Senate Inquiry: Barriers to consistent, timely and best practice assessment of attention deficit hyperactivity disorder (ADHD) and support services for people with ADHD

Addendum submission by Critical Psychiatry Network Australasia (CPNA)

Thank you for the opportunity to present to the Inquiry last month. As discussed, we wish to add a comment re the economic analysis prepared by Deloitte Access Economics for the Australian ADHD Professionals Association (AADPA) in 2019 (*The social and economic costs of ADHD in Australia*). The Deloitte report (and the modified analysis published by Sciberras et al. in 2022)[i] is highly relevant to term of reference *(i) the social and economic cost of failing to provide adequate and appropriate ADHD services*.

The Deloitte report is being used to support claims that *untreated* ADHD costs the Australian economy billions of dollars that could be saved by increasing diagnosis and treatment of ADHD. Such claims are misleading and, moreover, indicative of a simplistic, biased, non-evidence-based agenda. It is important to be aware that:

1. Most of the studies used in Deloitte's analysis focused on costs related to people who had been clinically diagnosed with ADHD in childhood and/or adulthood, and had received treatment. This should be obvious in relation to the estimates of treatment costs, but is ignored by some people. Furthermore, the sources used to estimate the *productivity costs* also mainly focus on treated people (and the titles of some of the source publications[ii] reflect this).
2. The Deloitte report has been seriously misrepresented as saying that the $20bn cost was caused by *untreated* ADHD. Notably the Royal Australian and New Zealand College of Psychiatrists' submission to your Inquiry stated 'In Australia, untreated ADHD has enormous economic costs to society with estimates of overall cost amounting to $20 billion per year'. Deloitte made no such claim; as noted above, they estimated and reported costs of ADHD, treated and untreated (and including the cost of treatment).
3. Misleading claims about the Deloitte report ignore the evidence that ADHD medications have very weak evidence of effectiveness and have substantial adverse effects including dependence. A recent study found that more than 90% of ADHD medication users experience adverse effects (average 5.8 symptoms in the past month), that are significantly correlated with reduced Quality of Life, reduced probability of employment, and increased work impairment.[iii]

We believe that the Senate Inquiry report should not only avoid endorsing misleading claims about the economic costs of untreated ADHD but also should explicitly address the common misinterpretation and misrepresentation.

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Schein J et al. Symptoms associated with ADHD/treatment-related adverse side effects and their impact on quality of life and work productivity in adults with ADHD. Curr Med Res Opin. 2023 Jan;39(1):149-159 doi: 10.1080/03007995.2022.2122228. Epub 2022 Sep 30. PMID: 36082503. (pdf attached); see also recent advice in a Therapeutics Letter about Adult ADHD from University of British Columbia's independent Therapeutic Initiative (pdf attached).

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RESEARCH ARTICLE

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Symptoms associated with ADHD/treatment-related adverse side effects and their impact on quality of life and work productivity in adults with ADHD

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ABSTRACT

Objective: Describe symptoms associated with ADHD/treatment-related adverse side effects among adults with ADHD in the US and assess their impact on quality of life (QoL) and work productivity.

Methods: An online survey among adults receiving ADHD medications in the US was conducted to collect information relating to symptoms associated with ADHD/treatment-related adverse side effects. Participants were recruited from the panel of a well-established market research firm, Dynata, from 26 July to 30 July 2021 and were included in the study if they met the eligibility criteria and were willing to participate in the survey. Correlations between symptoms and key outcomes (QoL/employment/work impairment) were estimated using linear regression analyses.

Results: Of 585 participants, 95.2% experienced ≥1 symptom associated with ADHD/treatment-related adverse side effects in the past month (average = 5.8 symptoms). The number of symptoms was significantly correlated with reduced QoL, reduced probability of being employed, and increased work/activity impairment. Among subgroups with insomnia/other sleep disturbances and emotional impulsivity/mood lability, 50.4% and 44.7% reported their symptoms had "a lot" or "extremely" negative impact on their overall well-being, respectively.

Conclusions: Symptoms associated with ADHD/treatment-related adverse side effects are common and have a substantial negative impact on QoL and reduces patients' probability of employment. Improved management of ADHD/treatment-related adverse side effects and more tolerable treatment options have the potential to improve QoL and work productivity among adults with ADHD.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder characterized by symptoms of inattention and/or hyperactivity–impulsivity that impair functioning and is estimated to affect 4.4% of adults in the United States (US)[1–3]. ADHD medications have demonstrated high effectiveness with medium-to-high effect sizes in meta-analyses (e.g. standardized mean difference of 0.7–1.2), especially for stimulants[4,5]. Frontline treatment for most adults with ADHD typically consists of pharmacological intervention with stimulants, which have been shown to be effective in reducing ADHD core symptoms[6,7]; other treatment options include non-stimulants as well as psychotherapy[6,8].

