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Senate suicide inquiry

TERMS OF REFERENCE:

1. The personal, social and financial costs of suicide in Australia;
2. The accuracy of suicide reporting in Australia, factors that may impede accurate identification and recording of possible suicides (and the consequences of any under-reporting on understanding risk factors and providing services to those at risk);
3. The appropriate role and effectiveness of agencies, such as police, emergency departments, law enforcement and general health services in assisting people at risk of suicide;
4. The effectiveness, to date, of public awareness programs and their relative success in providing information, encouraging help-seeking and enhancing public discussion of suicide;
5. The efficacy of suicide prevention training and support for front-line health and community workers providing services to people at risk;
6. The role of targeted programs and services that address the particular circumstances of high-risk groups;
7. The adequacy of the current program of research into suicide and suicide prevention, and the manner in which findings are disseminated to practitioners and incorporated into government policy; and
8. The effectiveness of the National Suicide Prevention Strategy in achieving its aims and objectives, and any barriers to its progress.

"If at first, the idea is not absurd, then there is no hope for it" Albert Einstein

"The world is not dangerous because of those who do harm but because of those who look at it without doing anything" Albert Einstein

This submission focuses on suicide caused by medication, usually but not always psychiatric medication. Drugs as diverse in structure and function as hypericum, (St John's Wort,) varenicline (Chantix), oseltamivir (Tamiflu), isotretinoin (Roaccutaine) mefloquine (Lariam), metoclopramide (Maxolon), zolpidem (Stilnox), calcium channel

blockers, reserpine, statins and interferon, all induce suicidal and homicidal thinking as an occasional side effect.[1,2]

Suicide caused and induced by medication is usually, but not always, akathisia suicide. Suicidality caused by psychiatric drugs is as different as can be from depressive suicide but some of my colleagues do not know how to make that distinction on clinical grounds. As with other iatrogenic conditions, organised medicine rails against their recognition, blaming the disease.

However, many epidemiological studies show that it is not the disease as untreated folk do better and do not commit suicide as do those on antidepressants or coming off them.

Many clinical studies show then at least with antidepressants, the treated condition usually carries no suicide risk until suicidogenic drugs are used.

This submission addresses not only this problem but also provides a solution: education independent of drug companies.

I would welcome a review of these data (I have more) by the chief scientist. Failure to recognise side effects and pharmaceutical industry fraud affect all sections of medicine. Attention to them will decrease costs and improve outcomes.

1. The personal, social and financial costs of suicide in Australia;

1.1. I am no expert in the financial cost of suicide, in the sense of productive lives cut short, however I have been involved in many cases where relatives have sued the Department of Health or private hospitals for negligence when patients have committed suicide in hospital having just been discharged. Information about that should be available from relevant state attorneys general through coroners who do not count them.

2. The accuracy of suicide reporting in Australia, factors that may impede accurate identification and recording of possible suicides (and the consequences of any under-reporting on understanding the risk factors and providing services to those at risk;

2.1. Suicide reporting in Australia is not accurate. It is always delayed but that is a universal problem attributable to the backlog in coroners' offices. Mr Bill Williams will provide a submission on the warned of an obvious suicide of his son that has been covered up not only by the coroner, but its causes have been covered up by everyone concerned. According to the Health Care Complaints Commission peer reviewers, he died of "standard psychiatric treatment".

2.2. It is generally known internationally that suicide is under reported. One of the reasons it is under reported is that there are not enough autopsies being done and the problem is that there are too few forensic pathologists.

2.3. The two toxicologists I regularly come up against in these cases when they appear in criminal courts go well outside of their expertise and advise courts and coroners that antidepressants (SSRIs) do not cause suicide. There are not familiar with product information, which admits that they double suicide in kids. Clinical trials and other research show they do the same in adults. So lack of relevant expertise is a problem.

2.4. The United States Food And Drug Administration (US FDA) has issued many public health advisories warning of increased rates of suicide by persons taking antidepressants and antiepileptic drugs toted as mood stabilisers compared with the same populations untreated or taking sugar pills.

2.5. The Australian Therapeutic Goods Administration (TGA) appears to be advised by vested interests (in the sense of persons who get research grants and other benefits from their makers and act as Key Opinion Leaders) and fails to issue these same advisories.

2.6. The main problem is that we are encouraged to prescribe drugs whose risks outweigh their benefits because producers control the production and distribution of information.

2.7. As well as that, it is assumed by coroners, that the people who are being treated with some sort of psychiatric medication are mentally ill and the mental illness causes the suicide. This is often not the case. Work stress does not cause suicide or at least it did not until it was medicalized and treated with drugs that do cause suicide.

2.8. Suicide is at least up to 12 times more likely to happen as a side effect of a medication than as a result of the conditions treated nowadays with antidepressants. Even if we agree that is only double or twice as likely, is that rational for an antidepressant that is supposed to prevent suicide? If the antidepressant indeed prevents some suicides (conceded) then we are both doubling death and redistributing it.

2.9. The science and details are provided later in this submission.

2.10. We can differentiate clinically between persons who commit suicide because of their illness and those who do so because of treatment induced akathisia. They are entirely different from those being treated for biological depression. It is being done in morgues in Sweden and parts of the USA.

2.11. We can now differentiate by a DNA test, a simple buccal swab, those who become suicidal and suicide because they have poor metaboliser status and cannot metabolise antidepressants from those who commit suicide for different reasons. There is already a literature on this and I making a further contribution with 115 genetically tested folk.

3. The appropriate role and effectiveness of agencies, such as the police, emergency departments, law enforcement and general health services in assisting people at risk of suicide;

3.1. It came home to me just how much the police in each state bear the cost of suicide attempts when I was interviewing a woman who made a claim for work stress. She had become (typically) violently suicidal on an antidepressant drug, Efexor (venlafaxine) prescribed for work stress and given out without information about its risks and side effects. Moreover, this woman, like virtually everyone else, was being co-prescribed medicines which competed for the metabolic pathways needed by venlafaxine and also inhibited these same pathways.

3.2. Pharmacogentic DNA studies by a swab demonstrated that the woman described above could not metabolise that drug or any other metabolised by the genes that she did not have. (I have 100+ others like her).

3.3. Her daughter, an ambulance officer in Western Sydney had accompanied her to the interview. What I had said made perfect sense to her. She told me, “That is all we ever do, we ambulance drivers. We take people who become suicidal on antidepressants to hospital."

3.4. Treatment with multiple drugs is called polypharmacy. This is very common in Australia. It may be that some medical schools failed to teach pharmacology or left the teaching of pharmacological therapies to the pharmaceutical industry.

3.5. It has been commented on in the Medical Journal of Australia that Australian doctors are not aware of the side effects and interactions of the medications they prescribe.

3.6. It comes home to me on a daily basis that most treating doctors in Australia have little notion of pharmacogenetics, pharmacokinetics and drug sensitivities.

3.7. When the outcome of unsuitable medication and inappropriate prescribing is suicide or homicide, this becomes a very serious problem indeed, and it fits within these terms of reference of this inquiry.

4. The effectiveness to date of public awareness programmes and their relative success in providing information, encouraging help-seeking and enhancing public discussion of suicide;

4.1. Certainly it is a good thing for the community to be aware of suicide and that people who are under great stress or who have been humiliated by life events might want to kill them.

4.2. This kind of suicide is not underpinned by mental illness and psychiatry has little to offer in the sense of medicine wearing a white coat. They need social support. Medication helps only the biologically, not the reactively, depressed, but the relative risk of suicide on antidepressant medication causes more suicides.

4.3. However because of pharmaceutical industry fraud (constantly litigated by the Department of Justice in USA with outcomes on their website) and misinformation, the Australian psychiatric community and governments have been persuaded to believe by *beyondblue* (whose earlier directors were funded by drug companies) that one can reduce suicides by medicalizing common human unhappiness and prescribing antidepressants to combat it.

4.4. I divert here to antidepressants. While both biological depression and human unhappiness can be expressed in the phrase “I am depressed” this phrase does not differentiate, for clinical purposes, those biological, melancholic depressive conditions that do respond to antidepressants from the predicament-driven, situational unhappiness that does not respond.

