FDA reviewed adverse event reports from the FDA Adverse Event Reporting System (FAERS) and the published literature, identifying patients that reported one or more vestibular symptoms such as dizziness, loss of balance, tinnitus, and vertigo. Patients who reported vestibular adverse reactions were healthy with no known major medical problems prior to taking mefloquine for malaria prophylaxis. Some patients did not suspect their symptoms were due to mefloquine and continued to take the drug after the symptoms started.

In many cases, these symptoms developed early in the course of treatment, sometimes after one or two doses of mefloquine. Dizziness, loss of balance, tinnitus, or vertigo persisted for months to years after mefloquine was discontinued, and permanent vestibular damage was diagnosed in some cases. These symptoms interfered with patients' daily activities and ability to work. Some cases described abnormal vestibular function tests and a diagnosis of vestibular damage. In some cases, the vestibular damage was thought to be caused by mefloquine use. Some patients reported recurrence of psychiatric and vestibular symptoms when they took mefloquine for the second time. **Patients who experienced vestibular symptoms usually had concomitant psychiatric symptoms such as anxiety, confusion, paranoia, and depression. Some of the psychiatric symptoms persisted for months to years after mefloquine was discontinued**" (no page no.).

Jousset, Rouge-Maillart, Turcant et al (2010)[8] in their report of a suicide related to mefloquine use, discussed the history of its use and adverse events which have been reported.

In 1989, the World Health Organization commissioned an investigation that confirmed the existence of such complications, with a prevalence estimated at 4.2/1000 treatments (WHO, 1989). The various effects observed were ranked in 3 categories:

- Slight complications: fatigue, loss of balance, concentration and memory difficulties, and sleep disorders;

- Moderate complications: vertigo, logorrhea, vision disturbances, anxiety, depression, agitation, and confusion;

[7] FDA (2013). FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. . Retrieved 15 April 2016, from http://www.fda.gov/drugs/drugsafety/ 077979

[8] Jousset N, Rouge-Maillart C, Turcant A, et al (2010). Suicide by skull stab wounds. Am J Forensic Med Pathol, 31(4): 378-81. 075197

- Serious complications: deep depression, suicidal ideation, panic attack, convulsions, manic behavior, acute psychosis with often paranoid delusions.

In 60% of reported cases, disorders appeared after the first intake of mefloquine. Serious complications were noticed only for curative treatments with doses equal to or greater than 1000 mg. As a result of these observations, the World Health Organization made the following recommendations (WHO, 1991): (a) mefloquine should be contraindicated in patients with previous psychiatric history or those having tasks requiring coordination or concentration, (b) particular care should be taken with mefloquine at high, curative dosages, and (c) for prophylaxis, mefloquine administration should begin at least 1 week before arrival in an endemic area.

Further studies confirmed these initial reports and revealed the existence of predisposition factors such as intercurrent infections, previous psychiatric diseases, or a previous history of epilepsy (Weinke et al, 1991; Bem et al, 1992; Barrett et al, 1996; van Riemsdijk et al, 2002). In addition, they showed that serious complications may also arise even at low-dose regimens intended for prophylaxis (risk estimated at 1/50,000 prescriptions). Such events are most often clustered around the beginning of treatment (in 90% of cases, they are observed within the first 3 weeks), but they may also supervene later and/or last long after mefloquine has been discontinued (Lebain et al, 2000; Grupp et al, 1994; Bygbjerg & Ronn, 1999; Lysack et al, 1998). Prospective trials that focused on the adverse effects of antimalarials found minor/moderate psychiatric effects related to mefloquine with a frequency of up to 1 of 140 patients (Meier et al, 2004; Bem et al, 1992; Ronn et al, 1998; van Riemsdijk et al, 2004; Potasman et al, 2000). They also pointed out the risk of severe complications including acute delusional crises with disorientation and hallucinations, manic-depressive psychosis, or deep depression.

No correlation seems to exist between blood levels of mefloquine and the occurrence of severe adverse effects (Schwartz et al, 2001). Up to date, approximately 20 reports of patients with serious complications have been published in France, without prior history of psychiatric illness in half of them (Lebain et al, 2000).

Randomised clinical trial

Soukhathammavong, Odermatt, Sayasone et al (2011)[9] conducted a randomised open-label trial between February and April, 2010, in the Saysetha district, Attapeu Province, Laos. Eligible patients were school children aged 10–15 years who had *Opisthorchis viverrini* infections. Patients were randomly assigned to one of five different treatment groups by use of a computer-generated randomisation code. They assessed efficacy as cure rate and egg reduction rate in intention-to-treat and per-protocol analyses. The trial was registered with Current Controlled Trials, ISRCTN23425032.

A total of 125 children were randomly assigned: 25 received mefloquine, 24 artesunate, 24 mefloquine–artesunate, 27 tribendimidine, and 25 praziquantel. 19 patients were lost to follow-up. In the intention to treat analysis, 14 patients receiving praziquantel were cured compared with none with mefloquine, one with artesunate (odds ratio 0·03, 95% CI 0·004–0·29), one with mefloquine–artesunate (0·03, 0·004–0·29), and 19 with tribendimidine (1·87, 0·60–5·85).

[9] Soukhathammavong P, Odermatt P, Sayasone S, et al (2011). Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, tribendimidine, and praziquantel in patients with opisthorchis viverrini: a randomised, exploratory, open-label, phase 2 trial. Lancet Infect Dis.;11(2):110-8. 078029

Egg reduction rate was 98·4% for praziquantel, 30·2% for mefloquine (egg reduction-rate ratio 1·61, 95% CI 0·21–0·72), 31·5% for artesunate (0·43, 0·23–0·80), 41·3% for mefloquine–artesunate (0·60, 0·31–1·10), and 99·3% for tribendimidine (1·00, 0·44–2·30). **Most adverse events were mild or moderate and affected all treatment groups; serious adverse events—vertigo, nausea, vomiting, and anxiety—were reported only by patients taking mefloquine or mefloquine– artesunate.**

Tribendimidine seems to be at least as efficacious as the drug of choice, praziquantel, for the treatment of *O viverrini* infections; both drugs were well tolerated. Mefloquine, artesunate, and mefloquine–artesunate did not show an effect on this liver fluke. Tribendimidine should be further investigated with large clinical trials.

Grande, Bernasconi, Erhart et al (2007)[10] carried out a randomised open label clinical trial comparing mefloquine-artesunate, the current first line treatment in this region, with dihydroartemisinin-piperaquine.

Between July 2003 and July 2005, 522 patients with P. falciparum uncomplicated malaria were recruited, randomized (260 with mefloquine-artesunate and 262 with dihydroartemisinin-piperaquine), treated and followed up for 63 days. PCR-adjusted adequate clinical and parasitological response, estimated by Kaplan Meier survival and Per Protocol analysis, was extremely high for both drugs (99.6% for mefloquine-artesunate and 98.4% and for dihydroartemisinin-piperaquine) (RR: 0.99, 95%CI [0.97-1.01], Fisher Exact p = 0.21). All recrudescences were late parasitological failures. Overall, gametocytes were cleared faster in the mefloquine-artesunate group (28 vs 35 days) and new gametocytes tended to appear more frequently in patients treated with dihydroartemisinin-piperaquine (day 7: 8 (3.6%) vs 2 (0.9%), RR: 3.84, 95%CI [0.82-17.87]). Adverse events such as anxiety and insomnia were significantly more frequent in the mefloquine-artesunate group, both in adults and children.

TABLE 1 ADVERSE EVENTS BY AGE AND TREATMENT GROUP WITHIN THE FIRST WEEK OF FOLLOW UP (GRANDE ET AL, 2007).

	ADULTS				CHILDREN			
	DHA-PPQ	MAS3	Relative Risk	p	DHA-PPQ	MAS3	Relative Risk	p-value
Nausea	77/161 (48%)	100/164 (61%)	0.78	0.02	49/101 (49%)	56/96 (58%)	0.83	0.17
Vomiting	29/161 (18%)	48/164 (29%)	0.62	0.02	24/101 (24%)	25/96 (26%)	0.91	0.71
Dizziness	122/161 (76%)	152/164 (93%)	0.82	<0.001	63/101 (62%)	66/96 (69%)	0.91	0.35
Anorexia	69/161 (43%)	77/164 (47%)	0.91	0.46	42/101 (42%)	35/96 (36%)	1.14	0.46
Abdominal pain	42/161(26%)	45/164(27%)	0.95	0.78	31/101 (31%)	34/96 (35%)	0.87	0.48
Insomnia	22/161 (14%)	71/164 (43%)	0.32	<0.001	5/101 (0.5%)	27/96 (28%)	0.18	<0.001
Somnolence	5/161 (3%)	0/164	.	0.02	3/101 (2.3%)	0/96	.	0.09
Anxiety	3/161 (1.2%)	24 (15%)	0.13	<0.001	0/101	5/96 (5%)	0	0.02

Dihydroartemisinin-piperaquine is as effective as mefloquine-artesunate in treating uncomplicated P. falciparum malaria but it is better tolerated and more affordable than mefloquine-artesunate (US$1.0 versus US$18.65 on the local market). Therefore, it should be considered as a potential candidate for the first line treatment of P. falciparum malaria in Peru.

[10] Grande T, Bernasconi A, Erhart A, et al (2007). A randomised controlled trial to assess the efficacy of dihdroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Peru. PLoS One, 2(10): e1101. 078030

Cohort studies

Adshead (2014)[11] conducted a prospective questionnaire-based cohort study of 150 deployed military personnel prescribed mefloquine as anti-malaria chemoprophylaxis. The primary study objective was to assess the rate of adverse reactions. In addition, an audit of mefloquine prescriptions and subsequent patient follow-up was conducted.

Among a cohort of 111 individuals taking mefloquine, 54% reported at least one adverse effect and 13% required a change in prescription to a second-line anti-malarial, due to significant side-effects. All females prescribed mefloquine reported at least one adverse reaction. There were two cases of clinically significant adverse reactions. Among those taking mefloquine, the two most common adverse effects experienced were vivid dreams (39%) and sleep disturbance (38%). Less common adverse side effects included nightmares, anxiety, headache, myalgia, nausea, vomiting and diarrhoea. Anxiety symptoms were reported in approximately 15% of the cohort.

There was a higher rate of adverse events reported amongst deployed military personnel than has been reported among civilian patients. This may be partly due to the stressful environment in which deployed personnel operate.

Wells, Smith, Smith et al (2006)[12] used standard military databases for mefloquine prescriptions and hospitalizations to investigate mefloquine safety among US service members from 2002 through 2004. Mefloquine-prescribed and deployed personnel (N=8,858) were compared with two reference groups. The reference groups comprised US service members who were not prescribed mefloquine and resided in Europe or Japan (N = 156,203) or had been otherwise deployed (N = 232,381). In comparison with active-duty US service members residing in Europe or Japan, mefloquine-prescribed service members were at statistically significant decreased hazard for any-cause hospitalization, as well as diseases of the respiratory and digestive systems, musculoskeletal system and connective tissue diseases, injuries and poisonings, ill-defined conditions, and mood disorders.

[11] Adshead Surg Lt S (2014). Clinical research. The adverse effects of mefloquine in deployed military personnel. J R Nav Med Serv, 100(3): 232-7. 077128

[12] Wells TS, Smith TC, Smith B (2006). Mefloquine use and hospitalizations among US service members, 2002-2004. Am J Trop Med Hyg, 74(5): 744-749. 077259

TABLE 2 RESULTS OF COX PROPORTIONAL HAZARDS ANALYSIS FOR HOSPITALIZATIONS AMONG US SERVICE MEMBERS PRESCRIBED MEFLOQUINE, 2002–2003 (WELLS ET AL, 2006).

Category (ICD-9-CM codes)	Cases			Mefloquine vs Europe/Japan*	Mefloquine vs deployed†
	Mefloquine (*n*)	Europe/Japan* (*n*)	Deployed† (*n*)	Hazard ratio (95% CI)‡	Hazard ratio (95% CI)§
Any cause¶	135	7,308	5,868	0.47 (0.39–0.56)	0.94 (0.79–1.12)
Infectious/parasitic (001–139)	11	386	438	1.06 (0.57–1.94)	1.08 (0.59–1.99)
Neoplasms (140–239)	5	240	251	0.90 (0.37–2.21)	1.13 (0.46–2.77)
Endocrine, nutritional, metabolic (240–279)	13	416	493	1.04 (0.59–1.82)	1.34 (0.77–2.35)
Blood and blood-forming organs (280–289)	4	316	360	0.51 (0.19–1.36)	0.65 (0.24–1.74)
Mental disorders (290–319)	37	1,280	1,314	0.76 (0.55–1.07)	1.23 (0.87–1.72)
Nervous system (320–389)	6	312	292	0.58 (0.26–1.32)	0.76 (0.34–1.73)
Circulatory system (390–459)	9	492	577	0.61 (0.31–1.18)	0.69 (0.35–1.34)
Respiratory system (460–519)	9	578	486	0.44 (0.23–0.86)	0.81 (0.42–1.58)
Digestive system (520–579)	23	1,280	1,122	0.52 (0.34–0.79)	0.90 (0.60–1.37)
Genitourinary system (580–629)	13	724	512	0.71 (0.40–1.26)	1.19 (0.67–2.13)
Skin and subcutaneous tissues (680–709)	9	272	294	0.88 (0.43–1.80)	1.31 (0.64–2.69)
Musculoskeletal and connective tissue (710–739)	30	1,149	984	0.68 (0.47–0.98)	1.28 (0.88–1.85)
Ill-defined conditions (780–799)	22	2,255	1,221	0.24 (0.16–0.37)	0.71 (0.46–1.09)
Injury and poisoning (800–999)	47	1,798	1,802	0.63 (0.47–0.84)	1.06 (0.79–1.43)

* US service members who resided in either Europe or Japan during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.
† US service members who deployed for 1 or more months during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.
‡ Hazard ratio for mefloquine-prescribed group, using the Europe/Japan reference group.
§ Hazard ratio for mefloquine-prescribed group, using the deployed reference group.
¶ Excludes complications of pregnancy, childbirth, and the puerperium, congenital anomalies, and certain conditions originating in the prenatal period (ICD-9-CM codes 630–676 and 740–779).

TABLE 3 RESULTS OF COX PROPORTIONAL HAZARDS ANALYSIS FOR HOSPITALIZATIONS AMONG US SERVICE MEMBERS PRESCRIBED MEFLOQUINE, SPECIFIC PSYCHOLOGICAL AND NEUROLOGICAL DIAGNOSES, 2002–2003 (WELLS ET AL, 2006).

Category (ICD-9-CM codes)	Cases			Mefloquine vs Europe/Japan*	Mefloquine vs deployed†
	Mefloquine (*n*)	Europe/Japan* (*n*)	Deployed† (*n*)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Somatoform disorders‡	0	25	10	—	—
Mood disorders§	6	388	412	0.37 (0.15–0.90)	0.50 (0.21–1.22)
Anxiety disorders¶	6	186	185	0.92 (0.40–2.10)	1.27 (0.55–2.91)
Post-traumatic stress disorder (309.81)	1	38	29	0.79 (0.11–5.91)	1.66 (0.21–12.85)
Mixed syndromes#	4	130	151	0.91 (0.33–2.51)	0.99 (0.36–2.73)
Substance use disorders**	19	634	741	0.72 (0.45–1.15)	1.20 (0.75–1.90)
Other disorders††	20	743	551	0.71 (0.45–1.13)	1.54 (0.96–2.46)
Personality disorders (301)	7	364	225	0.46 (0.21–1.05)	1.39 (0.60–3.20)
Adjustment reaction‡‡	13	453	305	0.78 (0.45–1.38)	1.68 (0.95–2.97)
Nystagmus (379.5)	0	0	2	—	—
Vertiginous syndromes (386)	1	4	6	3.17 (0.32–31.18)	5.53 (0.59–52.06)
Dizziness and giddiness (780.4)	0	42	21	—	—
Migraine (346)	3	93	52	1.36 (0.42–4.36)	2.09 (0.63–6.90)

* Residing in either Europe or Japan during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.
† Deployed for 1 or more months during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.
‡ ICD-9-CM codes 300.11, 300.7, 300.81, 306, 307.80–307.81, 309.82, 316.
§ ICD-9-CM codes 296.00, 296.2–296.3, 296.40–296.99, 298.0, 300.4–300.5, 311.
¶ ICD-9-CM codes 300.0, 300.2–300.3, 300.89–300.9, 309.81.
# ICD-9-CM codes 300.00, 300.09, 300.2–300.3, 300.89–300.9.
** ICD-9-CM codes 303, 304, 305.00–305.70.
†† ICD-9-CM codes 290–294, 295.30, 295.60, 295.62, 295.70, 295.90, 297.9, 298.8–298.9, 300.12, 300.14, 300.16, 300.19, 301, 302.7, 307.0–307.2, 307.4–307.6, 307.9–310, 312–315, 317, 319.
‡‡ ICD-9-CM codes 308–309.4, 309.83–309.9.

The anxiety disorders assessed according to the ICD-9 codes above were:

300.0 Anxiety states

300.00 Anxiety state, unspecified

300.01 Panic disorder without agoraphobia

300.02 Generalized anxiety disorder

300.09 Other anxiety states

300.2 Phobic disorders

300.20 Phobia, unspecified

300.21 Agoraphobia with panic disorder

300.22 Agoraphobia without mention of panic attacks

300.23 Social phobia

300.29 Other isolated or specific phobias

300.3 Obsessive-compulsive disorders

300.89 Other somatoform disorders

300.9 Unspecified nonpsychotic mental disorder

309.81 Posttraumatic stress disorder

These results suggest there is no association between mefloquine prescriptions and severe health effects, as measured by hospitalizations, across a wide range of outcomes.

Limitations

The results of this study should be considered within its limitations. Using a prescription database as a surrogate for mefloquine exposure created unique challenges, including potentially low sensitivity for identifying exposure. They attempted to minimize exposure misclassification by requiring a minimum pill count of at least seven tablets per mefloquine prescription to qualify as an exposure, yet they acknowledge this serves only as a proxy for having taken mefloquine. Among the deployed reference group, there may have been poor specificity in mefloquine exposure assessment because an unknown percentage of individuals in this population may have actually taken mefloquine while deployed. They also attempted to improve specificity of mefloquine exposure by using a reference group containing only nondeployed service members who resided in Europe or Japan. Although they chose to assess hospitalizations as the outcome measure for this study, this choice restricted analyses to those medical conditions that were of ample severity to require hospitalization, and it does not represent the entire spectrum of morbidity that may be associated with mefloquine. Finally, the study design called for a large number of analyses, which increases the likelihood of finding a statistically significant, but spurious, association.

Kitchener, Nasveld, Gregory and Edstein (2005)[13] described the tolerability of mefloquine in Australian soldiers for malaria prophylaxis, including a comparison with doxycycline. An open- label, prospective study and cross-sectional questionnaire and interview design was used in two contingents of Australian soldiers, each deployed to East Timor for peacekeeping duties over a 6-month period (April 2001–October 2001 and October 2001–May 2002). The outcome measures were withdrawals during the study; adverse events relating to mefloquine prophylaxis and willingness to use mefloquine again on deployment.

Of 1157 soldiers starting on mefloquine, 75 (6.5%) withdrew because of adverse responses to the drug. There were three serious adverse events of a neuropsychiatric nature, possibly relating to mefloquine. There were nine serious adverse events in the mefloquine arm of the study (four in the first contingent and five in the second) all occurring in men. Three of these men were withdrawn from the study because of neuropsychiatric symptoms possibly associated with mefloquine use. The first soldier had auditory hallucinations, which, on psychological assessment were consistent with his undisclosed history of auditory hallucinations preceding mefloquine use and the episode in East Timor. The second soldier experienced heat illness while on patrol, with symptoms of nausea, dizziness and abdominal discomfort. He was observed to have a generalised seizure. However, he was later found to

[13] Kitchener SJ, Nasveld PE, Gregory RM, et al (2005). Mefloquine and doxycycline malaria prophylaxis in Australian soliders in East Timor. MJA, 182(4): 168-71. 077980

have an undisclosed history of epilepsy. He recovered with rehydration and was returned to Australia. **The third soldier experienced depression, episodic anxiety, mild paranoia, short-term memory loss and suicidal ideation. Although he was taken off mefloquine and placed on doxycycline, his mental state continued to deteriorate. He was psychologically evaluated and returned to Australia. No panic attacks were reported as adverse health effects in this study.**

Fifty-seven per cent of soldiers using mefloquine prophylaxis reported at least one adverse event, compared with 56% using doxycycline. The most commonly reported adverse effects of both drugs were sleep disturbance, headache, tiredness and nausea. Of the 968 soldiers still taking mefloquine at the end of their deployments, 94% indicated they would use mefloquine again. Of 388 soldiers taking doxycycline prophylaxis who were deployed with the first mefloquine study contingent, 89% indicated they would use doxycycline again.

TABLE 4 ADVERSE EVENTS, BY BODY SYSTEM, REPORTED AMONG AUSTRALIAN SOLDIERS WHO WITHDREW FROM THE MEFLOQUINE TRIAL DUE TO ADVERSE EFFECTS OF THE DRUG* (KITCHENER ET AL, 2005).

Body system	First contingent withdrawals ($n = 52$)	Second contingent withdrawals ($n = 23$)
Gastrointestinal	6	4
Constitutional	9	9
Neuropsychiatric	42	20
Dermatological	3	3
Musculoskeletal	2	0

* Some participants reported more than one reason for withdrawing.

Mefloquine was generally well tolerated by Australian soldiers and should continue to be used for those intolerant of doxycycline.

van Riemsdijk, van der Klauw, van Heest, et al (1997)[14] conducted a prospective cohort study to investigate the neuro-psychiatric adverse effects of antimalarial drugs. Participants comprised persons who visited a Travel Clinic in Rotterdam over a period of 3 months. A total of 394 persons were taking mefloquine, 493 persons were taking proguanil and 340 persons were not taking antimalarial drugs who visited Africa, South America, Asia, or the Middle East.

All persons received a structured questionnaire within 14 days of their return to the Netherlands. The questionnaire consisted of questions regarding use of alcohol, smoking, general health, medical history, tropical diseases during the trip, and other medicines, and contained an extensive list of general complaints regarding all body systems at four levels of severity. A modified and validated version of the Profile of Mood States was included.

In the study period, 2541 persons visited the Travel Clinic, of whom 1791 (70%) were both eligible and willing to co-operate. Of these 1791, data were obtained from 1501 (84%). Insomnia was most frequently encountered in users of mefloquine and mouth ulcers in proguanil users. After adjustment for gender, age, destination, and alcohol use, the relative

[14] van Riemsdijk MM, van der Klauw MM, van Heest JA, et al (1997). Neuro-psychiatric effects antimalarials. Eur J Clin Pharmacol, 52(1): 1-6. 078031

risk for insomnia to mefloquine versus non-users of antimalarials was 1.6, and the excess risk was 6 per 100 users over an average period of 2 months. There were no significant differences between groups in depression, anxiety, agitation, and confusion. Stratification by gender demonstrated that insomnia was more common in women on mefloquine, but not in men. Also, women more frequently mentioned palpitations as an adverse event. After adjustment for age, destination, and alcohol use in women, the relative risks for insomnia and palpitations to mefloquine versus non-use of antimalarials were 2.4, and 22.5, respectively. When travellers were specifically asked for the adverse reactions they had experienced, anxiety, vertigo, agitation, and nightmares were significantly more frequently mentioned by mefloquine users.

TABLE 5 ADVERSE REACTIONS TO MEFOQUINE AND PROGUANIL IN TRAVELLERS (VAN RIEMSDIJK ET AL, 1997).

	Mefloquine (n = 394)	Proguanil (n = 493)	Relative risk (95% CI)
Anxiety	9	1	11.3 (1.4–88.5)*
Insomnia	1	–	$P > 0.05$
Palpitations	2	–	$P > 0.05$
Depression	3	–	$P > 0.05$
Vertigo	14	3	5.8 (1.7–20.2)*
Agitation	4	–	$P = 0.04$*
Nausea	17	21	1.0 (0.5–1.9)
Somnolence	3	3	1.3 (0.3–6.2)
Nightmares	6	–	$P = 0.008$*
Vision blurred	4	6	0.8 (0.2–2.9)
Rash	2	7	0.4 (0.1–1.7)
Confusion	1	1	1.3 (0.1–19.9)
Ataxia	2	–	$P > 0.05$
Diarrhoea	7	8	1.1 (0.4–3.0)
Dyspepsia	10	14	0.9 (0.4–2.0)
Mouth ulcers	2	19	0.1 (0.03–0.6)*
Any psychiatric ADR	17	3	7.1 (2.1–24.0)*
Any neurologic ADR	23	14	2.1 (1.1–3.9)*
Any gastrointestinal ADR	38	65	0.7 (0.5–1.1)

*Statistically significant

Insomnia was more commonly encountered during use of mefloquine than proguanil or during non-use of antimalarials.

Adverse Events Study

Ringqvist, Bech, Glenthoj et al (2015)[15] described long term effects of mefloquine in 73 subjects who reported to a Danish national register for mefloquine associated side effects. 16 subjects had a previous personal or family history of psychiatric disorder.

Using a 90-item symptoms questionnaire (SCL-90-R) significant results were displayed ($p < 0.01$) higher scores for the validated subscales anxiety, phobic anxiety, and depression in the adverse event group compared to the matched Danish control group (Table below). In the same subscales, i.e. anxiety, phobic anxiety, and depression, 55%, 51%, and 44% of the study subjects had scores above Danish cut-offs for caseness (i.e. clinically significant). The

[15] Ringqvist A, Bech P, Glenthoj B, et al (2015). Acute and long-term psychiatric side effects of mefloquine: A follow-up on Danish adverse event reports. Travel Medicine and Infectious Disease, 13: 80-8. 075202

subjects estimation of duration of symptoms indicated in the SCL-90-R are given in Table below. Out of 73 subjects, 30 subjects reported symptoms lasting more than 9 months. One subject reported delusional mood and delusions of reference for 9-11 months.

TABLE 6 THE SCL-90-R RETROSPECTIVE SCORES OF 73 CASES WITH ADVERSE REACTIONS TO MEFLOQUINE COMPARED TO DANISH NORMS MATCHED FOR AGE AND GENDER (N = 1090). EACH ITEM WAS RATED ON A FIVE-POINT SCALE OF DISTRESS (0-4) RANGING FROM "NOT AT ALL" THROUGH "EXTREMELY" (RINGQVIST ET AL, 2015).

	Adverse event group (n = 73)	Danish norms (n = 1090)	P
Somatization	0.90 ± 0.71	0.49 ± 0.53	<0.01
Obsessive-compulsive	1.08 ± 0.95	0.62 ± 0.60	<0.01
Interpersonal sensitivity	0.66 ± 0.80	0.55 ± 0.57	n.s.
Depression	1.18 ± 1.00	0.59 ± 0.64	<0.01
Anxiety	1.39 ± 1.03	0.40 ± 0.47	<0.01
Anger-hostility	0.51 ± 0.7	0.34 ± 0.41	n.s.
Phobia	0.77 ± 1.04	0.13 ± 0.33	<0.01
Paranoid ideation	0.4 ± 0.63	0.47 ± 0.59	<0.05
Psychotism	0.47 ± 0.51	0.22 ± 0.32	<0.01
Total SCL-90-R	2.09 ± 0.68	0.45 ± 0.43	<0.01

TABLE 7 SUBJECTS' ESTIMATION OF DURATION OF PHYSICAL SYMPTOMS, NIGHTMARES, COGNITIVE DYSFUNCTION, AND SYMPTOMS IN RESPONSE TO MEFLOQUINE IN THE SCL-90-R. THE STUDY POPULATION CONSISTED OF 73 CASES REPORTED FOR ADVERSE SIDE EFFECTS TO MEFLOQUINE (RINGQVIST ET AL, 2015).

	Cases indicating symptoms	1–2 days	3 days – 3 weeks	1–3 months	4–8 months	9 months – 3 years	Still symptoms
Nightmares	43	2	11	12	5	4	9
Cognitive dysfunction	42	2	10	7	3	6	14
SCL-90-R	68	2	18	12	6	13	17

Significant long-term mental health effects were demonstrated for the SF-36 subscales mental health, role emotional (RE), and vitality (VT) in the mefloquine group compared to Danish norms. The authors suggest that this could have been due to neurotoxic effects but could also be the result of having a stressful life event (the adverse drug reaction) or other unmeasured life events. The authors acknowledge that bias could have been introduced by retrospective collection of symptoms and non-random selection of study subjects.

Nested case-control studies

Schneider, Adamcova, Jick, et al (2013)[16] used the General Practice Research Database to conduct a follow-up study with a nested case-control analysis. They assessed the risk of developing first-time anxiety, stress-related disorders/psychosis, depression, epilepsy or peripheral neuropathies in patients using mefloquine, chloroquine and/or proguanil, or atovaquone/proguanil for malaria chemoprophylaxis, as compared to unexposed travelers.

Compared to non-users of antimalarials, the adjusted odds ratio in the nested case-control analysis for users of mefloquine, chloroquine and/or proguanil, or atovaquone/proguanil were

[16] Schneider C, Adamcova M, Jick SS, et al (2013). Antimalarial chemoprophylaxis and the risk of neuropsychiatric disorders. Travel Medicine and Infectious Disease, 11: 71-80. 075206

0.71 (95% CI 0.56-0.90), 1.04 (95% CI 0.74-1.46), and 0.73 (95% CI 0.61-0.86) for anxiety or stress-related disorders combined, 0.54 (95% CI 0.41-0.71), 1.06 (95% CI 0.71-1.59), and 0.75 (95% CI 0.62-0.91) for depression, 0.69 (95% CI 0.35-1.36), 1.41 (95% CI 0.54-3.67), and 0.75 (95% CI 0.42-1.36) for epilepsy, and 1.22 (95% CI 0.50-2.99), 1.59 (95% CI 0.41-6.15), and 1.05 (95% CI 0.54-2.03) for neuropathies, respectively.

The risk for phobia, anxiety or panic attacks was not elevated for users of mefloquine. The results for mefloquine, chloroquine and/or proguanil and atovaquone/proguanil are provided in the Table below. A sensitivity analysis stratifying the results by BMI did not show any increased risks for any BMI category (data not shown). The findings of a more detailed analysis of the group with anxiety and stress-related disorders are displayed in the second Table below. The risk of all outcomes was higher in females than in males across all exposure categories.

TABLE 8 ODDS RATIOS FOR ANTI-MALARIAL DRUG EXPOSURES IN RELATION TO ANXIETY OR STRESS-RELATED DISORDERS OR PSYCHOSIS, DEPRESSION, EPILEPSY AND NEUROPATHIES.

	Cases (%)	Controls (%)	OR (95% CI)	Adj. OR (95% CI)	*P*-value
Anxiety or stress-related disorders or psychosis					
Unexposed	537 (56.4)	2806 (49.1)	1.00 (ref)	1.00 (ref)	
Mefloquine	98 (10.3)	741 (13.0)	0.69 (0.54–0.87)	0.71 (0.56–0.90)	<0.01
Current	41 (4.3)	293 (5.1)	0.73 (0.52–1.03)	0.76 (0.53–1.08)	0.12
Past	57 (6.0)	448 (7.8)	0.67 (0.50–0.89)	0.68 (0.51–0.92)	0.01
Chloroquine/proguanil	47 (4.9)	238 (4.2)	1.04 (0.74–1.46)	1.04 (0.74–1.46)	0.83
Current	18 (1.9)	68 (1.2)	1.41 (0.82–2.41)	1.39 (0.81–2.40)	0.23
Past	29 (3.0)	170 (3.0)	0.90 (0.60–1.36)	0.90 (0.60–1.36)	0.62
Atovaquone/proguanil	266 (27.9)	1888 (33.1)	0.72 (0.61–0.85)	0.73 (0.61–0.86)	<0.01
Current	90 (9.5)	509 (8.9)	0.91 (0.71–1.16)	0.92 (0.72–1.18)	0.52
Past	176 (18.5)	1379 (24.1)	0.65 (0.54–0.78)	0.65 (0.54–0.79)	<0.01
Mixed exposure	4 (0.4)	39 (0.7)	0.53 (0.19–1.48)	0.56 (0.20–1.58)	0.27
Depression					
Unexposed	423 (57.2)	2181 (49.2)	1.00 (ref)	1.00 (ref)	
Mefloquine	68 (9.2)	640 (14.4)	0.54 (0.41–0.71)	0.54 (0.41–0.71)	<0.01
Current	16 (2.2)	248 (5.6)	0.33 (0.19–0.55)	0.32 (0.19–0.54)	<0.01
Past	52 (7.0)	392 (8.8)	0.67 (0.49–0.92)	0.68 (0.50–0.94)	0.02
Chloroquine/proguanil	33 (4.5)	159 (3.6)	1.07 (0.71–1.59)	1.06 (0.71–1.59)	0.78
Current	6 (0.8)	47 (1.1)	0.66 (0.28–1.58)	0.70 (0.29–1.66)	0.41
Past	27 (3.7)	112 (2.5)	1.23 (0.79–1.92)	1.21 (0.77–1.90)	0.41
Atovaquone/proguanil	210 (28.4)	1421 (32.0)	0.75 (0.62–0.91)	0.75 (0.62–0.91)	<0.01
Current	40 (5.4)	368 (8.3)	0.55 (0.39–0.78)	0.56 (0.40–0.80)	<0.01
Past	170 (23.0)	1053 (23.7)	0.83 (0.68–1.02)	0.83 (0.67–1.02)	0.07
Mixed exposure	5 (0.7)	33 (0.7)	0.80 (0.31–2.06)	0.84 (0.32–2.19)	0.72
Epilepsy					
Unexposed	45 (52.3)	241 (46.7)	1.00 (ref)	1.00 (ref)	
Mefloquine	14 (16.3)	107 (20.7)	0.71 (0.36–1.38)	0.69 (0.35–1.36)	0.28
Current	6 (7.0)	36 (7.0)	0.90 (0.35–2.31)	0.85 (0.33–2.20)	0.74
Past	8 (9.3)	71 (13.8)	0.62 (0.27–1.40)	0.61 (0.27–1.40)	0.24
Chloroquine/proguanil	7 (8.1)	24 (4.7)	1.60 (0.62–4.11)	1.41 (0.54–3.67)	0.48
Current	1 (1.2)	7 (1.4)	0.80 (0.10–6.67)	0.65 (0.08–5.48)	0.69
Past	6 (7.0)	17 (3.3)	1.89 (0.69–5.19)	1.70 (0.61–4.72)	0.31
Atovaquone/proguanil	20 (23.3)	138 (26.7)	0.78 (0.44–1.40)	0.75 (0.42–1.36)	0.34
Current	8 (9.3)	31 (6.0)	1.44 (0.61–3.41)	1.42 (0.59–3.42)	0.44
Past	12 (14.0)	107 (20.7)	0.59 (0.30–1.18)	0.56 (0.28–1.14)	0.11
Mixed exposure	0 (0.0)	6 (1.2)	NA	NA	NA
Neuropathy					
Unexposed	25 (44.6)	159 (47.3)	1.00 (ref)	1.00 (ref)	
Mefloquine	8 (14.3)	42 (12.5)	1.20 (0.50–2.89)	1.22 (0.50–2.99)	0.66
Current	5 (8.9)	16 (4.8)	2.01 (0.66–6.14)	2.27 (0.73–7.06)	0.15
Past	3 (5.4)	26 (7.7)	0.73 (0.21–2.59)	0.67 (0.18–2.43)	0.54
Chloroquine/proguanil	3 (5.4)	13 (3.9)	1.47 (0.39–5.58)	1.59 (0.41–6.15)	0.50
Current	0 (0.0)	3 (0.9)	NA	NA	NA
Past	3 (5.4)	10 (3.0)	1.88 (0.49–7.20)	2.36 (0.58–9.58)	0.23
Atovaquone/proguanil	20 (35.7)	121 (36.0)	1.04 (0.54–2.00)	1.05 (0.54–2.03)	0.89
Current	6 (10.7)	27 (8.0)	1.38 (0.51–3.70)	1.51 (0.54–4.21)	0.43
Past	14 (25.0)	94 (28.0)	0.93 (0.45–1.94)	0.91 (0.44–1.90)	0.80
Mixed exposure	0 (0.0)	1 (0.3)	NA	NA	NA

OR: odds ratio; adj. OR: odds ratio adjusted for smoking, BMI; 95% CI: 95% confidence interval.

TABLE 9 ODD RATIOS FOR ANTI-MALARIAL DRUG EXPOSURE IN RELATION TO PSYCHOSIS, PHOBIA, ANXIETY OR PANIC ATTACKS.

	Cases (%)	Controls (%)	OR (95% CI)	Adj. OR (95% CI)	*P*-value
Psychosis					
Unexposed	19 (42.2)	136 (50.4)	1.00 (ref)	1.00 (ref)	
Mefloquine	10 (22.2)	31 (11.5)	2.40 (0.98–5.86)	2.17 (0.85–5.59)	0.11
Chloroquine/Proguanil	1 (2.2)	12 (4.4)	0.59 (0.07–5.00)	0.47 (0.05–4.11)	0.49
Atovaquone/Proguanil	15 (33.3)	90 (33.3)	1.12 (0.52–2.37)	0.97 (0.44–2.14)	0.93
Mixed exposure	0 (0.0)	1 (0.4)	NA	NA	NA
Phobia					
Unexposed	92 (56.4)	464 (47.4)	1.00 (ref)	1.00 (ref)	
Mefloquine	16 (9.8)	114 (11.7)	0.70 (0.38–1.27)	0.73 (0.40–1.34)	0.30
Chloroquine/proguanil	7 (4.3)	35 (3.6)	1.04 (0.43–2.49)	1.06 (0.44–2.60)	0.89
Atovaquone/proguanil	48 (29.4)	360 (36.8)	0.66 (0.45–0.97)	0.64 (0.43–0.96)	0.03
Mixed exposure	0 (0.0)	5 (0.5)	NA	NA	NA
Anxiety					
Unexposed	293 (58.6)	1463 (48.8)	1.00 (ref)	1.00 (ref)	
Mefloquine	50 (10.0)	422 (14.1)	0.59 (0.43–0.82)	0.60 (0.43–0.83)	<0.01
Chloroquine/proguanil	23 (4.6)	130 (4.3)	0.87 (0.54–1.42)	0.86 (0.53–1.40)	0.54
Atovaquone/proguanil	131 (26.2)	962 (32.1)	0.66 (0.53–0.84)	0.66 (0.52–0.84)	<0.01
Mixed exposure	3 (0.6)	23 (0.8)	0.63 (0.19–2.13)	0.66 (0.20–2.24)	0.51
Panic attack					
Unexposed	121 (56.3)	657 (50.9)	1.00 (ref)	1.00 (ref)	
Mefloquine	18 (8.4)	150 (11.6)	0.64 (0.37–1.11)	0.68 (0.39–1.17)	0.17
Chloroquine/proguanil	10 (4.7)	52 (4.0)	1.04 (0.51–2.09)	1.06 (0.52–2.14)	0.87
Atovaquone/proguanil	65 (30.2)	423 (32.8)	0.84 (0.60–1.17)	0.86 (0.61–1.21)	0.38
Mixed exposure	1 (0.5)	8 (0.6)	0.67 (0.08–5.43)	0.88 (0.11–7.16)	0.90
Other					
Unexposed	12 (41.4)	86 (49.4)	1.00 (ref)	1.00 (ref)	
Mefloquine	4 (13.8)	24 (13.8)	1.10 (0.31–3.94)	1.80 (0.48–6.79)	0.38
Chloroquine/proguanil	6 (20.7)	9 (5.2)	5.17 (1.42–18.77)	6.39 (1.55–26.40)	0.01
Atovaquone/proguanil	7 (24.1)	53 (30.5)	0.96 (0.33–2.77)	1.04 (0.32–3.37)	0.94
Mixed exposure	0 (0.0)	2 (1.1)	NA	NA	NA

Other: Posttraumatic stress disorder, adjustment disorder, reaction to severe stress.
OR: odds ratio; adj. OR: odds ratio adjusted for smoking, BMI; 95% CI: 95% confidence interval.

The risk of neuropsychiatric disorders was similar for users and for non-users of anti-malarial chemoprophylaxis, with evidence for elevated risks in some subgroups.

Meier, Wilcock and Jick (2004)[17] conducted a population-based observational study using a database of medical records to quantify and compare the risk of psychiatric disorders during or after use of mefloquine with the risk during use of proguanil and/or chloroquine, or doxycycline.

The study population was drawn from the large UK-based General Practice Research Database (GPRD). Subjects were aged from 17–79 years and were exposed to mefloquine, proguanil, chloroquine or doxycycline (or a combination of these drugs) at some time between 1990 and 1999. A person-time and a nested case-control analysis was performed to assess the risk of developing a first-time diagnosis of depression, psychosis or panic attack during or after use of these antimalarial drugs.

Within the study population of 35 370 subjects (45.2% males), 580 subjects with a first-time diagnosis of depression (n = 505), psychosis (n = 16) or panic attack (n = 57) were identified and two subjects committed suicide. The incidence rates of first-time diagnoses of depression during current use of mefloquine, proguanil and/or chloroquine, or doxycycline, adjusted for age, gender and calendar year, were 6.9 (95% CI 4.5–10.6), 7.6 (95% CI 5.5–10.5) and 9.5

[17] Meier CR, Wilcock K, Jick SS (2004). The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials. Drug Saf, 27(3): 203-13. 075198

(95% CI 3.7–24.1)/1000 person-years, respectively. The incidence rates of psychosis or panic attacks during current mefloquine exposure were 1.0/1000 person-years (95% CI 0.3–2.9) and 3.0/1000 person-years (95% CI 1.6–5.7), respectively, approximately 2-fold higher (statistically nonsignificant) than during current use of proguanil and/or chloroquine, or doxycycline. The nested case-control analysis encompassed 505 cases with depression and 3026 controls, 16 cases with psychosis and 96 controls, and **57 cases with a panic attack** and 342 controls. Current use of mefloquine was not associated with an elevated risk of developing depression. In a comparison between patients currently using mefloquine with all past users of antimalarials combined, the risk estimate was elevated for current users of mefloquine for both psychosis (odds ratio [OR] 8.0, 95% CI 1.0–62.7; $p < 0.05$) and panic attacks (OR 2.7, 95% CI 1.1–6.5; $p < 0.05$).

TABLE 10 INCIDENCE RATES AND RELATIVE RISK ESTIMATES FOR DEPRESSION (N = 505), PSYCHOSIS (N = 16) OR PANIC ATTACK (N = 57). COMPARISON OF CURRENT OR RECENT USERS OF VARIOUS ANTIMALARIALS WITH THE REFERENCE GROUP OF ALL PAST USERS (MEIER ET AL, 2004).

Outcome	Cases	Person-years	IR/1000 person-years (95% CI)	RR (95% CI)
Depression				
All past use	353	36 863	9.6 (8.6–10.6)	1.0 (ref.)
Mefloquine current	21	3023.4	6.9 (4.5–10.6)	0.7 (0.5–1.1)
Mefloquine recent	32	3474.4	9.2 (6.5–13.0)	1.0 (0.7–1.4)
Proguanil and/or chloroquine current	35	4614.4	7.6 (5.5–10.5)	0.8 (0.6–1.1)
Proguanil and/or chloroquine recent	50	4807.7	10.4 (7.9–13.7)	1.1 (0.8–1.5)
Doxycycline current	4	423.0	9.5 (3.7–24.1)	1.0 (0.3–2.2)
Doxycycline recent	10	1225.6	8.2 (4.4–14.9)	0.8 (0.4–1.4)
Pychosis				
All past use	9	36 863	0.2 (0.1–0.5)	1.0 (ref.)
Mefloquine current	3	3023.4	1.0 (0.3–2.9)	4.1 (1.1–15.0)[a]
Mefloquine recent	1	3474.4	0.3 (0.1–1.6)	1.2 (0.2–9.3)
Proguanil and/or chloroquine current	2	4614.4	0.4 (0.1–1.6)	1.8 (0.4–8.2)
Proguanil and/or chloroquine recent	1	4807.7	0.2 (0.1–1.2)	0.9 (0.1–6.7)
Doxycycline current	0	423.0	0 (0.0–9.0)	
Doxycycline recent	0	1225.6	0 (0.0–3.1)	
Panic attacks				
All past use	27	36 863	0.7 (0.5–1.1)	1.0 (ref.)
Mefloquine current	9	3023.4	3.0 (1.6–5.7)	4.1 (1.9–8.6)[b]
Mefloquine recent	6	3474.4	1.7 (0.8–3.8)	2.4 (1.0–5.7)[a]
Proguanil and/or chloroquine current	6	4614.4	1.3 (0.6–2.8)	1.8 (0.7–4.3)
Proguanil and/or chloroquine recent	8	4807.7	1.7 (0.8–3.3)	2.3 (1.0–5.0)[a]
Doxycycline current	0	423.0	0 (0.0–9.0)	
Doxycycline recent	1	1225.6	0.8 (0.1–4.6)	1.1 (0.2–8.2)

a $p < 0.05$.

b $p < 0.001$.

IR = incidence rate; **ref.** = reference; **RR** = relative risk.

TABLE 11 ASSOCIATION BETWEEN ANTIMALARIAL DRUG EXPOSURE AND DEPRESSION, PSYCHOSIS OR PANIC ATTACK IN NESTED CASE-CONTROL ANALYSES (MEIER ET AL, 2004).

Exposure status	Study population		OR (95% CI)[a]	OR (95% CI)[b]
Depression	Cases (n = 505)[c]	Controls (n = 3026)[c]		
All past users combined	362	1960	1.0 (ref.)	
Mefloquine current	21	200	0.5 (0.3–0.9)[d]	0.9 (0.5–1.6)
Mefloquine recent	29	223	0.7 (0.5–1.1)	
Proguanil and/or chloroquine, current	33	259	0.7 (0.5–1.0)	1.0 (ref.)
Proguanil and/or chloroquine recent	46	312	0.8 (0.6–1.2)	
Doxycycline current	3	12	1.2 (0.3–4.3)	1.7 (0.4–6.6)
Doxycycline recent	8	52	0.7 (0.3–1.6)	
Psychosis	Cases (n = 16)	Controls (n = 96)		
All past users combined	9	61	1.0 (ref.)	
Mefloquine current	3	4	8.0 (1.0–62.7)[d]	9.8 (0.5–204)
Mefloquine recent	1	5	2.4 (0.1–39.1)	
Proguanil and/or chloroquine current	2	13	1.1 (0.1–8.5)	1.0 (ref.)
Proguanil and/or chloroquine recent	1	8	0.7 (0.1–7.8)	
Doxycycline current	0	2		
Doxycycline recent	0	3		
Panic attack	Cases (n = 57)	Controls (n = 342)		
All past users combined	28	227	1.0 (ref.)	
Mefloquine current	9	27	2.7 (1.1–6.5)[d]	1.7 (0.5–5.7)
Mefloquine recent	6	21	2.3 (0.8–6.1)	
Proguanil and/or chloroquine current	6	32	1.5 (0.6–3.9)	1.0 (ref.)
Proguanil and/or chloroquine recent	7	30	1.9 (0.7–4.9)	
Doxycycline current	0	1		
Doxycycline recent	1	4	2.0 (0.2–19.0)	

a Current or recent mefloquine, doxycycline or chloroquine and/or proguanil use, compared with all past users combined, adjusted for smoking status (non, current, ex, unknown) and BMI (<25, 25–29.9, 30+ kg/m²).

b Current mefloquine or doxycycline use compared with the reference group of current chloroquine and/or proguanil use, adjusted for smoking status (non, current, ex, unknown) and BMI (<25, 25–29.9, 30+ kg/m²).

c Cases and controls do not add up to 505 and 3026, respectively. Three cases and eight controls are not listed in the table as they had meaningless risk estimates due to mixed exposure (e.g. mefloquine recent and doxycycline past).

d $p < 0.05$.

BMI = body mass index; **OR** = odds ratio; **ref.** = reference.

The absolute risk of developing psychosis or panic attack appears low with all the antimalarials tested. No evidence was found in this large observational study that mefloquine use increased the risk of first-time diagnosis of depression when compared with the use of other antimalarials investigated in this study.

Cross-sectional studies

Durrheim, Gammon, Waner and Braack (1999)[18] conducted a retrospective survey to determine the use of antimalarial prophylaxis and the relative frequency of adverse events with different regimens in visitors to the Kruger National Park. The study was a retrospective postal survey of a cohort of 7,397 visitors during April 1996. Telephonic interviews were conducted with all respondents who reported neuropsychiatric adverse events necessitating medical attention, and their medical caregivers.

The most commonly used regimens were chloroquine and proguanil in combination (C&P) (35.6%) and mefloquine (18.4%). However, non-recommended regimens were also used by travellers to this chloroquine-resistant area, including chloroquine alone (15.7%). Adverse

[18] Durrheim D N, Gammon S, Waner S, Braack, L E. (1999). Antimalarial prophylaxis--use and adverse events in visitors to the Kruger National Park. South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde. 89(2):170-5.

events were reported by 23.8% of travellers and were more common in the C&P group than the mefloquine group (28.9% v. 25.0%, P = 0.0100). Gastro-intestinal side-effects were significantly more common in the C&P group (nausea (P = 0.0170), diarrhoea (P = 0.0008), mouth ulcers (P = 0.0000)), while neuropsychiatric side-effects were more common in the mefloquine group (depression (P = 0.0000), light-headedness (P = 0.0009), anxiety (P = 0.0060)). Only 30% of travellers reported using antimalarial drugs both regularly as prescribed and for 4 weeks after leaving the malaria area. The most commonly reported reason for changing prophylaxis was advice from a physician or pharmacist (41.9%).

Health professionals providing medical advice to prospective travellers to malarious areas must tailor recommendations based on the balance between malaria risk in a specific geographical area and the benefits and tolerance of protective measures. Mosquito-avoidance measures should always be advocated, but counselling on antimalarial prophylaxis will be guided by the malaria/prophylaxis (serious adverse events) risk ratio. Where drug measures are indicated, the importance of their correct use should be emphasised.

Case reports

Lobel, Coyne and Rosenthal (1998)[19] report three cases of iatrogenic/accidental overdose with mefloquine. Although serious side effects were noted, which lasted for 12 months or more, and permanently in one case, no anxiety symptoms were noted.

Nevin (2012)[20] report an adverse reaction to mefloquine chemoprophylaxis which was described as being characterised by prodromal symptoms of anxiety with subsequent development of psychosis, short-term memory impairment, confusion and personality change accompanied by complaints of disequilibrium and vertigo, with objective findings of central vestibulopathy. It is posited that these effects represent an idiosyncratic neurotoxic syndrome of progressive limbic encephalopathy and multifocal brainstem injury caused by the drug.

Within 12 h of taking his first 250 mg dose of a generic U.S. formulation of the drug, the patient experienced the onset of unease, anxiety, and foreboding, which increased over the next two days. By the third day he was reporting intermittent mumbling auditory hallucinations and a sense of the presence of a nearby nondescript female. On the fifth day he told his spouse in the U.S. by telephone that he felt “dark” and had the “devil inside” of him.

The patient had not read the mefloquine medication guide nor been issued the information wallet card provided by the drug’s generic manufacturer, and he was thus unaware his symptoms could be considered prodromal to a more serious event. The patient did not announce nor seek medical advice for these symptoms at his next supervised drug administration visit as he was highly reluctant to draw attention to his symptoms in a group setting or risk being perceived as non-compliant.

Shortly after his second supervised dose, he returned home by airplane for a week of scheduled training, where upon arrival his spouse noted him to be paranoid, distant, and confused, with a markedly changed personality. He explained that he felt “evil”. During this

[19] Lobel HO, Coyne PE, Rosenthal PJ (1998). Drug overdoses with antimalarial agents: prescribing and dispensing errors. JAMA, 280(17): 1483. 076985

[20] Nevin RL (2012). Limbic encephalopathy and central vestibulopathy caused by mefloquine: A case report. Travel Medicine and Infectious Disease, 10: 144-51. 075201

period he began suffering new onset sleep disturbance, and continued to experience anxiety, paranoia, and intermittent auditory hallucinations.

The patient continued to take the drug for up to 7 doses. Over subsequent weeks and months the psychiatric symptoms and his sleep disturbances gradually decreased in frequency and severity, and his physical symptoms including palpitations, tinnitus, vertigo and disequilibrium became relatively more prominent.

Ten months after symptom onset and at the conclusion of reported follow-up, the patient's improvement had plateaued. He remained restricted from driving due to persistent episodes of vertigo and disequilibrium. He walked with a cane at all times, which provided him dramatic relief from a sense of fatigue noted previously with only intermittent use of the cane when symptomatic. He complained of new onset, occasional visual illusions marked by a sudden loss of depth perception or the presence of "heat waves". He also complained of visual sensitivity to bright or flickering lights and crowds. He struggled with impairment in short-term spatial and working memory, which he would attempt to overcome by consolidating frequently misplaced objects at a central location, and by making prodigious notes to himself as reminders. The patient complained of personality change marked by increased irritability, and his spouse noted that he was simply "a different person".

Javorsky, Tremont, Keitner and Parmentier (2001)[21] reported the case of a 52-year-old master's-educated woman exhibited neuropsychiatric symptoms in close temporal relationship to using mefloquine prophylactically once a week for 3 week (250 mg) prior to and during a trip to Africa. She acutely developed anxiety, paranoia, visual hallucinations, confusion, and depressive symptoms during her return flight. She was initially treated as an outpatient with olanzapine, lorazepam, fluoxetine, and trazodone. When she continued to show suicidal ideation, other neuropsychiatric symptoms, and cognitive disturbances 3 months after her last dose of mefloquine, she was hospitalized for inpatient psychiatric treatment. Laboratory and infectious disease workup showed mildly elevated TSH (7.04 lU/ml) with normal free T3 and T4, and was positive for past exposure to hepatitis A. Brain MRI showed no abnormalities. Medical history was noncontributory. She had previously used mefloquine as a prophylaxis intermittently for about 4 years with no adverse reactions. While hospitalized, she was treated with risperidone and paroxetine and showed improvement in mood symptoms and cognition over 4 days. After initially living with her daughter following discharge, she returned to independent functioning.

Colebunders (2011)[22] described the case of 48 year old Kenyan woman who developed fear of flying which appeared to be related to the mefloquine she took as prophylaxis prior to the flight to Africa. The woman had lived in Belgium for more than a decade, and consulted with a physician at the Institute of Tropical Medicine in Antwerp. She planned to visit her family in Nairobi and asked for a letter stating that she might need oxygen during the flight. During two previous flights to Nairobi, she experienced difficulties breathing, palpitations, dizziness, weakness and anxiety. Each time the aircrew administered oxygen. She was very afraid that she might experience the same problems again. She was HIV seropositive and treated with tenofovir 300 mg daily, lamivudine 150mg daily, atazanavir 300mg daily and ritonavir 100 mg

[21] Javorsky DJ, Tremont G, Keitner GI, et al (2001). [Comment] Cognitive and neuropsychiatric side effects of mefloquine. J Neuropsychiatry Clin Neurosci, 13(2): 302. 077901
[22] Colebunders R (2011). Cured of fear of flying. Travel Medicine and Infectious Disease, 9(2): 82. 078032

daily. Her CD4 lymphocyte count was 936 cells/mL and her viral load < 20 copies/ml. Her body weight was 67 kg. Kidney function and liver tests were normal. There was no history of psychiatric or cardiac illness. Physical examination did not reveal any abnormalities. Prior to the two previous flights she took mefloquine 1 tablet per week starting 2 weeks before departure. It was explained to her that the problems she experienced were probably side effects of mefloquine and advised her to take doxycycline instead. She followed the physician's advice and there were no problems during the flight to Nairobi.

Biological mechanism

Dow, Hudson, Vahey and Koenig (2003)[23] investigated the possibility that the acute in vitro neurotoxicity of mefloquine might be mediated through a disruptive effect of the drug on endoplasmic reticulum (ER) calcium homeostasis. This study was conducted to try and explain the biochemical basis for the neurotoxicity of mefloquine.

Laser scanning confocal microscopy was employed to monitor real-time changes in basal intracellular calcium concentrations in embryonic rat neurons in response to mefloquine and thapsigargin (a known inhibitor of the ER calcium pump) in the presence and absence of external calcium. Changes in the transcriptional regulation of known ER stress response genes in neurons by mefloquine were investigated using Affymetrix arrays. The MTT assay was employed to measure the acute neurotoxicity of mefloquine and its antagonisation by thapsigargin.

At physiologically relevant concentrations mefloquine was found to mobilize neuronal ER calcium stores and antagonize the pharmacological action of thapsigargin, a specific inhibitor of the ER calcium pump. Mefloquine also induced a sustained influx of extra-neuronal calcium via an unknown mechanism. The transcription of key ER proteins including GADD153, PERK, GRP78, PDI, GRP94 and calreticulin were up-regulated by mefloquine, suggesting that the drug induced an ER stress response. These effects appear to be related, in terms of dose effect and kinetics of action, to the acute neurotoxicity of the drug in vitro.

Mefloquine was found to disrupt neuronal calcium homeostasis and induce an ER stress response at physiologically relevant concentrations, effects that may contribute, at least in part, to the neurotoxicity of the drug in vitro.

Animal study

Dow, Bauman, Caridha, Cabezas et al (2006)[24] conducted a study to investigate the potential neurological effects of mefloquine using six 7-week-old female rats which were given a single oral dose of the compound. Potential mefloquine-induced neurological effects were monitored using a standard functional observational battery, automated open field tests, automated spontaneous activity monitoring, a beam traverse task, and histopathology. Plasma mefloquine concentrations were determined 72 h after dosing by using liquid chromatography-mass spectrometry. Mefloquine induced dose-related changes in endpoints associated with spontaneous activity and impairment of motor function and caused degeneration of specific brain stem nuclei (nucleus gracilis). Increased spontaneous motor activity was observed only

[23] Dow GS, Hudson TH, Vahey M, et al (2003). The acute neurotoxicity of mefloquine may be mediated through a disruption of calcium homeostasis and ER function in vitro. Malar J, 2: 14. 077978
[24] Dow G, Bauman R, Caridha D, et al (2006). Mefloquine induces dose-related neurological effects in a rat model. Antimicrob Agents Chemother, 50(3): 1045-53. 077977

during the rats' normal sleeping phase, suggesting a correlate to mefloquine-induced sleep disorders. The threshold dose for many of these effects was 187 mg/kg of body weight. This dose yielded plasma mefloquine concentrations after 72 h that are similar to those observed in humans after the treatment dose. Collectively, these data suggest that there may be a biological basis for some of the clinical neurological effects associated with mefloquine.

Summary and conclusions

The quality of the evidence discussed below varies, however, it would appear that the better quality studies supports an association between mefloquine exposure and neuropsychiatric symptoms including agitation, nervousness and anxiety.

A number of reviews (McCarthy, 2015; USFDA, 2013;Jousset et al, 2010) reported on the neuropsychiatric adverse events of mefloquine reported in the literature. Anxiety symptoms are acknowledged as a moderate complication.

A randomised clinical trial (Soukhathammavong et al, 2011) assessing the efficacy of certain drugs including mefloquine and mefloquine-artesunate as a treatment for a liver fluke found that these drugs were not effective and also that only patients using these drugs reported serious adverse events of vertigo, nausea, vomiting, and anxiety**.** A randomised clinical trial (Grande et al, 2007) comparing efficacy of mefloquine-artesunate with dihydroartemisinin-piperaquine reported that anxiety symptoms were significantly more frequent in the mefloquine-artesunate group.

Adshead (2014) in a prospective study found that anxiety was a less commonly reported adverse side effect, with approximately 15% of the cohort of deployed personnel reporting it as a side effect. Interestingly, deployed personnel overall reported more adverse events than civilian samples.

The Millennium Cohort research group (Wells et al, 2006) used standard military database comparing personnel deployed and prescribed mefloquine to two reference groups who were not prescribed mefloquine – one group residing in Europe and Japan and the other group otherwise deployed. Their results suggested no association between issued mefloquine prescriptions and hospitalisation for an ICD-9 anxiety diagnosis. However, many limitations of this study were noted. They relied on prescription database data to indicate mefloquine use and adverse events which were severe enough to require hospitalisation were the only outcomes measured. They could not be sure that tablets prescribed were taken or that less severe to moderate adverse events were not reported which did not require hospitalisation.

An Australian study of soldiers deployed to East Timor (Kitchener et al, 2005) who used mefloquine for malaria prophylaxis were compared with a group who used doxycycline. Seventy-five soldiers from the total 1 157 soldiers studied withdrew due to adverse events. Three serious neuropsychiatric adverse events were reported, one soldier experiencing depression, episodic anxiety and paranoia. The nature of the milder neuropsychiatric adverse events were not discussed (n = 62).

von Riemsdijk et al (1997) used travel clinic data to compare the neuropsychiatric adverse effects of mefloquine vs proguanil. Comparing the mefloquine group (n=349) with the proguanil group (n=493), travellers taking mefloquine prophylaxis were significantly more likely to report any psychiatric adverse events (RR = 7.2; 95% CI 2.1-24.0).

Likewise, Ringquist et al, (2015), in a Danish national register study reporting adverse events of mefloquine found that the mefloquine adverse event group were significantly more likely to report anxiety symptoms as measured by the SCL-90-R questionnaire than the general Danish population.

The nested-case control study by Schneider, Adamcova, Jick, et al (2013) did not find a statistically significant association between the risk for phobia, anxiety or panic attacks in users of mefloquine, chloroquine and/or proguanil and atovaquone/proguanil. In a UK nested case-control study, Meier et al (2004) reported a significant increase in panic attacks in various sub-analyses in participants with current and or recent mefloquine use.

A cross-sectional study (Durrheim et al, 1999) and various case reports found associations between mefloquine use and anxiety symptoms as side effects.

The review by Quinn (2015) and two papers by Dow et al (2003; 2006) discuss various mechanisms which could explain the pathogenesis of neuropsychiatric events occurring during and after mefloquine use.

The majority of studies are supportive of an association. There is evidence strong enough to support a judgement of a probable causal relationship, but chance, bias or confounding cannot be ruled out with reasonable confidence.

Grade 2 level evidence

Other antimalarials

Summary of important issues

A request was received relating to tafenoquine seeking to have the contents of relevant Statements of Principles reviewed in terms of the use of tafenoquine as a causal or aggravating factor. The identified articles in the request for review were identified and scrutinised and further articles were also obtained.

The evidence regarding antimalarials causing anxiety/panic attacks or aggravating anxiety or panic disorders, excluding mefloquine discussed above, is very limited.

Randomised clinical studies

Llanos-Cuentas, Lacerda, Rueangweerayut et al (2014)[25] assessed the dose–response, safety, and tolerability of single-dose tafenoquine plus 3-day chloroquine for *P vivax* malaria radical cure. In this double-blind, randomised, dose-ranging phase 2b study, men and women (aged ≥16 years) with microscopically confirmed *P vivax* monoinfection (parasite density >100 to <100 000 per µL blood) were enrolled from community health centres and hospitals across seven sites in Brazil, Peru, India, and Thailand. Patients with glucose-6-phosphate dehydrogenase enzyme activity of less than 70% were excluded. Eligible patients received chloroquine (days 1−3) and were randomly assigned (1:1:1:1:1:1) by a computer-generated randomisation schedule to receive single dose tafenoquine 50 mg, 100 mg, 300 mg, or 600 mg, primaquine 15 mg for 14 days, or chloroquine alone. Randomisation was stratified by baseline parasite count (≤7500 and >7500 per µL blood). The primary efficacy endpoint was relapse-free efficacy at 6 months from initial dose (ie, clearance of initial infection without subsequent microscopically confirmed infection), analysed by intention to treat.

Between Sept 19, 2011, and March 25, 2013, 329 patients were randomly assigned to a treatment group (chloroquine plus tafenoquine 50 mg [n=55], 100 mg [n=57], 300 mg [n=57], 600 mg [n=56]; or to chloroquine plus primaquine [n=50]; or chloroquine alone [n=54]). Relapse-free efficacy at 6 months was 57·7% (95% CI 43−70) with tafenoquine 50 mg, 54·1% (40−66) with tafenoquine 100 mg, 89·2% (77−95) with tafenoquine 300 mg, 91·9% (80−97) with tafenoquine 600 mg, 77·3% (63−87) with primaquine, and 37·5% (23−52) with chloroquine alone. Tafenoquine 300 mg and 600 mg had better efficacy than chloroquine alone (treatment differences 51·7% [95% CI 35−69], p<0·0001, with tafenoquine 300 mg and 54·5% [38−71], p<0·0001, with tafenoquine 600 mg), as did primaquine (treatment difference 39·9% [21−59], p=0·0004). Adverse events were similar between treatments. 29 serious adverse events occurred in 26 (8%) of 329 patients; QT prolongation was the most common serious adverse event (11 [3%] of 329), occurring in five (2%) of 225 patients receiving tafenoquine, four (8%) of 50 patients receiving primaquine, and two (4%) of 54 patients receiving chloroquine alone, with no evidence of an additional effect on QT of chloroquine plus tafenoquine coadministration. **No anxiety symptoms or panic attacks associated with the drugs were reported.**

[25] Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, et al (2014). Tafenoquine plus chloroquine for the treatment and relapse prevention of plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. 078014

Single-dose tafenoquine 300 mg coadministered with chloroquine for *P vivax* malaria relapse prevention was more efficacious than chloroquine alone, with a similar safety profile. As a result, it has been selected for further clinical assessment in phase 3.

Nasveld, Edstein, Reid et al (2010)[26] described the study which represented the first phase III trial of the safety, tolerability, and effectiveness of tafenoquine for malaria prophylaxis. In a randomized (3:1), double-blinded study, Australian soldiers received weekly malaria prophylaxis with 200 mg tafenoquine (492 subjects) or 250 mg mefloquine (162 subjects) for 6 months on a peacekeeping deployment to East Timor. After returning to Australia, tafenoquine-receiving subjects received a placebo and mefloquine-receiving subjects received 30 mg primaquine daily for 14 days. There were no clinically significant differences between haematological and biochemical parameters of the treatment groups. Treatment-related adverse events for the two groups were similar (tafenoquine, 13.4%; mefloquine, 11.7%). Three subjects on tafenoquine (0.6%) and none on mefloquine discontinued prophylaxis because of possible drug-related adverse events. No diagnoses of malaria occurred for either group during deployment, but 4 cases (0.9%) and 1 case (0.7%) of *Plasmodium vivax* infection occurred among the tafenoquine and mefloquine groups, respectively, up to 20 weeks after discontinuation of medication. In a subset of subjects recruited for detailed safety assessments, treatment-related mild vortex keratopathy was detected in 93% (69 of 74) of tafenoquine subjects but none of the 21 mefloquine subjects. The vortex keratopathy was not associated with any effect on visual acuity and was fully resolved in all subjects by 1 year.

TABLE 12 NEUROPSYCHIATRIC EVENTS IN SUBJECTS ON TAFEOQUINE OR MEFLOQUINE (PROPHYLACTIC PHASE)[A] (NASVELD ET AL, 2010).

Adverse event	No. (%) of subjects by AE severity and treatment group					
	Mild		Moderate		Total	
	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine
Vertigo	22 (5)	7 (4)	0	1 (<1)	22 (5)	8 (5)
Somnolence	12 (2)	6 (4)	0	0	12 (2)	6 (4)
Abnormal dreams	7 (1)	2 (1)	0	0	7 (1)	2 (1)
Dizziness	5 (1)	2 (1)	0	0	5 (1)	2 (1)
Insomnia	4 (<1)	3 (2)	1 (<1)	0	5 (1)	3 (2)
Abnormal coordination	2 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)
Anxiety	2 (<1)	0	0	0	2 (<1)	0
Agitation	2 (<1)	0	0	0	2 (<1)	0
Euphoria	2 (<1)	0	0	0	2 (<1)	0
Tremor	2 (<1)	0	0	0	2 (<1)	0
Depression	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Paroniria	1 (<1)	0	0	0	1 (<1)	0
Amnesia	1 (<1)	0	0	0	1 (<1)	0

[a] In total, there were 492 tafenoquine subjects and 162 mefloquine subjects. There were no severe adverse events (AEs) of this type.

The table above shows the neuropsychiatric events reported by subjects taking tafenoquine or mefloquine during the study. Two subjects taking tafenoquine reported anxiety as a mild adverse reaction. Tafenoquine appears to be safe and well tolerated as malaria prophylaxis. Although the volunteers' precise exposure to malaria could not be proven in this study, tafenoquine appears to be a highly efficacious drug for malaria prophylaxis.

[26] Nasveld PE, Edstein MD, Reid M, et al (2010). Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother, 54(2): 792-8. 077907

Charles, Miller, Nasveld et al (2007)[27] examined the population pharmacokinetics of tafenoquine in Australian soldiers taking tafenoquine for malarial prophylaxis. The subjects (476 males and 14 females) received a loading dose of 200 mg tafenoquine base daily for 3 days, followed by a weekly dose of 200 mg tafenoquine for 6 months. Blood samples were collected from each subject after the last loading dose and then at weeks 4, 8, and 16. Plasma tafenoquine concentrations were determined by liquid chromatography-tandem mass spectrometry. Population modelling was performed with NONMEM, using a one-compartment model. Typical values of the first-order absorption rate constant (Ka), clearance (CL/F), and volume of distribution (V/F) were 0.243 h1, 0.056 litres/h/kg, and 23.7 litres/kg, respectively. The intersubject variability (coefficient of variation) in CL/F and V/F was 18% and 22%, respectively. The interoccasion variability in CL/F was 18%, and the mean elimination half-life was 12.7 days. A positive linear association between weight and both CL/F and V/F was found, but this had insufficient impact to warrant dosage adjustments. Model robustness was assessed by a nonparametric bootstrap (200 samples). A degenerate visual predictive check indicated that the raw data mirrored the postdose concentration-time profiles simulated (n 1 000) from the final model. Individual pharmacokinetic estimates for tafenoquine did not predict the prophylactic outcome with the drug for four subjects who relapsed with *Plasmodium vivax* malaria, as they had similar pharmacokinetics to those who were free of malaria infection.

No cases of adverse events relating to anxiety symptoms were reported (see table below).

TABLE 13 TAFENOQUINE PHARMACOKINETIC DATA FOR SIX SUBJECTS REPORTING AT LEAST ONE ADVERSE EFFECT CLASSIFIED AS SEVERE (*N* = 1) OR MODERATE (*N* = 5) (CHARLES ET AL, 2007).

Adverse event	Treatment duration (days)[a]	Cumulative dose (mg)[b]	Dosing stopped	C_{last} (ng/ml)[c]	CL/*F* (liters/h/kg)	*V*/*F* (liters/kg)	$t_{½}$ (days)
Severe event							
Diarrhea and/or abdominal pain	2	400	No	*	0.059	24.4	12.0
Moderate events							
Insomnia	1	200	No	*	0.059	23.2	11.3
Hyperesthesia	12	800	Yes	283	0.046	20.7	13.1
Abdominal pain	20	1,000	Yes	253	0.053	27.8	15.1
Depression	24	1,000	Yes	275	0.061	25.1	12.0
Vomiting and/or nausea	3	600	No	315	0.077	26.1	9.8

[a] Number of days from starting dosing until adverse event reported.
[b] Total amount of drug taken before adverse event reported.
[c] Last plasma tafenoquine concentration before adverse event reported. *, adverse event was reported before first plasma sample was drawn.

No obvious pattern existed between the plasma tafenoquine concentration and the pharmacokinetic parameter values for subjects with and without drug-associated moderate or severe adverse events. This validated population pharmacokinetic model satisfactorily describes the disposition and variability of tafenoquine used for long-term malaria prophylaxis in a large cohort of soldiers on military deployment.

Chloroquine plus proguanil is widely used for malaria chemoprophylaxis despite low effectiveness in areas where multidrug-resistant malaria occurs. Studies have shown that atovaquone and proguanil hydrochloride is safe and effective for prevention of falciparum malaria in lifelong residents of malaria-endemic countries, but little is known about non-

[27] Charles BG, Miller AK, Nasveld PE, et al (2007). Population pharmacokinetics of tafenoquine during malaria prophylaxis in healthy subjects. Antimicrob Agents Chemother, 51(8): 2709-15. 077898

immune travellers. **Hogh, Clarke, Camus et al (2000)**[28] reported on a double-blind equivalence trial, 1083 participants travelling to a malaria-endemic area were randomly assigned to two treatment groups: atovaquone-proguanil plus placebos for chloroquine and proguanil, or chloroquine, proguanil, and placebo for atovaquone-proguanil. Follow-up was by telephone 7 and 60 days after travel and at a clinic at 28 days. Serum samples were tested for antibodies to a malaria circumsporozoite protein. Blood and serum samples of participants with a potential malaria diagnosis were tested in a reference laboratory.

Seven days after travel, at least one adverse event was reported by 311 (61%) of 511 participants who received atovaquone-proguanil and 329 (64%) of 511 who received chloroquine-proguanil. People receiving atovaquone-proguanil had a lower frequency of treatment-related gastrointestinal adverse events (59 [12%] vs 100 [20%], p=0.001), and of treatment-related adverse events of moderate or severe intensity (37 [7%] vs 56 [11%], p=0.05). There were fewer treatment-related adverse events that caused prophylaxis to be discontinued in the atovaquone-proguanil group than in the chloroquine-proguanil group (one [0.2%] vs ten [2%], p=0.015).

Overall the two preparations were similarly tolerated. However, significantly fewer adverse gastrointestinal events were observed in the atovaquone-proguanil group in than in the chloroquine-proguanil group.

Cohort study

Terrell, Forde, Firth et al (2015)[29] conducted a study to identify which drug has a lesser impact on the travellers' ability to work as measured by self-reported severity of adverse effects via a questionnaire. This was a questionnaire-based two-arm cohort study. Participants were soldiers selected from 10 consecutive units training in Kenya during 2012 and 2013. The exposure was either doxycycline or mefloquine and the main outcome measure was impact upon ability to work. Each cohort was advised to take doxycycline or mefloquine with exceptions at the individual level where medically or occupationally advised.

Significantly more (p<0.0001) doxycycline users reported that one or more adverse effects had interfered with their ability to do their job than mefloquine users. Of the 867 mefloquine users, who reported on the impact of adverse effects, 109 (12.6%) reported that one or more adverse effects had impacted upon their ability to do their job, compared to 152 (22.2%) of the 685 doxycycline users who had reported on the impact of any adverse effects. Doxycycline symptoms were predominantly gastrointestinal and dermatological, whereas mefloquine symptoms were neuropsychiatric. Anxiety symptoms were not reported in this study and only one case of panic attack was reported in a participant taking doxycycline (see table below).

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[28] Hogh B; Clarke PD; Camus D; Nothdurft HD; Overbosch D; Gunther M; Joubert I; Kain KC; Shaw D; Roskell NS; Chulay JD; Malarone International Study Team. (2000). Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. Malarone International Study Team. Lancet; 356(9245):1888-94.

[29] Terrell AG, Forde ME, Firth R, et al (2015). Malaria chemoprophylaxis and self-reported impact on ability to work: mefloquine versus doxycycline. J Travel Med, 22(6): 383-8. 077918

TABLE 14 PARTICIPANTS REPORTING OTHER SYMPTOMS (TERRELL ET AL, 2015).

Symptom	Doxycycline	Mefloquine
Altered sensation—hands	4	
Altered sensation—head		1
Chest infection		1
Chest pain/shortness of breath	2	
Crabs	1	
Hot sweats	1	
Kidney/back pain		1
Loss of libido		1
Lump in groin		1
Mouth ulcer	1	
Muscle stiffness	1	
Nose bleeds		2
Panic attacks	1	
Shin splints		1
Sore throat		1
Vaginal rash	1	

Self-reported symptoms were common in those that responded and, while the true background rate of adverse effects (off any medication) is unknown, doxycycline had a significantly increased rate compared with mefloquine and was associated with a greater occupational impact. Therefore, this study supports the view that, for organizations which provide malaria chemoprophylaxis to employees free of charge, mefloquine should be the first-choice antimalarial drug where the only alternative is doxycycline.

Nasveld, Kitchener, Edstein and Reickmann (2002)[30] conducted a small prospective study comparing primaquine or tafenoquine efficacy in a group of Australian Defence Force personnel. On return from duty in North Solomons Province (including Bougainville Island), Papua New Guinea, 586 Australian Defence Force personnel received either primaquine (14-d) or tafenoquine (3-d) postexposure malaria prophylaxis. Within 12 months, 6 of the 214 volunteers receiving primaquine and 7 of 378 receiving tafenoquine had developed vivax malaria. Overall, volunteers preferred the shorter course of tafenoquine.

Drug tolerability was assessed by direct questioning and completion of a study diary by volunteers. Both drugs were associated with gastrointestinal disturbances such as nausea and abdominal pain. In this open-label design, tafenoquine produced more adverse events than primaquine. In contrast to primaquine, the adverse events associated with tafenoquine tended to be of greater intensity. However, they were transient in nature, generally non-troubling and did not interfere with the volunteers' daily activities. No neuropsychiatric symptoms were reported in this cohort.

Open-label, randomised, parallel-group clinical study

Elmes, Nasveld, Kitchener et al (2008)[31] reported on an open-label study, 1512 Australian Defence Force personnel received one of three tafenoquine 3 d regimens [400 mg once daily

[30] Kitchener SJ, Nasveld PE, Gregory RM, et al (2005). Mefloquine and doxycycline malaria prophylaxis in Australian soliders in East Timor. MJA, 182(4): 168-71. 077980

[31] Elmes NJ, Nasveld PE, Kitchener, et al (2008). The efficacy and tolerability of three different regimens of tefenoquine versus primaquine for post-exposure prophylaxis of plasmodium vivax malaria in the Southwest Pacific. Trans R Soc Trop Med Hygiene; 102:1095-1101. 077976

(od), 200 mg twice daily (bid), 200 mg od] or daily primaquine (22.5 mg) plus doxycycline (100 mg) over 14 d in Bougainville and in Timor-Leste for post-exposure prophylaxis. The relapse rate of subjects treated in Bougainville with tafenoquine (n = 173) was 1.2% (200 mg bid×3 d) and 2.3% (400 mg od×3 d), while primaquine plus doxycycline (n = 175) was 3.4%. For subjects treated in Timor- Leste with tafenoquine (n = 636), the relapse rate was 4.9% (200 mg od×3 d), 5.3% (200 mg bid×3 d) and 11.0% (400 mg od×3d), while primaquine plus doxycycline (n = 289) was 10.0%. The most frequent adverse events reported across all groups were nausea, abdominal distress and diarrhoea. No neuropsychiatric symptoms (including anxiety and/or panic attacks) were reported as adverse events. There was a dose-dependent reduction in adverse events with a reduced dose of tafenoquine, with the lowest dose (total 600 mg over 3 d) producing rates of adverse events equivalent to that of primaquine plus doxycycline. The much shorter dosing regimen of tafenoquine should increase compliance, which is often suboptimal with primaquine after leaving an endemic area.

Case Series

Atigari,Hogan and Healy (2013)[32] conducted a case series outlining three young individuals with no history of mental disorder who were treated for skin conditions with doxycycline, but developed suicidal ideation with an outcome of suicide in two of the cases. One of these individuals had CYP2C19*2 heterozygote genotype associated with a diminished cytochrome p450 enzyme activity and two of his siblings had developed severe anxiety previously while on doxycycline. Another had previously developed mood difficulties on a lower dose of doxycycline which resolved after discontinuation. In the third individual, a discontinuation of doxycycline has led to the resolution of symptoms without the need for psychotropic medications.

According to Atigari and colleagues (2013):

"Apart from anxiety no other psychiatric symptoms are listed as side effects in the British National Formulary (2013). However, in the recent years, there are increasing reports of psychiatric adverse events including cases of suicide (Doxycycline. Reported side effects, n.d.)". (Background, para. 2).

The table below demonstrates that there have been 317 adverse reports indicating a change in mental state on the US FDA database relating to doxycycline use and that 43 of these adverse events related to reports of anxiety.

[32] Atigari OV, Hogan C, Healy D (2013). Doxycycline and suicidality. BMJ Case Rep, : doi:10.1136/bcr-2013-200723. 077551

TABLE 15 FOOD AND DRUG ADMINISTRATION PSYCHIATRIC ADVERSE DRUG REPORTING FOR DOXYCYCLINE (ATIGARI ET AL, 2013).

Symptom	Number of reports	Symptom	Number of reports
Aggression	003	Feeling of despair	003
Agitation	018	Inappropriate affect	001
Anger	002	Irritability	016
Anhedonia	001	Mood altered	004
Anxiety	043	Mood swings	006
Anxiety disorder	001	Nervousness	010
Apathy	004	Obsessive thoughts	001
Crying	003	Panic attacks	011
Depersonalisation	006	Panic disorder	001
Depressed mood	013	Panic reaction	002
Depression	047	Paranoia	001
Depressed symptoms	001	Personality change	001
Derealisation	006	Psychotic disorder	004
Dysthymic disorder	001	Self-injurious behaviour	015
Fatigue	067	Suicide attempt	016
Fear	004	Thinking abnormal	002
Feeling jittery	003	Total reports indicating a change in mental state	317

Bhatia And Malik (1995)[33] reported a case series of 60 patients with chloroquine induced psychiatric complications. Psychosis was the most common complication followed by anxiety state and seizures. Four women developed anxiety symptoms, aged 28 to 32 years. They were on a dose of 2g of chloroquine and the side effect was noted 2 to 3 days after onset of the drug. Headache and sleeplessness were found to be more common among patients developing psychiatric complications of chloroquine. The symptoms disappeared within 2 to 21 days after the discontinuation of chloroquine.

[33] Bhatia MS and Malik SC (1995). Psychiatric complications of chloroquine. Indian Pediatrics, Vol 32 pp 351-353. 016496

Case report

Maxwell, Nevin, Stahl et al (2015)[34] described a case of chloroquine intoxication that appeared to be prolonged by subsequent use of multiple psychotropic medications. This case highlights important new considerations for the management of quinoline antimalarial intoxication.

While volunteering in Honduras, a 16-year-old female with an unremarkable medical history became ill during her ninth week of chloroquine prophylaxis (250 mg weekly). She had begun malaria prophylaxis 2 weeks prior to travel, and by her seventh week in Honduras had developed insomnia, paranoia, and confusion that progressed in severity over the next 2 days. Following a dose of diphenhydramine to aid sleep, her symptoms progressed to include hallucinations, irrational guilt and self persecution, suicidal ideation, and catatonic features. She was taken to a local neurologist where initial workup revealed a normal head CT, unremarkable lumbar puncture, normal complete blood count, negative infectious disease studies, and negative urine toxicology screen.

Upon repatriation to the United States 2 days later, she was admitted to the emergency room of a local hospital where olanzapine and lorazepam were administered for acute management of behavioural symptoms. Upon hospital admission, risperidone and fluoxetine were initiated with lorazepam continued on an as-needed basis for anxiety. On the second day, benztropine was added while lorazepam was replaced with clonazepam. Her mental status improved briefly by the evening of the second hospital day and she was able to converse with her family and recall many of her experiences over the prior week. However, by the morning of the third day, she had slipped back into a state of marked confusion, self-persecution, paranoia, suicidal ideation, visual and auditory hallucinations, delusional thinking, and catatonia. These progressed in a waxing and waning manner over the next 14 days.

Telgt, van der Ven, Schimmer et al (2005)[35] conducted a study to report serious psychiatric symptoms after standard chloroquine treatment following human malaria infection induced for research.

A 34-year-old healthy woman volunteered to participate in the study of malaria treatment. She was infected on day 0 with a chloroquine-susceptible strain of Plasmodium falciparum and was treated with a standard 3-day course of chloroquine from day 9 onward, following a positive blood smear (parasitemia 0.001%). On day 10, the blood smear became negative. On day 11, she developed a psychotic disorder not otherwise specified, most probably caused by chloroquine use, with symptoms of depersonalization and anxiety. The diagnosis of delirium was considered but ruled out because of clear consciousness with lack of diurnal fluctuations. She refused to take antipsychotic medication. Three weeks later, the woman still encountered serious concentration problems. All complaints gradually subsided over the next 4 months, after which she felt completely recovered. Plasma chloroquine concentrations were within the therapeutic range.