Pharmacological treatments for ADHD are associated with adverse side effects[1,9]. In the longest-running clinical trial of methylphenidate in adult ADHD to date[10], a higher proportion of patients receiving methylphenidate ($N = 205$) vs. placebo ($N = 209$) had sleep-related problems (e.g. insomnia [8.8 vs. 4.8%], restlessness [10.2 vs. 2.9%]), loss of appetite (22.4 vs. 3.8%), dry mouth (14.6 vs. 4.8%), weight loss (6.3 vs. 1.9%), and emotional dysregulation (e.g. irritability [6.8. vs 5.3%], depressed mood [19.0 vs. 12.9%]). Another clinical trial among children with ADHD has shown that clinically significant physiological adverse side effects, including insomnia, occurred more frequently among those who stayed on stimulant medication compared to those off medication[11]. In addition, many of these adverse side effects can be associated with the disease itself and it is challenging to distinguish whether they are related to the treatment or not. Regardless of the underlying cause, these ADHD/treatment-related adverse side effects may have important consequences on patients' well-being[12,13].

Prior studies on the potential impact of these ADHD/treatment-related adverse side effects have been conducted among children and adolescents (e.g. impact on overall functional impairment, school grades, health service utilization)[11,14–18], but their impact on the quality of life and work productivity of adult patients is less well characterized[19]. Importantly, it has been shown that ADHD/treatment-related

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adverse side effects may affect patients' persistence and adherence to treatment[20], which are crucial determinants of treatment outcomes. Thus, additional information on the impact of ADHD/treatment-related adverse side effects on the daily living of adults with ADHD is needed to better understand the burden and potential consequences associated with these adverse side effects, which may help improve the clinical management of this population. The current study aimed to describe symptoms associated with ADHD/treatment-related adverse side effects experienced by adults with ADHD receiving pharmacological treatment in the US through an online survey and assess their impact on participants' quality of life and work productivity using validated scales[21,22] and self-reported ratings.

Methods

Study design and data source

An online survey was conducted from 26 July to 30 July 2021 to collect de-identified, individual-level data from treated adults with ADHD living in the US. Participants were recruited from the panel of Dynata, a well-established market research firm. An invitation containing the survey link was sent to all US panel members who indicated having ADHD. The survey questionnaire comprised four sections: (1) Screening and informed consent form, which included questions to confirm respondent eligibility and willingness to participate in the study; (2) Core section, which included questions on individual characteristics and general outcomes; (3) Sleep disturbances–specific section, which included questions specific to insomnia and other sleep disturbances (completed by individuals who reported having symptoms of insomnia and other sleep disturbances during the past month); and (4) Emotional impulsivity–specific section, which included questions specific to emotional impulsivity/mood lability (completed by individuals who reported having symptoms of emotional impulsivity/mood lability during the past month). Prior to data collection, pilot testing was conducted with three eligible participants in the form of semi-structured virtual interviews to review the survey content, ensure comprehension, and refine questions as needed. This study was approved under the exemption category by the Western Copernicus Group Institutional Review Board.

Study population

Adults residing in the US were eligible to participate in this study if they were diagnosed with ADHD and were receiving a pharmacological therapy treatment approved by the US Food and Drug Administration (FDA) for the management of ADHD symptoms at the time of the study. To capture a study population that could more closely reflect patients with ADHD treated in the real world, patients on multiple medications and those with treatment-resistant ADHD (e.g. chronic patients) were not excluded. Participants must have been somewhat comfortable reading and understanding English.

Study measures and outcomes

Information on participants' demographic, clinical, and treatment characteristics (e.g. current and prior treatments, frequency and reasons for skipping or missing a dose of current pharmacological treatment), experiences with symptoms associated with ADHD/treatment-related adverse side effects in the past month (defined as undesirable symptoms experienced by patients while on treatment, which could be associated with the ADHD disease state or the ADHD treatment received; adverse side effects were identified from the FDA labels of various ADHD medications), and the reasons for whether or not the symptom(s) was discussed with a healthcare provider was collected. Health-related quality of life (HRQoL), employment status, and work productivity and activity impairment characteristics were also assessed. Specifically, HRQoL was assessed using the Adult Attention Deficit Hyperactivity Disorder Quality-of-Life (AAQoL) scale. The 29-item AAQoL scale includes four subscales—life productivity, psychological health, relationships, and life outlook[21]. The total and subscale scores ranged from 0 to 100, with a higher score indicating greater HRQoL. Participants' work productivity and activity impairment characteristics were measured using the Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP)[22]. WPAI-SHP outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

For participants who reported experiencing insomnia and other sleep disturbances or emotional impulsivity/mood lability in the past month, information on the characteristics of the respective symptoms (e.g. duration, frequency, treatment received for symptom management) and the participants' self-reported impact on quality of life and work productivity (based on the options of "not at all," "a little," "somewhat," "a lot," and "extremely") were collected.