4.5. When the worsening or new depression (in those treated for anxiety disorders or stress) has set in, the medication users (patients) are even more convinced that they are depressed. They need to be examined and shown that often they were not depressed before they got antidepressants which have worsening depression and suicidality among their side effects and that the culprit maybe the antidepressant. The US FDA Public Health Advisory of March 22, 2004 states

4.5.1. WARNINGS-Clinical Worsening and Suicide Risk

4.5.2. Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients.

4.5.3. .... Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial

few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

4.5.4. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

4.5.5. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

4.5.6. Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for [Drug Name] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

4.6. The full text FDA recommended advisory follows item 8. It needs to be implemented. Causation has since this first been established in both adults and kids.

4.6.1. Laughren, TP M.D. Director, Division of Psychiatry Products. HFD-130 FDA CDER **M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE.** November 16, 2006. **SUBJECT:** Overview for December 13 Meeting of Psychopharmacologic Drugs AdvisoryCommittee (PDAC). http://www.fda.gov/ohrms/DOCKETS/ac/06/briefing/2006-4272b1-01-FDA.pdf

4.7. Australian Product information (PI) is patchy in that for some antidepressants PI does not incorporate this information at all.

4.8. It is the population that gets worse with these symptoms that is blowing out both statistics and costs of mental illness. The criteria for major depression have an exclusion clause, which is "not caused by substance and medication." Diagnosticians too often ignore this.

4.9. I attach two seminal papers on antidepressant-induced suicide. The first is by suicidologists Roland Maris who assessed, by statistically scientific means, the clinical trials up to 2002. This is the better kind of science, meta-analyses of

clinical trials after setting up a null hypothesis, that antidepressants do not cause suicide.

4.10. The second is by Healy and Whittaker who assessed (scientifically) suicide rates in clinical trials presented to the United States Food and Drug Administration (US FDA).

4.10.1. Abstract: There has been a long-standing controversy about the possibility that selective serotonin reuptake inhibitor (SSRI) antidepressants might induce suicidality in some patients. To shed light on this issue, this paper reviews available randomised controlled trials (RCTs); meta-analyses of clinical trials and epidemiological studies that have been undertaken to investigate the issue further. The original clinical studies raising concerns about SSRIs and suicide induction produced evidence of a dose-dependent link on a challenge- de-challenge and rechallenge basis between SSRIs and both agitation and suicidality. Meta-analyses of RCTs conducted around this time indicated that SSRIs might reduce suicidal ideation in some patients. These same RCTs, however, revealed an excess of suicidal acts on active treatments compared with placebo, with an odds ratio of 2.4 (95% confidence interval 1.6–3.7). This excess of suicidal acts also appears in epidemiological studies. The data reviewed here make it difficult to sustain a null hypothesis that SSRIs do not cause problems in some individuals. Further studies or further access to data are indicated to establish the magnitude of any risk and the characteristics of patients who may be most at risk.

4.11. A list of studies of antidepressants and suicide is in the FDA paper linked in above.

4.12. By scientific evaluation I mean that these papers consist of determining causation by setting up a null hypothesis and seeing if it can be knocked down. The null hypothesis is that antidepressants do not cause suicide. The null hypothesis does not stand.

4.13. This is how good science is carried out. There are few doctors in Australian psychiatry outside of the universities who are capable of assessing clinical trials. My experience is that they are not listened to, nor heard over the louder voice of the pharmaceutical industry. As one of my internet group members reports from USA:

4.13.1. http://www.gooznews.com/node/3324

4.13.2. Putting Academic Detailing in Perspective by GoozNews ~ 15 Apr 2010 02:44pm

4.13.3. Top Senate and House Democrats issued a press release today praising the Agency for Healthcare Research and Quality for earmarking $29.5 million for grants to academics to spread the word on comparative effectiveness research. Academic detailing, championed by Jerry Avorn at Harvard, is a wonderful thing. But can it really offset the combined might of the marketing arms of Big Pharma, Big Bio and Big Device?

4.13.4. Do the math. The pharmaceutical industry, it has been conservatively estimated, has at least 50,000 detailers in the field. At a minimum, each one's annual salary, travel costs and associated support

materials comes to at least $150,000 a year. That's $7.5 billion for a small army of salespersons.

4.13.5. So how does $29.5 million a year stack up against that? Well, if it cost just $100,000 per academic detailer person-year (let's assume the professoriate works cheap), then the AHRQ program should enable the deployment of an equivalent of about 300 pharmaceutical truth bearers. 50,000 for the drug industry; 300 for the truth squad. Henry V had better odds at Agincourt.

4.14. The medical, but not the patient, community prefers the opinions of key opinion leaders, professors of psychiatry who are well remunerated by the pharmaceutical industry.

4.15. These academics were written up extensively by Roy Moynihan in considerable detail in his book, “Selling Sickness."

4.16. Professor Ian Hickie repeatedly states at public meetings on radio, on television, that suicide rates fell in Australia when antidepressants were introduced. I enclose this paper, *Hall et al.* The same Hall as did the inquiry into my reports for the TGA (see below). Hickie miss-cites his own research.

4.17. http://www.google.com.au/search?num=100&hl=en&q=Hickie+suicide+rates+fell&meta=&aq=f&aqi=&aql=&oq=&gs_rfai=

4.18. Hall and al. states:

4.18.1. Results While overall national rates of suicide did not fall significantly, incidence decreased in older men and women and increased in younger adults. In both men (rest= − 0.91; P < 0.01) and women (rest= − 0.76; P < 0.05) the higher the exposure to antidepressants the larger the decline in rate of suicide.

4.18.2. Conclusions: Changes in suicide rates and exposure to antidepressants in Australia for 1991-2000 are significantly associated. This effect is most apparent in older age groups, in which rates of suicide decreased substantially in association with exposure to antidepressants. The increase in antidepressant prescribing may be a proxy marker for improved overall management of depression. If so, increased prescribing of selective serotonin reuptake inhibitors in general practice may have produced a quantifiable benefit in population mental health.

4.18.3. http://www.bmj.com/cgi/eletters/326/7397/1008

4.18.4. http://www.google.com.au/search?num=100&hl=en&q=Hickie+suicide+rates+fell&meta=&aq=f&aqi=&aql=&oq=&gs_rfai=

4.19. The conclusions of this paper are not consistent with its text. A drug company funded the research. Suicide rates did not fall at all. They fell in older people for whom social services were being provided. Suicide rates rose slightly in young people. They have continued to rise, not only in younger people.

4.20. Claims of a falling rate by the NSW Department of Health are based on the highest suicide year, 1997 when two new suicidogenic drugs, olanzapine and risperidone (see below), were introduced on top of four or five new antidepressants and no caveats were about not using them together. The reasons for not so doing are both pharmacogentic and pharmacokinetic.

4.21. Sine the introduction of new generation antidepressants starting with Prozac in 2000 and 2001, suicide rates rocketed up among persons under

mental health care where antidepressants, atypical antipsychotics and antiepileptic drugs (toted as mood stabilisers) were being prescribed. A recent Meta analysis supports that US FDA advisories on suicide caused by epilepsy medications. See below.

4.21.1. THE "SECOND GENERATION": "ATYPICAL" ANTIPSYCHOTICS

4.21.2. More alarming information has emerged from David Healy's evaluation of the clinical trials presented to the FDA of new "atypical" antipsychotic drugs.[3] Because of their high cost ($300+ a month as opposed to $10 a month for haloperidol) they are limited to use for the Special Purpose (SP) of schizophrenia. In practice, they are very frequently prescribed unlawfully for all sorts of problems, with the best of intentions. They are problematic drugs. In the late 1980s, the FDA did not notice that one in 208 or 12 in 2,500 clinical trial subjects with schizophrenia committed suicide during the trials of Zyprexa, but only one on placebo and one on a comparator, most likely haloperidol. The subject numbers were so small that relative risk of suicide on Zyprexa could not be calculated reliably. The overall suicide rate for these trials, on a time-adjusted basis, was two to five times the norm for schizophrenics.