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[34] Maxwell NM, Nevin RL, Stahl S, et al (2015). Prolonged neuropsychiatric effects following management of chloroquine intoxication with psychotropic polypharmacy. Clin Case Rep, 3(6): 379-387. 076940

[35] Telgt DS, van der Ven AJ, Schimmer B, Droogleever-Fortuyn HA, Sauerwein RW. (2005). Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. Ann Pharmacother.; 39(3):551-4.

Chloroquine may achieve high concentrations in the brain and has a long half-life. As quinolines, the antimalarials may have the same pathologic activity as the fluoroquinolone antibiotics in acting as N-methyl-d-aspartate agonists and gamma-aminobutyric acid antagonists. Application of the Naranjo probability scale indicated that, in this patient, chloroquine was the probable cause of the serious psychiatric symptoms.

In the case above the anxiety symptoms appeared in close temporal proximity to the use of chloroquine, however, it is unclear how long the anxiety symptoms lasted. All psychiatric symptoms were resolved by four months.

Summary and conclusions

The randomised clinical trials (Llanos-Cuentos et al, 2014; Elmes et al, 2008; Charles et al, 2007; Hogh et al, 2000) reporting on anti-malarials, alone and/or in combination, did not report anxiety or panic attacks as identified adverse events. Apart from Nasveld and colleagues (2010) who reported 2 cases of mild anxiety in the tafenoquine group vs nil in the mefloquine group. It is unclear if this is a direct result of the drug, or a chance finding.

Terrell et al (2015) in a cohort study of soldiers training in Kenya in 2012 and 2013 reported one case of panic attack in users of doxycycline. No anxiety symptoms or panic attacks were reported in the mefloquine group. Nasveld et al (2002) in a comparison study of tafenoquine and primaquine use by Australian Defence personnel reported no anxiety symptoms or panic attacks as adverse events for either drug.

The nested-case control study by Schneider, Adamcova, Jick, et al (2013), summarised in the Mefloquine section above, did not find a statistically significant association between the risk for phobia, anxiety or panic attacks in users of mefloquine, chloroquine and/or proguanil and atovaquone/proguanil.

A case series (Atigari et al, 2013) reported on three occurrences of anxiety adverse events whilst taking doxycycline for a skin condition. They also reported statistics from the US FDA which identified 43 cases of anxiety associated with doxycycline use. Bhatia And Malik (1995) in a case series of 60 people with chloroquine neuropsychiatric side effects reported that four females suffered with anxiety symptoms believed to be related to the drug due to the close temporal relationship of symptom onset to the time of drug use and the resolution of symptoms after drug cessation.

A single case report (Maxwell et al, 2015) also cited a case of chloroquine intoxication with various neuropsychiatric symptoms including anxiety. Another case report by Telgt et al (2005) reported psychosis and anxiety induced by chloroquine use. Symptoms resolved within four months from onset.

The evidence for other anti-malarial drugs (excluding mefloquine) is limited. In a number of studies which focussed on tafenoquine use only 2 cases of mild anxiety were reported and it is unclear if this was a direct result of the medication. Grade 4 level evidence

A cohort study, a case series and the US FDA adverse events database reported various cases of doxycycline use resulting in anxiety symptoms. Grade 2 level evidence

A nested-case control study did not report an association between use of various anti-malarials (including mefloquine and chloroquine) and anxiety symptoms or panic attacks. A case series did report 4 cases of anxiety symptoms related to chloroquine use. Two case reports also found anxiety (as well as various other neuropsychiatric symptoms) as a side effect of chloroquine use. Grade 3 level evidence

Other Medication

Corticosteroids

Summary of important issues

This is a class of drugs with a well-recognised association with neuropsychiatric side effects.

Reviews

Bhangle, Kramer and Rosenstein (2013)[36] analysed the available literature regarding the neuropsychiatric (NP) disturbances associated with corticosteroid (CS) therapy; to determine the nature, severity, and frequency of these NP symptoms; and to identify the various risk factors involved in the development of CS-induced NP disturbances. They searched the available literature since the advent of corticosteroid therapy (1950) utilizing the PubMed database (www.pubmed.gov). Primary articles were identified, and they and their pertinent references were reviewed. Due to potential confusion between NP manifestations of CS therapy and central nervous system (CNS) involvement of systemic lupus erythematosus (SLE), a condition often treated with CS, a brief review of NP manifestations of SLE was also performed. The presentation of CS-induced neuropsychiatric disorders (CIPD) can be quite varied with depression, hypomania, and overt psychosis being the most common manifestations. CIPD can also include bipolar affective changes, delirium, panic attacks, agoraphobia, obsessive-compulsive disorder, anxiety, insomnia, restlessness, fatigue, catatonia, reversible dementia-like cognitive changes, impaired memory, and concentration. No factors have been identified that allow for the accurate prediction of development of CIPD. A dose-dependent relationship (increased risk when the daily prednisone-equivalent dose is >40 mg) has been observed in most cases of CIPD, although there have been case reports with lower doses, alternate-day therapy, and even inhaled CS. Women are more commonly affected with most symptoms occurring in the first 6 weeks of starting treatment. SLE has been the only specific illness that has been linked to a greater risk of CIPD and the NP manifestations of SLE may mimic those of CIPD, with most occurring in the first year of diagnosis. Antiribosomal P, antineuronal, or antiphospholipid antibodies are frequently seen in patients with SLE developing CIPD. Imaging and EEG abnormalities, the coexistence of non-CNS manifestations of SLE, and the presence of serious disturbances in memory and concentration are more suggestive of NP-SLE than CIPD. Although NP symptoms associated with the use of CS generally resolve with discontinuation of the medication, prophylaxis with lithium, and treatment with antidepressants, anticonvulsants and electroconvulsive therapy for severe mania and depression have been reported with successful outcomes.

Kenna, Poon, de los Angeles et al (2011)[37] reviewed adult case report data published during the past quarter-century on adverse corticosteroid-induced psychiatric effects, and present a case of corticosteroid-induced psychotic depression. PubMed and PsychLit databases were searched using the terms 'corticosteroids', 'steroids', and the generic names of corticosteroid medications with terms for psychiatric symptoms or syndromes, including psychosis, mania, hypomania, depression, apathy, anxiety, panic, depersonalization, delirium,

[36] Bhangle SD, Kramer N, Rosenstein ED. (2013). Corticosteroid-induced neuropsychiatric disorders: review and contrast with neuropsychiatric lupus. Rheumatology International. 33(8):1923-32.
[37] Kenna HA, Poon AW, de los Angeles CP, Koran LM. (2011). Psychiatric complications of treatment with corticosteroids: review with case report. Psychiatry & Clinical Neurosciences. 65(6):549-60.

confusion, hallucinations, delusions, paranoia, cognitive impairment and dementia. Fifty-five cases and a number of clinical trials investigating the incidence and treatment of these psychiatric symptoms and syndromes were identified. Data on incidence, drug dose, risk factors, course of illness and treatment (when present) were tabulated. They concluded that the cumulative data indicate that psychiatric complications of corticosteroid treatment are not rare and range from clinically significant anxiety and insomnia, to severe mood and psychotic disorders, delirium and dementia. While tapering or discontinuation of the corticosteroid treatment may remedy these adverse side-effects, psychotropic medications are often required because of the medical necessity of the corticosteroid or the severity of the psychiatric symptom. Further studies are needed to better understand the deleterious psychiatric effects associated with corticosteroids.

The systemic use of corticosteroids is connected with a variety of psychiatric and neurologic effects. Corticosteroids for intranasal administration (INCs) are considered to act locally and to exert minimal systemic effects. An unexpected cluster of case reports of neuropsychiatric disorders during intranasal corticosteroid use was reported to the World Health Organization Uppsala Monitoring Centre.

Pokladnikova, Meyboom, Vlcek and Edwards (2008)[38] investigated the possible connection between intranasal corticosteroid (INC) use and the development of neuropsychiatric disorders, as reported to the International Pharmacovigilance Programme.

All reports containing adverse event terms indicating neuropsychiatric disturbances in suspected connection with intranasal corticosteroids were retrieved from Vigibase and evaluated (April 2006). The case reports are heterogeneous and vary regarding source, documentation quality, and relationship likelihood.

A total of 429 reports were received from 16 countries (1980-April 2006), of neuropsychiatric events occurring in patients using INCs, representing 7.6% of the total of reports regarding these drugs in the same period. Frequently reported events were nervousness, anxiety, agitation, insomnia, emotional lability, depression, somnolence, confusion, convulsions, and migraine. Most reports concerned fluticasone propionate, beclometasone dipropionate, mometasone furoate, or budesonide. In 370 reports (86.2%), the INC was the sole suspect drug and in 220 (51.3%) it was the only drug used. In 97 of 108 patients who had discontinued use of the intranasal corticosteroid, the reaction abated. Of 41 patients, 32 had a relapse when the drug was reintroduced.

The data collected by the International Pharmacovigilance Programme suggest that the intranasal use of corticosteroids can be complicated by neuropsychiatric adverse reactions. Further study is needed to confirm the connection and to determine the frequency and risk factors of such reactions.

Retrospective medical records review

Corticosteroids are associated with numerous adverse drug reactions (ADRs). Long-term ADRs are well characterized, but there are limited data on the incidence and likelihood of

[38] Pokladnikova J, Meyboom RH, Vlcek J, Edwards RI. (2008). Intranasally administered corticosteroids and neuropsychiatric disturbances: a review of the international pharmacovigilance programme of the World Health Organization. Annals of Allergy, Asthma, & Immunology. 101(1):67-73.

short-term ADRs. **Mathis, Liu, Adamson, Nambi, and Patel (2007)**[39] sought to determine the incidence of ADRs potentially related to early administration of steroids in kidney and kidney-pancreas transplant recipients and to determine the probability that the ADR was due to the steroid. They retrospectively evaluated the records of all eligible kidney or pancreas-kidney transplants during 2003. ADRs were rated by two reviewers according to the Naranjo algorithm, and identified as "definite," "probable," "possible," or "doubtful." ADRs were identified in 100% of patients (n = 103) by 8.2 +/- 4.9 days. The mean ADRs per patient were 3.26 +/- 1.04. Weight gain occurred in 79.6%, hypertension in 71.8%, diabetes mellitus in 52.4%, hyperglycemia in 47.6%, leukocytosis in 31.1%, insomnia in 27.2%, anxiety in 10.7%, and psychosis in 1.9%. Based on mean interinvestigator score, leukocytosis was judged as "probable" and weight gain and psychosis were "possible to probable." Diabetes, hyperglycemia, hypertension, and insomnia were "possible" and anxiety was "possible to doubtful." These results provide evidence of the incidence and likelihood of early steroid-related ADRs.

Cohort Study

Barrimi, Aalouane, Arab et al (2013)[40] [In French]

Summary

To date, there is little data in the literature describing the anxiety and depressive disorders iatrogenic to corticosteroids. These disorders are common, underestimated, with potentially serious consequences that may jeopardize the patient's prognosis; their management is not consensual.

Objectives

The objective of our work is to determine the prevalence of anxiety and depressive disorders induced by corticosteroids, assessing their accountability to the corticosteroids and studying their risk factors.

Methods

We conducted a prospective longitudinal study over 12 months evaluating the prevalence of anxiety and depressive disorders in patients followed for chronic skin diseases treated with prolonged corticosteroid-therapy. Our patients were assessed using standardized instruments: the Mini International Neuropsychiatric Interview (MINI), the Hamilton Rating Scale for Anxiety (HAM-A) and the Beck Depression Inventory (BDI).

Results

Of 54 patients included, our study showed a high prevalence of anxiety and depressive disorders estimated at 27%. These disorders were divided into depressive disorder in 16% of cases, and anxiety disorder in 11% of cases. The early onset of these disorders was found during the first weeks of treatment. According to the Beck Depression Inventory (BDI), depression was moderate in 67% of cases; severe with suicide attempts in 22% of cases, and

[39] Mathis AS, Liu MT, Adamson RT, Nambi SS, Patel AM. (2007). Retrospective analysis of early steroid-induced adverse reactions in kidney and kidney-pancreas transplant recipients. Transplantation Proceedings. 39(1):199-201.

[40] Barrimi M, Aalouane R, Aarab C, et al (2013). Prolonged corticosteroid-therapy and anxiety-depressive disorders, longitudinal study over 12 months (Article in French). Encephale, 39(1): 59-65. 073349

mild in 11% of cases. According to the HAM-A, anxiety was mild in 33% of cases and moderate in 67% of cases. The disorders observed were mainly distributed into: 33% deep pemphigus, 27% lupus, 13% bullous pemphigoid and 13% dermatomyositis. In this study the statistically significant risk factors are dose of corticosteroids and personal psychiatric history of the patient; in addition, there is a high prevalence of disorders in patients whose age exceeds 40 years, female gender, and patients treated for deep pemphigus. The evolution after pharmacological treatment and supportive psychotherapy was favourable in most patients.

Conclusion

The psychiatric examination prior to prescription of long-term corticosteroid-therapy use should be standard practice to identify patients at risk, discuss the treatment modalities, and provide comprehensive care.

Case report

Iskandar, Wood, Ali and Alemu (2011)[41] report a case of panic attack induced by a single dose of prednisone. A 58-year-old white male with a history of type 2 diabetes mellitus, asthma, obstructive sleep apnoea, and chronic obstructive pulmonary disease was admitted to the hospital for gradually increased shortness of breath with exertion for the past 3 months. He denied any psychiatric history, current stressors, and use of alcohol or illegal drugs. Family history was non-contributory. Vital signs and results of laboratory tests were unremarkable. Current medications were albuterol 0.083% and ipratropium 0.02% inhalation solution as needed, oral cyanocobalamin 1000 ìg daily, formoterol inhaler 12 ìg twice daily, gabapentin 300 mg 3 times daily, mometasone inhaler 220 ìg daily, oral montelukast 10 mg at bedtime, oral omeprazole 20 mg at bedtime, and oral terazosin 2 mg at bedtime. The patient's as-needed medications had not been used for at least 48 hours prior to the administration of prednisone.

Thirty minutes after the patient first received prednisone 20 mg, he became restless, anxious, and agitated. He also reported palpitations, sweating, chest discomfort, shortness of breath, nausea, blurred vision, and feelings of derealization. The patient denied hallucinations or delusions. An electrocardiogram showed tachycardia. Vital signs were remarkable for blood pressure 150/105 mm Hg, pulse 140 beats/min, and respiratory rate 24 breaths/min. Improvement was seen in the panic state and vital signs returned to normal within 25 minutes after oral lorazepam 2 mg was administered. Upon questioning, the patient reported a similar episode after taking one dose of prednisone 60 mg approximately 4 years previously. After being discharged, the patient denied any further panic attacks at his 3- and 6-month visits. The patient met the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, diagnostic criteria for panic attack 30 minutes after he received prednisone.

Summary and conclusion

Bhangle et al (2013) reviewed the evidence related to corticosteroid-induced neuropsychiatric disorders. Both anxiety symptoms and panic attacks were acknowledged as adverse reaction to corticosteroids. Kenna et al (2011) reviewed adult case reports of psychiatric outcomes of corticosteroid outcomes. They concluded that neuropsychiatric adverse reactions were not

[41] Iskandar JW, Wood RL, Ali R, Alemu F. (2011). Panic attack induced by a single dose of prednisone. Annals of Pharmacotherapy. 45(11):1456-7.

rare and included clinically significant anxiety. Padladnikova et al (2008) reviewed the literature in regard to intra-nasal corticosteroid use and neuropsychiatric outcomes. The review supported an association between corticosteroid use and anxiety symptoms even when the drug is administered intra-nasally.

A retrospective medical records review (Mathi et al, 2007), a cohort study (Barrimi et al, 2013) and a case report (Iskandar et al (2011) reported corticosteroid-induced anxiety/panic attacks.

Anxiety could be causally linked to the baseline condition which has led to the need for the corticosteroid therapy and therefore the drug therapy could have a moderating role, rather than a mediating one. However, corticosteroids are well-known to have neuropsychiatric sequelae.

Grade 2 level

Anti-tumor necrosis factor therapy/Infliximab

Reviews

Lopez, Billioud, Peyrin-Biroulet and Peyrin-Biroulet (2013)[42] reviewed methods of assessment, prevalence, and predictors of nonadherence to anti-tumor necrosis factor therapy in inflammatory bowel diseases (IBD). Studies were identified through the electronic database of MEDLINE (up to January 2012) and the annual meetings of Digestive Disease Week, the American College of Gastroenterology, the United European Gastroenterology Week, and the European Crohn's and Colitis Organization.

Among 1783 citations identified, 13 studies evaluated adherence to biologics in IBD. Several methods were used to assess adherence to anti-tumor necrosis factor, including the medication possession ratio, the medication refill adherence, and the Morisky Medication Adherence Scale 8. Pooled adherence to anti-tumor necrosis factor therapy was 82.6%. Pooled adherence was 83.1% in adalimumab and 70.7% in infliximab-treated patients. Female gender, smoking, constraints related to treatment, anxiety, and moodiness were associated with nonadherence to both infliximab and adalimumab. Concomitant immunomodulator use and time since first infusion more than 18 weeks were predictors for nonadherence to infliximab. Regimen of 40 mg every other week, syringe use (versus pen), internal medicine center prescription (versus gastroenterology center prescription), retail pharmacy (versus speciality pharmacy) and new user (versus previous user) were predictors for adalimumab nonadherence.

More than three-quarters of patients with IBD adhere to biologics. Predictors of nonadherence include female gender, smoking, constraints related to treatment, **anxiety**, and moodiness. It is unclear from this review if any anxiety symptoms were related to a pre-existing condition, associated with the illness perse or the treatment medication.

Cohort study

Ertenli, Ozer, Kiraz et al (2012)[43] conducted a study to assess the effect of infliximab on depression, anxiety and quality of life in patients with active ankylosing spondylitis (AS). In this 6-week longitudinal study, 16 patients with AS were assessed. Active disease as defined by BASDAI ≥4.0 was sought for inclusion. Infliximab was administered 5 mg/kg at 0, 2 weeks and 6 weeks. Collected data included age, sex and date of onset of rheumatologic disease. Activity of disease was measured using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Biological activity was evaluated with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). ESR and CRP were assessed at baseline and day 42. The Hospital Anxiety and Depression scale (HADS), Beck Depression Inventory (BDI) and 36-item Short Form Health Survey (SF-36) were used to evaluate anxiety, depression and quality of life. BASDAI, SF-36, HADS and BDI were assessed prior to the initial infliximab dose and at 2nd, 14th and 42nd day. Seven (43.8%) AS patients had depression scores above the cut off value for both the HADS depression (HADS-D) and BDI and 4 (25 %) had high HADS anxiety scores at baseline. Significant time effect for BDI and HADS-D scores were observed.

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[42] Lopez A, Billioud V, Peyrin-Biroulet C, Peyrin-Biroulet L.(2013). Adherence to anti-TNF therapy in inflammatory bowel diseases: a systematic review. Inflamm Bowel Dis.;19(7):1528-33.
[43] Ertenli I, Ozer S, Kiraz S, Apras SB, Akdogan A, Karadag O, Calguneri M, Kalyoncu U. (2012). Infliximab, a TNF-α antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. Rheumatol Int.;32(2):323-30.

Although significantly lower BDI scores were found after first, second and third infusions of infliximab, compared to initial score, the significant decrease in HADS-D appeared after second and third infusions. A significant time effect for HADS-anxiety scores were found as well. Four of 16 (25%) patients with AS had high Mean HADS anxiety scores at baseline. On follow-up period, 2 of 16 patients (12.5%) at day 2, and neither of patients at day 14, and 42 had high anxiety scores.

All of the subscales of SF-36 improved significantly during the course, with an exception of role emotional, for which the difference approached to the significance. The change in BASDAI scores and CRP and ESR, in the treatment process, were not correlated with the change in depression and anxiety scores. Infliximab which is an anti-TNF-α drug, may be effective in the treatment of depression accompanying AS.

Case Reports

Saraceno, Faleri, Ruzzetti et al (2012)[44] conducted a study the aim of which was to evaluate the prevalence of panic disorders in psoriatic patients during infliximab (IFX) infusions. A retrospective study was performed on patients affected with psoriasis who were treated with IFX from 2002 to 2011 at a single centre. Panic disorders were defined using the clinical criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. A population of dermatological patients under treatment with IVG, rituximab, apheresis, intravenous corticosteroids and antibiotics was considered as the control group. A total of 141 patients were evaluated. Of these, 6 (4.25%) experienced panic attacks during the infusion; 16 (11.3%) had a medical history of panic attack and of those 5/16 (31%) experienced panic attacks during IFX infusion. In the control group panic attacks were not recorded. Six cases of patients in whom panic attacks were triggered by IFX infusion were reported. Premedication with oral benzodiazepine and a slow rate of infusion is recommended.

Summary and conclusion

It is difficult to disentangle the anxiogenic nature of the underlying condition from the direct relationship which the medication for treatment has on the mental state.

The review (Lopez et al, 2013) identified anxiety as a reason for non-compliance in treatment, but the cause of the anxiety is unclear. The cohort study (Ertenli et al, 2012) reported an improvement of anxiety symptoms with treatment. Saraceno et al (2012) reported six cases of panic attacks triggered by IFX infusion, 5 of these patients had an earlier history of panic attack.

On the case report evidence, suggest Grade 4 level evidence.

[44] Saraceno R, Faleri S, Ruzzetti M, Centonze D, Chimenti S. (2012). Prevalence and management of panic attacks during infliximab infusion in psoriatic patients. Dermatology. 225(3):236-41.

Interferon alpha

Summary of important issues

Interferon alpha is a drug known to cause neuropsychiatric effects. The evidence for the appearance of anxiety symptoms is limited.

Reviews

De Chouly De Lenclave, Foutrein and Bailly (2001)[45] conducted a review of the literature in relation to interferon alpha and the frequent somatic as well as neuropsychiatric side effects commonly reported. For about 30% of patients, various psychic disorders are noticed: personality disorders, mood disorders, anxiety states, suicidal tendencies, manic and psychotic symptoms. The appearance of psychiatric complications caused by interferon has been the subject of many publications. They have also raised the question of the toxicity mechanism which is still misunderstood today. This toxicity appears to be dose-dependent with variations depending on the daily dose given, the mode of administration, the combination with other chemotherapy treatments, the concomitance with a cerebral radiotherapy or a medical history of psychiatric disorders. Most of these effects occur after three weeks of treatment but non specific neuropsychiatric symptoms can be observed earlier.

Non-specific neuropsychiatric symptoms appear early but are difficult to detect, though they bring together a whole lot of clinical signs: asthenia, irritability, psychomotor slowdown, depressive mood or even a real "subsyndromic" depressive syndrome, anorexia, decline of the libido, concentration and attention problems, dizzy spells and headaches. Some authors have described intense and fluctuating of personality, mixing anxiety, irritability and disorder of drive control.

In regard to anxiety disorders they state that they are not described in any detail in the literature. They generally are already existing disorders (like phobic or obsessive compulsive disorders), reactivated or aggravated by the interferon-alpha molecule.

It is difficult to ascertain the relationship between the interferon-alpha treatment and neuropsychiatric complications because there is a lack of studies which address this relationship specifically. Nevertheless, it seems to be a causal relationship between the prescription of interferon and the appearance of psychiatric disorders. As a matter of fact, even if there is neither predictive criterion nor diagnosis of clinical type (set apart a dose effect), it is clear that there are diagnostic criteria of a chronological kind: delay of appearance and disappearance of side effects compatible with the kinetics of the molecule and test of positive reintroduction. The ascribed relationship is thus most likely an aetiological one, given the reported clinical observations and signs of direct cerebral toxicity described for interferon: induction of neurophysiological changes among healthy volunteers, reversible EEG impairments the second week of treatment, direct vascular and neurological toxicity. Eventually, authors have shown that the psychiatric morbidity could be more important among patients under treatment than in a control group.

The appearance of neuropsychiatric side effects during chemotherapy with the interferon-alpha molecule is a frequent complication, the consequences of which can prove tragic: involvement of the vital prognosis, family and professional relation disturbances, compliance

[45] De Chouly De Lenclave MB, Foutrein P, Bailly D. (2001). :[Alpha-interferon and mental disorders]. L'encéphale [Encephale]; Vol. 27 (4):308-17. [French]

problems, risks of psychiatric morbidity at short and middle terms.... In spite of the absence of rigorous controlled studies, the imputability to the interferon of the appearance of psychological disorders appears very likely.

Cohort study

Kovacs, Panczei, Balatoni et al (2015)[46]

Abstract

OBJECTIVE:

The most frequent serious psychological side effect of immune therapies is depression. In the present study, we tested whether social support, as a positive environmental effect, is able to moderate depression or anxiety symptoms in melanoma patients during adjuvant low-dose interferon treatment.

METHODS:

Hundred and twenty-seven melanoma patients with negative psychiatric history were included in our longitudinal study and followed up for one year. Depression and anxiety symptoms were measured six times during treatment: at baseline, at 1st, 3rd, 6th, 9th and 12th month of the therapy. In addition, social support was investigated with the Social Dimension Scale.

RESULTS:

Depressive symptoms significantly increased during the 12-month follow-up period ($p<0.001$). However, social support significantly moderated the depressogenic effect of low-dose interferon treatment ($p<0.001$). Patients with better social support showed attenuated increase of depression. **Anxiety showed no significant changes during the low-dose interferon treatment ($p=0.230$)**. Social support had no moderating effect on anxiety symptoms ($p=0.745$) during the follow up.

DISCUSSION:

Our data provide evidence that social support and interferon alpha treatment significantly interact in the development of depression. In addition, our study emphasises that enhancement of social support can reduce depressogenic side effects and increase compliance during adjuvant interferon treatment, and thus, psychological screening and psychooncological counselling should be incorporated in the treatment protocol.

Huckans, Fuller, Wheaton et al (2015)[47]

Abstract

OBJECTIVE:

[46] Kovács P, Pánczél G, Balatoni T, Liszkay G, Gonda X, Bagdy G, Juhasz G. (2015). Social support decreases depressogenic effect of low-dose interferon alpha treatment in melanoma patients. J Psychosom Res. 2015 Jun;78(6):579-84. doi: 10.1016/j.jpsychores.2015.03.005. Epub 2015 Mar 14.
[47] Huckans M, Fuller B, Wheaton V, Jaehnert S, Ellis C, Kolessar M, Kriz D, Anderson JR, Berggren K, Olavarria H, Sasaki AW, Chang M, Flora KD, Loftis JM. (2015). A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C. J Psychosom Res. 2015 Feb;78(2):184-92. doi: 10.1016/j.jpsychores.2014.07.020. Epub 2014 Aug 7.

To prospectively evaluate for changes in objective cognitive performance (attention, memory, and executive function) and psychiatric symptom severity (depression, anxiety, fatigue, and pain) in patients before, during and after interferon-alpha based therapy (IFN) for chronic hepatitis C virus infection (HCV).

METHODS:

33 HCV+ adults were evaluated two months before IFN initiation (baseline), three months into IFN, and six months following IFN termination (IFN+ Group). 31 HCV+ adults who did not undergo IFN therapy were evaluated at baseline and six months later (IFN- Group). At each evaluation, participants completed the Neuropsychological Assessment Battery (NAB) Attention, Memory and Executive Functions Modules, the Beck Depression Inventory, Second Edition (BDI), Generalized Anxiety Disorder Inventory (GADI), Fatigue Severity Scale (FSS), and Brief Pain Inventory (BPI).

RESULTS:

Compared with the IFN- Group, the IFN+ Group experienced significantly ($p<0.050$) increased symptoms of depression, anxiety, fatigue and pain during IFN therapy relative to baseline. In the IFN+ Group, psychiatric symptoms generally returned to baseline levels following IFN termination. Sustained viral response was associated with significantly lower depression and fatigue. No significant changes in cognitive performance were observed.

CONCLUSIONS:

During IFN, patients with HCV evidence significantly increased psychiatric symptoms, including symptoms of depression, anxiety, fatigue and pain. These psychiatric symptoms are generally short-term and remit following IFN termination, with increased benefit if viral clearance is achieved. However, IFN is not associated with significant declines in objective cognitive performance during or following IFN.

McNutt, Liu, Manatunga et al (2012)[48]

Abstract

In patients at high risk for recurrence of malignant melanoma, interferon-α (IFN-α), a stimulator of innate immunity, appears to induce distinct neurobehavioral symptom dimensions: a mood and anxiety syndrome, and a neurovegetative syndrome, of which the former is responsive to prophylactic administration of paroxetine. We sought to determine whether symptom dimensions (and treatment responsiveness) arise in patients with hepatitis C administered IFN-α and ribavirin. In a randomized, double-blind, 6-month study, 61 patients with hepatitis C eligible for therapy with IFN-α and ribavirin received the antidepressant paroxetine (n=28) or a placebo (n=33). Study medication began 2 weeks before IFN-α/ribavirin therapy. Neuropsychiatric assessments included the 10-item Montgomery-Asberg Depression Rating Scale (MADRS). The items of the MADRS were grouped into depression, anxiety, cognitive dysfunction, and neurovegetative symptom dimensions, and analyzed using a mixed model. By 2 weeks of IFN-α/ribavirin therapy, all four dimensions increased, with the symptom dimensions of anxiety and cognitive dysfunction fluctuating and worsening,

[48] McNutt MD, Liu S, Manatunga A, Royster EB, Raison CL, Woolwine BJ, Demetrashvili MF, Miller AH, Musselman DL. (2012). Neurobehavioral effects of interferon-α in patients with hepatitis-C: symptom dimensions and responsiveness to paroxetine. Neuropsychopharmacology. 2012 May;37(6):1444-54. doi: 10.1038/npp.2011.330. Epub 2012 Feb 22.

respectively, in both groups over time (anxiety, p=0.01; cognitive dysfunction, p<0.0001). The depression symptom dimension was significantly lower in the paroxetine treatment group (p=0.04); severity of the neurovegetative symptom dimension was similar in both groups. Similar to patients with malignant melanoma receiving high-dose IFN-α, the depression symptom dimension is more responsive to paroxetine treatment in individuals undergoing concomitant IFN-α/ribavirin therapy. However, the anxiety, cognitive dysfunction, and neurovegetative symptom dimensions appear less responsive to prophylactic paroxetine administration. Different neurobiologic pathways may contribute to the responsiveness of IFN-α-induced symptom dimensions to antidepressant treatment, requiring relevant psychopharmacologic strategies.

According to McNutt et al (2012)[49] the residual psychiatric symptoms (depressed mood, anxiety, insomnia) may last for up to at least 6 months after cessation of IFN-a treatment (Hosoda et al, 2000). p. 1444-5.

In regard to anxiety a number of limitations were noted in the study. “The anxiety and cognitive dysfunction symptom dimensions fluctuated and worsened, respectively, over 24 weeks. Of note is that the magnitude of these two symptom dimensions were not significantly different in subjects receiving paroxetine, despite the potential of this SSRI antidepressant to induce akathisia and anticholinergic associated impairment of cognitive performance (Teva Pharmaceuticals USA, 2011). Our estimation of the anxiety and cognitive dysfunction dimensions, however, may be erroneous in that a single MADRS item of ‘inner tension’ and another, ‘observed symptoms of concentration difficulties,’ were used to index these two symptom dimensions.

Another weakness of the study, which may have affected measurement of this symptom dimension, was that no inter-rater reliability for the MADRS was calculated among the sites, although all sites were required to review the same series of taped interviews and match their ratings to a standard metric. The likelihood that ribavirin was a contributing factor to the increasing magnitude of the anxiety and cognitive dysfunction symptom complexes in this study appeared small, given another large study, which showed, when compared with IFN-a therapy alone, that addition of ribavirin to IFN-a therapy for treatment of hepatitis C did not elevate the incidence of anxiety or impaired concentration (McHutchison et al, 1998). Given recent discoveries of hepatitis C virus within the brain, poor concentration may represent a neurocognitive ‘biomarker’ of central innate immune activation, given that significant differences have been documented in measures of concentration and information processing speed between patients with chronic hepatitis C infection, in comparison with patients who clear the virus and healthy volunteers (Forton et al, 2002)” (pp. 1450-1).

Summary and conclusion

The review by De Chouly and colleagues (2001) discuss the non-specific neuropsychiatric symptoms commonly reported with the use of interferon alpha. Anxiety symptoms are known to occur, however, the literature on this topic is poor.

A further literature search limited to ((Mesh terms interferons/adverse events) AND (anxiety or panic)) revealed a number of cohort studies (Kovacs et al, 2015; Huckans et al, 2015; McNutt

[49] McNutt MD, Liu S, Manatunga A, et al. (2012). Neurobehavioral effects of interferon-α in patients with hepatitis-C: symptom dimensions and responsiveness to paroxetine. Neuropsychopharmacology;37(6):1444-54. pp 1444-5.

et al, 2012) which were equivocal. Kovacs et al, found no association between drug exposure and anxiety symptoms and the other two studies supported an association, however, McNutt et al acknowledged that the measurement for anxiety which was used was not ideal.

Grade 3 – Grade 4 level evidence

Antiretrovirals - Efavirenz

Summary of important issues

A class of drug neuropsychiatric adverse event is not evident.

Reviews

A Medscape review (Bartlett & Ferrando, 2004) investigated the neurologic and psychiatric side effects association with HIV and highly active antiretroviral therapy (HAART). Side effects of HAART and complications of HIV infection may overlap significantly. Establishing etiology of neurologic (neuropathy and neuropathic pain, changes in cognition, dementia, and myelopathy) and psychiatric (neurocognitive disorders, depression, anxiety, substance abuse and dependence, and others) complications can present a significant challenge. In particular, the NNRTI efavirenz has been associated with neurologic and psychologic complaints that may be difficult to differentiate from preexisting mental illness, substance abuse, and HIV-related neuropsychiatric symptoms.

Unfortunately, many of the complications of HAART and those of the HIV infection itself may overlap, particularly in patients with advanced disease. Among health risks that may be associated with HIV or HAART are neurologic complications (neuropathy and neuropathic pain, changes in cognition, dementia, and myelopathy) and psychiatric complications (depression, anxiety, mania, and substance abuse and dependence).

Abers, Shandera and Kass (2014)[50] reviewed the literature concerning the neurological and psychiatric adverse effects of antiretroviral drugs. Antiretroviral drugs are associated with a variety of adverse effects on the central and peripheral nervous systems. The frequency and severity of neuropsychiatric adverse events is highly variable, with differences between the antiretroviral classes and amongst the individual drugs in each class. Two classes of drugs, the nucleoside reverse transcriptase inhibitor (NRTI) and the non-nucleoside reverse transcriptase inhibitor (NNRTI) were examined.

[50] Abers MS, Shandera WX, Kass JS (2014). Neurological and Psychiatric adverse effects of antiretroviral drugs. CNS Drugs, 28(2): 131-45. 078100

TABLE 16 SELECTED NEUROPSYCHIATRIC ADVERSE EVENTS ASSOCIATED WITH ANTIRETROVIRALS (ABERS ET AL, 2014).

Antiretroviral	Adverse event
Common (>10 %)	
Efavirenz	Dizziness, insomnia, vivid dreams, impaired concentration, lightheadedness, headache, aggression, anxiety
Zidovudine	Myopathy
NRTIs	Peripheral neuropathy
Ritonavir	Circumoral paraesthesias
Raltegravir	Myopathy
Occasional (1 to <10 %)	
Efavirenz	Memory loss, hallucinations, depression
Ritonavir	Peripheral neuropathy, dysgeusia
Enfuvirtide	Peripheral neuropathy
Raltegravir	Headache, dizziness, suicidality, nightmares
Rare (<1 %)	
Efavirenz	Mania
NRTIs	Mitochondriopathy syndromes

NRTIs nucleoside reverse transcriptase inhibitors

Abacavir, an NRTI, may cause central nervous system (CNS) manifestations, including mania and psychosis. Psychiatric complications of abacavir have been reported in six cases. Half of the cases were male, and their ages ranged from 11 to 47 years, with all but one case occurring in patients aged 37–47 years. In all cases, the symptoms began within 1 month of initiation of abacavir therapy. Commonly reported symptoms included depression, nightmares, hallucinations, mood changes, mania, anxiety and psychosis. Two patients reported suicidal ideation.

The non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz is perhaps the antiretroviral most commonly associated with CNS toxicity, causing insomnia, irritability and vivid dreams. As noted in the table above anxiety is a commonly reported adverse event. Recent studies have suggested that the risk of developing these adverse effects is increased in patients with various cytochrome P450 2B6 alleles.

Many studies have reported CNS toxicity in >50 % of patients taking efavirenz. However, the prevalence of CNS toxicity is difficult to determine, because of the inconsistent definition and detection methods used for ‘CNS toxicity’.

CNS toxicity usually begins within 2–4 weeks of initiating therapy. Symptoms appearing early in the course of therapy include dizziness, lightheadedness, sleep disturbance, vivid dreams, nervousness and irritability. These symptoms typically resolve 6–8 weeks later, without dose alteration [Sutterlin et al, 2010; cited in Abers et al, 2014]. After approximately 6 months of therapy, patients may begin to experience headache, decreased concentration and mood changes [Fumaz et al, 2002; cited in Abers et al, 2014].

In one study, patients taking efavirenz for 3 years were found to have higher than baseline levels of abnormal dreaming and anxiety, although their neuropsychological performance did

not decrease from baseline [Clifford et al, 2009; cited in Abers et al, 2014]. Conversely, another study of patients taking efavirenz for more than 1 year found that 47 % of patients were cognitively impaired, especially in executive functioning. Higher education was found to be a protective factor [Ciccarelli et al, 2011; cited in Abers et al, 2014].

Clifford et al. [2005; cited in Abers et al, 2014] found that CNS side effects during the first week of therapy were more commonly seen in patients taking efavirenz than in those on a non-efavirenz regimen ($p<0.001$). After the fourth week of therapy, there was no difference between the groups ($p = 0.038$). The investigators interpreted their findings as evidence supporting the decision to continue therapy in patients who experience CNS toxicity. In other studies, neuropsychiatric adverse effects have persisted for 1 year or longer, but the severity has decreased with time and has not appeared to diminish the patient's quality of life [(Fumaz et al, 2002; Hawkins et al, 2005; Blanch et al, 2001; Fumaz et al, 2005); cited in Abers et al, 2014].

Treisman and Kaplin (2002)[51] reviewed the evidence concerning the psychiatric complications of antiretroviral agents. Only efavirenz was identified as a drug which induced anxiety as a psychiatric side effect. They state:

"Psychiatric effects also have been noted with efavirenz, though they occur less frequently than neurologic effects. However, when efavirenz-associated psychiatric effects occur, they may be serious and may include anxiety, depression, and suicidal ideation [Colebunders & Verdonck, 1999; Staszerski, Morales-Ramirez, Tashima et al, 1999; Moyle, 1999]. A small study comparing patients who took efavirenz or PI for a mean of 45 weeks documented higher scores on psychometric scales of anxiety and hostility in the efavirenz group than in the PI group effects that were subtle but persistent [Hawkins, Grossman & Haubrich, 2000]" (p. 1205).

Randomised control study

Fumaz, Tuldra, Ferrer et al (2002)[52] assessed the impact of an efavirenz-containing regimen versus a protease inhibitor-containing regimen on quality of life, emotional status, and adherence of HIV-1-infected patients. In addition, the adverse events associated with these treatments, with a special focus on central nervous system disorders in the efavirenz treatment group were observed and reported. This prospective, randomized, two-arm, controlled study included 100 patients for whom initial treatment with a protease inhibitor-containing regimen failed. Patients were randomized to start treatment with two nucleoside retrotranscriptase inhibitors plus efavirenz (group 1; 51 patients) or two nucleoside retrotranscriptase inhibitors plus one or more new protease inhibitors (group 2; 49 patients). Quality of life was assessed by a five-point item adapted from the HIV questionnaire of the Medical Outcomes Study, emotional status was evaluated by the Profile of Mood State questionnaire, and patients self-reported adherence. Data were analyzed by both an as-treated method and an intention-to-treat-last observation carried forward method. Patients in group 1 reported the following findings at week 4: dizziness (66%), abnormal dreaming (48%), light-headedness (37%), and difficulty sleeping (35%). At week 24, dizziness (13%; $p <.001$),

[51] Treisman GJ, Kaplin AI (2002). Neurologic and psychiatric complications of antiretroviral agents. AIDS, 16: 1201-15. 078182

[52] Fumaz CR, Tuldra A, Ferrer M, et al (2002). Quality of life, emotional status, and adherence of HIV-1 -infected patients treated with efavirenz versus protease inhibitor - containing regimens. JAIDS, 29: 224-53. 078040

abnormal dreaming (18%; p =.002), light-headedness (13%; p =.01), difficulty sleeping (7%; p =.001), and **nervousness** (13%; p =.01) decreased in these patients. Irritability, abnormal dreaming, and **nervousness** persisted at week 48 in 13%, 10%, and 8% of group 1 patients, respectively. Patients in group 2 reported the following findings at week 4: light-headedness (8%), dizziness (5%), difficulty sleeping (4%), **nervousness** (4%), and headaches (3%). Patients in group 2 reported the following findings at week 48: difficulty sleeping (4%), **nervousness** (3%), headaches (3%), and light-headedness (2%).

TABLE 17 CENTRAL NERVOUS SYSTEM DISORDERS IN THE GROUP ASSIGNED TO EFAVIRENZ N (%) (FUMAZ ET AL, 2002).

Adverse event	Baseline (n = 51)	Week 4 (n = 45)	Week 12 (n = 43)	Week 24 (n = 43)	Week 36 (n = 40)	Week 48 (n = 37)
Dizziness	2 (4)	30 (66)[a]	16 (36)[a,c]	6 (13)	3 (7)[c]	2 (5)[c]
		34 (66)[a]	*21 (41)*[a,c]	*11 (21)*[a,c]	*9 (17)*[b,d]	*10 (19)*[b,d]
	[3.5 ± 2.9]	[11.7 ± 8.2]	9.8 ± 7.5]	[8.8 ± 6.8]	[7 ± 4.1]	[7.1 ± 5.4]
Nausea	3 (6)	7 (11)	5 (10)	5 (11)	—	—
		9 (17)	*7 (13)*	*7 (13)*		
	[7.3 ± 5.1]	[8.3 ± 5.4]	[7.1 ± 6.8]	[7.2 ± 6.1]		
Light-headedness	—	17 (37)[a]	8 (18)[d]	6 (13)	—	—
		21 (41)[a]	*12 (23)*[d]	*10 (19)*[d]		
		[15.6 ± 10.3]	[7.1 ± 4.1]	[7.1 ± 5.3]		
Somnolence	—	16 (35)[a]	6 (13)[c]	—	—	—
		16 (31)[a]	*6 (11)*[c]			
		[22.2 ± 10.3]	[10.2 ± 3.2]			
Difficulty of sleeping	4 (8)	16 (35)[a]	10 (22)[b]	3 (7)[c]	3 (7)[c]	—
		18 (35)[a]	*13 (25)*[b]	*6 (11)*[c]	*6 (11)*[c]	
	[7.2 ± 4.8]	17.3 ± 11.4]	[10 ± 2.3]	9.8 ± 6.3]	[7.2 ± 5.8]	
Abnormal dreaming	—	22 (48)[a]	10 (22)[c]	8 (18)[c]	6 (15)[c]	4 (10)[c]
		26 (50)[a]	*15 (29)*[c]	*13 (25)*[c]	*13 (25)*[c]	*11 (21)*[c]
		[15.04 ± 11.6]	[7 ± 2.2]	[7.3 ± 4.2]	[7.1 ± 5.5]	7.2 ± 4.8]
Impaired concentration	—	12 (26)[a]	5 (11)[b]	5 (11)[b]	—	—
		14 (27)[a]	*8 (15)*[a]	*8 (15)*[a]		
		[19.9 ± 12.9]	[7.3 ± 5.1]	[8 ± 6.3]		
Amnesia	—	2 (4)	—	—	—	—
		2 (4)				
		[2]				
Irrational thoughts	—	2 (4)	—	—	—	—
		2 (4)				
		[2]				
Hallucinations	—	2 (4)	—	—	—	—
		2 (4)				
		[2]				
Mood changes	—	7 (15)[a]	5 (11)[b]	7 (16)[a]	3 (7)	2 (5)
		11 (21)[a]	*10 (19)*[a]	*12 (23)*[a]	*8 (15)*[a]	*7 (13)*[a]
		[21.4 ± 10.1]	[15.5 ± 7.1]	[18.7 ± 7.5]	[15 ± 5.5]	[15 ± 4.3]
Nervousness	2 (4)	16 (35)[a]	8 (18)[a]	6 (13)	5 (12)[c]	3 (8)[c]
		18 (35)[a]	*11 (21)*[a]	*9 (17)*[b,d]	*8 (15)*[b,d]	*6 (11)*[c]
	[7 ± 5.4]	16.9 ± 10.8]	[15.2 ± 6.9]	[11.3 ± 8.9]	[7 ± 4.4]	[7.3 ± 5.4]
Irritability	—	13 (28)[a]	8 (18)[a]	8 (18)[a]	5 (12)[b]	5 (13)[b]
		17 (33)[a]	*13 (25)*[a]	*13 (25)*[a]	*10 (19)*[a]	*10 (19)*[a]
		[17.9 ± 10.5]	[20.6 ± 7.2]	[18.7 ± 7.5]	[7 ± 4.4]	[15 ± 6.2]
Euphoria	—	4 (8)	4 (9)	—	—	—
		4 (7)	*4 (7)*			
		[14.5 ± 10.8]	[7 ± 5.4]			
Headaches	1 (2)	6 (13)	3 (6)	2 (4)	—	—
		7 (13)	*4 (7)*	*4 (7)*		
	[2 ± 3.1]	[7 ± 5.3]	[7 ± 6.3]	[7.5 ± 6.3]		

Numbers in brackets indicate days per month, mean standard deviation.
Roman text indicates treated data.
Italic text indicates intention-to-treat last observation carried forward data.
[a] Comparisons with baseline; $p < .01$.
[b] Comparisons with baseline; $p < .05$.
[c] Comparisons with week 4; $P < .01$.
[d] Comparisons with week 4; $P < .05$.

In group 1, quality of life (p <.001) and emotional status (week 48; p =.004) improved, both of which were better than those in group 2 (p =.001). Both groups maintained high levels of medication adherence, and no significant differences in the number of patients who had viral loads of <200 copies/mL at week 48 were found (78% of group 1 patients vs. 85% of group 2 patients; p = not significant). At week 48, the mean CD4 cell count +/- SD was 497 +/- 224/mm3 in group 1 and 539 +/- 298/mm3 in group 2 (p = *not significant*). Despite similar immunologic and virologic outcomes, a second-line efavirenz-containing regimen improved quality of life of HIV-1-infected patients compared with a second-line protease inhibitor-containing regimen. However, close follow-up of patients receiving treatment with efavirenz-based regimens is recommended, especially for those with previous emotional disturbances due to central nervous system disorders in the short term and those with persistence of a low percentage of these disorders in the long term.

Clifford, Evans, Yang et al (2005)[53] conducted a study to characterise efavirenz-associated neurologic symptoms in a randomized, controlled study of initial antiretroviral treatment. The study design was a substudy of a randomized, double-blind, controlled trial of combination antiretroviral regimens (A5095) that was performed between March 2001 and January 2002 based in multicenter academic clinical trial units. The participants were HIV-infected patients who were initiating therapy in the context of a controlled trial. Neuropsychological performance measures, including the Digit Symbol Substitution Test and the Trail Making Test (Parts A and B); symptom questionnaires; standardized assessments of sleep quality, anxiety, and depression; and efavirenz plasma concentrations were measures of interest in the study.

Twenty of 303 (6.6%) enrolled participants prematurely discontinued the study. Neuropsychological performance improved in both groups over time without significant differences between patients who were receiving efavirenz and those who were not. The efavirenz group experienced more neurologic symptoms at week 1 (P < 0.001) but not at weeks 4, 12, or 24. A sleep index revealed that participants receiving efavirenz had more “bad dreams” during the first week of therapy (P =.038). No significant changes in anxiety or depressed mood were noted. Changes in efavirenz-associated neurologic symptoms were correlated to efavirenz plasma concentrations at week 1 but not at later time points. Twelve (6%) patients receiving efavirenz stopped taking the drug before the end of the study because of central nervous system symptoms.

All participants experienced substantial anxiety throughout the study; they observed clinically significant anxiety in greater than 80% of the patients at baseline and at each time point. Total anxiety scores increased in both groups. Changes in total anxiety scores from baseline were marginally different at week 1 (P =.073), with the patients receiving efavirenz experiencing fewer increases in anxiety. There was no significant difference with respect to changes in anxiety at weeks 4, 12, and 24. Neither absolute anxiety levels nor change in anxiety were significantly correlated to efavirenz levels.

In a large controlled trial, efavirenz use was associated with neurologic symptoms distinct from depression and anxiety that began early in therapy but resolved by week 4. Improvement in neuropsychological performance was comparable in patients who were receiving efavirenz and those who were not.

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[53] 078039 - Clifford DB, Evans S, Yang Y, et al (2005). Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Ann Intern Med, 143: 714-21.

Limitations

Participant selection may have been biased in favor of patients with fewer psychiatric complications. The study design permitted substitution of a new drug in place of efavirenz in cases of treatment-limiting toxicity.

Cross-sectional studies

Fumaz, Munoz-Moreno, Molto, Negredo et al (2005)[54] conducted a cross-sectional study to assess neuropsychiatric disorders and their relation to efavirenz plasma levels as well as quality of life, psychologic status, and adherence in HIV-infected patients on long-term efavirenz-based antiretroviral therapy.

The study compared 60 patients on an efavirenz-based approach (EFV group) and 60 patients on a protease inhibitor-containing regimen (PI group) for at least 1 year. Adverse events, efavirenz plasma levels, quality of life, psychologic status, and adherence were assessed.

The mean time on treatment was 91.1 ± 39.5 weeks in the EFV group and 119.9 ± 67.4 weeks in the PI group. Mild dizziness, sadness, mood changes, irritability, lightheadedness, **nervousness**, impaired concentration, abnormal dreams, and somnolence were reported more frequently in the EFV group than in the PI group ($P < 0.05$). Forty-nine of 60 patients presented with therapeutic efavirenz plasma levels (range: 1.0-4.0 mg/L). Efavirenz plasma levels were similar in subjects with and without neuropsychiatric disorders. No significant differences were found between the EFV group and the PI group regarding quality of life and psychologic status. Sixty percent of patients in the EFV group and 55% in the PI group reported adherence =95%.

[54] Fumaz CR, Munoz-Moreno JA, Molto J, et al (2005). Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. JAIDS, 38(5): 560-5. 078041

TABLE 18 ADVERSE EVENTS IN THE STUDY GROUPS (FUMAZ ET AL, 2005).

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Adverse Events	EFV Group n (%)	PI Group n (%)	*P*
Dizziness	13 (21.7)	3 (5)	**0.008**
Nephrolithiasis	—	4 (6.7)	0.118
Polineuropathy	15 (25)	11 (18.3)	0.402
Perioral paresthesia	—	1 (1.7)	0.999
Gastrointestinal disorders	11 (18.3)	18 (30)	0.122
Fatigue	22 (36.7)	15 (25)	0.185
Difficulty in erection	12 (20)	11 (18.3)	0.817
Loss of libido	14 (23.3)	11 (18.3)	0.530
Headaches	14 (23.3)	8 (13.3)	0.170
Sadness	22 (36.7)	9 (15)	**0.008**
Mood changes	16 (26.7)	7 (11.7)	**0.041**
Irritability	18 (30)	6 (10)	**0.007**
Euphoria	2 (3.3)	1 (1.7)	0.157
Lightheadedness	17 (28.3)	5 (8.3)	**0.005**
Nervousness	18 (30)	7 (11.7)	**0.015**
Impaired concentration	16 (26.7)	7 (11.7)	**0.041**
Abnormal dreams	29 (48.3)	1 (1.7)	**<0.001**
Difficulty in sleeping	17 (28.3)	11 (18.3)	0.213
Somnolence	15 (25)	6 (10)	**0.034**
Nausea	9 (15)	6 (10)	0.427

Statistically significant differences in univariate comparisons between the EFV group and the PI group are shown in bold.

Source: J Acquir Immune Defic Syndr © 2005 Lippincott Williams & Wilkins

Mild and clinically tolerable neuropsychiatric disorders may persist in patients after a mean of 2 years using an efavirenz-based approach. Quality of life and psychologic status remained good in both study groups. Interventions to enhance long-term adherence should be applied in clinical practice.

Summary and conclusion

Three reviews (Abers et al, 2014; Bartlett & Ferrando, 2004; Treisman & Kaplan, 2002) support a relationship between efavirenz and anxiety symptoms. Two randomised controlled trials (Clifford et all, 2005; Fumaz et al, 2002) also discussed and supported the association. A cross-sectional study (Fumaz et al, 2005) reported nervousness as an adverse event significantly occurring more often in the efavirenz treatment group then in the protease inhibitor group.

Abers et al (2014) also reported that anxiety was a commonly reported symptom associated with abacavir treatment. Although only six cases of neuropsychiatric adverse events due to the drug were reported.

No other HAART drugs were identified as causing anxiety symptoms.

The evidence in support of an efavirenz-induced anxiety disorder is strong and consistent. Grade 1 level evidence.

For abacavir use, only six cases have been reported in the literature of adverse events relating to neuropsychiatric symptoms. Grade 3 level evidence.

Oral contraceptive pill (OCP)

Summary of important issues

The **DSM-5**[55] states oral contraceptive medication is one of the medications that can evoke anxiety symptoms.

Reviews

Sirakov and Tomova (2015)[56]

Abstract [Article in Bulgarian]

Oral contraceptives are used since more than 50 years and are very popular due to offering more than 99% confidence in preventing pregnancy. Over 100 million women worldwide use oral contraceptives. In the UK 27% of women between 16 and 49 y. use pills. In the United States they are about 30%, in Germany - 40%, and in The Netherlands - 60%. According to a study by B. Pehlivanov, 2008, in Bulgaria only 4% of women use OC. (1) Despite the convenience and security, in the U.S.A. 29% of women taking OC interrupt prematurely their use (2), while the percentage of adolescents appears to be higher (3) Earlier studies of the reasons for refusal of OC focus on their influence on the menstrual cycle, as well as on some physical side effects such as the appearance of hair growth, weight gain, bloating etc. They paid very little attention to their impact on mood and sexual behavior of women (4). Newer studies suggest that the side effects associated with mood and sexual behavior proved more powerful factor leading to early termination of the use of OC (5). This paper is a review of the literature and evaluation of the facts presented in studies from different countries. They found a high incidence of symptoms such as anxiety, susceptibility to stress, mood changes, incl. depression, anxiety, increased irritability and affection of sexual desire of women. (6) There are many indications that OC-users are at increased risk of suicide and mental illnesses. (9).

Poromaa and Segebladh (2012)[57] conducted a review of combined oral contraceptives (COCs) and the prevalence of COC-related adverse mood symptoms and discussed the underlying biological mechanisms of proposed changes in mood and affect. The primary outcome was the prospective recording of depressed mood or anxiety by the use of validated questionnaires (depressed mood, anxiety, irritability, emotional well-being, mood swings). Studies relying on adverse event reporting or discontinuation rates were excluded. No studies relating to anxiety outcomes appeared to meet the selection criteria and therefore were not available for synthesis.

Precise estimates of COC-related adverse mood symptoms are not available due to the lack of placebo-controlled trials. In prospective trials the frequency of women who report deteriorated mood or deteriorated emotional well-being varies between 4 and 10%, but it can be assumed that the causal relation in these prevalence rates is overestimated. Adverse mood symptoms and somatic symptoms are most pronounced during the pill-free interval of the treatment cycles, but whether extended COC regimens would be more favourable in this respect is not known. COCs with anti-androgenic progestagens, such as drospirenone and

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[55] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783

[56] Sirakov M, Tomova E. (2015). [Oral contraceptives and mood/sexual disorders in women]. [Article in Bulgarian] Akush Ginekol (Sofiia). 2015;54(5):34-40. Abstract only

[57] Poromaa IS, Segebladh B (2012). Adverse mood symptoms with oral contraceptives. Acta Obstet Gynecol Scand, 91: 420-7. 078494

desogestrel, appear more favourable in terms of mood symptoms than progestagens with a more androgenic profile. Available data suggest that lower doses of ethinylestradiol could be beneficial.

Hormonal preparations have become one of the most popular methods used for controlling fertility. The literature over the last 40 years continues to reveal how their numerous side effects negatively impact many users and even society at large. Three large cohort trials were the first to demonstrate, on a grand scale, certain emotional and behavioural associations with contraceptive use. Current contraceptive use was associated with an increase rate in depression, divorce, tranquilizer use, sexual dysfunction, and suicide and other violent and accidental deaths. Despite the advent of more "user friendly" contraceptives, the discontinuation rate secondary to side effects has changed little through the years. While in rare cases hormonal preparations can be deadly to the user, there is substantial evidence that their negative effect issues more from their emotional and behavioural properties (Robinson et al, 2004).

Robinson, Dowell, Pedulla and McCauley (2004)[58] reviewed the results of seven studies which further characterize these prominent associations, particularly with hormonal contraception, in an attempt to demonstrate their association with the intrinsic pharmacologic properties of hormonal preparations. Hormonal contraceptive users, in contrast with non users, were found to have higher rates of depression, **anxiety**, fatigue, neurotic symptoms, sexual disturbances, compulsion, anger, and negative menstrual effects. The question of whether the association of these maladies is directly due to the effect of taking exogenous hormones versus the psychological impact of the contraceptive behaviour itself had yet to be studied. Seven small randomised-controlled trials were found in a review of the literature which studied this hypothesis in a direct way. They do not support the origination of these side effects being from the pharmacological properties of hormones. No association was found between hormone levels and emotional functioning in females. Psychiatric evaluations among IUD and oral contraceptive pill (OCP) users reveal no significant differences. Women who were given an OCP placebo experienced a similar side effect profile of OCP users. Different hormonal concentrations and combinations made no significant difference in the side effect profile. A study of women who were given either "weak female hormones" or a placebo failed to duplicate the side effect profile found in all of the other studies where the hormones were labelled as contraceptives. The evidence suggests that most of the side effects of hormonal contraception are a result of a psychological response to the practice of contraception. More study is warranted to further understand this psychological phenomenon, especially now that an effective non-contraceptive method of fertility regulation and more reliable psychological instruments are available. Furthermore, it is reasonable to hypothesize, given the present data that contraceptive activity itself is inherently damaging to women.

[58] Robinson SA, Dowell M, Pedulla D, McCauley L. (2004). Do the emotional side-effects of hormonal contraceptives come from pharmacologic or psychological mechanisms? Med Hypotheses.; 63(2):268-73.

Cross-sectional studies

Cheslack-Postava, Keyes, Lowe and Koenen (2015)[59] examined the association between oral contraceptive use (any current use, duration, and type) and major depressive disorder (MDD), generalized anxiety disorder (GAD), and panic disorder (PD) in a nationally representative sample of women in the USA. Data were drawn from 1,105 women aged 20–39 in the National Health and Nutrition Examination Surveys from 1999 to 2004. The associations between self-reported use of oral contraceptives in the past year and DSM-IV diagnosed and subthreshold MDD, GAD, and PD in the past year were assessed comparing oral contraceptive users to all non-users, former users, and former long-term users. Women using oral contraceptives had a lower past-year prevalence of all disorders assessed, other than subthreshold MDD. When adjusted for confounders, women using oral contraceptives in the past year had significantly lower odds of subthreshold PD, compared to former users (odds ratio (OR)=0.34, 95 % CI 0.14–0.84).

TABLE 19 ASSOCIATIONS OF PAST 12-MONTH MENTAL HEALTH DISORDERS WITH PAST-YEAR ORAL CONTRACEPTIVE USE AMONG US WOMEN AGED 20–39 IN 1999–2004 (CHESLACK-POSTAVA ET AL, 2015).

Outcome	Compared to all OC non-users		Compared to never OC users only	Compared to former OC users only
	cOR (95 % CI)	aOR (95 % CI)	aOR (95 % CI)	aOR (95 % CI)
Generalized anxiety disorder, diagnosis or subthreshold[a]	0.67 (0.40, 1.15)	0.80 (0.46, 1.39)	1.57 (0.77, 3.18)	0.66 (0.37, 1.21)
Panic disorder, diagnosis or subthreshold[b]	0.37 (0.17, 0.84)	0.47 (0.20, 1.08)	1.28 (0.41, 3.96)	0.34 (0.14, 0.84)
Major depression[c]				
Diagnosis	0.83 (0.49, 1.42)	0.81 (0.47, 1.40)	1.30 (0.51, 3.33)	0.66 (0.36, 1.20)
Subthreshold	1.08 (0.46, 2.52)	1.23 (0.48, 3.13)	2.17 (0.53, 8.97)	0.96 (0.34, 2.67)
Disorders combined[d]				
Diagnosis	0.69 (0.43, 1.10)	0.64 (0.38, 1.08)	1.03 (0.50, 2.11)	0.52 (0.29, 0.92)
Subthreshold	1.01 (0.64, 1.60)	1.15 (0.70, 1.90)	1.96 (0.96, 4.01)	0.90 (0.51, 1.58)

Each model is adjusted for those variables that were associated with both OC use and the specific outcome, as follows:

[a] aORs adjusted for age, BMI category, physical activity, and number of sexual partners in the past year

[b] aORs adjusted for education, past-year health insurance, chronic disease, and physical activity

[c] aORs adjusted for race/ethnicity, physical activity, BMI, chronic disease, and number of sexual partners in the past year

[d] aORs adjusted for race/ethnicity, physical activity, BMI, chronic disease, and number of sexual partners in the past year

[59] Cheslack-Postava K, Keyes KM, Lowe SR, et al (2015). Oral contraceptive use and psychiatric disorders in a nationally representative sample of women. Arch Womens Ment Health, 18(1): 103-11. 077734

TABLE 20 ASSOCIATION BETWEEN PAST-YEAR ORAL CONTRACEPTIVE USE, CATEGORIZED AS MONO- OR MULTIPHASIC, AND MENTAL HEALTH DISORDERS IN US WOMEN AGED 20– 39 (CHESLACK-POSTAVA ET AL, 2015).

OC formulation	GAD[a]	MDD[b]	
	Diagnosis or subthreshold OR (95 % CI)	Subthreshold OR (95 % CI)	Diagnosis OR (95 % CI)
No past-year OC use	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Monophasic	0.42 (0.11, 1.55)	1.79 (0.66, 4.90)	0.54 (0.21, 1.39)
Multiphasic	1.25 (0.57, 2.75)	0.40 (0.15, 1.10)	1.32 (0.60, 2.93)
p value (mono vs multi)	0.17	<0.01	

Reference group is all past-year OC non-users

[a] ORs adjusted for: age, BMI category, physical activity and number of sexual partners in the past year

[b] ORs adjusted for: race/ethnicity, physical activity, BMI, chronic disease and number of sexual partners in the past year

Effects estimates were strongest for monophasic (versus multiphasic) oral contraceptive users. Hormonal contraceptive use was associated with reduced risk of subthreshold PD. A potential mental health benefit of hormonal contraceptives has substantial public health implications; prospective longitudinal studies are needed to confirm whether hormonal contraceptive use improves mental health.

Summary and conclusion

The evidence for OC use being causally associated with anxiety or panic symptoms is inconsistent. DSM-5 asserts that OC can evoke anxiety symptoms. The Bulgarian review by Sirakov and Tomova (2015) suggests that anxiety symptomatology is a side-effect of oral contraceptive use. The review by Poromaa and Segebladh (2012) did not identify quality prospective studies which confirmed this assessment. The Robinson and colleagues (2004) review found that their assessment of seven small randomised control studies found that hormonal contraceptive users when compared to non-users had increased rates of anxiety and other symptoms. However, they interpret the evidence as suggesting that most of the side effects relate to psychological response rather than the direct result of the hormonal drugs, as different doses did not alter the effect. The cross-sectional study by Cheslack-Postava et al (2015) found that OC use in the past year was protective for the development of panic disorder or a subthreshold diagnosis in adjusted analysis.

Grade 4 level evidence

Benzodiazepine

Summary of important issues

Although an anxiogenic relationship with the use of benzodiazepine may seem counter-intuitive a limited body of literature supports this association.

Reviews

The **DSM-5**[60] states that panic or anxiety can occur in association with withdrawal from the anxiolytic medications.

Diazepam (Valium) is among the most successful drugs from the onset of the psychopharmacological revolution that began during the 1950s. Efficacious in treating a wide-spectrum of CNS disorders, including anxiety and epilepsy, it set the standard for pharmacotherapy in terms of potency, onset of action, and safety. In this review, **Calcaterra and Barrow (2014)**,[61] considered the legacy of diazepam to chemical neuroscience along with its synthesis, pharmacology, drug metabolism, adverse events and dependence, clinical use, and regulatory issues.

In regard to adverse events, they state:

“Serious and fatal adverse events associated with diazepam are extremely rare and are most often a consequence of interaction with another drug (such as opiates or alcohol). The most common fatal events are respiratory arrest and prolonged seizures resulting from prolonged habitual use, rather than acute overdose. In fact, reported cases of overdoses up to 2000 mg diazepam have resulted in an induced temporary coma with speedy recovery. More moderate adverse effects from chronic diazepam use include amnesia, dizziness, ataxia, confusion, sedation, depression, and tachycardia. Also, worsening of seizures or anxiety can occur in some patients being treated for epilepsy or anxiety disorders (Mullins, 1999; Greenblatt et al, 1978; Finkle et al, 1979)” (p. 256).

Cross-sectional studies

Nkogho,Mengue, Abdous, Berbiche, Preville and Voyer (2014)[62] examined the relationship between benzodiazepine dependence and anxiety disorders and depression in people aged 65 years and over. They referred to the data from the study on the health of seniors, a survey of a representative sample of 707 benzodiazepine users living in the community in Quebec, Canada. Benzodiazepine dependence, anxiety disorders and depression were measured using self-reported questionnaires based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth revised edition.

Seniors have consumed an average daily dose of 6.1±7.6mg diazepam equivalent to an average of 205±130 days. The prevalence of benzodiazepine dependence has been estimated at 9.5%. This dependence increases the risk of minor depression for females (RR =

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[60] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783

[61] Calcaterra NE & Barrow JC (2014). Classics in Chemical Neuroscience: Diazepam (Valium). ACS Chemical Neuroscience; 5, 253-260.

[62] Nkogho Mengue PG, Abdous B, Berbiche D (2014). Benzodiazepine dependence and the risk of depression and anxiety disorders: seniors' health study. [article in French]. L'Encéphale, 40(3): 216-22. 077735

4.36; 95% CI1.19 to 15.99). This dependence also resulted in a non-significant increased risk of generalised anxiety disorder in females (RR = 2.23; 95% CI 0.32-15.76).

TABLE 21 RELATIVE RISKS FOR THE ASSOCIATION BETWEEN BENZODIAZEPINE DEPENDENCE AND THE CUMULATIVE INCIDENCE OF ANXIETY AND DEPRESSION FOR MALES AND FEMALES (NKOGHO ET AL, 2014).

Caractéristiques	Hommes			Femmes		
	Incidence cumulée[a]	RR brut (IC 95 %)	RR ajusté[b] (IC 95 %)	Incidence cumulée[a]	RR brut (IC 95 %)	RR ajusté[b] (IC 95 %)
Troubles anxieux						
Anxiété généralisée	0/6	–	–	2/58	2,23 (0,32–15,76)	–
Trouble panique	0/6	–	–	0/58	–	–
Phobie spécifique	0/6	–		0/58	–	–
Phobie sociale	0/6	–	–	0/58	–	–
Agoraphobie sans panique	0/6	–	–	0/58	–	–
Trouble obsessionnel compulsif	0/6	–	–	0/58	–	–
Troubles dépressifs						
Dépression majeure	0/6	–	–	1/58	1,18 (0,22–6,27)	–
Dépression mineure	0/6	–	–	4/58	4,36 (1,19–15,99)	–

– : test statistique non applicable.
[a] Proportion de nouveaux-cas parmi les aînés dépendants aux benzodiazépines sur une période de 12 mois.
[b] Risque relatif (RR) ajusté pour l'âge, la scolarité, l'état civil, la région d'habitation, la santé mentale, les maladies chroniques et l
demi-vie d'élimination des benzodiazépines.

The results of this study suggest that the use of benzodiazepines is far from being optimal among seniors in Quebec. The proportion of seniors who develop an addiction is important. The results illustrate the need to develop and implement programs to improve the quality of benzodiazepine use among this population.

Summary and conclusion

Calcaterra & Barrow (2014) in their review which discussed the adverse events reported in Valium use, state that worsening of anxiety symptoms can occur with Valium use.

Nkogho et al (2014) in a French Canadian study reported only 2 cases of generalised anxiety disorder in the sample of benzodiazepine dependants. Medication-induced anxiety was not reported nor anxiety symptoms post-medication use.

Grade 4 level evidence

Caffeine

Summary of important issues

In experimental studies caffeine is used to induce anxiety and panic symptoms. The half-life of caffeine (time taken for the body to eliminate one-half of the caffeine) varies widely between people, depending on factors such as age, body weight, pregnancy status, medication intake and liver health. In healthy adults, the half-life is approximately 5 to 6 hours.

Systematic reviews

Vilarim, Araujo, Nardi (2011)[63] performed a systematic review of the literature, which consisted of retrospective searches of scientific articles related to the association between caffeine consumption and PD. They performed the searches in PubMed, BVS (Virtual Health Library [VHL]) and the ISI Web of Knowledge (ISIWEB), and the selected studies were published between 1991 and 2009. To set the exposure 'caffeine challenge test' for the outcome 'panic attack and/or anxiogenic effect', they used the following keywords in the searches: caffeine, caffeine challenge test, PD, panic attacks and anxiety disorder. Another strategy was a manual search in reference lists of identified articles selected by electronic search. The studies that they chose did not include pregnant women or individuals younger than 18 years of age. Using established strategy, the bibliographic search resulted in 1349 articles. However, only eight articles were selected to compose the current article. The others were excluded for several reasons (i.e., they did not fit into any of the criteria, they were literature reviews, they were repeats from one of the other databases or the articles were not available in their entirety). The criteria used to select articles for review were a randomized double-blind study design, written in English, Portuguese or Spanish, and using an oral administration of caffeine. Of the eight studies selected, four were from Brazil, one was from England, one was from Greece and two were from the USA. Sample sizes ranged between ten and 143 individuals. In terms of age, six studies reported the average age, one study reported the minimum and maximum ages and one study did not mention the participants' ages. The percentage of subjects lost during follow-up varied between 14.3% and 73.1%. However, the eight studies showed a positive association between caffeine and anxiogenic effects and/or PD (Table below).

[63] Vilarim MM, Araujo DMR, Nardi AE (2011). Caffeine challenge test and panic disorder: a systematic literature review. Expert Review of Neurotherapeutics, 11(8): 1185-95. 077737

TABLE 22 THE DISORDERS/SYMPTOMS EVALUATED AND THE SCALES AND RESULTS OF THE SELECTED STUDIES CONCERNING THE ASSOCIATION BETWEEN CAFFEINE AND PANIC DISORDER.

Study (year)	Disorders/symptoms evaluated	Scales	Results
Klein *et al.* (1991)	Panic disorder with or without agoraphobia	DSM-III, HDRS, NIMH panic attack inventory, NIMH rating scales for anxiety, depression and global impairment, and Zung SAS	Demonstrated that patients with panic disorder responded to caffeine with increased anxiety and panic attacks
			Although panic disorder patients in both caffeine and placebo conditions endorsed a significant
Beck & Berisford (1992)	Panic disorder	ADIS-R, DSM-III-R	number of panic symptoms and reported greater symptom severity relative to the normal controls, only the panic disorder/caffeine sample reported a significant increase in subjective anxiety
Bruce *et al.* (1992)	Panic disorder and generalized anxiety disorder	BSS, MRS, STAI	Patients with panic disorder showed different reactivity than normal patients, but were less reactive than patients with generalized anxiety disorder
Nardi *et al.* (2007)	Panic disorder, major depression and major depression with panic attacks	DSM-IV, DSQ, SCID, SUDS	Suggested that there is an association between panic attacks in panic disorder or major depression with panic attacks and hyper-reactivity to an oral caffeine challenge test
Nardi *et al.* (2007)	Panic disorder with agoraphobia	DSM-IV, SCID, SUDS	Suggested that there is an association between respiratory panic disorder subtype and hyperreactivity to an oral caffeine challenge test
Nardi *et al.* (2008)	Panic disorder	DSM-IV, DSQ, SCID, SUDS	Suggested that there is a genetic association between panic attacks after the intake of caffeine in panic disorder patients and their healthy first-degree relatives
Masdrakis *et al.* (2008)	Panic disorder with or without agoraphobia	DSM-IV, HDRS, SCID, SCLR-90-R, STAI	Indicated that patients with panic disorder who experience a panic attack after a 200 mg or a 400 mg caffeine challenge (compared with those patients with panic disorder who do not panic after both of these caffeine challenges) may present significantly higher nonspecific general psychopathology at baseline
Nardi *et al.* (2009)	Panic disorder, generalized social anxiety disorder and performance social anxiety disorder	DSM-IV, SCID, SUDS	Suggested that there is an association between panic disorder and an oral caffeine challenge test

ADIS-R: Anxiety Disorders Interview Schedule-Revised; BSS: Bodily Symptom Scale; DSM-III: Diagnostic and Statistical Manual of Mental Disorders III; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders III Revised; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV; DSQ: Diagnostic Symptom Questionnaire; HDRS: Hamilton Depression Rating Scale; MRS: Mood Rating Scale; NIMH: National Institutes of Mental Health; SAS: Self-rating Anxiety Scale; SCID: Structured Clinical Interview; SCLR-90-R: Symptom Checklist-90-Revised; STAI: State-Trait Anxiety Inventory; SUDS: Subjective Units of Disturbance Scale.

“Among the selected studies, 62.5% had administered doses of 480 mg of caffeine [Nardi et al, 2009; Nardi et al, 2008; Klein et al, 1991; Araujo et al, 2007; Nardi, Lopez et al, 2007; Nardi, Valenca et al, 2007] . The justification for more than half of studies administering 480 mg of caffeine was that it was a safe dose that had been tested in the laboratory to demonstrate the significant increase of anxiety in PD patients compared with normal controls [Uhde & Boulenger, 1989; Uhde, 1990]. With regard to the measurement scales, various types of instruments were used to assess PD, panic attacks and/or anxiety. Although no scale alone has been able to make a psychiatric diagnosis, they may offer a suggestive diagnosis of PD. As the scores can be confused with a number of clinical diseases, the validity of these scales is generally measured by their concordance with a 'gold standard' [Shear et al, 2000; Steiner et al, 1995]. In the eight studies selected, the most frequently used rating scales for PD were the DSM, Structured Clinical Interview and the Subjective Units of Disturbance Scale. All of the selected studies found a positive association between panic attacks and/or anxiogenic effects of a caffeine challenge test in patients with PD. This agreement may be attributed in part to the type of study design and the standard amount of caffeine offered. None of the studies controlled for confounding factors in the analysis. The small sample size was a limitation for four studies [Nardi et al, 2009; Klein et al, 1991; Beck & Berisford, 1992; Bruce et al, 1992] and two did not use sophisticated measurements of cognitive factors associated with PD [Nardi et al, 2009; Bruce et al, 1992]” (no page nos.).

Caffeine is present in coffee, tea, chocolate, cola soft drinks, guarana and cocoa, and is also found in medicines. Approximately 80% of the world's population consumes caffeine daily. Finland, Norway and Denmark are leaders in the consumption of coffee, with a total volume of approximately 13 kg per capita per year.

The Mayo Clinic Healthy Lifestyle webpage provides a comparison of levels of caffeine in various beverages (http://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/caffeine/art-20049372?pg=1&p=1 accessed 26 May 2016).

TABLE 23 TABLE OF CAFFEINE CONTENT IN MILLIGRAMS IN SELECTED BEVERAGES.[64]

BEVERAGE	*SIZE*	*CAFFEINE CONTENT*
COFFEE		
Brewed	8 oz. (237 mL)	95-200 mg
Brewed, decaffeinated	8 oz. (237 mL)	2-12 mg
Brewed, single-serve varieties	8 oz. (237 mL)	75-150 mg
Brewed, single-serve varieties, decaffeinated	8 oz. (237 mL)	2-4 mg
Espresso, restaurant-style	1 oz. (30 mL)	47-75 mg
Espresso, restaurant-style, decaffeinated	1 oz. (30 mL)	0-15 mg
Instant	8 oz. (237 mL)	27-173 mg
Instant, decaffeinated	8 oz. (237 mL)	2-12 mg
Specialty drink (latte or mocha)	8 oz. (237 mL)	63-175 mg
BREWED TEA		
Black tea	8 oz. (237 mL)	14-70 mg
Black tea, decaffeinated	8 oz. (237 mL)	0-12 mg
Green tea	8 oz. (237 mL)	24-45 mg
ICED TEA		
Instant, prepared with water	8 oz. (237 mL)	11-47 mg
Ready-to-drink, bottled	8 oz. (237 mL)	5-40 mg
SOFT DRINKS/SODAS		
Coca-Cola	12 oz. (355 mL)	23-35 mg
Diet Coke	12 oz. (355 mL)	23-47 mg
Diet Pepsi	12 oz. (355 mL)	27-37 mg
Mountain Dew, regular and diet	12 oz. (355 mL)	42-55 mg
7UP/Sprite/Lemonade	12 oz. (355 mL)	0 mg
Pepsi	12 oz. (355 mL)	32-39 mg

[64] Adapted from Mayo Clinic Healthy Lifestyle webpage (http://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/caffeine/art-20049372?pg=1&p=1 accessed 26 May 2016).

ENERGY DRINKS		
Red Bull, regular or sugar-free	8.4 oz. (248mL)	75-80 mg

Over the counter caffeine stimulants such as *no doz* may vary in caffeine dosage.

Review studies

Nehlig (2016)[65] in their review on the effects of coffee/caffeine on brain health report on caffeine consumption and its effects including anxiety. They state:

"High doses of caffeine can cause anxiety feelings, though this does not usually occur with low doses (Fredholm et al, 1999). Animal models of anxiety have confirmed caffeine's anxiogenic effect. Two studies in humans reported a caffeine-related increase in self-ratings of anxiety for social threat words (ie, hated and lonely) and negative facial expressions (ie, angry and fearful faces) (Smith et al, 2012). One study reported that the dose-dependent increase in anxiety after 75–300 mg caffeine occurred in men but not in women (Botella & Parra, 2003).

In a caffeine challenge test (480 mg caffeine given acutely), panic disorder patients and their healthy first-degree relatives were more sensitive than healthy volunteers to panic attack symptoms (Nardi et al, 2008). This response concords with the finding that a variant of the ADORA2A gene modulates caffeine-induced anxiety in people who habitually consume little caffeine. Frequent consumption of caffeine leads to centrally mediated tolerance to its anxiogenic effect, even in genetically susceptible people (Rogers et al, 2010)" (p. 91).

According to Nehlig (2016), the Food Regulation Authorities have concluded that coffee/caffeine consumption is not harmful if consumed at levels of 200 mg in one sitting (around 2½ cups of coffee) or 400 mg daily (around 5 cups of coffee). In addition, caffeine has many positive actions on the brain. It can increase alertness and well-being, help concentration, improve mood and limit depression. Caffeine may disturb sleep, but only in sensitive individuals. It may raise anxiety in a small subset of particularly sensitive people. Caffeine does not seem to lead to dependence, although a minority of people experience withdrawal symptoms. The table below provides examples of foods and beverages which contain caffeine and their levels.

[65] Nehlig A.(2016). Effects of coffee/caffeine on brain health and disease: What should I tell my patients? Pract Neurol.; 16(2):89-95.

TABLE 24 CAFFEINE CONTENT OF DIFFERENT FOODS AND DRINKS (NEHLIG, 2016).

	Mean concentration	Range (mg)
Filtered coffee	85 mg/125 mL	60–135
Instant coffee	65 mg/125 mL	35–105
Decaffeinated coffee	3 mg/125 mL	1–5
Espresso	60 mg/30 mL	35–100
Tea (leaves or bag)	32 mg/150 mL	20–45
Iced tea	20 (330 mL)	10–50
Hot chocolate	4 mg/150 mL	2–7
Caffeinated soft drinks	39 mg/330 mL	30–48
Sugar-free soft drinks	41 mg/330 mL	26–57
Energy drinks	80 mg/330 mL	70–120
Chocolate bar	20 (30 g)	5–36
Dark chocolate	60 mg/30 g	20–120
Milk chocolate	6 mg/30 g	1–15

The quantity of caffeine varies a lot for each food or drink. It is related to the brand but also for coffee and tea to the duration of infusion, filtration and mode of preparation.
Data from http://www.coffeeandhealth.org.

Roy-Byrne (2015)[66] in a review of the literature discusses true treatment resistance of anxiety disorder due to exogenous anxiogenic factors including caffeine overuse. The following excerpt is provided in regard to caffeine overuse:

"Excess caffeine intake is rarely a "cause" of anxiety but is a frequent aggravator/amplifier (Vilarim et al, 2011). Patients will often have accompanying fatigue (perhaps as part of a comorbid depression), which is a driver of caffeine use, and if they do not experience symptom aggravation coincident with the timing of intake, they will minimize this. It is important to note that dependence on caffeine not only produces anxiety as a caffeine effect, but may produce this as a withdrawal effect, greatly confusing the picture (Dews et al, 2002). Moreover, patients often are not aware of the caffeine content of some beverages, eg, the patient who was drinking several cans of Mello Yello daily, believing it was a relaxant and was unaware of the amount of caffeine he was ingesting.

Over-the-counter cold preparations contain phenylpropylamine and pseudoephedrine, obvious stimulants. Yet patients with unexplained dyspnea may believe they have allergies and take these medications frequently in order to treat their anxiety symptom, further exacerbating their dyspnea and anxiety symptoms. The use of energy drinks with combinations of both caffeine and stimulants is another important example. One night's total sleep deprivation has been shown to exacerbate panic (Roy-Byrne & Uhde, 1986), and relative sleep deprivation almost certainly plays an important role in aggravating anxiety. Relative deprivation of sleep likely plays an important role in the onset of first panic attack in college students, who may be

[66] Roy-Byrne P. (2015). Treatment-refractory anxiety; definition, risk factors, and treatment challenges. Dialogues Clin Neurosci.;17:191-206.

stressed by exams, perhaps taking caffeine to stay up and study, and then losing substantial amounts of sleep". (p. 196)

Ruxton (2014)[67] using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, conducted a systematic review to evaluate evidence from randomised controlled trials investigating the effects of caffeine on cognition, behaviour, mood and exercise performance in children. Observational studies and expert panel guidelines were also discussed.

One hundred and nine studies were found, with 11 randomised controlled trials and 13 observational studies meeting the criteria. High caffeine intakes (e.g. >5 mg kg^{-1} body weight day^{-1}) were associated with an increased risk of anxiety and withdrawal symptoms. However, smaller amounts were not linked with such effects and may benefit cognitive function and sports performance based on adult studies. The evidence suggests that children and adolescents should limit daily caffeine consumption to 2.5 mg kg^{-1} body weight day^{-1}, equating to one or two cups of tea or one small cup of coffee. Lower contributors of caffeine, such as tea, may be more appropriate for children because they contribute to daily fluid intakes and provide flavonoids. By contrast, caffeinated soft drinks may be less suitable options for children as a result of their acidity, higher caffeine content, presence of added sugar (in some cases) and absence of bioactive compounds.

In regard to the studies which assessed anxiety, Ruxton (2014) states:

"In a randomised cross-over study, 21 children took part in a baseline study and then received 2.5 mg kg^{-1}, 5.0 mg kg^{-1} caffeine or a placebo. Attention, dexterity and memory tests showed that caffeine improved performance on attention and motor task tests but led to some feelings of anxiety, although children felt less sluggish (Bernstein et al., 1994). Another study, providing children (n = 30) with up to 145 mg caffeine day^{-1} for 13 days, showed that discontinuation of caffeine led to significant reductions in reaction times for tasks that required sustained attention (Bernstein et al., 1998).