Statistical analyses

Information collected was reported descriptively overall and among subgroups of participants who experienced selected symptoms associated with ADHD/treatment-related adverse side effects (i.e. insomnia and other sleep disturbances; emotional impulsivity/mood lability). Means, medians, and standard deviations were reported for continuous variables; frequency counts and percentages were reported for categorical variables.

Linear regression analyses with stepwise variable selection were conducted to estimate the correlation between symptoms associated with ADHD/treatment-related adverse side effects and key outcomes of interest after adjusting for participant characteristics (i.e. gender, age, and education level). Specifically, ordinary least square regression models were used to estimate continuous response variables (i.e. the AAQoL score or the WPAI-SHP activity impairment score), and a logistic regression model was used to estimate a binary response variable (i.e. employment).

Table 1. Participant demographic and clinical characteristics.

Participant characteristics[a]	N 585	
Demographic characteristics		
Age, mean ± SD [median]	34.0 ± 11.3 [33.0]	
Gender, *n* (%)		
Female	342	(58.5%)
Male	237	(40.5%)
Other/non binary	6	(1.0%)
Race/ethnicity[b], *n* (%)		
Asian or Pacific Islander	26	(4.4%)
African American or Black	83	(14.2%)
Hispanic or Latino	65	(11.1%)
Native American or Alaskan Native	21	(3.6%)
White	435	(74.4%)
Other	4	(0.7%)
Prefer not to answer	1	(0.2%)
Region of residence, *n* (%)		
Northeast	83	(14.2%)
West	119	(20.3%)
Midwest	126	(21.5%)
South	257	(43.9%)
Education level, *n* (%)		
Less than high school	11	(1.9%)
High school	129	(22.1%)
College/some college	273	(46.7%)
Graduate school	170	(29.1%)
Prefer not to answer	2	(0.3%)
Relationship status, *n* (%)		
Single	209	(35.7%)
In a relationship, living with someone	328	(56.1%)
In a relationship, not living with someone	42	(7.2%)
Unknown/prefer not to answer	6	(1.0%)
Clinical characteristics		
Age at diagnosis, *n* (%)		
<13 years old	160	(27.4%)
13 17 years old	194	(33.2%)
≥18 years old	222	(37.9%)
Unknown/prefer not to answer	9	(1.5%)
Comorbidites[b], *n* (%)		
Anxiety disorder	384	(65.6%)
Depression	304	(52.0%)
Bipolar disorder	149	(25.5%)
High blood pressure	92	(15.7%)
Obsessive compulsive disorder	84	(14.4%)
Diabetes	67	(11.5%)
High cholesterol	63	(10.8%)

ADHD, attention deficit/hyperactivity disorder; SD, standard deviation.
Notes:
[a]Participant characteristics were measured at the time of data collection; [b]More than one option could be selected (i.e. responses were not mutu ally exclusive).

Table 2. Treatment characteristics.

Treatment characteristics[a]	N 585	
Current ADHD treatment		
Pharmacological treatment[b], *n* (%)	585	(100.0%)
Stimulants	548	(93.7%)
Non stimulants	105	(17.9%)
Combination therapy	226	(38.6%)
Multiple stimulants	158	(27.0%)
Combination of stimulants and non stimulants	68	(11.6%)
Duration of current pharmacological treatment, *n* (%)		
<1 month	14	(2.4%)
1 5 months	44	(7.5%)
6 12 months	101	(17.3%)
13 24 months	79	(13.5%)
>24 months	333	(56.9%)
Unknown/prefer not to answer	14	(2.4%)
Non pharmacological treatment[b,c], *n* (%)	475	(81.2%)
Prior ADHD treatment(s)		
Pharmacological treatment[b], *n* (%)	510	(87.2%)
Stimulants	476	(81.4%)
Non stimulants	119	(20.3%)
None	52	(8.9%)
Unknown/prefer not to answer	23	(3.9%)
Non pharmacological treatment[b,c], *n* (%)	479	(81.9%)

ADHD, attention deficit/hyperactivity disorder; SD, standard deviation.
Notes:
[a]Treatment characteristics were measured at the time of data collection; [b]More than one option could be selected (i.e. responses were not mutually exclusive).
[c]Non pharmacological treatment included psychotherapy interventions, aca demic or cognitive skills training, organizational skills training, school based interventions, social skills training, stress management training, and mindful ness training/meditation.