Table 4: Antipsychotic Drugs FDA Trials source FDA, David Healy[4]

Drug	Patient No.	Suicides	Suicidal Acts
Risperdal	2607	9	43
Comparator	601	1	5
Placebo	195	0	1
Zyprexa	2500	12	Not disclosed
Comparator	810	1 (2)	Not disclosed
Placebo	236	0 (1)	Not disclosed
Seroquel	2523	1	4
Comparator	426	0	2
Placebo	206	0	0
Sertindole	2194	5	20
Comparator	632	0	2
Placebo	290	0	1
Geodon zisapride	2993	6	Not disclosed
Comparator	951	Not disclosed	Not disclosed
Placebo	424	0	Not disclosed

The FDA trials and 52 subsequent studies evaluated in 2000, by John Geddes of Oxford University demonstrated no clear evidence that atypical antipsychotics were more effective or better tolerated than conventional antipsychotics.[5] Thirty-six, that being one in every 145 clinical trial subjects for Risperdal, Zyprexa, Seroquel,) and Sertindole died; most by suicide, yet these deaths are never mentioned in scientific literature or prescriber information. These deaths occurred even though two thirds of Zyprexa, nearly half the Risperdal and 80% of Seroquel subjects did not complete the trials because the drugs were poorly tolerated.[6] A rate of 27% akathisia in a trial of Zyprexa 10 mg was balanced by an equally high incidence of akathisia on placebo.[7]

This indicated that Eli Lilly either did not know what they were talking about (as akathisia is always a medication-induced phenomenon), or the participants had not fully recovered from whatever they had been taking before entry to the trial. Serious adverse events affected 84 subjects who took Risperdal.

None of this information appears in promotional material. Indeed 47 serious adverse events in 87,000 users of Zyprexa injectible included eight deaths. We are being assured that the deaths are not related to the Zyprexa but, given the number of suicides and deaths associated with the oral preparation, this seems to be improbable. The FDA issued a 'black box' warning about sudden death from the new antipsychotic medications, (including quetiapine and ariprazole) but only for the elderly, in spite of evidence that all age groups are adversely affected.[8,9] Further warnings are expected to advert to the extreme dangers of mixing them with SSRIs. Nor is it the case, as suggested, that Clozaril protects against suicide when compared with Zyprexa. Zyprexa itself is suicidogenic.[10] This comparison manoeuvre delays their obligation to issue full warnings for all children and adults. The PhaRMAs are stalling again as they did for antidepressants and as Merck did for Vioxx, when they suggested that a high heart attack rate on Vioxx, compared with Naproxen, occurred because the latter was protective. David Healy has pointed out that Zyprexa and Risperdal trials had the highest suicide rates in clinical trial history, but suicide risk does not feature in drug company promotional material. Geodon (ziprasidone) had the same suicide risk as SSRIs, about one in 500.

Only five Zyprexa schizophrenia trials were undertaken, but these generated 234 ghost written articles by prominent "opinion leaders" which were carefully placed in the prestigious journals, dependent for their viability on PhaRMA advertising.[11] None of these publications yielded any picture at all of the risk of suicide or suicidal acts on these drugs, let alone sudden death. "Endorsement Science" had become the means of promotion. The colourful capsules appeared on the cover of Time, in The Washington Times and The New York Times. The "Dopamine Theory of Schizophrenia" was alive and well in these endorsements, although by the time they were published it had no more scientific validity than the serotonin theory of depression.

4.22. The paper (Hall et al, Hickie) uses two numbers, the average daily dose of antidepressants and the suicide rate. This might, at best, simply be an association but even the association is not established in this paper. It does not and cannot establish causation.

4.23. The suicide rates cited in this are grouped in four-year tranches. They are never accurate immediately as it takes up to 2-3 years for coroners to report them, so each time the Australian Bureau of Statistics (ABS) reports an annual rate; it has to be amended as delayed reports come in.

4.24. At the same time suicide under mental healthcare where these drugs were being prescribed rose steadily until the way of counting mental health suicides changed.

From Tracking Tragedy reports

Reported suicide deaths of patients in contact with mental health services, and all suicide deaths in NSW 1993-2001.[12,13]

Year	Suicides in NSW	Suicides in mental health care	Percent of all NSW suicides
Suicides include inpatient suicides and suicides within 28 days of contact with mental health care. (Updated numbers in brackets)			
1993	676	68	10%
1994	798	72	9%
1995	747 (748)	100	13%
1996	811 (817)	136	17%
1997	946 (950)	166	18%
1998	827 (832)	143	17%
1999	846 (854)	173	20%
2000	738	156	21%
2001	775 (789)	159	21%
2002	643	117	?
2003	?	?	?
2004			
In 2004, the mode of counting changed to counting mental health and suicides of inpatients or within 7 days of contact with mental health care.			
2005		80-110	Information requests for this data have been denied
2006		80-110	
2007		80-110	
2008			
2009			

4.25. Between 2002 and 2009 the NSW Mental Health Sentinel Events Review Committee recorded well over 1000 suicides and 38 homicides committed by persons under public sector mental health care. It did not examine medication.

4.26. Suicide numbers under mental health care in NSW rose from 68 in 1993 to 173 in 1999 and 159 in 2001, a proportional increase from 10% to 21% of all suicides in NSW and one would expect pro rata to population rises in

4.27. The Review Committee found in that half the sample of patients died by suicide before the tenth day of their stay in mental health facilities, and 30% died within the first three days of their episode of care. By 2008, this Review Committee also examined 38 homicides committed by persons under public sector mental health care and nearly 2000 suicides.

4.28. A Victorian psychiatric unit had 13 suicides in 13 months in 2002-3 but this did not attract inquiry.[14]

4.29. Leaving aside suicide and its underpinning presentations and correlates, outcomes other then suicide for treated mental illness have been deteriorating.

4.30. The number of people under mental health care has also increased.

4.31. Persons too readily prescribed antidepressants for work stress and to cheer them up and some became psychotic, suicidal and homicidal and entered health care facilities where their symptoms, which are not subject to warnings by the TGA, were not recognised.

4.32. More often than not they are treated with more drugs requiring the same metabolic pathways and they add to a population of intractably mentally ill. These people are not mentally ill at all, they are neurotoxic and the condition is reversible. They remain suicidal and often go on to suicide.

4.33. The decade nominated in the *Hall et al.* paper contained two suicide peaks, that in 1997 appeared to be related to release of two atypical antipsychotics, which induced suicide and death see Healy below. Because of the introduction of four antidepressants in the years before, there would have been a large population of persons who were already hallucinating on antidepressants, to which, in my experience, atypicals are added at random.

4.34. The advertisements for Zyprexa during 1996 and 1997 simply stated, "Have you made the change yet?" The take up of new drugs was enormous. Australian doctors were not told of the drop out rates in clinical trials.

4.35. Mental Health Review Tribunals enforce these drugs in the face of patients telling them that they are suicidal. Enforced medication causes more to commit suicide.

4.36. These two 'atypical' drugs superimposed on antidepressants would have produced the 1996-7 peak. Of interest, is the fact that in 1996 and 1997 hanging became the most popular means of suicide? Hanging is strongly associated with akathisia. This anomaly demands further research. As the problems are ongoing, it would be easy to do it.

4.37. The atypicals would have been prescribed to an existing population of persons with functional psychosis as well as those with medication-induced hallucinations. The second group would have had the hallucinations because they could metabolise the medication or had been overmedicated with inhibitors.

4.38. The drop in suicide rates followed because only the new population now get them. People who understand epidemics understand this. The vulnerable

have accumulated and are affected so the initial rate of affectation is high and after that only new cases with personal vulnerability are affected.

4.39. The same phenomenon is seen in the United States in suicide statistics coming from the Centres of Disease Control, a rise in suicides among younger people.

4.40. To divert here: Every year about midyear, the Health Minister declares that suicide rates have fallen compared with the year before.

4.41. The rates from the year before have gone up as more deaths have been so described by coroners. The numbers that the Minister is talking about, midyear have not yet been finalised. However there is a lot of self-congratulation, “spin," going on.

4.42. A relative risk is how often an event of interest, suicide for example comes up in a clinical trial compared to the untreated population in the same trial.

4.43. If a vaccination programme had a relative risk of 1, that is, as many died from the vaccine as might die from the disease, it would soon be discarded. Even if the suicide rate were falling in Australia, it would be difficult to attribute its fall to medications that actually increase the suicide rate among those people taking them.

4.44. Antidepressants make people more vulnerable to suicide and this vulnerability persists. I enclose Janne Larssen’s studies of suicides and antidepressants in Sweden.