Behavioural effects were also seen in a cross-over trial of children (mean age 10.3 years; n = 38) where 'high caffeine consumers' (500 mg day^{-1} or more) and 'low consumers' received 5 mg kg^{-1} BW caffeine twice a day or placebo for 2 weeks. When not receiving caffeine, high consumers had higher anxiety scores and reduced autonomic arousal, whereas low consumers receiving the caffeine were perceived by their parents as being more emotional, inattentive and restless, although high consumers were not rated as changed (Rapoport et al., 1984)…

These studies suggest that caffeine habituation, dose, level of exposure and degree of withdrawal may influence how children respond to caffeine. Clearly, more well-designed studies are needed using the same randomised approach but larger sample sizes. There is also a need to study the effects of caffeine on children's behaviour from beverages as opposed to caffeine capsules, which create an artificial situation in terms of the speed of caffeine consumption, the amount consumed and associated fluid intake" (p. 349).

[67] Ruxton CH (2014). The suitability of caffeinated drinks for children: a systematic review of randomised controlled trials, observational studies and expert panel guidelines. J Hum Nutr Diet, 27(4): 342-57. 078620

More studies are needed to determine the intakes that represent a risk and whether there may be benefits for alertness and sports performance with moderate intakes of caffeine.

Testa, Giannuzzi, Sollazzo et al (2013)[68] review the literature concerning substance induced psychiatric and organic disorders including the hypotheses that attempt to explain the relationship between psychiatric disorders and substance abuse relationship. They examined: (1) common risk factors; (2) psychiatric disorders precipitated by substance use; (3) psychiatric disorders precipitating substance use (self-medication hypothesis); and (4) synergistic interaction. Substance induced psychiatric and organic symptoms can occur both in the intoxication and withdrawal state. Since ancient history, humans selected indigene psychotropic plants for recreational, medicinal, doping or spiritual purpose. After the isolation of active principles or their chemical synthesis, higher blood concentrations reached predispose to substance use, abuse and dependence.

Abuse substances have specific molecular targets and very different acute mechanisms of action, mainly involving dopaminergic and serotoninergic systems, but finally converging on the brain's reward pathways, increasing dopamine in nucleus accumbens (see Table below). The most common substances producing an addiction status may be assembled in depressants (alcohol, benzodiazepines, opiates), stimulants (cocaine, amphetamines, nicotine, caffeine, modafinil), hallucinogens (mescaline, LSD, ecstasy) and other substances (cannabis, dissociatives, inhalants). Anxiety disorders can occur in intoxication by stimulants, as well as in withdrawal syndrome, both by stimulants and sedatives. Finally, psychiatric and organic symptoms may be caused by prescription and doping medications, either as a direct effect or after withdrawal. Adverse drug reactions can be divided in type A, dose dependent and predictable, including psychotropic drugs and hormones; and type B, dose independent and unpredictable, usually including non psychotropic drugs, more commonly included being cardiovascular, antibiotics, anti-inflammatory and antineoplastic medications.

In regard to caffeine they state:

"The universal appeal of caffeine, a xanthine derivative, assumed by beverages such as coffee, tea and cola, is related to its mild psychostimulant properties. Even though the primary action of caffeine may be to block adenosine receptors, this leads to very important secondary effects on many classes of neurotransmitters, including noradrenaline, dopamine, serotonin, acetylcholine, glutamate, and GABA. **In a healthy person, caffeine promotes cognitive arousal and fights fatigue, but these same activating properties can produce symptomatic distress in a small subset of the population, with 50% presenting with symptoms of nervousness, excitation, abdomen pain, dry mouth, tremor, nausea, and jitteriness.** Susceptibility to this symptomatic distress is broadly determined by three factors: the dose consumed, individual vulnerability to caffeine, and pre-existing medical or psychiatric conditions (mood disorders in particular) that are aggravated by mild psychostimulant use. The caffeine excess produces persisting insomnia, nervousness, and mood fluctuations.

[68] Testa A, Giannuzzi R, Sollazzo F et al (2013). Psychiatric emergencies (part II): psychiatric disorders coesixting with organic diseases. Eur Rev Med Pharmacol Sci; 17(Suppl 1): 65-8.

TABLE 25 MAIN CLASSES OF COMMONLY ABUSED SUBSTANCES, THEIR MAIN SPECIFIC MOLECULAR TARGETS, AND SOME OF THEIR MECHANISM BY WHICH THEY ACTIVATE THE DOPAMINERGIC AND SEROTONERGIC SYSTEMS, LEADING TO INCREASE DOPAMINE IN NUCLEUS ACCUMBENS (TESTA ET AL, 2013).

Drug	Target	Mechanism
Depressants		
Alcohol, benzodiazepines and barbiturates	Multiple targets, including GABA and glutamate receptors	Facilitate GABAergic neurotransmission, which may disinhibit VTA dopamine neurons from GABA interneurons or may inhibit glutamate terminals that regulate dopamine release in nucleus accumbens.
Opiates(morphine, codeine and heroin)	μ-opioid receptor	Disinhibit neurons of the mesolimbic dopamine pathway by inhibiting GABA interneurons, that contain μ-opioid receptors in the ventral tegmental area, or directly activate nucleus accumbens neurons that contain μ-opioid receptor.
Stimulants		
Cocaine, amphetamine, methamphetamine or ecstasy	Dopamine transporter	Block dopamine transporter on the terminals of dopamine projecting neurons of the mesolimbic dopamine pathway (cocaine, crack), or release dopamine from the vesicles of dopamine terminals (amphetamine, methamphetamine).
Nicotine	Nicotinic receptors (predominantly α4β2 subtype)	Directly activates neurons of the mesolimbic dopamine pathway by stimulating their nicotine receptors, and indirectly activates them by stimulating the nicotine receptors in glutamatergic terminals to ventral tegmental area dopamine neurons.
Caffeine	Adenosine receptors (predominantly A2A subtype)	Inhibits adenosine A2A receptors interaction with dopaminergic transmission in the striatal GABAergic neurons projecting to the ventral pallidum, so decreasing GABA release in the nucleus accumbens.
Eugeroics (modafinil, adrafinil, and ampakines)	Multiple targets, including orexin trasmission, α1-adrenergic and glutamate receptors	Induce wakefulness by its action in the anterior hypothalamus, activating orexin neurons, which project to the entire CNS. Facilitate excitatory glutamatergic signalling and also amplify midbrain noradrenergic signals, cortical serotonin release and extracellular levels of dopamine, including the nucleus accumbens.
Hallucinogens		
Mescaline, psilocybin, LSD, ecstasy	Serotonin receptors	Enhance glutamatergic transmission in the cerebral cortex, responsible for the higher-level cognitive, perceptual, and affective distortions produced by these drugs, acting on serotonin receptors. The coeruleo-cortical noradrenergic system and the cerebral cortex are among the regions where hallucinogens have prominent effects.
Other substances		
Cannabinoids (marijhuana, hashish)	Cannabinoid CB1 and CB2 receptors	Regulate dopaminergic signalling through CB1 and CB2 receptors in nucleus accumbens neurons and in GABA and glutamate terminals to nucleus accumbens
Club Drugs o dissociatives (ketamine, gamma-hydroxybutyrate o GHB)	NMDA receptors (by ketamine) GHB receptors (by gamma-hydroxybutyrate)	Ketamine binds to the NMDA receptor, blocking calcium flow and increasing dopamine release in prefrontal cortex and midbrain. NMDA blockade has also been linked to activation of serotonin systems. GHB receptors have the highest density in the hippocampus, cortex, and dopaminergic areas (striatum, olfactory tracts, and substantia nigra). GHB acts increasing central dopamine levels, which could be associated with the reinforcing effects of GHB.
Inhalants or volatile solvents (toluene, benzene, chloroform, xylene, acetone, alkyl nitrites, butane, benzene, nitrous oxide, chlorofluorocarbons, halothane)	Multiple targets, including GABA receptors (predominantly GABAA subtype) and NMDA receptors (predominantly NR1 and NR2B subtypes)	Their anxiolytic effects depend on their positive modulation of GABA receptors. Induce subjective psychedelic effects blocking NMDA receptors. Increase dopamine levels in the prefrontal cortex, striatum and VTA, so producing their rewarding effects.

Symptoms of ADHD may be altered by caffeine as well. Psychosis can be induced in normal individuals ingesting caffeine at toxic doses, and psychotic symptoms can also be worsened in

schizophrenic patients using caffeine. Other symptoms affecting the cardiovascular system range from moderate increases in heart rate to more severe cardiac arrhythmia (Broderick et al, 2004). A number of drugs, including certain SSRIs, antipsychotics, antiarrhythmics, theophylline and quinolones, have been reported to be potent inhibitors of cytochrome P450, which participates in the metabolism of caffeine. This has important clinical implications, since the high potential for pharmacokinetic interactions. Withdrawal symptoms consist of dysphoric mood changes, fatigue, muscle pain, stiffness, lethargy, headache and nausea, with subjective psychological distress and significant impairment of psychomotor speed and cognitive performance tests (Silverman et al, 1992)" (pp. 71-2).

Caffeine is widely consumed in foods and beverages and is also used for a variety of medical purposes. Despite its widespread use, relatively little is understood regarding how genetics affects consumption, acute response, or the long-term effects of caffeine.

Yang et al (2010)[69] reviewed the literature on the genetics of caffeine from the following: (1) twin studies comparing heritability of consumption and of caffeine-related traits, including withdrawal symptoms, caffeine-induced insomnia, and anxiety, (2) association studies linking genetic polymorphisms of metabolic enzymes and target receptors to variations in caffeine response, and (3) case-control and prospective studies examining relationship between polymorphisms associated with variations in caffeine response to risks of Parkinson's and cardiovascular diseases in habitual caffeine consumers.

Twin studies find the heritability of caffeine-related traits to range between 0.36 and 0.58. Analysis of poly-substance use shows that predisposition to caffeine use is highly specific to caffeine itself and shares little common disposition to use of other substances. Genome association studies link variations in adenosine and dopamine receptors to caffeine-induced anxiety and sleep disturbances. Polymorphism in the metabolic enzyme cytochrome P-450 is associated with risk of myocardial infarction in caffeine users.

Modeling based on twin studies reveals that genetics plays a role in individual variability in caffeine consumption and in the direct effects of caffeine. Both pharmacodynamic and pharmacokinetic polymorphisms have been linked to variation in response to caffeine. These studies may help guide future research in the role of genetics in modulating the acute and chronic effects of caffeine.

Cross-sectional studies

Richards and Smith (2015)[70] used data from the Cornish Academies Project to investigate associations between caffeine (both its total consumption, and that derived separately from energy drinks, cola, tea, and coffee) and single-item measures of stress, anxiety, and depression, in a large cohort of secondary school children from the South West of England. After adjusting for additional dietary, demographic, and lifestyle covariates, positive associations between total weekly caffeine intake and anxiety and depression remained significant, and the effects differed between males and females. Initially, effects were also observed in relation to caffeine consumed specifically from coffee. However, coffee was found

[69] Yang A, Palmer AA, de Wit H (2010). Genetics of caffeine consumption and responses to caffeine. Psychopharmacology (Berl), 211(3): 245-57. 078668

[70] Richards G & Smith A. (2015). Caffeine consumption and self-assessed stress, anxiety, and depression in secondary school children. Journal ofPsychopharmacology; 29(12):1236-47.

to be the major contributor to high overall caffeine intake, providing explanation as to why effects relating to this source were also apparent.

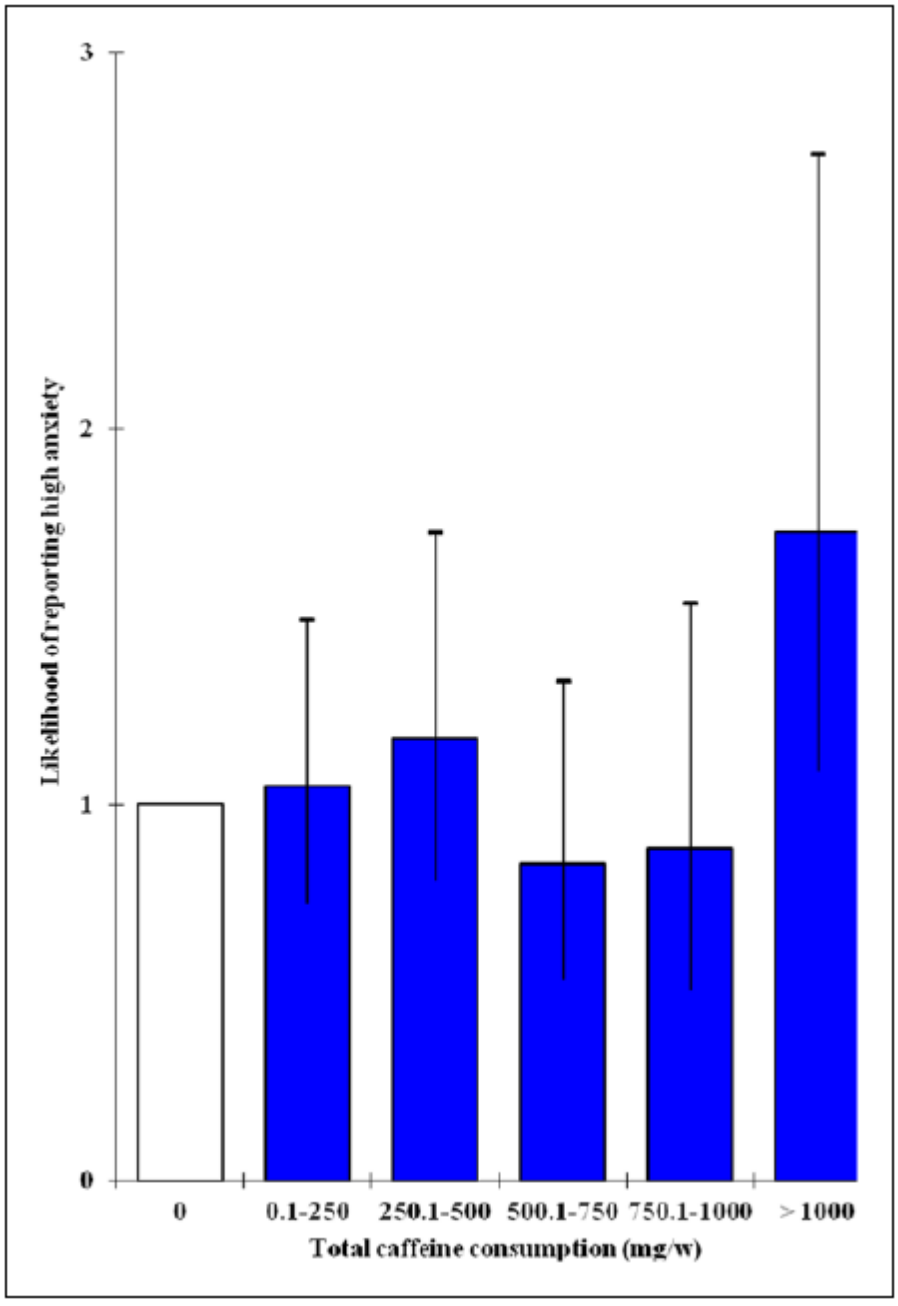

FIGURE 1 ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR MULTIVARIATE ASSOCIATIONS BETWEEN TOTAL WEEKLY CAFFEINE INTAKE AND ANXIETY (RICHARDS & SMITH, 2015).

Findings from the current study increase the knowledge regarding associations between caffeine intake and stress, anxiety, and depression in secondary school children, though the cross-sectional nature of the research made it impossible to infer causality.

Double-blind caffeine challenge test

Clemente-Suarez and Robles-Pérez (2015)[71] aimed to analyse the effect of a single dose of 400 mg of caffeine monohydrate on the psycho-physiological response and marksmanship of soldiers in close quarter combat (CQC). The heart rate, blood lactate concentration, cortical arousal, state anxiety and marksmanship of 19 soldiers in the Spanish Army (38.9 ± 4.1 years; 177.4 ± 5.3 cm; 78.8 ± 7.6 kg) before and after a CQC simulation in a double-blind procedure were analysed. Previous studies have researched the ergogenic effect (enhancing physical performance) of caffeine in different shooting actions, but none of them in a stressful combat action. Caffeine intake did not improve shooting performance in CQC; however, it increased cognitive and somatic anxiety levels.

State anxiety was evaluated using the CSAI-2R (Cox et al. 2003), consisting of 17 items that assess cognitive anxiety (CA), somatic anxiety (SA) and self-confidence (SC), with five, seven and five items, respectively. The response scale evaluated the intensity of each symptom on a scale of 1 (not at all) to 4 (very much). Higher scores on cognitive and SA subscales indicated a higher level of anxiety, whereas higher scores on the SC subscale indicated a higher level of SC. This questionnaire was approved in an independent study for the Spanish population, presenting an overall good fit of the model with a value of .97 for comparative and non-normed fit indices and .045 for root mean square error of approximation (Andrade, Lois, and Arce 2007).

CA and SA values increased significantly for both caffeine and placebo intake following the CQC simulation, but the values reached for caffeine intake were significantly higher than those for placebo ingestion (Table below).

TABLE 26 STATE ANXIETY VALUES PRE- AND POST CQC SIMULATION (CLEMENTE-SUAREZ ET AL, 2015)

	CA pre	CA post	SA pre	SA post	SC pre	SC post
Caffeine	5.7 ± 5.8	9.0 ± 5.3* (0.032) ** (0.017)	4.6 ± 7.8	9.0 ± 9.0* (0.011)	16.4 ± 6.3	17.0 ± 2.6
Placebo	4.2 ± 4.6	3.4 ± 4.6	1.3 ± 1.9	4.6 ± 3.9* (0.019)	17.7 ± 2.9	18.3 ± 3.0
F	.040	2.696	4.773	2.626	.452	.361
p	.844	0.014	.052	0.044	.612	.559

Notes: *$p < 0.05$ pre vs. post samples; **$p < 0.05$ caffeine vs. placebo; CA, cognitive anxiety; SA, somatic anxiety; SC, self-confidence; *F* and *p* values obtained in the ANOVA analysis of caffeine vs. placebo results.

Case report

Guarana (Paullinia cupana) is the climbing vine native to Amazon Basin, characterized by high caffeine content in its seeds. Guarana extract is a common ingredient of energy drinks used in order to boost energy and physical endurance and increase alertness. Severe caffeine intoxication is rare, but may be life-threatening mostly due to supraventricular and ventricular dysrhythmias.

Ciszowski, Biedroń and Gomólka (2014)[72] presented the case of intentional caffeine poisoning after ingestion of tablets containing guarana extract, complicated by atrial fibrillation. A 44-year-old man with no significant medical history was admitted to hospital about 21 h after

[71] Clemente-Suarez VJ, Robles-Pérez JJ. (2015). Acute effects of caffeine supplementation on cortical arousal, anxiety, physiological response and marksmanship in close quarter combat. Ergonomics;58(11):1842-50.
[72] Ciszowski K, Biedroń W, Gomólka E. (2014). Acute caffeine poisoning resulting in atrial fibrillation after guarana extract overdose. Przegl Lek;71(9):495-8.

ingestion of guarana extract containing 1.6 g of caffeine. Typical symptoms of caffeine toxicity, i.e. nausea, vomiting, anxiety and palpitations, occurred shortly after ingestion. On admission, he was conscious, with blood pressure of 136/86 mmHg, heart rate of 106-113 beats per minute, fever of 37.8 °C, and symmetrically increased deep tendon reflexes. QTc interval in electrocardiogram was prolonged to 0.542 s. Laboratory tests revealed hypokalemia, hyperglycemia, leukocytosis, as well as elevated creatinine and creatine phosphokinase levels. Approximately 45 h post ingestion, the patient developed atrial fibrillation with fast ventricular rhythm. Tachydysrythmia subsided after infusion of amiodarone and restoration of electrolyte balance. Echocardiogram revealed presence of asymmetrical hypertrophy of the left ventricle with the systolic anterior motion of the mitral valve and normal left ventricular outflow tract gradient suggesting non-obstructive hypertrophic cardiomyopathy.

Summary and conclusion

As outlined in the systematic review by Vilarim et al (2011) caffeine at high doses is given in experimental studies to subjects with panic disorder to illicit panic attacks and anxiety symptomatology.

The evidence is Grade 1 level.

The evidence for healthy individuals without a known mental health history is supportive of an association between caffeine exposure and anxiety symptoms. However, the dose of caffeine required to cause severe enough symptomatology to meet the SMIAD diagnostic criteria is difficult to ascertain.

Qualitative reviews (Nehlig, 2016; Roy-Byrne, 2015; Testa et al, 2013) support the anxiogenic properties of caffeine. Although specific details of the appropriate dose of caffeine to ilicit the response is not discussed. In regard to dose, Nehlig (2016) reported that the dose-dependent increase in anxiety after 75–300 mg caffeine occurred in men but not in women (Botella & Parra, 2003). In a caffeine challenge test (480 mg caffeine given acutely) was more likely to illicit panic disorder in panic disorder patients and their healthy first-degree relatives than healthy volunteers (Nardi et al, 2008). Nehlig (2016) also reported that the Food Regulation Authorities have concluded that coffee/caffeine consumption is not harmful if consumed at levels of 200 mg in one sitting (around 2½ cups of coffee) or 400 mg daily (around 5 cups of coffee). Interestingly, frequent consumption of caffeine leads to centrally mediated tolerance to its anxiogenic effect, even in genetically susceptible people.

The Ruxton (2014) systematic review of evidence related to the suitability of caffeine use in children found that the studies supported an association between high dose of caffeine and anxiety and withdrawal symptoms. High doses were measured differently in studies. 5.0 mg of caffeine per kilogram of body weight was considered in a randomised crossover study to induce anxiety. Habituation to caffeine appeared to reduce the anxiogenic effects of caffeine overtime in a cross-over trial. The participants were divided into high consumers (those who ingested 500 mg of caffeine or more per day) and low consumers. Both groups were given 5 mg/kg of caffeine twice a day or placebo for two weeks. The high consumers when not receiving caffeine reported high anxiety scores, perhaps indicating a withdrawal effect. The low consumers ingesting caffeine at this high dose were perceived by their parents as being more emotional, inattentive and restless, although high consumers were not rated as changed.

Yang et al (2010) reviewed twin studies which identified that genetics plays a role in the direct effects of caffeine at an individual level.

A cross-sectional study of a large cohort of secondary students (Richards & Smith, 2015) found in adjusted analysis that the association between weekly caffeine intake and anxiety and depression symptoms were significant at the 1 gram per week level.

A double blind caffeine challenge test (Clemente-Suarez & Robles-Pérez, 2015) in Spanish Army soldiers found that 1 dose of 400 mg of caffeine resulted in higher anxiety symptom ratings than at baseline.

A case report by Cizowski et al (2014) reported that a man who intentionally ingested 1.6 grams of caffeine from guarana extract presented with severe symptomatology, including anxiety, shortly after ingesting.

The evidence is consistent that caffeine exposure can cause the presentation of anxiety symptomatology. Individuals with existing anxiety or panic disorder diagnoses or a genetic vulnerability appear to require a lesser dose of caffeine to induce anxiety, likewise children/adolescents appear to also require a lesser dose. Tolerance to caffeine and withdrawal symptoms are described.

Grade 2 level evidence

Insulin Therapy

Summary of important issues

The **DSM-5**[73] states insulin is one of the medications that can evoke anxiety symptoms.

Cohort studies

Trento, Trevisan, Raballo et al (2014)[74] investigated depression, anxiety and cognitive impairment and their associations with clinical and socio-demographic variables in type 2 diabetes. The Zung Self-Rating Depression-Anxiety Scale and Mini-Mental State Examination (MMSE) were administered at baseline and after four years to 498 consecutive patients, 249 non-insulin treated (NIT) and 249 insulin treated (IT), aged 40-80 years.

At baseline, IT patients were older, had longer disease duration, higher HbA1c and did more glucose monitoring ($p < 0.001$, all) but their depression scores were lower than among NIT ($p = 0.006$), with no differences for anxiety or MMSE. After 4 years, 72 patients were lost to the follow-up, of whom 18 had died. 41 NIT had switched to insulin and increased BMI ($p = 0.004$), blood pressure ($p < 0.001$), retinopathy severity ($p = 0.03$) and microalbuminuria ($p = 0.0045$), but did not change their scores for depression, anxiety or MMSE. The remaining 171 NIT improved fasting glucose ($p = 0.006$), total cholesterol ($p < 0.0001$), triglyceride ($p = 0.0026$) and HbA1c ($p = 0.0006$). Despite increased prevalence of microalbuminuria and retinopathy ($p < 0.0001$, both), depression ($p = 0.04$) and MMSE ($p = 0.0007$) improved. Foot ulcers ($p = 0.03$), retinopathy ($p < 0001$), microalbuminuria ($p = 0.0047$) and hypertension ($p < 0.0001$) increased in the remaining 214 IT patients, in whom depression ($p = 0.0005$) and anxiety ($p < 0.0001$) worsened while MMSE improved slightly ($p = 0.0002$). On multivariate analysis, depression was associated with being a woman and anxiety with diabetes duration and lower schooling, which also affected MMSE scores.

The findings from this 4-year follow-up cohort study suggest that, despite clinical worsening of type 2 diabetes with progression of complications and the necessity to start insulin therapy in part of the patients, only anxiety increased with diabetes duration, while depression and anxiety worsened only in those already on insulin who developed more severe complications.

Depression was associated with female gender and worsening complications but not modified by diabetes duration or switching to insulin therapy. Diabetes duration and lower schooling may affect anxiety and cognitive impairment.

Summary and conclusion

Although DSM-5 states that insulin use can induce anxiety/panic attacks, the evidence summarised in the cohort study by Trento et al (2014) was equivocal. The 214 patients on insulin therapy did report worsening of anxiety symptoms in the follow-up period. But it is unclear if the increase in anxiety symptoms was due to the diabetes, needle anxiety or the insulin therapy. No other studies on this topic were identified in the literature.

Grade 4 level evidence

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[73] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783

[74] Trento M, Trevisan M, Raballo M, Passera P, Charrier L, Cavallo F, Porta M. (2014). Depression, anxiety, cognitive impairment and their association with clinical and demographic variables in people with type 2 diabetes: a 4-year prospective study. Journal of Endocrinological Investigation; 37(1):79-85.

Cardiovascular medications

Summary of important issues

Reviews

Huffman and Stern (2007)[75] review the evidence in relation to cardiovascular medications and purported neuropsychiatric adverse events. Huffman and Stern are critical of the literature which report on this subject. "First, neuropsychiatric symptoms are exceedingly common among patients with cardiovascular conditions. For example, approximately 15% of patients with recent myocardial infarction (MI), congestive heart failure (CHF), or recent coronary artery bypass graft (CABG) surgery suffer from major depressive disorder (MDD). Anxiety is also common among patients with coronary artery disease (CAD), especially among post-MI patients. Finally, delirium, which can present with psychotic symptoms, mood lability, and anxiety, is highly prevalent among hospitalized cardiac patients, especially among those undergoing surgery. Thus, it may appear that a particular cardiovascular medication frequently causes a particular neuropsychiatric syndrome, when in fact such a syndrome may occur commonly as part of the natural history of cardiac illness, and be unrelated to medication. In addition, the vast majority of studies that associate cardiovascular medications with neuropsychiatric consequences have been case reports and case series that may at best suggest a link between the taking of a medication and a clinical outcome. Such reports do not usually use standardized tools to evaluate the presence or severity of the reported neuropsychiatric symptoms; instead, they rely only on general reports of symptoms as observed by the authors. As we will discuss, well-controlled trials that examine the neuropsychiatric consequences of cardiovascular medications are relatively few and far between, and at times may contradict clinical reports" (p. 29).

Huffman and Stern (2007) assessed the evidence in relation to β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II blockers, calcium channel blockers, diuretics, centrally acting agents, α-adrenergic agents, vasodilators, antiplatelet and anticoagulant agents, selected antiarrhythmic medications (class I agents and class III agents) and lipid lowering agents and concluded the following in regard to drug-induced anxiety symptoms:

α-Adrenergic agents

The α1-adrenergic antagonists prazosin, doxazosin, and alfuzosin are used as antihypertensive agents and to treat symptoms of benign prostatic hypertrophy. In general, there are few adverse neuropsychiatric consequences associated with these medications. Fatigue is the most common neuropsychiatric effect, occurring in association with all α1 antagonists (Carruthers, 1994; MacDonald et al, 2004; Guay, 2004). This effect is relatively infrequent (presenting in approximately 5% to 15% of patients) (Carruthers, 1994; MacDonald et al, 2004), but it does occur more often than with placebo, and can lead to its discontinuation. Depression is not consistently associated with this class of agents, although there have been rare occurrences reported in association with prazosin use (Beers &

[75] Huffman JC & Stern TA. (2007). Neuropsychiatric consequences of cardiovascular medications. Dialogues in Clinical Neuroscience; 9(1):29-45.

Passman, 1990). Sleep disturbance and anxiety can occur with these agents, though such symptoms are usually mild (Pessina et al, 2006; Benson et al, 1983) (pp. 35-6).

Vasodilators

Hydralazine

Hydralazine, a systemic vasodilator, the use of which is usually reserved for patients with severe hypertension, occasionally has neuropsychiatric side effects. Fatigue or asthenia occur slightly more often with hydralazine than with placebo, although this effect is not prominent. Hydralazine has been associated on rare occasions with the direct onset of depression (Shrivastava, 2006), mild anxiety (Stevens et al, 1983), psychosis (Moser et al, 1953), and delirium (due to withdrawal of hydralazine that has led to acute hypertension in a patient receiving hydralazine for afterload reduction) (Black & Mehta, 1979).

Antiplatelet and anticoagulant agents

Aspirin (salicylic acid) has few neuropsychiatric consequences. It has not been consistently associated with mood symptoms, fatigue, sedation, anxiety, psychosis, or delirium when used at therapeutic doses.

Selected antiarrhythmic medications

Class I agents

Lidocaine (Class Ib)

Systemic use of lidocaine has been associated with a variety of neuropsychiatric effects. Lloyd and colleagues (Lloyd & Greenblatt, 1981), in a review of the neuropsychiatric effects of antiarrhythmics, report that delirium, psychotic symptoms, and anxiety may be consequences of lidocaine use. Furthermore, a specific review of 15 cases of adverse neuropsychiatric effects of lidocaine found that mood symptoms and apprehension/anxiety were the most common such effects; confusion and psychotic symptoms (hallucinations and delusions) were also common in this cohort (Saravay et al, 1987).

Class III agents

Amiodarone

In contrast to the above antiarrythmics, amiodarone has been increasingly used in recent years, especially for patients with atrial fibrillation (AF).Amiodarone is listed as a class III antiarrthymic agent that is thought to act via sodium, potassium, and calcium channel blockade. The structure of amiodarone is similar to that of thyroid hormone, and thyroid abnormalities occur in approximately 15% of patients taking amiodarone due to its high iodine content and its direct toxic effects on the thyroid (Martino et al, 2001); both hypothyroidism (more common) and hyperthyroidism may occur. Through this indirect mechanism, neuropsychiatric effects of amiodarone may occur, as hypothyroidism is commonly associated with fatigue and depressive symptoms (and occasionally psychosis) (Jackson, 1998), while hyperthyroidism can be associated with sleep disturbance, anxiety, apprehension, and, at times, depressive or maniform symptoms, with or without psychosis (Brownlie et al, 2000). In addition, amiodarone has been directly associated with delirium (Athwal et al, 2003; Barry & Franklin, 1999; Trohman et al, 1988; Anastasiou-Nana et al, 1986), depressive symptoms (Odelola, 1999; Ambrose & Salib, 1997) and fatigue (Durakovicet al, 1991); these effects have

not been studied comprehensively but do not appear to be frequent complications of amiodarone use.

Amiodarone is associated with thyroid abnormalities in 15% of patients, and untreated thyroid dysregulation can lead to a variety of mood, cognitive, and psychotic symptoms. In contrast, direct neuropsychiatric effects of amiodarone are uncommon.

HMG-CoA reductase inhibitors Statins

The statins appear to have few neuropsychiatric consequences, with occasional reports of anxiety, sleep disturbance (especially with lovastatin), and fatigue, but no other substantial neuropsychiatric effects (Davidson et al, 2000; Chung et al, 2001; Buajordet et al, 1997; Shaefer, 1998).

Shah, Iqbal, White and White (2005)[76] reviewed the literature in regard to psychiatric and cardiovascular medications, existing psychiatric comorbidities commonly reported in cardiac patients and the safety of these medications. They discussed the interaction of the drugs used in the management of these two varied but commonly coexistent group of diseases as well as their relative effects on either system. The data regarding the safe use of these medications based on the recommendations from the currently available evidence is summarised.

Many cardiac medications have been shown to influence the general mode, affect, and physical status of an individual. Of these, doxozosin, enalopril and nicardipine have been associated with the development of agitation and anxiety symptoms (see Table below).

TABLE 27 NEUROPSYCHIATRIC SIDE EFFECTS OF COMMON CARDIOVASCULAR MEDICATIONS (SHAH ET AL, 2005).

	Agitation/anxiety	Delirium	Depression	Hallucinations	Mania hypomania euphoria	Seizures	Sleep problems
Amiodarone		+	+				+
β-Blockers		+	+	+		+	++
Captopril		+	+	+	+		
Clonidine					+		+
Diltiazem		+	+	+	+		+
Digoxin		+		+	+	+	+
Doxazosin	+ (2.4%)	+					
Disopyramide		+		+		+	
Enalapril	+	+	+				
Felodipine			+				
Hydralazine			+		+		
Lidocaine		+				+	
Lisinopril			+				
Mexilitene		+				+	
Nicardipine	+ (rare)	+	+				
Nifedipine			+				+
Prazosin		+	+				
Procainamide			+	+	+		
Propanolol			+		+		
Quinapril			+				+
Reserpine		+			+		
Spironolactone		+					
Streptokinase			+	+			

[76] Shah SU, Iqbal Z, White A & White S (2005). Heart and mind: (2) psychotropic and cardiovascular therapeutics. Postgrad Med J; 81:33-40.

Cross-sectional studies

Johansen, Holmen, Stewart, Bjerkeset (2012)[77] investigated the associations between antihypertensive agents and symptoms of depression and anxiety in a large population sample. 55,472 participants in the Nord-Trondelag Health Study (HUNT 2, 1995-1997), Norway, who completed the Hospital Anxiety and Depression rating Scale, were divided into 3 groups according to their diastolic blood pressure and antihypertensive treatment status. A cut-off of >90 mmHg diastolic blood pressure was used to identify hypertensive status. Differences in anxiety and depression symptom levels in untreated and treated hypertensives (all treatments) versus the normotensive reference group were explained by differences in age and gender distribution in the three groups in this study.

TABLE 28 ODDS RATIOS (ORS) FOR SYMPTOMS OF DEPRESSION, ANXIETY, AND MIXED ANXIETY AND DEPRESSION IN HUNT 2 PARTICIPANTS ON DIFFERENT CLASSES OF ANTIHYPERTENSIVE MEDICATIONS COMPARED TO THE UNTREATED HYPERTENSIVE GROUP (DBP[90 MMHG) (JOHANSON ET AL, 2012).

	Beta blockers $n = 372$ OR (95% CI)	Calcium channel antagonists $n = 459$ OR (95% CI)	ACE-inhibitors $n = 257$ OR (95% CI)
Symptoms of depression			
Crude association	1.37 (0.90–2.07)	1.29 (0.88–1.90)	0.65 (0.33–1.27)
Age and gender adj.	1.28 (0.84–1.94)	1.07 (0.72–1.58)	0.56 (0.28–1.10)
Final model	1.20 (0.78–1.83)	1.04 (0.70–1.53)	0.54 (0.28–1.08)
Symptoms of anxiety			
Crude association	1.23 (0.86–1.77)	1.11 (0.79–1.56)	0.88 (0.54–1.43)
Age and gender adj.	1.28 (0.88–1.84)	1.27 (0.89–1.79)	0.95 (0.58–1.55)
Final model	1.10 (0.75–1.62)	1.29 (0.90–1.84)	0.99 (0.60–1.64)
Mixed symptoms of anxiety and depression			
Crude association	1.50 (1.01–2.29)	1.30 (0.90–1.90)	1.00 (0.58–1.74)
Age and gender adj.	1.49 (1.00–2.22)	1.31 (0.89–1.93)	1.00 (0.58–1.74)
Final model	1.12 (0.73–1.74)	1.31 (0.86–1.97)	1.06 (0.59–1.90)

Analyses restricted to those on single drug treatment only

Final model adjusted for age, gender, cohabitation status, level of education, employment, exercise, daily smoking, monthly drinking frequency, BMI, previous mental health help-seeking, previous depressive syndrome, and psychotropic drug use. Participants with established or suspected cardiovascular disease, were excluded from the study

However, the receipt of two or more antihypertensive drugs was associated with depressive symptoms alone (OR = 1.40, 95% CI = 1.03-1.90), but not with symptoms of anxiety (OR = 1.14, 95% CI = 0.83-1.57) or mixed anxiety and depression (OR = 1.19, 95% CI = 0.82-1.72) in the fully adjusted model, compared to untreated hypertension.

[77] Johansen A, Holmen J, Stewart R, Bjerkeset O. (2012). Anxiety and depression symptoms in arterial hypertension: the influence of antihypertensive treatment. the HUNT study, Norway. European Journal of Epidemiology; 27(1):63-72.

TABLE 29 ODDS RATIOS (ORS) FOR SYMPTOMS OF DEPRESSION, ANXIETY, AND MIXED ANXIETY AND DEPRESSION IN HYPERTENSIVES TREATED WITH SINGLE AND MULTIPLE ANTIHYPERTENSIVES AGENTS COMPARED TO UNTREATED HYPERTENSIVES (UHT, REF) (JOHANSEN ET AL, 2012.

	Antihypertensive monotherapy OR (95% CI)	Antihypertensive therapy with 2 or more agents OR (95% CI)
Depression (HADS-D ≥ 8 and HADS-A < 8)		
Crude association[a]	1.09 (0.85–1.41)	1.72 (1.28–2.31)
Age and gender adj.[a]	0.94 (0.73–1.23)	1.46 (1.08–1.98)
Final model[a,c]	0.90 (0.67–1.18)	1.40 (1.03–1.90)
Crude association[b]	1.18 (0.98–1.42)	1.60 (1.28–1.01)
Age and gender adj.[b]	0.96 (0.79–1.17)	1.33 (1.05–1.68)
Anxiety (HADS-A ≥ 8 and HADS-D < 8)		
Crude association[a]	1.10 (0.89–1.36)	0.99 (0.73–1.34)
Age and gender adj.[a]	1.21 (0.97–1.51)	1.13 (0.83–1.54)
Final model[a]	1.19 (0.94–1.49)	1.14 (0.83–1.57)
Crude association[b]	1.07 (0.91–1.27)	1.03 (0.79–1.34)
Age and gender adj.[b]	1.14 (0.96–1.36)	1.13 (0.82–1.30)
Mixed symptoms of anxiety and depression: HADS-A ≥ 8 and HADS-D ≥ 8		
Crude association[a]	1.34 (1.06–1.70)	1.17 (0.84–1.64)
Age and gender adj.[a]	1.36 (1.06–1.73)	1.20 (0.85–1.69)
Final model[a]	1.29 (0.99–1.68)	1.19 (0.82–1.72)
Crude association[b]	1.13 (0.94–1.36)	1.04 (0.81–1.35)
Age and gender adj.[b]	1.12 (0.92–1.36)	1.03 (0.79–1.34)

Results from analyses of dataset with [a] complete confounder information ($n = 7,757$) and [b] missing confounder information ($n = 12,287$)

[c] Final model adjusted for age, gender, cohabitation status, level of education, employment, exercise, daily smoking, monthly drinking frequency, BMI, previous mental health help-seeking, previous depressive syndrome, and psychotropic drug use. Participants with established or suspected cardiovascular disease were excluded from the study

Antihypertensive monotherapy (all agents) nor any single antihypertensive drug class were associated with symptoms of depression, anxiety, or mixed anxiety and depression. There may be a positive association between multi antihypertensive drug use and symptoms of depression, whereas this was not found in persons with symptoms of anxiety or mixed anxiety and depression. This might reflect poor antihypertensive treatment adherence leading to polypharmacy, or other unfavourable health behaviours in people with symptoms of pure depression.

Limitations

"The study also has some limitations. Anxiety and depression symptoms were self-reported, and results cannot be directly compared to studies using clinical diagnoses of anxiety and depressive disorders. Further, misclassification between the three categories could have occurred, since the use of antihypertensive drugs was based on self-report and stress-induced situational hypertension cannot be excluded. In particular, poorer antihypertensive treatment compliance in persons with symptoms of depression could have contributed to misclassification. Still, we expect the risk of misclassification to be low, as the HUNT study focused especially on hypertension and all participants were explicitly asked whether they were treated for hypertension or not. Unfortunately, the high number of participants made the gold standard of 24 h-measurement of blood pressure not feasible in our study. Nevertheless, the standard method used in HUNT, with blood pressure measured three times by especially trained nurses, is better than in most clinical settings.

Due to the cross-sectional design, the direction of causality underlying any association between hypertension, antihypertensive treatment and symptoms of depression and/or anxiety cannot be inferred. It may also be argued that prescription bias might operate in our study. For

some time, beta blockers have been under suspicion of causing depression, and, for that reason, physicians may have been reluctant to prescribe this drug to those with current or previous depression. Our results, however, showed there was little difference between the study groups regarding previous mental health help-seeking. Furthermore, analyses were adjusted for self-reported previous depression and the use of psychotropic drugs. Finally, selecting only those using a single antihypertensive drug when assessing the drug classes lead to reduced statistical power, and associations might have gone undetected" (p. 68).

Alpha adrenergic antagonists

Review studies

Tam, Worcel and Wyllie (2001)[78]

Abstract

Although yohimbine (YOH) has been available for the treatment of male erectile dysfunction (ED) for longer than Viagra, there is a perception that little is known about the clinical performance of the drug. This review attempts, by comprehensive analysis of the literature, to cover the clinical, pharmacological, and therapeutic profiles of YOH, relevant to its potential utility in the management of patients with ED. Relatively few well-designed studies have been completed. From these, however, it can be concluded that YOH as monotherapy possesses only modest efficacy in ED patients. In acute and chronic (long-term) studies, YOH has been found to be relatively free of side effects over the dose range predicted to be effective in ED. At much higher doses, the most frequently observed effects, consistent with the primary pharmacological action of the drug, are elevation of blood pressure, a slight anxiogenic action, and increased frequency of urination. These side effects are all easily reversible on termination of YOH therapy. There is increasing evidence that the erectogenic action of YOH can be augmented by concomitant administration of agents that augment the release and/or action of nitric oxide in the corpus cavernosum. YOH has yet to be studied in female sexual dysfunction. Overall, the benefit risk profile of YOH would indicate that it has potential, more probably as part of a combination strategy, e.g., with a drug that enhances the nitric oxide pathway, in the treatment of ED.

Controlled trials

Fox, Anderson, Tuit et al (2012)[79]

Abstract

BACKGROUND:

Stress, alcohol cues, and dysregulated stress responses increase alcohol craving and relapse susceptibility, but few pharmacologic agents are known to decrease stress- and cue-induced alcohol craving and associated stress dysregulation in humans. Here we report findings from a preliminary efficacy study of the alpha-1 receptor antagonist, prazosin, in modulating these relapse-relevant factors in alcohol-dependent individuals.

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[78] Tam SW, Worcel M, Wyllie M. (2001). Yohimbine: a clinical review. Pharmacol Ther. 2001 Sep;91(3):215-43.

[79] Fox HC, Anderson GM, Tuit K, Hansen J, Kimmerling A, Siedlarz KM, Morgan PT, Sinha R. (2012). Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin Exp Res.;36(2):351-60.

METHODS:

Seventeen early abstinent, treatment-seeking alcohol-dependent individuals (12 men and 5 women) were randomly assigned to receive either placebo or 16 mg daily prazosin in a double-blind, placebo-controlled manner over 4 weeks. During week 4, all patients participated in a 3-day laboratory experiment involving 5-minute guided imagery exposure to stress, alcohol cue, and neutral-relaxing/control conditions, 1 exposure per day, on consecutive days in a random, counterbalanced order. Alcohol craving, anxiety, negative emotion, cardiovascular measures, and plasma hypothalamic-pituitary-adrenal (HPA; cortisol, adenocorticotropic hormone) were assessed repeatedly in each session.

RESULTS:

The prazosin group (n = 9) versus the placebo group (n = 8) showed significantly lower alcohol craving, anxiety, and negative emotion following stress exposure. The placebo group also showed significantly increased stress- and cue-induced alcohol craving, anxiety, negative emotion, and blood pressure (BP), as well as a blunted HPA response relative to the neutral condition, while the prazosin group showed no such increases in craving, anxiety, negative emotion, and BP, and no blunted HPA response to stress and alcohol cue exposure.

CONCLUSIONS:

Prazosin appears efficacious in decreasing stress- and cue-induced alcohol craving and may normalize the stress dysregulation associated with early recovery from alcoholism. Further research to assess the efficacy of prazosin in reducing alcohol craving and stress-related relapse risk is warranted.

Cross-sectional studies

Sommer, Braumann, Althoff et al (2011)[80]

Abstract

INTRODUCTION:

Several clinical studies suggest antidepressive and anxiolytic effects of regular endurance training. The mechanisms by which exercise exerts these effects are still unclear. It was hypothesized that athletes might show a diminished reaction to psychosocial stress and noradrenergic stimulation.

METHODS:

12 male athletes and 12 healthy untrained male controls underwent a challenge paradigm on 3 separate days: the alpha-2-receptor antagonist yohimbine (0.4 mg/kg), placebo or a psychosocial stress test (SST) were administered. Responses were measured by psychometric scales, plasma cortisol, blood pressure and heart rate.

RESULTS:

Before testing, psychometric variables and cortisol levels were not different between the 2 groups. In comparison to placebo conditions, both the social stress test and the administration

[80] Sommer M, Braumann M, Althoff T, Backhaus J, Kordon A, Junghanns K, Ehrenthal D, Bartmann U, Hohagen F, Broocks A. (2011). Psychological and neuroendocrine responses to social stress and to the administration of the alpha-2-receptor antagonist, yohimbine, in highly trained endurance athletes in comparison to untrained healthy controls. Pharmacopsychiatry; 44(4):129-34.

of yohimbine were followed by significant increases of anxiety symptoms, plasma cortisol, heart rate and blood pressure in both groups. However, these responses were not significantly different between the group of athletes and the control group.

DISCUSSION:

These results do not support the hypotheses that high aerobic fitness is associated with attenuated psychological and neuroendocrine responses to yohimbine or to psychosocial stress.

Quek, Low, Razak and Loh (2000)[81] assessed and evaluated the level of depression, anxiety and psychiatric status in patients with lower urinary tract symptoms (LUTS) before and after treatment by surgery or drugs. The study included 123 patients (mean age 64.6 years, SD 7.95) with LUTS who were treated medically (with a-blockers, i.e. terazosin, prazosin, doxazosin and alfuzosin), and 52 patients (mean age 69.6 years, SD 7.94) with LUTS and confirmed to have benign prostatic hyperplasia (BPH) who underwent transurethral resection of the prostate (TURP). Both groups were assessed at baseline and 3 months after treatment using standardized questionnaires (the Beck Depression Inventory, the State-Trait Anxiety Inventory and the General Health Questionnaire-12).

Patients before TURP were significantly more depressed, worried and psychiatrically morbid than were those before medical treatment. Three months after medical and surgical treatment, there was significantly less depression, anxiety and psychiatric morbidity in the TURP than in the medication group. There was no significant increase in anxiety symptoms after medical treatment (see table below).

[81] Quek KF, Low WY, Razack AH, Loh CS (2000). The psychological effect of treatments for lower urinary tract symptoms. BJU International; 86:630-3.

TABLE 30 THE CHARACTERISTICS OF THE PATIENTS IN EACH GROUP AND THE MEAN AND DISTRIBUTION OF SCORES FOR THE VARIOUS ASSESSMENTS BEFORE AND 3 MONTHS AFTER TREATMENT (QUEK ET AL, 2000).

Variable/ score	*Before treatment*		*After treatment*	
	α-blockers	*TURP*	*α-blockers*	*TURP*
Number	123	52	123	52
% at age (years)				
<50	4.1	–		
50–59	44.7	36.5		
60–69	26.8	15.4		
70–79	23.6	42.3		
>80	0.8	5.8		
Ethnicity (%)				
Chinese	56.9	51.9		
Indian	24.4	19.2		
Malays	14.6	26.9		
Others	4.1	1.9		
BDI score, *n* (%)				
0–9	87 (70.7)	15 (28.9)	91 (74.0)	30 (57.7)
10–18	30 (24.4)	23 (44.2)	24 (19.5)	19 (36.5)
19–29	6 (4.9)	13 (25.0)	8 (6.5)	3 (5.8)
30–63	0	1 (1.9)	0	0
Mean	8.02	14.08	7.78	9.65
SD	5.53	7.52	5.83	5.78
Mean (SD) anxiety level				
State	35.5 (7.9)	41.0 (6.5)	34.7 (8.6)	33.5 (4.7)
Trait	38.4 (5.8)	41.4 (5.0)	38.6 (7.8)	38.7 (4.7)
Total	74.0 (12.6)	82.4 (10.7)	73.5 (14.9)	72.2 (8.5)
Mean psychiatric morbidity (GHQ-12)				
Mean	10.33	13.5	10.12	8.79
SD	3.76	4.51	3.82	1.33

TURP is a better treatment than medication for minimising anxiety, depression and psychiatric morbidity after treatment in patients with LUTS, but causes greater psychological stress before treatment.

Enalopril

Randomised clinical trial

Muldoon, Waldstein, Ryan et al (2002)[82]

Abstract

OBJECTIVE:

To describe and compare the effects of six different antihypertensive medications on cognitive performance.

DESIGN:

Prospective, randomized, and double-blind with treatment cross-over.

SETTING:

University hypertension clinic and neuropsychology laboratory.

PARTICIPANTS:

[82] Muldoon MF, Waldstein SR, Ryan CM, Jennings JR, Polefrone JM, Shapiro AP, Manuck SB. (2002). Effects of six anti-hypertensive medications on cognitive performance. J Hypertens.; 20(8):1643-52.

Ninety-eight Caucasian men between 25 and 55 years of age with mild-to-moderate essential hypertension (88 of whom completed the study), and 32 normotensive men with similar socio-demographic characteristics.

INTERVENTIONS:

Six-week treatment periods with atenolol, metoprolol, hydrochlorothiazide, methyldopa, enalapril and verapamil, and 2-week placebo baseline and wash-out periods.

MAIN OUTCOME MEASURES:

In-depth neuropsychological assessments and several mood questionnaires were completed during placebo (baseline) periods and active treatment periods. Practice effects due to repeated neuropsychological testing were estimated from data collected concurrently in the normotensive participants.

RESULTS:

The antihypertensive treatments lowered blood pressure comparably and did not affect mood or anxiety. Small treatment effects were noted in four of seven domains of cognitive performance. Irrespective of medication type, treatment reduced the simple motor speed (P < 0.001), and slowed completion of two tests measuring perceptuo-motor speed and mental flexibility (P </= 0.05). Manual dexterity declined somewhat with metoprolol and methyldopa (P = 0.01). In contrast, all antihypertensive agents favorably affected performance on several tests that require working memory (P < 0.01). Performance on other tests assessing grip strength, learning and memory, attention and executive function was not affected.

CONCLUSION:

Short-term treatment with standard antihypertensive medications was associated with some small decrements in psychomotor performance and small improvements in working memory, without notable drug-class differences. Long-term effects await further study.

Fowler, Webster, Lyons et al (1993)[83]

Abstract

1. The safety and efficacy of amlodipine vs enalapril as monotherapy was evaluated in patients with moderate/severe hypertension (supine DBP 105-125 mm Hg, SBP 140-220 mm Hg). 2. After 2 weeks placebo treatment 31 patients were randomised by the technique of minimisation in an observer-blind study to receive once daily treatment with either amlodipine (15 patients) 5-10 mg, or enalapril (16 patients) 5-20 mg for 8 weeks. The study design concluded with 2 weeks placebo treatment. In addition to clinic measurements, home blood pressure monitoring (Copal UA-251) was performed during the study. 3. Clinic supine systolic blood pressure was reduced from 177 to 152 mm Hg (amlodipine) and 183 to 169 mm Hg (enalapril) (95% CI for the intergroup difference -22.1, 0.3, P = 0.06) after 8 weeks treatment. 4. Clinic supine diastolic blood pressure was reduced from 110 to 93 mm Hg (amlodipine) and 109-102 mm Hg (enalapril) (95% CI for the intergroup difference -17.7, -2.7, P < 0.01) after 8 weeks treatment. 5. Home blood pressure recordings confirmed these reductions in blood pressure. Although the reduction in blood pressure was greater for the amlodipine treated

[83] Fowler G, Webster J, Lyons D, Witte K, Crichton WA, Jeffers TA, Wickham EA, Sanghera SS, Cornish R, Petrie JC. (1993). A comparison of amlodipine with enalapril in the treatment of moderate/severe hypertension. Br J Clin Pharmacol.;35(5):491-8.

group, the differences between treatments were not statistically significant. 6. Both drugs were reasonably well tolerated. **The adverse events occurring most frequently in the amlodipine group were headache (5), peripheral oedema (3), upper respiratory infection (3) and anxiety (2). The adverse events occurring most frequently in the enalapril treated patients were headache (6), dizziness (3) and upper respiratory infection (2).** The anxiety symptoms in the amlodipine group was rated as severe (see Table below).

TABLE 31 SUMMARY OF THE SEVERITY OF ADVERSE EVENTS REPORTED AND PATIENTS WITHDRAWN DURING THE ACTIVE TREATMENT PHASES (FOWLER ET AL, 1993).

	Number of adverse events on amlodipine				*Number of adverse events on enalapril*			
Adverse events	*Mild*	*Moderate*	*Severe*	*Withdrawn*	*Mild*	*Moderate*	*Severe*	*Withdrawn*
Headache	2	2	1	1	2	2	1	0
Respiratory infection	0	3	0	0	0	2	0	0
Lethargy	1	1	0	0	0	1	0	0
Nocturia	0	1	0	0	0	0	0	0
Oedema	1	0	2	1	0	0	0	0
Flushing	0	0	2	1	1	0	0	0
Indigestion	0	1	0	0	0	0	0	0
Chest pain	1	0	0	0	0	0	0	0
Anxiety	0	0	1	0	0	0	0	0
Palpitations	0	0	0	0	0	0	1	1
Epistaxis	0	0	0	0	1	0	0	0
Dizziness	0	0	0	0	0	2	0	0
Numb hands and feet	0	0	0	0	0	0	1	1
Conjunctivitis	0	0	0	0	1	0	0	0
Skin rash	0	0	0	0	1	0	0	0
Depression	0	0	0	0	1	0	0	0
Arthralgia	0	0	0	0	0	0	1	0

Nicardipine

The review by Shah et al (2005) suggests that anxiety may be an adverse event on taking nicardipine in rare cases. A search of the literature in PubMed using the terms (nicardipine AND (anxiety OR panic)) did not reveal any relevant articles to support an association, although a number of abstracts mentioned an anxiolytic effects of the calcium channel blocker class of drugs.

Summary and conclusion

The two reviews (Huffman and Stern, 2007; Shah et al, 2005) reported on neuropsychiatric adverse events associated with cardiovascular drugs. Both studies identified that psychiatric disorders are commonly reported comorbidly with cardiovascular disorders and hence reported psychiatric disorders in close temporal relation to the onset of drug therapy may be caused by the disorder itself, rather than the treatment. With this caveat in mind, a number of drug-induced adverse events of anxiety symptoms have been identified.

Johansen et al (2012) reported no associations between antihypertensive agents and anxiety symptoms in their adjusted findings from the large cross-sectional study.

A more in depth search of the literature for alpha adrenergic antagonists, enalopril and nicardipine did not find further support for the associations noted in the reviews above. It is suggested that these drugs therefore would be Grade 4 level evidence.

Relying on the review evidence summarised above, it is suggested that the following drugs/class of drugs be considered for inclusion in the SoPs – Grade 2-3 level evidence:

(a) hydralazine
(b) lidocaine
(c) statins

Antiepileptics

Summary of important issues

Reviews

Mula, Pini and Cassano (2007)[84] in a systematic review reported on the efficacy of antiepileptic drugs (AEDs) as a treatment for some anxiety disorders. Mula et al (2007) conducted an updated MEDLINE search (January 1970 to September 2006) using the terms "panic disorder," "agoraphobia," "posttraumatic stress disorder," "obsessive-compulsive disorder," "generalized anxiety disorder," "social phobia," "phobia," "carbamazepine," "phenobarbital," "phenytoin," "valproate," "lamotrigine," "topiramate," "vigabatrin," "tiagabine," "gabapentin," "levetiracetam," and "pregabalin" which showed more than 70 articles and 38 published studies. Only articles published in English were reviewed. They assigned level 1 evidence to meta-analysis and replicated randomized controlled trials, level 2 to at least 1 randomized controlled trial, level 3 to uncontrolled trials with 10 or more subjects, and level 4 to anecdotal case reports. The strongest evidence was demonstrated for pregabalin in social phobia and generalized anxiety disorder, lamotrigine in posttraumatic stress disorder, and gabapentin in social anxiety. The available data about gabapentin in panic disorder are somewhat mixed, and more definitive conclusion would require additional studies. This review suggested that AEDs can be an alternative treatment in some anxiety disorders. Further investigation is needed to determine in what circumstances they should be used in individuals who are partially responsive or nonresponsive to conventional therapy. The three drugs with the strongest evidence suggested for anxiety treatment are not proposed as drugs which could induce anxiety.

Piedad, Rickards, Besag and Cavanna (2012)[85] conducted a systematic review of the Antiepileptic drugs (AEDs) literature which revealed evidence for both positive and negative effects on depression, anxiety, aggression, psychosis and sleep in patients with epilepsy. Topiramate, vigabatrin, levetiracetam, tiagabine and zonisamide have been associated primarily with adverse psychotropic effects, whilst gabapentin, pregabalin, lacosamide and lamotrigine, in particular, have demonstrated a more beneficial psychotropic profile, especially with regard to affective symptoms. AEDs can have both beneficial and adverse psychotropic effects. They act on neurotransmitter systems, neuronal ion permeability and other targets, although the exact mechanisms are not generally fully elucidated.

[84] Mula M, Pini S, Cassano GB (2007). The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. J Clin Psychopharmacol, 27: 263-72. 078633

[85] Piedad J, Rickards H, Besag FM, Cavanna AE. (2012). Beneficial and adverse psychotropic effects of antiepileptic drugs in patients with epilepsy: a summary of prevalence, underlying mechanisms and data limitations. CNS Drugs. 2012 Apr 1;26(4):319-35.

TABLE 32 SUMMARY OF REPORTED PSYCHOTROPIC EFFECTS OF ANTIEPILEPTIC DRUGS IN EPILEPSY (PIEDAD ET AL, 2012).

Reference	Psychotropic effects[a]	Study characteristics
Carbamazepine (CBZ)		
Dam et al.[16]	No psychotropic effects	*N*=100; weekly, fortnightly and monthly clinical exam for 52–56 wks in a randomized, double-blind, parallel-group monotherapy study
Berg et al.[17]	↑ Anxiety, irritability, sleep disturbance vs PHT and VPA ($p<0.02$)	*N*=18; BC at baseline, 1 and 6 mos in a prospective, randomized parallel-group study
Brodie et al.[18]	Sleepiness (22%, $p<0.05$ vs LTG), depression (9%, p=NS vs LTG)	*N*=129; weekly and fortnightly clinical exam for 48 wks in a randomized, double-blind, parallel-group monotherapy study
Pulliainen and Jokelainen[19]	↓ Anxiety ($p=0.005$), depression ($p=0.002$) vs baseline	*N*=16; POMS at baseline, 6 and 24 mos in a prospective, single-blind parallel-group study
Chadwick[20]	Agitation (5.7%), depression (3.1%), insomnia (2.2%), somnolence (32.3%)	*N*=226; incidence of ICD-10 coded PAEs in a prospective, randomized, double-blind parallel-group study for 6 mos
Carisbamate		
Trenité et al.[21]	No effects vs baseline on depression scale	*N*=18; POMS at days 1, 2 and 3 in a prospective, single-blind, placebo-controlled add-on study
Diazepam (DZP, rectal solution)		
Dreifuss et al.[22]	Euphoria (6.7%), nervousness (2.2%), somnolence (33.3%)	*N*=45; clinical exam after acute administration of DZP in a randomized, double-blind, placebo-controlled, parallel-group add-on study
Kriel et al.[23]	Somnolence (25.0%), nervousness (2.9%)	*N*=68; clinical exam within 3 days of acute administration of DZP in a randomized, double-blind, placebo-controlled, parallel-group add-on study
Felbamate (FBM)		
Ketter et al.[24]	↑ Anxiety (56.3%) vs placebo ($p=0.007$)	*N*=30; ZARS, HDRS, YMRS, BHS, CGI and BPRS weekly in 2 wk randomized, double-blind, placebo-controlled, parallel-group study then chronic treatment
Weintraub et al.[25]	Depression (3.6%)	*N*=28; incidence of PAEs in a retrospective review of clinical notes
Gabapentin (GBP)		
Crawford et al.[26]	Drowsiness (44%)	*N*=25; monthly clinical exam for 3 mos in a randomized, double-blind, dose crossover add-on study
Chadwick et al.[27]	Somnolence (12.1%), emotional lability (6.9%)	*N*=58; clinical exam in a 26 wk randomized, double-blind, placebo-controlled, parallel-group add-on study
Dimond et al.[28]	Improvement of general well-being (especially affective symptoms)	*N*=423; retrospective review of the 'general condition' of patients from 5 randomized, placebo-controlled studies
Harden et al.[29]	↓ Depression vs baseline ($p=0.04$)	*N*=40; CDRS, BDI, HDRS and HARS at baseline and 3 mos in a prospective, placebo-controlled add-on study
Weintraub et al.[25]	Irritability (0.6%)	*N*=160; incidence of PAEs in a retrospective review of clinical notes
Lacosamide (LCS)		
Ben-Menachem et al.[7]	Somnolence (9.7%)	*N*=321; clinical exam in an 18 wk randomized, double-blind, placebo-controlled, parallel-group add-on study

Continued next page

Table Continued

Reference	Psychotropic effects[a]	Study characteristics
Biton et al.[30]	Somnolence (0% oral vs 5.1% IV preparation)	*N* = 21 (oral), 39 (IV); clinical exam at baseline and day 3 in a 3 day randomized, double-dummy, parallel add-on study
Halász et al.[8]	No psychotropic effects	*N* = 322; clinical exam in a 16 wk randomized, double-blind, placebo-controlled, parallel-group add-on study
Lamotrigine (LTG)		
Brodie et al.[18]	Sleepiness (12%, p < 0.05 vs CBZ), depression (5%, p = NS vs CBZ)	*N* = 131; weekly and fortnightly clinical exam for 48 wks in a randomized, double-blind, parallel-group monotherapy study
Gilliam et al.[31]	No psychotropic effects	*N* = 43; 2- to 4-weekly clinical exam in a 12 wk randomized, double-blind, parallel-group monotherapy study
Sadler[32]	Insomnia (6.4%)	*N* = 109; retrospective review of clinical notes in an add-on study
Parmeggiani et al.[33]	Anxiety (4.9%), somnolence (4.9%)	*N* = 41; clinical exam every 4 wks for 8 mos then every 6 mos until 12–48 mos in a prospective add-on study
Edwards et al.[34]	↓ Depression (BDI, CDRS, POMS) after adjunctive and monotherapy phases, consistently > VPA; somnolence (7.7%), emotional lability (7.7%)	*N* = 65; BDI, CDRS and POMS at baseline, 10 and 32 wks in a randomized, double-blind, parallel-group add-on and monotherapy study
Biton et al.[35]	Emotional lability (16.7%), somnolence (5.6%), insomnia (5.6%)	*N* = 18; 3- to 7-weekly clinical exam in a 32 wk randomized, double-blind, parallel-group monotherapy study
Cramer et al.[36]	Improvement of symptoms of seizure-related anxiety vs baseline	*N* = 143; QOLIE-31 at baseline and 12 wks in a prospective study
Cramer et al.[37]	↓ Anger, anxiety, depression POMS sub-scores after adjunctive (p < 0.0001) and monotherapy phases (p < 0.003)	*N* = 155; POMS at baseline, 16 and 28 wks in a prospective add-on and monotherapy study
Ettinger et al.[38]	↓ Depression (BDI-II, p = 0.01; POMS, p = 0.03) vs placebo, somnolence (5.7%)	*N* = 32; BDI-II, POMS and CDRS at baseline and 19 wks in a prospective, randomized, double-blind, placebo-controlled, parallel-group add-on study
Weintraub et al.[25]	Irritability (1.3%), depression (1.5%), anxiety (1.6%), behavioural change (1.1%), psychosis (0.4%)	*N* = 547; incidence of PAEs in a retrospective review of clinical notes
Fakhoury et al.[39]	↓ Depression (p < 0.01) in all psychometric scales after adjunctive and monotherapy phases vs baseline, except for BDI-II and NDDI-E after adjunctive phase	*N* = 158; BDI-II, CES-D, NDDI-E, POMS at baseline, 19 and 36 wks in a prospective add-on and monotherapy study
Kalogjera-Sackellares and Sackellares[40]	↓ Depression (MADRS, p = 0.002, p = 0.01; MMPI-D, p = 0.033, p = NS), anxiety (STAI State, p = 0.014, p = 026; STAI Trait, p = 0.025, p = NS) at 5 wks and 3 mos vs baseline	*N* = 13; MADRS, STAI and MMPI-D at baseline, 5 wks and 3 mos in a prospective add-on study
Labiner et al.[41]	↓ vs LEV in aggression (POMS, p = 0.024), irritability (IDAS, p < 0.05); depression (POMS, IDAS, NDDI-E, all p < 0.05); somnolence (5.3%), insomnia (6.1%), irritability (6.1%), depression (3.0%)	*N* = 132; POMS, STAXI, BDI-II, IDAS, NDDI-E, ESS, AEP at baseline and 20 wks in a randomized, double-blind, parallel-group add-on study
Kwan et al.[42]	Somnolence (4%), insomnia (5%), depression (4%, HADS sub-score > PGB, p = 0.0186), anxiety (2%, HADS sub-score > LTG, p = 0.0025), sleep disorder (2%)	*N* = 330; clinical exam and HADS at baseline and 56 wks in a randomized, double-blind, parallel-group monotherapy study

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Table Continued

Reference	Psychotropic effects[a]	Study characteristics
Levetiracetam (LEV)		
Cramer et al.[43]	Improvement in anxiety ($p=0.0003$) vs placebo	$N=246$; QOLIE-31 at baseline and 18 wks in a prospective, randomized, placebo-controlled, double-blind add-on study
Ben-Menachem and Gilland[44]	Irritability (7.1%), psychosis (1.0%), somnolence (36.8%)	$N=98$; incidence of psychiatric symptoms at 3 mo intervals for 12 mos in a prospective add-on study
Betts et al.[45]	Depression (1.7%), aggression (4.2%), insomnia (4.2%), somnolence (21.8%)	$N=119$; retrospective review of clinical notes, which detailed psychiatric symptoms at 6 and 12 mos in an add-on study
Cramer et al.[46]	Anxiety (2.7%), depression (3.8%), aggression (2.3%)	$N=769$; retrospective review of psychiatric symptoms in placebo-controlled studies
Mula et al.[47]	Affective disorder (2.5%), psychosis (1.2%), aggression (3.7%), anxiety (0.6%)	$N=517$; retrospective review of clinical notes, which detailed incidence DSM-IV-coded PAEs
Mula et al.[48]	Affective disorder (1.7%), aggression (7.6%), emotional lability (1.7%)	$N=118$; incidence DSM-IV-coded PAEs unrelated to other AEDs in a prospectively followed cohort
Opp et al.[49]	Aggression (10.5%), mood (2.8%), sleep disturbances (26.9%)	$N=285$; retrospective review of clinical notes, which detailed psychiatric symptoms in an add-on study
Mazza et al.[50]	↓ Depression, anxiety, sleep vs baseline (all $p<0.05$)	$N=25$; MADRS, HDRS, ZDRS, HARS and ZARS at 5 wks and 3 mos in a prospective add-on study
Weintraub et al.[25]	Irritability (9.0%), depression (4.0%), anxiety (1.6%), behavioural change (0.5%), psychosis (1.3%)	$N=521$; incidence of PAEs in a retrospective review of clinical notes
Labiner et al.[41]	↓ Aggression vs baseline but < LTG (POMS, $p=0.024$); ↑ irritability, depression and anxiety (IDAS) vs baseline; somnolence (11.8%), insomnia (4.4%), irritability (9.6%), depression (5.9%)	$N=136$; POMS, STAXI, BDI-II, IDAS, NDDI-E, ESS, AEP at baseline and 20 wks in a randomized, double-blind, parallel-group add-on study
de la Loge et al.[51]; Levisohn et al.[52]	Somnolence (14.1%), aggression (12.5%; higher CBCL sub-scores vs placebo, $p=0.013$), insomnia (6.3%), altered mood (6.3%), anxiety (6.3%)	$N=64$; clinical exam and CBCL at baseline and 12 wks in a randomized, placebo-controlled, double-blind, parallel-group add-on trial
Loreclezole		
Rentmeester et al.[53]	Sleepiness (3.1%), improved mood (3.1%)	$N=32$; clinical exam (frequency not reported) in a 12 wk, randomized, placebo-controlled, double-blind, parallel-group add-on study
Oxcarbazepine (OXC)		
Dam et al.[16]	Emotional lability (1.1%)	$N=94$; weekly, fortnightly and monthly clinical exam for 52–56 wks in a randomized, double-blind, parallel-group monotherapy study
McKee et al.[54]	Sedation (7.0%)	$N=43$; 3-wkly clinical exam in a 6 wk randomized, placebo-controlled, double-blind, crossover add-on study
Schachter et al.[55]	Somnolence (15.7%)	$N=51$; daily clinical exam in a 10 day randomized, placebo-controlled, double-blind, parallel add-on study
Mazza et al.[56]	↓ Depression (CDRS, $p=0.02$); ↓ depression (BDI, HDRS) and anxiety (HARS) but changes, $p=$ NS vs baseline	$N=40$; CDRS, BDI, HDRS, HARS at baseline and 3 mos in a prospective, controlled add-on study
Weintraub et al.[25]	Depression (4.3%), anxiety (1.2%), behavioural change (0.6%)	$N=162$; incidence of PAEs in a retrospective review of clinical notes

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Reference	Psychotropic effects[a]	Study characteristics
Phenobarbitone		
Thilothammal et al.[57]	Hyperactivity (21.6%), aggression (21.6%)	*N*=51; monthly clinical exam for 3 mos in a randomized, double-blind, parallel monotherapy study
Phenytoin (PHT)		
Berg et al.[17]	↓Anxiety, irritability, sleep disturbancevs. CBZ ($p<0.02$)	*N*=14; BC at baseline, 1 mo and 6 mos in a prospective, randomized parallel study
Pulliainen and Jokelainen[19]	↓Anxiety (p 0.005), depression (p 0.002) vs baseline	*N*=15; POMS at baseline, 6 and 24 mos in a prospective, single-blind parallel-group study
Thilothammal et al.[57]	Sedation (23.1%)	*N*=52; monthly clinical exam for 3 mos in a randomized, double-blind, parallel-group monotherapy study
Pregabalin (PGB)		
Kwan et al.[42]	Somnolence (17%), insomnia (5%), depression (3%, HADS sub-score<LTG $p=0.0186$), anxiety (1%, HADS sub-score<LTG $p=0.0025$), sleep disorder (1%)	*N*=330; clinical exam and HADS at baseline and 56 wks in a randomized, double-blind, parallel-group monotherapy study
Primidone		
Lopez-Gomez et al.[6]	Higher depression scores in patients treated with primidone vs patients not treated with primidone ($p<0.001$)	*N*=241; MADRS and BDI in a 6 mo, prospective add-on study
Tiagabine (TGB)		
Dodrill et al.[58]	↑Mood function vs baseline ($p<0.027$)	*N*=123; neuropsychological tests including POMS and MRS at 2 and 5 mos in a prospective add-on study
Trimble et al.[59]	Affective disorder (40%), psychosis (60%)	*N*=5; retrospective review of clinical notes for patients who developed affective or psychotic disorder during an add-on study
Sackellares et al.[60]	Psychosis (8.4%), somnolence (1.1%)	*N*=356; incidence of COSTART-coded PAEs from combined randomized, placebo-controlled, double-blind, parallel-group add-on studies
Weintraub et al.[25]	Irritability (10.5%), depression (5.3%), anxiety (5.3%), psychosis (5.3%)	*N*=19; incidence of PAEs in a retrospective review of clinical notes
Topiramate (TPM)		
Elterman et al.[61]	Somnolence (29.3%), emotional lability (29.3%), mood problems (24.4%), aggression (24.4%), nervousness (24.4%)	*N*=41; incidence of WHOART-coded PAEs in a 16 wk randomized, double-blind, placebo-controlled, parallel-group add-on study
Khan et al.[62]	Psychosis (6.3%)	*N*=80; retrospective review of clinical notes for patients developing psychosis during an add-on study
Sachdeo et al.[63]	Somnolence (87.5%), nervousness (43.8%), behavioural problems (43.8%)	*N*=48; clinical exam in an 11 wk randomized, double-blind, placebo-controlled, parallel-group add-on study
Aldenkamp et al.[64]	Depression (4.2%), changes in POMS scores (p=NS)	*N*=24; clinical exam and POMS at baseline and 20 wks in a randomized, observer-blinded, parallel add-on study
Trimble et al.[59]	Affective disorder (47.1%), psychosis (52.9%)	*N*=34; retrospective review of clinical notes for patients who developed affective or psychotic disorder during an add-on study
Guberman et al.[65]	Somnolence (15%), nervousness (9%)	*N*=171; 2- to 4-wkly clinical exam in a randomized, placebo-controlled, double-blind, parallel-group add-on study
Christensen et al.[66]	Aggression (16.9%), anxiety (27.7%), sleep disturbance (33.8%), depression (12.3%)	*N*=65; incidence of WHOART-coded PAEs at baseline and 5 mos in a prospective add-on study

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Reference	Psychotropic effects[a]	Study characteristics
Kanner et al.[67]	Depression (5.0%), aggression (5.7%), psychosis (1.5%)	*N*=596; incidence WHOART-coded PAEs at 6 mo intervals until discontinuation in a prospective add-on study
Mula et al.[68]	Affective disorder (10.7%), psychosis (3.7%), aggression (5.6%), anxiety (3.9%)	*N*=431; retrospective review of clinical notes, which detailed incidence WHOART and DSM-IV-coded PAEs
Grošelj et al.[69]	Depression (7.0%), insomnia (2.3%)	*N*=43; clinical exam at baseline and every 3 mos for 13 mos in a prospective study
Weintraub et al.[25]	Irritability (2.7%), depression (2.7%), behavioural change (1.8%)	*N*=112; incidence of PAEs in a retrospective review of clinical notes
Valproate (VPA)		
Richens and Ahmad[70]	Drowsiness (45%)	*N*=20; weekly clinical exam for 16 wks in randomized, placebo-controlled, double-blind crossover add-on study
Berg et al.[17]	↓Anxiety, irritability, sleep disturbance and when vs CBZ ($p<0.02$)	*N*=15; BC at baseline, 1 mo and 6 mos in a prospective, randomized parallel-group study
Thilothammal et al.[57]	Hyperactivity (12.5%)	*N*=48; monthly clinical exam for 3 mos in a randomized, double-blind, parallel-group monotherapy study
Gilliam et al.[31]	Somnolence (2.3%)	*N*=44; 2-4-wkly clinical exam in a 12 wk randomised, double-blind, parallel-group monotherapy study
Aldenkamp et al.[64]	Insomnia (3.4%), irritability (3.4%), changes in POMS scores (p=NS)	*N*=29; clinical exam and POMS at baseline and 20 wks in a randomized, observer-blinded, parallel-group add-on study
Edwards et al.[34]	Nominal changes to depression scales after adjunctive and monotherapy phases, consistently < LTG; somnolence (23.5%), emotional lability (10.3%)	*N*=68; BDI, CDRS and POMS at baseline, 10 and 32 wks in a randomized, double-blind, parallel-group add-on and monotherapy study
Biton et al.[35]	Emotional lability (5.0%), somnolence (15.0%), insomnia (10.0%)	*N*=20; 3- to 7-wkly clinical exam in a 32 wk randomized, double-blind, parallel-group monotherapy study
Vigabatrin (VGB)		
Dodrill et al.[71]	No changes vs baseline scores on depression scale	*N*=146; neuropsychological tests including POMS and MRS at wks 6 and 18 in a prospective, randomized, placebo-controlled and double-blind add-on study
Wong[72]	Aggression (7.5%), anxiety (6%), depression (6.8%), psychosis (7.5%)	*N*=133; retrospective review of electronic clinical notes, which detailed incidence of psychiatric symptoms
Chadwick[20]	Agitation (7.0%), depression (6.6%), insomnia (6.6%), somnolence (25.7%)	*N*=220; incidence of ICD-10 coded PAEs in a prospective, randomized and double-blind parallel-group study for 6 mos
Levinson and Devinsky[73]	Psychosis (2.5%, $p=0.028$), aggression (3.0%), mania (1.0%), depression (12.1%, $p<0.001$), anxiety (9.4%) vs placebo	*N*=406; retrospective review of incidence of psychiatric symptoms during placebo-controlled, double-blind add-on studies
Veggiotti et al.[74]	↓Aggression vs baseline (100%)	*N*=10; *ad hoc* tests for behavioural psychotic disturbances in patients developing psychosis at 3 mo intervals for 12 mos in a prospective add-on study
Guberman and Bruni[75]	Agitation (14.4%), somnolence (11.3%)	*N*=97; POMS, MRS and neurological and physical exam every 2–14 wks for 12 mos in a prospective, randomized, placebo-controlled, double-blind add-on study

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Reference	Psychotropic effects[a]	Study characteristics
Trimble et al.[59]	Affective disorder (44.0%), psychosis (56.0%)	*N* = 50; retrospective review of clinical notes for patients who developed affective or psychotic disorder during an add-on study
Weintraub et al.[25]	No psychotropic effects	*N* = 13; incidence of PAEs in a retrospective review of clinical notes
Zonisamide (ZNS)		
Schmidt et al.[76]	Somnolence (14.1%, > placebo p = 0.05), abnormal thinking (11.3%, p 0.019), nervousness (9.9%, p = NS)	*N* = 71; clinical exam in a 12 wk randomized, double-blind, placebo-controlled, parallel-group add-on study
Faught et al.[77]	Somnolence (15.3%), psychosis (1.7%)	*N* = 118; 2- to 8-weekly clinical exam in a 20 wk randomized, double-blind, placebo-controlled, parallel-group add-on study
Weintraub et al.[25]	Irritability (2.6%), depression (4.2%), anxiety (1.6%), behavioural change (0.5%), psychosis (1.6%)	*N* = 192; incidence of PAEs in a retrospective review of clinical notes

a Some patients developed more than one psychiatric disorder (e.g. psychotic depression), which indicates severity, although their individual prevalence was not indicated.

AEP = adverse events profile (SR)[41]; **BC** = Behaviour Checklist (CR), a scored checklist of childhood difficulties derived from Quay[78]; **BDI-II** = Beck Depression Inventory (2nd edition; SR)[79,80]; **BHS** = Bunney-Hamburg Scale (CR)[81]; **BPRS** = Brief Psychiatric Rating Scale (CR)[82]; **CBCL** = Child Behaviour Checklist (PR)[83]; **CDRS** = Cornell Dysthymia Rating Scale (CR)[84]; **CES-D** = Centre for Epidemiological Studies Depression Scale (SR)[85]; **CGI** = Clinical Global Impression scale (CR), which measures symptom severity and treatment response/efficacy[86]; **CR** = clinician-rated; **ESS** = Epworth Sleepiness Scale (SR)[87]; **HADS** = Hospital Anxiety and Depression Scale (SR)[88]; **HARS** = Hamilton Anxiety Rating Scale (CR)[89]; **HDRS** = Hamilton Depression Rating Scale (CR)[90]; **ICD-10** = *International Classification of Diseases* (10th Edition)[12]; **IDAS** = Irritability-Depression-Anxiety Scale (SR)[91]; **IV** = intravenous; **MADRS** = Montgomery-Åsberg Depression Rating Scale (CR)[92]; **MMPI-D** = Minnesota Multiphasic Personality Inventory Depression sub-scale (CR)[93]; **MRS** = Mood Rating Scale (SR)[94]; **N** = number of patients treated with the active drug; **NDDI-E** = Neurological Disorders Depression Inventory in Epilepsy (SR);[95] **NS** = not significant; **P** = probability values; **PAEs** = psychiatric adverse events; **POMS** = Profile of Mood States (SR)[96]; **PR** = parent-rated; **QOLIE-31** = Quality of Life in Epilepsy 31-item questionnaire (SR), which measures for example mood, sociality and well-being[97]; **SR** = self-rated; **STAI** = Spielberger State-Trait Anxiety Inventory (SR)[98]; **STAXI** = State-Trait Anger Expression Inventory (SR)[99]; **WHOART** = WHO Adverse Reaction Terminology[100,101]; **YMRS** = Young Mania Rating Scale (CR)[102]; **ZARS** = Zung Anxiety Rating Scale (CR)[103]; **ZDRS** = Zung Depression Rating Scale (SR)[104]; ↑ indicates increase in psychopathology; ↓ indicates decrease in psychopathology.

The table above summarises the studies included in the systematic review by Piedad et al (2012). In regard to anxiety, carbamazepine reported conflicting results. Only one study of felbamate reported increased anxiety For lamotrigine a majority of studies reported anxiety effects of the drug. For levetiracem anxiety symptoms were minimal or reduced across studies. One of four studies for tiagabine reported anxiety symptoms. Two studies of topiramate reported anxiogenic effects. Vigabatrin reported two studies with elevated anxiety symptoms associated with the drug. Only one study if zonisamide reported anxiety symptoms at low levels – 1.6% prevalence.

This review identifies specific methodological issues with studies that have reported on the psychotropic effects of AEDs, suggesting that some of the findings might be inconclusive or unreliable because of confounding factors, particularly the presence of psychiatric history. More rigorous double-blind, randomized, placebo-controlled trials on larger numbers of patients with epilepsy, with clear inclusion/exclusion criteria, that are specifically designed to investigate psychotropic changes are more likely to produce results that inform clinical practice and direct future research.

Beyenburg, Mitchell, Schmidt et al (2005)[86] reviewed the literature as it relates to anxiety in epilepsy patients. Up to 50 or 60% of patients with chronic epilepsy have various mood disorders including depression and anxiety. Whereas the relationship between epilepsy and depression has received much attention, less is known about anxiety disorders. The

[86] Beyenburg S, Mitchell AJ, Schmidt D, Elger CE, Reuber M. (2005). Anxiety in patients with epilepsy: systematic review and suggestions for clinical management. Epilepsy & Behavior; 7(2):161-71.

relationship between anxiety disorders and epilepsy is complex. It is necessary to distinguish between different manifestations of anxiety disorder: ictal, postictal, and interictal anxiety.

• Anxiety as an ictal phenomenon (for instance, as an isolated aura or simple partial seizure causing the patient to experience fear/panic, especially from temporal lobe epilepsy with involvement of the amygdala);

• Anxiety as a postictal phenomenon (for instance, soon after recovery from a fit, often in association with clouding of consciousness or reduced orientation); and

• Anxiety as an interictal phenomenon with a possible indirect relationship to epilepsy (for instance, as an adjustment reaction, a seizure phobia, a side effect of anticonvulsant medication, or a consequence of epilepsy surgery).