Results

Demographic and clinical characteristics

A total of 585 eligible adults with ADHD completed the survey and were included in the analyses. The mean age of the participants was 34 years; 58.5% of the participants were female; 74.4% were White, 14.2% were African American or Black, and 11.1% were Hispanic or Latino. The participants were from across all US regions (South: 43.9%, Midwest: 21.5%, West: 20.3%, Northeast: 14.2%), 29.1% had a graduate degree, and 63.2% were in a relationship. Based on information reported by the participants, 37.9% were first diagnosed with ADHD as adults, 65.6% had comorbid anxiety disorder, and 52.0% had comorbid depression (Table 1).

ADHD treatment characteristics

As per the study eligibility criteria, all participants were receiving a pharmacological treatment at the time of data collection, with 93.7% receiving stimulants, 17.9% receiving non-stimulants, and 38.6% receiving combination therapy, including 11.6% who were receiving both stimulants and non-stimulants; 56.9% of participants were treated with their current ADHD medication for more than 24 months (Table 2). Most participants (73.2%) reported at least sometimes skipping or missing a planned dose of their current pharmacological treatment, with 19.7% reporting skipping or missing a planned dose at least half of the time. Of those skipping or missing a planned dose, the main reported reasons were problems with obtaining prescription (54.4%), forgot to take it (51.4%), timing of dosing conflicts with daily routine and/or other activities (25.0%), and experienced or to avoid potentially experiencing undesirable effects (19.9%).

The majority of participants (81.2%) were also receiving non-pharmacological treatments for their ADHD (e.g. psychotherapy interventions, academic or cognitive skills training, organizational skills training). Furthermore, 87.2% of participants had previously received other ADHD medications, including stimulants (81.4%) and non-stimulants (20.3%), and 81.9% had previously received non-pharmacological treatments (Table 2).

Symptoms associated with ADHD/treatment-related adverse side effects

A vast majority (95.2%) of participants reported experiencing at least one symptom associated with ADHD/treatment-related adverse side effects in the past month, with an average of 5.8 symptoms per participant. Among the symptoms most