4.45. Dr Grace Jackson in her book, “Rethinking Psychiatric Drugs” also cites evidence of this phenomenon that antidepressants make people more vulnerable to future depression.

4.46. It is my experience that when I have taken people safely off antidepressants (if they have been suicidal and homicidal on them); it takes a full two years to recover.

4.47. Some other people who have taken themselves off after being advised of the nature of their problems have phoned me 2 years later to say, “Doctor, I’m just beginning to feel like myself."

4.48. The side effect of antidepressants that leads to suicide (and homicide and violence) is called akathisia. This is what DSM says about akathisia.

4.49. The subjective distress resulting from akathisia is significant and can lead to non-compliance with neuroleptic treatment. Akathisia may be associated with dysphoria, irritability, aggression or suicide attempts. Worsening of psychotic symptoms or behavioural dyscontrol may lead to an increase in neuroleptic medication dose, which may exacerbate the problem. Akathisia can develop very rapidly after initiating or increasing neuroleptic medication. The development of akathisia appears to be dose dependent and to be more frequently associated with particular neuroleptic medications.

4.50. Acute akathisia tends to persist for as long as neuroleptic medications are continued, although the intensity may fluctuate over time. The reported prevalence of akathisia among individuals receiving neuroleptic medication has varied widely (20%-75%). Variations in reported prevalence may be due to a lack of consistency in the definition of cases, neuroleptic prescribing practices, study design, and the demographics of the population being studied.

4.51. This is what Wikipedia, which I think is the better definition, says about akathisia.

4.51.1. Akathisia (or "acathisia") is an often extremely unpleasant subjective sensation of "inner" restlessness that manifests itself with an inability to sit still or remain motionless, hence its the origin of its name: Greek a (without) + akathisia (to sit). It is a common side effect of certain drugs, notably typical or atypical antipsychotics (also called major tranquillisers), such as haloperidol (Haldol®) and droperidol, olanzapine (Zyprexa®); SSRIs, such as paroxetine (Paxil®); tricyclic antidepressants, certain antihistamines, such as promethazine and diphenhydramine (Benadryl®); and certain anti-emetic drugs, particularly the dopamine blockers (e.g. metoclopramide (Reglan®) and prochlorperazine (Compazine®)).

4.51.2. Akathisia may range in intensity from a mild sense of disquiet or anxiety (which may be easily overlooked) to a total inability to sit still with overwhelming anxiety and severe dysphoria (manifesting as an almost indescribable sense of terror and doom). In the most severe cases, dysphoria can be so severe that the patient is literally compelled to take action, leading, possibly, to suicide attempts. It is not unknown to have patients literally run out of a hospital or emergency room.

4.51.3. Akathisia is often misdiagnosed and can lead the patient to commit suicide in or outside the hospital.

4.51.4. Causes:

* *typical or atypical antipsychotics (also called major tranquillisers), such as haloperidol (Haldol®) and droperidol, olanzapine (Zyprexa®);*
* *SSRIs, such as paroxetine (Paxil®);*
* *tricyclic antidepressants, certain antihistamines, such as promethazine and diphenhydramine (Benadryl®);*
* *and certain anti-emetic drugs, particularly the dopamine blockers (e.g. metoclopramide (Reglan®) and prochlorperazine (Compazine®)).*

Treatment includes the discontinuation or reduction of dose of the causative agent and the use of typical or atypical antipsychotics (also called major tranquilizers) to reduce the agitation and anxiety. Unfortunately, these neuroleptics are often the cause of the condition and are known to cause irreversible akathisia in some cases. While the administration of these drugs may temporarily ameliorate the symptoms, there is a serious risk of worsening the condition over the longterm.

Therefore, some consider the drug of choice for the treatment of akathisia to be propranolol, along with other beta blockers such as metoprolol. The antihistamine cyproheptadine is also effective, though with shorter effect than beta blockers. Second-line treatments include benztropine and benadryl, though excess use of benadryl may worsen symptoms. ***Most of the clinical cases of akathisia can be prevented by not administering the drugs that cause the condition.*** *This page was last modified 22:32, 30 December 2005*

4.52. According to DSM, between 25% to 75% of persons taking psychiatric drugs develop akathisia. Akathisia is poorly understood by Australian-trained psychiatrists.

4.53. It does not seem to be taught much in Australia. It seems to me to stand to reason that, once akathisia, behavioural dyscontrol and intense restlessness, suicidal and violent ideation and toxic hallucinosis have set in, then a person is not going to recover from whatever they were suffering from before, which with the new generation drugs was any of anxiety, schizophrenia, mania, depression, work stress, or whatever the drug has been prescribed for.

4.54. As this condition, akathisia or 'supersensitivity psychosis" which is much the same as withdrawal akathisia, is not recognised by Australian psychiatrists, it has become epidemic. It increases suicide rates. Akathisia (but not schizophrenia or mania) has “suicide attempts” as one of its criteria and between 1 attempt in 20 and 1 attempt in 40 is successful. And all generate morbidity and costs.

4.55. Burgess et al. reported that, after psychiatric services were introduced to 100 developing countries, suicide rates rose in all of them.[15]

4.56. This is because nearly all psychiatric drugs induce akathisia. Akathisia is a delirium associated with suicide attempts based on a death wish and suicide induction. Some users of psychiatric drugs will develop akathisia and some people with akathisia will kill themselves whereas they might not have done so if not treated with medication.

4.57. This does not suggest treatment should be withheld; it should be given but with more understanding and more care and regular warnings.

4.58. Text books such as Kaplan and Sadock III (1980) (and all editions since) state:

4.58.1. *Akathisia is a subjective desire to be in constant motion. A manifestation of drug sensitivity, it may be confused with psychotic agitation and incorrectly treated by increasing the dose of the offending medication. The symptom subsides promptly when the offending medication is discontinued and replaced by another one better tolerated by the patient*.

4.59. Current DSM since 1994 for antidepressants and neuroleptics:

4.59.1. Associated Features and Disorders of akathisia

4.59.2. The subjective distress resulting from akathisia is significant and can lead to noncompliance with neuroleptic treatment. Akathisia may be associated with dysphoria, irritability, aggression or suicide attempts. Worsening of psychotic symptoms or behavioural dyscontrol may lead to an increase in neuroleptic medication dose, which may exacerbate the problem. Akathisia can develop very rapidly after initiating or increasing neuroleptic medication.

4.59.3. The development of akathisia appears to be dose dependent and to be more frequently associated with particular neuroleptic medications.

4.59.4. *Acute akathisia tends to persist for as long as neuroleptic medications are continued, although the intensity may fluctuate over time. The reported prevalence of akathisia among individuals receiving*

neuroleptic medication has varied widely (20%-75%). Variations in reported prevalence may be due to a lack of consistency in the definition of cosiness, neuroleptic prescribing practices, study design, and the demographics of the population being studied.

4.60. But my Australian colleagues do not seem to read basic undergraduate text books, or they simply deny their validity.

4.61. I have made between 400 to 500 fully de-identified medico-legal reports to the Adverse Drug Reactions Advisory Committee (ADRAC) of persons mostly normal folk, treated for pain, injuries or work stress, or anxiety, pain, anorexia or shyness (none of which carry a suicide risk) who had become suicidal and homicidal after using prescribed antidepressants.

4.62. My 400-500 comprise only a small proportion of 10,000 such reports made by other people. I have them on CD ROM and can email.

4.63. The Therapeutic Goods Administration (TGA) simply ignored these reports until I placed 90 in front of the Secretary of Health and Aging Ms Jane Halton who called and inquiry. The report can be accessed here:

4.64. http://www.tga.gov.au/alerts/medicines/pdseap-report2009.htm

4.65. This report confirmed what I was saying culprit drugs and interactions.

4.66. The report has not been taken up by departments of health nor circulated by the Royal Australian College of Psychiatrists (RANZCP). Nor have any further or better advisories been produced. What conflicts of interest, what inertias are operating here?

4.67. While working in a rural psychiatric unit, I made, to ADRAC, the adverse drug reactions advisory committee, 193 reports of homicidal and suicidal admissions over 2 years. 163 were admissions some multiple, 30 were medico-legal cases who had had admissions as well.

4.68. I came mainly on Tuesday and probably captured 60% or 70% of the admissions simply keeping notes of medicines being taken by suicidal and homicidal patient as they were being admitted or that I saw or talked to or was consulted about in various situations. These were the drugs in use:

4.69.