Preexisting vulnerability factors, neurobiological factors, iatrogenic influences (antiepileptic drugs, epilepsy surgery), and psychosocial factors are all likely to play a role, but with considerable individual differences.

TABLE 33 POSITIVE AND NEGATIVE PSYCHOTROPIC EFFECTS OF ANTIEPILEPTIC DRUGS[A] (BEYENBURG ET AL, 2005).

Substance	GABAergic mode of action[b]	Antiglutamatergic mode of action	Negative effects	Positive effects
Barbiturates	++	–	Sedation, depression, cognitive impairment	Anxiolytic, hypnotic
Benzodiazepines	+++	–	Confusion, irritability, depression, cognitive impairment	Anxiolytic, hypnotic, minor antimanic and antidepressant effects
Carbamazepine (CBZ)	+	+	Depression, sexual dysfunction, manic episodes, irritability, somnolence	Antimanic, moderate antidepressant effect, anxiolytic in animal models
Ethosuximide	–	–	Sedation, anxiety, behavioral abnormalities, psychoses	
Felbamate	+	++	Apathy, depression, agitation, psychoses, irritability, anxiety and panic	Activating, increased attention and concentration
Gabapentin	–	–	Sedation, somnolence	Anxiolytic,"mood stabilizer," no cognitive impairment
Lamotrigine	–	++	Irritability, additive toxic effects in combination therapy with CBZ, insomnia	"Mood stabilizer," positive psychotropic effects, anxiolytic in animal models
Levetiracetam	?	?	Irritability, reversible psychosis (including anxiety), somnolence	Anxiolytic effects in animal experiments
Oxcarbazepine	?	+	Somnolence	Less cognitive impairment than with CBZ
Phenytoin	–	–	Sedation, confusion (including anxiety), depression	
Pregabalin	–	–	Sedation, somnolence	Anxiolytic, no impairment
Tiagabine	+++	–	Sedation, psychoses (very rare), depression	Anxiolytic
Topiramate	+	++	Sedation, psychoses, anxiety, cognitive dysfunction	"Mood stabilizer"
Valproate	+	+	Sedation, somnolence, depression (very rare)	Antimanic, moderate antidepressant effects, anxiolytic
Vigabatrin	+++	–	Sedation, psychoses (including anxiety), depression	Anxiolytic?
Zonisamide	+	–	Somnolence, agitation, psychoses (including anxiety), depression	"Mood stabilizer"?

Source. Modified from Refs.[87,105].
[a] The list of anxiolytic antiepileptic drugs includes barbiturates and benzodiazepines, which should be considered only after careful consideration of the risk of adverse effects and the development of tolerance.
[b] Effects: –, none; +, minor; ++, clear; +++, major; ?, questionable.

The relationship between antiepileptic drugs (AEDs) and psychiatric symptomatology is complex (see Table above). "AEDs can exacerbate anxiety or have beneficial mood-stabilizing and anxiolytic effects. Several AEDs (valproate, tiagabine, gabapentin, and pregabalin) have been used in trials for the treatment of anxiety disorders with variable

success [Blanco et al, 2003; Carta et al, 2003; Kinrys et al, 2003; Lauria-Horner & Pohl, 2003; Pande et al, 2003, 2000; Rosenthal, 2003]. It remains unclear why some AEDs increase anxiety in some patients with epilepsy. There is some evidence that a history of psychiatric disorder increases the vulnerability to psychiatric side effects of AEDs [Marsh & Rao, 2002]. Ketter et al. [1999] formulated the hypothesis that substances with predominantly glutamatergic mechanisms of action cause ‘‘activation’’ (leading to such effects as weight loss, increase in anxiety, improvement of depressive symptoms), whereas AEDs that enhance GABAergic neurotransmission (like barbiturates, benzodiazepines, valproate, tiagabine, and vigabatrin) cause sedation, cognitive slowing, weight gain, and alleviation of anxiety [Ketter et al, 1999]. Unfortunately, this approximate division of AEDs into those with sedating and those with ‘‘activating’’ properties is too simplistic from a clinical point of view. Vigabatrin, for instance, is an incontrovertibly GABAergic substance, but causes anxiety in some patients. AEDs clearly have several relevant mechanisms of action and probably others that are not yet known. In general, the anxiolytic and mood-stabilizing potential of AEDs is more powerful than their anxiogenic effects. In line with this observation, anxiety symptoms are sometimes seen when AEDs are discontinued [Ketter et al, 1994].(p. 167).

Despite the high prevalence of anxiety disorders in patients with epilepsy, there are no systematic treatment studies or evidence-based guidelines for best treatment practice. Nevertheless, a practical approach based on the temporal relationship between anxiety and epileptic seizures allows clinicians to consider appropriate treatment strategies to reduce the psychiatric comorbidity in patients with epilepsy.

Case reports

Muether, Welsandt and Dietlein (2011)[87] [Article in German]

AB We report a case of acute myopic recurrence in a 38-year-old patient in a state of panic with a condition corresponding to LASIK 4 months earlier. The patient had commenced topiramate treatment 1 week previously, which is an antiepileptic drug also approved for migraine treatment. The symptoms were due to a rare topiramate-induced side effect (SE) with ciliochoroidal effusion, anterior shift of the lens-iris diaphragm and induced myopia. Cessation of topiramate led to complete remission of this idiosyncratic reaction, however, the patient's anxiety was impressive. Ocular administration of Topiramate-SE should thus be clarified.

Damsa, Warczyk, Cailhol et al (2006)[88] reported the case of a 27-year-old female with bipolar II diagnosed who had been stabilised for 3 months with lithium, 1200 mg/day. A weight gain justified a change of medication to topiramate. In view of the clinical experience of one of the authors in using topiramate for bipolar disorders, the patient was stabilised at 150mg/day using a graded regimen with an initial dose of 25 mg/day, increasing by 25 mg weekly. During topiramate therapy, the patient remained euthymic and lost 3 kg over 4 weeks. However when 150 mg/day was reached, she experienced panic attacks that included shortness of breath increased heart rate and muscle tightness. She had no history of panic attacks before introduction of topiramate. The panic attacks stopped entirely 2 weeks after discontinuation of

[87] Muether PS, Welsandt G, Dietlein TS. (2011). Panic after LASIK: acute medication-induced myopic recurrence after refractive surgery]. [German]. Ophthalmologe; 108(2):164-6. [Abstract only].
[88] Damsa C, Warczyk S, Cailhol L, Kelley-Puskas AM, Cicotti A, Lazignac C, Andreoli A. (2006). Panic attacks associated with topiramate. Journal of Clinical Psychiatry; 67(2):326-7.

topiramate, and the patients refused further mood-stabilising drugs. Two months after topiramate was discontinued, she experienced a hypomanic episode which necessitated hospitalisation. With the patient's compliance, topiramate was reintroduced by a psychiatrist sceptical of the association between panic attacks and topiramate. When the topiramate dose was increased from 100 to 150 mg/day, the patient again experienced panic attacks. The panic attacks disappeared one week after switching medication from topiramate to lamotrigine, 15 mg/day. The patient remained euthymic with the change of medication and experienced no further panic attacks.

Levetiracetam

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Efficacy and Safety of Levetiracetam and Carbamazepine as Monotherapy in Partial Seizures.

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Abstract

Introduction. Levetiracetam (LEV) is a newer antiepileptic drug with better pharmacokinetic profile. Currently, it is frequently used for the treatment of partial seizures. The present study was undertaken to compare the efficacy and safety of LEV and Carbamazepine (CBZ) in partial epilepsy. Methods. This was a prospective, open labeled, randomized study. It was conducted in participants suffering from partial seizures after the approval of ethics committee and written informed consent. The first group received Tab LEV (500 to 3000 mg/day) and the second group received Tab CBZ (300 to 600 mg/day). The primary outcomes were efficacy and safety. The secondary outcome was the Quality of Life (QOL). Efficacy was assessed by comparing the seizure freedom rates at the end of 6 months. Safety profile was evaluated by comparing the adverse effects. QOL was assessed by QOLIE-10 scale. Results. The overall seizure freedom rate at the end of 6 months was 71.42% in CBZ group compared to 78.57% in LEV group ($p = 0.2529$). Both LEV and CBZ reported a similar incidence of adverse reactions. LEV group reported more behavioral changes like increased aggression and anxiety. Also, it showed better QOL compared to the CBZ group. Conclusion. LEV monotherapy and CBZ monotherapy demonstrated similar efficacy for treatment of partial epilepsy and were found to be well tolerated.

Epilepsy Behav. 2015 Apr;45:64-7. doi: 10.1016/j.yebeh.2015.03.018. Epub 2015 Apr 7.

Self-reported aggressiveness during treatment with levetiracetam correlates with depression.

Mula M, Agrawal N, Mustafa Z, Mohanalingham K, Cock HR, Lozsadi DA, von Oertzen TJ.

Abstract

PURPOSE:

The purpose of this study was to identify clinical correlates of self-reported aggressiveness (SRA) in patients with epilepsy treated with levetiracetam (LEV) with special reference to the role of depression.

METHODS:

A consecutive sample of adult outpatients with epilepsy was assessed with the Neurological Disorder Depression Inventory for Epilepsy, the Adverse Event Profile (AEP), and the Emotional Thermometer.

RESULTS:

From a total sample of 163 consecutive patients treated with LEV, SRA at any level (from rarely a problem to always) was associated with a 7-fold increased risk of being depressed (95% CI: 3.0-17.5; p<0.001). Self-reported aggressiveness was reported as "always" a problem by 9.8% of the patients. In these patients, apart from depression, SRA was associated with high AEP total scores (55.1 vs. 39.3; p<0.001) and polytherapy (43.8% vs. 19.8%; p=0.034). Anxiety scores were not elevated (4.9 vs. 3.6; p=0.183).

CONCLUSIONS:

Self-reported aggressiveness during treatment with LEV is not an isolated symptom but is associated with depressed mood. Anxiety-mediated mechanisms do not seem to be involved.

Epilepsia. 2012 Jan;53(1):111-9. doi: 10.1111/j.1528-1167.2011.03300.x. Epub 2011 Nov 2.

Adjunctive levetiracetam in children, adolescents, and adults with primary generalized seizures: open-label, noncomparative, multicenter, long-term follow-up study.

Delanty N1, Jones J, Tonner F.

Abstract

PURPOSE:

To evaluate the long-term efficacy and tolerability of adjunctive levetiracetam (LEV) in patients with uncontrolled idiopathic generalized epilepsy (IGE).

METHODS:

This phase III, open-label, long-term, follow-up study (N167; NCT00150748) enrolled patients (4 to <65 years) with primary generalized seizures (tonic-clonic, myoclonic, absence). Patients received adjunctive LEV at individualized doses (1,000-4,000 mg/day; 20-80 mg/kg/day for children/adolescents weighing <50 kg). Efficacy results are reported for all seizure types [intention-to-treat (ITT) population, N = 217] and subpopulations with tonic-clonic (n = 152), myoclonic (n = 121), and/or absence (n = 70) seizures at baseline.

KEY FINDINGS:

One hundred twenty-five (57.6%) of 217 patients were still receiving treatment at the end of the study. Mean (standard deviation, SD) LEV dose was 2,917.5 (562.9) mg/day. Median (Q1-Q3) exposure to LEV was 2.1 (1.5-2.8) years, and the maximum duration was 4.6 years. Most patients were taking one (124/217, 57.1%) or ≥2 (92/217, 42.4%) concomitant antiepileptic drugs (AEDs). Seizure freedom of ≥6 months (all seizure types; primary efficacy end point) was achieved by 122 (56.2%) of 217 patients, and 49 (22.6%) of 217 patients had complete seizure freedom. Seizure freedom of ≥6 months from tonic-clonic, myoclonic, and absence seizures was achieved by 95 (62.5%) of 152, 75 (62.0%) of 121, and 44 (62.9%) of 70 patients, respectively. Mean (SD) maximum seizure freedom duration was 371.7 (352.4) days. At least one treatment-emergent adverse event (TEAE) was reported by 165 (76%) of 217 patients; most TEAEs were mild/moderate in severity, with no indication of an increased

incidence over time. Seventeen (7.8%) of 217 patients discontinued medication because of TEAEs. The most common psychiatric TEAEs were depression (16/217, 7.4%), insomnia (9/217, 4.1%), nervousness (8/217, 3.7%), and anxiety (7/217, 3.2%).

SIGNIFICANCE:

Adjunctive LEV (range 1,000-4,000 mg/day) demonstrated efficacy as a long-term treatment for primary generalized seizures in children, adolescents, and adults with IGE, and was well tolerated.

J Clin Psychiatry. 2006 Oct;67(10):1573-6.

Safety and efficacy of levetiracetam for patients with panic disorder: results of an open-label, fixed-flexible dose study.

Papp LA.

Abstract

OBJECTIVE:

To examine the safety and efficacy of the anticonvulsant levetiracetam in the treatment of patients with panic disorder.

METHOD:

In an open-label, fixed-flexible dose study, 18 patients with panic disorder with or without agoraphobia (DSM-IV diagnostic criteria) were treated with levetiracetam for 12 weeks. Outcome was assessed with standard rating instruments (Clinical Global Impressions-Severity of Illness scale [CGI-S], Clinical Global Impressions-Improvement scale [CGI-I], and the 14-item Hamilton Rating Scale for Anxiety [HAM-A]) and by the number of panic attacks during the previous week. The study was conducted in 2 outpatient clinics in New York City from January 2004 through July 2005.

RESULTS:

Of the 13 patients completing the study, 11 were rated "very much" or "much" improved on the CGI-I. Panic attack frequency, anxiety (HAM-A), and global severity (CGI-S) ratings also demonstrated significant improvement (all $p < .00$). For most patients, clinical benefits were apparent after only 1 to 2 weeks of treatment. Levetiracetam was well tolerated with minimal side effects.

CONCLUSION:

Given its favorable pharmacokinetics, side effect profile, and, if confirmed, early onset of action and efficacy, levetiracetam might represent significant progress in the pharmacologic management of panic disorder.

Vigabatrin

Neuropsychopharmacology. 2001 Nov;25(5):699-703.

Vigabatrin decreases cholecystokinin-tetrapeptide (CCK-4) induced panic in healthy volunteers.

Zwanzger P1, Baghai TC, Schuele C, Ströhle A, Padberg F, Kathmann N, Schwarz M, Möller HJ, Rupprecht R.

Abstract

Vigabatrin increases gamma aminobutyric acid (GABA) levels by irreversible inhibition of the GABA-catabolizing enzyme GABA-transaminase (GABA-T). Preclinical studies suggest anxiolytic effects in vigabatrin treated rats. Anxiolytic effects in patients with panic disorder (PD) could therefore be expected. To evaluate putative anxiolytic properties of vigabatrin in humans, CCK-4-induced panic symptoms were studied in healthy volunteers before and after vigabatrin treatment. After placebo-controlled administration of 50 microg CCK-4, ten healthy volunteers received vigabatrin for seven days with a daily dosage of 2 g. The treatment period was followed by a second CCK-4 challenge. Panic and anxiety were assessed using the Acute Panic Inventory (API) score and a DSM-IV derived panic-symptom-scale (PSS). ACTH and cortisol plasma levels were determined during the CCK-4 challenge. All subjects reported a marked reduction of CCK-4-induced panic symptoms and anxiety after seven days of vigabatrin treatment both in the API- and PSS-scores. Moreover, there was a significant attenuation of CCK-induced elevation of ACTH and cortisol levels following vigabatrin treatment. In conclusion, our data show that GABA-transaminase inhibitors exert anxiolytic effects in CCK-4-induced panic in healthy volunteers and suggest that GABA transaminase inhibitors might be useful in ameliorating panic symptoms also in patients with PD.

Neurology. 1999 Oct 22;53(7):1503-11.

Psychiatric adverse events during vigabatrin therapy.

Levinson DF1, Devinsky O.

Abstract

OBJECTIVE:

To determine the incidence of psychiatric adverse events associated with vigabatrin therapy, we reviewed data from US and non-US double-blind, placebo-controlled trials of vigabatrin as add-on therapy for treatment-refractory partial epilepsy.

METHODS:

"Verbatim" terms from investigators' reports had been translated into standard "preferred" terms using an adverse event dictionary. Terms for psychiatric events were then combined into categories for analysis of rates during vigabatrin versus placebo treatment.

RESULTS:

Compared with placebo, vigabatrin subjects had a higher incidence of events coded as depression (12.1% versus 3.5%, $p < 0.001$) and psychosis (2.5% versus 0.3%, $p = 0.028$); there were no significant differences between treatment groups for aggressive reaction, manic symptoms, agitation, emotional lability, anxiety, or suicide attempt. Although depression and psychosis were typically observed during the first 3 months, most studies were 12 to 18 weeks long, so that definitive conclusions could not be reached about timing of events. Psychosis was generally transient and reported to be responsive to reduction or discontinuation of vigabatrin or to neuroleptic treatment. Depression was typically mild. Serious depression, defined as discontinued from the study, hospitalized, or suicide attempt, or coded as psychotic depression, occurred in only 9 of the 49 vigabatrin-treated patients with depression.

CONCLUSIONS:

Vigabatrin use in treatment-refractory partial epilepsy is associated with increased occurrence of depression and of psychosis, although the frequency of psychosis is apparently lower than previously reported. Clinical experience suggests that these adverse events respond to reduction of vigabatrin dose or to counteractive psychotropic treatment.

Summary and conclusion

Beyenburg et al (2005) in their review identified various antiepileptic drugs which have been reported to cause anxiety and/or panic. A systematic review by Piedad et al (2012) reported that certain drugs were associated with anxiogenic effects, however, methodological wealmeses and counfoundig by other factors cannot be discounted. The two case reports above also discuss the anxiogenic properties of topiramate, which is also identified in the Beyenburg paper. Mula et al (2007) report on the anxiolytic effects of some anticonvulsants and the drugs with the strongest evidence in support of these effects were not suggested as inducing anxiety.

Specific literature searches of more recent literature focussing on AEDs and anxiety was conducted. The levetiracetam literature was equivocal with mixed reports, one study found no elevated anxiety scores, one study reported minimal side-effects and in one study 7 out of 217 patients reported anxiety as a psychiatric treatment-emergent adverse event. Two older studies of vigabatrin use and anxiety and panic found that vigabatrin reduced panic and anxiety symptoms after seven days of use in one study. In the other study there were no difference in anxiety symptoms between when comparing the drug and placebo groups.

Relying on the review evidence summarised above, it is suggested that the following drugs/class of drugs be considered for inclusion in the SoPs – Grade 3 level evidence & topiramate Grade 2 level evidence:

(a) felbamate - RH
(b) phenytoin - RH
(c) topiramate
(d) zonisamide - RH

Anaesthetic agents

Summary of important issues

Reviews

Niesters, Martini and Dahan (2014)[89] review the literature in regard to ketamine as an agent for chronic pain syndromes. The anaesthetic ketamine is used to treat various chronic pain syndromes, especially those that have a neuropathic component. Low dose ketamine produces strong analgesia in neuropathic pain states, presumably by inhibition of the N-methyl-D-aspartate receptor although other mechanisms are possibly involved, including enhancement of descending inhibition and anti-inflammatory effects at central sites. Current data on short term infusions indicate that ketamine produces potent analgesia during administration only, while three studies on the effect of prolonged infusion (4-14 days) show long-term analgesic effects up to 3 months following infusion. The side effects of ketamine noted in clinical studies include psychedelic symptoms (hallucinations, memory defects, panic attacks, anxiety symptoms), nausea/vomiting, somnolence, cardiovascular stimulation and, in a minority of patients, hepatoxicity. The recreational use of ketamine is increasing and comes with a variety of additional risks ranging from bladder and renal complications to persistent psychotypical behaviour and memory defects. Blind extrapolation of these risks to clinical patients is difficult because of the variable, high and recurrent exposure to the drug in ketamine abusers and the high frequency of abuse of other illicit substances in this population. In clinical settings, ketamine is well tolerated, especially when benzodiazepines are used to tame the psychotropic side effects.

The World Health Organisation (WHO; 2015)[90] Expert Committee on Drug Dependence : thirty-sixth report reported on the side effects of ketamine including the ability to induce anxiety symptoms as follows:

3.24 - Ketamine (INN)

Substance identification

Ketamine is (±)-2-(*o*-chlorophenyl)-2-(methylamino)-cyclohexanone. It contains a chiral centre, resulting in two enantiomers: S-(+)-ketamine and R-(–)-ketamine. Usually, the racemate is marketed, but the more active S-(+)-enantiomer is increasingly present in commercially available preparations.

Previous review

Ketamine had been pre-reviewed by the ECDD at its thirty-third meeting, at which a recommendation was made for a critical review. At its thirty-fourth meeting, the ECDD carried out a critical review of ketamine and concluded that the information available was not sufficient to warrant scheduling. Also in view of the activities of the Commission on Narcotic Drugs regarding ketamine in its forty-ninth session held in March 2006, at the thirty-fourth meeting, the ECDD requested the Secretariat to produce an updated version of the critical review and

[89] Niesters M, Martini C, Dahan A. (2014). Ketamine for chronic pain: risks and benefits. British Journal of Clinical Pharmacology; 77(2):357-67.
[90] WHO (2015). WHO Expert Committee on Drug Dependence : thirty-sixth report (WHO technical report series ; no. 991), Geneva, Switzerland. *Pre-Layout Version*

present it to the next Committee meeting. At its thirty-fifth meeting, and on the basis of the critical review undertaken, the Committee decided that bringing ketamine under international control was not appropriate. At its fifty-seventh session in March 2014, the Commission on Narcotic Drugs adopted Resolution 57/10 on preventing the diversion of ketamine from legal sources while ensuring its availability for medical use. The Commission stated a concern regarding the threat to the well-being of people and society posed by the diversion of ketamine and by the rising trend in the abuse and trafficking of that substance. A notification was made by the Government of the People's Republic of China, under Article 2, Paragraph 1 of the Convention on Psychotropic Substances (1971), concerning the proposed recommendation for international control of ketamine. The information provided by China with its notification to the Secretary-General was brought to Expert Committee's attention.

Similarity to known substances and effects on the central nervous system

Ketamine is an anaesthetic that binds to the so-called phencyclidine (PCP) -binding site of the N-methyl-D-aspartate (NMDA)-receptor complex as a non-competitive antagonist. Several studies indicate that opioid receptors are also involved in the pharmacological analgesic effects of ketamine. In non-fatal intoxications, anxiety (especially in first-time users), agitation, changes of perception (e.g. loss of notion of danger or visual disturbances), disorientation and impairment of motor function, such as ataxia and dystonic reaction have been described. Reported intoxications typically involve other drugs and ketamine was the sole intoxicant in only a very limited number of fatalities (pp. 43-4).

Case report

Klein and Benveniste (1999)[91] described three cases of peripheral nerve blockade with ropivacaine that resulted in unusual symptoms of CNS toxicity. In three patients, unexpected behavioural changes occurred during administration of ropivacaine. The patients became extremely agitated, anxious, and screamed, and they did not respond to verbal commands. This case report shows that ropivacaine may cause CNS toxicity that differs from classical signs of local anaesthetic-induced toxicity. This effect might be related to the unique structure of ropivacaine, which is formulated in an S-enantiomer preparation. It has been shown that S-enantiomers bind differently to receptors in both the CNS and cardiovascular systems. This property may account for the disinhibition of select neural pathways that are specifically involved in mediation of anxiety and aggression.

Ackerman, Phero and Juneja (1989)[92] reported panic disorder/anxiety symptoms following the administration of 2-chloroprocaine. The patient was a 25-year-old woman, who delivered a live male baby with epidural analgesia. She received 8 ml of 0.25% bupivacaine and 10 ml of 1% lidocaine during labour without complications. Sixteen hours postpartum, she was taken to the operating room for tubal ligation. She received 20 ml of epidural 3% 2-chloroprocaine in 3-ml incremental doses until a bilateral T4 sensory level was obtained. Within 3 minutes of receiving the total local anaesthetic, the patient reported that the "operating room ceiling was falling" and that she was "going to die." She became confused and agitated and was subsequently given a general anaesthetic, from which she emerged without sequelae. The

[91] Klein SM, Benveniste H. (1999). Anxiety, vocalization, and agitation following peripheral nerve block with ropivacaine. Regional Anesthesia & Pain Medicine; 24(2):175-8.
[92] Ackerman WE, Phero JC, Juneja MM (1989). Panic disorder following 2-chloroprocaine. Am J Psych, 146(7): 940-1. 078484

patient had no history of psychiatric problems before this admission. The authors stated that they have had three additional panic reactions under similar circumstances in the preceding 12 months before this case when epidural 2-chloroprocaine was used for patients requiring elective Caesarean section.

Summary and conclusion

In the article by Niesters et al (2014) the adverse events associated with ketamine use as an anaesthetic agent for chronic pain syndromes is discussed, with panic attacks and anxiety symptomatology identified as known neuropsychiatric side effects of the drug.

Two case reports were also identified which discussed peripheral nerve blockade with ropivacaine that resulted in unusual anxiety symptoms (Klein & Benveniste, 1999) and cases of anxiety symptoms subsequent to the administration of epidural 2-chloroprocaine.

Ketamine – Grade 2 level evidence

Ropivacaine & 2-chloroprocaine – Grade 3 level evidence

Antipsychotic medication

Summary of important issues

Case reports

Hori and Shiraishi (1999)[93] reported a case involving a 35-year-old man with an 11-year history of paranoid schizophrenia, referred to as Mr. A. The patient experienced chronic delusions of persecution, auditory hallucination and avolition. Although he maintained contact and had sufficient insight to continue pharmacotherapy, he was overly sensitive to such adverse effects of the drug as drug-induced parkinsonism following increases in the dose of antipsychotics. Limited improvement in response to previous treatment led to the initiation of risperidone at 3 mg/day. Nemonapride was concurrently reduced from 18 mg to 9mg a day and 6 mg/day biperiden was discontinued. Two days after the switch to risperidone, Mr. A complained of an inexplicable sadness, anxiety and awareness of actuality. He denied depressive mood but was very afraid and ashamed of his present condition to the point where he could not work properly. This change was intolerable to him and a week later the regimen was switched back to the previous one, with the result being a disappearance of symptoms 2 days later.

Approximately 10 months later, Mr. A complained of worsening auditory hallucinations and agreed to a second attempt at risperidone treatment. This time the biperiden was continued and the nemonapride was gradually tapered off. At the same time, risperidone was started from 1 mg/day and increased to 2 mg/day. Hallucinations and avolition showed an immediate, though slight improvement, and as a result, the dose was increased 2 weeks later to 3 mg/day. Two days following this increase, only anxiety reappeared and subsequently persisted despite switching back to the previous dose of nemonapride. The dosage was then decreased to 2 mg/day, and subsequently symptoms disappeared.

Hanna, Fluent and Fischer (1999)[94] also report some cases of low dose of risperidone added to other medications to treat two adolescent boys with obsessive compulsive disorder (OCD) and a childhood history of separation anxiety disorder, and one prepubertal boy with a history of attention deficit hyperactivity disorder and escalating behaviour suggestive of mania. Each patient developed anxiety symptoms which were diagnosed as a re-emergence of severe separation anxiety in two cases and a new diagnosis in the boy with a history of attention deficit hyperactivity disorder. The separation anxiety resolved when risperidone was discontinued. The response was similar to that described in Tourette's disorder patients treated with haloperidol and pimozide. Two of the patients were treated subsequently with olazapine without a recurrence of separation anxiety.

Summary and conclusion

The cases reported above support risperidone-induced anxiety symptomatology. Hori and Shiraishi (1999) reported the case where rechallenge with the drug some 10 months later resulted in the re-emergence of anxiety symptoms. Grade 3 level evidence

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[93] Hori M, Shiraishi H. (1999). Risperidone-induced anxiety might also develop 'awakening' phenomenon. Psychiatry & Clinical Neurosciences; 53(6):682.

[94] Hanna GL, Fluent TE, Fischer DJ. (1999). Separation anxiety in children and adolescents treated with risperidone. Journal of Child & Adolescent Psychopharmacology; 9(4):277-83.

Antidepressants

Summary of important issues

Mixed presentations of depression and anxiety are commonly reported. Some study designs support anxiety presentation in close temporal relationship to the commencement of the antidepressant drug, however, other studies support the anxiolytic effects of these same drugs.

Reviews

Mihanović, Restek-Petrović, Bodor, et al (2010)[95]

Antidepressants and antipsychotics can cause side effects in various organs and organic systems, and in the central nervous system, which can also be clinically manifested by suicidal behavior as well. Tricyclic antidepressants particularly of imipramine and clomipramine can have pro-suicidal effect, which is believed to be the consequence of their own hypothetic asynchronous cognitive-psychomotor pharmacodynamic action. Antidepressants from the group of selective serotonin reuptake inhibitors can at the beginning of administration as monotherapy also have pro-suicidal effects in patients with hints of suicidality or suicidal behavior, by increasing the intensity of already present suicidal predictors, such as dysphoria, anxiety, impulsiveness, agitation etc. Antipsychotics can act stimulatingly upon predictors of suicidal behavior, that is, pro-suicidal in an indirect way through side effects they cause indirect pro-suicidal neurological and consecutive psychological impact, as it is called. It is particularly valid for classic antipsychotics causing primarily neurological, i.e. extrapyramidal side effects, along which consecutive psychological side effects can occur as well. However, new antipsychotics in comparison to classic ones, have less pronounced neurological, extrapyramidal symptoms and signs but more somatic-metabolic side effects, and thereby their action can be mostly manifested as indirect pro-suicidal neurological and somatic-metabolic as well as consecutive psychological activity.

Serretti, Calati, Goracci et al (2010)[96]

A wide debate is ongoing regarding whether antidepressant effects should be considered a general property of these agents or whether they exclusively belong to the context of target symptoms. The aim of the present review is to summarize findings on antidepressant influences on healthy volunteers, focusing on changes in psychological and cognitive functions. Differences have been detected between acute and chronic treatments. Acute treatment has been found to lead to positive bias in emotion processing and facilitation in negative emotion recognition. Chronic treatments have been found to stabilise some changes induced by acute treatment, such as increased social behaviours. Regarding antidepressant modulation of affective symptomatology contrasting results have been reported suggesting that the link between action on cognitive processes and mood may be not direct. In fact, meta-analyzing data on mood and anxiety symptoms no difference was detected between subjects receiving placebo and SSRIs. However, meta-analyzing data on negative affects, a significant decrease was detected in subjects receiving SSRIs in comparison with subjects receiving

[95] Mihanović M, Restek-Petrović B, Bodor D, Molnar S, Oresković A, Presecki P. (2010). Suicidality and side effects of antidepressants and antipsychotics. . Psychiatr Danub. 2010 Mar;22(1):79-84.
[96] Serretti A, Calati R, Goracci A, Di Simplicio M, Castrogiovanni P, De Ronchi (2010). Antidepressants in healthy subjects: what are the psychotropic/psychological effects? Eur Neuropsychopharmacol. 2010 Jul;20(7):433-53.

placebo. In summary, antidepressants seem to exert a detectable influence also in healthy subjects.

Sinclair, Christmas, Hood et al (2009)[97]

BACKGROUND: Early worsening of anxiety, agitation and irritability are thought to be common among people commencing antidepressants, especially for anxiety disorders. This phenomenon, which may be termed jitteriness/anxiety syndrome, is cited as an explanation for early treatment failure and caution in using selective serotonin reuptake inhibitors (SSRIs). However, we believe that it is inconsistently defined and that robust evidence to support the phenomenon is lacking.

AIMS: To review systematically all evidence relating to jitteriness/anxiety syndrome to identify: constituent symptoms; medications implicated; disorders in which it was reported; incidence; time course; management strategies; relationship of this syndrome to therapeutic response; distinction between syndrome and akathisia; relationship between syndrome and suicide; and genetic predispositions.

METHOD: A systematic search identified articles and these were included in the review if they addressed one of the above aspects of jitteriness/anxiety syndrome.

RESULTS: Of 245 articles identified, 107 articles were included for review. No validated rating scales for jitteriness/anxiety syndrome were identified. There was no robust evidence that the incidence differed between SSRIs and tricyclic antidepressants, or that there was a higher incidence in anxiety disorders. Published incidence rates varied widely from 4 to 65% of people commencing antidepressant treatment. Common treatment strategies for this syndrome included a slower titration of antidepressant and the addition of benzodiazepines. Conclusive evidence for the efficacy of these strategies is lacking. There was conflicting and inconclusive evidence as to whether the emergence of this syndrome had a predictive value on the response to treatment. It appears to be a separate syndrome from akathisia, but evidence for this assertion was limited. The effect of jitteriness/anxiety syndrome on suicide rates has not been evaluated. Three studies examined genetic variations and side-effects from treatment, but none was specifically designed to assess jitteriness/anxiety syndrome.

CONCLUSIONS: Jitteriness/anxiety syndrome remains poorly characterised. Despite this, clinicians' perception of this syndrome influences prescribing and it is cited to support postulated mechanisms of drug action. We recommend systematised evaluation of side-effects at earlier time points in antidepressant trials to further elucidate this clinically important syndrome.

Shah, Iqbal, White and White (2005)[98] reviewed the literature in regard to psychiatric and cardiovascular medications, existing psychiatric comorbidities commonly reported in cardiac patients and the safety of these medications. The table below outlines known general side effects of the antidepressants which include anxiety symptoms.

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[97] Sinclair LI, Christmas DM, Hood SD, Potokar JP, Robertson A, Isaac A, Srivastava S, Nutt DJ, Davies SJ. (2009). Antidepressant-induced jitteriness/anxiety syndrome: systematic review. Br J Psychiatry. 2009 Jun;194(6):483-90.

[98] Shah SU, Iqbal Z, White A & White S (2005). Heart and mind: (2) psychotropic and cardiovascular therapeutics. Postgrad Med J; 81:33-40.

TABLE 34 COMMONLY USED ANTIDEPRESSANTS, DOSAGES, GENERAL AND CARDIOVASCULAR SIDE EFFECTS (SHAH ET AL, 2005).

Agent	Starting dose	Maximum dose	General side effects	Cardiovascular effects
Serotonin reuptake inhibitors				
Sertraline	12.5–25 mg/day	200 mg/day	Sexual dysfunction, nausea, diarrhoea, headache	Benign bradycardia
Fluoxetine	5–10 mg/day	80 mg/day	Anxiety, agitation, insomnia, somnolence, sedation	
Paroxetine	10 mg/day	50 mg/day	Tremor	
Tricyclics				
Amitriptyline	10–25 mg at bedtime	300 mg/day	Sedation, somnolence, dry mouth, blurry vision	Increase QT, PR, QRS intervals, decreased T wave amplitude
Imipramine	10–25 mg at bedtime	300 mg/day	Constipation, urinary retention	Tachycardia, arrhythmias
Nortriptyline	10 mg/day	150 mg/day	Anxiety, insomnia, weight gain	Postural hypotension
Desipramine	25 mg/day	300 mg/day		
Psychostimulants				
Methylphenidate	2.5 mg twice a day	20 mg twice a day	Anxiety, agitation, insomnia Anorexia, paranoia	Tachycardia (mild), hypertension (mild)
Other agents				
Bupropion	75 mg/day	150 mg three times a day	Anorexia, nausea, anziety, agitation, insomnia, seizures	
Venlafaxine	12.5 mg twice a day	125 mg three times a day	Headache, sexual dysfunction, anxiety, insomnia, somnolence, dizziness	Hypertension (dose related)
Trazadone	25 mg/day	600 mg/day	Sedation, nausea, headache, priapism (rare)	Postural hypotension, arrhythmias (rare)
Mirtazapine	15 mg every hour of sleep	45 mg every hour of sleep	Sedation, somnolence, dry mouth, anticholinergic effects, dizziness agranulocytosis (rare)	

Meta-analysis

Andrisano, Chiesa and Serretti (2013)[99]

Selective serotonin reuptake inhibitors and venlafaxine are currently considered as first-line agents for patients with panic disorder (PD). However, a systematic comparison of newer antidepressants for the treatment of PD is lacking thus far. Eligible studies focusing on PD patients treated with newer antidepressants were entered in the Cochrane Collaboration Review Manager. Our primary outcome measure was the mean change in panic symptoms from the baseline to the endpoint in patients treated with antidepressants as compared with those treated with placebo. Secondary outcome measures included the mean change in the overall anxiety scores and dropout rates. Sensitivity analyses were also carried out. Fifty studies focusing on 5236 patients were included. The following antidepressants were significantly superior to placebo for PD patients with the following increasing order of effectiveness: citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine for panic symptoms and paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine for overall anxiety symptoms. Aside from reboxetine and fluvoxamine, all drugs were associated with significantly lower dropout rates as compared with placebo. Several clinical variables moderated clinical outcomes. However, because of some inconsistencies across the studies and limited evidence for some drugs under investigation, further head-to-head comparisons are required.

[99] Andrisano C, Chiesa A, Serretti A. (2013). Newer antidepressants and panic disorder: a meta-analysis. Int Clin Psychopharmacol. 2013 Jan;28(1):33-45.

Cohort Studies

Li, Pfeiffer, Hoggatt et al (2011)[100] assessed demographic and clinical factors associated with emergent anxiety following a new antidepressant start among Department of Veterans Affairs (VA) Health System patients with depression. Using a retrospective cohort design, data was obtained from 328,888 VA patients with depression who were newly prescribed 1 of the 7 most commonly used antidepressant drugs between April 1999 and September 2004 from the VA National Depression Registry.

[100] Li Z, Pfeiffer PN, Hoggatt KJ, Zivin K, Downing K, Ganoczy D, Valenstein M. (2011). Emergent anxiety after antidepressant initiation: a retrospective cohort study of Veterans Affairs Health System patients with depression. Clinical Therapeutics. 33(12):1985-1992.e1.

TABLE 35 UNADJUSTED AND ADJUSTED HAZARD RATIOS AND THEIR 95% CONFIDENCE INTERVALS (CIS) FOR ANXIETY DEVELOPMENT (ANXIETY INDICATED BY EITHER ANTIANXIETY MEDICINE OR ANXIETY DIAGNOSIS) (N=328,888) (LI ET AL, 2011).

	Unadjusted		Adjusted	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Antidepressants				
Bupropion	1.09*	(1.02, 1.18)	0.94	(0.87, 1.01)
Citalopram	1.09**	(1.04, 1.17)	1.10*	(1.04, 1.16)
Fluoxetine	1.03	(0.97, 1.11)	0.97	(0.90, 1.04)
Mirtazapine	1.54**	(1.39, 1.71)	1.42**	(1.28, 1.58)
Paroxetine	1.28**	(1.20, 1.37)	1.25**	(1.17, 1.34)
Venlafaxine	1.30**	(1.17, 1.44)	1.16*	(1.05, 1.28)
Sertraline	1	1	1	1
Age				
≥65	1	1	1	1
45–65	1.69**	(1.44, 1.81)	1.55**	(1.38, 1.72)
<45	2.04**	(1.92, 2.13)	1.72**	(1.59, 1.85)
Hispanic				
Yes	1	1	1	1
No	0.86**	(0.78, 0.94)	0.95	(0.86, 1.04)
Service connection[a]				
Yes	1	1	0.95	(0.86, 1.05)
No	0.98	(0.93, 1.02)	1	1
Charlson score				
0	1	1	1	1
1	0.77**	(0.73, 0.80)	0.99	(0.95, 1.03)
2	0.72**	(0.67, 0.77)	1.11**	(1.05, 1.18)
3	0.63**	(0.57, 0.69)	1.20**	(1.12, 1.29)
Major depression				
No	1	1	1	1
Yes	1.66**	(1.59, 1.74)	1.40**	(1.33, 1.47)
Medicare				
Yes	1	1	1	1
No	1.58**	(1.50, 1.65)	1.11**	(1.04, 1.18)
Personality disorder				
No	1	1	1	1
Yes	1.72**	(1.51, 1.97)	1.12	(0.98, 1.29)
Total inpatient psych stays[b]				
0	1	1	1	1
1	1.71**	(1.57, 1.86)	1.29**	(1.16, 1.42)
2	1.90**	(1.66, 2.18)	1.46**	(1.23, 1.73)
Psychiatric disorder days[c]	1.004**	(1.002, 1.005)	1.00	(0.99, 1.00)
# psycotropic medicines in last 12 months				
0	1	1	1	1
1	1.23**	(1.17, 1.30)	1.23**	(1.16, 1.30)
2	1.31**	(1.18, 1.46)	1.27**	(1.14, 1.42)
Alcohol abuse				
No	1	1	1	1
Yes	1.43**	(1.35, 1.52)	1.09*	(1.02, 1.17)
Any other substance abuse				
No	1	1	1	1
Yes	1.44**	(1.34, 1.55)	1.01	(0.92, 1.11)

The prevalence of emergent anxiety was examined, defined as either a new anxiety diagnoses or by new antianxiety medication starts, during the 12 weeks following new antidepressant start. In multivariate analyses, the hazard ratios for emerging anxiety associated with patient characteristics and specific antidepressant agents was assessed.

Approximately 3% of patients developed clinically significant anxiety within 12 weeks of starting an antidepressant drug regimen. Younger age (age <45 years and 45-64 years) was associated with higher risks for emergent anxiety than older age (>65 years) (hazard ratio [HR] = 1.72 and 1.55; 95% CI, 1.59-1.85, and 1.38-1.72, respectively). Female gender was associated with higher risks than male gender (HR = 1.17; 95% CI, 1.10-1.26), and white and other races compared with black race were associated with higher risks of emergent anxiety (HR = 1.49 and 1.13; 95% CI, 1.30-1.59 and 1.04-1.23, respectively). Finally, filling antidepressant drug prescriptions in years subsequent to 1999 was associated with lower risks of emergent anxiety.

Only a small proportion of patients developed emergent anxiety following a new antidepressant start, resulting in a new diagnosis or antianxiety medication use. Anxiety occurred more often in young adults, whites, and women.

Summary and conclusion

Mihanovic et al (2010) in their review of suicidality and side effects of antidepressants state that SSRIs can on initiation of the drug have pro-suicide effects due to an increasing intensity of already present suicidal predictors such as dysphoria, anxiety, impulsiveness and agitation etc.

Serretti et al (2010) in their summary of findings regarding antidepressants influence on mood and anxiety symptoms detected no difference between subjects receiving placebo and SSRIs.

Sinclair et al (2009) in their systematic review discussed the evidence regarding antidepressant-induced jitteriness/anxiety syndromes. They are critical of the studies 1. No validated rating scales for jitteriness/anxiety syndrome were identified; 2. There was no robust evidence that the incidence differed between SSRIs and tricyclic antidepressants, or that there was a higher incidence in anxiety disorders; 3. Published incidence rates varied widely from 4 to 65% of people commencing antidepressant treatment. They suggest that newer clinical trials are required which assess for jitteriness/anxiety syndromes using valid measures early and repeatedly during the trial to elucidate the relationship further.

The meta-analysis (Andrisano et al, 2013) found that a number of anti-depressants were significantly superior to placebo for PD patients with the following increasing order of effectiveness: citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine for panic symptoms and paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine for overall anxiety symptoms.

According to Shah et al (2005) a number of antidepressant drugs report anxiety as an adverse reaction (e.g., fluoxetine, nortriptyline, methylphenidate, bupropion, venlafaxine). Li et al (2011) in their large retrospective cohort study also identify a number of antidepressant drugs with anxiety symptoms reported as side effects. In the adjusted multivariate analysis anxiety development was significantly associated with bupropion, mirtazapine, paroxetine, and venlafaxine.

The evidence is in conflict. Mihanovic et al (2010), Shah et al (2005) and Li et al (2011) are supportive of an association between certain antidepressants inducing an anxiety syndrome. However, two reviews and a meta-analysis are not supportive of a relationship. With Andrisano et al (2013) reporting that certain antidepressants were superior treatment for anxiety and panic symptoms. Methodological concerns in identifying induced anxiety in studies is also highlighted (Sinclair et al, 2009).

Grade 4 level evidence

Antiparkinsonian medications

Summary of important issues

Evidence is limited to case reports.

Case reports

De Cerqueira and Nardi (2011)[101] reported the case of a 38-year-old female patient with young-onset Parkinson's disease, who presented with panic attack-like episodes that may have been induced by pramipexole. At age 28, she was diagnosed with Parkinson's disease which was well-controlled for 10 years on L-dopa and carbidopa. At 38 years of age she presented with motor fluctuations of off-period dystonia in her foot in the early morning. On examination, it was shown that she had a "pill-rolling" tremor, rigidity, and a dearth of movement in her left hand and leg, as well as mild postural instability. Treatment with pramipexole was prescribed at 0.125 mg three times per day as an add-on therapy. Approximately 1 hour after her first dose of pramipexole, the patient developed an episode of palpitations, shortness of breath, paresthesias, chills, dizziness, and a sense of impending death that lasted 30 minutes. These symptoms disappeared spontaneously, but she decided to withdraw the pramipexole. However, 1 week later, the pramipexole was reintroduced, and another similar episode occurred. These episodes disappeared after pramipexole withdrawal, and the patient had no further episodes during a 6-month follow-up period.

Alonso-Navarro, Jimenez-Jimenez, Pilo-de-la-Fuente and Plaza-Nieto (2009)[102] reported the case of a 73-year-old female patient with advanced Parkinson's disease who developed panic attack like episodes related with a treatment with ropinirole. The patient was diagnosed 9 years before in another hospital. She reported previous history of left ear surgery because of otosclerosis, amygdalectomy, and a mixed anxiety-depression disorder since age 57, which was treated with mirtazapine 30 mg twice a day and lorazepam 2 mg/d. She was not taking other drugs or herbals, with the exception of carbidopa/L-dopa. She had neither previous personal history of panic attacks nor family history of psychiatric illnesses.

In February 2008, a treatment with ropinirole (starting with 0.25 mg/d and increasing the dose weekly up to 1 mg 3 times per day) was prescribed. When the patient reached this dose, she developed, after each intake of 1 mg of ropinirole, sudden episodes consisting of anguish, feelings of imminent death, crying, dizziness, chest and perineal pain, dyspnea, tachypnea, and high blood pressure (160/80 mm Hg) lasting 1.5 to 2 hours. These episodes disappeared after ropinirole withdrawal. The reintroduction of ropinirole (starting with 0.125 mg/d and increasing the dose weekly up to 1 mg 3 times per day) reproduced these episodes again after reaching 1 mg 3 times daily. Transdermic rotigotine at increasing doses was started (initial dose, 2 mg/d and increasing the dose weekly up to 8 mg/d). This drug was well tolerated. The patient did not experience new episodes like those previously described after 3 months of follow-up.

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[101] de Cerqueira AC, Nardi AE. (2011). Panic attack-like episodes possibly induced by pramipexole in a patient with young-onset Parkinson's disease. Journal of Neuropsychiatry & Clinical Neurosciences; 23(3):E21.

[102] Alonso-Navarro H, Jimenez-Jimenez FJ, Pilo-de-la-Fuente B, Plaza-Nieto JF. (2009). Panic attack-like episodes possibly associated with ropinirole. Clinical Neuropharmacology; 32(4):237-8.

Alonso-Navarro and Jimenez-Jimenez (2007)[103] reported the case of a 62-year-old female patient with early Parkinson's disease who developed panic attack-like episodes related with pramipexole. The patient was recently diagnosed with PD and developed a panic attack-like episode according to the DSM-IV criteria, that was temporally related to oral pramipexole administration. This side effect was reproduced, with higher intensity, after a second attempt to use this drug at higher doses, but was not elicited by levodopa. The patient had neither other previous diseases nor pre-existing psychiatric symptoms, and she had no family history of psychiatric disorders.

Summary and conclusion

Three case reports describe the onset of anxiety and panic symptoms after the introduction of anti-Parkinsonian drugs (2 cases of pramipexole use and one of ropinirole use) and the re-emergence of these symptoms on rechallenge with the drugs

Grade 2 level evidence

[103] Alonso-Navarro H, Jimenez-Jimenez FJ. (2007). Panic attack like episodes possibly associated with pramipexole therapy in Parkinson's disease. European Journal of Neurology; 14(5):e1.

Sympathomimetics

Summary of important issues

Reviews

The **DSM-5**[104] states sympathomimetic medication is one of the medications that can evoke anxiety symptoms.

Case reports

Nelson, Bryant and Aks (2012)[105] reported a novel case of systemic toxicity with sympathomimetic excess and rhabdomyolysis after use of Melanotan II. Melanotan products are purchased via the Internet and have three main formulations (Melanotan I, Melanotan II, and bremelanotide). Melanotan I increases melanogenesis and eumelanin content to produce sunless tanning. Melanotan II also increases skin pigmentation but also produces spontaneous penile erections and sexual stimulation. Bremelanotide is a variation of Melanotan II that is specifically designed for sexual stimulation.

A 39 year-old Caucasian male injected subcutaneously 6 mg of Melanotan II purchased over the Internet in an attempt to darken his skin during wintertime. This dose was six times the recommended starting dose per the patient. In the emergency department two hours post injection, he complained of diffuse body aches, sweating, and a sensation of anxiety. Vital signs included BP 151/85 mmHg, HR 130 bpm that peaked at 146 bpm, and temperature of 97.8°F. Physical exam demonstrated a restless and anxious appearing male with mydriasis, diaphoresis, tachycardia, and diffuse muscle tremors. Pertinent laboratory values were creatinine 2.25 mg/dL, CPK 1760 IU/L, troponin 0.23 ng/mL, WBC 19.1 k/µL. Urinalysis demonstrated 3 + blood with red cell casts but 0-2 RBC/hpf. Qualitative urine drug screen was negative for metabolites of cocaine and amphetamines but positive for opiates. The patient received benzodiazepines for agitation and anxiety and had improvement in his symptoms. He was admitted to the ICU and during hospitalization his CPK elevated to 17773 IU/L 12 hours later. He continued to receive intravenous fluids with sodium bicarbonate for rhabdomyolysis and his CPK decreased to 2622 IU/L with improvement of creatinine to 1.23 mg/dL upon discharge from the ICU after 3 days. The substance, which he injected, was analysed via mass spectrometry and was confirmed to be Melanotan II when compared with an industry purchased standard sample.

This unique case highlights the potential of systemic toxicity with sympathomimetic excess, rhabdomyolysis, and renal dysfunction from Melanotan II use. Melanotan II use resulted in systemic toxicity including apparent sympathomimetic symptoms, rhabdomyolysis, and renal dysfunction. The patient also presented with agitation and anxiety and was treated for these symptoms.

Pseudoepineprhine

Int J Sports Physiol Perform. 2012 Sep;7(3):237-41. Epub 2011 Nov 29.

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[104] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783

[105] Nelson ME, Bryant SM, Aks SE (2012). Melanotan II injection resulting in systematic toxicity and rhabdomyolysis. Clinical Toxicology, 50: 1169-73. 078464

Effect of pseudoephedrine on 800-m-run times of female collegiate track athletes.

Berry C, Wagner DR.

Abstract

CONTEXT:

Pseudoephedrine (PSE) is an over-the-counter decongestant that might have ergogenic effects. The World Anti-Doping Agency has prohibited large doses (>150 µg/mL) of PSE, while the National College Athletic Association (NCAA) does not include it on their banned-substance list.

PURPOSE:

This study examined the effect of body-weight dosing of PSE on 800-m-run times of NCAA female runners.

METHODS:

Fifteen NCAA female track athletes volunteered to participate in the randomized, double-blind, crossover design. Participants were given 2.5 mg/kg PSE or placebo in trials separated by a week. Ninety minutes postingestion, participants completed an 800-m individual time trial on an indoor track. Finishing time was recorded with an automated video timing device. Heart rate and anxiety state scores were recorded immediately after each trial.

RESULTS:

Fourteen runners completed both trials, and 1 was an outlier: N=13. Despite the dose being well above normal therapeutic levels (144±17 mg), there was no significant difference (P=.92) in 800-m times between PSE (2:39.447±9.584) and placebo (2:39.372±9.636) trials, in postexercise heart rate (P=.635; PSE=177.9±14.5 beats/min, placebo=178.4±18.5 beats/min), or in anxiety-state levels (P=.650; PSE=38.4±11.6, placebo=38.1±8.8).

CONCLUSION:

A 2.5-mg/kg dose of PSE had no effect on 800-m performance for female NCAA runners. More research is needed to determine if PSE should be a specified banned substance.

Ventolin (albuterol/salbutamol)

Ventolin is a bronchodilators, and more specifically, β2-adrenergic agonists with sympathomimetic effects. The literature commonly reports anxiety as a moderate to severe side effect of this treatment.

Clin Neuropharmacol. 2003 Jul-Aug;26(4):207-12.

Albuterol improves response to levodopa and increases skeletal muscle mass in patients with fluctuating Parkinson disease.

Uc EY1, Lambert CP, Harik SI, Rodnitzky RL, Evans WJ.

Abstract

Animal studies indicate that beta(2)-adrenergic receptor agonists enhance transport of levodopa across the blood-brain barrier. Preliminary studies showed improved response to levodopa in patients with Parkinson disease (PD) who were given albuterol as adjunctive therapy. Beta(2)-adrenergic agonists may offer additional benefits to PD patients via their

skeletal muscle anabolic effects, particularly those who experience decreased muscle strength and weight loss. Nondemented, fluctuating PD patients receiving levodopa but not experiencing severe dyskinesias underwent the following tests at baseline and 14 weeks after treatment with albuterol sulfate (4 mg four times a day, orally): Unified Parkinson's Disease Rating Scale motor, tapping, and stand-walk-sit tests every 30 minutes between 8 am and 5 pm; body composition analyses using whole-body plethysmography and computed tomography of the thigh; muscle strength tests; and the Parkinson's Disease Questionnaire (PDQ-39). Results were analyzed using paired t-tests (2 tailed), repeated-measures analysis of variance, and the Wilcoxon signed-rank test. Seven of 8 enrolled patients completed the study; 1 patient withdrew because of headache and anxiety. The area under the curve for all-day UPDRS motor scores improved by 9.8 +/- 9.1% (mean +/- standard deviation; $P < 0.05$) and tapping improved by 7.6 +/- 8.1% ($P < 0.05$). The effect was more pronounced when only the response to the first levodopa dose (area under the curve, 8-11 am) was analyzed: 13.0 +/- 9.8% and 9.8 +/- 9.6% respectively. Thigh muscle cross-sectional area increased significantly as measured by computed tomography (5.3 +/- 3.2%, $P < 0.01$), as did fat-free mass by whole-body plethysmography combined with total-body water determination (9.5 +/- 2.9%, $P < 0.05$). There was no significant improvement in the stand-walk-sit test, muscle strength tests, other UPDRS sections, daily OFF time, or PDQ-39. Four patients were rated as having a mild global improvement (+1 point) on a -3 to +3-point scale, and 3 of them chose to continue albuterol beyond the termination of the study. The mean heart rate increased from 78.3 +/- 9.3 beats/minute to 85.6 +/- 8.7 beats/minute ($P < 0.05$). No laboratory abnormalities or electrocardiographic changes were induced by albuterol in any subject. This open-label pilot study suggests that albuterol increases muscle mass and improves the therapeutic response to levodopa in patients with fluctuating PD. A double-blind, placebo-controlled study is needed to confirm the effects and safety profile of beta(2)-agonists in PD.

Am J Emerg Med. 1998 Nov;16(7):637-42.

Salbutamol treatment of acute severe asthma in the ED: MDI versus hand-held nebulizer.

Rodrigo C1, Rodrigo G.

Abstract

The objectives of this study were to compare the efficacy of salbutamol delivered by either metered-dose inhaler plus spacer (MDI-spacer) or by wet nebulization (NEB), and to determine the relationships between physiologic responses and plasma salbutamol concentrations. Asthmatic patients presenting to the emergency department (ED) with acute severe asthma (forced expiratory volume in the first second [FEV1] less than 50% of predicted) were enrolled in a randomized, double-blind, parallel-group study. The MDI-spacer group received salbutamol, delivered via MDI into a spacer device, in four puffs actuated in rapid succession at 10-minute intervals (2.4 mg/h). The NEB group was treated with nebulized salbutamol, 1.5 mg, via nebulizer at 15-minute intervals (6 mg/h). Doses were calculated on the basis of the percentage of total dose that reaches the lower airway with both methods. The protocol involved 3 hours of this treatment. Mean peak expiratory flow rate (PEFR) and FEV1 improved significantly over baseline values for both groups ($P=.01$). However, there were no significant differences between both groups for PEFR and FEV1 at any point studied. The examination of the relationships between cumulative dose of salbutamol and change in FEV1 showed a significant linear relationship ($P=.01$) for both methods (MDI $r=.97$; NEB $r=.97$). The regression equations showed that for every 1 mg of salbutamol by MDI-spacer, 2.5 mg are

needed from nebulization to have equal therapeutic response. At the end of treatment, the salbutamol plasma levels were 10.1+/-1.6 ng/ml for the MDI-spacer group and 14.4+/-2.3 ng/ml for the NEB group (P=.0003). Both groups showed a nonsignificant heart rate decrease. A significant group-by-time interaction means that differences between groups increased with time (P=.04). Additionally, the NEB group presented a higher incidence of tremor (P=.03) and anxiety (P=.04), reflecting larger systemic absorption of salbutamol. These data indicate that when doses used are calculated on the basis of the percentage of total drug that reaches the lower airway, there was equivalent bronchodilatation after salbutamol administered by either MDI-spacer or nebulization in patients with acute severe asthma. However, nebulizer therapy produced greater side effects related to the increase in salbutamol absorption and higher plasma level.

Med J Aust. 1978 May 6;1(9):465-9.

A study of 208 patients in premature labour treated with orally administered salbutamol.

Hastwell GB, Halloway CP, Taylor TL.

Abstract

Orally administered salbutamol (8 mg every six hours) is a simple, acceptable and effective method of inhibiting labour. Of 208 patients, 89.4% had pregnancy prolonged for longer than two days. The pregnancy was prolonged for one week in 77.5%, and for two weeks in 66.8% of patients. Tremor and anxiety occurred in 68.3% of patients, and tachycardia greater than 110 beats per minute in 21.2%, but these proved tolerable if the patient was forwarned. Haemorrhages, both ante partum, and post partum, were apparently reduced. Glycosuria and pre-eclampsia were uncommon. Urinary oestriol levels were not significantly altered. Perinatal mortality was 58 per 1000 live and still births. The babies were active at delivery, but prone to hypothermia. The incidence of respiratory distress syndrome (4.1%) was low, particularly in babies born within four hours of the last salbutamol administration. Low Apgar scores were also uncommon in this group.

Theophylline and derivatives

Practitioner. 2016 Jan;260(1789):17-20, 2-3.

Anxiety in older adults often goes undiagnosed.

Koychev I, Ebmeier KP.

Abstract

Anxiety disorder in the elderly is twice as common as dementia and four to six times more common than major depression. Anxiety is associated with poorer quality of life, significant distress and contributes to the onset of disability. Mortality risks are also increased, through physical causes, especially cardiovascular disease, and suicide. Diagnosing anxiety disorders in older adults remains a challenge because of the significant overlap in symptoms between physical disorders (shortness of breath; abdominal and chest pain; palpitations) and depression (disturbed sleep; poor attention, concentration and memory; restlessness). Good history taking is crucial in elucidating whether the complaint is of new onset or a recurrence of

a previous disorder. The presence of comorbid depression should be clarified. If present, its temporal relationship with the anxiety symptoms will indicate whether there is an independent anxiety disorder. A medication review is warranted, as a number of drugs may be causative (calcium channel blockers, alpha- and beta-blockers, digoxin, L-thyroxine, bronchodilators, steroids, theophylline, antihistamines) or may cause anxiety in withdrawal (e.g. benzodiazepines). Substance and alcohol abuse should be excluded, as withdrawal from either may cause anxiety. A new or exacerbated physical illness may be related to anxiety. Medical investigations will help clarify the extent to which a particular somatic symptom is the result of anxiety.

Int J Clin Pharmacol Ther. 1997 Mar;35(3):107-11.

Oral doxophylline in patients with chronic obstructive pulmonary disease.

Villani F, De Maria P, Ronchi E, Galimberti M.

Abstract

Doxophylline, or 2-(7'-theophyllinemethyl)1,3-dioxolane, is a theophylline derivative which has shown interesting bronchodilating activity, and it appears to determine few adverse effects. The aim of the present investigation was to evaluate clinical therapeutic effects of the drug in the treatment of 2 groups of patients suffering from moderate to severe chronic obstructive pulmonary disease differing in acute response to the inhaled beta 2-agonist salbutamol and to compare changes of lung function tests to serum concentration of doxophylline. We studied 67 patients with chronic obstructive pulmonary disease (median age 63 years, 9 females and 58 males) who were all clinically stable at the time of the study. Patients were separated into 2 groups on the basis of their reaction to inhalation of 200 micrograms of salbutamol: those with an increased FEV1 of more than 20% from baseline value (group 1), and those with no increase (group 2). Doxophylline was administered orally at the dose of 400 mg 3 times daily. Serum levels of doxophylline were determined by high-pressure liquid chromatography. Spirometry and blood gas analysis were performed before and 10 days after treatment. Four patients stopped drug use because of side effects (3 for dyspepsia and 1 for anxiety). In group 1 (34 patients), a significant increase in SVC, FVC, FEV1, FEF 25-75% and PEFR was observed. In group 1 (29 patients), only PEFR significantly increased. No modifications in blood gas analysis were observed. The mean serum level of doxophylline was 14 micrograms/ml in group 1 and 9 micrograms/ml in group 2: the difference was statistically significant. The relation between serum levels of doxophylline and FVC showed an increase in the parameter up to the concentration of 12-13 micrograms/ml, after which a plateau phase was observed. On the basis of our data, doxophylline appears to have an interesting bronchodilating effect in patients responsive to the inhaled beta 2-agonist salbutamol. The lower limit of the therapeutic range seems to be 12-13 micrograms/ml. The upper limit of the therapeutic range was not determined because it was not possible to obtain serum samples when side effects occurred.

Summary and conclusion

The sympathomimetic effects of Melanotan II in this report above resulted in drug-induced anxiety symptoms. It is suggested that this drug may be best catered for in the idiosyncratic

drug factor in the SoP. No other studies relating to sympathomimetics and anxiety/panic attacks were identified on literature search.

A number of drugs cause sympathomimetic effects – and a search was conducted to identify studies which report on anxiogenic effects of these drugs. A small cross-sectional study of athletes taking pseudoephedrine did not find raised anxiety symptoms when exposed participants were compared to placebo users. Anxiety is commonly reported as a moderate to severe side effect of salbutamol. In a study where salbutamol was given as an adjunct therapy for Parkinson's disease only one patient withdrew due to headache and anxiety. In a randomised double blind study of asthmatics in an ED setting comparing metered dose spacer Ventolin with wet nebulizer Ventolin the nebulizer group presented with a significantly higher incidence of anxiety – reflecting larger systemic absorption of the drug. Salbutamol used to prolong pregnancy in a study of 208 premature labours reported tremor and anxiety in 68% of the patients.

A paper by Koychev and Ebmeier (2016) discuss anxiety in the elderly and the commonly used drugs with may contribute to anxiety in older age – theophylline is identified as a anxiogenic agent. COPD patients participated in a trial of doxophylline efficacy in two groups – one with an increased FEV1 on more than 20% from baseline on challenge with 200mg of salbutamol and group 2 were there was no increase on challenge with salbutamol. In this trial only four patients stopped drug use because of side effects (3 for dyspepsia and 1 for anxiety).

This class of drugs commonly report restlessness and anxiety as an adverse event.

Grade 2 level evidence

Idiosyncratic drug factor

Summary of important issues

A search of MIMS Online was conducted on 28 April 2016 using the term "anxiety" restricting the search to Adverse Reactions. 1228 drugs were identified.

Summary and conclusion

The generic drug factor is appropriate given the large number of drugs which can result in anxiety/panic attack symptoms. This is supported by the large number of case reports canvassed in the briefing paper.

Grade 1 level evidence.

Withdrawal

Summary of important issues

The **DSM-5**[106] states that panic or anxiety can occur in association with withdrawal from the following classes of substances: alcohol; opioids; sedatives, hypnotics, and anxiolytics; stimulants (including cocaine); and other (or unknown) substances.

A search of Micromedex on 1 July 2016 using the term “drug withdrawal which causes anxiety” identified 230 results. Another search using the term “drugs that cause drug withdrawal” resulted in 96 identified drugs.

Reviews

Nicotine

Taylor, McNeill, Girling et al (2014)[107] investigated change in mental health after smoking cessation compared with continuing to smoke. They conducted a systematic review and meta-analysis of observational studies. Data sources were Web of Science, Cochrane Central Register of Controlled Trials, Medline, Embase, and PsycINFO for relevant studies from inception to April 2012. Reference lists of included studies were hand searched, and authors were contacted when insufficient data were reported. Eligibility criteria for selecting studies longitudinal studies of adults that assessed mental health before smoking cessation and at least six weeks after cessation or baseline in healthy and clinical populations.

A total of 26 studies that assessed mental health with questionnaires designed to measure anxiety, depression, mixed anxiety and depression, psychological quality of life, positive affect, and stress were included. Follow-up mental health scores were measured between seven weeks and nine years after baseline. Anxiety, depression, mixed anxiety and depression, and stress significantly decreased between baseline and follow-up in quitters compared with continuing smokers: the standardised mean differences (95% confidence intervals) were anxiety −0.37 (95% confidence interval −0.70 to −0.03); depression −0.25 (−0.37 to −0.12); mixed anxiety and depression −0.31 (−0.47 to −0.14); stress −0.27 (−0.40 to −0.13). Both psychological quality of life and positive affect significantly increased between baseline and follow-up in quitters compared with continuing smokers 0.22 (0.09 to 0.36) and 0.40 (0.09 to 0.71), respectively). There was no evidence that the effect size differed between the general population and populations with physical or psychiatric disorders.

Smoking cessation is associated with reduced depression, anxiety, and stress and improved positive mood and quality of life compared with continuing to smoke. The effect size seems as large for those with psychiatric disorders as those without. The effect sizes are equal or larger than those of antidepressant treatment for mood and anxiety disorders.

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[106] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783

[107] Taylor G, McNeill A, Girling A, et al (2014). Change in mental health after smoking cessation: systematic review and meta-analysis. BMJ, 348(g1151): doi: 10.1136/bmj.g1151. 074776

Benzodiazepine

Benyamina, Naassila and Bourin (2012) [108] reported that benzodiazepine withdrawal is associated with various side effects including anxiety. This article discussed the beneficial anxioloytic effects of a drug used in cases of benzodiazepine withdrawal. The antipsychotic cyamemazine is a potent serotonin 5-HT(2A) receptor (5-HT(2AR)) antagonist. A positron emission tomography (PET) study in human patients showed that therapeutic doses of cyamemazine produced near saturation of 5-HT(2AR) occupancy in the frontal cortex, whereas dopamine D(2) occupancy remained below the level for motor side effects observed with typical antipsychotics. Recently, numerous studies have revealed the involvement of 5-HT(2AR) in the pathophysiology of anxiety and a double-blind, randomized clinical trial showed similar efficacy of cyamemazine and bromazepam in reducing the anxiety associated with benzodiazepine withdrawal. Therefore, we reviewed the above articles about 5-HT(2AR) and anxiety in order to understand better the anxiolytic mechanisms of cyamemazine in benzodiazepine withdrawal. The 5-HT(2AR) is the most abundant serotonin receptor subtype in the cortex. Non-pharmacological studies with antisense oligodeoxynucleotides and genetically modified mice clearly showed that cortical 5-HT(2AR) signaling positively modulates anxiety-like behavior. With a few exceptions, most other studies reviewed here further support this view. Therefore, the anxiolytic efficacy of cyamemazine in benzodiazepine withdrawal can be due to a 5-HT(2AR) antagonistic activity at the cortical level.

SSRIs

Finfgeld (2002)[109] discussed SSRI discontinuation syndrome. Based on 49,335 reports from many countries, researchers identified 947 cases of SSRI discontinuation symptoms associated with paroxetine (derived from a total of 10,020), 271 linked to fluoxetine (derived from a total of 33, 731), and 170 related to sertraline (derived from a total of 5,638) (Stahl et al., 1997). Additional findings suggest the incidence of SSRl discontinuation symptoms may be as high as 30% for some agents (Haddad, 1998).

To help clinicians identify SSRI discontinuation syndrome early, the mnemonic FINISH has been suggested, which is based on six core symptoms. They include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal (i.e., anxiety or agitation) (Berber, 1998). These symptoms may occur after an SSRI prescription is purposefully discontinued or in cases in which individuals miss one or more doses (Michelson et al., 2000). For example, clients may withhold their medication to temporarily diminish sexual side effects or may skip doses due to carelessness or intentional noncompliance.

Recently, efforts have been made to clearly articulate diagnostic criteria for SSRI discontinuation syndrome. The two proposed criteria in the Table below (Black et al., 2000; Haddad, 1998) are similar. Differences are most notable under criterion B. The times of onset differ (i .e., 1 to 10 days versus 1 to 7 days), and there are some variations in the list of symptoms. For exampie, Black et al. (2000) include visual disturbances and gait instability, which are absent in Haddad's (1998) list.

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[108] Benyamina A, Naassila M, Bourin M. (2012). Potential role of cortical 5-HT(2A) receptors in the anxiolytic action of cyamemazine in benzodiazepine withdrawal. Psychiatry Res. 2012 Jul 30;198(2):307-12. doi: 10.1016/j.psychres.2012.01.009. Epub 2012 Mar 14.

[109] Finfgeld DL. (2002). Selective serotonin reuptake inhibitor. Discontinuation syndrome. Journal of Psychosocial Nursing & Mental Health Services; 40(12):14-8.

TABLE 36 PROPOSED DIAGNOSTIC CRITERIA FOR SSRI DISCONTINUATION SYNDROME (FINFGELD, 2002).

Criterion	Black et al. (2000)	Haddad (1998)
A	Discontinuation of or reduction in dose of an SSRI after a period of use of at least 1 month.	A course of treatment when an SSRI is stopped or interrupted, or the dose is reduced after a period of use of 4 or more weeks.
B	Two or more of the following symptoms develop within 1 to 7 days of Criterion A: • Dizziness, light-headedness, vertigo, or feeling faint. • Nausea and/or emesis. • Headache. • Tremor. • Fatigue. • Anxiety. • Shock-like sensations or paresthesia. • Insomnia. • Irritability. • Diarrhea. • Gait instability. • Visual disturbances.	Two or more of the following symptoms develop within 1 to 10 days of Criterion A: • Dizziness or light-headedness. • Vertigo. • Nausea or vomiting. • Headache. • Tremor. • Lethargy. • Anxiety or agitation. • Tingling (i.e., paresthesia). • Numbness or "electric" shock-like sensations. • Insomnia. • Irritability. • Diarrhea. • Sweating.
C	The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or important areas of functioning.	The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D and E	The symptoms are not due to a general medical condition and are not better accounted for by recurrence of symptoms of the mental disorder for which the SSRI originally was prescribed or by concurrent discontinuation (or reduction in use) of another psychoactive substance.	The symptoms are not due to a general medical condition or the direct physiological effects of another substance (e.g., a medication or drug of misuse) that has been recently commenced, stopped, or altered in dosage. The disorder is not better accounted for by an exacerbation, relapse, or recurrence of the psychiatric disorder for which the SSRI was prescribed.

Randomised double blind study

Caffeine

Rogers, Hohoff, Heatherley et al (2010)[110] assessed the anxiogenic effect of caffeine in individuals with specific genetic profiles. Caffeine, a widely consumed adenosine A(1) and A(2A) receptor antagonist, is valued as a psychostimulant, but it is also anxiogenic. An association between a variant within the ADORA2A gene (rs5751876) and caffeine-induced anxiety has been reported for individuals who habitually consume little caffeine. This study investigated whether this single nucleotide polymorphism (SNP) might also affect habitual

[110] Rogers PJ, Hohoff C, Heatherley SV, Mullings EL, Maxfield PJ, Evershed RP, Deckert J, Nutt DJ. (2010). Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. Neuropsychopharmacology; 35(9):1973-83.

caffeine intake, and whether habitual intake might moderate the anxiogenic effect of caffeine. Participants were 162 non-/low (NL) and 217 medium/high (MH) caffeine consumers. In a randomized, double-blind, parallel groups design they rated anxiety, alertness, and headache before and after 100 mg caffeine and again after another 150 mg caffeine given 90 min later, or after placebo on both occasions. Caffeine intake was prohibited for 16 h before the first dose of caffeine/placebo. Results showed greater susceptibility to caffeine-induced anxiety, but not lower habitual caffeine intake (indeed coffee intake was higher), in the rs5751876 TT genotype group, and a reduced anxiety response in MH vs NL participants irrespective of genotype. Apart from the almost completely linked ADORA2A SNP rs3761422, no other of eight ADORA2A and seven ADORA1 SNPs studied were found to be clearly associated with effects of caffeine on anxiety, alertness, or headache. Placebo administration in MH participants decreased alertness and increased headache. Caffeine did not increase alertness in NL participants. With frequent consumption, substantial tolerance develops to the anxiogenic effect of caffeine, even in genetically susceptible individuals, but no net benefit for alertness is gained, as caffeine abstinence reduces alertness and consumption merely returns it to baseline. Anxiety as a symptom of caffeine withdrawal was not reported.

Cohort Studies

Tobacco

Leventhal, Ameringer, Osborn et al (2013)[111] conducted a study to parse the broad variation in anxiety and depressive symptoms into conceptually discrete components and explore their relative predictive influence on affective patterns of acute tobacco withdrawal. A within-participant experimentally manipulated tobacco abstinence design was used involving: (i) a baseline visit at which past-week depression and anxiety symptoms were assessed and (ii) two counterbalanced experimental visits-one after ad lib smoking and one after 16-h of tobacco abstinence-at which state affect was assessed. Participants were community-dwelling adults (N=187) smoking 10+ cig/day for at least two years without an active mood disorder. Anxiety-related general distress symptoms (e.g., tension, nervousness) predicted greater abstinence-induced increases in various negative affective states but not changes in positive affect (betas .17-.33). Depression-related general distress symptoms (e.g., sadness, worthlessness) predicted greater abstinence-induced increases in acute depressed affect only (betas .24-.25). Anhedonic symptoms (e.g., diminished interest, lack of pleasure) predicted larger abstinence-induced decreases in acute positive affect only (betas .17-.20). Anxious Arousal symptoms (e.g., shakiness, heart racing) predicted larger abstinence-induced increases in fatigue and depressive affect (betas .15-.24). Different components of anxiety and depressive symptoms are associated with unique affective patterns of acute tobacco withdrawal. These results provide insight into the affective mechanisms underlying tobacco dependence and could inform smoking cessation treatment approaches tailored to individuals with emotional distress.

[111] Leventhal AM, Ameringer KJ, Osborn E, Zvolensky MJ, Langdon KJ. (2013). Anxiety and depressive symptoms and affective patterns of tobacco withdrawal. Drug & Alcohol Dependence; 133(2):324-9.

Leyro and Zvolensky (2013)[112] evaluated nicotine withdrawal symptoms elicited by 12 hours of smoking deprivation on anxious and fearful responding to bodily sensations among daily smokers with and without panic disorder (PD). It was hypothesized that smokers with PD who were experiencing greater levels of nicotine withdrawal would experience the greatest levels of fearful responding to, and delayed recovery from, a 10% carbon dioxide-enriched air (CO_2) biological challenge procedure. Participants were 58 adults who reported smoking 19.72 cigarettes daily (SD = 7.99). Results indicated that nicotine withdrawal and PD status interacted to predict greater postchallenge panic attack symptoms. Also, individuals with PD initially evidenced a quicker decrease in subjective anxiety following the challenge, but their rate of recovery decelerated over time as compared to those without PD. There was, however, no significant interaction for change in subjective anxiety pre- to postchallenge.

Retrospective chart study

Dopamine agonist

Rabinak and Nirenberg (2010)[113] reported and characterised a dopamine agonist (DA) withdrawal syndrome (DAWS) in Parkinson disease. They conducted a retrospective cohort study in an outpatient tertiary movement disorders clinic. The participants consisted of 93 nondemented patients with Parkinson disease enrolled in a prospective study of nonmotor and motor disease manifestations. The main outcome measure was the presence of DAWS, defined as a severe, stereotyped cluster of physical and psychological symptoms that correlate with DA withdrawal in a dose-dependent manner, cause clinically significant distress or social/occupational dysfunction, are refractory to levodopa and other Parkinson disease medications, and cannot be accounted for by other clinical factors.

Of 40 subjects treated with a DA, 26 underwent subsequent DA taper. Of these 26 subjects, 5 (19%) developed DAWS and 21 (81%) did not. All subjects with DAWS had baseline DA-related impulse control disorders. Symptoms of DAWS resembled those of other drug withdrawal syndromes and included anxiety, panic attacks, agoraphobia, depression, dysphoria, diaphoresis, fatigue, pain, orthostatic hypotension, and drug cravings. Subjects with DAWS as compared with those without DAWS had higher baseline DA use (mean [SD], 420 [170] vs 230 [180] DA levodopa equivalent daily doses [DA-LEDD], respectively; P = .04) and higher cumulative DA exposure (mean [SD], 1800 [1200] vs 700 [900] DA-LEDD-years, respectively; P = .03). Subjects with DAWS also had considerably lower Unified Parkinson's Disease Rating Scale motor scores than those without DAWS (mean [SD], 21 [5] vs 31 [10], respectively; P = .007), despite comparable disease duration (mean [SD], 7.3 [7] vs 6.3 [4] years, respectively; P = .77) and similar total dopaminergic medication use (mean [SD], 830 [450] vs 640 [610] total LEDD, respectively; P = .52) in the 2 groups.

Dopamine agonists have a stereotyped withdrawal syndrome that can lead to profound disability in a subset of patients. Physicians should monitor patients closely when tapering these medications.

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[112] Leyro TM, Zvolensky MJ. (2013). The interaction of nicotine withdrawal and panic disorder in the prediction of panic-relevant responding to a biological challenge. Psychology of Addictive Behaviors; 27(1):90-101.

[113] Rabinak CA, Nirenberg MJ (2010). Dopamine agonist withdrawal syndrome in Parkinson diseas. Arch Neurol, 67(1): 58-63. 073330

Marijuana

Bonn-Miller and Moos (2009)[114] examined the role of anxiety symptoms immediately following substance abuse treatment in the relation between frequency of pre-treatment marijuana use and relapse to marijuana use at 12-months post-treatment among 1288 male patients who used marijuana within the 3 months prior to admission to treatment. Consistent with expectation, more frequent marijuana use at intake predicted more anxiety symptoms at discharge. Anxiety symptoms at discharge predicted relapse to marijuana use at 12-month follow-up, but did not mediate the relation between intake marijuana use and relapse. Results are discussed in relation to better understanding the role of increased anxiety during discontinuation of regular marijuana use in the prediction of relapse to marijuana.

Cross-sectional studies

Tramadol

El-Hadidy and Helaly (2015)[115] conducted a study to address the chronic sequel of tramadol dependence over at least 5 years duration with a large dose (more than 675 mg/day, three tablets or more, each tablet of 225 mg). The study was aimed to check the physical and psychiatric status during tramadol dependence and 3 months after complete treatment. The present study was applied on 79 patients with single tramadol-dependence dose of 675 mg or more for 5 years or more. The physical and psychological impact of tramadol abuse before and after 3 months of stoppage of the drug was observed.

The blood chemistry was nearly within normal parameters, although slight nonsignificant rise in liver enzymes was reported in some cases. Patients during tramadol dependence period were angry, hostile, and aggressive. On the other hand, after treatment the main problem observed was the significant increase in comorbid anxiety, depressive, and obsessive-compulsive symptoms, but no increase was found in psychotic symptoms. Tramadol-dependence dose was more important than duration of use in psychiatric illness.

Tramadol dependence on high dose could be physically safe to some limit, but psychiatrically it has many side effects.

Nicotine

Hogle, Kaye and Curtin (2010)[116] state that stress response neuroadaptation has been repeatedly implicated in animal addiction models for many drugs, including nicotine. Programmatic laboratory research that examines the stress response of nicotine-deprived humans is necessary to confirm that stress neuroadaptations observed in animal models generalize to humans. They conducted two experiments which tested the prediction that nicotine deprivation selectively increases startle response associated with anxiety during unpredictable threat but not fear during imminent, predictable threat. Dependent smokers (n = 117) were randomly assigned to 24-hour nicotine-deprived or nondeprived groups and participated in one of two experiments wherein electric shock was administered either

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[114] Bonn-Miller MO; Moos RH. (2009). Marijuana discontinuation, anxiety symptoms, and relapse to marijuana. Addictive Behaviors; 34(9):782-5.
[115] El-Hadidy MA, Helaly AM. (2015). Medical and Psychiatric Effects of Long-Term Dependence on High Dose of tramadol. Substance Use & Misuse; 50(5):582-9.
[116] Hogle JM, Kaye JT, Curtin JJ. (2010). Nicotine withdrawal increases threat-induced anxiety but not fear: neuroadaptation in human addiction. Biological Psychiatry; 68(8):719-25.

unpredictably (noncontingent shock; Experiment 1) or predictably (cue-contingent shock; Experiment 2).

Nicotine deprivation increased overall startle response in Experiment 1, which involved unpredictable administration of shock. Age of first cigarette and years of daily smoking were significant moderators of this deprivation effect. Self-reported withdrawal symptoms also predicted startle response during unpredictable shock. In contrast, nicotine deprivation did not alter overall or fear-potentiated startle in Experiment 2, which involved predictable administration of shock.

These results provide evidence that startle response during unpredictable threat may be a biomarker of stress neuroadaptations among smokers in nicotine withdrawal. Contrast of results across unpredictable versus predictable shock experiments provides preliminary evidence that these stress neuroadaptations manifest selectively as anxiety during unpredictable threat rather than in every stressful context. Individual differences in unpredictable threat startle response associated with withdrawal symptoms, age of first cigarette, and years daily smoking link this laboratory biomarker to clinically relevant indexes of addiction risk and relapse.

Caffeine

Caffeine, the only licit psychoactive drug available to minors, may have a harmful impact on students' health and adjustment, yet little is known about its use or effects on students, especially from a developmental perspective. **Luebbe and Bell (2009)**[117] examined caffeine use in 5th- and 10th-grade students in a cross-sectional design, and relations and potential mediators of caffeine use to depression and anxiety symptoms were investigated. Children (n = 135) and adolescents (n = 79) completed a measure of naturalistic use of caffeinated and noncaffeinated beverages. Furthermore, daily availability, perceived benefits, and stimulating, psychological, and withdrawal effects of caffeinated and noncaffeinated beverages were assessed. Measures of depression and anxiety were also administered.

Fifth and 10th graders used caffeine frequently. Depression was positively related to caffeine use for both cohorts, though mediated by caffeine withdrawal effects. **Surprisingly, anxiety was unrelated to use.** Fifth graders reported less daily access to caffeine, but more psychological and stimulating effects of caffeine than 10th graders. **Anxiety as a withdrawal effect was not discussed.**

Although both children and adolescents experience negative caffeine-related outcomes, intake is seemingly not greatly limited in either cohort. In particular, youth appear vulnerable to increased depressive symptoms with increasing caffeine consumption. Implications for school policy regarding students' caffeine use are discussed.

Methamphetamine

Mood disturbances in methamphetamine (MA) abusers likely influence drug use, but the neurobiological bases for these problems are poorly understood. **London, Simon, Berman,**

[117] Luebbe AM, Bell DJ. (2009). Mountain Dew or mountain don't?: a pilot investigation of caffeine use parameters and relations to depression and anxiety symptoms in 5th- and 10th-grade students. Journal of School Health; 79(8):380-7.

Mandelkern et al (2004)[118] assessed regional brain function and its possible relationships with negative affect in newly abstinent MA abusers. Two groups were compared by measures of mood and cerebral glucose metabolism ([18F]fluorodeoxyglucose positron emission tomography) during performance of a vigilance task. Participants were recruited from the general community to a research center. Seventeen abstaining (4-7 days) MA abusers (6 women) were compared with 18 control subjects (8 women). Self-reports of depressive symptoms and anxiety were measured, as were global and relative glucose metabolism in the orbitofrontal, cingulate, lateral prefrontal, and insular cortices and the amygdala, striatum, and cerebellum.