Count	New Gen Antidepresents	Atypicals	Mood Stabillsers	Typical Antipsychotics	Benzodiazepines	Antiparkinsonian	Pre 1990 Antidepressants	Pain Medications	NSAIDS:	MAOIs	Substance Abuse Meds	Anti Emetics	Antihistamines	CNS Stimulants	Oddments	Unknown	
4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
102	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	A
29	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	AB
4	X	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	ABC
1	X	X	X	X	-	X	-	-	-	-	-	-	-	-	-	-	ABCDG
1	X	X	X	X	X	-	-	-	-	-	-	-	-	-	-	-	ABCDH
2	X	X	-	X	X	-	-	-	-	-	-	-	-	-	-	-	ABCH
1	X	X	-	X	X	-	X	-	-	-	-	-	-	-	-	-	ABCHN
1	X	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	ABD
1	X	X	X	-	X	-	-	-	-	-	-	-	-	-	-	-	ABDH
4	X	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	ABH
3	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	AC
1	X	-	-	X	-	-	-	-	-	-	-	X	-	X	-	-	ACFL
2	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	AD
1	X	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	AH
1	X	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	AK
1	X	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	AM
1	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	AO
1	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	AP
13	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	B
7	-	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	BC
1	-	X	-	X	-	X	-	-	-	-	-	-	-	-	-	-	BCG
1	-	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	BD
1	-	X	-	-	-	-	-	-	-	-	-	-	X	-	-	-	BI
1	-	X	-	-	-	-	-	-	X	-	-	-	-	-	-	-	BK
4	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	C
1	-	-	-	X	-	X	-	-	-	-	-	-	-	-	-	-	CG
2	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	N

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I was unable to collect information co-prescribed medications at that time but a current study I am conducting on 100 clinically identical persons suggests that polypharmacy combined with genetic polymorphism are causing this suicidality problem to be greater then it was in clinical trials. In clinical trials no other drugs were in use and subjects were interviewed weekly and removed when and if they became suicidal.

4.70. These 100 persons had become suicidal and homicidal on antidepressants. I examined their medications and their metabolizing genes. I will return to this work in progress later.

4.71. The Administration and the NSW Department of Health knew full well what I have been doing.

4.72. They have been informed more times that DFAT was informed about the Wheat Board paying bribes to Saddam Hussein. It seems that there is no one who will take responsibility.

4.73. I continued to blow the whistle on SSRI-induced akathisia suicides in the face of severe warnings but I was about as successful as middle management at Lehman Brothers had been when they tried to warn the Securities Commission of the company's debt situation, or Mr Markopolos who spent 7 years begging the US Securities Commission to stop Madoff's Ponzi Scheme.

4.74. If people do not want to see, they do not see.

4.75. I made submissions to each of 5 NSW Health Ministers. Only Dr Andrew Refshauge believed me; he knew me well, has worked with me and had read my PhD thesis on another iatrogenic disorder RSI. But he retired suddenly.

4.76. The other health ministers ignored my submissions, as did the NSW Department of Health, the RANZCP and various state parliamentary committees.

4.77. In so doing they ignored Product Information (better in USA than here) textbook psychiatry, peer reviewed literature, meta-analyses of clinical trials and US FDA Advisories and Canadian Advisories.

4.78. I reported some 30 cases of persons making SSRI-induced, multiple and, in some cases, successful suicide attempts to the Medical Board of NSW. The Health care complaints commission engaged peer reviewers who could not spell akathisia, who could not find anything wrong with the prescribing even though my reports soon included four deaths.

4.79. That is, 4 people died by suicide after I had warned of their treatment. 8 died in two years one a Prozac (fluoxetine) homicide victim. The Supreme Court Judge believed me. All this was ignored. Why? Is someone being threatened?

4.80. I was told that in all cases this was Standard Psychiatric Care. When multiple suicide deaths occur under Standard Psychiatric Care, then what constitutes Standard Psychiatric Care needs to be re-evaluated, not covered up like

4.81. I reviewed the suicide rates in clinical trials and follow up studies for antidepressants and atypicals.

4.82. In 2003 in the state of New South Wales (NSW), Australia, the Director of the NSW Centre for Mental Health, Professor Beverley Raphael, revealed that "the numbers of people requiring psychiatric treatment fronting at hospital emergency departments had doubled in the past decade"

4.83. The suicide rate immediately after discharge was 100 times the rate for the general population; for patients with depression, it was up to 500 times. The suggestion was that the patients were not fully recovered.

4.84. More likely, they were taking antidepressants and unable to metabolise them.

4.85. The number of "seriously mentally ill persons" increased again by 15% in the 4 years to 2005, and the demand for mental health services has continued to increase by 4% annually since that time.

4.86. The Mental Health Council of Australia (http://www.mhca.org.au) reported that costs of mental health in Australia had reached $1.5 billion, having increased by 26% during 2009.

4.87. In the U.S., *Preda et al.* (2001) found that 10% of admissions to a psychiatric unit were for antidepressant-induced mania and psychosis. They are precursors of antidepressant-induced suicide.

4.88. As this epidemic of "mental illness" unfolded in lockstep with the ever-increasing use of psychiatric drugs, Whitaker asked: "Is our drug-based paradigm of care fuelling this modern-day plague?"

4.89. Indeed, in 2004, the U.S. Food and Drug Administration (US FDA) issued public health advisories warning of "worsening depression and suicidality" in adults on antidepressants.

4.90. Review of reported rates of suicide in clinical trials of selective serotonin reuptake Inhibitors (SSRIs and atypical neuroleptics)

4.91. Suicide accompanying akathisia (the Greek word for "cannot sit down") first emerged with reserpine in clinical trials for anxiety and depression in the 1950s.

4.92. In lower doses, when given to mentally healthy persons for hypertension, reserpine also caused suicide.

4.93. Suicide caused by tri- antidepressants (TCAs) was recognised soon after their introduction and this was a subject of textbook psychiatry in 1960. "*during early convalescence following initiation of treatment with tricyclic antidepressants, the risk of suicide once more becomes serious as retardation fades."* **Clinical Psychiatry, by Mayer-Gross, Slater, and Roth, 1960, p. 231**]:

4.94. Clinical trials for SSRIs revealed a relative risk (RR) of suicide over placebo ranging from 2 to 10. All these are referenced in Lines of Evidence provided.

4.95. As early as 1989, paroxetine trial data demonstrated an eightfold increase in suicide risk, a risk not acknowledged until 2006. A homicide had occurred in clinical trials for each of paroxetine and fluoxetine.

4.96. Without differentiating suicide on active substance from suicide in withdrawal, Khan et al. (2003) reported 77/48,277 suicides (159/100,000) in antidepressant trials presented to the US FDA from which subjects with a history of suicidality had been excluded.

4.97. Healy et al, after court-ordered access to the same trial data, separated withdrawal suicides from those in placebo run-in and found a relative risk of suicide of between 2 and 3 with antidepressant use over placebo. This means

that a person is two to three times more likely to commit suicide than if that person were untreated or took placebo.

4.98. Healy et al. related suicides not to the duration of treatment nor to the underlying diagnosis but to the number of patients treated, suggesting a personal vulnerability factor. We now know it is genetic.

4.99. Further evaluation of follow-up and epidemiological studies in the community revealed that around 1 in 500 persons given SSRIs committed suicide in trials and follow-up studies (range 173-269/100,000, mean 219/100,000).

4.100. Their conclusion was modest: “It is no longer possible to support the null hypothesis that SSRIs do not cause suicide.” The highest estimate of the suicide rate for mood disorders in the community consistent with general suicide rates is 68/100,000 but more likely 30/100,00.

4.101. The available information from clinical settings, emergency rooms, morgues, Daubert Hearings and clinical trials establishing that “SSRIs cause suicide” meets the scientific standard of proof. This makes no sense for an antidepressant, but that does not seem to bother regulators or prescribers.

4.102. *Hall et al.* found that with the increase in antidepressant prescribing in Australia, suicide rates rose in younger adults.

4.103. In 1997, the year that olanzapine and risperidone came into use, the national rate was 14.6/100,000, an increase of 9% from the previous year, while NSW reported a rate of 15.1/100,000.