Abusers of MA provided higher self-ratings of depression and anxiety than control subjects and differed significantly in relative regional glucose metabolism: lower in the anterior cingulate and insula and higher in the lateral orbitofrontal area, middle and posterior cingulate, amygdala, ventral striatum, and cerebellum. **In MA abusers, self-reports of depressive symptoms covaried positively with relative glucose metabolism in limbic regions (eg, perigenual anterior cingulate gyrus and amygdala) and ratings of state and trait anxiety covaried negatively with relative activity in the anterior cingulate cortex and left insula. Trait anxiety also covaried negatively with relative activity in the orbitofrontal cortex and positively with amygdala activity.**

Abusers of MA have abnormalities in brain regions implicated in mood disorders. Relationships between relative glucose metabolism in limbic and paralimbic regions and self-reports of depression and anxiety in MA abusers suggest that these regions are involved in affective dysregulation and may be an important target of intervention for MA dependence.

Case reports

Kratom

Kratom (Mitragyna speciosa) has been used for medicinal and recreational purposes. It has reported analgesic, euphoric and antitussive effects via its action as an agonist at opioid receptors. It is illegal in many countries including Thailand, Malaysia, Myanmar, South Korea and Australia; however, it remains legal or uncontrolled in the UK and USA, where it is easily available over the Internet.

McWhirter and Morris (2010)[119] described a case of kratom dependence in a 44-year-old man with a history of alcohol dependence and anxiety disorder. He demonstrated dependence on kratom with withdrawal symptoms consisting of anxiety, restlessness, tremor, sweating and cravings for the substance. A reducing regime of dihydrocodeine and lofexidine proved effective in treating subjective and objective measures of opioid-like withdrawal phenomena, and withdrawal was relatively short and benign. There are only few reports in the literature of supervised detoxification and drug treatment for kratom dependence.

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[118] London ED, Simon SL, Berman SM, Mandelkern MA, et al. (2004). Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. Archives of General Psychiatry; 61(1):73-84.

[119][119] McWhirter L, Morris S. (2010). A case report of inpatient detoxification after kratom (Mitragyna speciosa) dependence. European Addiction Research. 16(4):229-31, 2010.

Venlafaxine

Boyd (1998)[120] reviewed the Adverse Drug Reaction Advisory Committee (ADRAC) reports of venlafaxine (antidepressant) adverse events related to withdrawal reactions. Between 1996 and 1998 13 patients aged 25 to 60 years (median age – 41 years) had been taking venlafaxine for treatment of depression for 2 to 12 months before a decision was made to cease treatment. Four of the 13 patients recovered from their symptoms within two weeks and two required return to venlafaxine and a tapered withdrawal. Anxiety was noted as a withdrawal symptom by three patients.

TABLE 37 WITHDRAWAL REACTIONS ASSOCIATED WITH VENLAFAXINE REPORTED TO ADRAC, 1996 TO MARCH 1998 (BOYD, 1998).

Age/ Sex	Daily dose (mg)	Indication	Duration of therapy	Symptoms	Outcome
60/M	70	Severe depression	About 12 months	Nightmares	Recovered after a 2-month tapered dose
39/F	112.5	Depression	Not known	Nausea, dizziness, anxiety, spatial disorientation, impaired coordination	Unknown, but taking 18.75 mg venlafaxine on alternate days*
42/M	37.5	Depression and anxiety	2 months	Headache, hypomania	Recovered quickly after oral chlorpromazine treatment†
39/F	150	Depression	4 months	Vertigo, insomnia, nightmares	Not yet recovered*
42/F	150	Depression	4 months	Headache, drowsiness, nightmares, postural hypotension, blurred vision	Recovered 2 weeks after venlafaxine ceased
46/M	225	Depression	2 months	Dizziness, numbness, headache, anxiety, ataxia	Recovered†
25/F	600	Depression	12 months	Nausea, headache	Recovered†
54/F	150	Depression	6 months	Sweating, nightmares, cramps, anxiety	Recovered within 4 days
45/F	75	Depression	8 months	Nausea, vomiting, malaise, dizziness, ataxia, emotional lability	Recovered within a week
51/F	75	Depression	7 months	Nausea, dizziness	Not yet recovered*
40/F	75	Depression	7 months	Dizziness, arthralgia	Unknown*
25/F	75	Depression	7 months	Nausea, dizziness, cramps, diarrhoea, somnolence, lethargy	Recovered after 5 days
38/M	75	Depression	8 months	Paraesthesia, hyperaesthesia, syncope	Not yet recovered*

ADRAC = Adverse Drug Reactions Advisory Committee. * At the time the report was submitted to ADRAC. † Time-to-recovery information not available on report submitted to ADRAC.

Summary and conclusion

There is a diverse literature relating to various drugs/substances which can induce anxiety symptomatology on withdrawal. The DSM-5 states that alcohol; opioids; sedatives, hypnotics, and anxiolytics; stimulants (including cocaine); and other (or unknown) substances may induce substance/medication-induced anxiety disorder. But other prescription medications (SSRIs, dopamine agonists, venlafaxine) are also known to have this effect.

The evidence for commonly used legal substances is not supportive - nicotine/smoking withdrawal is equivocal and for caffeine is not supported.

Nicotine/Smoking

The Taylor systematic review (2014) which assessed 26 high quality longitudinal studies found that smoking cessation was associated with decreased anxiety. Other studies assessed above did report an association between nicotine withdrawal/smoking cessation and anxiety symptomatology. Leventhal et al (2013) in a short-term (16H abstinence) tobacco withdrawal

[120] Boyd IW. (1998). Venlafaxine withdrawal reactions. Medical Journal of Australia; 169(2):91-2.

study found that anxiety symptoms was associated with this acute tobacco withdrawal. Leyro and Zvolensky found in a small study of smokers averaging 20 cigarettes per day that nicotine withdrawal and PD status interacted when abstaining smokers were challenged with 10% CO_2. At post-challenge this group had greater panic attack symptoms.

Hogle et al (2010) reported that nicotine deprivation increased overall startle response in Experiment 1, which involved unpredictable administration of shock. Age of first cigarette and years of daily smoking were significant moderators of this deprivation effect. Self-reported withdrawal symptoms also predicted startle response during unpredictable shock. In contrast, nicotine deprivation did not alter overall or fear-potentiated startle in Experiment 2, which involved predictable administration of shock.

Caffeine

Rogers et al (2010) did not report anxiety as a symptom of caffeine withdrawal. Luebbe and Bell (2009) also did not report anxiety as a caffeine withdrawal symptom. Although studies of children reported in the Caffeine Section did report a suspected withdrawal effect with anxiogenic features and reviews note that a withdrawal effect can occur.

Similar to the idiosyncratic drug factor proposed above, I believe for inclusiveness and sensible operationalisation of this drug withdrawal factor it is prudent to not list the drugs/substances in the SoP factor as there is a potential for various illicit drugs, prescription drugs and other substances to induce substance/medication-induced anxiety disorder – as outlined in the Micromedex search referenced above. This is in line with the approach taken by the RMA with substance/medication-induced depressive disorder.

The evidence for various drugs/substances in withdrawal to induce substance/medication-induced anxiety disorder is strongly supported. Grade 1

Illicit Drugs – Drugs of Abuse

Opioids

Summary of important issues

Although some of these medications are prescribed for legitimate medical purposes – drugs in the relevant class of drugs are commonly used illegally, are drugs of abuse and dependence and drug withdrawal can be particularly problematic with some of these substances.

Assessing the evidence relating to illicit drug use and adverse events ascribed to specific substances is complex due to the high rates of polysubstance abuse in the samples assessed.

The **DSM-5**[121] states that panic or anxiety can occur in association with intoxication with the following classes of substances: alcohol, caffeine, cannabis, phencyclidine, other hallucinogens, inhalants, stimulants (including cocaine), and other (or unknown) substances.

Clinical trials

Wallace, Kosek, Staats et al (2008)[122] conducted a phase II, multicenter, open-label study with a 5-week titration phase and an extension phase to assess the safety and efficacy of adding intrathecal ziconotide to intrathecal morphine in patients being treated with a stable intrathecal morphine dose. Participants were outpatients with suboptimal pain relief receiving stable intrathecal morphine doses (2-20 mg/day).

Intrathecal morphine dosing remained constant during the titration phase. Ziconotide therapy began at 0.60 microg/day and was titrated to a maximum of 7.2 microg/day. During the extension phase, ziconotide and intrathecal morphine dosing were adjusted at the investigator's discretion.

Safety was assessed primarily via adverse event reports. Efficacy was analyzed via percentage change on the visual analog scale of pain intensity and in weekly systemic opioid consumption.

Twenty-six patients were enrolled. Treatment-emergent adverse events were generally mild or moderate; the most common (> or = 15% of patients in either study phase) study drug-related (i.e., ziconotide/morphine combination [or ziconotide monotherapy in the extension phase only]) events were confusion, dizziness, abnormal gait, hallucinations, and **anxiety**. The mean percentage improvement in visual analog scale of pain intensity scores was 14.5% (95% confidence interval: -9.4% to 38.5%) from baseline to week 5 and varied during the extension phase (range: -0.4% to 42.8%). Mean percentage change from baseline in systemic opioid consumption was -14.3% at week 5 and varied considerably during the extension phase.

Ziconotide, combined with stable intrathecal morphine, may reduce pain and decrease systemic opioid use in patients with pain inadequately controlled by intrathecal morphine alone.

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[121] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783

[122] Wallace MS, Kosek PS, Staats P Fisher R, Schultz DM, Leong M. (2008). Phase II, open-label, multicenter study of combined intrathecal morphine and ziconotide: addition of ziconotide in patients receiving intrathecal morphine for severe chronic pain. Pain Medicine; 9(3):271-81.

Jensen, Handberg, Helbo-Hansen, Skaarup et al (2008)[123] tested the hypothesis that the addition of ketamine to i.v. patient-controlled morphine reduces the amount of morphine required for pain-control during the first 24 h after embolization of the uterine arteries (UAEs). Fifty-six patients undergoing UAE embolization for treatment of symptomatic uterine leiomyomata were randomized to receive either 2 mg/ml of morphine (Control group, n=30) or 2 mg/ml of both morphine and ketamine (Ketamine group, n=26) by i.v. patient-controlled analgesia (IV-PCA). Pump settings were bolus dose 1 ml, lockout 10 min, no background infusion. In addition, all patients received diclofenac and acetaminophen for pain relief. Pain scores, morphine consumption and adverse events like nausea, vomiting, itching, visual disturbances, **anxiety**, dreaming and hallucinations, if any, were recorded for 24 h after embolization.

The mean +/- SD 24-h consumption of patient-controlled morphine was 38.3 +/- 21.0 mg in the Ketamine group vs. 33.3 +/- 18.3 mg in the Control group. The difference between the means was 5.0 mg (95% confidence interval: -5.7; 15.6). One patient in the Ketamine group vs. none in the Control group experienced auditory hallucinations.

Studying an unselected group of patients undergoing embolization of the UAEs for treatment of symptomatic uterine leiomyomata under conditions of basal analgesia with acetaminophen and diclofenac, they failed to demonstrate any morphine-sparing effect of IV-PCA ketamine and morphine compared with IV-PCA morphine alone.

Naef, Curatolo, Petersen-Felix, Arendt-Nielsen et al (2003)[124] conducted a study to measure the analgesic effect of delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination (THC-morphine) in humans using experimental pain models. THC (20 mg), morphine (30 mg), THC-morphine (20 mg THC+30 mg morphine), or placebo were given orally and as single doses. Twelve healthy volunteers were included in the randomized, placebo-controlled, double-blinded, crossover study. The experimental pain tests (order randomized) were heat, cold, pressure, single and repeated transcutaneous electrical stimulation. Additionally, reaction time, side-effects (visual analog scales), and vital functions were monitored. For the pharmacokinetic profiling, blood samples were collected. THC did not significantly reduce pain. In the cold and heat tests it even produced hyperalgesia, which was completely neutralized by THC-morphine. A slight additive analgesic effect could be observed for THC-morphine in the electrical stimulation test. No analgesic effect resulted in the pressure and heat test, neither with THC nor THC-morphine. Psychotropic and somatic side-effects (sleepiness, euphoria, **anxiety**, confusion, nausea, dizziness, etc.) were common, but usually mild.

Adverse Event Surveillance

In 1994, the Drug Abuse Advisory Committee (DAAC) of the Food and Drug Administration (FDA) concluded that Ultram (tramadol hydrochloride) could be marketed as an analgesic drug without scheduling under the Controlled Substances Act based upon extensive pre-clinical, clinical and European epidemiological data. However, to guard against unexpectedly

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[123] Jensen LL, Handberg G, Helbo-Hansen HS, Skaarup I, Lohse T, Munk T, Lund N. (2008). No morphine sparing effect of ketamine added to morphine for patient-controlled intravenous analgesia after uterine artery embolization. Acta Anaesthesiologica Scandinavica; 52(4):479-86.

[124] Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. (2003). The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain; 105(1-2):79-88.

high levels of abuse in the United States, the DAAC recommended that an independent steering committee (ISC) be appointed to proactively monitor abuse/dependence. In the event that high rates of abuse were found, this ISC was given the authority to immediately recommend to the FDA that Ultram be scheduled.

TABLE 38 FEATURES AND SYMPTOMS OF TYPICAL AND ATYPICAL WITHDRAWAL FROM ULTRAM (SENAY ET AL, 2003).

Typical opioid withdrawal[a] ($N = 367$)	Atypical withdrawal[b] ($N = 55$)	% Frequency[c]
Abdominal cramps Anxiety	Severe anxiety and panic attacks	32.8
Bone pain Depression Diarrhea Goose flesh Insomnia Lacrimation Nausea Restlessness Rhinorhea Sweating	Unusual CNS symptoms Confusion Delusions Depersonalization Derealization Paranoia	27.2
	Unusual sensory phenomena Numbness Tingling Parathesia Tinnitus	25.4
	Hallucinations Tactile Visual Auditory	20.0

[a] DSM-IV requires that 3 or more of these symptoms are present to meet the definition ofwithdrawal or physical dependence.

[b] Often combined with typical opioid withdrawal signs and symptoms. Listed in order of decreasing prevalence.

[c] Total adds to more than 100% since multiple signs were frequently reported.

Senay, Adams, Geller, Inciardi et al (2003)[125] reported that in the course of the surveillance project, the ISC received reports of withdrawal following abrupt discontinuation of Ultram and in some instances, following dose reductions. In most cases, the withdrawal symptoms consisted of classical opioid withdrawal, but in some cases were accompanied by withdrawal

[125] Senay EC, Adams EH, Geller A, Inciardi JA, Munoz A, Schnoll SH, Woody GE, Cicero TJ. (2003). Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. Drug & Alcohol Dependence; 69(3):233-41.

symptoms not normally observed in opiate withdrawal, such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion and unusual sensory experiences such as numbness and tingling in one or more extremities (see Table above). Withdrawal symptoms of either type were one of the more prevalent adverse events associated with chronic Ultram use, comprising nearly 40% of all adverse events reported with Ultram. Most of these consisted of typical opiate withdrawal symptoms, but 1 in 8 cases presented as atypical. These results indicate that physicians and other healthcare professionals need to be aware of the potential of Ultram to induce withdrawal of the classical opioid type, and that atypical withdrawal may also occur.

Cross-sectional studies

Ahmadi and Ahmadi (2005)[126] evaluated the rate of current substance-induced anxiety disorder in opioid dependents. It was designed to determine the prevalence of DSM-IV-based substance-induced anxiety disorder, generalized anxiety disorder, and substance- induced depression. The settings were private and government clinics. Five hundred unpaid opioid dependents who voluntarily sought treatment participated in the study. They utilized the research version of the structured clinical interview for DSM-IV Axis I Disorders (SCID-I).

The mean age of the subjects (487 men and 13 women) was 33.4 years, ranging from 16 to 67. The majority (341, 68.2%) had voluntary jobs or were self-employed, and 67 (13.4%) were unemployed. The majority (299, 59.8%) had education at the level of primary, secondary, or high school, and only 19 (3.8%) were illiterate. **Of the subjects, 105 (21%) had substance-induced anxiety disorder**, 11 (2.2%) had generalized anxiety disorder, and 274 (54.8%) had substance-induced depression. Of the subjects 319 (63.8%) reported more than 5 years use of opioid. Of the patients, only 16 (3.2%) reported no episode of abstinence, and the majority (484, 96.8%) reported one or more episodes of abstinence. About 4.2% (21) reported less than 1 g per day, and the majority (86.4%, 432) reported between 1 to 5 g per day current use of opioids.

TABLE 39 FREQUENCY DISTRIBUTION OF OPIOID DEPENDENTS BY CURRENT ANXIETY DISORDER AND DEPRESSION (AHMADI & AHMAD, 2005).

Anxiety Disorder/Depression	*N*	%
Substance-induced anxiety disorder	105	21
Generalized anxiety disorder	11	2.2
Substance-induced depression	274	54.8
Total	336	67.2

Ahmadi, Farrashbandi, Menzies, Majdi et al (2005)[127] assessed the rate of current mood disorders and anxiety disorders in outpatient opioid addicts. The data were collected from five hundred unpaid opioid-dependent patients who were seeking treatment and referred to private

[126] Ahmadi M, Ahmadi J (2005). Substance-induced anxiety disorder in opioid dependents. Addictive Disorders & Their Treatment, 4(4): 157-9. 077733

[127] Ahmadi J, Farrashbandi H, Majdi B, et al (2005). Prevalence of mood and anxiety disorders in a sample of Iranian outpatient opioid addicts. German Journal of Psychiatry, 8(1): 5-7. 078094

and government clinics. The Research version of structured clinical interview for DSM-IV Axis I Disorders (SCID-I) was used.

The mean age of the subjects (487 men and 13 women) was 53.4 yr., ranging from 16 to 67. The majority (68.2%) had private sector job and 13.4% were unemployed. Most of them (59.8%) had education at the level of primary, guidance or high school and only 3.8% were illiterate. Three hundred and thirty-six (67.2%) subjects were diagnosed as having mood disorders, of those 274 (54.8%) had substance induced depression, 37 (7.4%) major depression, 14 (2.8%) dysthymia, 5 (1%) depression due to general medical condition, 3 (0.6%) cyclothymia, (0.6%) bipolar mood disorder, type I, and none was diagnosed as having bipolar mood disorder, type II. **One hundred and five (21%) subjects were diagnosed as having substance-induced anxiety disorders**, and 11 (2.2%) as generalised anxiety disorders. Of the participants 319 (63.8%) reported more than 5 years use of opioid abuse. Of the subjects only 16 (3.2%) reported no episode of abstinence and the majority 484 (96.8%) reported one or more episodes of abstinences. About 4.2% (21) reported less than 1 gm per day and the majority 86.4% (432) reported between 1 to 5 gm per day current use of opioid. Due to high rates of mood disorders in opioid-dependent subjects, psychiatric services should be open and accessible to the patients, especially those who voluntarily seek help and treatment.

Case report

Sansone and Sansone (2002)[128] report two cases where two middle-aged females developed panic attacks after vicodin use and in one case, repeat panic attacks when she was re-exposed at a later time. Both cases had a history of panic disorder.

Case One

Mrs. M., a 45-year-old, white, married female had a 4-year history of panic disorder, with attacks characterized by tachycardia, flushing, diaphoresis, nausea, tremulousness, intense anxiety, fears of “going crazy,” and wanting to “run away.” Attacks did not include light-headedness, respiratory changes, paresthesias, chest tightness, or depersonalization. The attacks were 10–15 minutes in duration, accompanied by agoraphobia (particularly fears of leaving home at night), and precipitated by psychosocial stressors. Mother and two brothers were diagnosed with panic disorder; father was alcoholic and committed suicide. In the developmental history, there was no separation anxiety, or sexual or physical abuse. However, the patient underwent ongoing emotional abuse as well as witnessed violence in the home (step-father) during junior and senior high school.

The patient experienced a single episode of major depression following a miscarriage at age 26. Mrs. M. had undergone several surgical procedures during her lifetime including two Caesarian sections, hysterectomy and surgical revision, D&C, removal of wisdom teeth, and laparoscopy for endometriosis. When panic symptoms began four years ago, the patient was treated with sertraline 100 mg per day with robust results.

During an outpatient procedure for the removal of a lipoma, the patient received Vicodin for pain control. During the first 48 hours, Mrs. M. received a total of 5 doses of the analgesic, and no more, thereafter. At 96 hours, she began to experience panic attacks, identical in character

[128] Sansone RA, Sansone LA. (2002). Exacerbation of panic disorder symptoms following Vicodin exposure. General Hospital Psychiatry; 24(6):448-9.

to the prior attacks. The attacks continued for several days but remitted within 24 hours following intervention with lorazepam 0.5 mg, which was continued for 5 doses every 12 hours.

Case Two

Mrs. S., a 41-year-old, white, married female, experienced the onset of panic attacks at age 17. Attacks, 10–15 minutes in duration, were characterized by chest tightness, tachycardia, diarrhea, diaphoresis, dyspnea, intense anxiety, tremulousness, “a rush of adrenaline,” derealization, flushing, apprehension, fears of going crazy, and a sense of doom. The patient denied lightheadedness or nausea, but described agoraphobic symptoms (i.e., fears of leaving home, traveling on the highway, being in a plane). As with the first patient, Mrs. S. experienced exacerbation of panic symptoms with psychosocial stressors. Father reported panic attacks during his college years. Mrs. S. experienced some separation anxiety as a child. As an adolescent, Mrs. S. had subsyndromal anorexia nervosa. Mrs. S. had undergone several surgeries including a hysterectomy, two Caesarian sections, excision of breast lumps, tubal ligation, appendectomy, laparoscopy, and hemorrhoidectomy. Initially, the patient had been treated for panic disorder with daily clonazepam for years, which was weaned and limited to an as-needed basis. Mrs. S. was taking sertraline 50 mg per day, in addition to as-needed clonazepam (one-half of a 0.5 mg tablet, 20 doses per year) with total symptom remission.

Three years ago, following a fall, Mrs. S. was evaluated in the emergency room and diagnosed with a bruised arm. She was prescribed Vicodin and after administration, began to experience sub-threshold panic symptoms (i.e., intense anxiety, unable to sit down, pacing). The patient stopped the analgesic and symptoms receded in several hours. Three years later, the patient was unknowingly prescribed Vicodin following carpal tunnel surgery. After two doses, 6 hours apart, the patient experienced the same symptoms, which lasted about one hour, as with the previous exposure. Mrs. S. did not take any more Vicodin and symptom remission was complete.

Summary and Recommendation

Three clinical trials (Wallace et al, 2008; Jensen et al, 2008; Naef et al, 2003) which assessed the efficacy and side effects of opioid medication combined with other therapies (ziconotide, ketamine and THC). Anxiety was reported as a side effect of the combined drugs.

An adverse event survey (Senay et al, 2003) reported anxiety and panic attacks as symptoms of tramadol withdrawal and reduction of dose, in some circumstances.

Ahmadi and Ahmadi (2005) and Ahmadi et al (2005) reported high rates of substance-induced anxiety in opioid-dependant participants in their cross-sectional studies.

Sansone and Sansone (2002) detailed 2 cases of women with well-controlled panic disorder who developed acute and dramatic exacerbations of panic symptoms following exposure to Vicodin.

Grade 2 level evidence

Cannabis

Systematic reviews

Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

Whiting, Wolff, Deshpande, Di Nisio, Duffy, Hernandez et al (2015)[129] conducted a systematic review of the benefits and adverse events (AEs) of cannabinoids. Twenty-eight databases from inception to April 2015 were searched. Randomized clinical trials of cannabinoids for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, **anxiety** disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome.

Study quality was assessed using the Cochrane risk of bias tool. All review stages were conducted independently by 2 reviewers. Where possible, data were pooled using random-effects meta-analysis.

Patient-relevant/disease-specific outcomes, activities of daily living, quality of life, global impression of change, and AEs. In regards to substance-induced anxiety symptoms, the table below reports that 12 studies (N=1 242) using cannabinoids vs placebo reported anxiety symptoms but the results were not significant Summary OR 1.98 (95% CI 0.73-5.35) with moderate heterogeneity (I^2 = 54%).

[129] Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al (2015). Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA;313(24):2456-73.

TABLE 40 SUMMARY ESTIMATES FROM META-ANALYSES FOR EACH AE ASSESSED: ODDS OF PARTICIPANTS EXPERIENCING AE WITH CANNABINOID VS PLACEBO OR ACTIVE COMPARISON (WHITING ET AL, 2015).

	No. of Studies (No. of Patients)	Summary OR (95% CI)	I^2, %
General AE categories			
Any	29 (3714)	3.03 (2.42-3.80)	31
Serious	34 (3248)	1.41 (1.04-1.92)	0
Withdrawal due to AE	23 (2755)	2.94 (2.18-3.96)	2
MedDRA high-level grouping[164]			
Gastrointestinal disorders	10 (1960)	1.78 (1.43-2.22)	0
Infections and infestations	7 (1681)	1.13 (0.87-1.46)	0
Psychiatric disorders	8 (1672)	3.10 (1.81-5.29)	55
Nervous system disorders	10 (1521)	3.17 (2.20-4.58)	46
Musculoskeletal and connective tissues disorders	7 (1310)	1.32 (0.75-2.32)	34
General disorders and administration site conditions	6 (1208)	1.78 (1.34-2.36)	0
Death	5 (929)	1.01 (0.51-2.00)	0
Ear and labyrinth disorders	3 (922)	2.72 (1.55-4.75)	0
Respiratory, thoracic, and mediastinal disorders	5 (851)	0.80 (0.46-1.39)	0
Cardiac disorders	7 (833)	1.42 (0.58-3.48)	0
Blood disorders	3 (543)	1.42 (0.20-10.25)	18
Injury, poisoning and procedural complications	3 (543)	1.18 (0.48-2.93)	0
Renal and urinary disorders	3 (470)	2.45 (2.27-2.65)	0
Investigations	2 (427)	1.55 (0.36-6.71)	0
Metabolism and nutrition	2 (427)	2.37 (1.00-5.61)	0
Neoplasms, benign, malignant, and unspecified	2 (427)	0.99 (0.47-2.08)	0
Skin and subcutaneous	3 (405)	0.85 (0.34-2.13)	0
Eye disorders	1 (339)	1.42 (0.46-4.33)	NA
Reproductive system	1 (246)	1.55 (0.20-11.92)	NA
Hepatobiliary disorders	1 (181)	3.07 (0.12-76.29)	NA
Mental status change	3 (106)	2.49 (0.49-12.64)	0
Other body systems	1 (42)	2.59 (0.34-19.47)	NA
Injection site pain	1 (32)	2.49 (0.92-6.68)	NA
Individual AEs			
Dizziness	41 (4243)	5.09 (4.10-6.32)	18
Dry mouth	36 (4181)	3.50 (2.58-4.75)	28
Nausea	30 (3579)	2.08 (1.63-2.65)	0
Fatigue	20 (2717)	2.00 (1.54-2.62)	0
Somnolence	26 (3168)	2.83 (2.05-3.91)	27
Euphoria	27 (2420)	4.08 (2.18-7.64)	49
Depression	15 (2353)	1.32 (0.87-2.01)	0
Vomiting	17 (2191)	1.67 (1.13-2.47)	0
Diarrhea	17 (2077)	1.65 (1.04-2.62)	15
Disorientation	12 (1736)	5.41 (2.61-11.19)	0
Asthenia	15 (1717)	2.03 (1.35-3.06)	0
Drowsiness	18 (1272)	3.68 (2.24-6.01)	44
Anxiety	12 (1242)	1.98 (0.73-5.35)	54
Confusion	13 (1160)	4.03 (2.05-7.97)	0
Balance	6 (920)	2.62 (1.12-6.13)	0
Hallucination	10 (898)	2.19 (1.02-4.68)	0
Dyspnea	4 (375)	0.83 (0.26-2.63)	0
Paranoia	4 (492)	2.05 (0.42-10.10)	0
Psychosis	2 (37)	1.09 (0.07-16.35)	25
Seizures	2 (42)	0.91 (0.05-15.66)	0

Abbreviations: AE, adverse event; I^2, measures of heterogeneity; NA, not applicable; OR, odds ratio; MedDRA, medical dictionary for regulatory activities.

A total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. There was an increased risk of short-term AEs

with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

Cannabinoids were associated with an increased risk of short-term AEs, including anxiety, however, the results were not statistically significant.

Reviews

Hoch, Bonnet, Thomasius et al (2015)[130] conducted a selective literature review based on a search of the PubMed database, with special emphasis on systematic reviews, meta-analyses, cohort studies, randomised controlled trials (RCTs), case-control studies, and treatment guidelines.

The delta-9-tetrahydrocannabinol content of cannabis products is rising around the world as a result of plant breeding, while cannabidiol, in contrast, is often no longer detectable. Various medical conditions can arise acutely after cannabis use, depending on the user's age, dose, frequency, mode and situation of use, and individual disposition; these include panic attacks, psychotic symptoms, deficient attention, impaired concentration, motor incoordination, and nausea. In particular, intense use of high doses of cannabis over many years, and the initiation of cannabis use in adolescence, can be associated with substance dependence (DSM-5; ICD-10), specific withdrawal symptoms, cognitive impairment, affective disorders, psychosis, **anxiety** disorders, and physical disease outside the brain (mainly respiratory and cardiovascular conditions). At present, the most effective way to treat cannabis dependence involves a combination of motivational encouragement, cognitive behavioural therapy, and contingency management (level 1a evidence). For adolescents, family therapy is also recommended (level 1a evidence). No pharmacological treatments can be recommended to date, as evidence for their efficacy is lacking.

Hoch et al (2015) state, “For cannabis withdrawal syndrome to be diagnosed, at least two mental symptoms (e.g., irritability, restlessness, anxiety, depression, aggressiveness, loss of appetite, sleep disturbances) and at least one vegetative symptom (e.g., pain, shivering, sweating, elevated body temperature, chills) must be present. The symptoms are at their most intensive in the first week and can persist for as long as a month. Clinically, withdrawal from cannabis is usually uncomplicated” (p. 272).

“More evidence exists for a connection between cannabis use and anxiety disorders, particularly panic disorders. The risk of an anxiety disorder was significantly elevated in persons who consumed cannabis weekly up to the age of 29 years (OR 3.2, 95% CI 1.1 to 9.2) (e60) (evidence level: 2b). Furthermore, epidemiological investigations have revealed a 2.5– to 6-fold risk of anxiety disorders in those dependent on cannabis” (p. 275).

[130] Hoch E, Bonnet U, Thomasius R, Ganzer F, Havemann-Reinecke U, Preuss UW. Risks associated with the non-medicinal use of cannabis. Dtsch Arztebl Int. 2015 Apr 17;112(16):271-8. doi: 10.3238/arztebl.2015.0271.

TABLE 41 SIGNS AND SYMPTOMS OF ACUTE CANNABINOID INTOXICATION (HOCH ET AL, 2015).

Acute cannabinoid intoxication

Dysfunctional behavior or distorted perceptions can be recognized by the presence of at least one of the following:

1. Euphoria and disinhibition
2. Anxiety or agitation
3. Mistrust or paranoid delusions*
4. Altered sense of time (a feeling that time is passing extremely slowly or a feeling of racing thoughts)
5. Limited power of judgment
6. Attention disorder
7. Impaired reaction time
8. Acoustic, optic, or tactile illusions
9. Hallucinations without lack of orientation
10. Depersonalization
11. Derealization
12. Impaired personal performance

Moreover, at least one of the following signs may be present:
Appetite loss, dry mouth, conjunctival injection, tachycardia

*May persist for as long as a week; the other symptoms subside within a few hours of cannabis consumption

Further research is needed to elucidate the causal relationships between intense cannabis use and potential damage to physical and mental health.

Vorspan, Mehtelli, Dupuy et al (2015)[131] provided the most recent literature results on the association of substance use disorders (SUDs) and anxiety, and evidence for one explicative model or the other when available. For substances with sedative properties (alcohol, benzodiazepines, cannabis, opioids), both evidence for a self-medication and for a toxic effect exist. For substances with psychostimulant properties (tobacco, cocaine, and amphetamines), the literature favours the toxic hypothesis to explain the association with anxiety disorders. We give practical steps for the recognition of these dual diagnoses and present therapeutic issues, although the strategies are rarely evidence based.

The co-occurrence of SUDs and anxiety disorders has been now well established. This association is frequent and can be explained by three models: the shared vulnerability factors model, the self-medication model, and the substance-induced model. General population epidemiological studies provide strong evidence of the frequency of the association for the most used substances: tobacco, alcohol, cannabis, and to a lesser extent sedatives, opiates,

[131] Vorspan F, Mehtelli W, Dupuy G, Bloch V, Lépine JP. (2015). Anxiety and substance use disorders: co-occurrence and clinical issues. Curr Psychiatry Rep. 2015 Feb;17(2):4. doi: 10.1007/s11920-014-0544-y.

and cocaine. For substances that are less commonly used in the general population, the frequency of the co-occurrence can more precisely be studied in clinical samples.

According to Vorspand et al (2015), "The association between anxiety disorders and SUD is now well established. Epidemiological studies from the general population have demonstrated a high rate of association with AUD, tobacco smoking, cannabis UD, sedative dependence, prescription opioids, and cocaine UD. Studies conducted in clinical samples allow a deeper investigation on the direction of the co-occurrence. Alcohol, like cannabis, benzodiazepines, and opiates, all of them sedative compounds, is at the same time a self-medication and a cause of anxiety disorders. There are more pieces of evidence that tobacco smoking and cocaine, both stimulants, provoke anxiety disorders, especially panic disorder. Whatever their direction, those dual diagnoses have bad prognoses and are poorly responsive to usual treatments" (Conclusion section, no page no.).

Coscas, Benyamina, Reynaud, Karila (2013)[132] [Article in French]

Cannabis is the most widely used illicit substance, especially among young people. Cannabis use is extremely commonplace and frequently comorbid with psychiatric disorders that raise questions about the etiology. The use of cannabis is an aggravating factor of all psychiatric disorders. Psychiatric complications are related to the age of onset, duration of exposure and individual risk factors of the individual (mental and social health). The panic attack is the most common complication. The link with psychosis is narrow that leads to increased prevention for vulnerable populations. Cannabis is also an indicator of increased depressive vulnerability and an aggravating factor for bipolar disorder.

Karila, Roux, Rolland, et al (2014)[133] reported that cannabis can frequently have negative effects in its users, which may be amplified by certain demographic and/or psychosocial factors. Acute adverse effects include hyperemesis syndrome, impaired coordination and performance, anxiety, suicidal ideations/tendencies, and psychotic symptoms. Acute cannabis consumption is also associated with an increased risk of motor vehicle crashes, especially fatal collisions. Evidence indicates that frequent and prolonged use of cannabis can be detrimental to both mental and physical health. Chronic effects of cannabis use include mood disorders, exacerbation of psychotic disorders in vulnerable people, cannabis use disorders, withdrawal syndrome, neurocognitive impairments, cardiovascular and respiratory and other diseases.

Polysubstance use

Zvolensky, Bernstein, Marshall and Feldener (2006)[134] briefly reviewed and summarised key aspects of this literature, with a specific focus on panic-spectrum psychopathology (panic attacks, panic disorder, and agoraphobia) and its associations with tobacco, alcohol, and marijuana use, abuse, and dependence. A heuristic theoretical model for better understanding the panic-substance use relations also is offered. Extant data suggest clinically meaningful

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[132] Coscas S, Benyamina A, Reynaud M, Karila L. [Psychiatric complications of cannabis use]. Rev Prat. 2013 Dec;63(10):1426-8. [Article in French] **Abstract only**

[133] Karila L, Roux P, Rolland B, Benyamina A, Reynaud M, Aubin HJ, Lançon C1. Acute and long-term effects of cannabis use: a review. Curr Pharm Des. 2014;20(25):4112-8.

[134] Zvolensky MJ, Bernstein A, Marshall EC, Feldner MT (2006). Panic attacks, panic disorder, and agoraphobia- Associations with substance use, abuse, and dependence. Curr Psych Reports, 8- 279-85. 049075

bidirectional associations are evident between panic problems and premorbid risk factors for such problems and various forms of tobacco, alcohol, and marijuana use.

Cohort studies

Patton, Coffey, Carlin et al (2002)[135] conducted a prospective cohort study to determine whether cannabis use in adolescence predisposes to higher rates of depression and anxiety in young adulthood. The study was a seven wave cohort study over six years set in 44 schools in the Australian state of Victoria. Participants consisted of a statewide secondary school sample of 1601 students aged 14-15 followed for seven years. The main outcome measure reported was the Interview measure of depression and anxiety (revised clinical interview schedule) at wave 7.

Some 60% of participants had used cannabis by the age of 20; 7% were daily users at that point. Daily use in young women was associated with an over fivefold increase in the odds of reporting a state of depression and anxiety after adjustment for intercurrent use of other substances (odds ratio 5.6, 95% confidence interval 2.6 to 12). Weekly or more frequent cannabis use in teenagers predicted an approximately twofold increase in risk for later depression and anxiety (1.9, 1.1 to 3.3) after adjustment for potential baseline confounders. In contrast, depression and anxiety in teenagers predicted neither later weekly nor daily cannabis use.

Patton and colleagues followed a sample of Australian secondary students (aged 14–15 years) over seven years and found that 68 per cent of daily cannabis users suffered from a mixed state of depression and anxiety. This translated to a fourfold increased risk of depression and anxiety compared to non-users, after controlling for other drug use, pre-existing symptoms and antisocial behaviour (Patton *et al.* 2002). However, these findings were only evident for females in the sample.

Frequent cannabis use in teenage girls predicts later depression and anxiety, with daily users carrying the highest risk. Given recent increasing levels of cannabis use, measures to reduce frequent and heavy recreational use seem warranted. Frequent recreational use of cannabis has been linked to high rates of depression and anxiety in cross sectional surveys and studies

A strong association between daily use of cannabis and depression and anxiety in young women persists after adjustment for intercurrent use of other substances. Frequent cannabis use in teenage girls predicts later higher rates of depression and anxiety. Depression and anxiety in teenagers do not predict later cannabis use; self medication is therefore unlikely to be the reason for the association.

Zvolensky, Bernstein, Sachs-Ericsson et al (2006)[136] evaluated lifetime associations between cannabis use, abuse, and dependence and panic attacks after controlling for alcohol abuse, polysubstance use, and demographic variables.

Data for this study were obtained as part of a large statewide survey, the Colorado Social Health Survey (CSHS). Participants were contacted using randomly sampled household

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[135] Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M and Hall W (2002). Cannabis use and mental health in young people- cohort study. BMJ, 325(7374) pp 1195-1198. 025590

[136] Zvolensky MJ, Bernstein A, Sachs-Ericsson N, Schnmidt NB, et al (2006). Lifetime associations between cannabis, use, abuse, and dependence and panic attacks in a representative sample. Journal of Psychiatric Research, 40(6)- 477-8. 048511 -

addresses (72% response rate) and interviews took place in participants' homes. Participants consisted of a representative sample from the Colorado general adult population (ii = 4745; 52% female). The Diagnostic Interview Schedule was administered to obtain diagnoses.

After controlling for polysubstance use, alcohol abuse, and demographic variables, lifetime history of cannabis dependence, but not use or abuse, was significantly related to an increased risk of panic attacks. Additionally, among participants reporting a lifetime history of both panic attacks and cannabis use, the age of onset of panic attacks (M = 19.0 years of age) was significantly earlier than for individuals with a lifetime panic attack history but no cannabis use (M = 27.6 years of age).

Structured interview data suggest lifetime cannabis dependence is significantly associated with an increased risk of panic attacks.

Summary and Recommendation

While the systematic review by Whiting et al (2015) reported a non-significant summary OR for anxiety symptoms as an adverse event of cannabis use, other studies were supportive of an association. Hoch et al's (2015) review supported a strong association between cannabis use and anxiety disorders, in regard to intoxication, dependence and withdrawal. Vorspan et al (2015) also supported the finding of Hoch and colleagues. Two other reviews Coscas et al (2013) and Karila et al (2014) reported that panic attack is a common adverse event associated with cannabis use. The Australian prospective cohort study of adolescents (Patton et al, 2002) reported a strong association between daily use of cannabis and depression and anxiety in young women, not in young men. The study by Zvolensky et al (2006) suggests that lifetime cannabis use is significantly associated with panic attacks.

Overall the evidence is supportive of an association – Grade 2 level evidence

Synthetic Cannabinoids

Review Studies

Synthetic cannabinoids

Brewster and Collins (2014)[137] conducted a review to heighten the awareness of the increased use and risks of synthetic cannabinoids (SCs) and associated clinical manifestations among adolescents and young adults.

Reviewed case studies suggest that the use of SCs have unpredictable negative psychological and physiological effects. Predominant manifestations reported were anxiety, agitation, paranoia, hallucinations, tachycardia, nausea and vomiting, and diaphoresis.

Synthetic cannabinoids (SC) are a heterogeneous group of compounds developed to probe the endogenous cannabinoid system or as potential therapeutics. Clandestine laboratories subsequently utilized published data to develop SC variations marketed as abuseable "designer drugs." In the early 2000's, SC became popular as "legal highs" under brand names such as "Spice" and "K2," in part due to their ability to escape detection by standard cannabinoid screening tests. The majority of SC detected in herbal products have greater binding affinity to the cannabinoid CB1 receptor than does Δ9-tetrahydrocannabinol (THC), the primary psychoactive compound in the cannabis plant, and greater affinity at the CB1 than the CB2 receptor. In-vitro and animal in-vivo studies show SC pharmacological effects 2-100 times more potent than THC, including analgesic, anti-seizure, weight-loss, anti-inflammatory, and anti-cancer growth effects. SC produce physiological and psychoactive effects similar to THC, but with greater intensity, resulting in medical and psychiatric emergencies.

According to **Castaneto, Gorelick. Desrosiers et al (2014)**[138] in their review of the published literature, human adverse effects include nausea and vomiting, shortness of breath or depressed breathing, hypertension, tachycardia, chest pain, muscle twitches, acute renal failure, anxiety, agitation, psychosis, suicidal ideation, and cognitive impairment (see Table below). Long-term or residual effects are unknown. Due to these public health consequences, many SC are classified as controlled substances. However, frequent structural modification by clandestine laboratories results in a stream of novel SC that may not be legally controlled or detectable by routine laboratory tests.

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[137] Brewer TL, Collins M. A review of clinical manifestations in adolescent and young adults after use of synthetic cannabinoids. J Spec Pediatr Nurs. 2014 Apr;19(2):119-26. doi: 10.1111/jspn.12057. Epub 2013 Dec 10.

[138] Castaneto MS, Gorelick DA, Desrosiers NA, et al (2014). Synthetic cannabinoids: epidemiology, pharmacodynamics and clinical implications. Drug Alcohol Depend, 1: 12-41. 078332

TABLE 42 SYNTHETIC CANNABINOID (SC) ACUTE AND SUB-ACUTE INTOXICATION DOCUMENTED FROM CASE REPORTS/SERIES AND RETROSPECTIVE CASE REVIEWS (CASTENETO ET AL, 2014).

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	11	M	13-27	Spice	UNK	tachycardia(6), anticholinergic toxidrome(4), agitation/irritability(4), tremor(4), confusion(3), pallor(2), mydriasis(2), hypertension(2)	UNK	UNK	(−)UDS(3); SC not tested for all	BDP(3), supportive care (10)	(Banerji et al., 2010)
USA	1	M	18	K2 Summit	30gm (sm)	tremors, blurred vision, nausea, vomiting, incoherent speech	30 min	4.5h	(−)UDS, 0.5μg/L JWH-018(serum)	anti-emetics, IVF	(Canning et al., 2010)
Germany	1	M	21	UNK	40mg (sm)	blurred vision, unsteady gait, excessive sweating, heart palpitations, anxiety	"within min"	<24h	(−)UDS	lorazepam (2mg, IV), IVF	(Müller et al., 2010)
Russia	3	2M 1F	22±1	Tropical Synergy	~1g each	reddened conjunctivae, tachycardia, anxiety, paranoia, hallucinations, short-term memory & sense of time impairment	UNK	UNK	(−)UDS, (+)JWH-018 metabolites (urine)	UNK	(Sobolevsky et al., 2010)
USA	1	F	17	JWH-018	UNK (sm)	"violent" & "crazy", hallucinations, lower extremities numbness, muscle twitches, elevated pulse, dilated pupils	15 min	2h	(+)THC (urine), SC not tested	lorazepam (2mg, IV)	(Vearrier and Osterhoudt, 2010)
USA	1	M	20	Spice	UNK (sm)	anxiety, tachycardia, diaphoresis	UNK	UNK	(−)UDS, SC not tested	supportive care	(Benford and Caplan, 2011)
USA	11	10M 1F	15-19	UNK	UNK (sm)	euphoria(11), irritability(4), anxiety(3), numbness(2), anger(1), sadness(1), memory impairment(11), change of auditory(1) & visual (5) perception, paranoia(2), palpitations(3), muscle trembles(1) & weakness(1), blackouts(1), restlessness(1), stimulation(10	UNK	UNK	UNK	UNK	(Castellanos et al., 2011)

Table Continued

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
Germany	13	12M 1 F	14-28	Spice, Smoke, Jamaican Gold, Monkees-go bananas, Ninja	UNK (sm)	shaking, acute psychosis, seizers, muscle jerking, muscle pains, hypokalemia	UNK	UNK	(+)JWH-018(7), JWH-081(4), JWH-122(4); all serum, concentration UNK	UNK	(Hermanns-Clausen et al., 2011)
USA	10	M	21-25	UNK	UNK (sm)	auditory hallucinations(4), paranoid delusions(9), odd or flat affect(6), blocked thoughts(4), disorganized speech(6) & behavior(7), alogia(3), suicidal ideation(4), insomnia(6), psychomotor retardation(6) & agitation(3), anxiety(2)	UNK	UNK	(+)THC(4), (−)UDS(6), SC not tested	antipsychotics (7), hospitalizetion (6-10d)	(Hurst et al., 2011)
USA	1	M	23	Spice	UNK (sm)	nonsensical speech, paranoia, disorganized thoughts	<48h	<72h	(−)UDS	psychiatric referral, supportive care	(Johnson et al., 2011)
USA	1	M	48	JWH-018 (powder)	UNK (po with ETOH)	seizure, tachycardia, refractory supraventricular tachycardia (1 day later)	30min	<48h	(−)UDS, 74.3µg/L JWH-018 pentanoic (urine)	lorazepam (IV), electrocardioversion; ET intubation	(Lapoint et al., 2011)
Italy	10	UNK	14-55	Spice, N-joy, Forest Green (contained JWH-122)	UNK	agitation (7), confusion (6), hallucination (4), dyspnea (1), coma(2), seizure(1), mydriasis(2), xerostomia(2), vertical nystagmus(1), psychomotor agitation(2), vomiting (1)	UNK	<24h	(+)JWH-018 (blood), (+)JWH-250 (blood & urine); number of samples UNK	UNK	(Locatelli et al., 2011)
USA	1 1 1	M M M	16 16 16	K2 K2 K2	UNK (sm) UNK (sm) UNK (sm)	chest pain for 3d, diagnosed with elevated ST-segment & troponin (25µg/L) intermittent chest pain × 3d lasting ~30min, diagnosed with elevated ST-segment & troponin (11.6µg/L) intermittent chest pain × 3d lasting1-2h, elevated troponin (12µg/L)	1d after sm within 1 wk after sm 4d after sm	3d UNK 1 wk	(+)THC, SC not tested (−)UDS, SC not tested (+)THC, (+)JWH-018, JWH-073 metabolites (urine)	supportive care, coronary angiography supportive care, coronary angiography supportive care	(Mir et al., 2011)
USA	9	UNK	UNK	UNK	UNK	tachycardia, hypokalemia, agitation/irritability, hallucination, pallor, nausea, mydriasis	UNK	8-24h	(−)UDS, (+)JWH-018, JWH-073 metabolites (urine)	BDP, IVF, anti-emetics, potassium supplement	(McCain et al., 2011)

Table Continued

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	3	UNK	UNK	Bad Mojo	UNK (sm)	psychosis	UNK	>12h	UNK	supportive care	(Rodgman et al., 2011)
USA	2	F	20, 22	Banana Cream Nuke	½ packet (sm)	anxiety, palpitations/tachycardia	"shortly after smoking"	1h	(−)UDS, SC not tested	supportive care	(Schneir et al., 2011)
USA	1 1 1	M M M	25 23 19	UNK UNK UNK	UNK (sm) UNK (sm) UNK (sm)	"eyes-crossed & flailing arms", unresponsive to verbal stimuli, dilated pupils unresponsive, muscle spasm, depressed breathing paranoia, delusions, short-term memory impairment	45min UNK 1h	3h <24h <24h	(−)UDS, (+)JWH-018 metabolites (urine) (−)UDS, (+)JWH-018, JWH-073 metabolites (urine) (−)UDS, (+)JWH-018 & JWH-073 metabolites	lorazepam (4mg, IV), IVF airway management, ICU admission, 5 mg haloperidol supportive care	(Simmons et al., 2011)
USA	1	M	17	K9 Pure Fire (contained JWH-073, JWH-018)	UNK (sm)	Hallucinations, dizziness, difficulty breathing, tachycardia, chest pressure that lasted for 3 days	10 min	<24h	(−)UDS, SC not tested	nitroglycerin, supportive care	(Young et al., 2011)
USA	1 1 1	M F M	19 19 23	Space Space Spice	UNK (sm) UNK (sm) UNK (sm)	paranoia, hallucinations, agitation, tachycardia, hyperglycemia mild drowsiness, short-term memory impairment, hyperglycemia anxiety, agitation, breathing difficulty, hyperventilation, tachycardia, injected sclera	2h UNK UNK	<6h <6h	(−)UDS, SC not tested (−)UDS, (+)APAP, (+)DXM, (+) doxylamine, (+)levorphenol, SC not tested (−)UDS, SC not tested	lorazepam (2mg, IV) supportive care lorazepam. IVF, anti-emetic	(Bebarta et al., 2012)
USA	1 1 1	F M M	16 18 16	K2 Spice Spice	UNK (sm) UNK (sm) UNK (sm)	catatonia, tachycardia, (+) vertical nystagmus headache, dizziness, profuse sweating, agitation, aggression, restlessness, tachycardia, hyperventilation disorientation, agitation, slowed speech	UNK UNK UNK	<24h <24h <24h	(−)UDS, SC not tested (−)UDS, SC not tested (−)UDS, SC not tested	diphenhydramine (50mg, IV), lorazepam (2mg IV × 2 dose) diphenhy-dramine (50mg, IV), lorazepam (2mg, IV) lorazepam (4mg IV), IVF	(Cohen et al., 2012)

Table Continued

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	1	M	17	K2	UNK (sm)	dizziness, confusion, lethargy, vomiting, tachycardia	"immediately after 1 inhalation"	UNK	(−)UDS, SC not tested	IVF, naloxone (2mg, IV), supportive care	(Faircloth et al., 2012)
USA	3	M	20-30	K2, XXX, K2 Blond, Black Box, Smoke n' Skulls, Zombie, Blueberry	3g/d (sm)	similar(1) or elevated "high" than cannabis(2)	UNK	UNK	UNK	UNK	(Gunderson et al., 2012)
USA	1 1	F F	19 17	Bayou Blaster® Humboldt Gold	UNK (sm)	jerking motions of extremities, agitation, altered mental status, somnolence, tachycardia agitation, hallucinations, myoclonic jerking, aggression, tachycardia, flushed skin, dilated pupils, "inappropriate laughter"	"immediately after smoking" UNK	<3h <3h	(−)UDS, SC not tested (−)UDS, SC not tested	admitted to mental health ward; discharged after 4 days	(Harris and Brown, 2012)
USA	1 1	M M	17 15	K2 K2	UNK (sm) UNK (sm)	hypertonia, apnea, cyanosis, confused, swollen red eyes, tachycardia, chest & back pain loss of consciousness, tachycardia, headache, fatigue	UNK UNK	<12h	(−)UDS, SC not tested (−)UDS, SC not tested	adenosine (6 mg, IV), APAP IVF	(Heath et al., 2012)
Germany	29	25M 4F	14-30	Bonzai, Jamaican Gold, Lava Red, Maya, Monkees go bananas tropical car perfume, Ninja Strong, OMG, Spice, Smoke, Space,	UNK (sm)	Poisoning severity score (PSS) 1 (n=9):drowsiness, vertigo, ataxia, restlessness, paraesthesia, mild visual or auditory hallucinations mild muscular tenderness or pain, tachycardia, mild change in blood pressure, vomiting, diarrhea, abdominal pain, mild hypoglycemia, mild electrolyte imbalance, short-term hypothermia PSS2 (n=18): unconsciousness, brief apnea or slowed breathing, confusion, agitation, hallucination, delirium, seizures, visual and auditory hallucinations, dystonia, rhabdomyolysis or chest pain, sinus brady or tachycardia, irregular EKG,	1-20h	UNK	2.3µg/L CP47,497-C8 (1), <0.1-13µg/L JWH-018 (8), 0.11µg/L JWH-073(1), 1.2-42µg/L JWH-081(7), 0.17-40µg/L(11), 2.5-190µg/L JWH-210(11), 0.1-1.1 JWH-250(4), 0.2µg/L AM694; all measured in serum	Supportive care (29), BDP (8), IVF (5), anti-emetics (2), potassium supplement (5), neuroleptics (1), psychiatric care (1), ET (1)	(Hermanns-Clausen et al., 2013b)

Table Continued

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
						prolonged coughing, bronchospasm, difficulty breathing, vomiting, diarrhea, abdominal pain, electrolyte imbalance, moderate hypoglycemia, and prolong hypothermia					
USA	1 1	M M	19 15	Climax Silver-K2	"pinch" (sm) UNK (sm)	seizure, unresponsive, aggression, "abnormal" speech, slow & shallow breathing, loss of consciousness loss of consciousness, shallow breathing	UNK UNK	UNK UNK	(−)UDS, SC not tested (−)UDS< SC not tested	supportive care ET intubation, supportive care	(Jinwala and Gupta, 2012)
USA	1	F	18	KS	UNK (sm)	panic attack, paranoia, chest pain, hyperventilation, nausea	UNK	UNK	(−)UDS, SC not tested	supportive care	(McGuiness and Newell, 2012)
USA	1	M	20	Black Mamba	UNK (sm)	tonic-clonic seizures, dry skin, drowsiness, elevated pulse	"immediately after smoking	<3h	(+)AM2201 metabolites (urine)	IVF, supportive care	(McQuade et al., 2012)
USA	1	M	59	Spice	1.5g/d (sm)	"flashbacks" combat-related trauma, re-admitted 3wk later for hallucinations, then 2d later, total 3 admissions	UNK	<24h /visit	(−)UDS, SC not tested	BDP, gabapentin (400mg QID), hydroxyzine (25mg TID PRN), apiprazole (10mg qD), benztropine (1mg BID), bupropion (150mg BID)	(Peglow et al., 2012)
USA	1	M	48	Spice	3g(sm)	tonic-clonic seizures, tachycardia, diaphoresis, mydriasis	UNK	<24h	(−)UDS, 140mg/dL BAC (serum), (+)JWH-018 metabolites (urine)	lorazepam (4mg IV)	(Pant et al., 2012)
USA	1	M	19	Happy Tiger (contained JWH-018, JWH-081, JWH-250, AM2201)	UNK (sm)	convulsions, vomiting	"immediately after smoking"	<24h	(−)UDS, SC not tested	midazolam (5mg IV), supportive care	(Schneir and Baumbacher, 2012)

Table Continued

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	1	M	20	K2	UNK (sm)	agitation, confusion, suicidal ideation, self-inflicted wounds, hyperventilation, tachycardia	UNK	<24h	(−)UDS, SC not tested	supportive care	(Thomas et al., 2012)
USA	1	M	48	K2 Summit	0.3g (po with milk)	Sedated, nauseous, "detached," flushed, loss of consciousness, tonic-clonic seizure, tachycardia, depressed breathing, hyperthermia, supraventricular tachycardia	45 min	<48h	(−)UDS, SC not tested	lorazepam (IV), electrocardioversion, ET intubation	(Tofighi and Lee, 2012)
Hong Kong	1	M	36	K2	0.5g/d (sm)	agitation, profuse sweating, tachycardia, delusion, elevated blood pressure	UNK	<24h	(−)UDS, (+)DXM, (+)ephedrine, (+)promethazine, SC not tested	midazolam (IM)	(Tung et al., 2012)
USA	1	M	21	MadHatter, Kite, Scooby Snax	UNK (sm)	fainted while driving, tachycardia, elevated blood pressure, dyspnea & hyperventilation	UNK	UNK	(+)THC (urine), 0.75µg/L AM2201, JWH-122, JWH-210 (blood), (+)AM2201 & JWH-018 metabolites (urine)	ICU admission, airway management, antibiotics, steroids	(Alhadi et al., 2013)
USA	1 1	F F	22 26	K2 Peak Extreme	UNK (sm) UNK (sm)	palpitations, dyspnea, "angor animi," dysarthria, difficulty standing, drowsiness, inattention, left face & hemi-body weakness, & hemianesthesia, diagnosed with ischemic stroke confirmed by CT scan left facial weakness, left-sided numbness, dysfluency, hemi-anesthesia, left visual neglect, diagnosed with ischemic stroke confirmed by CT scan	"while smoking" <24h	UNK UNK	(+)THC, BDP, & salicylates (urine) (−)UDS	supportive care warfarin, supportive care	(Bernson-Leung et al., 2013)
USA	1	M	20	Spice	UNK (sm)	uncommunicative, unable to follow instruction, combatant	UNK	UNK	(−)UDS, SC not tested	IVF, lorazepam (2mg) admission, supportive care	(Berry-Caban et al., 2013)

Table Continued

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	1 1 1 1	M M M M	20 23 26 30	Spice Spice Spice Spice	UNK (sm) UNK (sm) UNK (sm) UNK (sm)	nausea, vomiting for 2d; history of smoking SC within the last few weeks nausea, vomiting for 2 d; history of SC within few weeks nausea, vomiting, diarrhea, lower abdominal pain × 2d; history of SC intake × 2yr, but changed "supplier" in last week nausea, vomiting, diarrhea, abdominal pain × 3d; history of SC intake × 1yr, but changed "supplier" in few wks.	48h 48h 48h 72h	UNK UNK UNK UNK	(−)UDS, SC not tested (−)UDS, SC not tested (−)UDS, SC not tested (−)UDS, SC not tested	renal biopsy, inpatient admission, supportive care renal biopsy, inpatient admission, supportive care renal biopsy, inpatient admission, supportive care inpatient admission, supportive care	(Bhanushali et al., 2013)
USA	16	15M 1 F	15-33	Blueberry, Clown Loyal, Flame 2.0, Mad Monkey, Mr. Happy, Phantom Wicked, Spice Gold	UNK (sm)	nausea(15), vomiting(15), abdominal(8) & flank(4) pain, back pain(2)	"within h or days"	UNK	42µg/L XLR-11 pentanoic acid (blood, n=1), 35-35µg/L XLR-11, 38-102µg/L XLR-11 pentanoic acid metabolite (serum, n=2), 6µg/L UR-144 (serum, n =1), 400-529µg/L XLR-11 pentanoic acid (urine, n=2); SC not tested for n=9	renal biopsy(8), hemodialysis (5), corticosteroid (4)	(Centers for Disease Control and Prevention, 2013a)

Case series

Besli, Ikiz, Yildrim and Saltik (2015)[139]

Abstract

BACKGROUND:

Synthetic cannabinoids, referred to as "Bonzai" in Turkey, are relatively new recreational drugs of abuse. Although the use of synthetic cannabinoids has been dramatically increasing in young populations in many countries, their adverse effects are not well known.

OBJECTIVES:

To report on the clinical features and social history of pediatric patients with a diagnosis of synthetic cannabinoid intoxication and to highlight the dangers of these drugs to public health.

METHODS:

We retrospectively reviewed 16 cases presenting to our Emergency Department with synthetic cannabinoid intoxication in the last 10 months. Usage characteristics and the psychoactive, physical, and metabolic effects of synthetic cannabinoids were analyzed.

RESULTS:

The mean age of the 16 patients with a diagnosis of synthetic cannabinoid intoxication was 15.4 ± 1.7 years (15 males, 1 female). The most common physical symptoms were eye redness, nausea/vomiting, sweating, and altered mental status; the main psychoactive findings were agitation, anxiety, hallucinations, and perceptual changes. We observed hypotension and bradycardia in 8 (50%) and 5 (31.3%) of the patients, respectively. Although most patients were discharged from the Emergency Department, 25% were transferred to an intensive care unit. They all had reduced school attendance and performance. The rates of cigarette smoking and alcohol drinking were also significantly higher.

CONCLUSION:

Synthetic cannabinoids are unsafe and potentially harmful drugs of abuse; they may even cause life-threatening effects. It is important for pediatricians to be familiar with the signs and symptoms of consumption of synthetic cannabinoid products. Education of parents, teachers, and adolescents about the potential health risks of using these products is essential.

Case reports

"Spice" refers to various synthetic cannabinoid-containing products that seem to have rapidly become popular recreational drugs of abuse. Very little medical literature currently exists detailing the adverse effects and Emergency Department presentations associated with "spice" use.

Schneir, Cullen and Ly (2011)[140] report two cases of patients who presented to the Emergency Department with, predominantly, anxiety after recreationally using a "spice" product that we subsequently confirmed to contain the synthetic cannabinoids, JWH-018 and

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[139] Besli GE, Ikiz MA, Yildirim S, Saltik S. (2015). Synthetic Cannabinoid Abuse in Adolescents: A Case Series. J Emerg Med. 2015 Nov;49(5):644-50. doi: 10.1016/j.jemermed.2015.06.053. Epub 2015 Aug 17.

[140] Schneir AB, Cullen J, Ly BT. (2011). Spice" girls: synthetic cannabinoid intoxication. Journal of Emergency Medicine; 40(3):296-9.

JWH-073. CONCLUSION: We suspect that use of "spice" products may increase. Although anxiety was a prominent presentation in both of the patients described here, undoubtedly, future studies will describe the manifestations of intoxication and toxicity with the various synthetic cannabinoids.

Summary and Recommendation

The reviews by Brewster and Collins (2014) and Castaneto et al (2014) report anxiety symptoms as a common side effect of synthetic cannabinoids use. One case of panic attack induced by synthetic cannabinoids is also reported by Castaneto et al (2014). A recent case series by Besli et al (2015) reported on 16 adolescent patients who used synthetic cannabinoids, anxiety symptoms were a major psychoactive finding in these intoxicated patients. The case report by Schneir et al (2011) also reports two cases of “spice” induced anxiety symptoms.

Due to the lack of specificity of type of drug it is suggested at this time that it be graded as a Grade 3 - 4 level evidence. The generic drug factor can be used by claimants who have a substance/medication-induced anxiety disorder from exposure to these substances.

Cocaine

Cross-sectional studies

Zubaran, Foresti, Thorell and Franceschini (2013)[141] conducted a study to investigate anxiety symptoms among crack cocaine and inhalant users in southern Brazil. The study investigated two groups of volunteers of equal size (n=50): one group consisted of crack cocaine users, and the other group consisted of inhalant users. Research volunteers completed the Portuguese versions of the State-Trait Anxiety Inventory (STAI), Hamilton Anxiety Rating Scale (HAM-A), and Self-Report Questionnaire (SRQ).

Both crack and inhalant users experience significant symptoms of anxiety. Inhalant users presented significantly more anxiety symptoms than crack users according to the HAM-A questionnaire only. In contrast to the results of the HAM-A, the STAI failed to demonstrate a significant difference between the two groups of substance users. SRQ scores revealed that crack and inhalants users had significant degrees of morbidity.

A significant difference regarding anxiety symptomatology, especially state anxiety, was observed among inhalant and crack users. Anxiety and overall mental psychopathology were significantly correlated in this sample. The results indicate that screening initiatives to detect anxiety and additional psychiatric comorbidities among crack and inhalant users are feasible and relevant.

Williamson, Gosop, Powis et al (1997)[142] contacted and interviewed a sample of drug users (n = 158) in non-clinical community settings about their use of Ecstasy, cocaine powder, and amphetamines and the adverse effects of these drugs. Subjects reported a wide range of adverse effects including anxiety problems, depression, mood swings, feelings of paranoia, and panic attacks. Sleep and appetite disturbances were the most commonly reported problems. About half of all subjects reported depression and paranoid feelings associated with their stimulant use. Many of those reporting problems stated that these were mild. However, for all drugs, a substantial minority of users reported adverse effects which they rated as 'severe'. Between 30 and 55% of the sample reported having had at least one 'severe' adverse effect (30% cocaine, 35% Ecstasy and 55% amphetamine).

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[141] Zubaran C, Foresti K, Thorell MR, Franceschini PR. (2013). Anxiety symptoms in crack cocaine and inhalant users admitted to a psychiatric hospital in southern Brazil. Revista Da Associacao Medica Brasileira. 59(4):360-7.

[142] Williamson S, Gossop M, Powis B, Griffiths P, Fountain J, Strang J. (1997). Adverse effects of stimulant drugs in a community sample of drug users. Drug Alcohol Depend.;44(2-3):87-94.

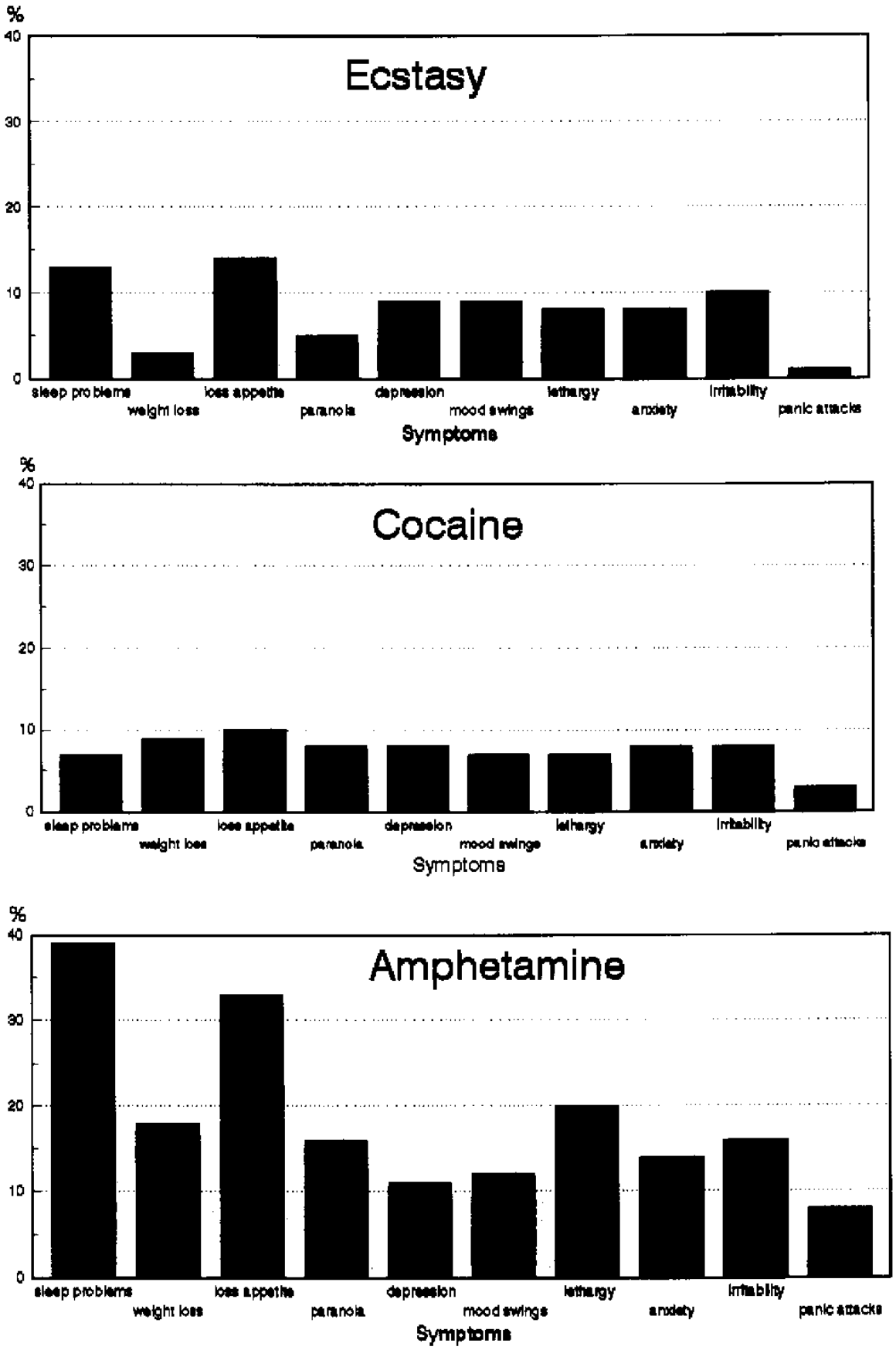

FIGURE 2 NUMBER OF PARTICIPANTS REPORTING SEVERE ADVERSE EFFECTS (WILLAIMSON ET AL, 1997).

There were clear differences between the different drugs in the likelihood and reported severity of adverse effects. Amphetamine use was associated with significantly more adverse effects and with more severe adverse effects than Ecstasy or cocaine. Cocaine powder was associated with the least severe adverse effects. A common pattern of drug use involved the use of depressant drugs such as opiates and benzodiazepines in addition to stimulants. The stimulant and depressant users were more likely than the stimulants-only users to use stimulants by injection and more likely to report adverse effects associated with stimulant use. The stimulant and depressant users were also more likely to have been treated for a drug problem. Approximately a quarter of the sample stated that they had stopped using stimulants up to the point of interview as a result of their bad experiences.

Summary and Recommendation

The DSM-5 state that cocaine is a drug which induces anxiety and or panic attacks in some users.

Both studies summarised above compare groups of cocaine users to other drug users. Zubaran et al (2013) compared anxiety symptomatology in a group of crack cocaine users with inhalant users. Anxiety symptoms were significantly higher in the inhalant group when reviewing the Hamilton Anxiety Rating Scale (HAM-A) results, however, not significantly different when the STAI results were compared between groups. Anxiety was highly correlated with both groups.

Williamson et al (1997) compared groups of ecstasy, cocaine and amphetamine use. Anxiety symptoms were reported by all groups and polysubstance use was common.

Grade 2 level evidence

MDMA - 3, 4- methylenedioxymethamphetamine - Ecstasy, E or XTC

Reviews

The **Drug Info Clearing House (2005)**[143] summarise the literature in regard to the neuropsychiatric side effects of ecstasy and state:

Ecstasy users report a wide range of psychological effects, positive (as mentioned above) and negative, which include anxiety, depression, depersonalisation, confusion, perceptual side effects such as "flashbacks" and hallucinations, aggression and impulsivity, motivational deficits, panic attacks and paranoia (Montoya, Sorrentino, Lukas & Price 2002).

Many of these psychological effects seem to be consistent with the cumulative evidence that ecstasy has toxic effects on serotonergic pathways in the brain (Morgan, Mofie, Fleetwood & Robinson 2002). **The most commonly reported symptoms are panic attacks/anxiety** and toxic psychoses. **Panic attacks usually tend to occur within the first hour of ecstasy consumption** (Williamson, Gossop, Powis, Griffiths et al. 1997). According to McCann and Ricaurte (1991), individuals with genetic predisposition to panic attacks are more vulnerable to experiencing an attack while using ecstasy. In such cases, the risk is that ecstasy use may trigger panic disorder.

With regard to toxic psychoses, Gouzoulis, von Bardeleben, Rupp, Kovar et al. (1993) showed that ecstasy caused psychosis when given to a healthy volunteer. While other cases have been reported (self reports), it is known that these individuals also presented with premorbid psychological dysfunctions (Gamma et al. 2000). In another study, heavy ecstasy users indicated significantly higher scores on a psychological symptoms list, compared to nonusers. These include obsessive-compulsive patterns, anxiety, psychosis, somatisation and loss of pleasure from sexual activity (Parrott 2001). Further findings suggest high levels of depression among users (MacInnes, Handley & Harding 2001; Verheyden, Maidment & Curran 2003). Gender differences were also identified, with women being more susceptible than men to "flashbacks", hallucinations (Liechti & Vollenwieder 2001) and low mood following a weekend of ecstasy use (Verheyden et al. 2002; Maxwell 2005). In conclusion, it would appear that more is unknown rather than known with regard to the long-term effects of ecstasy on humans, and further well-designed research is needed to clarify such effects.

Cross-sectional studies

Scott, Hides, Allen, Burke and Lubman (2010)[144] conducted a study to determine the relationship between ecstasy use and depressive/anxiety symptomatology after controlling for known environmental and genetic (polymorphism of the serotonin transporter gene) risk factors for depression and anxiety disorders. Participants consisted of a community sample of 184 18-35-year olds who had taken ecstasy at least once in the past 12 months. Participants completed an interview and questionnaires and provided a saliva sample. Mood symptoms were assessed using the Mood and Anxiety Symptom Questionnaire. Timeline methods were

[143] Drug Info Clearing House (2005). Prevention. Ecstasy and related drugs. Prevention Research Quarterly: current evidence evaluated, 078185

[144] Scott RM, Hides L, Allen JS, Burke R, Lubman DI. (2010). Depressive and anxiety symptomatology in ecstasy users: the relative contribution of genes, trauma, life stress and drug use. Psychopharmacology. 209(1):25-36.

used to collect information on lifetime and recent ecstasy use, as well as recent other drug use and life stress. Trauma exposure was measured using the Composite International Diagnostic Interview--Trauma List. Genomic DNA was extracted from participant saliva samples. Neither lifetime nor recent ecstasy use was associated with the severity of current mood symptoms, either alone or in combination with genetic risk factors. Rather, lifetime trauma, recent stressful life events, the frequency of tobacco use and recent polydrug use significantly predicted the severity of depressive and anxiety symptoms. These results highlight the need to consider the role of environmental factors when examining the relationship between ecstasy use and mood symptoms. Whether ecstasy exacerbates such symptoms in vulnerable individuals requires further investigation using prospective designs.

Lamers, Bechara, Rizzo and Ramaekers (2006)[145]

AB Repeated ecstasy (MDMA) use is reported to impair cognition and cause increased feelings of depression and anxiety. Yet, many relevant studies have failed to control for use of drugs other than MDMA, especially marijuana (THC). To address these confounding effects we compared behavioural performance of 11 MDMA/THC users, 15 THC users and 15 non-drug users matched for age and intellect. We tested the hypothesis that reported feelings of depression and anxiety and cognitive impairment (memory, executive function and decision making) are more severe in MDMA/THC users than in THC users. MDMA/THC users reported more intense feelings of depression and anxiety than THC users and non-drug users. Memory function was impaired in both groups of drug users. MDMA/THC users showed slower psychomotor speed and less mental flexibility than non-drug users. THC users exhibited less mental flexibility and performed worse on the decision making task compared to non-drug users but these functions were similar to those in MDMA/THC users. It was concluded that MDMA use is associated with increased feelings of depression and anxiety compared to THC users and non-drug users. THC users were impaired in some cognitive abilities to the same degree as MDMA/THC users, suggesting that some cognitive impairment attributed to MDMA is more likely due to concurrent THC use.

Verheyden, Maidment and Curran (2003)[146]

AB The regular use of ecstasy (3,4-methylenedioxymethamphetamine, MDMA) has been associated with depressed mood, anxiety and hostility, but it is not known whether such effects persist after people stop using the drug. Furthermore, little is known about what factors might influence the decision to quit using MDMA. The aim of the present study was to examine the reasons why ex-users had stopped using this drug and to assess their current levels of depression, anxiety, anger and aggression. Telephone interviews were conducted with people who used to take MDMA on a regular basis but who no longer used the drug. The participants comprised sixty-six ex-users who used to take MDMA regularly (at least once every 2 months over a period of at least 1 year), but who had not taken MDMA for at least 1 year (average 3 years). Participants were asked about why they had quit MDMA. They also completed questionnaires to assess trait mood. Ex-users could be divided into two groups based on their reason for quitting: (i) those who had quit for mental health reasons and (ii)

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[145] Lamers CT, Bechara A, Rizzo M, Ramaekers JG. (2006). Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. Journal of Psychopharmacology. 20(2):302-11.

[146] Verheyden SL, Maidment R, Curran HV. (2003). Quitting ecstasy: an investigation of why people stop taking the drug and their subsequent mental health. Journal of Psychopharmacology. 17(4):371-8.

those who had quit for circumstantial reasons. Approximately half of those in the mental health group scored in the range for clinical depression. In that group, current levels of depression and anxiety correlated significantly with the cumulative amount of MDMA that they had taken several years previously. These findings suggest that some users may either be more vulnerable to the adverse effects of MDMA or have pre-existing mental health problems for which they self-medicate by using ecstasy. The present study shows that some ex-users experience an impairment to mental health that persists for years after they stop using this drug.

Summary and conclusion

Assessing the literature in regard to illicit drugs and mental health outcomes is difficult as a vast majority of illicit drug uses do not restrict their use to one specific drug of choice. Commonly polydrug use is identified in the literature.

The review by the The Drug Info Clearance House (2005) identifies anxiety symptoms and panic attacks as commonly reported side effects of “ecstasy” use. The Scott et al (2010) cross-sectional study suggested that other factors such as lifetime trauma, recent stressful life events, the frequency of tobacco use and recent polydrug use significantly predicted the severity of anxiety symptoms. Lamers et al (2006) reported that MDMA use is associated with increased feelings of anxiety compared to THC users and non-drug users. Verheyden et al (2003) reported that regular users of “ecstasy” (once every two months for at least a year) who cease using MDMA did so for either mental health reasons or circumstantial reasons. In the mental health group, the ex-users reported current levels of anxiety which correlated significantly with the cumulative amount of MDMA taken several years previously. The study design was not prospective so interpretation of these results in unclear. Some users may be more vulnerable to the adverse effects of MDMA or pre-existing mental health problems preceding the use may lead the users to self-medicate with the drug.

Grade 2 level evidence

Methamphetamine

Data-base records study

"Designer drugs have become increasingly prevalent among recreational drug users. In particular, amphetamines and MDMA are used across many settings (Guillaume and Pavic, 2011). Besides these substances, a wide variety of new related substances have appeared on the illicit market. Among the 256 new psychoactive substances identified in Europe from 2012 to 2014, 80 were phenethylamines or cathinones. In the same time, members of the French drug abuse monitoring network (Système national d'identification des toxiques et substances, SINTES) have identified 94 new psychoactive substances. In January, 2013, 27 substances in the phenethylamine family (including 15 synthetic cathinones) were circulating in France (Lahaie et al., 2013).

Phenethylamines are a large family of chemical structures that are molecular variants of the core compounds, i.e., amphetamines, MDMA, etc. The phenethylamine skeleton (1) consists of an aromatic ring with a side chain of two carbons ending by an amine group, as shown in Fig. 1. Slight modifications in this structure, partially induced by natural products, can change the pharmacological activity. Phenethylamines may thus undergo two major changes. First, substitution of the alpha carbon by a methyl gives rise to amphetamine derivatives (2), which have an optimal structure for psychostimulant activity (Hill and Thomas, 2011). The2C and D series are obtained by substitutions of the benzene cycle at positions 2 and 5 by methoxy groups and at position 4 by a variable substituent, respectively on phenethylamine (3) oramphetamine (4) (Hill and Thomas, 2011; Maurer, 2010; Shulgin,1991). These series have tetrahydrobenzodifuranyl and benzodifuranyl analogs (5) called "FLY" (Corazza et al., 2011). Finally, the NBOMe series which groups N-benzyl derivatives of the 2Cseries (6) has appeared more recently on the drug market (Elz et al., 2002; Heim, 2003). Ring substitutions increase the affinity for 5HT2a receptors, thus providing the hallucinogenic properties (Trachsel, 2012). Specifically, substitution of the aromatic ring by a methylenedioxy group at positions 3 and 4 produces MDMA and derivatives (7). This kind of substitution has given rise to anew pharmacological class called entactogens that express psychostimulant/hallucinogenic properties. Entactogens generally do not cause hallucinations (except at high doses for some of them), but instead promote socialization and a desire for contact with oneself and others (Ghysel-Laporte et al., 2012; Freudenmann andSpitzer, 2004; Gouzoulis-Mayfrank, 2001). Finally, both methylene-dioxyphenethylamines and amphetamines may be substituted by a ketone function on the β carbon to lead to cathinones. Synthetic cathinone may have the same structural changes as non-ketonated homologues (Kelly, 2011; Coppola and Mondola, 2012)." (Le Roux et al, 2015; pp. 46-7)

Le Roux, Bruneau, Lelievre, Bretaudeau Deguigne et al (2015)[147] conducted a study to describe typical aspects of phenethylamine poisoning in order to better inform patient care. Phenethylamine poisoning cases reported to the Poison Control Center of Angers, France, from January, 2007 to December, 2013 were examined. Clinical findings were examined in 105 patients, including phenethylamine used, symptoms and final outcome. Patients were predominantly male (80%), with mean age 26+/-8 years.

[147] Le Roux G, Bruneau C, Lelievre B, et al (2015). Recreational phenethylamine poisonings reported to a French poison control center. Drug & Alcohol Dependence; 154:46-53.

MDMA (38%), amphetamine (18%) and methamphetamine (14%) were the most commonly reported. Synthetic cathinones (10%) and the 2C series (7%) were also found. Substances most commonly associated with phenethylamine poisoning were cannabis (27%), ethanol (20%) and cocaine (9%). The most frequently reported symptoms included anxiety (see Table below) and hallucinations (49%), mydriasis and headache (41%), tachycardia (40%) and hypertension (15%). Complications such as seizures (7%), cardiac arrest (5%), toxic myocarditis (1%) and hemorrhagic stroke (1%) were also observed. Of the cases, the Poison Severity Score was: null or low, 66%, moderate, 21%, severe or fatal, 13%. Of the patients, 77% received hospital care and 12.4% were admitted to an intensive care unit. Analytical confirmations were obtained for all severe cases. While 93% of patients recovered, there were 5 deaths and 2 patients presented with neurological sequelae.

TABLE 43 SYMPTOMS OBSERVED IN PHENETHYLAMINE POISONINGS REPORTED TO THE ANGERS PCC BETWEEN 2007 AND 2013 (LE ROUX ET AL, 2015).