4.104. The national suicide rate had previously peaked at 17.5/100,000 in 1963, a few years after tricyclics had become available for the treatment of “biological” depression.

4.105. The decade after the introduction of antidepressants contained two peaks in suicide rates.

4.106. A 2006 US FDA review of 273 antidepressant trials found that on average, suicide on antidepressants was double to several times that on placebo. In fact, that review understated the problem, as suicides in withdrawal (a danger period) were coded as “placebo” suicides.

4.107. Khan et al. (2001) found that in trials presented to the US FDA for licensing of risperidone, olanzapine and quetiapine, 26/10,118 subjects (257/100,000) had committed suicide and 51/10,118 (563/100,000) had attempted.

4.108. This problem could be explained by the wide range of half-life of olanzapine of (9-56 hours) and the high prevalence of poor metabolisers (PMs) and intermediate metabolisers (IMs) at CYP450 450 2D6, required for risperidone metabolism.

4.109. Slow metabolism causes delayed effects and poor compliance over groups, but not necessarily of appropriately dosed individuals.

4.110. Via the Freedom of Information Act, Whitaker gained access to US FDA data and to more extensive drug trial dossiers for the same atypicals and reported that 1 in every 145 patients who entered the trials *died* as a result of adverse reactions to these three drugs, Zyprexa (olanzapine) Risperdal (risperidone) and drugs (690/100,000), but these deaths were never mentioned in the scientific literature.

4.111. Science writer and Pulitzer Prize winner Robert Whitaker, via the Freedom of Information Act gained access to FDA data on the drug trials for the Atypicals Risperdal, Seroquel and Zyprexa. Whitaker found that:

4.112. One in every 145 patients who entered the trials *died*, and yet those deaths were never mentioned in the scientific literature. From what is published, most were suicides.

4.113. The trials were structured to favour the Atypicals and most of the study reports were discounted by the FDA as being biased.

4.114. One in every thirty-five patients in Risperdal trials experienced a serious adverse event, defined by the FDA as a life threatening event or one that required hospitalization. These included suicide attempts.

4.115. Twenty-two percent of patients in Zyprexa trials suffered serious adverse events. 28% on 15 mg daily suffered from akathisia. This is in US product information but Australian doctors have not been told, indeed have been told that EPSEs (extra pyramidal side effects including akathisia) are lower in atypicals then in old drugs,

4.116. This is cited in the Allen Jones, "whistleblower document" on TMAP, **http://psychrights.org/Drugs/AllenJonesTMAPJanuary20.pdf** and has been confirmed by personal communication.

4.117. Healy accessed dossiers in archives and reported that for olanzapine, 20/2500 (800/100,000 i.e. 1 in 200) died, of 2500 remaining after two thirds had failed to complete 6-week trials for undisclosed reasons.

4.118. 12 of those 20, that 12/2500 died by suicide, (480/100.000) and no records of suicide attempts were found by Professor Healy in the archives. Suicide attempts were not reported.

4.119. PI from the US FDA website revealed that 67/3100 (2,161/100,000) took overdoses of olanzapine and 66 survived. But were these suicide attempts? I suspect so as I have seen a lot of Zyprexa (olanzapine) suicide attempts. .

4.120. Total deaths in risperidone trials were not disclosed but there were 9/2,607 suicides (345/100,000) and 47 attempts (1802/100,000) after 50% of subjects failed to complete.

4.121. Overall there were 1-2 suicides on each of placebo and comparator, haloperidol even though 38% of subjects had previously been intolerant of it.

4.122. Jackson also reported that two thirds of starters dropped out of the four olanzapine trials, of which only two were considered acceptable for its licensing by the US FDA.

4.123. Breggin (2003) reviewed the literature on suicidality; violence and mania caused by SSRIs and described the typical syndromes associated with their use.

4.124. He also identified the reasons that sufferers themselves were unaware that they had side effects.

4.125. Current mental health outcomes compared with those of 20, 50 or 100 years ago.

4.126. Hospitalised suicide attempts in New South Wales (NSW) (now renamed "Intentional self-harm hospitalisations" more than trebled between 1989-90 and 2006-7, increasing from 55 to 155/100,000, increasing with the release of each new psychiatric drug.

4.127. Healy reported on suicide rates in schizophrenia and other psychoses and found a 20-fold increase in the 1994-1998 cohort over the 1875-1920 cohort each suicide was underpinned by 20-40 attempts.

4.128. Between 1980 and 2006, mortality among mental health patients rose in Australia and USA.

4.129. By 2007, confirmed data from the Australian Therapeutic Goods Administration (TGA) included 399 deaths and 9532 adverse reports involving anti-psychotics in the previous 15 years. Many involved children, for whom SSRIs and atypicals had either not been approved or had been approved for special purposes or specific conditions. Some were likely suicides.

4.130. A report of a Psychiatric Drug Safety Expert Advisory Panel including Hall of Hall et al, was commissioned by the TGA, it looked at genetically based interactions, did not comment on the prevalence of diminished metabolisers.

4.131. It criticised polypharmacy while reiterating that antidepressants “do more good than harm." It has never been circulated by the RANZCP or anyone else.

4.132. The TGA appears to be on the side of the their clients drug companies. (I can provide detail). This may improve information.

4.133. New TGA powers reach Parliament: The TGA will be able to demand that sponsors show compliance with conditions placed on medicines registrations under proposed amendments to the Therapeutic Goods Act.

4.134. A register of press reports and legal judgements of deaths, suicides, homicides and toxic behaviours caused by antidepressants are maintained at **www.ssristories.com** but authorities make no attempt to collect this information. Sub-lethal ADRs, suicide attempts fill hospitals, generating privatised profits and socialised costs.

4.135. Many medicines are metabolised by the P450 cytochrome system, 1000 enzymes determined by 50 different genes. Not every person has all the genes and all the enzymes. Genetics of the metabolism, of transporter and neuro-receptor systems, may reveal why different people respond differently to the same substances. Some cannot deal with particular medicines at all and react catastrophically to one or two doses, while others need more. A, B, and O blood typing provides an analogy in that unless the blood group of both donor and recipient has been matched, a blood transfusion might by chance be a success, might kill some recipients, and others would sicken.

4.136. In relation to metabolism, the population can be broadly divided by genetic testing into PMs, IMs, extensive metabolisers (EMs) and UMs for one or more of three relevant cytochromes. The term "diminished metaboliser" highlights the vulnerability of both PMs and IMs and may be a preferable, more informative depiction.

4.137. If the genes producing the relevant cytochrome (CYP450) enzymes are defective, or inhibited by another drug, the enzyme is not produced and the blood level of the drug that should be metabolised by that enzyme system rises. It then may exceed the range, known as the “therapeutic window” within which it might be effective, and above which it is toxic, hence ineffective.

4.138. Some EMs, after taking a CYP inhibitor, develops blood levels associated with PMs over time. Young women, with endogenous and exogenous oestrogens, are particularly vulnerable to antidepressant and olanzapine toxicity, as oestrogens inhibit some relevant CYPs.

4.139. Both high and rapidly changing levels of drugs are linked to unpredictable and violent side effects, those listed in each drug's PI. Extrapyramidal side effects (EPSEs), including akathisia, develop faster in persons with diminished metabolism and in children, who are toxin-naïve, having not yet induced cytochrome metabolism.

4.140. Ordinary drug-drug interactions, not genetic variances, ought to account for most adverse drug reactions. The fundamental requirement for safe prescribing is that doctors understand that metabolism is a finite resource, with 30-fold inter-individual variance. They must know which drugs are substrates of various CYPs and which other drugs compete for, induce or inhibit that metabolism.

4.141. Conditions which affect metabolism include co-prescribed medications that induce or inhibit the enzymatic pathways, age, nutrition, stress, liver disease, hormones (natural and extraneous); the sequence in which drugs have been prescribed or taken away; the route of administration; the range of the drug half-life in any population; potentially multiple metabolic pathways; the size of the therapeutic window; the duration of therapy and the duration of inhibition which may persist after discontinuation.

4.142. Suicide is the measurable tip of an iceberg of psychiatric phenomena, which demand care. These phenomena are listed in the "label information" approved by the US FDA and in an abridged version in MIMS.

4.143. The PI accessed through the website of the US FDA for olanzapine and venlafaxine (2007 version) combined lists adverse effects as abnormal/changed/toxic/dyscontrolled behaviour, overdose, adjustment disorder, aggression, agitation, akathisia, alcohol abuse, amnesia, antisocial reaction, anxiety, coma, confusion, delirium, delusions, dementia, depersonalisation, nightmares, euphoria, hallucinations, homicidal ideation, insomnia, impulse control difficulties, intentional injury, libido up or down, manic reaction, obsessive/compulsive, paranoia, paroniria (weird dreaming and thinking), personality disorder, phobias, psychosis, psychotic depression, serotonin toxicity, speech disorder, schizophrenic/schizophreniform reaction, stuttering, sudden death, substance misuse, suicidal ideation, suicide attempt and suicide [68]. Australian doctors are not told half of this in Australian Product, "MIMS," information.

4.144. Serotonergic toxicity involves non-specific mental state changes, palpitations, breathing difficulties, night sweats in the company of neurological signs, lack of coordination, tremors and cognitive and memory problems.

4.145. Suicide attempts, hospital admissions, ambulance use, presentations and demands on mental health services, courts, jail time and hospital time were huge but incalculable. More than half the resources of the rural unit had been taken up with iatrogenic disorders. Statistics about increased demand suggest it might be as high as two thirds of costs of mental health in Australia.

4.146. If the deaths, suicides and their antecedent states that appeared in clinical trials translate into the community, the Report of NSW Mental Health Sentinel Events Review Committee is an understatement, as it deals only with the public sector. The rise in demand, as documented by the NSW Department of Health, parallels suicide and its precursor states as they manifested in clinical trials.

4.147. Clinical trials are closely monitored but, in the Australian community, neither patients nor prescribers know what side effects are to be expected or how they are produced. Treating doctors have not been told of the possibility that suicidal violence is an ADR, nor that they need to understand pharmacokinetics, pharmacogentics and CYP450 problems in any population. Indeed, patients in the community, often unsupervised, are more likely to be adversely affected than clinical trial subjects. The latter are interviewed weekly about side effects, and quietly withdrawn from the trial if they develop suicidal ideation or akathisia.

4.148. This information about rates of sudden death, dropout and suicide has been withheld from patients, prescribers and coroners in Australia. This knowledge would make it impossible to obtain informed consent for some medicines. Unaware of dropout rates in the trials for the atypicals, Mental Health Review Tribunals enforce these drugs by injection when patients, finding them intolerable, refuse to take them by mouth. As a last resort for non-recovering patients, electroconvulsive therapy (ECT) is enforced, at a rate, which has doubled over the last decade. Prescribers no longer withdraw medication whose side effects include worsening depression before embarking on ECT. Yet 30 years ago this information was known and withdrawal was always undertaken.

4.149. Completed suicides, violence and completed homicides by patients under mental health care in Australia have increased at least sixfold as psychiatric patients have become more violent. To avoid potentially catastrophic side effects, prescribers need to start low, go slow, watch and warn. Education about the roles of cytochromes, substrates, inducers and inhibitors and CYP450 I have since been generously supported by Healthscope Molecular, a cytochrome laboratory.

4.150. All this is in Product Information (PI) and known to those who read it and beyond that.

4.151. People who

5. The efficacy of suicide prevention training and support for front line health and community workers;

5.1. If the causes of suicidality, that is antidepressant and neuroleptic induced akathisia are not known then it stands to reason that targeted programmes will not be successful.

5.2. There are 167 common drugs that have psychiatric side effects. Australian doctors do not appear to be unaware of them.

5.3. Common inducers of suicidal akathisia include: Lipitor (atorvastatin), conjugated oestrogens, ace inhibitors, Tagamet (cimetidine) as well as all psychiatric drugs.

5.4. There are further problems in that pharmacogenetic principles are poorly recognised even at the TGA where one might expect to see experts with high-level skills and influence.

5.5. Some people can do quite well on antidepressants until another drug is introduced into their regime.

5.6. People become toxic on psychiatric medication not only because of the genetic problems but also because of co-prescribed medication.

5.7. Ms Jane Halton, Secretary of the Department of Health and Aging ordered a 'secret' inquiry by Therapeutic Goods Administration into 90 reports I had made in the form of fully de-identified medicolegal reports on workers compensation

and injury claimants who had been normal before they had received antidepressants and suicidal and akathisic after.

5.8. The Expert report was fair but the authors found, inexplicably given the 90 tragedies in front of them, that antidepressants did more good than harm. This view can not be deduced from evidence in front to them evidence or the scientific as opposed to pharmaceutical industry information generated the literature,

5.9. Some medicines available over the counter have very strong interactions with some antidepressants. It is possible to doing quite well on, for instance, Zoloft (sertraline) until Nexium (esomeprazole) is introduced and then suicidality and violence will occur. Other over the counter drugs that interact with prescribed drugs include non steroidal anti-inflammatories and even paracetamol. This is poorly known and this information needs to be distributed by pharmacists.

5.10. Labels ought to be put on all of these drugs to warn against the combined use of those and other drugs that require the same metabolic pathways or inhibits.

6. The role of targeted programs and services that address the particular circumstances of high-risk groups.

6.1. There is a report which urgently needs to be implemented:

Australian Centre for Health Research. Improving the Quality Use of Medicines in Australia Realising the Potential of Pharmacogenomics. October 2008. This report expects a ten year run in. it can be found on http://www.achr.com.au/pdfs/PharmacogenomicsReportFINALDec2008.pdf

6.2. The role of pharmacists needs to be expanded. Pharmacists should not be allowed to dispense incompatible drugs without alerting the patient and the doctor.

6.3. The 2009 Report of the Psychiatric Drug Safety Expert Advisory Panel, which addressed drug-drug interactions, and the dangers of polypharmacy (while repeating that antidepressants do more good than harm) have not been circulated, nor has the RANZCP drawn attention to it. It needs to be implementated.

6.4. Iatrogenesis in medicine is a neglected field of research. Guidelines must be based on sound scientific evidence, taking into account not only what is available in published ghost-written papers and PHARMA-funded trial reports but also what is revealed in the primary knowledge obtained from drug applications made available to experts during litigation against psychotropic drug promoters and through court-ordered inspections. Patients whose biology does not allow them to metabolise psychotropic drugs and who become psychotic, suicidal and often violently toxic and homicidal on those drugs contribute significantly to the crisis in mental health.

6.5. Patients suspected of being in this condition need to be identified and recalled to prevent them from killing themselves.

6.6. Coroners need to be informed officially of these problems, so they can count and attribute suicides properly.

6.7.

7. The role of targeted programmes and services that address the particular circumstances of high-risk groups. The adequacy of the current programme of research into suicide and suicide prevention, and the manner in which

findings are disseminated to practitioners and incorporated into government policy; and

7.1. If iatrogenic, medication induced akathisia suicide has to be kept a secret, then all programs will be inadequate. I cite the TGA report into my reports which contains a set of recommendations which should be implemented immediately with the report from Deloitte.

7.2. It may be the case that this "Pharma Science" was produced at least in part by academics that had links to or benefits from the pharmaceutical industry.

7.3. An understanding of genetic pharmacology and the concept of the "window of opportunity" are essential for safe prescribing in psychiatry. Toxic states may become chronic when treated with more toxins. Polypharmacy is not an appropriate response to failure to recover or to side effects of medicines, psychiatric or other.

7.4. Education about the roles of cytochromes, substrates, inducers and inhibitors and CYP450 testing is essential and should not be delayed. To avoid potentially catastrophic side effects, prescribers need to start low, go slow, watch and warn.

7.5. Medical faculties, continuing medical educators and licensing agencies charged with issuing advisories must share the responsibility for failing to teach practical pharmacogenetics.

7.6. At work here is the phenomenon of being unable to accept new medical knowledge, known as "reverse gullibility", which has been recognised frequently since Semmelweiss drew attention to iatrogenic deaths from puerperal sepsis. Understanding and accepting the implications of pharmacogenetics represents a paradigm shift, which will result in great deal of accepted "knowledge" being discarded.

7.7. Paradigm shifts are always resisted,

8. The effectiveness of the National Suicide Prevention Strategy in achieving its aims and objectives, and any barriers to its progress.