Symptom	All cases *n* (%)	No other substances *n* (%)	Associated substances *n* (%)
Tachycardia	42 (40)	19 (42)	23 (38)
Mydriasis	30 (28)	12 (27)	18 (30)
Hallucinations/delirium	27 (26)	11 (24)	16 (27)
Fear/anxiety	24 (23)	9 (20)	15 (25)
Restnessless/excitement	22 (21)	4 (9)	18 (30)
Sleepiness/mental clouding	16 (15)	8 (18)	8 (13)
High blood pressure	16 (15)	7 (16)	9 (15)
Nausea/vomiting	14 (13)	8 (18)	6 (10)
Headache	13 (12)	7 (16)	6 (10)
Cyanosis	11 (10)	7 (16)	4 (7)
Sleep disorders	9 (9)	4 (9)	5 (8)
Hypoesthesia/paresthesia	8 (8)	6 (13)	2 (3)
Malaise	7 (7)	4 (9)	3 (5)
Seizures	7 (7)	1 (2)	6 (10)
Cardiac rhythm trouble	6 (6)	3 (7)	3 (5)
Disorientation	6 (6)	2 (4)	4 (7)
Excessive sweating	6 (6)	4 (9)	2 (3)
Hyperthermia (>38 °C)	5 (5)	4 (9)	1 (2)
Localized hypertonia	5 (5)	1 (2)	4 (7)
Cardiac arrest	5 (5)	2 (4)	3 (5)
Myosis	5 (5)	0 (0)	5 (8)
Coma (GSC 9–14)	5 (5)	2 (4)	3 (5)
Chills	5 (5)	5 (1)	1 (2)
Lower abdominal pain	4 (4)	2 (4)	2 (3)
Aspiration pneumonia	4 (4)	1 (3)	3 (5)
Chest pain/chest tightness	4 (4)	0 (0)	4 (7)
Character disorders	4 (4)	3 (7)	1 (2)
Dyspnea	4 (4)	2 (4)	2 (3)
Precordial algia	4 (4)	2 (4)	2 (3)
Memory issues	4 (4)	2 (4)	2 (3)
Euphoria	3 (3)	1 (2)	2 (3)
Bradycardia	3 (3)	1 (2)	2 (3)
Respiratory acidosis	3 (3)	1 (2)	2 (3)
Dizziness	3 (3)	2 (4)	1 (2)
Dryness of mucous membranes	3 (3)	1 (2)	2 (3)
Acute renal failure	3 (3)	1 (0)	2 (3)
Hypothermia below 35 °C	3 (3)	1 (0)	2 (3)
Hepatitis	3 (3)	1 (0)	2 (3)
Coma (GSC 4–8)	3 (3)	1 (0)	2 (3)
Anuria	3 (3)	1 (0)	2 (3)
Low blood pressure	3 (3)	2 (4)	1 (2)
Glare	2 (2)	1 (2)	1 (2)
Abnormal movements	2 (2)	1 (2)	1 (2)
Circulatory shock	2 (2)	1 (2)	1 (2)
Erythema/rash	2 (2)	0 (0)	2 (3)
Asthenia	2 (2)	0 (0)	2 (3)
Apnoea	2 (2)	0 (0)	2 (3)
Metabolic acidosis	2 (2)	0 (0)	2 (3)
Extremity tremors	2 (2)	0 (0)	2 (3)
Acute pulmonary edema	2 (2)	1 (2)	1 (2)
Heart failure	2 (2)	1 (2)	1 (2)
Dehydration	2 (2)	1 (2)	1 (2)
Withdrawal syndrome	1 (1)	0 (0)	1 (2)
Acute respiratory syndrome	1 (1)	0 (0)	1 (2)
Rhabdomyolysis	1 (1)	0 (0)	1 (2)
Hypersalivation	1 (1)	0 (0)	1 (2)
Hemoptysis	1 (1)	0 (0)	1 (2)
Hematoma	1 (1)	0 (0)	1 (2)
Congestion/hypersecretion	1 (1)	0 (0)	1 (2)
Drunkenness	1 (1)	0 (0)	1 (2)
Coma (GSC 3)	1 (1)	0 (0)	1 (2)
Bradypnea/breathing pause	1 (1)	0 (0)	1 (2)

Phenethylamine poisonings may be severe in young and healthy individuals. Physicians, toxicologists and analysts should be aware of new phenethylamine consumption trends in order to inform management of patient care and to contribute to a more responsive drug policy.

Cross-sectional studies

Akindipe, Wilson and Stein (2014)[148] used a structured diagnostic interview to assess the prevalence and pattern of co-morbid psychiatric disorders in individuals with methamphetamine dependence; and identified risk factors for this comorbidity. One hundred adult volunteers with a diagnosis of methamphetamine dependence and without co-morbid medical disorders were consecutively recruited from three drug rehabilitation centres. Each volunteer was assessed with a socio-demographic questionnaire and evaluated for psychiatric comorbidity using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). A regression model was used to determine predictors of psychiatric comorbidity. Co-morbid psychiatric disorders were present in 36.0% of the sample; these included mood disorders (16.0%), psychotic disorders (13.0%) and **anxiety disorders (7.0%). One in four of these disorders were assessed as being substance-induced.** However no substance-induced anxiety disorder was diagnosed in this group of individuals with methamphetamine dependence.

Independent predictors of psychiatric comorbidity included being male (OR=10.04, 95% C.I=2.07-48.63, p=0.004), younger (OR=0.87, 95% C.I=0.77-0.99, p=0.04), and having a previous psychiatric disorder (OR=18.45, 95% C.I=3.81-89.33, p<0.001). Mood, psychotic, and anxiety disorders are common in individuals with methamphetamine dependence. Risk factors for such comorbidity can be identified. These findings underscore the need for an integrated model of care addressing both substance use disorders and psychiatric comorbidity.

Salo, Flower, Kielstein et al (2011)[149] assessed the prevalence of psychiatric comorbidity in a large sample of methamphetamine (MA)-dependent subjects using a validated structured clinical interview, without limitation to sexual orientation or participation in a treatment program. The secondary aim was to assess whether the prevalence of psychiatric comorbidities varied by gender. Structured clinical interviews (SCIDs) were administered to 189 MA-dependent subjects and lifetime prevalence of DSM-IV diagnoses was assessed. Across the sample, 28.6% had primary psychotic disorders, 23.8% of which were substance-induced; 13.2% had MA-induced delusional disorders and 11.1% had MA-induced hallucinations. A substantial number of lifetime mood disorders were identified that were not substance-induced (32.3%), whereas 14.8% had mood disorders induced by substances, and 10.6% had mood disorders induced by amphetamines. **Of all participants, 26.5% had anxiety disorders and 3.7% had a substance-induced anxiety disorder, all of which were induced by MA.** Salo et al (2011) summarised the available studies of MA use and substance-use disorder as follows:

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[148] Akindipe T, Wilson D, Stein DJ. (2014). Psychiatric disorders in individuals with methamphetamine dependence: prevalence and risk factors. Metabolic Brain Disease. 29(2):351-7.
[149] Salo R, Flower K, Kielstein A, et al (2011). Psychiatric comorbidity in methamphetamine dependence. Psychiatry Res, 186(2-3): 356-61. 078081

"Limited information is available on the prevalence of anxiety disorders associated with MA use. In the Shoptaw study cited above, 25% of MA users reported a lifetime prevalence of substance-induced anxiety disorders (Shoptaw et al., 2003). One Australian study reported that 76% of 301 regular amphetamine users reported experiencing severe anxiety and 33% had panic attacks after initiation of MA use (48% reported severe anxiety and 11% had panic attacks before they began MA use; Hall et al., 1996). The NESARC (Conway et al., 2006) described earlier reported a lifetime prevalence for anxiety disorders of 50% among amphetamine users, but the percentage of substance-induced anxiety disorders was not reported" (no page nos).

TABLE 44 PREVALENCE OF LIFETIME ANXIETY AND OTHER DISORDERS IN 189 METHAMPHETAMINE (MA) DEPENDENT SUBJECTS (SALO ET AL, 2011).

	Full Sample	Women	Men
Substance-induced anxiety disorder			
Methamphetamine	7 (3.7%)	0	7 (5.5%)
Unknown substance	0	0	0
Anxiety disorders	**46 (24.3%)**	**22(34.9%)**	**24 (19.0%)**
Post traumatic stress disorder	23 (12.2%)	12 (19.0%)	11 (8.7%)
Generalized anxiety disorder	14 (7.4%)	9 (14.3%)	5 (4.0%)
Obsessive-compulsive disorder	7 (3.7%)	1 (1.6%)	6 (4.8%)
Panic disorder without agoraphobia	5 (2.6%)	3 (4.8%)	2 (1.6%)
Panic disorder with agoraphobia	5 (2.6%)	4 (6.3%)	1 (0.8%)
Conversion disorder	2 (1.1%)	1 (1.6%)	1 (0.8%)
Anxiety NOS	2 (1.1%)	1 (1.6%)	1 (0.8%)
Other disorders	**14 (7.4%)**	**4 (6.3%)**	**10 (7.9%)**
Adjustment disorder	5 (2.6%)	1 (1.6%)	4 (3.2%)
Eating disorder	5 (2.6%)	2 (3.2%)	3 (2.4%)
Mental disorder due to general medical condition	3 (1.6%)	1 (1.6%)	2 (1.6%)
Hypochondriasis	1 (0.5%)	0	1 (0.8%)

Male subjects reported a higher percentage of MA-induced delusions compared to female abusers. Given the impact of MA psychosis and other drug-induced symptoms on hospitals and mental health services, the description and characterization of comorbid psychiatric symptoms associated with MA use is of paramount importance.

Summary and conclusion

The adverse events data base study by Le Roux and colleagues (2015) of phenethylamine poisoning which includes methamphetamine, MDMA and other designer drugs reported anxiety as a commonly reported side effect.

Akindipe et al (2014) did not report any cases of comorbid substance-induced anxiety disorder in their sample of methamphetamine dependant individuals, however, other anxiety disorders were identified. Chronic use of methamphetamine may result in development of other more robust anxiety disorders, with acute exposures resulting in the substance-induced anxiety diagnoses. In conflict with Akindipe's results, Salo et al (2011) reported in their sample that 26.5% had anxiety disorders and 3.7% had a substance-induced anxiety disorder, all of which were induced by MA. They also cite a number of studies which support the development of substance-induced anxiety in methamphetamine users.

Grade 2 level evidence

Inhalants

Summary of important issues

According to the **DSM-5**[150] panic or anxiety can occur in association with intoxication with inhalants. Some medications that evoke anxiety symptoms include anaesthetics; and volatile substances (such as gasoline and paint) may also induce panic or anxiety symptoms.

I conducted a search of pubmed using the terms (("Inhalant Abuse"[Majr]) AND (anxiety or panic)) and only one article was identified. A less restrictive search using the terms (("Inhalant Abuse") AND (anxiety or panic)) was conducted and 9 articles were identified, but only one was judged to be relevant and obtained.

Reviews

Testa, Giannuzzi, Sollazzo et al (2013)[151] in their review of the literature concerning substance induced psychiatric and organic disorders state:

“Inhalants (or volatile solvents) such as glues and adhesives (toluene, benzene, chloroform, etc.), cleaning agents (tetrachloroethylene, trichloroethane, xylene), solvents (acetone, ethyl acetate, alkyl nitrites), gases (butane, isopropane), aerosols (chlorofluorocarbons), gasoline (benzene, xylene), and anaesthetics (nitrous oxide, halothane, enflurane, desflurane, isoflurane, ethyl chloride), are very lipophilic molecules which when inhaled produce changes in mental status, prevalently analgesia and euphoric-oniroide status. Inhalant use disorders are among the least prevalent and dangerous substance use disorders, their lifetime prevalence being estimated in about 10% among teenagers, up to 50% of whom may develop dependence.

Panic attack and generalized anxiety disorder represent the most common adverse psychiatric events associated to intoxication by inhalants, which generally produces a syndrome similar to alcohol intoxication, consisting of dizziness, slurred speech, euphoria, lethargy, slowed reflexes, slowed thinking and movement, incoordination, tremor, generalized muscle weakness, involuntary eye movement, blurred vision, stupor, coma and death” (p. 74).

Cross-sectional Studies

Zubaran, Foresti, Thorell et al (2013)[152] investigated anxiety symptoms among crack cocaine and inhalant users in southern Brazil. The study investigated two groups of volunteers of equal size (n = 50): one group consisted of crack cocaine users, and the other group consisted of inhalant users. Research volunteers completed the Portuguese versions of the State-Trait Anxiety Inventory (STAI), Hamilton Anxiety Rating Scale (HAM-A), and Self-Report Questionnaire (SRQ).

Both crack and inhalant users experience significant symptoms of anxiety. Inhalant users presented significantly more anxiety symptoms than crack users according to the HAM-A questionnaire only. In contrast to the results of the HAM-A, the STAI failed to demonstrate a

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[150] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783

[151] Testa A, Giannuzzi R, Sollazzo F et al (2013). Psychiatric emergencies (part II): psychiatric disorders coesixting with organic diseases. Eur Rev Med Pharmacol Sci; 17(Suppl 1): 65-8.

[152] Zubaran C, Foresti K, Thorell MR, et al (2013). Anxiety symptoms in crack cocaine and inhalant users admitted to a psychiatric hospital in southern Brazil. Rev Assoc Med Bras, 59(4): 360-7. 078230

significant difference between the two groups of substance users. SRQ scores revealed that crack and inhalants users had significant degrees of morbidity.

A significant difference regarding anxiety symptomatology, especially state anxiety, was observed among inhalant and crack users. Anxiety and overall mental psychopathology were significantly correlated in this sample. The results indicate that screening initiatives to detect anxiety and additional psychiatric comorbidities among crack and inhalant users are feasible and relevant.

According to Zubaran et al (2013):

“Anxiety disorders are commonly associated with inhalant use. The reported prevalence rate of generalized anxiety disorder among inhalant users is 20.5% (Evren et al, 2006). Data from a national epidemiological survey revealed that inhalant users had a significant lifetime prevalence of anxiety disorders (36%) (Wu et al, 2007). Female inhalant users presented higher lifetime prevalence rates of any anxiety disorder in comparison with male users (53% versus 30%), including panic disorder without agoraphobia (25% versus 11%), and specific phobia (28% versus 14%). Female inhalant users also were more likely to have met the criteria for three or more anxiety disorders (15% versus 8%) in the past year (Wu et al, 2007). In addition, adolescents with inhalant abuse or dependence are significantly more likely to have abuse or dependence of alcohol, hallucinogens, nicotine, cocaine, and/or amphetamines, and are more likely to have attempted suicide compared with other adolescent patients who reported never using inhalants (Sakai et al, 2004). **Toluene is the main component of inhalants used by youth in Brazil, including homeless youth, as confirmed by urinary levels of hippuric acid** (Thiesen & Barros, 2004; Thiesen et al, 2007)” (p. 360).

Perron and Howard (2009)[153]

Abstract

AIMS:

To compare adolescent inhalant users without DSM-IV inhalant use disorders (IUDs) to youth with IUDs (i.e. abuse or dependence) across demographic, psychosocial and clinical measures.

DESIGN:

Cross-sectional survey with structured psychiatric interviews.

SETTING:

Facilities (n = 32) comprising the Missouri Division of Youth Services (MDYS) residential treatment system for juvenile offenders. Participants Current MDYS residents (n = 723); 97.7% of residents participated. Most youth were male (87%) and in mid-adolescence (mean = 15.5 years, standard deviation = 1.2, range = 11-20); more than one-third (38.6%, n = 279) reported life-time inhalant use.

MEASUREMENTS:

[153] Perron BE, Howard MO. (2009). Adolescent inhalant use, abuse and dependence. Addiction.;104(7):1185-92.

Antisocial behavior, temperament, trauma-exposure, suicidality, psychiatric symptoms and substance-related problems.

FINDINGS:

Among life-time inhalant users, 46.9% met criteria for a life-time DSM-IV IUD (inhalant abuse = 18.6%, inhalant dependence = 28.3%). Bivariate analyses showed that, in comparison to non-users, inhalant users with and without an IUD were more likely to be Caucasian, live in rural or small towns, have higher levels of anxiety and depressive symptoms, evidence more impulsive and fearless temperaments and report more past-year antisocial behavior and life-time suicidality, traumatic experiences and global substance use problems. A monotonic relationship between inhalant use, abuse and dependence and adverse outcomes was observed, with comparatively high rates of dysfunction observed among inhalant-dependent youth. Multivariate regression analyses showed that inhalant users with and without an IUD had greater levels of suicidal ideation and substance use problems than non-users.

CONCLUSIONS:

Youth with IUDs have personal histories characterized by high levels of trauma, suicidality, psychiatric distress, antisocial behavior and substance-related problems. A monotonic relationship between inhalant use, abuse and dependence and serious adverse outcomes was observed.

Summary and conclusion

The list of chemicals which are used as inhalants and can be abused is very long and not always discussed in detail in the literature. In the studies above, any history of psychiatric illness preceding the inhalant use/abuse is not evaluated. In general inhalant users are adolescent when first use occurs, but as confirmed by Zubaran et al (2013) polysubstance abuse is common in the inhalant users.

The review by Testa et al (2013) states that panic attack and generalized anxiety disorder represent the most common adverse psychiatric events associated to intoxication by inhalants. In the cross-sectional study by Zubaran et al (2013) found that crack and inhalant users experience significant symptoms of anxiety. Inhalant users presented significantly more anxiety symptoms than crack users according to the HAM-A questionnaire only. In contrast to the results of the HAM-A, the STAI failed to demonstrate a significant difference between the two groups of substance users. Perron and Howard (2009) found in bivariate analyses comparing inhalant users with and without an IUD to non-users, that users were more likely to have higher levels of anxiety and depressive symptoms.

The studies support an association between inhalant use and IUD inducing anxiety symptoms which would be at a level to reach the substance/medication-induced anxiety disorder diagnosis.

Other illicit drugs

Reviews

The World Health Organisation (WHO; 2012)[154] Expert Committee on Drug Dependence : thirty-fifth report reported an association between a piperazine derivative and anxiety and panic attacks induced by toxic effects of the drug.

4.3.3 1-(3-Chlorophenyl)piperazine (mCPP)

1-(3-Chlorophenyl)piperazine (mCPP) is a piperazine derivative with stimulant (including euphoric) and hallucinogenic properties. mCPP has never been licensed as a medicine but is a known metabolite of some antidepressants and is a tranquillizer. Its use was first reported in the mid-2000s across Europe but has since been reported in various other countries (e.g., the United States). mCPP is sometimes sold as “legal ecstasy” or as a “legal high” or as “ecstasy” itself. Such products can contain other piperazine derivatives as well as other psychoactive substances including MDMA. Very few user reports involving the use of mCPP alone have been documented. However, the toxic effects reported include: nausea, hallucinations, headache and most frequently, anxiety and panic attacks. There are no published reports of non-fatal or fatal hospital admissions. In Europe, a few cases reported to monitoring centres have mentioned hot flushes, some respiratory problems and coma, but all these cases also involved other unspecified substances. No specific studies have been performed to determine the abuse or dependence potential of mCPP but, in animal discrimination studies, it has been found to mimic TFMPP, ethanol and MDMA, but not lysergic acid diethylamide (LSD). Its abuse and dependence potential in humans is unclear.

The World Health Organisation (WHO; 2015)[155] Expert Committee on Drug Dependence : thirty-sixth report reported various drugs which induce anxiety and panic attacks.

3.13 - 3,4-Methylenedioxypyrovalerone (MDPV)

Substance identification

3,4-Methylenedioxypyrovalerone (MDPV) is chemically (R,S)-1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one.

Previous review

MDPV had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO’s attention that MDPV is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

MDPV is structurally related to pyrovalerone. Key features related to the mechanisms of action are comparable with cocaine-like psychostimulants, which includes potent dopamine

[154] WHO (2012). WHO Expert Committee on Drug Dependence : thirty-fifth report (WHO technical report series ; no. 973), Canada p. 13.
[155] WHO (2015). WHO Expert Committee on Drug Dependence : thirty-sixth report (WHO technical report series ; no. 991), Geneva, Switzerland. *Pre-Layout Version*

transporter (DAT) and norepinephrine transporter (NET) selective transporter blockage. MDPV is a potent locomotor stimulant in mice, which has also been shown to lead to increases of extracellular dopamine in mesolimbic reward pathways using microdialysis studies. MDPV appears to show a profile of high abuse liability. Adverse effects reported from MDPV use pointed towards the observation of a potent and potentially long-lasting psychostimulant-type toxidrome and include severe agitation, violent behaviour, tachycardia, psychosis, profuse diaphoresis, paranoia and anxiety. Non-fatal and fatal intoxications involving MDPV have been reported (pp. 28-29).

3.14 - Methylone (BK-MDMA)

Substance identification

Methylone(beta-keto-MDMA) is chemically (R,S)-1-(1,3-benzodioxol-5-yl)-2-(methylamino) propan-1-one.

Previous review

Methylone had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that methylone is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

Methylone is the beta-keto analogue of MDMA. Key features related to the mechanisms of action are comparable with psychostimulants and medicinal products that target the monoaminergic system. Some of its pharmacological properties overlap with those reported for mephedrone. These include the ability to act as a non-selective substrate at transporters of serotonin, dopamine and norepinephrine. Although its catecholamine-related properties appear to be less pronounced than those observed with methamphetamine, the behavioural profile of methylone was observed to be similar to that of amphetamine-type psychostimulants. Methylone shows potential for abuse liability. Adverse effects reported in connection with methylone use pointed towards the observation of a psychostimulant-type toxidrome and include tachycardia, hypertension, paranoia, anxiety, bruxism and muscle tension and aching. Non-fatal and fatal intoxications involving methylone have been reported (pp. 30-31).

3.23 - Methiopropamine (MPA)

Substance identification

Methiopropamine (MPA) is chemically 1-(thiophen-2-yl)-2-methylaminopropane, which is a structural analogue of methamphetamine in which the phenyl group has been replaced with a thiophene ring.

Previous review

MPA had not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that MPA is clandestinely manufactured, poses an especially serious risk to public health and society, and has no recognized therapeutic use by any party. Preliminary data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use.

Similarity to known substances and effects on the central nervous system

MPA shows some structural and pharmacological similarities to methamphetamine. It functions primarily as a norepinephrine and dopamine reuptake inhibitor and, secondarily, as a serotonin reuptake inhibitor. MPA is a central nervous system stimulant and displays methamphetamine-like properties including stimulation, alertness and increase of focus and energy. Side-effects following administration that have been reported are tachycardia, anxiety, panic attacks, perspiration, headache, nausea, difficulty in breathing, vomiting, difficulty urinating and sexual dysfunction. Although some non-fatal and fatal intoxications involving MPA have been reported in the literature, they have also involved other drugs or else data to allow assessment have been limited (pp. 42-3).

Summary and conclusion

The three drugs (MDPV, BK-MDMA, MPA) above identified by WHO in their technical reports are newer designer drugs which are appearing on the market. BK-MDMA and MPA would be covered under the *amphetamines and amphetamine-type substances, including methamphetamine and 3,4-methylenedioxymethamphetamine (ecstasy)* group in the drug factor. The MDPV drug would sit in a psychostimulant drug class and may be better placed to be picked up by the generic drug factor.

Grade 2-3 level evidence

Alcohol

Summary of important issues

The **DSM-5**[156] states that panic or anxiety can occur in association with intoxication with alcohol and various other substances and also during withdrawal.

The literature supports a complex interactive relationship between alcohol intoxication/use/dependence and anxiety symptoms. A large body of evidence examines the anxiolytic effects of alcohol. [157] [158] Plebani et al (2012)[159] discusses the complex relationship in more detail, stating that alcohol can create, exacerbate, reduce, or have no effect on anxiety. A large body of research supports this statement, as do prominent theories of the acute effects of alcohol on mood, cognition, and behaviour. But Plebani does note that there is a paucity of good quality research to disentangle the relationship.

Review studies

Vorspan, Mehtelli, Dupuy et al (2015)[160] contends that the co-occurrence of substance use disorders (SUDs) and anxiety disorders has been now well established. This association is frequent and can be explained by three models: the shared vulnerability factors model, the self-medication model, and the substance-induced model. General population epidemiological studies provide strong evidence of the frequency of the association for the most used substances: tobacco, alcohol, cannabis, and to a lesser extent sedatives, opiates, and cocaine. Vorspan et al (2015) provided the most recent literature results on the association of SUDs and anxiety, and evidence for one explicative model or the other when available. For substances with sedative properties (alcohol, benzodiazepines, cannabis, opioids), they state that both evidence for a self-medication and for a toxic effect exist.

Specifically in regard to alcohol use disorder and anxiety research they state:

"Alcohol is the most widely used psychotropic substance in the world, with a prevalence of alcohol use as high as 80 % in most developed countries. The prevalence of alcohol use disorder (AUD) is debated, with lifetime prevalence rates ranging from 3 to 6 % in European countries and from 14 to 24 % in the USA according to similarly well-conducted epidemiological studies. The rate may be overestimated because most temporary problematic drinking meets AUD criteria [1]. That puts lifetime AUD to the prevalence of lifetime anxiety disorders [2••], which is also around 20–25 % of the general population. Thus, the co-occurrence of those equally frequent disorders could happen by chance only. But it is now strongly established that the co-occurrence of those two types of disorders is more frequent than expected if it was only by chance. ORs for the comorbidity between AUDs and anxiety are most often between 2 and 3 but can rise to 10 for the association with agoraphobia and

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[156] American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. DSM-5, 5th Edition,. American Psychiatric Publishing, Inc. 070783

[157] Gilman JM, Ramchandani VA, Davis MB, Bjork JM, Hommer DW. (2008). Why we like to drink: a functional magnetic resonance imaging study of the rewarding and anxiolytic effects of alcohol. J Neurosci.;28(18):4583-91.

[158] Parrott DJ, Gallagher KE, Zeichner A. (2012). Liquid courage or liquid fear: alcohol intoxication and anxiety facilitate physical aggression. Subst Use Misuse.;47(7):774-86.

[159] Plebani JG, Ray LA, Morean ME, Corbin WR, MacKillop J, Amlung M, King AC. (2012). Human laboratory paradigms in alcohol research. Alcohol Clin Exp Res.;36(6):972-83.

[160] Vorspan F, Mehtelli W, Dupuy G, et al (2015). Anxiety and substance use disorders: co-occurrence and clinical issues. Curr Psych Reports, 17: 4. 078389

generalized anxiety disorder (GAD) in patients defined as having alcohol dependence, even when the ORs are adjusted with other psychiatric disorders. In the recent years, the published papers are reanalyzing previous epidemiological studies, conducted in representative samples of the general population, in the USA (ECA Epidemiology Catchment Area, NCS National Comorbidity Survey, NESARC National Epidemiologic Survey in Alcohol and Related Conditions), in Europe (ZCSYA Zurich Cohorts Study of Young Adults, ESEMeD European Study of the Epidemiology of Mental Disorders, NESDA Netherlands Study of Depression and Anxiety), and in Australia (NSMHWB Australian National Survey of Mental Health and Wellbeing of Adults). Those new analyses provide interesting findings on specific risk factors that are associated with the comorbidity: younger age and early onset of both diseases, male gender, vulnerability factors (family history of alcohol problems, family history of anxiety or mood disorder, being single, childhood trauma, sensation seeking, or low conscientiousness), and other comorbid addictions.

As the age of onset of anxiety disorders and AUD are overlapping (childhood and early adolescence), epidemiological studies that have several waves of interview are of particular interest to try to distinguish between the self-medication and the alcohol-induced hypotheses. But they find results supporting both. Among results supporting the self-medication model, it has been shown that young adolescents with excessive timidity, inhibited behavior, or already diagnosed anxiety disorder (according to most studies: GAD and social phobia; and less replicated: panic disorder, PTSD, simple phobia) have higher risk of later AUD, with ORs around 2, when compared to the rest of the general population. Over 10 years, pre-existing anxiety disorders are predictive of transition from AUD to alcohol dependence (OR 3). But on the other hand, some prospective data derived from those studies support a toxic effect of alcohol, mainly when alcohol dependence criteria are chosen. Alcohol dependence is diagnosed when several social or medical complications are present and when several quit attempts have failed, which implicate an older age of onset if compared to AUD. Alcohol dependence remains a strong predictor of incident GAD, social phobia, and panic disorder (OR 2 for each disorder). Thus, the co-occurrence of anxiety disorders and AUD is well demonstrated but remains complex, with a highly prevalent association, and both a self-medication and a toxic effect are demonstrated" (Part 1. Epidemiology From the General Population).

"Comorbid anxiety disorders (panic disorder, agoraphobia, simple phobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder) are very common in clinical samples, ranging from 5 to 30 % in samples of alcohol use disorder (AUD) patients. In samples of anxiety disorder patients, the prevalence of AUD is usually 7–10 %, but up to 50 % of patients report self-medication of anxiety symptoms with alcohol. AUD predicts worse outcomes following treatment and must be considered as a risk factor for suicide. Clinical studies provide numerous pieces of evidence for both the self-medication hypothesis with a short-term anxiolytic effect of alcohol and for a toxic effect of prolonged alcohol consumption (abuse or dependence) that increases anxiety and induces anxiety symptoms among other withdrawal symptoms. Studies have tried to define optimal therapeutic strategies in case of a dual diagnosis" (Part 2. Studies Conducted in Clinical Samples).

Cosci et al (2007)[161] in a systematic review of the evidence relating to alcohol use disorders and panic disorder also reported a bidirectional relationship as discussed by Vorspan and colleagues (2015). They found that panic disorder with agorophobia and alcohol use disorders can both serve to initiate the other via independent mechanisms.

Kushner, Abrams and Borchardt (2000)[162] in another review of the literature relating to the relationship between anxiety disorders and alcohol use disorders also support the findings that anxiety disorder and alcohol disorder can both serve to initiate the other, especially in cases of alcohol dependence versus alcohol abuse alone.

Cohort studies

Haynes, Farrell, Singleton et al (2005)[163] examined whether excessive alcohol consumption is a risk factor for anxiety and depression in the general population, and whether anxiety and depression are risk factors for excessive alcohol consumption. Data were analysed from the 18-month follow-up of the Psychiatric Morbidity Among Adults Living in Private Households, 2000 survey.

Anxiety and depression was used as a diagnostic category, as most people with significant psychiatric problems have symptoms of both, and many meet the criteria for more than one diagnosis. The CIS–R has been validated as a measure of common mental disorders (Lewis et al, 1992), covering diagnoses of depressive illness, generalised anxiety disorder, obsessive– compulsive disorder, panic disorder, phobias, and mixed anxiety and depressive disorder. It comprises 14 sections, with possible scores within each ranging from 0 to 4 (except the section on depressive ideas which has a maximum score of 5). A total score of 12 or more was used to indicate the presence of disorder. Owing to questions relating only to the previous week, a true measure of incident anxiety and depression was not obtainable for the period between baseline and follow-up, as cases may have presented and then subsequently recovered. However, this phrase, or ‘new onset’, will be used as shorthand with the understanding that a random misclassification may have occurred. It is recognised that the CIS–R can be used to diagnose generalised anxiety disorder, and yet produce a score less than 12. This occurred in very few cases at baseline, and so the ensuing degree of bias was small.

Alcohol use was classified in four ways:

(a) hazardous drinking: AUDIT score 58;

(b) above government guidelines: more than 21 units per week for men or more than 14 units per week for women;

(c) binge-drinking: six or more drinks on one occasion on at least a monthly basis (same definition used for men and women);

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[161] Cosci F, Schruers KRJ, Abrams K, Griez EJL (2007). Alcohol use disorders and panic disorder- a review of the evidence of a direct relationship. J Clin Psychiatry, 68(6)- 874-80. 048538

[162] Kushner MG, Abrams K, Borchardt C (2000). The relationship between anxiety disorders and alcohol use disorders- a review of major perspectives and findings. Clinical Psychology Review, 20-149-171. 041514

[163] Haynes JC, Farrell M, Singleton N, et al (2005). Alcohol consumption as a risk factor for anxiety and depression: results from the longitudinal follow-up of the National Psychiatric Morbidity Survey. British Journal of Psychiatry; 187:544-51.

(d) dependence: AUDIT score 510 and SAD–Q 54.

Further analyses examined the association between anxiety and depression at baseline and alcohol use (binge-drinking, hazardous drinking or dependence) at follow-up. Individuals who were classified as binge drinkers (n=752), hazardous drinkers (n=669), or dependent on alcohol (n=309) at baseline were excluded from these additional analyses.

Hazardous and dependent drinking were not associated with onset of anxiety and depression at follow-up. Binge-drinking was non-significantly associated with incident anxiety and depression (adjusted OR=1.36, 95% CI 0.74-2.50). Abstainers were less likely to have new-onset anxiety and depression at follow-up.

Unadjusted analyses suggested that those who reported binge-drinking at least once per month were more likely to develop anxiety and depression at follow-up than non-binge drinkers (odds ratio=1.58, 95% CI 0.97–2.56). However, when adjusted for baseline CIS–R and potential confounders, this association was attenuated (odds ratio=1.36, 95% CI 0.74–2.50). Stratifying by gender showed some differences (Table below). Men who binged at least once per month had a threefold increased risk of anxiety and depression at follow-up after adjustment for confounders. In contrast, no excess was observed for female binge drinkers. However, a test for interaction did not provide statistical support (P=0.30).

Anxiety and depression or sub-threshold symptoms at baseline were not associated with incident hazardous or binge-drinking at follow-up, but there was weak evidence linking sub-threshold symptoms with onset of alcohol dependence (adjusted OR=2.04, 95% CI 0.84-4.97).

TABLE 45 GENDER-SPECIFIC ASSOCIATIONS: ALCOHOL CONSUMPTION AND ANXIETY AND DEPRESSION AT FOLLOW-UP (HAYNES ET AL, 2005).

Baseline variable	Men			Women		
	n	Odds ratio[1]	95% CI	*n*	Odds ratio[1]	95% CI
Hazardous drinking						
Never drank (or not in past 12 months)	57	0.19	0.04–0.92	112	0.42	0.17–1.06
AUDIT <8	342	1.00		616	1.00	
AUDIT ⩾8	312	0.85	0.38–1.90	139	0.53	0.22–1.27
Above government guidelines						
Never drank (or not in past 12 months)	57	0.20	0.04–0.93	112	0.45	0.18–1.13
Drink but not above guidelines	546	1.00		714	1.00	
Drink in excess of guidelines	107	1.28	0.50–3.26	41	0.60	0.18–2.05
Binge-drinking – monthly						
Never drank (or not in past 12 months)	57	0.32	0.07–1.50	112	0.42	0.17–1.07
No	322	1.00		571	1.00	
Yes	332	3.28	1.28–8.37	184	0.70	0.31–1.55
Frequency of binge-drinking						
Never drank (or not in past 12 months)	57	0.36	0.08–1.66	112	0.31	0.11–0.82
Drink alcohol but do not binge drink	196	1.00		378	1.00	
Binge – less than monthly	126	1.27	0.54–2.97	193	0.41	0.16–1.07
Binge – monthly	85	4.78	1.40–16.4	104	0.35	0.11–1.15
Binge – weekly (or daily)	247	3.14	1.07–9.26	80	0.60	0.22–1.63
Dependent (AUDIT ⩾10 and SAD–Q ⩾4)						
Never drank (or not in past 12 months)	57	0.21	0.04–0.96	112	0.45	0.18–1.14
Not dependent	490	1.00		714	1.00	
Dependent	164	1.29	0.53–3.14	41	0.75	0.18–3.06

AUDIT, Alcohol Use Disorders Identification Test; SAD–Q, Severity of Alcohol Dependence Questionnaire; CIS–R, Clinical Interview Schedule – Revised.
1. Adjusted for baseline CIS–R, age, gender, ethnicity, marital status, educational qualifications, employment status, social class, housing tenure, life events, type of area (urban/rural), weekly income, size of primary support group, current smoking habits, illicit drug use in the previous year, use of psychotropic drugs or therapy, and consultations with mental health professional(s) in the past year.

Excessive alcohol consumption was not associated with the onset of anxiety and depression but abstinence was associated with a lower risk. Sub-threshold symptoms were weakly associated with new-onset alcohol dependence. Analyses stratified by gender suggested that men who binge drank (on at least a monthly basis) had a threefold increased odds of anxiety and depression at follow-up compared with men who did not binge drink. No such association was observed for women.

Alati, Lawlor, Najman, Williams, Bor and O'Callaghan (2005)[164] determined the nature of the association between alcohol consumption and symptoms of anxiety and depression in women. The study was a prospective cohort of women (n = 4527) who received antenatal care at a major public hospital (Mater Misericordiae Hospital) in South Brisbane between 1981 and 1984 and who have follow-up data on alcohol use, depressive and anxiety symptoms over a 14-year period.

[164] Alati R, Lawlor DA, Najman JM, et al (2005). Is there really a 'J-shaped' curve in the association between alcohol consumption and symptoms of depression and anxiety? Findings from the Mater-University Study of Pregnancy and its outcomes. Addiction; 100(5):643-51.

Depression and anxiety were assessed at all phases of the study using the Delusions-Symptoms-States Inventory (DSSI) (Bedford & Foulds 1978; cited in Alati et al, 2005). The DSSI items were administered to the mother in the form of a self-report questionnaire. The DSSI was developed by clinicians and validated against a clinical sample (Bedford & Foulds 1977; cited in Alati et al, 2005). It contains a depression subscale which has been found to correlate strongly with other scales of depression including the Beck's Depression Inventory (Najman et al. 2000; cited in Alati et al, 2005). In this sample, the depression subscale obtained Cronbach's a values of 0.78 at the first clinic visit, 0.86 at 5-year follow-up and 0.88 at 14-year follow-up, whereas the internal consistency of the anxiety subscale was 0.76 at first clinic visit, 0.83 at 5-year follow-up and 0.84 at 14-year follow-up. In this study in the main analyses maternal symptoms of depression were defined as having three or more of seven of the symptoms in the DSSI depression subscale and symptoms of anxiety were defined similarly as having three or more of seven of the symptoms in the anxiety subscale. In order to ensure that the results were not driven by the choice of cut-off for defining a case, we also conducted sensitivity analyses in which all analyses were repeated with both outcomes defined by two or more, four or more and five or more symptoms.

At each assessment the women were asked how frequently they consumed alcohol (six pre-specified categories from never to daily) and how much they consumed at each session (six prespecified categories from none to seven or more standard drinks). These data were used to categorize the women into four categories that were similar to those used in the previous British prospective study: abstainers; light drinkers (>none to five drinks per week); moderate drinkers (six to 20 drinks per week) and heavy drinkers (greater than 20 drinks per week) (Power et al. 1998 ;cited in Alati et al, 2005).

At the 5-year follow-up there was a 'J-shaped' association between alcohol consumption and both symptoms of depression and of anxiety. Although for anxiety disorder only the abstainers in fully adjusted analysis reported a statistically significant result (OR 1.24; 95% CI 1.04 – 1.46) (see table below). At the 5-year follow-up the prevalence of depressive and anxiety symptoms among those who were abstainers at both baseline and 5-year follow-up was similar to that among those who had been previous drinkers and then become abstainers (P = 0.67). In age-adjusted analyses at baseline and 5-year follow-up heavy drinking was significantly associated with anxiety symptomatology; however, when also controlling for smoking, family income, marital status and relationship quality the results became none significant.

Similarly, the prevalence of these symptoms was the same at the 14-year follow-up comparing those who had been abstainers at baseline, 5-year and 14-year follow-up to those who had previously consumed alcohol but were then abstainers. At the baseline assessment and the 14-year follow-up alcohol consumption was linearly and positively associated with depressive symptoms with increasing prevalence of symptoms with greater consumption, but not with anxiety.

TABLE 46 MULTIVARIABLE ASSOCIATIONS BETWEEN ALCOHOL CONSUMPTION AND SYMPTOMS OF DEPRESSION AND ANXIETY AT EACH OF THE THREE STAGES OF THE STUDY AMONG THOSE WITH COMPLETE DATA ON ALL COVARIATES, N = 4205 (ALATI ET AL, 2005).

	Baseline [mean (SD) age = 25.0 (5.0)]		*5-year follow-up [mean (SD) age = 30.2 (5.1)]*		*14-year follow-up [mean (SD) age = 39.7 (5.2)]*	
	Age-adjusted OR (95% CI)	*Fully adjusted[a] OR (95% CI)*	*Age-adjusted OR (95% CI)*	*Fully adjusted[a] OR (95% CI)*	*Age-adjusted OR (95% CI)*	*Fully adjusted[a] OR (95% CI)*
Depression						
Abstainers	0.85 (0.65, 1.10)	0.88 (0.67, 1.15)	1.27 (1.01,1.62)	1.35 (1.06, 1.72)	1.00 (0.95, 1.83)	1.00 (0.78, 1.29)
Light drinkers	1.00	1.00	1.00	1.00	1.00	1.00
Moderate drinkers	1.16 (0.78, 1.72)	0.91 (0.62, 1.37)	1.55 (1.01, 2.39)	1.42 (0.92, 2.20)	1.32 (0.95, 1.83)	1.30 (0.93, 1.80)
Heavy drinkers	1.39 (0.65, 2.97)	0.92 (0.42, 2.00)	2.52 (1.08, 5.85)	2.07 (0.89, 4.87)	1.43 (0.83, 2.47)	1.31 (0.75, 2.26)
P-value for linear trend	0.05	0.67	0.77	0.52	0.10	0.19
P-value for non-linear association	0.96	0.64	0.006	0.01	0.45	0.51
Anxiety						
Abstainers	0.92 (0.77, 1.10)	0.94 (0.78, 1.13)	1.19 (1.00, 1.40)	1.24 (1.04, 1.46)	1.05 (0.88, 1.25)	1.07 (0.90, 1.27)
Light drinkers	1.00	1.00	1.00	1.00	1.00	1.00
Moderate drinkers	1.17 (0.87, 1.56)	1.01 (0.75, 1.36)	1.44 (1.05, 1.97)	1.34 (0.98, 1.85)	1.07 (0.83, 1.37)	1.04 (0.81, 1.33)
Heavy drinkers	2.02 (1.18, 3.45)	1.59 (0.92, 2.76)	2.16 (1.08, 4.30)	1.85 (0.92, 3.71)	1.12 (0.73, 1.72)	1.02 (0.67, 1.57)
P-value for linear trend	0.01	0.18	0.83	0.62	0.88	0.72
P-value for non-linear association	0.30	0.47	0.003	0.006	0.72	0.80

[a]Adjusted for family income, smoking, marital status and relationship quality.

The nature of the association between alcohol consumption and symptoms of depression and anxiety may vary across their life course in women. Previous drinkers who become abstainers do not appear to be at any higher risk of symptoms of depression or anxiety compared to those who always abstained, suggesting that increased symptoms in abstainers at age 30 is not due to 'sick quitters'. **The association of high alcohol consumption with symptoms of depression and anxiety may be confounded by low income and smoking.**

Cross-sectional studies

Caldwell, Rodgers, Jorm, Christensen et al (2002)[165] examined levels of affect, depression and anxiety over the full range of alcohol consumption in young adults. The study was a cross-sectional design which reported findings from the first wave of a prospective, longitudinal study. The general population sample comprised of 2 404 young adults (aged 20-24 years). living in the Canberra region. Various measures were utilised in this study including: Consumption categories from AUDIT quantity/frequency items: (1) non-drinkers (no alcohol in the past year), (2) occasional drinkers (monthly or less), (3) lower-level drinkers (up to 14 standard drinks per week for men and seven for women), (4) higher-level drinkers (up to 28 and 14 standard drinks per week, respectively), and (5) those drinking at hazardous or harmful levels (over 28 and 14 standard drinks per week, respectively). Measures included: the Goldberg Depression and Anxiety scales, the Positive and Negative Affect Schedule, and the Alcohol Use Disorders Identification Test.

For men, both non/occasional and hazardous/harmful consumption were associated with lower levels of positive affect and higher levels of anxiety and depression. The higher levels of distress evident for male abstainers were related to being less extroverted and less healthy and not to past hazardous/harmful alcohol consumption, current tobacco or marijuana use. **For women, only hazardous/harmful drinkers were found to have higher levels of depression and negative affect, no significant association with anxiety was noted.** Hazardous/harmful consumption was related to using marijuana, tobacco and recent stressful events in both men and women.

[165] Caldwell TM, Rodgers B, Jorm AF, Christensen H, Jacomb PA, Korten AE, Lynskey MT. (2002). Patterns of association between alcohol consumption and symptoms of depression and anxiety in young adults. Addiction; 97(5):583-94.

TABLE 47 MEAN (AND SE) GOLDBERG AND PANAS SCORES BY ALCOHOL CONSUMPTION FOR MEN, WITH AND WITHOUT ADJUSTMENT FOR POSSIBLE CONFOUNDERS (CALDWELL ET AL, 2002).

Mental health variable	*Non-/ occasional n = 294*	*Light n = 606*	*Moderate n = 126*	*Hazardous/ harmful n = 70*
Depression (unadjusted)***	**2.84 (0.13)**	2.32 (0.09)	2.51 (0.20)	**3.61 (0.27)**
(1) adjusted (tobacco, marijuana, life events)***	**2.96 (0.16)**	2.32 (0.12)	2.32 (0.19)	**3.06 (0.26)**
(2) adjusted (tobacco, marijuana)***	**3.02 (0.16)**	2.32 (0.12)	2.28 (0.20)	**3.20 (0.27)**
(3) adjusted (extraversion, PCS-12, paid work)***	2.60 (0.14)	2.32 (0.11)	2.55 (0.21)	**3.60 (0.27)**
(4) excluding (past and present haz/harmful drinkers)**	**2.93 (0.13)**	2.32 (0.10)	2.21 (0.27)	
Anxiety (unadjusted)**	**3.35 (0.15)**	2.98 (0.10)	3.18 (0.23)	**4.17 (0.31)**
(1) adjusted (tobacco, marijuana, life events)**	**3.51 (0.18)**	2.98 (0.13)	2.96 (0.22)	3.52 (0.30)
(2) adjusted (tobacco, marijuana)**	**3.58 (0.19)**	2.98 (0.14)	2.91 (0.23)	**3.70 (0.31)**
(3) adjusted (extraversion, PCS-12, paid work)**	3.13 (0.17)	2.98 (0.13)	3.21 (0.24)	**4.17 (0.31)**
(4) excluding (past and present haz/harmful drinkers)	**3.41 (0.15)**	2.98 (0.11)	3.02 (0.31)	
Positive affect (unadjusted)*	**32.77 (0.40)**	34.06 (0.28)	33.41 (0.62)	**31.93 (0.83)**
(1) adjusted (tobacco, marijuana, life events)**	**32.42 (0.52)**	34.06 (0.39)	33.72 (0.65)	32.47 (0.87)
(2) adjusted (tobacco, marijuana)**	**32.40 (0.52)**	34.06 (0.39)	33.74 (0.65)	32.41 (0.86)
(3) adjusted (extraversion, PCS-12 Paid work, BAS-funseeking)*	34.11 (0.41)	34.06 (0.33)	32.88 (0.60)	**31.80 (0.79)**
(3b) adjusted (BAS-funseeking, extraversion)*	33.89 (0.38)	34.06 (0.26)	32.79 (0.57)	**31.85 (0.77)**
(4) excluding (past and present haz/harmful drinkers)*	**32.59 (0.42)**	34.06 (0.31)	33.60 (0.85)	
Negative affect (unadjusted)	18.08 (0.37)	17.43 (0.26)	17.38 (0.57)	18.76 (0.76)

Depression (SD = 2.26), anxiety (SD = 2.58), positive affect (SD = 6.95), negative affect (SD = 6.40).
The bold figures indicate the consumption categories which differ significantly from light drinkers ($p < 0.05$).
Asterisks refer to overall significance levels for overall alcohol consumption: * < 0.05, ** < 0.01, *** < 0.001.

Higher levels of distress are already evident in male non-drinkers in early adulthood. The findings counter theories that distress in non-drinkers is due to past hazardous/harmful alcohol consumption, marijuana or tobacco use, or characteristics in common with hazardous/harmful drinkers. Alcohol use disorders and mental health problems are pertinent issues for young adults. However, more understanding is needed of the experiences of non-drinkers in an alcohol consuming culture.

Low, Lee, Johnson, Williams and Harris (2008)[166] conducted a cross-sectional study to test the association between current anxiety with alcohol versus cannabis abuse disorders. The study used clinician-administered, structured assessment--using the Primary Care Evaluation of Mental Disorders--to evaluate anxiety, mood and substance abuse disorders among 632 adolescents recruited from primary care settings.

Results show a strong association between current anxiety and alcohol [odds ratio = 3.8; 95% confidence interval (CI) 1.2-11.8], but not cannabis (odds ratio = 1.4; 95% CI 0.4-4.7) abuse (see Table below).

“Due to the cross-sectional design of this study, evidence supporting the pathway or evolution to this association cannot be provided here. There is little research in the age group of 13–17 given alcohol use is illegal in North America and most parts of Europe. However, research on

[166] Low NC, Lee SS, Johnson JG, Williams JB, Harris ES. (2008). The association between anxiety and alcohol versus cannabis abuse disorders among adolescents in primary care settings. Family Practice; 25(5):321-7.

the next older age group (young adults) may shed some light on certain aspects of the association.

Research in young adults (~18 to early 20s) has shown complexity in the relationship between anxiety, motives to drink (e.g. for coping/stress management) and alcohol use (Schmidt et al, 2007; Hussong et al, 2005; Lewis et al, 2008; Ham et al, 2007). Some findings have supported social anxiety as a risk for alcohol use, whereas others have not. Two large nationally representative epidemiologic studies have examined the perspective that anxiety plays a primary role leading to alcohol misuse, also known as 'alcohol as self-medication for anxiety'. Bolton et al. (2006) observed that in a sample of ~8000 persons (aged 15–54) those with anxiety who self-medicated with drinking had higher rates of alcohol abuse. Falk et al. (2008) looked at the temporal sequencing of the onset of specific anxiety and mood disorders with respect to alcohol misuse (abuse and dependence) in the NESARC sample of nearly 20 000 (over-sampled for 18- to 24-year olds). They found that specific phobia and social anxiety were the only two disorders to precede alcohol misuse, while panic disorder and generalized anxiety disorder increased the risk of persistent alcohol dependence" (p. 325).

TABLE 48 ASSOCIATION BETWEEN ANXIETY AND ALCOHOL AND CANNABIS ABUSE DISORDERS (LOW ET AL, 2008).

	Alcohol abuse	Cannabis abuse
	Odds ratio (95% CI)	Odds ratio (95% CI)
Main effect		
Anxiety disorder	3.8 (1.2–11.8)	1.4 (0.4–4.7)
Covariates		
Mood disorder	0.6 (0.2–2.0)	2.0 (0.8–4.8)
Sex (0 = male, 1 = female)	0.6 (0.3–1.2)	0.5 (0.2–1.0)
Age	1.2 (0.9–1.6)	1.7 (1.2–2.3)
Ethnicity	0.7 (0.5–1.1)	0.8 (0.5–1.2)
Sampling site	1.0 (0.9–1.2)	1.1 (0.5–1.1)

This association in adolescents reflects the importance for increased awareness of anxiety symptoms and alcohol use patterns in primary care. The lack of association of anxiety with cannabis abuse in this group may reflect differences in cannabis' anxiolytic properties or that this young group has had less exposure thus far. Given adolescence is a time of especially rapid psychosocial, hormonal and brain development, primary care may provide an opportunity for further investigation and, potentially, early screening and intervention.

Summary and conclusion

Vorspan et al (2015) in their review support the association between alcohol exposure at the level of dependence and anxiety symptomatology. The relationship may be bi-directional with studies supporting anxiety preceding alcohol use disorder and developing as a consequence of it. This is supported by two earlier reviews (Cosci et al, 2007; Kushner et al, 2000).

The two cohort studies (Haynes et al, 2005; Alati et al, 2005) did not report statistically significant associations between alcohol consumption at any level and anxiety symptoms for women. Haynes and colleagues did report a significant association between binge drinking on at least a monthly basis and anxiety for men, when compared with men who did not binge drink.

The cross-sectional study (Caldwell et al, 2002) supported Haynes results regarding men and hazardous/harmful alcohol consumption; but not for women. Low et al (2008) in their cross-sectional study of adolescents found that current anxiety and alcohol abuse were strongly associated. A gender specific analysis was not carried out by Low et al.

A number of studies suggest a J-shaped relationship between alcohol use and anxiety, with those who abstain and those who consume high levels of alcohol reporting stronger associations. But this relationship is not consistently reported.

The evidence for binge drinking on at least a monthly basis and anxiety onset was supported by a prospective cohort study and a cross-sectional study. Grade 2-3 level evidence

The available studies also supported an association between alcohol use disorder and anxiety onset.

Other Substances/Gases

Nicotine/smoking

Summary of important issues

There has been a large amount of studies published on this topic – however the evidence is not consistent and a dose-response relationship is only reported in a few studies. A bi-directional causal relationship is suggested by a number of authors.

Systematic reviews

Moylan et al (2012)[167] undertook a systematic review of population-based observational studies that utilized recognized structured clinical diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD)) for anxiety disorder diagnosis to investigate the relationship between cigarette smoking, nicotine dependence and anxiety disorders.

In total, 47 studies met the predefined inclusion criteria, with 12 studies providing prospective information and 5 studies providing quasiprospective information. The available evidence suggests that some baseline anxiety disorders are a risk factor for initiation of smoking and nicotine dependence, although the evidence is heterogeneous and many studies did not control for the effect of comorbid substance use disorders. The identified evidence however appeared to more consistently support cigarette smoking and nicotine dependence as being a risk factor for development of some anxiety disorders (for example, panic disorder, generalized anxiety disorder), although these findings were not replicated in all studies. A number of inconsistencies in the literature were identified.

Although many studies have demonstrated increased rates of smoking and nicotine dependence in individuals with anxiety disorders, there is a limited and heterogeneous literature that has prospectively examined this relationship in population studies using validated diagnostic criteria. The most consistent evidence supports smoking and nicotine dependence as increasing the risk of panic disorder and generalized anxiety disorder. The literature assessing anxiety disorders increasing smoking and nicotine dependence is inconsistent. Potential issues with the current literature are discussed and directions for future research are suggested.

Multiple studies have demonstrated that rates of smoking and nicotine dependence are increased in individuals with anxiety disorders. However, significant variability exists in the epidemiological literature exploring this relationship, including study design (cross-sectional versus prospective), the population assessed (random sample versus clinical population) and diagnostic instrument utilized.

“The available prospective evidence associating smoking and nicotine dependence as risk factors for incident anxiety disorders is limited and heterogeneous. However, smoking has been demonstrated as a risk factor for grouped anxiety disorders, panic disorder and generalized anxiety disorder in a number of studies, although these findings are not replicated in all studies. Data from the Oregon Adolescent Depression Project were utilized to assess the

[167] Moylan S, Jacka FN, Pasco JA, et al (2012). Cigarette smoking, nicotine dependence and anxiety disorders: a systematic review of population-based, epidemiological studies. BMC Med, : Epub. 070553

relationship between baseline smoking status and incident ADs. Goodwin et al. [2005] demonstrated an association between increased odds of PD diagnosis at age 24 in those with daily smoking at baseline versus those not smoking daily (OR 5.1 (2.4 to 10.5)), which remained significant after controlling for other ADs and parental risk factors. No other associations were found.

Utilizing data from the Detroit Epidemiologic Study, Breslau et al. [1999] found increased risk of subsequent PD onset in individuals with prior daily smoking even when controlling for gender and MDD (HR 13.13 (4.41 to 39.10)). In addition, prior daily smokers who continued to smoke were more likely to experience incident PD (HR 14.46 (4.81 to 43.5)) when controlled for gender and MDD.

In the New York Adolescent Cohort, relationships were discovered between odds of adult ADs when grouped (OR 10.78 (1.48 to 78.55)), GAD (OR 5.53 (1.84 to 16.66) and PD (OR 15.58 (2.31 to 105.14) when comparing baseline > 1 pack per day smokers versus < 1 pack per day smokers [Johnson et al, 2000]. Data from the EDSP studies [Isensee et al, 2003] demonstrated relationships between increased incident PD, agoraphobia, SP and PTSD when comparing baseline ND smokers versus non-users, however all associations became non-significant when controlled for comorbid conditions at baseline (depressive disorders, panic attacks, other ADs, alcohol and drug disorders, and eating disorders). In the NESARC study, Chou et al. [2011] assessed the relationship between ND at baseline and subsequent ADs, finding no associations. Cuijpers et al. [2007] utilized data from the NEMESIS to investigate the relationship between incident ADs (expressed as incident rate ratios) and past smoking status. Smoking at 1-year follow-up was associated with increased incidence of grouped ADs (IRR 1.77 (1.10 to 2.86)) and GAD (IRR 3.80 (1.09 to 13.21)) after controlling for demographics and other risk factors. No other relationships were found" (see Table below) (Section: Smoking and nicotine dependence as risk factors for later anxiety disorders).

TABLE 49 PROSPECTIVE LONGITUDINAL STUDIES INVESTIGATING INFLUENCE OF SMOKING AND NICOTINE DEPENDENCE (ND) ON SUBSEQUENT RISK OF ANXIETY DISORDERS (MOYLAN ET AL, 2012).

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Breslau et al, 1999 [14]	Sample randomly drawn from 21-30 yr old individuals from a large HMO (general population) as part of the Detroit Epidemiologic Study (DES)(n=1007) ; and Participants a part of the National Comorbidity Survey (NCS), a stratified, multistage probability sample of US non-institutionalised residents age 15-54. Respondents (n= 4411) who undertook the tobacco use component of the NCS survey were included.	Prospective Follow up: DES: Baseline assessment occurred in 1989 (n=1007) Follow up 1 = 1990 Follow up 2 = 1992 Follow up 3 = 1994 (Complete follow up data available for n=974)	NIMH-DIS, revised to cover DSM-III-R criteria by face to face interviews for the DES; and M-CIDI for DSM-III-R criteria (NCS)	Self Report Smoking: Daily smoking = smoking daily for >=1 month	HR of PD onset: Prior Daily smoking vs. Prior No Daily smoking Prior daily smokers who continued to smoke vs. Prior daily smokers who didn't continue to smoke Prior daily smokers who quit vs. Prior daily smokers who didn't quit	HR of PD onset: Adjusted HR (95% CI)*: DES: Prior daily smoking vs. No prior daily smoking = HR 4.73 (2.36-9.49)*, HR 13.13 (4.41-39.10)** DES: Prior daily smokers who continued to smoke vs. Prior daily smokers who didn't continue to smoke = HR 14.46 (4.81 - 43.5)** DES: Prior daily smokers who quit vs. Prior daily smokers who didn't quit = HR 0.51 (0.12-2.28)** NCS: Prior daily smoking vs. No prior daily smoking = HR 2.93 (1.84-4.66)** NCS: Prior daily smokers

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						who continued to smoke vs. Prior daily smokers who didn't continue to smoker = HR 3.18 (1.99-5.10)** NCS: Prior daily smokers who quit vs. Prior daily smokers who didn't quit = HR 1.82 (0.69-4.28)** Daily Smoking to PD: DES HR 13.13 (4.41-39.10); NCS : HR 2.93 (1.84-4.66) *Adjusted for gender ** Adjusted for gender and major depressive disorder
Chou et al, 2011 [25]	Study population drawn from Nationally representative sample (NESARC), addressing only those aged 60 yrs or older (n= 8012). , community dwelling adults aged over 60 years.	Wave 1 of NESARC performed in 2000-2001. Wave 2 of NESARC performed in 2004-2005. Mean interval	AUDADIS-IV for DSM-IV criteria	ND using AUDADIS-IV	Odds of Incident AD: Baseline ND vs. No Baseline ND	Odds of Incident AD (prospective): OR (99% CI): PD: ND Baseline vs. No ND Baseline = OR 1.07 (0.32-3.58)

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
		between waves 36.6 months (SD= 2.62)				Specific Phobia: ND Baseline vs. No ND Baseline = OR 1.69 (0.73-3.94) SP: ND Baseline vs. No ND Baseline = OR 2.76 (0.84-9.07) GAD: ND Baseline vs. No ND Baseline = OR 1.20 (0.53-2.71)
Cuijpers et al, 2007 [27]	Participants aged 18-64 drawn from the NEMESIS study (Netherlands Mental Health Survey and Incidence Study), a multistage, stratified, random population sample of 90 municipalities (n=4796 at final followup)	Baseline assessment (n= 7076) Time 1 Follow up at 1 year (n= 5618) Time 2 Follow up at 3 years(n= 4796)	CIDI for DSM-III-R diagnosis	Self Report: Past year smoking assessed at Time 1 & Time 2. Categories of smokers: Non-smokers 1-9 cigarettes daily 10-19 cigarettes	Incident Rate Ratios of AD's: Smoking at time 1 vs. Non smoking at time 1	Grouped & Individual AD's (prospective) Adjusted Incident Rate Ratio (95% CI)* of new onset AD: Grouped AD: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 1.88 (1.15-3.06)*, p<0.05 Grouped AD: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 1.77 (1.10-2.86)** p<0.05

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
				daily >20 cigarettes daily		GAD: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 4.57 (1.53-13.67)* p<0.01 GAD: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 3.80 (1.09-13.21)** p<0.05 PD: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 1.15 (0.31-4.17)* PD: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 0.94 (0.28-3.24)** Agoraphobia: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 13.52 (0.91-13.65)* Agoraphobia: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 4.07 (0.88-18.85)** SP: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 1.37 (0.34 - 5.53)*

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						SP: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 1.26 (0.31-5.21)** Specific Phobia: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 1.59 (0.84-3.02)* Specific Phobia: Smoking at Time 1 vs. Non Smoking at Time 1 = IRR 1.50 (0.82-2.73)** * Adjusted for gender, age, education level, employment status ** Adjusted for gender, age, education level, employment status, childhood trauma, parental psychopathology, somatic illnesses, locus of control & neuroticism
Goodwin et al, 2005 [13]	Participants drawn from time 3 of the Oregon Adolescent Depression Project (n=904).	Participants initially assessed between age 14-18	Children were assessed at time 1 using the K-	Self Report at each assessment:	Odds of Individual AD's at time 3:	Individual Anxiety Disorder (Prospective) OR (95% CI):

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
	Participants randomly selected from 9 senior high schools in Western Oregon.	(time 1), and followed for two further follow up assessments at 1 year (time 2) and at their 24th birthday (time 3)	SADS and additional questions to elicit DSM-III-R diagnoses; At time 3 participants assessed with the Longitudinal Interval Follow-Up Evaluation* to elicit diagnoses to DSM-IV criteria	Life time cigarette use Current frequency of cigarette smoking Highest previous frequency of cigarette smoking (every day, 3-6 times per week, 1-2 times a week, not at all); From this participants divided into 4 categories: 1) daily smoking lifetime at baseline, 2) daily smoking lifetime at	Daily smoking at time 1 & Ever smoking at time 1 vs. Never smoking time 1	Odds of PD at time 3: Daily smoking time 1 vs. No Daily smoking) = OR 5.1 (2.4-10.5), p<0.05 Odds of PD at time 3: Ever smoking at time 1 vs. Never smoking at time 1 = OR 1.8 (0.4 - 8.8) Odds of Specific Phobia at time 3: Daily smoking time 1 vs. No Daily smoking time 1 = OR 1.7 (.6-4.6) Odds of SP at time 3: Daily smoking time 1 vs. No Daily smoking time 1 = OR 1.7 (0.8-3.9) Odds of SP at time 3: Ever smoking time 1 vs. Never smoking time 1 = OR 1.0 (0.3-3.5) Odds of PTSD at time 3: Daily smoking time 1 vs. No Daily smoking time 1 = OR 1.3 (0.7-2.3)

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
				Time 3, 3) ever lifetime smoking at baseline and 4) ever lifetime smoking at time 3		Odds of PTSD at time 3: Ever smoking time 1 vs. Never smoking time 1 = OR 1.3 (0.6-2.8) Adjusted OR (95% CI)*: Odds of PD at time 3: Daily Smoking time 1 vs. No Daily Smoking = OR* 4.2 (2.0-8.9) Odds of PD at time 3: Daily Smoking time 1 vs. No Daily Smoking = OR** 3.7 (1.6-8.9) * Adjusted for other anxiety disorders (Specific Phobia, SP, Separation Anxiety disorder, PTSD (lifetime) ** Adjusted for other anxiety disorders (Specific Phobia, SP, Separation Anxiety disorder, PTSD (lifetime) , and parental anxiety,

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						parental smoking, and the interaction between the two.
Isensee et al, 2003 [22]	Participants drawn from the Early Developmental Stages of Psychopathology Study (EDSP), a community sample from metropolitan Munich (n= 3021) of adolescents and young adults aged 14 - 24.	Baseline assessment occurred in 1995. Follow up assessment 1 occurred between 1996/1997 - Average 19.7 months post baseline assessment Follow up assessment 2 occurred between 1998/1999.	M-CIDI for DSM-IV criteria diagnosis	Nicotine dependence: M-CIDI for DSM-IV criteria Self Report: Smoking assessment: Regular smoking defined as daily use for at least 4 weeks Smoking behavior, Age of onset, Age at commencement regular smoking:	Odds of Incident AD: By smoking status at baseline	Odds of Incident AD (prospective): Adjusted OR (95% CI)*: Odds of Incident PD: Occasional User (baseline) vs. Non User (baseline) = OR 0.3 (0-1.3) Odds of Incident PD: Non ND smoker (baseline) vs. Non User (baseline) = OR 1.1 (0.2-5.7) Odds of Incident PD: ND smoker (baseline) vs. Non User (baseline = OR 3.3 (1.0-10.5), p<0.05** Odds of Incident PD: Adjusted HR (95% CI): ND vs. no ND baseline: HR 1.7 (0.7-3.9) (Cox regressions with time-

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
				Categories of smoker: 1) Non-users (No lifetime smoking) 2) Occasional user (Have used but never daily for 4 weeks) 3) Non-dependent regular smokers (Daily smoking >4 weeks in lifetime but not DSM-IV ND) 4) Dependent regular smokers (Daily smoking >4 weeks in		dependent covariates) Odds of Incident Agoraphobia: Occasional User (baseline) vs. Non User (baseline) = OR 2.0 (0.6-6.5) Odds of Incident Agoraphobia: Non ND smoker (baseline) vs. Non User (baseline) = OR 2.6 (0.7-9.9) Odds of Incident Agoraphobia: ND smoker (baseline) vs. Non User (baseline = OR3.7 (1.1-12.1), p<0.05** Odds of Incident SP: Occasional User (baseline) vs. Non User (baseline) = OR 0.7(0.3-1.6) Odds of Incident SP: Non ND smoker (baseline) vs. Non User (baseline) = OR

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
				lifetime & DSM-IV ND)		1.3 (0.5-3.1) Odds of Incident SP: ND smoker (baseline) vs. Non User (baseline = OR2.5 (1.1-5.4), p<0.05** Odds of Incident GAD: Occasional User (baseline) vs. Non User (baseline) = OR 0.4 (0.0-1.8) Odds of Incident GAD: Non ND smoker (baseline) vs. Non User (baseline) = OR 0.1 (0.0-0.5), p<0.05 Odds of Incident GAD: ND smoker (baseline) vs. Non User (baseline = OR 3.6 (0.9-13.3) Odds of Incident OCD: Occasional User (baseline) vs. Non User (baseline) = OR 0.4 (0.0 -

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						3.5) Odds of Incident OCD: Non ND smoker (baseline) vs. Non User (baseline) = OR 0.2 (0.0-3.7) Odds of Incident OCD: ND smoker (baseline) vs. Non User (baseline = OR 4.2 (0.6-29.1) Odds of Incident PTSD: Occasional User (baseline) vs. Non User (baseline) = OR 3.0 (0.7-11.6) Odds of Incident PTSD: Non ND smoker (baseline) vs. Non User (baseline) = OR 2.2 (0.3-13.3) Odds of Incident PTSD: ND smoker (baseline) vs. Non User (baseline = OR 5.1 (1.2-21.5), p<0.05**

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						Odds of Incident Specific Phobia: Occasional User (baseline) vs. Non User (baseline) = OR 1.2 (0.7-2.0) Odds of Incident Specific Phobia: Non ND smoker (baseline) vs. Non User (baseline) = OR 1.3 (0.5-3.1) Odds of Incident Specific Phobia: ND smoker (baseline) vs. Non User (baseline = OR 2.5 (1.1-5.4), p<0.05** * Adjusted for age & gender ** Association failed to reach significant when controlled for comorbidity at baseline (depressive disorders, panic attacks, other AD, alcohol and illicit drug

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						disorders, eating disorders)
Johnson et al, 2000 [17]	Community based sample of youths (n = 688) randomly selected from upper New York State in 1975.	Initially assessed during 1983 (Mean Age 14 yrs) and followed at two subsequent time points, between 1985-86 (Mean Age 16 yrs) and 1991-1993 (Mean Age 22 yrs)	Diagnostic Interview Schedule for Children (DIS-C) to DSM-III criteria	Self Report: Cigarette Smoking categorised: < 1 pack (1-19 cigarettes day) vs. >1 pack (20+ cigarettes a day)	Odds of AD occurrence in Adulthood: Smoking >1 pack vs. Smoking <1 pack daily in adolescence	Group Anxiety Disorder (Prospective) Adjusted OR (95% CI)*: Odds of Adult AD: Smoking > 1 pack vs. Smoking <1 pack = OR 10.78 (1.48-78.55) Odds of Adult GAD: Smoking > 1 pack vs. Smoking <1 pack = OR 5.53 (1.84-16.66) Odds of Adult OCD: n/a Odds of Adult PD: Smoking > 1 pack vs. Smoking <1 pack = OR 15.58 (2.31-105.14) Odds of SP: Smoking > 1 pack vs. Smoking <1 pack = OR 0.44 (0.04-4.62) * Adjusted for age, sex, difficult childhood temperament, alcohol and drug use, anxiety, and depressive disorders

STUDY	Study Population	Prospective Follow Up	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						during adolescence, and parental smoking, educational level and psychopathology

“Breslau et al. [2004] utilized the NCS, including respondent recall about their age of smoking and ND onset, to assess the effect of these parameters on developing ADs. Adjusting for demographic characteristics, pre-existing daily smoking (defined as onset > 1 year prior to disorder onset) was associated with increased odds of PD (OR 2.6 (1.2 to 5.4)) and agoraphobia (OR 4.4 (2.3 to 8.2)). The role of ND was assessed across all ADs. In this analysis, ND smokers and non-ND smokers maintained increased odds of PD and agoraphobia, but no other ADs. The only other associations were found in relation to past smokers (without ND) who exhibited decreased odds of PTSD (OR 0.2 (0.1 to 0.5)) when controlled for demographics and other pre-existing psychiatric disorders. Breslau et al. [2004] extended their study by comparing the age of smoking onset (early vs not early; see Table below for definitions), standardized pack years of smoking and time since quitting against odds of AD diagnosis. No association was found between early onset smoking and ADs, but increased years since quitting was associated with decreased odds of subsequent PD (OR 0.5 (0.4 to 0.7)), agoraphobia (OR 0.5 (0.5 to 0.8)) and SP (OR 0.6 (0.4 to 0.8)). The associations between standardized pack years of smoking were not significant in all ADs except PD, where increased pack years of smoking appeared protective in current smokers but a risk factor in past smokers, and GAD where increased pack years was associated with increased odds of GAD in both current and past smokers.

In a separate analysis utilizing a subsample of NCS data, Breslau et al. [1999] investigated the interaction between smoking characteristics and subsequent onset of PD. Significant relationships were discovered between prior daily smoking (HR 2.93 (1.84 to 4.66)) and smoking persistence in prior daily smokers (HR 3.18 (1.99 to 5.10)) and subsequent onset of PD. In addition, pre-existing ND was associated with increased odds of subsequent PTSD onset (OR 2.24 (1.78 to 2.83)) in the aforementioned study drawn from the VET registry [Koenen et al, 2005]” (Section: Smoking and nicotine dependence and risk of incident anxiety disorders).

TABLE 50 QUASIPROSPECTIVE STUDIES INVESTIGATING INFLUENCE OF SMOKING AND NICOTINE DEPENDENCE (ND) ON SUBSEQUENT RISK OF ANXIETY DISORDERS (MOYLAN ET AL, 2012).

STUDY	Study Population	Prospective/Retrospective Follow up Process	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Breslau et al , 2004 [33]	Data from the NCS (outlined previously)	Utilised recall of age of onset smoking & PD	M-CIDI	Smoking status from NCS (outlined previously) Early onset of daily smoking was defined as onset falling in the earliest 10% of the age of onset distribution of all same sex members of the smoker's birth cohort who smoked daily	Risk of Individual AD onset: Pre-exisiting daily smoker (onset>1yr prior) vs. non-daily smoking ND smoker vs. Non-ND smoker / ND (Past) non-smoker vs. Non-ND (past) non-smoker Temporal relationship of smoking to AD: Current smoker, past smoker or recent quitter.	Odds of AD onset: Adjusted OR (95% CI)*: PD: Pre-existing daily smoking (onset >1 yr prior) vs. non-daily smoking = OR 2.6 (1.2-5.4)* ND smoker vs. non-daily smoker = OR 2.7 (1.2-6.0)** Non ND smoker vs. non-daily smoker = OR 2.3 (1.2-4.4)** ND past smoker vs. non-daily smoker = OR 0.4 (0.2-0.9)** Non ND past smoker vs. non-daily smoker= OR 0.7 (0.3-1.8)** Current smoker vs. past smoker = Wald Chi2 34.1, p<0.05 ND vs. non ND = Wald Chi2 0.3 Agoraphobia: Pre-existing daily smoking (onset >1 yr prior) vs. non-daily smoking = OR 4.4 (2.3-8.2)* ND smoker vs. non-daily smoker = OR 2.8 (1.5, 5.3)** Non ND smoker vs. non-daily smoker = OR 3.4 (1.9, 5.9)** ND past smoker vs. non-daily smoker = OR 2.6 (0.8, 8.0)** Non ND past smoker vs. non-daily smoker= OR 1.0 (0.5, 2.2)**

STUDY	Study Population	Prospective/Retrospective Follow up Process	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						Current smoker vs. past smoker = Wald Chi2 4.0, p<0.05 ND vs. non ND = Wald Chi2 0.3 Specific Phobia: Pre-existing daily smoking (onset >1 yr prior) vs. non-daily smoking = OR 1.4 (0.7-2.8)* ND smoker vs. non-daily smoker = OR 0.6 (0.2, 2.2)** Non ND smoker vs. non-daily smoker = OR 1.4 (0.7, 2.9)** ND past smoker vs. non-daily smoker = OR 0.6 (0.2, 1.7)** Non ND past smoker vs. non-daily smoker = OR 0.5 (0.2, 1.1)** Current smoker vs. past smoker = Wald Chi2 3.4 ND vs. non ND = Wald Chi2 0.6 SP: Pre-existing daily smoking (onset >1 yr prior) vs. non-daily smoking = OR 1.1 (0.5 -2.4)* ND smoker vs. non-daily smoker =OR 0.4 (0.1, 1.1)** Non ND smoker vs. non-daily smoker = OR 0.8 (0.4, 1.6)** ND past smoker vs. non-daily smoker = OR 2.7 (0.7, 9.9)** Non ND past smoker vs. non-daily smoker = OR 3.0 (0.8, 11.2** Current smoker vs. past smoker = Wald Chi2 0.5 ND vs. non ND = Wald Chi2 1.1 GAD:

STUDY	Study Population	Prospective/Retrospective Follow up Process	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						Pre-existing daily smoking (onset >1 yr prior) vs. non-daily smoking = OR 2.7 (0.9-8.1)* ND smoker vs. non-daily smoker = OR 1.5 (0.6, 4.3)** Non ND smoker vs. non-daily smoker = OR 3.4 (0.9, 12.1)** ND past smoker vs. non-daily smoker = OR 1.5 (0.4, 5.8)** Non ND past smoker vs. non-daily smoker = OR 0.8 (0.2, 3.0)** Current smoker vs. past smoker = Wald Chi2 3.8 ND vs. non ND = Wald Chi2 0.1 PTSD: Pre-existing daily smoking (onset >1 yr prior) vs. non-daily smoking = OR 1.3 (0.6-2.9)* ND smoker vs. non-daily smoker = OR 1.1 (0.3, 3.3)** Non ND smoker vs. non-daily smoker = OR 0.9 (0.4, 1.9)** ND past smoker vs. non-daily smoker = OR 0.9 (0.3, 2.6)** Non ND past smoker vs. non-daily smoker= OR 0.2 (0.1, 0.5)** Current smoker vs. past smoker = Wald Chi2 7.1, p<0.05 ND vs. non ND = Wald Chi2 6.7, p<0.05 * Adjusted for race, gender, age, education and same year onset. ** Adjusted for race, gender, age, education, pre-existing psychiatric disorders

STUDY	Study Population	Prospective/Retrospective Follow up Process	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						Odds of AD by smoking characteristics: Adjusted OR(95% CI)*: PD: Early smoking onset vs. non early smoking onset = OR 1.2 (0.5-3.0)* Standardised Pack years in current smokers = OR 0.8 (0.6, 0.9)* Standardised Pack years in past smokers = OR 1.4 (1.0, 2.0)* Standardised Years since quitting = OR 0.5 (0.4, 0.7)* Agoraphobia: Early smoking onset vs. non early smoking onset = OR 1.5 (0.6-3.3)* Standardised Pack years in current smokers = OR 1.0 (0.8, 1.2)* Standardised Pack years in past smokers = OR 1.1 (0.8, 1.4)* Standardised Years since quitting = OR 0.5 (0.5, 0.8)* Specific Phobia: Early smoking onset vs. non early smoking onset = OR 1.2 (0.4-3.4)* Standardised Pack years in current smokers = OR 1.0 (0.8, 1.3)* Standardised Pack years in past smokers = OR 0.9 (0.4, 1.9)* Standardised Years since quitting = OR 0.9 (0.6, 1.3)*

STUDY	Study Population	Prospective/Retrospective Follow up Process	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
						SP: Early smoking onset vs. non early smoking onset = OR 2.4 (0.9-6.1)* Standardised Pack years in current smokers = OR 0.8 (0.6, 1.2)* Standardised Pack years in past smokers = OR 0.8 (0.5, 1.2)* Standardised Years since quitting = OR 0.6 (0.4, 0.8)* GAD: Early smoking onset vs. non early smoking onset = OR 1.1 (0.4-3.1)* Standardised Pack years in current smokers = OR 1.3 (1.0, 1.6)* Standardised Pack years in past smokers = OR 1.4 (1.0, 1.8)* Standardised Years since quitting = OR 1.2 (0.9, 1.6)* PTSD: Early smoking onset vs. non early smoking onset = OR 1.8 (0.9-3.8)* Standardised Pack years in current smokers = OR 0.7 (0.6, 0.8)* Standardised Pack years in past smokers = OR 1.1 (0.8, 1.6)* Standardised Years since quitting = OR 1.0 (0.8, 1.2)* *Adjusted for ever smoking, race, gender, age, education and other pre-existing psychiatric disorders

STUDY	Study Population	Prospective/Retrospective Follow up Process	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Breslau et al, 1999 [14]	Sample randomly drawn from 21-30 yrold individuals from a large HMO (general population) as part of the Detroit Epidemiologic Study (DES)(n=1007) ; and Participants a part of the National Comorbidity Survey (NCS), a stratified, multistage probability sample of US non-institutionalised residents age 15-54. Respondents (n= 4411) who undertook the tobacco use component of the NCS survey were included.	Prospective Followup: DES: Baseline assessment occurred in 1989 (n=1007) Follow up 1 = 1990 Follow up 2 = 1992 Follow up 3 = 1994 (Complete follow up data available for n=974)	NIMH-DIS, revised to cover DSM-III-R criteria by face to face interviews for the DES; and M-CIDI for DSM-III-R criteria (NCS)	Self Report Smoking: Daily smoking = smoking daily for >=1 month	HR of PD onset: Prior Daily smoking vs. Prior No Daily smoking Prior daily smokers who continued to smoke vs. Prior daily smokers who didn't continue to smoke Prior daily smokers who quit vs. Prior daily smokers who didn't quit	HR of PD onset: Adjusted HR (95% CI)*: DES: Prior daily smoking vs. No prior daily smoking = HR 4.73 (2.36-9.49)*, HR 13.13 (4.41-39.10)** DES: Prior daily smokers who continued to smoke vs. Prior daily smokers who didn't continue to smoke = HR 14.46 (4.81 -43.5)** DES: Prior daily smokers who quit vs. Prior daily smokers who didn't quit = HR 0.51 (0.12-2.28)** NCS: Prior daily smoking vs. No prior daily smoking = HR 2.93 (1.84-4.66)** NCS: Prior daily smokers who continued to smoke vs. Prior daily smokers who didn't continue to smoker = HR 3.18 (1.99-5.10)** NCS: Prior daily smokers who quit vs. Prior daily smokers who didn't quit = HR 1.82 (0.69-4.28)** Daily Smoking to PD: DES HR 13.13 (4.41-39.10); NCS : HR 2.93 (1.84-4.66) *Adjusted for gender ** Adjusted for gender and major depressive disorder

STUDY	Study Population	Prospective/Retrospective Follow up Process	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Koenen et al, 2005 [31]	Sample drawn from national VET registry, a male-male twin pair registry of vietnam veterans where both siblings subsequently served in the Vietnam war era. Data taken from the Harvard Twin Study of Drug Abuse and Dependence (n=6744).	Retrospective data of age of onset utilised from the DISC to undertake prospective predictions	DISC 3 for DSM-III-R criteria	ND by DISC-3 for DSM-III-R criteria	Odds of PTSD onset (amongst those trauma exposed): ND vs. no ND (onset prior to trauma)	Odds of PTSD onset: Adjusted OR (95% CI)*: ND vs. no ND = OR 2.24(1.78-2.83)*, p<.001 * Time dependent covariates were conduct disorder, major depression, alcohol and drug abuse/dependence * Estimates for ND were adjusted for zygosity, minority race, father did not graduate from high school, mother did not graduate from high school, maternal/paternal depression, maternal/paternal alcohol problems, maternal/paternal drug problems, and maternal/paternal problems with the law.

TABLE 51 CROSS-SECTIONAL STUDIES INVESTIGATING ASSOCIATIONS BETWEEN ANXIETY DISORDERS, NICOTINE DEPENDENCE (ND) AND SMOKING (MOYLAN ET AL, 2012).

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Acierno et al 1996 [35]	Sample drawn from the National Women's Study, a national household probability sample (n= 4008) adult women in the United States. This study utilised wave 3 assessment (n= 3006)	National Women's Study PTSD module for DSM-III-R criteria Current PTSD = present during 6 months prior to Wave 3 assessment	Self Report smoking: Lifetime smoking = yes to "have you ever smoked cigarettes, at least occasionally?" Current smoking = yes to "do you currently smoke cigarettes, at least occasionally?"	Risk of smoking: Lifetime smoking: Lifetime PTSD vs. no Lifetime PTSD Current smoking: Lifetime PTSD vs. No Lifetime PTSD Current PTSD vs. No Current PTSD	Risk of smoking: Adjusted OR (95% CI)*: Lifetime smoking: Lifetime PTSD vs. No Lifetime PTSD = OR 2.25 (1.78-2.84)*, p<0.01 Current smoking: Lifetime PTSD vs. No Lifetime PTSD = OR 2.16 (1.373 -2.70)*, p<0.01, OR 1.34 (1.04-1.71)**, p<0.05 Current PTSD vs. No Current PTSD = OR 2.28 (1.62-3.22)*, p<0.01 * Adjusted for race and education status ** Adjusted for race and education status, OR after stepwise introduction of lifetime depression & lifetime assault
Acierno et al, 2000 [34]	Sample drawn from the National Survey of Adolescents (n=4023). Adolescents aged 12-17 from the US.	PTSD using a modified National Womens Study PTSD module to DSM-IV criteria	Self Report: Curent Smoking = Smoking at least 15 of the last 30 days (yes/no)	Odds of smoking: PTSD vs. no PTSD by gender	Odds of Smoking: Unadjusted OR (95% CI): Boys: Odds of Smoking PTSD vs. no PTSD = OR 2.10, p<0.05 Girls: Odds of Smoking PTSD vs. no PTSD = OR 4.22, p<0.001 When analysis are incorporated into a multivariate analysis including age, race, familial drug and alcohol problems, physical assault and sexual assault and witnessed

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					violence, a diagnosis of PTSD no longer predicts smoking status for either boys or girls.
Breslau 1995 [36]	Random sample of 1200 people drawn from 400,000 members of HMO's in southeast Michigan, Age 21-30 yrs.	NIMH-DIS, revised to cover DSM-III-R criteria by face to face interviews	Smoking: Smokers = Respondents who ever smoked for >=1 month ND: From the DIS for DSM-III_R criteria	Co-morbidity between Grouped Anxiety Disorders and ND (Odds Ratios) Risk of Anxiety Disorders (grouped): ND smokers vs. non smokers Non ND smokers vs. non smokers	Risk of ND: Adjusted OR (95% CI)*: MEN: Grouped Anxiety Disorder: ND vs. No ND = OR 2.2 (1.3-3.9), p<0.05 FEMALES: Grouped Anxiety Disorder: ND vs. No ND = OR 2.6 (1.8-3.9), p<0.05 ALL: Grouped Anxiety Disorder: ND smoker vs. non smoker = OR 2.4 (1.7-3.5), p<0.05* Grouped Anxiety Disorder: Non ND smoker vs. non smoker = OR 1.4 (1.0-2.0) * Adjusted for gender and other substance abuse
Breslau et al, 1991 [37]	21-30 year old individuals drawn from a large HMO (general population) as part of the Detroit Epidemiologic Study (N=1007)	NIMH-DIS, revised to cover DSM-III-R criteria by face to face interviews	Nicotine Dependence defined according to DSM-III-R criteria.	Risk of AD occurrence: Mild ND vs. non-ND; Moderate ND vs. non-ND	Grouped Anxiety Disorders Unadjusted OR (95% CI): Mild ND vs None: OR (95%CI) = 1.63 (1.10-2.42) Mod vs. None: OR (95%CI) = 4.63 (2.84-7.53) Adjusted* OR (95% CI): Mild vs. None: OR (95% CI) = 1.46(0.97-2.21) Mod vs none: OR (95% CI) = 4.18 (2.51-6.96)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Any Dependence = OR (95%CI) = 2.03 (1.39-2.97) *OR's adjusted for gender and other substance use
Breslau et al, 1999 [14]	Sample randomly drawn from 21-30 yrold individuals from a large HMO (general population) as part of the Detroit Epidemiologic Study (DES)(n=1007) ; and Participants a part of the National Comorbidity Survey (NCS), a stratified, multistage probability sample of US non-institutionalised residents age 15-54. Respondents (n= 4411) who undertook the tobacco use component of the NCS survey were included.	NIMH-DIS, revised to cover DSM-III-R criteria by face to face interviews for the DES; and M-CIDI for DSM-III-R criteria (NCS)	Self Report Smoking: Daily smoking = smoking daily for >=1 month	Lifetime association between Daily smoking & PD	Lifetime association between Daily Smoking & PD: Adjusted OR (95% CI)*: DES: Daily Smoking & PD = OR 4.24 (2.23-8.06)* NCS: Daily Smoking & PD = OR 1.60 (1.27-2.18)* *Adjusted for gender ** Adjusted for gender and major depressive disorder
Brown et al, 1996	Data drawn from the Oregon Adolescent Depression Project. Participants at Time 1 (n=1709).	Children were assessed at time 1 using the K-SADS and additional questions to elicit DSM-III-R diagnoses	Self Report at each assessment: Smokers dichotomised (Smoking* vs. Non-smoking) * Smoker defined as smoking >=3 episodes per week; Non-Smoking as	Odds of smoking: AD vs. No AD	Odds of smoking (cross-sectional): Unadjusted and Adjusted OR (95% CI)*: Odds of smoking: AD vs. No AD = OR 1.11 (0.62-1.99) Odds of smoking: AD vs. No AD = OR 0.98 (0.54-1.77)* Odds of smoking: AD vs. No AD = OR 0.65 (0.33-1.27)**

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
			smoking <3 episodes per week		* Adjusted for age, gender, race, number of biological parents in household, parental education ** Adjusted for age, gender, race, number of biological parents in household, parental education, other psychiatric disorders
Carroll et al, 2009 [38]	Sample drawn from the Vietnam Experience Study, a cross-sectional analysis of military personal from the Vietnam War Era (1964-1977) (n= 4256)	DIS (v3A) for DSM III criteria.	Smoking status ascertained "using standard questions" Correlation between smoking and GAD. Direct correlation not reported in actual study - only in discussion text. Correlation GAD & Smoking:	Correlation between smoking and GAD. Direct correlation not reported in actual study - only in discussion text	Correlation GAD & Smoking: Comparative significance testing only: Current Smokers: GAD vs. No GAD = p<0.001 (Results reported in discussion only - no further information)
Costello et al, 1999 [32]	Data from the Great Smoky Mountains Study (GSMS), a longitudinal study of 4500 children and adolescents, recruited from a representative sample of 9-, 11- and 13 yr olds from North Carolina. Multiple waves of data were collapsed to form 3 month substance use and psychiatric diagnoses.	Child and Adolescent Psychiatric Assessment administered to assess DSM-III-R & DSM-IV criteria	Child or Parental report of smoking: Cigarette smoking present if child smoked on average >=1 cigarette a day for 3 months	Prevalance of smoking: Anxiety disorder vs. no disorder	Prevalence of smoking: Prevalence and significance testing: GIRLS: Prevalence of smoking: Grouped Anxiety Disorders vs. No Disorder = 12.8% vs. 8.2% BOYS: Prevalence of smoking: Grouped Anxiety Disorders vs. No Disorder = 16.1% vs. 11.5%
Cougle et al, 2010 [39]	Study population drawn from the National Comorbidity Study Replication (NCS-R), a	WMH-CIDI for DSM-IV criteria	Self report smoking: Categories:	Risk of Smoking & Quitting: AD vs. no AD (same diagnosis)	Risk of smoking: Unadjusted & Adjusted OR (95% CI)*: SP:

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
	representative sample of English speaking adults from the United States (n= 5692). Interviewed between 2001-2003.		Lifetime smoking = Ever smoked tobacco daily or nearly daily for at least 2 months 12 month smoking (Yes) = Smoking at >= 300 days in last 12 months Heavy smoking = >=20 cigarettes on typical day during past 12 months or during year that most heavily smoked WMH-CIDI utilised to determine 12-month and lifetime DSM-IV ND.		Lifetime ever smoked daily AD vs. Lifetime ever smoked daily (not AD) = OR 1.43 (1.22-1.67), p<0.01; AOR 1.23 (1.06-1.43)*, p<0.05, AOR 1.01 (0.87-1.18)** Lifetime smoked heavily AD vs. Lifetime smoked heavily (not AD) = OR 1.57(1.37-1.80), p<0.01; AOR 1.45 (1.24-1.70)*, p<0.01; AOR 1.19 (1.01-1.39)**, p<0.05 ND AD vs. ND (not AD) = OR 2.59 (2.05-3.28), p<0.01; AOR 1.82 (1.39-2.38)*, p<0.01; AOR 1.31 (1.01-1.71)**, p<0.05 Unsuccessful quit attempt AD vs. Unsuccessful quit attempt (not AD) = OR 2.02 (1.66-2.44), p<0.01; AOR 1.50 (1.21-1.85)*, p<0.01; AOR 1.36 (1.10-1.66)**, p<0.01 12-month smoke daily AD vs. 12-month smoke daily (not AD) = OR 1.84 (1.47-2.30), p<0.01; AOR 1.28 (1.02-1.60)*, p<0.05; AOR 1.12 (0.09-1.39)** 12-month smoke heavily AD vs. 12-month smoke heavily (not AD) = OR 1.90 (1.56-2.31), p<0.01; AOR 1.25 (0.98-1.59)*; AOR 1.08 (0.84-1.39)** 12-month ND AD vs. 12-month ND (not AD) = OR 3.08 (2.05-4.62), p<0.01; AOR 1.77 (1.14-2.76)*, p<0.05; AOR 1.45 (0.92-2.30)** PD: Lifetime ever smoked daily AD vs. Lifetime ever smoked daily (not AD) = OR 1.71 (1.35-2.19), p<0.01; AOR 1.43(1.07-1.91)*, p<0.05; AOR 1.24 (0.95-1.61)**

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Lifetime smoked heavily AD vs. Lifetime smoked heavily (not AD) = OR 1.62 (1.20-2.18), p<0.01; AOR 1.34 (0.97-1.87)*; AOR 1.19 (0.87-1.63)** ND AD vs. ND (not AD) = OR 2.50 (1.89-3.31), p<0.01; AOR 1.38 (0.98-1.94)*; AOR 1.14 (0.82-1.58)** Unsuccessful quit attempt AD vs. Unsuccessful quit attempt (not AD) = OR 1.99 (1.58-2.52), p<0.01; AOR 1.37 (1.04-1.80)*, p<0.05; AOR 1.29 (0.99-1.68)** 12-month smoke daily AD vs. 12-month smoke daily (not AD) = OR 2.32 (1.76-3.04), p<0.01; AOR 1.59 (1.13-2.22)*, p<0.01; AOR 1.42(1.04-1.94)**, p<0.05 12-month smoke heavily AD vs. 12-month smoke heavily (not AD) = OR 2.29 (1.71-3.06), p<0.01; AOR 1.45 (0.95-2.21)*; AOR 1.29 (0.84-1.96)** 12-month ND AD vs. 12-month ND (not AD) = OR 2.95 (1.72-4.09), p<0.01; AOR 1.19 (0.67-2.11)* ; AOR 1.05 (0.58-1.93)** GAD: Lifetime ever smoked daily AD vs. Lifetime ever smoked daily (not AD) = OR 1.73 (1.45-2.07), p<0.01; AOR 1.50 (1.24-1.82)*, p<0.01; AOR 1.23 (1.05-1.61)**, p<0.05 Lifetime smoked heavily AD vs. Lifetime smoked heavily (not AD) = OR: 1.70 (1.42-2.03), p<0.01; AOR 1.41 (1.18-1.68)*, p<0.01; AOR 1.21 (0.98-1.45)**

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					ND AD vs. ND (not AD) = OR 3.12 (2.61-3.72), p<0.01; AOR 2.12 (1.70-2.65)*, p<0.01; AOR 1.59 (1.21-1.98)**, p<0.01 Unsuccessful quit attempt AD vs. Unsuccessful quit attempt (not AD) = OR 2.23 (1.86-2.68), p<0.01; AOR 1.73 (1.38-2.16)*, p<0.01; AOR 1.58 (1.24-2.03)**, p<0.01 12-month smoke daily AD vs. 12-month smoke daily (not AD) = OR 2.04 (1.58-2.64), p<0.01; AOR 1.55 (1.15-2.08)*, p<0.01; AOR 1.27 (0.92-1.76)** 12-month smoke heavily AD vs. 12-month smoke heavily (not AD) = OR 2.75 (2.21-3.43), p<0.01; AOR 2.09 (1.59-2.75)*, p<0.01; AOR 1.68 (1.28-2.22)**, p<0.01 12-month ND AD vs. 12-month ND (not AD) = OR 3.83 (2.69-5.47), p<0.01; AOR 2.28 (1.54-3.39)*, p<0.01; AOR 1.75 (1.10-2.79)**, p<0.05 PTSD: Lifetime ever smoked daily AD vs. Lifetime ever smoked daily (not AD) = OR 1.96 (1.53-2.50), p<0.01; AOR 2.96 (1.49-2.58)*, p<0.01; AOR 1.58 (1.21-2.06)**, p<0.01 Lifetime smoked heavily AD vs. Lifetime smoked heavily (not AD) = OR 1.76 (1.32-2.33), p<0.01; AOR 1.83 (1.30-2.58)*, p<0.01; AOR 1.45 (1.03-2.03)**, p<0.05 ND AD vs. ND (not AD) = OR 2.95 (2.15-4.05), p<0.01; AOR 2.11 (1.42-3.14)*, p<0.01; AOR 1.47 (1.01-2.16)**, p<0.05

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Unsuccessful quit attempt AD vs. Unsuccessful quit attempt (not AD) = OR 2.03 (1.53-2.68), p<0.01; AOR 1.61 (1.16-2.24)*, p<0.01; AOR 1.46 (1.05-2.01)**, p<0.05 12-month smoke daily AD vs. 12-month smoke daily (not AD) = OR 2.16(1.70-2.74), p<0.01; AOR 1.70 (1.29-2.24)*, p<0.01; AOR 1.46 (1.08-1.97)**, p<0.05 12-month smoke heavily AD vs. 12-month smoke heavily (not AD) = OR 2.51 (1.96-3.21), p<0.01; AOR 2.04 (1.46-2.86)*, p<0.01; AOR 1.74 (1.23-2.45)**, p<0.01 12-month ND AD vs. 12-month ND (not AD) = OR 4.41 (2.86-6.81), p<0.01; AOR 2.82 (1.91-4.16)*, p< 0.01; AOR 2.39 (1.63-3.50)**, p<0.01 * Adjusted for age, sex, race, education, income, marital status ** Adjusted for age, sex, race, education, income, marital status, depression, alcohol and drug abuse/dependence
Cuijpers et al, 2007 [27]	Participants aged 18-64 drawn from the NEMESIS study (Netherlands Mental Health Survey and Incidence Study), a multistage, stratified, random population sample of 90 municipalities (n=4796 at final followup)	CIDI for DSM-III-R diagnosis	Self Report: Past year smoking assessed at Time 1 & Time 2. Categories of smokers: Non-smokers 1-9 cigarettes daily 10-19 cigarettes daily >20 cigarettes daily	Cross sectional risk of smoking by AD diagnosis (12month and lifetime diagnosis).	Risk of smoking: Relative Risk (95% CI): Relative Risk of Smoking: 12 month Grouped AD vs. population= RR: 1.33 (1.18-1.50) p<0.001; Relative Risk of Smoking: Lifetime Grouped AD vs. population= RR 1.26 (1.15-1.37 p<0.001) Relative Risk of smoking: 12 month GAD vs. population = RR 1.46 (0.99-2.15) NS;

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Relative Risk of smoking: Lifetime GAD vs. population = RR 1.33 (1.11-1.59) p<0.01 Relative Risk of smoking: 12 month PD vs. population = RR: 149 (1.19-1.87) p<0.01; Relative Risk of smoking: Lifetime PD vs. population = RR: 1.26 (1.08-1.47) p<0.01 Relative Risk of smoking: 12 month Agoraphobia vs. population = RR 1.68 (1.39-2.03), p<0.001; Relative Risk of smoking: Lifetime Agoraphobia vs. population = RR 1.43 (1.25-1.64) p<0.001 Relative Risk of smoking: 12 month SP vs. population = RR 1.44 (1.20-1.73) p<0.001; Relative Risk of smoking: Lifetime SP vs. population = RR 1.31 (1.17-1.47), p<0.001 Relative Risk of smoking: 12 month Specific Phobia vs. population = RR 1.21 (1.03-1.42) p<0.05; Relative Risk of smoking: Lifetime Specific Phobia vs. population = RR 1.19 (1.07-1.33) p<0.01 Relative Risk of smoking: 12 month OCD vs. population = RR: 1.00 (0.53-1.87) Relative Risk of smoking: Lifetime OCD vs. population = RR 1.12 (0.82-1.53)
Degenhardt et al, 2001 [40]	Adults drawn from a representative sample of the Australian population (n=10641)	CIDI for DSM-IV	Self Report: Never Smoker Former Smoker Current Smoker	Risk of AD occurrence by smoking rates	Grouped Anxiety Disorders Unadjusted OR (95% CI): Former Smokers vs. Never Smokers: OR (95% CI) = 1.13 (0.92-1.40) Current smokers vs. Never smokers: OR (95% CI) = 2.54 (2.13-3.03)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Adjusted OR (95% CI)*: Former Smokers vs. Never Smokers: OR (95% CI) = 1.01 (0.79-1.28) Current smokers vs. Never smokers: OR (95% CI) = 1.50 (1.21-1.87) *Adjusted for gender, age, education, marital status, employment status, other drug use, neuroticism score
Dierker et al, 2007 [42]	Sample of Puerto Rican adolescents Age 11-17 yrs (n=498) selected from random sample of 8568 children who received mental health and substance abuse services through the public health system and through private sector Managed Behavioral Health Organizations between Jan 1 1998 and May 31 1998.	Spanish Diagnostic Interview Schedule for Children (DISC-IV) for DSM-IV criteria - Both parents (DISC-P) and youths (DISC-Y) were interviewed.	Tobacco module of DISC-Y utilised to determine lifetime and past year smoking information. Smokers categorised into: 1) Never users 2) Experimenters (>=1 use, No weekly use) 3) Regular users (Weekly use for 1 month, no Nicotine Dependence) 4) Nicotine Dependent	Risk of smoking: AD vs. No AD	Group Anxiety Disorders (cross-sectional) Unadjusted and Adjusted OR (95% CI)*: Risk of smoking: AD vs. No AD: Experimenters vs. Never users = OR 1.3 (0.73-2.14) Risk of smoking: AD vs. No AD: Experimenters vs. Never users = OR 1.0 (0.54-1.95)* Risk of smoking: AD vs. No AD: Non ND regular smokers vs. Never users = OR 2.6 (1.43-4.68) p<0.001 Risk of smoking: AD vs. No AD: Non ND regular smokers vs. Never users = OR 2.5 (1.21-5.14) p<0.05* Risk of smoking: AD vs. No AD: ND regular smokers vs. Never users = OR 1.8 (0.97-3.34 Risk of smoking: AD vs. No AD: ND regular smokers vs. Never users = OR 1.2 (0.53-2.64)* * Adjusted for age, gender and poverty status

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Dierker et al, 2008 [41]	Sample drawn from the National Epidemiologic Survey of Alcohol Related Conditions (NESARC). Data utilised is from Adults age 18-25.	AUDADIS-IV for DSM-IV Criteria	AUDADIS-IV for ND	Odds of 12 month ND: AD vs. No AD	Odds of ND: Unadjusted and Adjusted OR (95% CI): Odds of ND: Lifetime GAD vs. no GAD = OR 2.8 (1.55-5.02); AOR 1.3 (0.57-2.77)* Lifetime PD vs. No PD= OR 3.6 (2.12-5.96); AOR 1.5 (0.79-2.96)* Lifetime SP vs. No SP = OR 3.4 (1.94-6.07); AOR 1.5 (0.74-2.87)* Lifetime Specific Phobia vs. No Specific Phobia: OR 3.4 (2.37-4.93); AOR 1.8 (1.16-2.88)* * Adjusted for other psychiatric disorders, smoking and demographic characteristics
Durai et al 2011 [43]	Sample drawn from US army veterans across multiple US centres (n=17250). All participants aged 65yrs and older and male and identified as suffering from depression, anxiety or at-risk drinking behavior.	Composite diagnosis established using the Veterans Health Administration Clinical Guidelines for Major Depressive Disorder including Comorbidities of Substance Use and PTSD (1997). Utilised a total of 4 questions - 1 from the Quick Diagnostic schedule and 3 from the PTSD check list	Current smoking status (yes/no). Definition not provided	Risk of smoking: PTSD vs. No PTSD (Combines No Trauma and No Trauma/PTSD groups)	Risk of smoking: Adjusted OR (95% CI)*: Risk of smoking: PTSD vs. No PTSD = OR 2.0 (1.5-2.8) *Adjusted for study site
Farrell et al, 2003 [44]	National Households survey, UK: 10, 018 individuals in private	CIS-R for ICD-10 criteria. Scores >12 classified as "Mixed AD"; algorithms	DIS adopted for ND diagnosis to ICD-10 criteria	Prevalence of AD: ND vs. non ND Prevalence of smoking:	Risk of AD: Prevalence and significant testing:

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
	households, 755 permanent institution residents, 1061 national survey homeless individuals.	utilised to establish individual AD diagnosis from CIS-R. DIS adopted for ND diagnosis to ICD-10 criteria		AD by category of smoking	Mixed AD: ND vs. non ND = 10.2% vs. 6.2%, p<0.001 GAD: ND vs. non ND = 4.1% vs. 2.4%, p<0.001 Phobia: ND vs. non ND = 1.5% vs. 0.8%, p<0.001 PD: ND vs. non ND = 1.5% vs. 0.5%, p<0.001

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Glassman et al, 1990 [45]	Sample drawn randomly from the St Louis Epidemiological Catchment Area Sample (n=3213)	DIS for DSM-III criteria	Self Report Smoking: Smokers = Ever smoked daily for > 1 month	Risk of smoking: AD vs. No AD (Including and Excluding patients with MDD)	Risk of smoking: Unadjusted OR (95%): Smoking: PD vs. No PD (Including MDD diagnosis) = OR 1.57 (0.86-2.84) PD vs. No PD (Excluding MDD diagnosis) = OR 2.13 (0.81-5.65) OCD vs. No OCD (Including MDD diagnosis) = OR 1.33 (0.80-2.24) OCD vs. No OCD (Excluding MDD diagnosis) = OR 1.74 (0.87-3.51) Agoraphobia vs. No Agoraphobia (Including MDD diagnosis) = OR 1.76 (1.20-2.56) Agoraphobia vs. No Agoraphobia (Excluding MDD diagnosis) = OR 1.23 (0.80-1.89) SP vs. No SP (Including MDD diagnosis) = 1.19 (0.90-1.58) SP vs. No SP (Excluding MDD diagnosis) = 1.03 (0.76-1.40)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Grabe et al, 2001 [46]	Sample (n=4075) drawn randomly from residents aged 18-64yrs from general population of Northern German city of Lubeck	M-CIDI for DSM-IV criteria	ND by WHO-CIDI for DSM-IV criteria	Risk of ND: OCD vs. no OCD (by gender)	Risk of ND: Adjusted OR (95% CI)*: Males: No comorbid ND and OCD cases Females: OCD vs. No OCD = 7.5 (2.9-20)*, p<0.05 *Adjusted for age

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Grant et al, 2004 [47]	Sample of civilian, non-institutionalised people aged 18yrs and older from the USA, drawn from the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (n= 43093)	Computerised survey module of the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV (AUDADIS-IV) for DSM-IV criteria	ND by the AUDADIS-IV for DSM-IV criteria Self report smoking: Lifetime smokers = smoked at least 100 cigarettes in lifetime Current smokers = smoked during year preceeding interview Total number of cigarettes calculated from (how often did you smoke / how many cigarettes when you did smoke?)	Risk of Individual AD: ND vs. no ND (by gender)	Risk of Grouped & Individual AD: Unadjusted OR (95% CI): Grouped AD: ND vs. no ND (All) = OR 2.7 (2.4-3.0) ND vs. no ND (MALES) = OR 2.8 (2.4-3.3) ND vs. no ND (FEMALES) = OR 2.9 (2.5-3.3) PD with Agoraphobia: ND vs. no ND (All) = OR 4.6 (3.4-6.2) ND vs. no ND (MALES) = OR 4.1 (2.4-7.0) ND vs. no ND (FEMALES) = OR 5.2 (3.6-7.5) PD without Agoraphobia: ND vs. no ND (All) = OR 3.9 (3.2-4.8) ND vs. no ND (MALES) = OR 3.5 (2.4 - 5.1) ND vs. no ND (FEMALES) = OR 4.5 (3.5-5.7) SP: ND vs. no ND (All) = OR 2.6 (2.2-3.1) ND vs. no ND (MALES) = OR 2.3 (1.8-3.1) ND vs. no ND (FEMALES) = OR 3.0 (2.4-3.7) Specific Phobia: ND vs. no ND (All) = OR 2.6 (2.3-2.9)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					ND vs. no ND (MALES) = OR 3.0 (2.5-3.6) ND vs. no ND (FEMALES) = OR 2.6 (2.3-3.0) GAD: ND vs. no ND (All) = OR 3.4 (2.8-4.2) ND vs. no ND (MALES) = OR 3.4 (2.4-4.8) ND vs. no ND (FEMALES) = OR 3.8 (3.1-4.7)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Grant et al, 2005 [48]	Sample of civilian, non-institutionalised people aged 18yrs and older from the USA, drawn from the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (n= 43093)	Diagnosis assessed using the AUDADIS-IV for DSM-IV criteria	Nicotine Dependence measured using the AUDADIS-IV	Risk of ND: GAD (12 month and Lifetime) vs. No GAD	Risk of ND: Adjusted OR (95% CI)*: 12month GAD: ND vs. no ND = AOR 2.9 (2.34-3.52)* Lifetime GAD: ND vs. no ND = OR 2.5 (2.15-2.88) *Adjusted for age, race-ethnicity, sex, marital status, education, income, urbanicity, region of country
Gwynn et al, 2008 [49]	Sample drawn from the NYC-HAYNES study, a population based cross sectional survey of New York City's non-institutionalised adult residents aged 20yrs or older. Participants included in this study (n=1817) were those who completed mental health diagnostic assessment..	WHO CIDI for DSM-IV & ICD-10 criteria	Smoking assessed through an audio-computer assisted self-interview. No actual definition provided.	Risk of Smoking: GAD vs. No Diagnosis of GAD or MDD (Major Depressive Disorder)	Risk of Smoking: Prevalence (95% CI) and significance testing: Current Smoking: GAD vs. No GAD/MDD = 49% (33.9-64.2) vs. 21% (18.7-23.3), p<0.01

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Hapke et al, 2005 [50]	Sample drawn randomly from residents aged 18-64yrs from general population of Northern German city of Lubeck (n= 4072)	M-CIDI for DSM-IV criteria	Self Report Smoking: Current smokers = at least 1 cigarette/day for >= 4 weeks within the previous 4 weeks Former smokers = at least 1 cigarette/day >= 4 weeks but not in previous 4 weeks Never smokers = never smoked at least 1 cigarette/day for period of >=4 weeks Quit Rates = % of smokers who did not continue smoking in last 4 weeks.	Risk of Smoking & Quitting PTSD vs. No Traumatic Experience History (by Gender)	Risk of Smoking: Adjusted OR (95% CI)*: Ever Smoking: ALL: PTSD vs. No Trauma History = OR 2.12 (1.16-3.90)* Males: PTSD vs. No Trauma History = OR 1.49 (0.4-5.60)* Females: PTSD vs. No Trauma History = OR 2.79 (1.4-5.58)* Current Smoking: All: PTSD vs. No Trauma History = OR 2.76 (1.60-4.77)* Males: PTSD vs. No Trauma History = OR 2.42 (0.75-7.74)* Females: PTSD vs. No Trauma History = OR 3.10 (1.67-5.77)* ND: All: PTSD vs. No Trauma History = OR 2.70 (1.57-4.65)* Males: PTSD vs. No Trauma History = OR 1.61 (0.48-5.40)* Females: PTSD vs. No Trauma History = OR 3.68 (1.98-6.85)* Current ND: All: PTSD vs. No Trauma History = OR 4.52 (2.56-7.98)* Males: PTSD vs. No Trauma History = OR 4.26 (1.26-14.33)*

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Females: PTSD vs. No Trauma History = OR 4.81 (2.50-9.25)* Quit Rates (Of Ever smokers): All: PTSD vs. No Trauma History = OR 0.38 (0.17-0.84)* Males: PTSD vs. No Trauma History = OR 0.33 (0.07-1.70)* Females: PTSD vs. No Trauma History = OR 0.43 (0.17-1.05)* * Adjusted for age and gender(where appropriate)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Isensee et al, 2003 [22]	Participants drawn from the Early Developmental Stages of Psychopathology Study (EDSP), a community sample from metropolitan Munich (n= 3021) of adolescents and young adults aged 14 - 24.	M-CIDI for DSM-IV criteria diagnosis	Nicotine dependence: M-CIDI for DSM-IV criteria Self Report: Smoking assessment: Regular smoking defined as daily use for at least 4 weeks Smoking behavior, Age of onset, Age at commencement regular smoking: Categories of smoker: 1) Non-users (No lifetime smoking) 2) Occasional user (Have used but never daily for 4 weeks) 3) Non-dependent regular smokers (Daily smoking >4 weeks in lifetime but not DSM-IV ND) 4) Dependent regular smokers (Daily smoking >4 weeks in lifetime & DSM-IV ND)	Odds of Smoking: Grouped and Individual AD vs. No AD's	Odds of Smoking (cross-sectional): Adjusted OR (95% CI)*: PD: Odds of Smoking: Occasional User vs. Non User = OR 9.8 (1.2-74.7), p<0.05 Odds of Smoking: Non ND smoker vs. Non user = OR 13.8 (1.7-108.6), p<0.05 Odds of Smoking: ND regular smoker vs. Non user = OR 28.0 (3.7-208.4) p<0.05 Agoraphobia: Odds of Smoking: Occasional User vs. Non User = OR 0.8 (0.3 -1.8) Odds of Smoking: Non ND smoker vs. Non user = OR 0.8 (0.3-2.1) Odds of Smoking: ND regular smoker vs. Non user = OR 2.8 (1.3-5.8) p<0.05** SP: Odds of Smoking: Occasional User vs. Non User = OR 0.9 (0.6-1.5) Odds of Smoking: Non ND smoker vs. Non user = OR 0.9 (0.5-1.6) Odds of Smoking: ND regular smoker vs. Non user = OR = 1.9 (1.2-3.1) p<0.05** GAD: Odds of Smoking: Occasional User vs. Non User = OR 1.4 (0.4-4.1) Odds of Smoking: Non ND smoker vs. Non user = OR 4.2 (1.5-11.5) p<0.05**

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Odds of Smoking: ND regular smoker vs. Non user = OR: 7.4 (2.9-19.0) p<0.05 OCD: Odds of Smoking: Occasional User vs. Non User = OR 0.7 (0.1-2.3) Odds of Smoking: Non ND smoker vs. Non user = OR 1.3 (0.3-4.9) Odds of Smoking: ND regular smoker vs. Non user = OR 1.1 (0.3-4.1) PTSD: Odds of Smoking: Occasional User vs. Non User = OR 0.8 (0.2-3.0) Odds of Smoking: Non ND smoker vs. Non user = OR 0.7 (0.1-3.1) Odds of Smoking: ND regular smoker vs. Non user = OR 6.4 (2.3-17.4) p<0.05** Specific Phobia: Odds of Smoking: Occasional User vs. Non User = OR=1.0 (0.7-1.4) Odds of Smoking: Non ND smoker vs. Non user = OR 0.8 (0.5-1.3) Odds of Smoking: ND regular smoker vs. Non user = OR 2.0 (1.4-2.8) p<0.05** * Adjusted for age & gender ** Association failed to reach significant when controlled for comorbidity at baseline (depressive disorders, panic attacks, other AD, alcohol and illicit drug disorders, eating disorders)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
John et al, 2004 [51]	4072 residents aged 18-64 drawn randomly from general population of Northern German city of Lubeck (pop 217,000) - mean age was 41.8 yrs, 50.2% male:	Respondents examined using Munich version of CIDI (M-CIDI) for DSM-IV diagnoses	Smoking categories established: Never smokers = never smoked in their life Never daily smokers = never smoked daily for >=1 month Former daily smokers = have smoked daily for >=1 month in lifetime, but not in last 4 weeks Daily smokers = daily smoking for last 4 weeks prior to interview	Rates of smoking categories vs. grouped anxiety disorders (cross-sectional at baseline)	Risk of AD: Adjusted OR (95% CI)*: MALES: Grouped Anxiety Disorders: Never daily smokers vs. never smokers = OR 1.3 (0.7-2.5)* Grouped Anxiety Disorders: Former daily smokers vs. never smokers = OR 2.1 (1.1-3.9), p<0.05* Grouped Anxiety Disorders: Never daily smokers vs. never smokers = OR 1.9 (1.1-3.5), p<0.05* FEMALES: Grouped Anxiety Disorders: Never daily smokers vs. never smokers = OR 1.3 (0.9-1.8)* Grouped Anxiety Disorders: Former daily smokers vs. never smokers = OR 1.6 (1.2-2.4), p<0.01* Grouped Anxiety Disorders: Never daily smokers vs. never smokers = OR 1.9 (1.4-2.6), p<0.001* ALL: Grouped Anxiety Disorders: Never daily smokers vs. never smokers = OR 1.1 (0.8-1.5)* Grouped Anxiety Disorders: Former daily smokers vs. never smokers = OR 1.4 (1.0-1.9), p<0.05*

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Grouped Anxiety Disorders: Never daily smokers vs. never smokers = OR 1.6 (1.2-2.0), p<0.05* * Adjusted for age

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Kandel et al, 1997 [53]	Children and adolescents (604 females, 681 males, n=1285), mean age (12.9 SD 2.6) recruited from probability samples of 4 US locations in 1992.	NIMH DISC 2.3, assessing against DSM-III-R criteria	Self Report of Substance Abuse	% of AD by 4 categories of cigarette use: No lifetime use No use in past 6 month Less than daily use in last 6 months Daily use in last 6 months.	Group Anxiety Disorder % AD: "No Use"= 12.2% % AD: No use last 6 months=7.7% Less than Daily use last 6 months =17.1% Daily use in last 6 months= 39.1% AD diagnosis: Less than Daily use in last 6 months vs. Daily Use in last 6 months (p<0.01) Adjusted OR*: AD Daily Use in last 6 months vs. Non-Daily Use in Last 6 months = 3.9 (no CI's provided) p<0.01 *Adjusted for age, gender, ethnicity, and household income
Kandel et al, 2001 [52]	Sample drawn from the 1994, 1995 and 1996 National Household Surveys on Drug Abuse - Cross-sectional surveys of multistage probability samples of the US population 12 years and over (data only utilised for those over 18 years)	Anxiety disorders (GAD, Panic Attack with agoraphobia) utilising modified questionnaires (derived from the CIDI) for DSM-III-R criteria	Self report: Never smoker Former smoker Non ND current smoker ND current smoker	Adjusted OR for any Anxiety Syndrome: Smoking characteric vs. Never used	Odds of AD: Adjusted OR (95% CI)*: Any Anxiety Syndrome (GAD & PA with Agoraphobia): Former smoker vs. never smoker = AOR 1.1 (0.9-1.4)* Non ND smoker vs. never smoker = AOR 1.4 (1.2-1.7)* ND smoker vs. never smoker = AOR 2.6 (2.1-3.2)* * Adjusted for sociodemographic variables

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Lasser et al, 2000 [54]	Participants a part of the National Comorbidity Survey (1), a stratified, multistage probability sample of US non-institutionalised residents age 15-54. Respondents (n= 4411) who undertook the tobacco use component of the NCS survey were included.	Modified CIDI for DSM-III	Self report smoking status: Lifetime smokers (Ever smoked daily for >=1 month) Current smokers (Smoked "fairly regularly" in last month) Peak consumption of cigarettes/day reported.	Rate of smoking by group: Lifetime and past month AD diagnosis vs. No mental illness	Rate of Smoking: Percentage and Chi2 test of difference between groups: SP: Rate of Smoking: Lifetime SP vs. no Mental Illness: Current Smokers = 39.5% vs. 22.5%, p<=0.0001 Rate of Smoking: Lifetime SP vs. no Mental Illness: Lifetime Smokers = 54.0% vs. 39.1%, p<=0.0001 Quit Rate: Lifetime SP vs. no Mental Illness: Quit Rate = 33.4% vs. 42.5%, p<=0.01 Rate of Smoking: Past month SP vs. no Mental Illness: Current Smokers = 31.5% vs. 22.5%, p<=0.01 Rate of Smoking: Past month SP vs. no Mental Illness: Lifetime Smokers = 44.5% vs. 39.1%, p>0.05 Quit Rate: Past month SP vs. no Mental Illness: Quit Rate = 29.2% vs. 42.5%, p<=0.05 Agoraphobia: Rate of Smoking: Lifetime Agoraphobia vs. no Mental Illness: Current Smokers = 38.4% vs. 22.5%; p<=0.0001 Rate of Smoking: Lifetime Agoraphobia vs. no Mental Illness: Lifetime Smokers = 58.9 vs. 39.1%; p<=0.0001

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Quit Rate: Lifetime Agoraphobia vs. no Mental Illness: Quit Rate = 34.5% vs. 42.5%, p>0.05 Rate of Smoking: Past month Agoraphobia vs. no Mental Illness: Current Smokers = 48.1% vs. 22.5%; p<=0.0001 Rate of Smoking: Past month Agoraphobia vs. no Mental Illness: Lifetime Smokers = 63.2% vs. 39.1%; p<=0.0001 Quit Rate: Past month Agoraphobia vs. no Mental Illness: Quit Rate = 32.9% vs. 41.4%, p>0.05 PD: Rate of Smoking: Lifetime PD vs. no Mental Illness: Current Smokers = 35.9% vs. 22.5%; p<0.001) Rate of Smoking: Lifetime PD vs. no Mental Illness: Lifetime Smokers = 61.3% vs. 39.1%; p<=0.0001 Quit Rate: Lifetime PD vs. no Mental Illness: Quit Rate = 33.4% vs. 41.4%, p>0.05 Rate of Smoking: Past month PD vs. no Mental Illness: Current Smokers = 42.6% vs. 22.5%, p<0.001 Rate of Smoking: Past month PD vs. no Mental Illness: Lifetime Smokers = 63.5% vs. 39.1% p<=0.0001 Quit Rate: Past month PD vs. no Mental Illness: Quit Rate = 33.3% vs. 41.4%, p<=0.05 Specific Phobia:

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Rate of Smoking: Lifetime Specific Phobia vs. no Mental Illness: Current Smokers = 40.3% vs. 22.5%, p<0.001 Rate of Smoking: Lifetime Specific Phobia vs. no Mental Illness: Lifetime Smokers = 57.8% vs. 39.1%, p<=0.0001 Quit Rate: Lifetime Specific Phobia vs. no Mental Illness: Quit Rate = 30.3% vs. 41.4%, p>0.05 Rate of Smoking: Past month Specific Phobia vs. no Mental Illness: Current Smokers = 36.8% vs. 22.5%, p<=0.0001 Rate of Smoking: Past month Specific Phobia vs. no Mental Illness: Lifetime Smokers = 55.2% vs. 39.1%, p<=0.0001 Quit Rate: Past month Specific Phobia vs. no Mental Illness: Quit Rate = 33.3% vs. 41.4%, p<=0.05 PTSD: Rate of Smoking: Lifetime PTSD vs. no Mental Illness: Current Smokers = 45.3% vs. 22.5%, p<0.001 Rate of Smoking: Lifetime PTSD vs. no Mental Illness: Lifetime Smokers = 63.3% vs. 39.1%, p<=0.0001 Quit Rate: Lifetime PTSD vs. no Mental Illness: Quit Rate = 28.4% vs. 41.4%, p<0.01 Rate of Smoking: Past month PTSD vs. no Mental Illness: Current Smokers = 44.6% vs. 22.5%, p<=0.0001

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Rate of Smoking: Past month PTSD vs. no Mental Illness: Lifetime Smokers = 58.1% vs. 39.1%, p<=0.0001 Quit Rate: Past month PTSD vs. no Mental Illness: Quit Rate = 23.2% vs. 41.4%, p<=0.01 GAD: Rate of Smoking: Lifetime GAD vs. no Mental Illness: Current Smokers = 46.0% vs. 22.5%; p<0.001 Rate of Smoking: Lifetime GAD vs. no Mental Illness: Lifetime Smokers = 68.4% vs. 39.1%, p<=0.0001 Quit Rate: Lifetime GAD vs. no Mental Illness: Quit Rate = 32.7% vs. 41.4, p<0.05 Rate of Smoking: Past month GAD vs. no Mental Illness: Current Smokers = 54.6% vs. 22.5%; p<=0.0001 Rate of Smoking: Past month GAD vs. no Mental Illness: Lifetime Smokers = 76.8% vs. 39.1%, p<=0.0001 Quit Rate: Past month GAD vs. no Mental Illness: Quit Rate = 28.9% vs. 41.4%, p<=0.05 * All results Adjusted for gender, age and geographical region

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Lawrence et al, 2010 [6]	Study Population drawn from the Australian National Survey of Mental Health and Wellbeing, a random population sample (n= 8841) of participants aged 16-85 living in private dwellings in Australia.	CIDI (v3) for ICD-10 and DSM-IV criteria. ICD-10 criteria utilised for this study. 12 month mental disorders were identified as having a lifetime diagnosis and having established symptoms in 12 months prior to survey. Severity of AD measured using the World Mental Health Survey severity measure	Self report smoking: Current smokers= Smoked daily or less than daily Daily smokers = Smoked daily Non-daily smokers were asked if they had ever smoked.	Proportion of current and daily smokers by AD diagnosis and severity	Prevalence of smoking in Grouped and Individual AD: Prevalence % (95% CI): Grouped AD: Prevalence of Current Smoking = 33.4% (31.0-35.9) Prevalence of Daily Smoking = 28.4% (24.4-31.8) PD: Prevalence of Current Smoking = 39.6% (33.4-45.8) Prevalence of Daily Smoking = 27.7% (19.7-34.6) Agoraphobia: Prevalence of Current Smoking = 37.0% (32.7-41.4 Prevalence of Daily Smoking = 34.2% (25.8-42.6) SP: Prevalence of Current Smoking = 32.9% (29.6 - 36.2) Prevalence of Daily Smoking = 28.7% (23.4-34.0) GAD: Prevalence of Current Smoking = 45.8% (39.0-52.7) Prevalence of Daily Smoking = 42.1% (32.0-52.1)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					OCD: Prevalence of Current Smoking = 41.4% (33.1-49.2) Prevalence of Daily Smoking = 32.7% (21.2-44.2) PTSD: Prevalence of Current Smoking = 33.7% (30.2-37.1) Prevalence of Daily Smoking = 27.9% (22.6-33.3) Prevalence of smoking in Grouped AD by severity: Prevalence % (95% CI) and significance testing: AD by severity: Prevalence of Current smokers (mild vs. moderate vs. severe AD) = 26.8% (20.7-32.9) vs. 31.8% (24.5-39.2) vs. 29.1% (41.0-57.2), p<0.0001 Prevalence of Daily smokers (mild vs. moderate vs. severe AD) = 21.9% (16.1-27.7) vs. 27.2% (20.0-34.4) vs. 41.7% (33.6-49.8), p<0.043

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Morris et al, 2006 [55]	111,984 individuals aged 12 and older who accessed the Colorado public mental health system during 2003-2004 fiscal years.	Diagnosis confirmed from coded patient records (criteria not specified)	Smoker if endorsed current tobacco use on clinical assessment record	Risk of smoking: AD vs. "Other Primary Diagnosis"* * Reference category included all those without a primary diagnosis or schizophrenia, schizoaffective disorders, bipolar disorder, depression or dysthymia	Risk of smoking: Adjusted OR (95% CI)*: AD vs. Other Primary Diagnosis = OR 0.95 (0.91-1.00), p>0.05 *Adjusted for gender, age, race/ethnicitity
Nelson et al, 1998 [56]	14-24 year old individuals drawn from German Government registers (n=3021)	Munich-CIDI (M-CIDI) utilising DSM-IV and ICD-10 criteria	Self-Report for smoking: Ever Use vs. Regular Use (used daily for >4 weeks) Nicotine Dependence = DSM-IV	Risk of AD occurrence: Non-ND / Regular Use vs. No Use ND / Regular Use vs. No Use % No Use vs. % Reg Use (Non-ND vs. ND)	Grouped Anxiety Disorders Unadjusted OR (95% CI): Non-ND / Regular Use vs. No Use: OR (95% CI) = 1.10 (0.81-1.48) ND / Regular Use vs. No Use: OR (95% CI) = 1.94 (1.49-2.53) % No Use= 11.5% vs. Non-ND Use (13.4%) vs. ND Use (23%) p<0.05 (No Use vs. Any Use); p<0.05 (Non-ND Use vs. ND Use)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Op Den Velde et al 2002 [57]	Sample drawn randomly (n=182) from respondents to an approach of study investigating wellbeing of the known 813 men who had previously registered as part of the Dutch civilian resistance living ("Stichting 1940-1945) in the Netherlands during 1986-1988. These were compared against 252 males aged 55-64 who had been included in a general Netherlands Central Bureau for Statistics survey	SCID for DSM-III-R criteria	Self report smoking: Information from "number of cigarettes smoked daily" to calculate weekly rates	Risk of smoking (rates of cigarette consumption): PTSD vs. no PTSD (veterans)	Risk of smoking (rates of cigarette consumption): Rates (%) and significant testing: Rates of Smoking: PTSD vs. No PTSD: 0 cigarettes per week = 43.1% vs. 66.0% PTSD vs. No PTSD: 1-35 cigarettes per week = 6.9% vs. 2.0% PTSD vs. No PTSD: 36-105 cigarettes per week = 26.4% vs. 12.0% PTSD vs. No PTSD: 106-175 cigarettes per week = 15.3% vs. 18.0% PTSD vs. No PTSD: >175 cigarettes per week = 8.3% vs. 2.0% X^2 = 9.61, df=4, P = 0.05

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Schmitz et al, 2003 [58]	Population drawn from the German National Health Interview and Examination Survey: a cross-sectional, stratified, nationally representative survey of non-institutionalised Germans aged 18-79 (n=4181)	CIDI for DSM-IV criteria	Self report smokers: Categories: Non smokers Non ND Current smokers ND Current smokers	Prevalence of 12 month AD (All, Pure, Comorbid) by smoking categories	Prevalence of AD: Prevalence 12 month diagnosis % (SE): Never smokers: Prevalence of all AD = 11.9% (0.8) Prevalence of pure AD = 6.2% (0.6) Prevalence of comorbid AD = 5.7% (0.5) Non ND Current smokers: Prevalence of all AD = 13.5% (1.0) Prevalence of pure AD = 7.3% (0.8) Prevalence of comorbid AD = 6.1% (0.7) ND smokers: Prevalence of all AD = 28.3% (2.5) Prevalence of pure AD = 11.8% (1.8) Prevalence of comorbid AD = 16.5% (1.9) Prevalence 1 month diagnosis % (SE): Never smokers: Prevalence of all AD = 7.3 (0.6)% Prevalence of pure AD = 4.1% (0.5) Prevalence of comorbid AD = 3.2% (0.4) Non ND Current smokers: Prevalence of all AD = 8.5% (0.8) Prevalence of pure AD = 5.6% (0.7)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					Prevalence of comorbid AD = 2.9% (0.5) ND smokers: Prevalence of all AD = 18.6% (2.1) Prevalence of pure AD = 8.3% (1.5) Prevalence of comorbid AD = 10.3% (1.6)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Schumann et al, 2004 [59]	Participants drawn from the German Transitions in Alcohol Consumption and Smoking Study (n= 4072). Participants aged 18-64 were drawn randomly from general population of Lubeck, Germany.	M-CIDI for DSM-IV	Smoking information gathered from M-CIDI: Smokers categorised into: 1) ND Cigarette Ever smokers (M-CIDI ND and at least 1 cigarette/day for >=4 weeks at some stage) 2) Non-ND Cigarette Ever smokers (No M-CIDI ND but at least 1 cigarette/day for >=4 weeks at some stage) 3) Current Cigarette smokers (at least 1 cigarette/day for >=4 weeks within the previous 4 weeks) 4) Former smokers (at least 1 cigarette/day for 4 weeks but not in previous 4 weeks) 5) Never smokers (never at least 1 cigarette/day for period of =>4 weeks)	Risks of AD: By smoking categories	Grouped and Individual Anxiety Disorders (cross-sectional): Unadjusted OR (95% CI): Grouped AD's: Risk of Disorder: Non ND Ever smoker vs. Never smoker = OR 1.04 (0.84-1.28) Risk of Disorder: ND Ever smoker vs. Non ND Ever smoker = OR 2.20 (1.78-2.73), p<0.05 PD: Risk of Disorder: Non ND Ever smoker vs. Never smoker = OR 1.16 (0.67-2.03) Risk of Disorder: ND Ever smoker vs. Non ND Ever smoker = OR 2.92 (1.79-4.79),p <0.05 SP: Risk of Disorder: Non ND Ever smoker vs. Never smoker = OR 0.59 (0.33-1.07) Risk of Disorder: ND Ever smoker vs. Non ND Ever smoker = OR 3.07 (1.70-5.57), p<0.05 Specific Phobia: Risk of Disorder: Non ND Ever smoker vs. Never smoker = OR 1.04 (0.82-1.33) Risk of Disorder: ND Ever smoker vs. Non ND Ever smoker = OR 2.09 (1.63-2.68), p<0.05

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					GAD: Risk of Disorder: Non ND Ever smoker vs. Never smoker = OR 1.18 (0.43-3.26) Risk of Disorder: ND Ever smoker vs. Non ND Ever smoker = OR 4.26 (1.85-9.84), p<0.05 PTSD: Risk of Disorder: Non ND Ever smoker vs. Never smoker = OR 1.48 (0.75-2.94) Risk of Disorder: ND Ever smoker vs. Non ND Ever smoker = OR 2.08 (1.13-3.83), p<0.05

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Sonntag et al, 2000 [23]	Participants drawn from the Early Developmental Stages of Psychopathology Study (EDSP), a community sample from metropolitan Munich (n= 3021) of adolescents and young adults aged 14 - 24.	M-CIDI for DSM-IV criteria diagnosis	Nicotine dependence: M-CIDI for DSM-IV criteria Self Report: Smoking assessment: Regular smoking defined as daily use for at least 4 weeks Smoking behavior, Age of onset, Age at commencement regular smoking: Categories of smoker: 1) Non-users (No lifetime smoking) 2) Occasional user (Have used but never daily for 4 weeks) 3) Non-dependent regular smokers (Daily smoking >4 weeks in lifetime but not DSM-IV ND) 4) Dependent regular smokers (Daily smoking >4 weeks in lifetime & DSM-IV ND)	Odds of smoking (by categories & gender): SP vs. No SP	Odds of Smoking (cross-sectional): Adjusted OR (95% CI)*: MEN: Odds of smoking: SP vs. no SP: Occasional Users = OR 0.72 (0.34-1.50) Odds of smoking: SP vs. no SP: Non-dependent regular smokers = OR 0.74 (0.29-1.87) Odds of smoking: SP vs. no SP: ND regular smokers = OR 1.88 (0.89-3.98) FEMALES: Odds of smoking: SP vs. no SP: Occasional Users = OR 1.05 (0.62-1.79) Odds of smoking: SP vs. no SP: Non-dependent regular smokers = OR 0.90 (0.45-1.82) Odds of smoking: SP vs. no SP: ND regular smokers = OR 2.53 (1.4-4.58) p<0.05 ALL: Odds of smoking: SP vs. no SP: Occasional Users = OR: 0.86 (0.56-1.32) Odds of smoking: SP vs. no SP: Non-dependent regular smokers = OR 0.81 (0.46-1.41) Odds of smoking: SP vs. no SP: ND regular smokers = OR 2.07 (1.29-3.29) p<0.05 * Adjusted for age

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Tobias et al, 2008 [7]	Nationally representative sample (n=12992) from New Zealand (The 2003-4 New Zealand Mental Health Survey)	M-CIDI for DSM-IV criteria	Self Report smoking: 3 categories: Current smoker Ex-smoker Never smoker Tobacco consumption estimated utilising the Kessler 10-item Scale of Psychological distress (cross referenced with smoking intensity questions from a later New Zealand Health Survey)	Prevalence of current smoking: AD by gender Proportion of cigarettes consumed by individuals with AD	Prevalence of current smoking: Prevalence (Grouped AD) (95% CI): ALL: Prevalence of current smoking = 30.4% (27.7-33.0) Proportion of total cigarettes consumed by people with AD = 16.0% (14.1-17.9) MALES: Prevalence of current smoking = 28.7% (24.4-33.1) Proportion of total cigarettes consumed by people with AD = 10.5% (8.4 to 12.6) FEMALES: Prevalence of current smoking = 30.6% (27.6-33.6) Proportion of total cigarettes consumed by people with AD = 21.1% (18.4 to 23.8)

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Vesga-Lopez, 2008 [60]	Sample of civilian, non-institutionalised people aged 18yrs and older from the USA, drawn from the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (n= 43093)	Diagnosis assessed using the AUDADIS-IV for DSM-IV criteria	Nicotine Dependence measured using the AUDADIS-IV	Risk of ND (comparisons by gender): Males vs. Females = ND vs. no ND	Gender Risk of ND Adjusted OR (95% CI)*: 12month GAD: Males ND vs. Females ND = OR 1.2 (0.8-1.7) Lifetime GAD: Males ND vs. Females ND = OR 1.4 (1.1-1.9), p<0.05 * Adjusted for age, race-ethnicity, sex, marital status, education, income, urbanicity, region of country
Wittchen et al, 1999 [61]	Early Developmental Stages of Psychopathology Study (EDSP), community sample of 3021 adolescents and young adults with two follow up surveys at 15 to 30 months after baseline	M-CIDI for DSM-IV criteria	ND by M-CIDI for DSM-IV criteria	Risk of ND: SP (Lifetime) vs. no SP (Lifetime) (by Any SP, Generalized SP or Non-Generalized SP)	Risk of ND: Adjusted OR (95% CI)*: ND: SP (Any) vs. No SP (Any) = 2.0 (1.4-2.9)*, p<0.05 SP (Gen) vs. No SP (Gen) = 2.9 (1.6–5.3)*, p<0.05 SP (Non-Gen) vs. No SP (Non-Gen) = 1.7 (1.1-2.6)*, p<0.05 * Adjusted for age

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
Wu et al, 2010 [62]	Samples drawn from two surveys in the United States: The NIMH Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) and Westchester Study. Sample (n= 781) of adolescents was drawn from the randomly selected population of 1458 children (Age 9yrs to 17yrs) in 1992.	DISC 2.3 to DSM-III-R criteria (child and parent interview)	Parental and Child Self Report smoking: Lifetime smoking Past 12month smoking Frequent Smoking = >=1 cigarette daily in last 6 months	Risk of Frequent Smoking: AD vs. no AD	Risk of Frequent Smoking: Adjusted OR (95%CI)*: BOYS: Grouped AD: Frequent Smoking AD vs. Frequent Smoking (no AD) = AOR 3.0 (1.3-7.0)*, p<0.05; AOR 2.9 (1.2-6.9)**, p<0.05 SP: Frequent Smoking AD vs. Frequent Smoking (no AD) = AOR 4.9 (1.6-15.1)*, p<0.01; AOR 4.8 (1.6-14.8)**, p<0.01 Agoraphobia: Frequent Smoking AD vs. Frequent Smoking (no AD) = N/A Over Anxious Disorder/GAD: Frequent Smoking AD vs. Frequent Smoking (no AD) = AOR 2.9 (1.0-8.8)*; AOR 2.8 (0.9-8.5)** OCD: Frequent Smoking AD vs. Frequent Smoking (no AD) = AOR 1.1 (0.1-9.2)*; AOR 1.1 (0.1-9.4)** GIRLS: Grouped AD: Frequent Smoking AD vs. Frequent Smoking (no AD) = AOR 3.3 (1.3-8.0)*, p<0.05; AOR 2.4 (0.9-6.5)** SP: Frequent Smoking AD vs. Frequent Smoking (no AD) = AOR 0.8 (0.2-3.3)*; AOR 0.5 (0.1-2.0)** Agoraphobia: Frequent Smoking AD vs. Frequent Smoking (no AD) = AOR 3.2 (0.7-14.1)*; AOR 3.0 (0.6-13.7)** Over Anxious Disorder/GAD: Frequent Smoking AD vs. Frequent Smoking (no AD) = AOR 6.5 (2.1-20.3)*, p<0.01; 4.4 (1.2-15.8)**, p<0.05

STUDY	Study Population	Definition of Anxiety Disorder Diagnosis	Definition of Smoking Status or Nicotine Dependence	Parameters Measured	Results
					OCD: Frequent Smoking AD vs. Frequent Smoking (no AD) = AOR 13.0 (2.3-73.2)*, p<0.001; AOR 7.4 (1.1-47.8)**, p<0.05 Significant Gender Difference existed for SP, p<0.505* & p<0.138** * Adjusted for age, ethnicity, public assistance, not living with both biological parents, parental drug/alcohol problems and site ** Adjusted for age, ethnicity, public assistance, not living with both biological parents, parental drug/alcohol problems, site, depressive disorders

A large number of studies have reported cross-sectional relationships between cigarette smoking, nicotine dependence and anxiety disorders. Many demonstrate higher rates of smoking and nicotine dependence in those with anxiety disorders, and vice versa. However, their utility is limited due to their inherent inability to provide insight into direction of causality.

Almost all studies included in this review for Moylan et al (2012) reported cross-sectional associations between smoking and/or ND and ADs. Studies providing cross-sectional information are listed in the Table above.

In regard to dose-response Moylan et al (2012) states:

"A demonstrated dose-dependent relationship would support a causal association between cigarette smoking and subsequent onset of ADs. Breslau demonstrated that increased standardized pack years of smoking were associated with increased odds of GAD, but decreased odds of PD [Breslau et al, 2004] in dose dependent fashion" (no page numbers).

Cigarette smoking increases the risk of panic disorder with or without agoraphobia's emerging. Although the cause of this comorbidity remains controversial, the main explanations are that (1) cigarette smoking promotes panic by inducing respiratory abnormalities/lung disease or by increasing potentially fear-producing bodily sensations, (2) nicotine produces physiologic effects characteristic of panic by releasing norepinephrine, (3) panic disorder promotes cigarette smoking as self-medication, and (4) a shared vulnerability promotes both conditions.

Cosci, Knuts, Abrams et al (2010)[168] conducted a review to survey the literature in order to determine the validity of these explanatory models. Studies were identified by searching English language articles published from 1960 to November 27, 2008, in MEDLINE using the key words: nicotine AND panic, tobacco AND panic, and smoking AND panic.

Twenty-four studies were reviewed and selected according to the following criteria: panic disorder with or without agoraphobia and nicotine dependence, when used, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, Fourth Edition, or Fourth Edition, Text Revision; no additional comorbidity or, if present, adjustment for it in the statistical analyses; use of adult or adolescent samples; comparison with a nonclinical control group or application of a crossover design. Non-significant results or trends only were reported as no difference. Data on anxiety disorders or substance abuse in general were not included.

Cosci et al (2010) state

"Breslau and coworkers (1991) evaluated a random sample of young adults and found that nicotine-dependent smokers are at a higher risk of developing panic than nonsmokers. Moreover, the higher the level of nicotine dependence, the higher the risk of panic.

When the NCS (APA, 2000) and the Epidemiologic Study of Young Adults datasets were analysed (Breslau & Klein, 1999), a significantly higher risk of panic occurrence (either panic attacks or panic disorder) was found in subjects with pre-existing smoking if compared to

[168] Cosci F, Knuts IJ, Abrams K, et al (2010). Cigarette smoking and panic: a critical review of the literature. J Clin Psychiatry, 70(5): 606-15. 078716

nonsmokers and in subjects who persist in smoking after panic onset compared to nonsmokers.

Examining subjects with a history of panic and a history of daily smoking, Bernstein et al (2007) found that the earlier the age at onset of daily smoking, the greater the risk of developing panic disorder.

Longitudinal studies have found similar results. In one study, adolescents who smoked 20 cigarettes or more per day were at elevated risk of panic disorder with agoraphobia during both adolescence and early adulthood when compared with those who smoked fewer than 20 cigarettes per day (Johnson et al, 2000).

Nondependent regular smokers and dependent smokers were at higher risk of panic attacks than nonsmokers, and an elevated risk was maintained in dependent smokers when compared to occasional smokers (Isensee et al, 2003).

Current smokers, with or without nicotine dependence, were at higher risk of panic disorder occurrence than non-smokers, while being a former smoker seemed to reduce such a risk. Examining the relationship between time elapsed since quitting and the risk of the first onset of panic disorder in past daily smokers, using a standardized variable that counts the number of years passed beginning with the year after quitting, researchers found that the likelihood of panic was reduced by one-half with each standard deviation unit of time elapsed since quitting (Breslau et al, 2004). Thus, the authors showed some evidence that smoking cessation might reduce the risk of subsequent panic" (p 611).

Cosci and colleagues (2010) concluded that panic and cigarette smoking each appear to have the capacity to serve as a causal factor/facilitator in the development of the other. Although the temporal pattern and the pathogenetic explanations of such a co-occurrence are still being discussed, cigarette smoking tends to precede the onset of panic and to promote panic itself.

Proposed theories

Several explanations have been proposed for this relationship between smoking and panic disorder: (i) cigarette smoking may lead to the onset of panic by inducing respiratory abnormalities or lung disease. Thus, smoking may increase the risk of panic because, according to the false suffocation alarm theory it induces an overreaction to suffocation signals; (2) nicotine may produce physiologic effects characteristic of panic attacks by promoting the release of norepinephrine into the brainstem; (3) smoking may modify the expression of panic disorder by increasing potentially fear-producing bodily sensations. Thus, individuals with panic disorder who usually perceive themselves as being physically unhealthy would more likely react with exaggerated anxiety.

A different, less frequent, reverse pathway of primary panic and secondary nicotine dependence cannot be excluded. One hypothesis for this pathway is that panic disorder patients smoke as a means of self-medicating their symptoms, because of the anxiolytic (pharmacologic) effects of nicotine or because of cognitive mechanisms (smoking narrows the focus of attention and diverts one from stressful cognitions). A shared vulnerability has been also advanced suggesting that personality, and in particular neuroticism, may be responsible for such a co-occurrence.

Mendelian randomised analysis

Bjorngaard, Gunnell, Elvestad et al (2013)[169] investigated the causal relationship between smoking and symptoms of anxiety and depression in the Norwegian HUNT study using the rs1051730 single nucleotide polymorphism (SNP) variant located in the nicotine acetylcholine receptor gene cluster on chromosome 15 as an instrumental variable for smoking phenotypes. Among smokers, this SNP is robustly associated with smoking quantity and nicotine dependence. In total, 53 601 participants were genotyped for the rs1051730 SNP and provided information on smoking habits and symptoms of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS).

Self-reported smoking was positively associated with the prevalence of both anxiety and depression, and the measured polymorphism was positively associated with being a current smoker and the number of cigarettes smoked in current smokers. In the sample as a whole, risk of anxiety increased with each affected T allele [odds ratio (OR) 1.06, 95% confidence interval (CI) 1.02–1.09, p=0.002] but there was no association with depression (p=0.31). However, we found no clear association of the polymorphism with either anxiety (OR 1.03, 95% CI 0.97–1.09, p=0.34) or depression (OR 1.02, 95% CI 0.95–1.09, p=0.62) among smokers.

As there was no association of the smoking-related rs1051730 SNP with anxiety and depression among smokers, the results suggest that smoking is not a cause of anxiety and depression.

Cohort studies

Mojtabai and Crum (2013)[170] examined the association between regular cigarette smoking and new onset of mood and anxiety disorders. Logistic regression analysis was used to detect associations between regular smoking and new-onset disorders during the 3-year follow-up among 34 653 participants in the longitudinal US National Epidemiologic Survey on Alcohol and Related Conditions (2001–2005). Instrumental variable methods were used to assess the appropriateness of these models.

Regular smoking was associated with an increased risk of new onset of mood and anxiety disorders in multivariable analyses ($F_{df=5,61} = 11.73$; $P < .001$). Participants who smoked a larger number of cigarettes daily displayed a trend toward greater likelihood of new-onset disorders. Age moderated the association of smoking with most new-onset disorders. The table below showed a significant trend between most anxiety disorders and increasing levels of smoking. The association was mostly statistically significant and generally stronger in participants aged 18 to 49 years but was smaller and mostly nonsignificant in older adults.

Mojtabai and Crum concluded that a strong association between regular cigarette smoking and increased risk of new-onset mood and anxiety disorders among younger adults is supported by their findings.

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[169] Bjørngaard JH, Gunnell D, Elvestad MB, et al (2013). The causal role of smoking in anxiety and depression: a Mendelian randomization analysis of the HUNT study. Psychol Med, 43(4): 711-9. 074512

[170] Mojtabai R, Crum RM (2013). Cigarette smoking and onset of mood and anxiety disorders. Am J Public Health, 103(9): 1656-65. 070479

TABLE 52 ASSOCIATION OF SMOKING WITH NEW ONSET OF MENTAL DISORDERS AT FOLLOW-UP: US NATIONAL EPIDEMIOLOGIC SURVEY ON ALCOHOL AND RELATED CONDITIONS, 2001–2005 (MOJTABAI & CRUM, 2013).

Disorders	AOR[a] (95% CI)	Overall Test, $F_{df=5,61}$	Test of Trend, $F_{df=1,65}$
Any mood or anxiety disorder		11.73***	29.88***
Nonsmokers (Ref)	1.00		
Ex-smokers	1.18** (1.06, 1.31)		
Smokers, 1–9 cigarettes/d	1.49** (1.18, 1.86)		
Smokers, 10–19 cigarettes/d	1.30** (1.11, 1.53)		
Smokers, 20–29 cigarettes/d	1.64*** (1.41, 1.90)		
Smokers, ≥30 cigarettes/d	1.84*** (1.43, 2.38)		
New onset of major depressive episodes		2.86*	11.62**
Nonsmokers (Ref)	1.00		
Ex-smokers	1.05 (0.88, 1.24)		
Smokers, 1–9 cigarettes/d	1.31 (0.91, 1.90)		
Smokers, 10–19 cigarettes/d	1.11 (0.83, 1.47)		
Smokers, 20–29 cigarettes/d	1.40* (1.08, 1.81)		
Smokers, ≥30 cigarettes/d	1.93** (1.27, 2.95)		
New onset of dysthymia		9.05***	27.53***
Nonsmokers (Ref)	1.00		
Ex-smokers	1.08 (0.69, 1.68)		
Smokers, 1–9 cigarettes/d	1.95 (0.95, 4.03)		
Smokers, 10–19 cigarettes/d	2.87*** (1.67, 4.95)		
Smokers, 20–29 cigarettes/d	4.26*** (2.45, 7.40)		
Smokers, ≥30 cigarettes/d	4.31*** (2.00, 9.32)		
New onset of manic episodes		5.95***	24.46***
Nonsmokers (Ref)	1.00		
Ex-smokers	1.07 (0.75, 1.50)		
Smokers, 1–9 cigarettes/d	1.07 (0.65, 1.76)		
Smokers, 10–19 cigarettes/d	1.44 (0.96, 2.15)		
Smokers, 20–29 cigarettes/d	2.28*** (1.52, 3.41)		
Smokers, ≥30 cigarettes/d	2.83** (1.60, 5.02)		
New onset of generalized anxiety disorder		1.77	5.55*
Nonsmokers (Ref)	1.00		
Ex-smokers	1.05 (0.86, 1.30)		
Smokers, 1–9 cigarettes/d	1.37 (0.84, 2.22)		
Smokers, 10–19 cigarettes/d	1.05 (0.78, 1.41)		
Smokers, 20–29 cigarettes/d	1.46* (1.08, 1.97)		
Smokers, ≥30 cigarettes/d	1.55 (1.00, 2.40)		
New onset of panic disorder		5.95***	13.52***
Nonsmokers (Ref)	1.00		
Ex-smokers	1.56** (1.16, 2.10)		
Smokers, 1–9 cigarettes/d	2.03** (1.21, 3.41)		
Smokers, 10–19 cigarettes/d	2.04*** (1.40, 2.97)		
Smokers, 20–29 cigarettes/d	2.59*** (1.69, 3.95)		
Smokers, ≥30 cigarettes/d	2.64** (1.45, 4.82)		

Continued

Table Continued

New onset of social anxiety disorder		3.85**	7.54**
Nonsmokers (Ref)	1.00		
Ex-smokers	1.25 (0.90, 1.72)		
Smokers, 1–9 cigarettes/d	1.51 (0.91, 2.51)		
Smokers, 10–19 cigarettes/d	1.85** (1.19, 2.89)		
Smokers, 20–29 cigarettes/d	2.11*** (1.42, 3.11)		
Smokers, ≥ 30 cigarettes/d	1.95* (1.03, 3.72)		
New onset of specific phobias		5.96***	17.62***
Nonsmokers (Ref)	1.00		
Ex-smokers	1.09 (0.84, 1.42)		
Smokers, 1–9 cigarettes/d	1.83* (1.12, 3.00)		
Smokers, 10–19 cigarettes/d	1.72** (1.23, 2.40)		
Smokers, 20–29 cigarettes/d	1.79** (1.26, 2.55)		
Smokers, ≥ 30 cigarettes/d	2.35** (1.45, 3.80)		
New onset of posttraumatic stress disorder		3.03*	2.76
Nonsmokers (Ref)	1.00		
Ex-smokers	1.37* (1.05, 1.80)		
Smokers, 1–9 cigarettes/d	1.43 (0.85, 2.39)		
Smokers, 10–19 cigarettes/d	1.33 (0.86, 2.06)		
Smokers, 20–29 cigarettes/d	2.17** (1.45, 3.25)		
Smokers, ≥ 30 cigarettes/d	1.35 (0.71, 2.60)		

Note. AOR = adjusted odds ratio; CI = confidence interval.
[a]Analyses adjusted for baseline variables of gender, age, race/ethnicity, household income, education, marital status, physical illness (cardiovascular, gastrointestinal, arthritis), residence (metropolitan central city, other metropolitan, nonmetropolitan), region (Northeast, Southwest, West, South), lifetime history of other mental disorders, alcohol disorders, and nonalcohol drug disorders.
*$P < .05$; **$P < .01$; ***$P < .001$.

The author's cite a number of limitations associated with their study and hence the findings should be interpreted in the context of these limitations. The onset of smoking might have preceded the onset of mental disorders by many years. The time lag between the onset of regular smoking and the onset of new mental disorders may have important implications. For example, participants who have just started smoking may be more vulnerable than those who have smoked regularly for many years. A more detailed assessment of the effect of smoking on onset of mental disorders would require studying a large cohort of participants recruited at an early age and assessed at multiple time points across the life span. Smoking history and mental disorder symptoms were both assessed by self-report and were thus prone to recall bias. Past research has shown that reports of lifetime mental disorders are especially prone to such biases.

In the context of these limitations, the data provide supporting evidence from a large, longitudinal, population-based survey on the link between regular smoking and the onset of mental disorders. These findings add to a growing literature on the mental health

consequences of smoking and further suggest that these consequences might be limited to the younger age group.

Summary and conclusion

The systematic review by Moylan et al (2012) presented the evidence relating to anxiety disorders and smoking and/or nicotine dependence. The six prospective studies in the table above reported inconsistent findings. Chou et al (2011) found no statistically significant associations between ND at baseline and subsequent ADs. The other five studies reported some significant findings but similar findings weren't replicated in each study. For example the DES data found a statistically significant protective association for quitters vs non-quitters in PD onset, but the NCS data did not find significant findings in this sub-analysis (Breslau et al, 1999). Cuijpers et al (2007) reported that grouped anxiety disorders were significantly associated with smoking, as was GAD, but other individual anxiety disorders were not. Goodwin and colleagues (2005) found that PD was significantly associated with smoking in an adolescent sample but other anxiety disorders were not associated with smoking. Insensee et al (2003) only found significant associations for ND smokers vs non-users for PD, agoraphobia, social phobia, PTSD and specific phobia; but not for current smokers. For those with GAD diagnoses the results for ND smokers vs non-users were not significant, but for non-ND smokers vs non-users a statistically significant result was reported. Johnson et al (2000) reported that the odds of developing AD, PD, and GAD was significant in those with > 1 pack year of cigarette smoking vs < 1 pack year of cigarette smoking. The cross-sectional studies reviewed by Moylan et al (2012) were equally equivocal as the prospective data and the direction of causality cannot be determined in those with a positive association. Some studies did provide evidence of a dose-response but not for all anxiety disorders measured.

Cosci et al (2010) in a systematic review of literature relating to ND and PD with or without agoraphobia concluded that a bi-directional causal relationship exists, with PD and smoking each appearing to serve as a causal factor the other.

Bjorngaard et al (2013) conducted a genetic study to identify if certain genotypes known to be associated with smoking were associated with anxiety. They concluded that smoking is not a cause of anxiety.

In a recent cohort study by Mojtabal and Crum (2013) examined the relationship between current smoking and risk of new onset of anxiety disorder, and found a positive association, particularly strong in the 18-49 year old age group. They also reported a significant dose response between increasing levels of smoking and new anxiety disorder onset, for most categories.

A consistent association has been observed between nicotine dependence/smoking and various anxiety disorders, although a literature related to SMIAD was not identified. Due to the heterogeneity of measurements across studies and the inconsistencies noted across studies it is difficult to determine a judgement of a probable/convincing causal relationship or a judgement of a possible causal relationship. Although does response relationships are reported across various studies including the recent cohort study above.

Grade 2-3 level evidence

Carbon monoxide poisoning

Summary of important issues

Only one study was identified in the literature which did not report on psychiatric history prior to exposure.

Cohort studies

Jasper, Hopkins, Duker and Weaver (2005)[171] longitudinally assessed the prevalence of depression and anxiety following carbon monoxide (CO) poisoning and the contributions of mode of poisoning (accidental versus suicide attempt), cognitive sequelae, and oxygen dose (hyperbaric oxygen versus normobaric oxygen) to depression and anxiety. CO is the most common cause of poisoning in the United States and may result in neuropathologic changes and cognitive and neurologic sequelae, yet little is known regarding affective outcomes. Jasper et al (2005) prospectively assessed affect in 127 CO-poisoned patients. Self-report inventories of depression and anxiety were administered at 6 weeks and at 6 and 12 months post CO poisoning. The primary outcome was prevalence of depression and anxiety at 6 weeks. To determine the effect of mode of poisoning, cognitive sequelae, and oxygen dose, odds ratio estimates were calculated at all three times using logistic regression.

Depression and anxiety were present in 45% of patients at 6 weeks, 44% at 6 months, and 43% at 12 months. Patients with suicide attempt and cognitive sequelae had higher prevalence of depression and anxiety at 6 weeks. At 12 months, there were no differences in depression or anxiety regardless of mode of poisoning, presence of cognitive sequelae, or oxygen dose.

CO poisoning may result in significant depression and anxiety that persist to at least 12 months. Patients with cognitive sequelae and suicide attempt had a higher rate of depression and anxiety at 6 weeks (which may have been pre-existing and related to the suicide attempt) but not at 12 months.

Jasper et al (2005) summarised the case studies previously published on this topic (see Table below), A major limitation of the evidence provided by Jasper and colleagues is the unavailability of the psychiatric histories of the participants and cases. It is unclear if the anxiety symptoms are a new presentation related to the CO exposure or a pre-existing condition.

[171] Jasper BW, Hopkins RO, Duker HV, Weaver LK. (2005). Affective outcome following carbon monoxide poisoning: a prospective longitudinal study. Cognitive & Behavioral Neurology; 18(2):127-34.

TABLE 53 CASE STUDIES OF PATIENTS WITH AFFECTIVE CHANGES FOLLOWING CARBON MONOXIDE POISONING (JASPER ET AL, 2005).

Author (year)	Cases (n)	Depression	Anxiety	Personality Change	Cognitive Change	Suicide Attempt	Time from CO
Bruno et al (1993)[16]	1	+			+	−	4 y
	2	+	+		+	−	4 y
Deckel (1994)[68]	1				+	−	4 y
	2	+		+	+	−	2 y
Dunham and Johnstone (1999)[33]	1	+	+		+	−	6–7 y
	2	+	+		+	−	6–7 y
	3	−	+		+	−	6–7 y
	4	+	+		+	−	6–7 y
Escalona et al (1997)[39]	1		+			+	6 mo
Garland and Pearce (1967)[28]	1	+			+	−	7 and 12 mo
	2	+			+	−	10 and 16 mo
	3	+			+	−	10 mo
	4	+				−	10 and 16 mo
Jaeckle and Nasrallah (1985)[35]	1	+			+	−	1–9 w and 1 y
Jefferson (1976)[37]	1	+	+		+	−	1 mo and 1 y
	2	+	+		+	−	1 mo and 1 y
Jerrett & Steffens (1995)[69]	1	+			+	−	4 y
Lugaresi et al (1990)[40]	1			+	+		10 mo and 1 y
	2			+	+	+	3 mo
	3			+	+		1, 6, and 12 mo
Mori et al (1996)[19]	1	−	−	+	−	−	11 and 12 mo
Smith & Mellick (1975)[70]	1	+			+	+	6 wk
	2	+			+	+	11 wk
	3	+			+	+	1 and 2 mo
	4	+			+	+	2 y
Thomson, Mardel, Jack, & Shields (1992)[71]	1	+		+	+	+	3 d and 5 wk
Thorpe (1994)[72]	1			+	+	−	Admit
Vieregge et al (1989)[36]	1				+	−	8 d and 18 mo
	2				+	−	18 h and 8 mo
	3				+	−	2 d, 8 and 18 mo
	4				+	−	4 d and 4 mo

This table shows case studies of patients with affective changes following carbon monoxide poisoning. Study inclusion criteria were age ≥16 years, carbon monoxide poisoning, and reports of affective outcome.

Empty cells, no data available; (+), present; (−), absent; Anxiety, anxiety or anxiety disorders (eg, obsessive–compulsive disorder); Cognitive change, any cognitive impairment such as memory, IQ, visuospatial, apraxia/dyspraxia, agnosia, acalculia, concentration, executive function, etc.

Summary and conclusion

The longitudinal study above has a number of methodological concerns, the most concerning of which is that it is unclear if the anxiety symptoms reported are directly related to the CO exposure or a pre-existing condition suffered prior to exposure.

Grade 5A level evidence

Carbon dioxide (CO_2)

Summary of important issues

Carbon dioxide is commonly used in experimental settings to induce panic attacks and anxiety symptoms. Fewer studies report on "healthy" participants and the long-term effects of this exposure.

Placebo-controlled study

The study of carbon dioxide (CO_2) inhalation in psychiatry has a long and varied history, with recent interest in using inhaled CO_2 as an experimental tool to explore the neurobiology and treatment of panic disorder. As a consequence, many studies have examined the panic-like response to the gas either using the single or double breath 35% CO_2 inhalation or 5-7% CO_2 inhaled for 15-20 min, or rebreathing 5% CO_2 for a shorter time. However, this lower dose regime produces little physiological or psychological effects in normal volunteers. For this reason, **Bailey, Argyropoulos, Kendrick and Nutt (2005)**[172] studied the effects of a higher concentration of CO_2, 7.5%, given over 20 min. Twenty healthy volunteers were recruited to a double blind, placebo-controlled study where air and 7.5% CO_2 were inhaled for 20 min. Cardiovascular measures and subjective ratings were obtained.

Visual analogue rating scales (VAS) were used, measured on 100 mm line, anchored from 0 (''not at all'') to 100 (''the mostyever''). The individual items were labeled as: alert, anxious, fearful, relaxed, happy, feel like leaving the room, feel paralysed, tense, irritable, nervous, worried. These scales provide a good estimate of rapid changes of aspects of mood states [Bond and Lader, 1974; cited in Bailey et al 2005]. The panic symptom inventory (PSI) lists 34 symptoms related to panic anxiety and the associated autonomic arousal, with the option of rating 0=not at all, 1=slight, 2=moderate, 3=severe, or 4=very severe. It has been used in studies of panic provocation [Bell et al., 2002; Nutt et al., 1990; cited in Bailey et al, 2005] and previous 35% CO_2 studies [Argyropoulos et al., 2002; cited in Bailey et al, 2005]. The PSI was adapted from Clark and Hemsley [1982] and was administered at baseline for peak effects of inhalation and at the end of each inhalation. The Spielberger State Anxiety Inventory (SSAI) [Spielberger, 1983; cited in Bailey et al, 2005] was used to measure state anxiety at baseline and 10 min after the end of each inhalation period.

When compared to air, inhaling 7.5% CO_2 for 20 min increases systolic blood pressure and heart rate, indicating increased autonomic arousal. It also increases ratings of anxiety and fear and other subjective symptoms associated with an anxiety state.

For peak effects of CO2, 10 of 11 ratings of the VAS are significantly different from air (Table below). The subjective reporting of 'alertness' was not significantly different between the gases at this, or any other, time point.

[172] Bailey JE, Argyropoulos SV, Kendrick AH, Nutt DJ. (2005). Behavioral and cardiovascular effects of 7.5% CO2 in human volunteers. Depression & Anxiety; 21(1):18-25, 2005.

TABLE 54 VAS DATA, CHANGE FROM BASELINE VALUES FOR PEAK EFFECTS OF GAS (BAILEY ET AL, 2005).

Rating	Peak air	Peak CO_2
Anxious	2 (2.1)	25 (5.8)[b]
Fear	1 (2.9)	24 (4.5)[b]
Feel like leaving	3 (2.5)	23 (5.8)[b]
Happy	−10 (2.9)	−27 (4.0)[c]
Irritable[a]	2 (2.1)	16 (6.9)[d]
Nervous[a]	5 (2.3)	17 (3.4)[c]
Paralysed	4 (2.6)	15 (4.2)[c]
Relaxed	−13 (5.5)	−35 (4.9)[b]
Tense	4 (2.9)	29 (5.1)[b]
Worried[a]	1 (1.6)	18 (4.7)[c]

Values are expressed as mean (*sem*); $n = 20$.
[a] $n = 12$.
Wilcoxon signed rank test: [b] $P = .001$; [c] $P = .01$; [d] $P < .05$.

At >20 min after start of inhalation, 7 of 11 ratings were significantly different for air and CO_2 (Table below). There were no significant changes from baseline at the +30 minute time point.

TABLE 55 VAS DATA, CHANGE FROM BASELINE VALUES FOR +20 MIN OF GAS (BAILEY ET AL, 2005).

Rating	Peak air	Peak CO_2
Anxious	−2 (2.4)	7 (2.8)[c]
Fear	8.7 (3.2)	3.5 (6.3)
Feel like leaving	1 (1.9)	12 (4.5)[b]
Happy	−5 (4.5)	−16 (2.8)[c]
Irritable[a]	−1 (2.3)	4.6 (3.0)[d]
Nervous[a]	−1.7 (2.5)	2.1 (2.4)
Paralysed	2 (1.1)	7 (1.9)[d]
Relaxed	1 (5.7)	−29 (4.9)[b]
Tense	−2 (3.5)	16 (5.7)[c]
Worried[a]	−2.1 (1.6)	0.8 (2.6)

Values are expressed as mean (*sem*); $n = 20$.
[a] $n = 12$.
Wilcoxon Signed rank test: [b] $P = .001$; [c] $P = .01$; [d] $P < .05$.

Three subjects (participants 12, 17 and 18) scored highly on the PSI in response to 7.5% CO_2. These individuals demonstrated a marked sensitivity to the gas, but recovered rapidly with no sequelae. Individual variability of response is shown in Figure below.

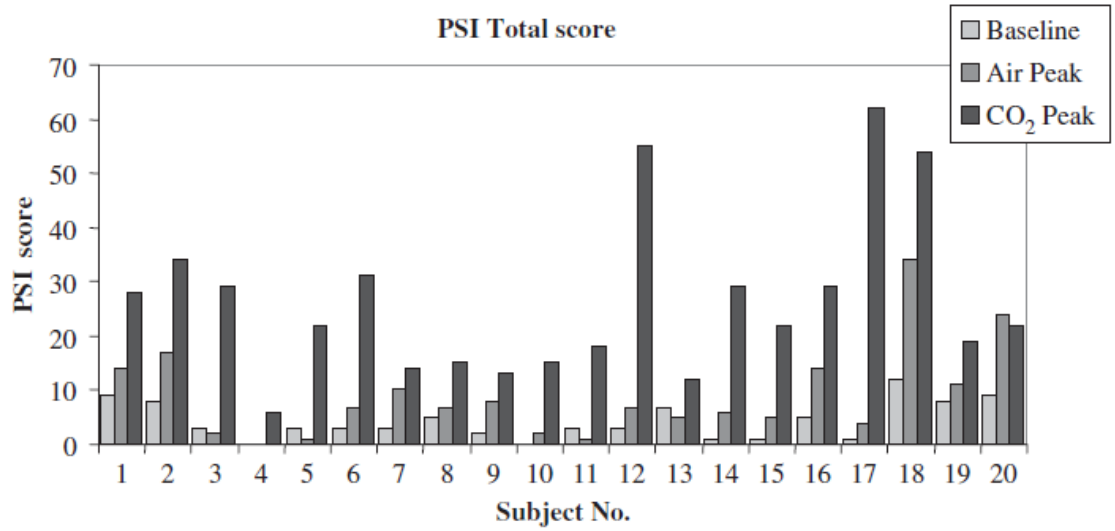

FIGURE 3 PSI TOTAL SCORE FOR BASELINE, PEAK RESPONSE OF AIR AND CO2 INHALATION FOR EACH SUBJECT UNDERGOING THE PROCEDURE (BAILEY ET AL, 2005).

The data from the Spielberger state anxiety inventory suggested that a residual anxiety is still present for up to 10 min after completion of the CO2 inhalation, as indicated by the significant increase in the score (Figure below). This is not reflected in the VAS scores, however, and it must be noted that the mean Spielberger score is still within the range for normal volunteers, with anxious patients reporting a mean score of 49 [Spielberger, 1983; cited in Bailey et al, 2005].