8.1. The National Suicide Prevention Strategy has been unsuccessful. This appears to me to be because it is trapped in a paradigm where common human events and unhappiness are medicalised unhappiness, re-branded as "depression" to be treated with pills.

8.2. For example, the RANZCP guidelines to the treatment of Depression 2003 are based on the fraudulent Parma consortium TMAP. The RANZCP needs to be counselled and informed.

9. Post script

In May of 2004, the US FDA demanded that the makers of the drugs listed below carry this warning in detail below. Australian Product information still does not conform in most cases, the TGA was advised, judging from the citations by person closely connected to the pharmaceutical industry by grants that the black box warning for adolescents children was not required**.**

Labeling Change Request Letter for Antidepressant Medications

Dear xxx : Please refer to your new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [Drug Name].

We additionally refer to the September 13, and 14, 2004 meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee to

discuss reports of the occurrence of suicidality in clinical trials for various antidepressant drugs in pediatric patients with major depressive disorder and other psychiatric disorders.

Based upon the recommendations made by the committee members, we believe that additional labeling changes are warranted in order to caution practitioners, patients, family members or caregivers about an increased risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders who are taking antidepressant medications.

Therefore, we are requesting revisions to your labeling in order to incorporate the committee's recommendations. Specifically, we are requesting the following changes to product labeling.

[This new section should be added to the beginning of the package insert with bolded font and enclosed in a black box]

DRUG NAME

Suicidality in Children and Adolescents

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Drug Name] is not approved for use in pediatric patients except for patients with [Any approved pediatric claims here]. (See Warnings and Precautions: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials

[The following language would replace the current language under the **WARNINGS-Clinical Worsening and Suicide Risk** section.]

WARNINGS-Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. A causal role for antidepressants in inducing suicidality has been established in pediatric patients.

Pooled analyses of short-term placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk

arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Ideally, such observation would include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for [Drug Name] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

[This language will be included for those drugs for which tapering is recommended.] If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION -- Discontinuation of Treatment with **[Drug Name]**, for a description of the risks of discontinuation of **[Drug Name]**.

Rule out bipolar disorder to the extent possible: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a

conversion is unknown. However, prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

[The following language would replace the current language under the **PRECAUTIONS**-Information for Patients section.]

PRECAUTIONS-Information for Patients

Physicians should inform patients and caregivers about the benefits and risks associated with treatment with **[Drug Name]** and should counsel them in its appropriate use. A patient Medication Guide is available for **[Drug Name]** . The prescriber should instruct patients and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Physicians are advised to discuss the following issues with patients for whom they prescribe **[Drug Name]** and to ask them to alert their physician if these occur:

Clinical Worsening and Suicide Risk: Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Pediatric Use

[This section will include either (1) a general statement for drugs for which pediatric data have not been submitted to FDA, as follows: "Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS -- Clinical Worsening and Suicide Risk)," or (2) more specific language regarding pediatric efficacy data that have been evaluated by FDA.]

Anyone considering the use of **[Drug Name]** in a child or adolescent must balance the potential risks with the clinical need.

These labeling revisions should be submitted in the form of a "Supplement - Changes Being Effected" within 30 days from the date of this letter.

Additionally, please be advised that we will also be requesting a Medication Guide in the format as outlined under 21 CFR 208 for all drugs in this therapeutic class. This Medication Guide would replace, if applicable, any patient package insert. We would also require that your product be distributed in unit-of-use packaging to ensure that every patient receives the Medication Guide. Additional information pertaining to the specifics of this Medication Guide will be forthcoming in the next 2-3 weeks.

*T*he NSW Department of Health has been repeatedly advised of antidepressant suicide since January of 2004, and a region has been so advised since 1997.

Both were more influenced by what he Department of health agreed (obviously with what it was doing) than the science, which seemed to go over its had.

Antidepressant Use in Children, Adolescents, and Adults List of Antidepressant Drugs with Medication Guides (I am using American names here)

Anafranil (clomipramine)

Asendin (amoxapine)

Aventyl (nortriptyline)

Celexa (citalopram hydrobromide)

Cymbalta (duloxetine)

Desyrel (trazodone HCl)

Elavil (amitriptyline)

Effexor (venlafaxine HCl)

Emsam (selegiline)

Etrafon (perphenazine/amitriptyline) fluvoxamine maleate

Lexapro (escitalopram oxalate)

Limbitrol (chlordiazepoxide/amitriptyline)

Ludiomil (maprotiline)

Marplan (isocarboxazid)

Nardil (phenelzine sulfate)

nefazodone HCl

Norpramin (desipramine HCl)

Pamelor (nortriptyline)

Parnate (tranylcypromine sulfate)

Paxil (paroxetine HCl

Pexeva (paroxetine mesylate)

Prozac (fluoxetine HCl)

Remeron (mirtazapine)

Sarafem (fluoxetine HCl)

Seroquel (quetiapine)

Sinequan (doxepin)

Surmontil (trimipramine)

Symbyax (olanzapine/fluoxetine)

Tofranil (imipramine)

Tofranil-PM (imipramine pamoate)

Triavil (perphenazine/amitriptyline)

Vivactil (protriptyline)

Wellbutrin (bupropion HCl) Zoloft (sertraline HCl)

Zyban (bupropion HCl)

Suicidal Behavior and Ideation and Antiepileptic Drugs Update 5/5/2009:

The following is a recent advisory from the US FDA, one of a series, which have been systematically ignored by the TGA.

Suicidal Behavior and Ideation and Antiepileptic Drugs. Update 5/5/2009: Class label changes.

Manufacturers of antiepileptic drugs (AEDs) or anticonvulsant drugs will update product labelling to include a warning about **an increased risk of suicidal thoughts or actions** and will develop a Medication Guide to help patients understand this risk. These changes affect all approved AEDs except those indicated only for short-term use.

Drugs with updated labels: The approved AEDs affected by these safety label changes are

Carbatrol,

Celontin,

Depakene,

Depakote ER,

Depakote sprinkles,

Depakote tablets,

Dilantin, Equetro,

Felbatol, Gabitril,

Keppra,

Keppra XR,

Klonopin,

Lamictal,

Lyrica,

Mysoline,

Neurontin,

Peganone,

Stavzor,

Tegretol,

Tegretol XR,

Topamax,

Tranxene,

Tridione,

Trileptal,

Zarontin,

Zonegran, and generics.

FDA approved updated labeling for these drugs on April 23, 2009: The following is a list of antiepileptic drugs* included in the analyses:

<u>Carbamazepine</u> (marketed as Carbatrol, Equetro, Tegretol, Tegretol XR)

Felbamate (marketed as Felbatol)

Gabapentin (marketed as Neurontin)

Lamotrigine (marketed as Lamictal)

Levetiracetam (marketed as Keppra)

Patient Information Sheet

Oxcarbazepine (marketed as Trileptal)

Pregabalin (marketed as Lyrica)

Tiagabine (marketed as Gabitril)

Topiramate (marketed as Topamax)

Valproate (marketed as Depakote, Depakote ER, Depakene, Depacon)

Zonisamide (marketed as Zonegran).

Drugs with Medication Guides

New comprehensive Medication Guides were approved on April 23, 2009, for

Lamictal,

Lyrica,

Topamax,

Zonegran and

Keppra.

Comprehensive Medication Guides are being developed for the other drugs and should be available by the end of 2009.

Advice for healthcare professionals

Epilepsy and other illnesses for which antiepileptic drugs are prescribed are associated with an increased risk of suicidal thoughts and behavior. If suicidal thoughts or behavior emerge during treatment with AEDs, the prescriber should consider whether these symptoms may be related to the illness being treated.

All patients who currently are taking or starting on any antiepileptic drug for any indication should be monitored for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression.

Background

Since issuing safety alerts on December 16, 2008 and January 31, 2008 (see below), FDA has been working with the manufacturers of drugs in this class to better understand the suicidality risk.

As described in the January 31, 2008, Information for Health Care Professionals Sheet on AEDS, eleven antiepileptic drugs were included in FDA's original pooled analysis of placebo-controlled clinical studies in which these drugs were used to treat epilepsy as well as psychiatric disorders and other conditions.

The increased risk of suicidal thoughts or behavior was generally consistent among the eleven drugs, with varying mechanisms of action and across a range of indications. This observation suggests that the risk applies to all antiepileptic drugs used for any indication.

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