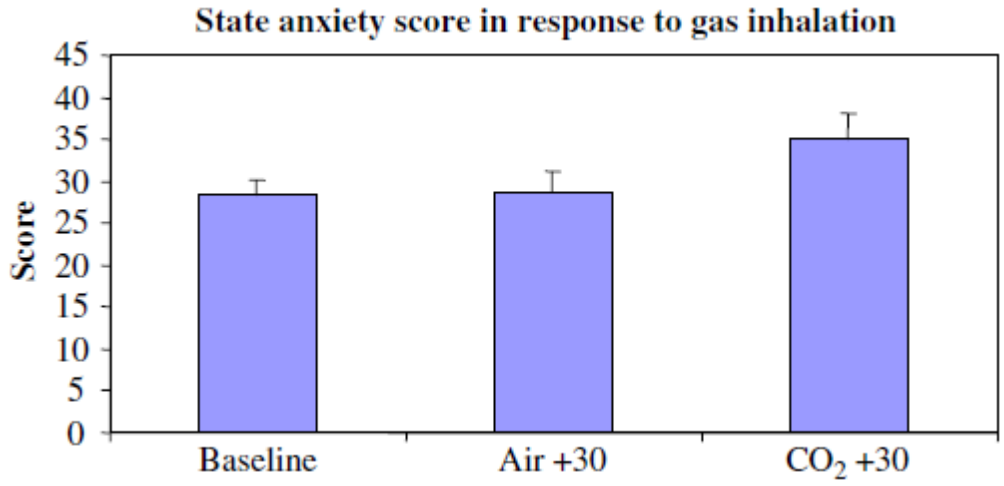

FIGURE 4 MEAN TOTAL SCORE FOR SPIELBERGER STATE ANXIETY INVENTORY FOR BASELINE, AIR Þ30 MIN AND CO2 Þ30 MIN. SIGNIFICANT DIFFERENCES BETWEEN BASELINE AND POST-CO2 INHALATION (P¼.009) AND POST AIR COMPARED TO POST-CO2 (P¼.002) (BAILEY ET AL, 2005).

These results indicate that carbon dioxide exposure can result in anxiety and panic symptoms in healthy controls, however, the VAS scores showed that anxiety symptoms returned to normal 10 minutes after exposure and the state anxiety scores at peak exposure never reached levels above normal range.

The inhalation of 7.5% CO_2 for 20 min is safe for use in healthy volunteers and produces robust subjective and objective effects. It seems promising as an anxiety provocation test that

could be beneficial in the study of the effects of anxiety on sustained performance, the discovery of novel anxiolytic agents, and the study of brain circuits and mechanisms of anxiety.

Garner, Attwood, Baldwin and Munafo (2012)[173] supported the findings above that healthy particpants report subjective anxiety symptoms and autonomic arousal whilst exposed to CO_2. They expanded the study concept by also examining the effect of 7.5% CO_2 inhalation (vs. air) on the efficiency of discrete attention networks implicated in anxiety: alerting (maintaining an alert state), orienting (the selection of information from sensory input) and executive control (resolving cognitive conflict). Twenty-three healthy human participants completed a computerized Attention Network Test (ANT) during inhalation of 7.5% CO_2 enriched and normal/medical air. Gas was administered blind to participants with inhalation order counterbalanced across participants. Measures of heart rate, blood pressure and subjective mood/anxiety were obtained at baseline and following each inhalation period. CO2 inhalation increased anxiety, autonomic arousal and the efficiency of alerting and orienting attention network function. Autonomic response to CO_2 correlated with increased orienting; and CO_2-induced anxiety, autonomic arousal and orienting network function increased with chronic (trait) anxiety. They concluded that the evidence found that CO_2 modulates attention mechanisms involved in the temporal detection and spatial location of salient stimuli converges with evidence that CO_2 triggers fear behaviour in animals via direct innervation of a distributed neural network that facilitates environmental hypervigilance.

Unfortunately the study did not assess anxiety or autonomic responses post-CO_2 exposure so the time it took to return to baseline levels is not reported.

Cohort studies

Perna, Cocchi, Allevi et al (1999)[174] conducted a follow-up study to investigate the potential priming effect of the 35% CO_2 challenge on the development of anxiety disorders and/or panic attacks in healthy first-degree relatives of panic patients across a period of 3-4 years subsequent to the challenge. Thirty-one relatives who underwent the 35% CO_2 challenge 3-4 years before and 14 relatives, free from psychiatric diagnoses in the same period, were directly re-evaluated for the presence of anxiety disorders and panic attacks. None developed anxiety disorders and only 1, among relatives previously tested with the 35% CO_2 challenge, reported sporadic panic attacks. Perna et al (1999) concluded that the 35% CO_2 challenge is a safe research paradigm in the investigation of healthy subjects with a familial vulnerability to panic.

Summary and conclusion

The two blinded controlled studies above (Bailey et al, 2005; Garner et al, 2012) reported an association between carbon dioxide exposure and subjective anxiety symptoms in healthy subjects. Bailey reported that ten minutes after exposure to carbon dioxide the subjective symptoms of anxiety returned to baseline levels. Garner stated that the anxiety and autonomic responses were raised during exposure to the carbon dioxide levels. The cohort

[173] Garner M, Attwood A, Baldwin DS, Munafo MR. (2012). Inhalation of 7.5% carbon dioxide increases alerting and orienting attention network function. Psychopharmacology; 223(1):67-73.
[174] Perna G, Cocchi S, Allevi L, Bussi R, Bellodi L. (1999). A long-term prospective evaluation of first-degree relatives of panic patients who underwent the 35% CO_2 challenge. Biological Psychiatry; 45(3):365-7.

study by Perna et al (1999) found that exposure to carbon dioxide in subjects which reported a positive response to anxiety etc. years earlier did not lead to anxiety or panic disorder diagnoses later in life, although one participant did have periodic panic attacks. This report of panic attacks in one individual could be a chance finding.

No persistent symptomatology significant as an anxiety disorder was reported in the studies above.

Grade 4 – 5a level evidence

Ozone concentrations

Summary of important issues

Only one study on this topic was identified in the literature search.

Data-base records study

Cho, Choi, Sohn, Suh et al (2015)[175] investigated the association of ambient air pollution with the risk of panic attack-related emergency department visits. Using health insurance claims, we collected data from emergency department visits for panic attacks in Seoul, Republic of Korea (2005-2009). Daily air pollutant concentrations were obtained using automatic monitoring system data. We conducted a time-series study using a generalized additive model with Poisson distribution, which included spline variables (date of visit, daily mean temperature, and relative humidity) and parametric variables (daily mean air pollutant concentration, national holiday, and day of the week). In addition to single lag models (lag1 to lag3), cumulative lag models (lag0-1 to lag0-3) were constructed using moving-average concentrations on the days leading up to the visit. The risk was expressed as relative risk (RR) per one standard deviation of each air pollutant and its 95% confidence interval (95% CI). A total of 2320 emergency department visits for panic attacks were observed during the study period. The adjusted RR of panic attack-related emergency department visits was 1.051 (95% CI, 1.014-1.090) for same-day exposure to ozone. In cumulative models, adjusted RRs were 1.068 (1.029-1.107) in lag0-2 and 1.074 (1.035-1.114) in lag0-3. The ambient ozone concentration was significantly associated with emergency department visits for panic attacks.

This study design cannot establish a causal relationship, and only demonstrates an association.

Summary and conclusion

The study design does not allow causal associations to be drawn. It could be another exposure (e.g., air pollution per se) rather than ozone levels which account for any correlation.

Grade 4 – 5a level evidence

[175] Cho J, Choi YJ, Sohn J, Suh M, Cho SK, Ha KH, Kim C, Shin DC. (2015). Ambient ozone concentration and emergency department visits for panic attacks. Journal of Psychiatric Research; 62:130-5.

Organic solvent exposure

Summary of important issues

A contentious exposure for veteran groups, particularly the reseal/deseal exposed personnel.

Cohort Study

Nordling Nilson, Karlson, Nise, Malmberg and Orbæk (2010)[176] conducted a study to clarify the long-term effects of occupational exposure to organic solvents by means of a longitudinal follow-up of a group of previously toluene-exposed printers and their referents initially examined in the mid-1980s [Orbaek & Nise, 1989].[177] Specifically, the following questions were addressed: does long-term occupational exposure to toluene lead to aggravated cognitive impairment later in life? More specifically, will printers with long-term exposure to toluene before 1980 be found to have deteriorated more in their cognitive performance than their unexposed referents when re-examined 20 years later? An additional aim was to examine whether printers would report more complaints of cognitive dysfunction and mood disturbances, and poorer social adjustment compared with the referents.

The initial study in 1983/1984 included 30 male rotogravure printers and a reference group of 50 sugar refinery workers and 22 railway carriage repair shop workers, employed and active at work when examined.178 All subjects still alive in 2003 were approached with a letter of invitation, followed by a personal telephone call to each printer and to referents of similar age. Exclusion criteria were (a) present or past exposure to organic solvents in referents (to a greater extent than is usually seen among these workers); and (b) diagnosed disease that markedly affects CNS functions, e.g. cerebrovascular disorders, brain tumour, multiple sclerosis, Parkinson's disease, Alzheimer's disease, long-term severe epileptic disease, sleep apnoea and high alcohol intake.

Seven printers and 14 referents had died; one printer and two referents could not be located; eight printers and 20 referents declined participation because of poor somatic health (six printers and four referents) or for unspecified reasons; two printers and seven referents were excluded because of CNS disease (stroke, Alzheimer's disease, Parkinson's disease and sleep apnoea). Of the available referents only individuals at an equivalent age range were included in the examinations. This was motivated by the wish to avoid statistical adjustment for the cofactor age on the presumed not linear detrimental effects of the previous exposure. Altogether 12 rotogravure printers and 19 referents participated in the follow-up study; response rates were 55% of the available printers and 41% of the available referents of similar age.

Working conditions for the printers had been thoroughly investigated in the mid-1980s, including assessment of present and past solvent exposure for printers, mainly to toluene, and for the referents in the early 1980s. The exposure situation since then was followed up. Semi-structured interviews by a senior occupational hygienist on telephone or during personal meetings with all subjects focused on work tasks, chemical handling and the general working

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[176] Nilson LN, Karlson B, Nise G, et al (2010). Delayed manifestations of CNS effects in formerly exposed printers - a 20-year follow-up. Neurotoxicology and Teratology, 32(6): 620-26. 074424

[177] Orbaek P, Nise G. Neurasthenic complaints and psychometric function of toluene-exposed rotogravure printers. Am J Ind Med. 1989-16(1)-67-77 032171

[178] Orbaek P, Nise G. Neurasthenic complaints and psychometric function of toluene-exposed rotogravure printers. Am J Ind Med. 1989-16(1)-67-77 032171

environment during the person's whole working life. Possible exposure during leisure time was explored as well. The information collected at the present interviews and the data from the 1980s were used to calculate each individual's cumulative exposure to solvents and other potentially neurotoxic exposure. The time-weighted average (TWA) exposure was estimated from measurement reports and information on preventive measures at the different workplaces. The hygienic effect (HE)—the quota of the estimated TWA solvent exposure and the occupational exposure limit of the given solvent — was used when calculating total solvent exposure (Swedish OELs 2000 were used). The cumulative solvent exposure was calculated as the sum of the estimated HE from solvent exposure during each year, multiplied by the time actually having worked in contact with the solvent. The cumulative exposure of lead, the only other chemical with a neurotoxic effect present, was assessed in the same way.

At the site visit all participants were examined by a specialist in occupational and environmental medicine. The medical interview and clinical examination concerned general health status and focused specifically on signs of somatic disease with known negative CNS effect, psychiatric disorder and alcohol or drug overuse. Where needed, and with the subject's written consent, additional information on a subject's diagnosis was obtained from hospital records. The interview assessed various areas of health including, cardiovascular, dyspnoea and respiratory questions; cerebrovascular symptoms; and alcohol intake, smoking habits and drug use.

Two main dimensions, symptoms and social interaction, were assessed as self-reports by various questionnaires:

The Symptom Checklist (SCL-35); an abridged version of the SCL-90 for assessment of psychosomatic and emotional distress comprising the 35 items which form the three subscales of somatization, depression and anxiety. Respondents are asked to indicate to what extent they have been distressed by each symptom during the last week on a 5-point Likert scale. Scale scores are computed as the average of the item scores. A suite of neuropsychiatric tests were also conducted.

The printers were found to have deteriorated more than their referents in cognitive functioning affecting reasoning and associative learning. No relevant additional exposure during the lengthy time period between assessments could explain this discrepancy. In addition, printers performed significantly worse than the referents in verbal memory and sustained attention at follow-up, where also a dose-effect relationship was noted for reasoning. While the printers did not report more subjective cognitive complaints than the referents, a slightly higher depression score was noted for the printers. Anxiety symptoms were not noted to be significantly different in the two groups.

TABLE 56 Self-rated symptoms and social network [a] (Nordling Nilson et al, 2010).

	Printers (n — 12)		Referents (n — 19)		M-W
	Md	Q1-Q3[b]	Md	Q1-Q3	p
Euroquest-9	1.78	1.44-2.22	1.67	1.44-1.89	0.29
SCL					
Somatization	0.29	0.02-0.65	0.17	0.00-0.42	0.37
Depression	0.42	0.19-0.88	0.23	0.00-0.33	0.05
Anxiety	0.20	0.10-0.53	0.10	0.10-0.40	0.39
ISSI[c] total score	0.79	0.76-0.83	0.85	0.75-0.92	0.27
AVAT[d]	1.00	0.67-1.00	1.00	0.83-1.00	0.64
ADAT[e]	1.00	0.93-1.00	1.00	0.80-1.00	0.31
AVSI[f]	0.33	0.33-0.63	0.50	0.33-0.83	0.08
ADSI[g]	1.00	1.00-1.00	1.00	0.88-1.00	0.54

[a] Groups were compared with Mann-Whitney *U* Test (M-W).
[b] Q1-Q3 — items 1-3 from the Euroquest-9.
[c] ISSI — Interview schedule of social integration.
[d] AVAT — Availability of attachment.
[e] ADAT — Adequacy of attachment.
[f] AVSI — Availability of social integration.
[g] ADSI — Adequacy of social integration.

On the SCL subscales assessing psychosomatic and emotional distress (table above) the printers did not report a higher anxiety score compared with the referents (p=0.39).

Long term occupational exposure to organic solvents may induce chronic solvent-induced encephalopathy (CSE), characterized by mild to severe cognitive impairment, generally seen as the key diagnostic feature. Psychiatric disorders are often diagnosed in subjects with CSE, but were never studied in more detail. **Visser, Wekking, de Boer, de Joode et al (2011)**[179] designed a study to establish the prevalence rates of DSM IV mood, anxiety, and alcohol and substance related disorders in patients with CSE. In CSE, n=203 (consecutively recruited between 2002 and 2005), defined according to the criteria of the World Health Organisation (WHO), one month prevalence rates of DSM IV mood, anxiety, and life time alcohol/substance related disorders were assessed using the Structured Clinical Interview for DSM IV disorders (SCID). These prevalences were compared with those from an age and gender matched community sample (n=3212) while controlling for insufficient neuropsychological test effort.

Solvent exposure data were calculated for current study in the CSE patients. An exposure-index was derived from the exposure duration in years, the supposed workplace concentrations, both based on the occupational history presented by the patient to an occupational hygienist, and from the Occupational Exposure Limits (OEL), resulting in a number of OEL-weighted exposure years ('OEL-years'). In estimating workplace concentration attention was given to the occurrence of concentration peaks and to the use of personal protective devices. If there were various jobs or specific job tasks in the patient's history, the total exposure index resulted from the summation of the job specific exposure indices. Finally, exposure was categorized as: <5, 5–9, 10–20, and >20 OEL-years.

[179] Visser I, Wekking EM, de Boer AG, de Joode EA, van Hout MS, van Dorsselaer S, Ruhé HG, Huijser J, van der Laan G, van Dijk FJ, Schene AH. (2011). Prevalence of psychiatric disorders in patients with chronic solvent induced encephalopathy (CSE). Neurotoxicology;32(6):916-22.

In CSE, prevalence rates for major depressive disorder (n=36, relative risk (RR)=7.4), dysthymia (n=15, RR=6.0), panic disorders (n=18, RR=7.1), agoraphobia (n=7, RR=5.5) and generalized anxiety disorder (n=19, RR=15.8) were increased. Reduced prevalence rates were found for alcohol related disorders (n=21, RR=0.3). Insufficient neuropsychological test effort was not associated with increased prevalence rates of DSM IV disorders in subjects suspected of CSE.

TABLE 57 MOOD, ANXIETY, AND ALCOHOL A SUBSTANCE RELATED DISORDERS (DSM IV) IN PATIENTS WITH CHRONIC SOLVENT INDUCED ENCEPHALOPATHY (CSE) AND IN THE MATCHED REFERENCE POPULATION. PREVALENCE RATES (%), RELATIVE RISKS (RR), AND 95% CONFIDENCE INTERVALS (CI). CSE TOTAL N = 203; MATCHED REFERENCE POPULATION TOTAL N = 3212 (VISSER ET AL, 2011).

Diagnosis	CSE patients n (%)	Reference population n (%)	RR	CI
A. Mood disorders				
Major depressive disorder	36 (18)	65 (2)	7.4	5.2–11.2
Dystymia	15 (7)	39 (1)	6.0	3.4–10.9
B. Anxiety disorders				
Panic disorder	18 (9)	27 (1)	7.1	3.9–12.7
Agoraphobia	7 (4)	20 (1)	5.5	2.3–12.9
Social phobia	5 (3)	93 (3)	0.9	0.4–2.1
Simple phobia	2 (1)	100 (3)	0.3	0.8–1.3
GAD	19 (10)	19 (1)	15.8	8.5–29.4
OCD	0	11	–	–
C. Alc-sub related disorders				
Alc abuse/dependence	21 (10)	939 (30)	0.3	0.2–0.5
Sub abuse/dependence	7 (3)	124 (4)	0.9	0.4–1.9

OCD = obsessive compulsive disorder.
GAD = generalized anxiety disorder.
Alc = Alcohol.
Sub = Substance.

In conclusion, in this first large scale study in patients with CSE, prevalence rates of DSM IV mood and anxiety disorders were elevated as compared with those in the general community, while the prevalence rates of alcohol related disorders were reduced. Further study must determine whether CSE, and mood and anxiety disorders, share a same, solvent induced, neurobiological pathway, supporting the use of a more inclusive diagnostic approach. Additionally, randomised controlled trials are needed for the urgent issue of how to treat mood and anxiety disorders in CSE patients effectively.

Attia, D'Este, Schofield et al (2006)[180] sought to contrast mood disorder symptoms in F-1 11 aircraft Deseal/Reseal maintenance personnel with appropriate comparisons in a retrospective cohort designed study. Participants completed a comprehensive health assessment, including measures of mood disorder, self-reported mood symptom questionnaire items, and review of anxiolytic and depression medication. Multiple logistic regression was conducted for each outcome using exposure group and potential confounders as explanatory variables. There was high agreement between self-reported mood disturbance and objective tests.

Information about expo-sure dose was gathered using the Exposure Questionnaire. Respondents nominated program and task types and duration of participation for each task, selecting from five expo-sure dose categories, where the minimum was less than 1 month and

[180] Attia JR, D'Este C, Schofield PW, Brown AM, Gibson R, et al (2006). Mental health in F-111 maintenance workers- the Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP) General Health and Medical Study. J Occup Environ Med; 48:682-691. 040848

the maximum was greater than 24 months. The midpoint of each expo-sure category was obtained for each participant, with 0.5 months selected for those reporting less than one month involvement and 30 months selected for those reporting more than 24 months involvement. The largest recorded value of all activities within a program was selected and summed across all programs for each individual providing a pseudo continuous measure where the minimum possible exposure was 0.5 month and the maximum possible was 120 months.

The exposed group was more likely to self-report previous diagnoses of depression/anxiety, had higher use of antidepressant medications, and had increased risk of diagnosis of depression/anxiety. Results were consistently strong against both comparison groups, with the exposed more likely to have mental distress and social dysfunction when compared with the Australian population.

TABLE 58 CRUDE AND ADJUSTED ODDS RATIOS FOR EACH MOOD AND MENTAL HEALTH OUTCOME (ATTIE ET AL, 2006).

Outcomes	Amberley Crude OR (95% CI)	Amberley Adjusted OR (95% CI)	Richmond Crude OR (95% CI)	Richmond Adjusted OR (95% CI)	*P* Value for the Adjusted Model
Kessler (K-10): Medium/high probability of having anxiety or depression	2.1 (1.6–2.8)	2.6 (1.9–3.6)	2.4 (1.9–3.1)	2.4 (1.9–3.2)	<0.0001
General Health Questionnaire (GHQ): High probability of mental illness	2.0 (1.5–2.6)	2.8 (2.0–3.8)	2.1 (1.7–2.7)	2.1 (1.6–2.7)	<0.0001
Self-Reported Depression: Reported previous physician diagnosis	1.8 (1.3–2.3)	2.0 (1.4–2.7)	2.2 (1.6–2.9)	2.2 (1.6–3.0)	<0.0001
Self-Reported Anxiety: Reported previous physician diagnosis	1.8 (1.3–2.45)	2.0 (1.4–2.8)	2.0 (1.5–2.8)	2.1 (1.5–2.9)	<0.0001
CIDI Depression: Diagnosed as having been or being depressed	1.5 (1.1–2.1)	1.8 (1.2–2.6)	2.1 (1.6–2.8)	2.0 (1.4–2.7)	<0.0001
CIDI Anxiety: Diagnosed as having had or having anxiety	1.7 (1.3–2.4)	1.8 (1.2–2.5)	2.7 (1.9–3.7)	2.4 (1.7–3.5)	<0.0001
Antidepressants: Self-reported taking medication	1.6 (1.0–2.4)	1.6 (1.0–2.6)	2.1 (1.3–3.2)	2.0 (1.3–3.2)	0.005
Neurasthenia diagnostic criteria met	1.4 (0.89–2.3)	1.2 (0.71–2.0)	2.7 (1.6–4.7)	2.5 (1.4–4.4)	0.004

There is robust evidence for an association between F-1 11 Deseal/Reseal exposure and impaired mental health, including anxiety symptomatology.

Case-control studies

Morrow, Gibson, Bagovich et al (2000)[181] conducted a study to determine whether the prevalence of current and past DSM-IV axis I psychiatric disorders is higher among persons with a history of exposure to organic solvents than among a demographically similar group of nonexposed control subjects. Thirty-eight solvent-exposed subjects and 39 nonexposed healthy control subjects were evaluated for axis I disorder with the Structured Clinical Interview for DSM-IV.

A significantly higher number of solvent-exposed subjects (71%) met criteria for current DSM-IV axis I disorder in comparison with control subjects (10%). The most prevalent diagnosis in exposed subjects was within the **anxiety and mood clusters**, with a high percentage (36%) of exposed subjects meeting criteria for a dual diagnosis of mood and anxiety disorder. There were no differences between the groups in past psychiatric disorders or current or past substance abuse or dependence.

[181] Morrow LA, Gibson C, Bagovich GR, Stein L, (et al). Increased incidence of anxiety and depressive disorders in persons with organic solvent exposure. Psychosomatic Medicine, 62 pp 746-750. 030334

The rates of past psychiatric disorders among solvent-exposed subjects are similar to those among normal control subjects, but the prevalence of current DSM-IV axis I psychiatric disorders is significantly higher among exposed subjects than among control subjects.

Indulski, Sinczuk-Walczak, Szymczak and Wesolowski (1996)[182] examined the nervous system of workers chronically exposed to mixtures of organic solvent at concentrations within or slightly exceeding the minimum alveolar concentration (MAC) values, used in the manufacture of paints and lacquers. The tests were performed on a group of 175 people, 107 men aged 22-59 (mean = 41.25), and 68 women aged 20-55 (mean = 38.62). The period of employment was mean = 17.34 years and cumulative dose index 16.97 for males; for females, the corresponding values were mean = 14.75 and mean = 11.42, respectively. The control group included 175 people (107 men and 68 women) not exposed to chemicals matched according to sex, age, and work shift distribution. The neurological examinations included subjective and objective examinations of the nervous system, electroencephalographic (EEG) and visual evoked potential (VEP) evaluations. The assessment of organic solvent exposure was performed according to the method described in PN89/Z-04008/07, and the solvent mixtures were shown to contain xylenes, ethyltoluenes, trimethylbenzenes, propylbenzene, ethylbenzene, toluene, aliphatic hydrocarbons and the components of painter's naphtha. **The most frequent complaints among the exposed males included headache, vertigo, concentration difficulties, sleep disorders, sleepiness during the day, increased emotional irritability, mood swings with a tendency to anxiety**. The objective neurological examinations did not reveal organic lesions in the central or peripheral nervous systems. Generalised and paroxysmal changes were most common recordings in the abnormal EEG. VEP examinations revealed abnormalities, primarily in the latency of the response evoked. The results of this study suggest that exposures to concentrations within MAC values, or below 1.5 of the MAC values of organic solvents mixtures used in the manufacture of paints and lacquers produce subclinical health effect in the nervous system.

Cross-sectional studies

LoSasso, Rapport, Axelrod and Whitman (2002)[183] evaluated neuropsychologic performance among women occupationally exposed to products commonly used in nail studios. Organic solvents and (meth)acrylates commonly used in nail studios have known neurotoxic properties. Few studies have examined the potential for cognitive and neurosensory effects of occupational exposure to these substances, and none has addressed exposure occurring in the cosmetics industry.

Participants in this study included nail-salon technicians (n = 33) and demographically similar controls who had no known history of exposure to toxic chemicals (n = 35). The groups were administered psychologic, neuropsychologic, and neurosensory tests. Aspects of the workplace environment (e.g., square footage of the salon, adequacy of ventilation, and hours worked) also were assessed.

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[182] Indulski JA , Sińczuk-Walczak H , Szymczak M , Wesołowski W. (1996). Neurological and neurophysiological examinations of workers occupationally exposed to organic solvent mixtures used in the paint and varnish production. International Journal of Occupational Medicine and Environmental Health; 9(3):235-244.

[183] LoSasso GL, Rapport LJ, Axelrod BN, Whitman RD (2002). Neurocognitive sequelae of exposure to organic solvents and (meth)acrylates among nail-studio technicians. Neuropsychiatry Neuropsychol Behav Neurol, 15(1) pp 44-55. 033558

Multivariate analysis of variance revealed that the nail technicians performed more poorly than did controls on tests of attention and processing speed (p = 0.015; eta(2) = 0.20). Olfaction among the nail technicians was below expected performance based on normative data (p < 0.001). A trend toward poorer performance by the nail technicians was observed on the MANOVA investigating executive functioning; individual tests within that domain may be worthy of future investigation (ps = 0.03-0.10). **No significant group differences were observed in the domains of learning and memory, visuospatial ability, or fine motor coordination, or on measures of depression and anxiety.** Multiple regression indicated that level of occupational exposure as measured by time worked in the industry, adequacy of ventilation, and workplace size predicted 29% of the variance of performance on attentional tasks (p = 0.04).

Exposure to low-level neurotoxicants common to nail studios may result in mild cognitive and neurosensory changes similar to those observed among solvent-exposed workers in other settings, but anxiety does not appear to be elevated in this group compared to controls.

Sassine, Mergler, Larribe and Belanger (1996)[184]

[Article in French]

Abstract

Emotional instability which might be an early symptom of more severe disorders, is one of the first manifestations of chronic exposure to organic solvents. The present study measures the association between exposure to styrene and mood states of active workers. A total of 128 workers (85% of the total population) from 3 factories where styrene is used, participated on a voluntary basis. They filled out the following self-administered questionnaires: Profile of Mood States (POMS), Psychiatric Symptom Index and Well-being Index. **The results indicate a significant relationship between post work-shift urinary mandelic acid (biological indicator of styrene exposure) and the scores obtained on the POMS scales of tension-anxiety (Spearman's rank correlation rho = 0.30; p < 0.01)**, anger-hostility (rho = 0.29; p < 0.01), fatigue-inertie (rho = 0.34; p < 0.01), and confusion-bewilderment (rho = 0.23; p = 0.04), as well as the Psychological Distress Index (rho = 0.30; p < 0.01). All scores were adjusted for the effects of 4 potentially confounding variables: age, schooling, alcohol and cigarette consumption. These indicators of mood states do not constitute a diagnosis of mental disease but reveal progressive deterioration of well being associated with neurotoxic exposure in the workplace.

Escalona, Yanes, Feo and Maizlish (1995)[185] conducted a study to assess the applicability of the World Health Organization (WHO) Neurobehavioral Core Test Battery (NCTB), they evaluated 53 male and 29 female Venezuelan workers exposed to mixtures of organic solvents in an adhesive factory, and 56 male and 11 female workers unexposed to any type of neurotoxic chemical. The average age of unexposed workers was 30 years and 33 years for those exposed, average schooling for both groups was 8 years, and the mean duration of exposure was 7 years. The NCTB, which assesses central nervous system functions, is

[184] Sassine MP, Mergler D, Larribe F, Bélanger S. (1999). [Mental health deterioration in workers exposed to styrene]. [Article in French]. Rev Epidemiol Sante Publique;44(1):14-24. [ABSTRACT ONLY].

[185] Escalona E, Yanes L, Feo O, Maizlish N. (1995). Neurobehavioral evaluation of Venezuelan workers exposed to organic solvent mixtures. Am J Ind Med;27(1):15-27.

composed of seven tests that measure simple motor function, short-term memory, eye-hand coordination, affective behaviour, and psychomotor perception and speed. The battery includes: profile of mood states (POMS); Simple Reaction Time for attention and response speed; Digit Span for auditory memory; Santa Ana manual dexterity; Digit-Symbol for perceptual motor speed; the Benton visual retention for visual perception and memory; and Pursuit Aiming II for motor steadiness. In each of 13 subtests, the exposed group had a poorer performance than the nonexposed group. The range of differences in mean performance was between 5% and 89%, particularly in POMS (tension-anxiety, anger-hostility, depression-rejection, fatigue-inertia, confusion-bewilderment), Simple Reaction Time, Digit-Symbol, and Santa Ana Pegboard ($p < .05$). **In multivariate regression analyses, controlling for the effects of age, sex, and education, significantly poorer performance in the exposed was found for tension-anxiety, hostility, depression, and confusion moods in the POMS, and in digit-symbol and simple reaction time ($p < .05$). These alterations were also dose-related using years of exposure in analyses of covariance.**

TABLE 59 NEUROBEHAVIORAL FUNCTION IN WORKERS EXPOSED AND NONEXPOSED TO SOLVENT MIXTURES, VENEZUELA ESCALONA ET AL, 1995).

	Exposed		Nonexposed				Years of Exposure[c]	
Test	Mean[a]	(SD)	Mean	(SD)	p	Effect[b]	F(2,142)	p
Profile of mood states[d]								
tension-anxiety	10.4	(6)	8.1	(5)	.02	↓	3.7	.03
depression	8.9	(9)	4.7	(5)	.001	↓	6.4	.002
hostility	7.7	(8)	4.3	(4)	.004	↓	5.6	.005
vigor	19.0	(4)	18.8	(5)	.83	↓	0.5	.64
fatigue	5.5	(5)	4.1	(4)	.07	↓	6.2	.03
confusion	5.9	(4)	3.4	(3)	.001	↓	10.9	.001
Simple Reaction Time (msec)	303	(13)	265	(36)	.001	↓	13.5	.001
Digit Symbol (no. correct)	38.3	(13)	43.9	(12)	.002	↓	6.3	.002
Digit Span (forward + backward)	9.4	(2)	9.5	(2)	.84	↓	0.2	.79
Santa Ana (no. completed)[e]								
preferred	30.4	(6)	43.7	(12)	.01	↓	3.1	.05
nonpreferred	20.5	(6)	49.5	(7)	.001	↓	19.8	.001
Benton (no. correct)	5.8	(1)	6.2	(2)	.19	↓	1.3	.27
Pursuit Aiming (no. completed)	171	(74)	181	(62)	.36	↓	1.1	.33

[a]Analysis of covariance, means adjusted for age, sex, and education.
[b]↓ = poorer performance in the exposed group.
[c]Analysis of covariance (age, sex, education adjusted) with years of exposure categories: none; 1–9; 10 or more.
[d]Profile of Mood States scale: 1 = best to 20 = worst.
[e]Analysis of covariance, means adjusted for age, sex, education, and plant variables.

TABLE 60 PREVALENCE (IN LAST YEAR) OF SUBJECTIVE SYMPTOMS AMONG WORKERS EXPOSED AND NONEXPOSED TO SOLVENT MIXTURES, VENEZUELA (ESCALONA ET AL, 1995).

	Exposed		Nonexposed		Relative	
Item	N	%	N	%	Risk	95% CI
Tired after work	34	51	28	34	1.5[a]	1.0, 2.2
Tired after waking up	13	19	8	10	2.0	.9, 4.5
Day dreaming	24	36	27	33	1.1	.7, 1.7
Falling asleep at TV	25	37	14	17	2.2[b]	1.2, 3.9
Insomnia	10	15	11	13	1.1	.9, 4.5
Wakeful sleep	29	43	32	39	1.1	.9, 4.5
Forgetful of routine items	20	30	11	13	2.2[a]	1.2, 4.3
Confused thinking	10	15	4	5	3.1[a]	1.0, 9.3
Forget what you were thinking	15	22	11	13	1.7	.8, 3.7
Difficulty concentrating	12	18	12	15	1.2	.6, 2.6
Depressed	13	19	12	15	1.3	.7, 2.7
Indifference	15	22	20	24	.9	.5, 1.7
Paranoid thoughts	10	15	9	11	1.4	.6, 3.2
Feeling isolated	12	18	9	11	1.6	.7, 3.6
Irritable	16	24	11	13	1.8	.9, 3.6
Anxious	19	28	13	16	1.8	.9, 3.4
Headache	16	24	13	16	1.5	.8, 2.9
Vertigo	10	15	7	9	1.8	.7, 4.4
Palpitations	21	31	8	10	3.2[b]	1.5, 6.8
Excessive sweating	24	36	15	18	1.9[a]	1.1, 3.4
Loss of appetite	7	10	8	10	1.1	.4, 2.8
Diarrhea	4	6	3	4	1.6	.4, 7.0
Constipation	8	12	14	17	.7	.3, 1.6
Stomach ache	11	19	14	17	1.0	.5, 2.0
Paresthesia in fingers	8	12	6	7	1.6	.6, 4.5
Paresthesia in legs/feet	10	15	6	7	2.1	.8, 5.3
Paresthesia in hands/arms	12	18	5	6	2.9[a]	1.1, 7.9
Weakness in hands/arms	9	13	5	6	2.2	.8, 6.3
Weakness in legs/feet	9	13	5	6	2.2	.8, 6.3
Dropping objects from hands	5	7	1	1	6.1	.7, 51
Hand tremors	10	15	8	10	1.5	.6, 3.7
Difficulty walking in the dark	15	22	11	13	1.7	.8, 3.4
Changes in the sense of smell	7	10	8	10	1.1	.4, 2.8
Changes in the sense of taste	12	18	12	15	1.2	.6, 2.6
Paresthesia in the face	4	6	1	1	4.9	.6, 43
Facial tic	9	13	3	4	3.7[a]	1.1, 13
Nightmares	34	51	26	32	1.6[b]	1.1, 2.4

[a] $p < .05$.
[b] $p < .01$ (2-tailed test).

Compared to the nonexposed, the exposed subjects demonstrated an increased frequency of subjective symptoms of fatigue, difficulties with memory, confusion, paraesthesias in upper and lower extremities, and sleep disturbances. They concluded that the methodology was applicable to the population studied. The tests of the NCTB were accepted by the subjects and were administered satisfactorily, except for occasional difficulties in verbal comprehension in subtests of POMS, which is the only test that requires more demanding verbal skills. The magnitude of the behavioural deficits is consistent with the probable high level of exposure and with the range of deficits previously reported in workers with long-term solvent exposures.

Morrow, Kamis and Hodgson (1993)[186] investigated psychiatric symptomatology, self-concept, locus of control, and daily events in persons with a history of exposure to mixtures of organic solvents. Exposed subjects were more likely than controls to report depression, anxiety, fatigue, confusion, and somatic concerns, which in turn were associated with certain exposure-related variables (e.g., cacosmia). The exact range of exposure was not detailed. However, the level discussed met a diagnosis of solvent neurotoxicity. There were no differences between the groups in self-concept, locus of control, or ratings of daily hassles and uplifts. Exposed persons may be able to accurately identify what they perceive as changes that are due to the exposure (e.g., anxiety) without attributing these specific adverse outcomes to dispositional variables.

Bowler, Mergler, Rauch et al (1991)[187] reported on a group of workers from the production and manufacture of microelectronic components industry. The work which is carried out primarily by women workers, require extensive use of organic solvents. Affective and personality disturbances frequently have been associated with organic solvent toxicity. A group of women, former microelectronics workers (N = 70), primarily of Hispanic origin (77.1%) but raised in the United States, were evaluated for affective and personality disturbance with the MMPI. Profiles were analysed, and diagnostic classification was performed blind. Results showed that (1) 85.7% of the profiles indicated abnormally high clinical elevations; and (2) MMPI profile classification revealed four clinical diagnostic groups: somatoform (24.3%), depression (15.7%), anxiety (28.6%), and psychotic (14.3%). These findings indicate significant psychopathology among these women, who formerly had worked in a microelectronics plant. The patterns of impairment present similarities to previous reports of organic solvent toxicity.

Case reports

Dager, Holland, Cowley and Dunner (1987)[188] describe three cases of idiosyncratic response to occupational solvent exposure, with symptoms characteristic of panic disorder (DSM-III). The specific treatment and prognostic implications of this panic-like reaction to solvents are discussed. Sodium lactate infusion is proposed as an objective test to aid in the diagnosis. The cases related to reasonably acute exposure, as detailed below.

Case 1 . Mr. A, a 28-year-old married man, was self referred for treatment of panic attacks. Seven years earlier, 1 month after starting a job as an aircraft mechanic, he had experienced the acute onset of confusion, disorientation, lightheadedness, tunnel vision, depersonalization, derealization, cold sweats, tachycardia, palpitations, dyspnoea, tremor, and fear of dying, which lasted approximately one-half hour.

At that time the patient was working with methyl ethyl ketone and toluene. He continued to experience similar reactions when in close proximity to these solvents. He also began to experience attacks outside the work place; they were most commonly associated with driving but also occurred without apparent precipitant. Extensive medical evaluation uncovered no objective pathological finding except CAT scan evidence of mild ventriculomegaly. Because of

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[186] Morrow LA, Kamis H, Hodgson MJ. (1993). Psychiatric symptomatology in persons with organic solvent exposure. J Consult Clin Psychol;61(1):171-4.
[187] Bowler RM, Mergler D, Rauch SS, Harrison R, Cone J. (1991). Affective and personality disturbances among female former microelectronics workers. J Clin Psychol;47(1):41-52.
[188] 076196 - Dager SR, Holland JP, Cowley DS, et al (1987). Panic disorder precipitated by exposure to organic solvents in the work place. Am J Psychiatry, 144(8): 1056-8.

this finding, which was not corroborated by clinical evidence of dementia or gait or urinary disturbance, the patient had been given a diagnosis of presumed normal pressure hydrocephalus, and 4 years earlier a shunt procedure had been performed. After surgery the attacks continued unabated with increasing frequency, up to a maximum of 20 attacks per day that usually lasted 1 to 10 minutes. Progressive phobic avoidance also occurred, presumably due to the panic attacks.

As part of his evaluation for panic disorder, Mr. A had a lactate infusion (6). Normal saline was infused for 15 minutes as a control and then was changed under single blind conditions to 0.5 M sodium lactate, 10 cc/kg over 20 minutes. Five minutes after the switch to lactate, the patient became acutely symptomatic, with symptoms indistinguishable from a typical attack. He was stabilized on nortriptyline, 150 mg/day, and alprazolam, 6 mg/day, and the attacks ceased. He continued to work in the same setting for 1 year and remained panic free.

Case 2. Ms. B, a 36-year-old married woman who had worked the past 7 years in an electronics assembly plant, was referred from the occupational medicine clinic for further evaluation. The plant had recently introduced a new process for cleaning soldered parts that used a solution containing alkylaryl polyether alcohol, organic phosphate ester, and iso-octyl phosphate acid. While standing over a container of this solution, Ms. B had experienced the acute onset of nausea, diarrhoea, disorientation, visual disturbances, leg cramps, tremor, dyspnoea, a lump in the throat, choking, chest tightness, weakness, disorientation, and fear of dying. The initial reaction lasted for approximately a week, with fluctuating recurrence of symptoms. For the next year she continued to experience two or three attacks per day that lasted approximately 5 minutes. The attacks were usually related to olfactory stimulation associated with supermarkets, traffic, and beauty salons but also occurred spontaneously. Ms. B experienced progressive phobic avoidance and was unable to work. She had no prior psychiatric problems or family history of psychiatric illness. Extensive medical evaluation revealed no pathological findings.

A lactate infusion was performed as previously described. After 5 to 10 minutes of receiving lactate, Ms. B experienced the onset of chest pain, coldness, difficulty in breathing, palpitations, twitching, depersonalization, difficulty speaking, and confusion. The symptoms were similar to but milder than a typical attack. The patient began a regimen of desipramine, 250 mg/day, and the attacks ceased within 2 months. Further follow-up data were not available.

Case 3. Ms. C, a 34-year-old married woman who had previously worked as a licensed practical nurse, was referred from the occupational medicine clinic for further evaluation. Five months earlier, she had experienced the acute onset of disorientation, muscle tension, dry mouth, sweating, lightheadedness, palpitations, lethargy, fatigue, and panic while working in a poorly ventilated room around paint fumes and paint thinner that contained toluene. At that time she was hospitalized overnight and given oxygen. There were at least 15 subsequent attacks that were temporally related to olfactory stimulation associated with gasoline, paint, and cleaning solutions. Ms. C also began to experience attacks that were not related to solvent exposure, including one during a bowling tournament. The frequency of attacks had increased to more than one per week, and there were progressive symptoms of generalized anxiety and phobic avoidance. The patient quit work after maintaining steady employment for the preceding 14 years. There was no prior history of psychiatric illness or significant medical

illness. The patient denied a family history of psychiatric illness. Extensive medical workup revealed no objective pathological findings.

A lactate infusion was performed as previously described. Ms. C remained asymptomatic throughout the infusion. Treatment with imipramine, 250 mg/day, resulted in complete resolution of attacks. Because of the subsequent onset of a bigeminal arrhythmia, which was thought to be secondary to the anticholinergic effects of imipramine, the patient was switched to trazodone, with continued resolution of attacks. The patient has since resumed work and has not experienced further attacks for 2 years while continuing trazodone treatment.

Summary and conclusion

The evidence concerning organic solvent exposure and the development and/or exacerbation of anxiety and/or panic attack symptomatology is generally supportive of an association.

The very small prospective study by Nording Nilson et al (2010) did not support an association between long term solvent exposure and anxiety symptoms. The cohort study of Visser and colleagues (2011) found that participants with chronic solvent-induced encephalopathy were more likely to report a number of anxiety diagnoses then matched referents. This is suggestive that chronic exposure which does not meet the diagnosis of chronic solvent encephalopathy may present with anxiety symptoms. The Attia et al (2006) Australian retrospective cohort study of the air craft maintenance workers (re-seal/de-seal exposure) found that the solvent exposed group were significantly more likely to self-report previous diagnoses of depression/anxiety and had an increased risk of depression and anxiety when compared to the control groups. However, this study relied on self-reported exposure with doses ranging from the minimum possible exposure was 0.5 month and the maximum possible was 120 months.

Morrow et al (2000) in a small case-control study found that solvent exposed participants were significantly more likely to meet criteria for DSM-IV disorders that the control group. The most prevalent diagnoses were in the anxiety and mood clusters. The rates of previous psychiatric diagnoses were similar in both groups. Indulski et al (1996) compared workers chronically exposed to organic solvents to age-, sex- and work shift-matched to an unexposed referent group. Mood swings with a tendency for anxiety were one of the most frequently reported complaints. No valid measure of psychiatric symptom assessment was used. The reported symptoms may have been part of an over-arching diagnosis of chronic solvent encephalopathy.

The cross-sectional study of nail salon workers and demographically similar controls found that no significant difference between measures of depression and anxiety were observed between the groups. The French study by Sassine et al (1996) measured the effects of chronic exposure to styrene and mood states of active workers. A significant relationship between post work-shift urinary mandelic acid (biological indicator of styrene exposure) and the scores obtained on the POMS scales of tension-anxiety were reported. Escalano et al (1995) compared solvent exposed workers in an adhesive factory to an unexposed group of workers. They found in multivariate regression analyses, controlling for known confounders, a significantly poorer performance for tension-anxiety in the POMS in the exposed group. These alterations were also dose-related using years of exposure in analyses of covariance. Morrow et al (1993) found that subjects exposed to organic solvents were more likely to report anxiety than controls. Bowler et al (1991) also reported anxiety in 28.6% of women occupationally

exposed to organic solvents. Three cases described by Dager et al (1987) report panic attacks in close temporal relation to occupational solvent exposure which persisted to a diagnosis of panic disorder.

In general the studies are small and not of high methodological quality (relying on self-report of symptoms and not controlling for known confounders), but report an association between chronic organic solvent exposure and anxiety outcomes. Most of the studies related to occupational exposure of some years. The syndrome of chronic solvent encephalopathy is commonly reported to include comorbid depression and anxiety symptoms and diagnoses which add support to the association. The studies described all focus on chronic organic solvent exposure, apart from the reseal-deseal study which reports varying levels of exposure and the case reports above which report acute occupational exposure.

Grade 3 level evidence

Dioxin/phenoxyherbicides (Agent orange)/Pesticides

Summary of important issues

Reviews

Blanc-Lapierre, Bouvier, Garrigou, Canal-Raffin, Raherison, Brochard and Baldi (2012)[189] [Article in French]

Abstract

BACKGROUND:

Given the neurotoxic properties of pesticides, suggested by experimental results and clinical observations, many epidemiological studies have investigated neurological effects following acute or chronic exposure to pesticides. This review provides an overview of current knowledge about pesticide effects on the central nervous system: neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis), cognitive disorders, and psychiatric disorders (mood disorders, anxiety, depression and suicide).

RESULTS:

Parkinson's disease, the most widely studied in relation with pesticide exposure, particularly with insecticides and herbicides, was observed to be a risk factor of the disease. Evidence is scarce for Alzheimer's disease and amyotrophic lateral sclerosis, but quite consistent. Cognitive and psychiatric disorders were often observed in relation with organophosphate insecticide exposure. Cognitive disorders were found associated with acute and chronic exposures, and psychiatric disorders mostly with poisonings. These epidemiologic studies were limited by a lack of detailed and reliable exposure assessment. The role of genetic susceptibilities has been recently observed, but must be further investigated.

Lessenger and Reese (1999)[190] conducted a review of the literature and considered three illustrative cases which showed misunderstandings in the pathophysiology of the enzyme and procedures for effective testing and monitoring of acetylcholinesterase (AChE) levels.

According to Lessenger and Reese (1999), the effects on the central nervous system of prolonged acetylcholine action by organophosphates and carbamates include restlessness, tremors, staggering gait, mental confusion, seizures, cardiovascular failure, and respiratory depression (Table below; Feldman et al, 1997; cited in Lessinger & Reese, 1999). Among long-term pesticide applicators, there is evidence of reduced cognitive function even when clinical symptoms of excessive cholinergic activity are not present.

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[189] Blanc-Lapierre A, Bouvier G, Garrigou A, et al (2012). Chronic central nervous system effects of pesticides: state-of-the-art. Revue d Epidemiologic et de Sante Publique, 60(5): 389-400. [Abstract] 078156

[190] Lessenger JE, Reese BE (1999). Rational use of cholinesterase activity testing in pesticide poisoning. J Am Board Fam Med, 12: 307-14. 078147

TABLE 61 SIGNS AND SYMPTOMS OF ACETYLCHOLINESTERASE INHIBITING AGENT POISONING (LESSENGER & REESE, 1999).

System	Sign or Symptom
Autonomic nervous system	
Muscarinic	Respiratory tract secretions
	Sweating
	Salivation
	Lacrimation
	Miosis
	Bradycardia
	Hypotension
	Urinary incontinence
	Gastrointestinal spasms
Nicotinic	Muscular fasciculation followed by respiratory muscle weakness
Central nervous system	
Mild	Mental confusion
	Staggering gait
	Restlessness
	Anxiety
	Insomnia
	Tremors
Moderate	Convulsions
Severe	Respiratory depression
	Circulatory collapse

Systematic Reviews

Takahashi and Hashizume (2014)[191] conducted a study to conduct a systematic review of the published literature and to estimate whether or not there is a causal relationship between occupational exposure to organophosphate pesticides (OPs) and either neurological impairment or depressive symptoms. Various databases [EMBASE, MEDLINE, Global Health and PsycINFO (1980 to April 2014)], were sourced to obtain relevant studies i.e., observational studies (cross-sectional, cohort and case–control studies) with exposed and unexposed groups. Participants were people who occupationally use OPs for more than 1 month and their family. Results of neurological core test batteries or depressive symptoms such as headaches, anxiety and dizziness were assessed.

[191] Takahashi N & Hashizume M. (2014).A systematic review of the influence of occupational organophosphate pesticides exposure on neurological impairment. BMJ Open 2014;4:e004798. doi:10.1136/bmjopen-2014-004798

After an extensive search of various literature databases, one author screened titles and abstracts, searched the relevant publications manually and conducted data extraction. All extracted data from the selected articles were synthesised for analysis. Quality appraisal was conducted using the Newcastle Ottawa Scale.

Of the 1024 articles retrieved by database search, 24 studies that met the inclusion and exclusion criteria were selected for analysis. Of the selected studies, 17 were cross-sectional and the remaining 7 were cohort and nested case–control studies. The geographical areas included in the studies were the USA (10 studies), the UK (4 studies), Africa (4 studies), Asia (3 studies), Europe (2 studies) and South America (1 study). Each of the included studies used different exposure and outcome assessments such as neurological scores and depressive symptoms, making it difficult to compare the results exactly. Most studies showed that exposed groups had poorer results than unexposed groups; however, owing to the inconsistent neurological test batteries, there was not enough pooling evidence to conduct a meta-analysis. Only one study included in the review (Levin et al, 1976) reported on anxiety. This study found that anxiety scores of the pesticide applicators were significantly higher ($p<.05$) that that of the farmers. However, there was no significant difference in measures of depression.

Case-control studies

Pesticides remain an integral part of agricultural activities worldwide. Although there have been a number of studies over the last two decades concerning the adverse effects of pesticide poisoning and chronic long term exposures on neurobehavioral function, the impact of recent pesticide poisoning and long term pesticide exposure on neurobehavioral function in Chinese farm workers has not been reported. China is the largest user of pesticides worldwide and figures suggest 53,300-123,000 Chinese people are poisoned every year.

Zhang, Wu, Yao et al (2016)[192] conducted a case-control study to examine the impact of recent pesticide poisoning on neurobehavioral function and the relationship between years worked in agriculture and lower performance on neurobehavioral tests. Pesticides were identified according to trade name and active ingredients, focusing on insecticides, herbicides, and fungicides. Insecticide sprayers in the study group applied mixed preparations containing organophosphates, pyrethroids, and carbamates.

A total of 121 farm workers who self-reported recent pesticide poisonings within the previous 12 months (case group) and 80 farm workers who reported no pesticide poisoning in the previous 12 months (control group) were recruited from three areas of Jiangsu Province, China. Cases and controls were matched by area, gender, age, education, working years, tobacco use, alcohol use, and general physical condition. Participants were excluded if they had reported amyotrophic lateral sclerosis, Parkinson's disease, retinopathy or macular degeneration, or were taking medicines which could affect nervous system functioning, as these conditions may influence the results of neurobehavioral testing.

The World Health Organisation (WHO) recommended neurobehavioural core test battery (NCTB) was used to assess neurobehavioral functioning among cases and controls. Student's t tests and two-way covariance analysis (ANCOVA) were used to test for significant differences in the neurobehavioral test results between the groups. **Scores on the Profile of**

[192] 078154 - Zhang X, Wu M, Yao H, et al (2016). Pesticide poisoning and neurobehavioral function among farm workers in Jiangsu, people's republic of China. Cortex, 74: 396-404.

Mood States (POMS) in the recently poisoned group were significantly higher for anger-hostility, depression-dejection, tension-anxiety and lower for vigor-activity compared to controls (p < .05). Digit span, digit symbol, Benton visual retention and pursuit aiming scores were all significantly lower among the recently poisoned group compared to the controls (p < .05). Two-way ANCOVA indicated significantly lower performance in correct pursuit aiming and higher error pursuit aiming amongst the recently poisoned group and those who had worked for more than 30 years in agriculture (p < .05). These findings provide important preliminary epidemiological evidence regarding the association between occupational pesticide exposure and neurobehavioral functioning in Chinese farm workers.

"There are several limitations to be considered when interpreting the results of this study. First, the information on occupational pesticide poisoning in the past 12 months was collected through a cross-sectional survey. Recall bias might lead to an inaccurate estimation of recent pesticide poisoning. In addition, the effect of recent pesticide poisoning on neurobehavioral function might be underestimated because individuals in the control group could have experienced pesticide poisoning in the past. It may be difficult for them to remember and self-report all pesticide poisoning incidents over a 30-40 year period. However, if we assume that some of the control group workers also experienced pesticide poisoning but did not report it in our study, this recall bias would be more likely to obscure any association between recent pesticide poisoning and neurobehavioral function. Another limitation of this study is the fact that our sample of participants came from only one province in China and so the sample size was small and it is unclear how representative they were of all farm workers in China. Finally, it was not possible to determine which types of pesticides caused the neurobehavioral deficits described herein. Further investigation is necessary to differentiate the neurobehavioral effects of specific classes of pesticide" (p. 402).

van Wijngaarden (2003)[193]

Abstract

Some studies have suggested a role of pesticide exposure in the development of neurobehavioral disorders. This case-control study examined the association between mortality from mental disorders and occupational exposure to pesticides. The study population consisted of 7756 deaths and 330,452 eligible controls identified from US death certificate files for the years 1988 through 1992. Exposure assignment was based on job title reported on the death certificates. Employment in jobs potentially involving pesticide exposure was weakly associated with the risk of death from mental disorders (OR = 1.46; 95% CI = 1.33–1.60). This association was stronger among women (OR = 2.65; 95% CI = 1.89–3.71), in particular for deaths from **neurotic disorders** (OR = 4.32; 95% CI = 2.44–7.64). These results must be interpreted with caution, however, because the impact of social and work-related factors other than pesticide exposure is not known.

Beshwari, Bener, Ameen et al (1999)[194] conducted a study to determine the effect of pesticides on farm workers and to identify some risk factors associated with pesticide

[193] van Wijngaarden E. (2003). Mortality of Mental Disorders in Relation to Potential Pesticide Exposure. Journal of Occupational & Environmental Medicine; 45:564-568.
[194] Beshwari MMM, Bener A, Ameen A, Al-Mehdi AM et al (1999). Pesticide related health problems and disease among farmers in the United Arab Emirates. International Journal of Environmental Health Research; 9:213-221.

conditions may cause adverse health effects in farm workers in the United Arab Emirates. This case-control study consisted of 103 farm workers (case) and 105 non-farm workers (control), matched for age, sex and nationality selected from A1-Ain city, Dubai, Sharjah and Fujairah Emirates. Indian-subcontinent workers represented the majority among farmers (90.3%) and non-farmers (82.9%). While the majority of farmers were illiterate and had low level of education, the non-farmers slightly shifted towards a higher level of education ($p < 0.0001$). Most of the farmers were living in prefabricated houses (50.5%) and were washing the harvested product (72.8%) before eating. Farmers had higher prevalence of symptoms than non-farmers, being significantly greater for diarrhoea ($p < 0.016$), nausea/vomiting ($p < 0.003$), rash ($p < 0.002$), red/irritated eye/blurred vision ($p < 0.024$), increased anxiety ($p < 0.003$), dizziness ($p < 0.0001$), headache ($p < 0.024$), muscular symptoms ($p < 0.015$), memory loss ($p < 0.0001$), drowsiness ($p < 0.003$), fatigue ($p < 0.001$), dyspnoea ($p < 0.005$), and insomnia ($p < 0.001$). Also, farm workers had higher prevalence respiratory symptoms than non-farm workers being significantly greater for cough, phlegm, breathlessness, sinusitis, throat discomfort, chronic bronchitis, asthma diagnosis by doctor, allergic rhinitis, skin pruritus (tinea, contact dermatitis) and eczema. In conclusion, this study determined possible exposure and associated risk factors with pesticides among farmers and there is evidence that some of the illnesses obtained in this study could be related to excessive exposure to pesticides.

TABLE 62 REPORTED SYMPTOMS AMONG FARMERS AND NON-FARMERS (BESHWARI ET AL, 1999).

Symptoms	*Farmer* n = *103* *Yes (%)*	*Non-farmer* n = *105* *Yes (%)*	*Odds Ratio*	*95% Confidence interval*	p-*value significance*
Diarrhoea	21 (20.4)	9 (8.6)	2.73	1.18–6.29	0.016
Nausea/vomiting	17 (16.5)	4 (3.8)	4.99	1.61–15.39	0.003
Rash	25 (24.3)	8 (7.6)	3.88	1.66–9.09	0.002
Red eye/irritated eye/blurred vision	27 (26.2)	14 (13.3)	2.30	1.13–4.71	0.02
Increased sweating	21 (20.4)	12 (11.4)	1.98	0.91–4.28	NS
Increased anxiety	23 (22.3)	8 (7.6)	3.48	1.47–8.21	0.003
Dizziness	29 (28.2)	7 (6.7)	5.48	2.27–13.21	0.0001
Headache	46 (44.7)	31 (29.5)	1.92	1.08–3.41	0.03
Muscular symptoms	44 (42.7)	28 (26.7)	2.05	1.14–3.67	0.02
Chest pain	19 (18.4)	11 (10.5)	1.93	0.86–4.29	NS
Excessive salivation	14 (13.6)	12 (11.4)	1.21	0.53–2.77	NS
Difficulty breathing	13 (12.6)	12 (11.4)	1.11	0.48–2.58	NS
Ataxia	4 (3.9)	2 (1.9)	2.08	0.37–11.61	NS
Memory loss	16 (15.5)	0	2.20	1.88–2.57	0.0001
Drowsiness	15 (14.6)	3 (2.9)	5.79	1.62–20.67	0.003
Fatigue	31 (30.1)	12 (11.4)	3.33	1.60–6.95	0.001
Dyspnoea	14 (13.6)	3 (2.9)	5.34	1.48–19.21	0.005
Insomnia	27 (26.2)	9 (8.6)	3.78	1.68–8.53	0.001
Skin disorders	12 (11.7)	8 (7.6)	1.60	0.58–4.52	NS
Variables to assess recall bias					
Taste change	7 (6.8)	1 (1.0)	7.58	0.91–62.77	0.03
Friable nails	11 (10.7)	6 (5.7)	1.97	0.70–5.55	NS

Amr, Halim and Moussa (1997)[195] conducted a study to assess the prevalence of psychiatric disorders and symptoms in Egyptian pesticide applicators and formulators in comparison to a control group.

The participants were a group of 208 pesticide formulators working in 2 different plants, 172 pesticide applicators, and 223 control subjects (72 from an urban textile factory who were matched with the pesticide formulators and 151 from a rural area who were matched with the pesticide applicators). The control subjects were chosen from the same communities as the exposed population and were matched for age and socioeconomic and educational levels. None of the control subjects had a prior history of direct exposure to pesticides, either at work or in the community. All subjects were assessed in the field by two psychiatrists. One administered the GHQ and the other assigned the DSM-III-R diagnosis (if one was assigned).

The pesticide plants were formulating organochlorine, organophosphate, carbamate, synthetic pyrethroid, and other multipurpose chemical compounds. The randomly selected formulators were directly exposed to these chemicals for at least 40 hr per week for at least 9 months of the year for at least 2 consecutive years.

Pesticide applicators were randomly selected from workers involved in the annual application of pesticides (carbamates, pyrethroids, organophosphates, and organochlorines, singly or in combination) for at least 2 consecutive years at two large-scale ‘‘model farms’’ belonging to the Ministry of Agriculture.

The study aimed to screen for psychiatric morbidity using a standardized screening tool, the General Health Questionnaire, and a widely recognized system of diagnosis and classification, the revised third edition of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-III-R). Significantly higher frequencies of psychiatric disorders were found in the exposed groups. The predominant diagnosis was depressive neurosis; the most frequent symptoms were irritability and erectile dysfunction. Theoretical and practical implications of these findings are discussed.

TABLE 63 GHQ DIMENSIONS IN PESTICIDE APPLICATORS AND MATCHED CONTROL SUBJECTS (AMR ET AL, 1997).

GHQ dimension	Pesticide applicators (n = 172), mean ± SD	Control subjects (n = 151), mean ± SD	Statistical significance	
			t	P
Somatic symptoms	2.54 ± 1.72	2.29 ± 1.98	3.47	<0.001
Anxiety and insomnia	2.24 ± 1.47	1.47 ± 2.0	3.11	<0.01
Social dysfunction	1.19 ± 1.67	0.68 ± 1.52	2.87	<0.01
Severe depression	0.93 ± 1.53	0.46 ± 0.13	33.13	<0.0001
GHQ total score	6.99 ± 6.34	4.19 ± 5.43	4.11	<0.0001

[195] Amr MM, Halim ZS, Moussa SS. (1997). Psychiatric disorders among Egyptian pesticide applicators and formulators. Environmental Research;73:193-199.

The scores of pesticide applicators and their matched control subjects on different GHQ dimensions are shown in the table above. The applicators scored significantly higher than control subjects on all dimensions, including anxiety and insomnia. Similar results were found for the GHQ total score.

This study lends some support to an association between heavy, long-term occupational exposure with pesticides and anxiety symptoms. This study focussed primarily on depressive diagnoses.

Limitations

However, certain methodologic issues must be considered. First, this series consisted only of applicators and formulators, who are heavily and continuously exposed. Thus, the generalizability of the findings must be recognized as being limited to a special group of subjects. In other words, the findings do not necessarily apply to other high-risk populations or under different exposure conditions. Second, the study investigators were actively looking for psychiatric morbidity and therefore might have overdiagnosed the condition of interest. Third, subjects were assessed using an open clinical interview and diagnoses were made according to a local system of classification. This made communication of results quite difficult and the screening procedure less standardized. (p. 196)

Cross-sectional studies

Sapbamrer and Nata (2014)[196] conducted a cross-sectional study to investigate health symptoms related to occupational pesticide exposure and agricultural tasks in rice farmers. Data on demographic variables and health symptoms associated with pesticide exposure were collected from 182 rice farmers (exposed subjects) and 122 non-farmers (controlled group) using interviews and measuring whole blood acetylcholinesterase (AChE) activity during August and October 2012.

Rice farmers had a significantly lower median AChE activity than the controls (9,594 vs. 10,530 U/L, respectively) and a significantly higher prevalence of difficulty in breathing and chest pain [odds ratio (OR) 2.8, P<0.01 and OR 2.5, P<0.05, respectively]. The prevalence of dry throat and cramp was associated with those farmers who sprayed and mixed pesticides (OR 2.5 and 2.6 for dry throat, OR 2.5 and 2.9 for cramp, respectively; P<0.01). The prevalence of numbness and diarrhoea was associated with those farmers who scattered seed (OR 2.2, P<0.01 and OR 3.6, P<0.05, respectively). **The prevalence of numbness and increasing anxiety was also associated with those farmers who harvested crops (OR 3.6, P<0.01 and OR 3.0, P<0.05, respectively).**

The findings suggest that occupational pesticide exposure and agricultural tasks in the paddy field may be associated with the increasing prevalence of respiratory tract and muscle symptoms. This possibility warrants further investigation in more detail.

"There are several limitations to this study. Firstly, farmers were exposed to other pesticides in addition to OPs and carbamates, such as fungicides and pyrethroids. Consequently, it is difficult to determine which types of pesticides caused the health symptoms described herein. Secondly, The AChE activity in almost all of our subjects was in the normal range, indicating that they had been exposed—if at all—to only low levels of OPs and carbamates. This low

[196] Sapbamrer R & Nata S. (2014). Health symptoms related to pesticide exposure and agricultural tasks among rice farmers from northern Thailand. Environ Health Prev Med; 19:12-20.

level of exposure may not high enough to produce definitive symptoms, thereby limiting the interpretation of our data. Thirdly, health symptoms have multiple causes and may not be attributed to pesticide exposure. Numbness may be due to ergonomic problems, and dry throat may be due to infectious agents as well as pesticides. Finally, the study design did not control a number of confounding factors, such as gender, education level, exposure to previous OPs, carbamate poisoning, and underlying diseases. Thus, these factors may also account for (some of) the symptoms reported" (p. 19).

Malekirad, Faghih, Mirabdollahi et al (2013)[197] conducted a cross-sectional study to establish the organophosphate (OP) toxicity in 187 occupationally exposed farmers in terms of neurocognitive impairment, mental health status, clinical symptoms, diabetes, and haematological factors. The exposed group was compared to 187 healthy age-, sex-, and education-matching controls. Neurocognitive impairment was measured using the Subjective Neurocognition Inventory (SNI) and mental health status using the General Health Questionnaire-28 (GHQ-28). The subjects were also tested for fasting blood glucose (FBG), blood urea nitrogen (BUN), cholesterol (CL), triglycerides (TG), creatinine, oral glucose tolerance test (GTT), high-density lipoprotein (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). The exposed farmers showed higher FBG ($p<0.001$), BUN ($p=0.007$), CL ($p<0.001$), oral GTT ($p<0.001$), and lower AST ($p<0.001$), ALP ($p<0.001$), and creatinine ($p=0.004$) than controls. The rates of anxiety/ insomnia and severe depression were also significantly higher in the farmers than in controls ($p=0.015$ and $p<0.001$, respectively). Meanwhile, the rate of social dysfunction was significantly lower than in controls ($p<0.001$). Disorders affecting psychomotor speed, selective attention, divided attention, verbal memory, nonverbal memory, prospective memory, spatial functioning, and initiative/energy were all lower in the farmers ($p<0.001$). Farmers showed clinical symptoms eczema, saliva secretion, fatigue, headache, sweating, abdominal pain, nausea, superior distal muscle weakness, inferior distal muscle weakness, inferior proximal muscle weakness, breath muscle weakness, hand tingling, foot tingling, epiphoria, polyuria, miosis, dyspnoea, bradycardia, and rhinorrhoea, which all significantly correlated with the number of working years. These findings indicate that farmers who work with OPs are prone to neuropsychological disorders and diabetes.

Wesseling, van Wendel de Joode, Keifer et al (2010)[198] examined symptoms of psychological distress, including suicidal ideation, among banana workers in Costa Rica previously exposed to a cholinesterase inhibiting pesticide. A total of 78 workers who had received medical attention 1-3 years previously for occupational pesticide poisoning were recruited: 54 had been exposed to organophosphate, 24 to carbamate, and 43 and 35, respectively, had single and multiple poisoning episodes with a cholinesterase inhibitor. Referents were 130 non-poisoned workers randomly selected from company payrolls. Psychological distress symptoms during the month prior to interview were obtained using the Brief Symptom Inventory (BSI), which has a general severity index and nine subscale scores. Differences in abnormal BSI scores (T score≥63) were assessed through multivariate logistic

[197] Malekirad AA, Faghih M, Mirabdollahi M, et al (2013). Neurocognitive, mental health, and glucose disorders in farmers exposed to organophosphorus pesticides. Arh Hig Rada Toksikol, 64: 1-8. 078155
[198] Wesseling C, van Wendel de Joode B, Keifer M, et al (2010). Symptoms of psychological distress and suicidal ideation among banana workers with a history of poisoning by organophosphate or n-methylcarbamate pesticides. Occup Environ Med, 67(11):778-84. 078157

regression for all poisoned and for subcategories of poisoned as compared to non-poisoned workers.

Organophosphate poisoned workers reported significantly more symptoms than non-poisoned on all but one symptom dimension. Significant trends of increasing symptoms with increasing number of previous poisonings were seen for somatisation, obsessive-compulsiveness, interpersonal sensitivity, depression and anxiety. The logistic regression models yielded significantly higher probability for abnormal BSI scores among the organophosphate poisoned subjects than among the referents in the symptom dimensions of somatisation, obsessive-compulsiveness, interpersonal sensitivity, depression, hostility, anxiety, phobia and psychoticism as well as the general severity index, whereas among the carbamate poisoned workers only somatisation was significantly increased as compared to the reference population (table below).

TABLE 64 PREVALENCE OF ABNORMAL SCORES (T SCORES ≥63) FOR PSYCHOLOGICAL DISTRESS ASSESSED WITH THE BRIEF SYMPTOM INVENTORY (BSI) BY EXPOSURE CATEGORIES OF POISONED BANANA WORKERS ACCORDING TO TYPE OF CHOLINESTERASE INHIBITOR, AND ADJUSTED ORS COMPARING POISONED TO NEVER POISONED BANANA WORKERS (WESSELING ET AL, 2010).

	Referents, N=130		All poisoned, N=78			Organophosphate poisoned, N=54			Carbamate poisoned, N=24		
BSI dimensions	Prevalence T score ≥63, n (%)	OR	Prevalence T score ≥63, n (%)	OR*	95% CI	Prevalence T score ≥63, n (%)	OR*	95% CI	Prevalence T score ≥63, n (%)	OR*	95% CI
Somatisation	46 (35.4)	1.00	46 (61.5)	2.92	1.64 to 5.22	34 (63.0)	3.10	1.61 to 6.00	14 (58.3)	2.56	1.05 to 6.21
Obsessive-compulsiveness	38 (29.2)	1.00	38 (48.7)	2.54	1.39 to 4.62	29 (53.7)	3.18	1.61 to 6.24	9 (37.5)	1.58	0.63 to 3.97
Interpersonal sensitivity	28 (21.5)	1.00	28 (35.9)	2.04	1.09 to 3.82	24 (44.4)	2.91	1.48 to 5.76	4 (16.7)	0.73	0.23 to 2.31
Depression	38 (29.2)	1.00	36 (46.2)	2.08	1.16 to 3.72	27 (50.0)	2.42	1.26 to 4.66	9 (37.5)	1.45	0.59 to 3.60
Anxiety	36 (27.7)	1.00	35 (34.9)	1.85	1.01 to 3.42	27 (50.0)	2.24	1.14 to 4.41	8 (33.3)	1.41	0.54 to 3.54
Hostility	25 (19.2)	1.00	25 (32.1)	1.98	1.04 to 3.78	19 (35.2)	2.28	1.12 to 4.63	6 (25.0)	1.50	0.53 to 4.23
Phobia	54 (41.5)	1.00	40 (51.3)	1.48	0.84 to 2.61	31 (57.4)	1.90	1.00 to 3.61	9 (37.5)	0.84	0.34 to 2.07
Paranoid ideation	33 (25.4)	1.00	25 (32.1)	1.36	0.72 to 2.54	18 (33.3)	1.44	0.71 to 2.92	7 (29.2)	1.21	0.46 to 3.18
Psychoticism	56 (43.1)	1.00	39 (50.0)	1.32	0.75 to 2.32	32 (59.3)	2.19	1.12 to 4.30	7 (29.2)	0.54	0.21 to 1.40
General severity index	42 (32.3)	1.00	43 (55.1)	2.57	1.44 to 4.59	34 (63.0)	3.56	1.84 to 6.92	9 (37.5)	1.26	0.51 to 3.11

*Adjusted for age, education, recent and cumulative exposure, alcohol, head injury, time of day of examination and examiner.

The prevalence of abnormal scores and corresponding adjusted ORs significantly increased over the categories of number of poisonings for the five symptom dimensions of somatisation, obsessive- compulsiveness, interpersonal sensitivity, depression and anxiety as well as the general severity index (table below). After stratification by organophosphate and carbamate poisoning, trends for organophosphate poisoned workers remained significant for the same dimensions.

TABLE 65 PREVALENCE OF ABNORMAL SCORES (T SCORES ≥63) FOR PSYCHOLOGICAL DISTRESS ASSESSED WITH THE BRIEF SYMPTOM INVENTORY (BSI) BY NUMBER OF POISONINGS, AND ADJUSTED ORS COMPARING POISONED TO NEVER POISONED BANANA WORKERS (WESSELING ET AL, 2010).

	Referents, N=130		1 Poisoning, N=43			≥2 Poisonings, N=35			
BSI dimensions	Prevalence T score ≥63, n (%)	OR	Prevalence T score ≥63, n (%)	OR*	95% CI	Prevalence T score ≥63, n (%)	OR*	95% CI	p Value (χ^2 trend
Somatisation	46 (35.4)	1.00	23 (53.5)	2.10	1.04 to 4.22	25 (71.4)	4.57	2.02 to 10.33	<0.001
Obsessive-compulsiveness	38 (29.2)	1.00	18 (41.9)	1.97	0.94 to 4.11	20 (57.1)	3.40	1.56 to 7.43	0.007
Interpersonal sensitivity	28 (21.5)	1.00	13 (30.2)	1.57	0.72 to 3.41	15 (42.9)	2.75	1.24 to 6.11	0.036
Depression	38 (29.2)	1.00	17 (39.5)	1.58	0.77 to 3.25	19 (54.3)	2.88	1.34 to 6.18	0.019
Anxiety	36 (27.7)	1.00	18 (41.9)	1.57	0.74 to 3.31	17 (48.6)	2.25	1.03 to 4.89	0.034
Hostility	25 (19.2)	1.00	14 (32.6)	2.03	0.94 to 4.39	11 (31.4)	1.93	0.83 to 4.44	0.111
Phobia	54 (41.5)	1.00	24 (55.8)	1.78	0.89 to 3.56	16 (45.7)	1.19	0.56 to 2.15	0.264
Paranoia ideation	33 (25.4)	1.00	10 (23.3)	0.72	0.31 to 1.69	15 (42.9)	2.21	0.98 to 5.00	0.092
Psychoticism	56 (43.1)	1.00	20 (46.5)	1.15	0.58 to 2.30	19 (54.5)	1.57	0.74 to 3.32	0.494
General severity index	42 (32.3)	1.00	23 (53.5)	2.41	1.19 to 4.87	19 (54.3)	2.79	1.30 to 6.00	0.005

*Adjusted for age, education, recent and cumulative exposure, alcohol, head injury, time of day of examination and examiner.

This cross-sectional study showed a relationship between acute occupational poisoning with organophosphates and psychological distress including suicidal ideation. Stronger designs are needed to address causality.

Levin, Rodnitzky and Mick (1976)[199] assessed psychiatric manifestations of exposure in workers less substantially exposed to organophosphate compounds and showing no obvious signs of toxicity. Commercial pesticide sprayers and farmers recently exposed to organophosphate agents were compared to control subjects on personality tests, a structured interview, and cholinesterase level. The commercial sprayers but not the exposed farmers showed elevated levels of anxiety and lower plasma cholinesterase than control subjects. Assessment of other behavioural manifestations and red blood cell cholinesterase failed to disclose other group differences. These findings are viewed as tentative until confirmed by additional study, but they point to the possibility that organophosphate compounds may produce subtle defects in workers who are not obviously toxic. The findings do not justify public alarm but do suggest an area warranting more systematic and definitive investigation.

Case series

Hong, Hong, Han, Lee, Gil et al (2008)[200] assessed twelve cases of suspected chronic pesticide intoxication, with medically unexplained physical symptoms. Complete blood cell count (CBC), blood chemistry, routine urinalysis, chest X-ray, ECG, gastrofiberscopy, abdominal ultrasonography, neuroselective sensory nerve conduction threshold, and psychological assessment were performed on 12 farmers who believe themselves to have suffered from chronic pesticide intoxication.

No specific abnormalities were observed on CBC, routine urinalysis, chest X-ray, ECG, gastroscopy, abdominal ultrasonography, or peripheral nerve conduction velocity test. They persistently manifested helplessness, depression, and anxiety. The results of both psychological assessment and general physical examination revealed the following clinical features: depression (8 cases), multiple chemical hypersensitivity syndrome (2 cases),

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[199] Levin HS, Rodnitzky RL, Mick DL (1976). Anxiety associated with exposure to organophosphate compounds. Arch Gen Psych, 33: 225-8. 078162

[200] Hong Z-R, Hong S-Y, Han M-J, et al (2008). Clinical observation of 12 farmers who believe themselves to have suffered from chronic pesticide intoxication. The Korean Journal of Internal Medicine, 23: 1-4. 078158

alcoholism (1 case), and religious preoccupation (1 case). Although the authors state that the cases ongoing mood was marked with helplessness, depression, and tendency toward anxiety. Anxiety was not assessed formally with the instruments used in this study.

Animal study – Biological plausibility

Judge, Savy, Campbell, Dodds et al (2016)[201]

The neurotransmitter serotonin (5-HT) is involved in mood disorder aetiology and it has been reported that (organophosphate) OP exposure affects 5-HT turnover. The aim of this study was to elucidate the mechanism underlying OP effects on the adult 5-HT system. First, acute in vivo administration of the OP diazinon (0, 1.3, 13 or 39 mg/kg intraperitoneal (i.p.)) to male Hooded Lister rats inhibited the activity of the cholinergic enzyme acetylcholinesterase in blood and in the hippocampus, dorsal raphe nucleus (DRN), striatum and prefrontal cortex. Diazinon-induced cholinesterase inhibition was greatest in the DRN, the brain's major source of 5-HT neurones. Second, acute in vivo diazinon exposure (0 or 39 mg/kg i.p.) increased the basal firing rate of DRN neurones measured ex vivo in brain slices. The excitatory responses of DRN neurones to a1-adrenoceptor or AMPA/kainate receptor activation were not affected by in vivo diazinon exposure but the inhibitory response to 5-HT was attenuated, indicating 5-HT1A autoreceptor down-regulation. Finally, direct application of the diazinon metabolite diazinon oxon to naive rat brain slices increased the firing rate of DRN 5-HT neurones, as did chlorpyrifos-oxon, indicating the effect was not unique to diazinon. The oxon-induced augmentation of firing was blocked by the nicotinic acetylcholine receptor antagonist mecamylamine and the AMPA/kainate glutamate receptor antagonist DNQX. Together these data indicate that 1) acute OP exposure inhibits DRN cholinesterase, leading to acetylcholine accumulation, 2) the acetylcholine activates nicotinic receptors on 5-HT neurones and also on glutamatergic neurones, thus releasing glutamate and activating 5-HT neuronal AMPA/kainate receptors 3) the increase in 5-HT neuronal activity, and resulting 5-HT release, may lead to 5-HT1A autoreceptor down-regulation. This mechanism may be involved in the reported increase in risk of developing anxiety and depression following occupational OP exposure.

Recommendation and conclusion

Blanc-Lapieerre et al, (2012) in a review stated that psychiatric disorders due to pesticide exposure were mostly associated with poisonings. Lessenger and Reese (1999) in their review of the literature relating to pesticides poisoning identify anxiety as a symptom of acetylcholinesterase inhibiting agent poisoning.

The Takahashi and Hashizuma (2014) systematic review focussed on depression as an outcome of organophosphate pesticide exposure, however, one study (Levin et al, 1976) found that anxiety scores of the pesticide applicators were significantly higher than the farmers assessed in the study.

Four case-control studies reported on the relationship between pesticide exposure and anxiety. Zhang et al (2016) found that the cases in the recently poisoned group were significantly higher for their scores on the Profile of Mood States tension-anxiety subscale. van Wijngaarden (2003) examined the association between mortality from mental disorders and occupational exposure to pesticides. The study reported that employment in jobs potentially

[201] Judge SJ, Savy CY, Campbell M, et al (2016). Mechanism for the acute effects of organophosphate pesticides on the adult 5-HT system. Chemico-Biological Interactions; 245:82-89.

involving pesticide exposure was weakly associated with the risk of death from mental disorders (OR = 1.46; 95% CI = 1.33–1.60). This association was stronger among women (OR = 2.65; 95% CI = 1.89–3.71), in particular for deaths from neurotic disorders (OR = 4.32; 95% CI = 2.44–7.64), which would include anxiety disorders. Beshwari et al (1999) in a Saudi Arabian study of farmers found that farmers had higher prevalence of symptoms than non-farmers. They had significantly greater increased anxiety symptoms (p<0.003). Likewise, the Egyptian study (Amr et al, 1997) of pesticide applicators and formulators had higher levels of anxiety and insomnia than matched controls ($p < 0.01$).

Three cross-sectional studies found associations between pesticide exposure and later anxiety. Sapbamrer and Nata (2014) compared rice farmers with non-farmers and found the prevalence of numbness and increased anxiety was associated with farmers who had harvested crops. Rice farmers had a significantly reduced serum median AChE than controls assumed to be due to pesticide exposure. Makekirad et al (2013) compared an exposed farmer group to matched controls. They noted that the rates of anxiety/insomnia were higher in the farmers ($p = 0.015$) than in controls. Wesseling et al (2010) compared banana workers with a history of pesticide (organophosphates or carbamate) poisoning to a group of non-exposed workers. Significant trends of increased symptoms with the increased number of previous poisonings was reported for anxiety.

The case series by Hong et al (2008) of suspected chronic pesticide intoxication in 12 farmers found that the12 subjects persistently manifested anxiety as one of the presenting symptoms. However, no objective measure of anxiety was carried out.

An animal study by Judge et al (2016) discusses the effect which OPs have on the serotonergic system as a means of explained the biological plausibility of OP exposure causing anxiety and depressive symptoms.

The evidence above is strongest for high level exposure (poisoning) with OP pesticides resulting in anxiety symptoms. Other pesticides are not consistently reported to show an effect. There is a dose response reported of increased symptoms with the increased number of previous OP poisonings in the Wesseling study. Methodologically these studies may suffer from issues in regard to confounding from other risk factors. Farmers may suffer with a higher rate of anxiety symptoms due to issues not directly related to the pesticide exposure, the impact of social and work-related factors other than pesticide exposure is not known.

Grade 3 level evidence

Posttraumatic stress disorder & Mefloquine

Summary of important issues

The request for review application received from Rear Admiral Robyn Walker also suggested that there may be an association between posttraumatic stress disorder and mefloquine.

Reviews

There is a small body of literature which discusses a relationship between PTSD and mefloquine use (McCarthy, 2015; Peterson et al, 2011; Nevin, 2015), although studies which specifically investigate this relationship are unavailable.

A number of the authors (McCarthy, 2015; Nevin, 2014; 2015) suggests the neuropsychiatric effects of mefloquine can confound the diagnosis of PTSD. Nevin (2014) states:

“Many of the symptoms of the mefloquine toxic syndrome, including vivid nightmares, personality and affective change, disordered sleep, irritability, anger, difficulties with concentration, dissociation, and amnesia, may mimic prior Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria B-D, as well as DSM-5 criteria B-E for posttraumatic stress disorder (PTSD), and may last long after discontinuation of dosing. According to a publication by the Centers for Disease Control and Prevention, these symptoms “may confound the diagnosis and management of posttraumatic stress disorder (Magill et al, 2012).” As mefloquine has been commonly prescribed to military personnel during combat deployments (Nevin, 2010), risk of intoxication may therefore have frequently coexisted with pervasive exposure to DSM-IV and DSM-5 criterion A stressors, particularly confounding the PTSD diagnosis in military and veteran populations exposed to the drug” (p. 278).

"How commonly the symptoms of mefloquine intoxication might have complicated the PTSD diagnosis in military settings is unclear. An underpowered (Phillips-Howard & Bjorkman, 1990; cited in Nevin, 2014) retrospective study of US military personnel found an increased risk of hospitalization for diagnosed anxiety disorders and PTSD among those with prior mefloquine exposure as compared to those deployed without mefloquine exposure (Wells et al, 2006), but the results of this study were not statistically significant. Despite formal recommendations, no similar study of outpatient encounters has been published (Armed Forces Epidemiological Board, 2014; cited in Nevin, 2014), and no long-term studies of veterans have been performed to rule out a higher incidence of such disorders after mefloquine exposure" (Nevin, 2014:283)

Nevin (2014) and McCarthy (2014) hypothesise that exposure to mefloquine toxicity could predispose users to other neuropsychiatric disorders such as posttraumatic stress disorder and anxiety disorders. At this time there is no evidence to support this hypothesis.

Summary and Conclusions

At this time the literature does not support an association between mefloquine use and the onset or worsening of PTSD. Rather the three reviews cited above suggest that the neuropsychiatric effects of mefloquine use may mimic PTSD diagnostic criteria and that efforts must be made to differentiate between a “mefloquine toxic syndrome” and PTSD. Grade 5A level evidence.

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