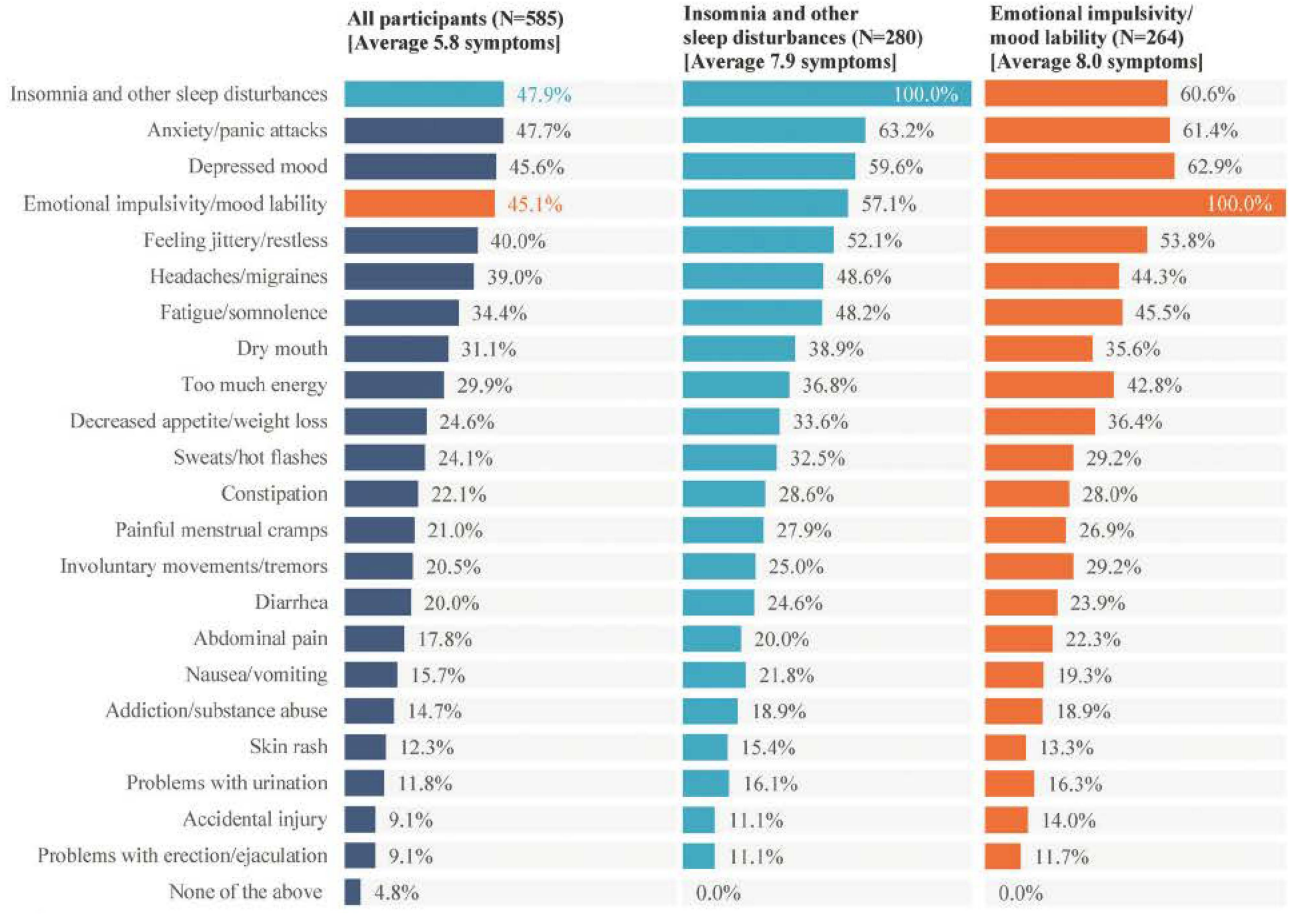

Figure 1. Symptoms associated with ADHD/treatment related adverse side effects experienced in the past month.

frequently experienced by the participants were insomnia and other sleep disturbances (47.9%), anxiety/panic attacks (47.7%), depressed mood (45.6%), and emotional impulsivity/mood lability (45.1%). The subgroups of participants with insomnia and other sleep disturbances and with emotional impulsivity/mood lability had an average of 7.9 and 8.0 symptoms in the past month, respectively. More than half of participants in these subgroups also experienced anxiety/panic attacks, depressed mood, and feeling jittery/restless (Figure 1).

Among participants who experienced at least one symptom in the past month ($N = 557$), 35.7% did not discuss at least one symptom with their healthcare provider; this proportion was 17.5% among those with insomnia and other sleep disturbances and 19.3% among those with emotional impulsivity/mood lability. For participants who did not discuss at least one symptom with their healthcare provider, frequently reported reasons included symptoms were tolerable or not important enough to discuss (44.7%), choosing to manage the symptoms without the help of a healthcare provider (34.0%), thought it was more important to manage ADHD symptoms and/or other conditions (30.9%), planned to discuss the symptoms, but have not had time yet (28.7%), and did not want to take additional medications (25.5%).

HRQoL

Overall, the mean AAQoL score was 46.4 points among the participants, with a mean score ranging from 37.8 to 57.4 points in the four AAQoL domains (Table 3). Among subgroups, participants with insomnia and other sleep disturbances or emotional impulsivity/mood lability had numerically lower scores (42.9 and 42.6 points, respectively) than the overall sample in all AAQoL domains (Table 3).

The number of symptoms associated with ADHD/treatment-related adverse side effects was significantly correlated with a reduction in HRQoL. Specifically, each additional symptom experienced in the past month was associated with a decrease of 1.6 points in the total AAQoL score ($p < .001$; Table 3). Of note, a reduction of ~8 points is considered clinically important in adults with ADHD[23]; this corresponds to ~5 symptoms based on each symptom contributing to a 1.6-point decrease in the AAQoL score.

Employment

Overall, 67.4% of participants were employed and the average number of hours worked per week was 26.7 hours. Among subgroups, participants with insomnia and other sleep disturbances or emotional impulsivity/mood lability had a numerically lower rate of employment (60.0 and 60.2%, respectively) than the overall sample (Table 3).

The number of symptoms associated with ADHD/treatment-related adverse side effects was significantly correlated with a reduction in the probability of being employed. Specifically, each additional symptom experienced in the

Table 3. Impact of ADHD/treatment adverse side effects on HRQoL, employment, and work productivity and activity impairment.

a) Descriptive statistics

	All participants N 585	Participants with selected symptoms: Insomnia and other sleep disturbances N 280	Participants with selected symptoms: Emotional impulsivity/ mood lability N 264
Health related quality of life[a]			
AAQoL score[b], mean ± SD [median]	46.4 ± 16.9 [44.8]	42.9 ± 15.1 [42.2]	42.6 ± 14.6 [41.4]
Life productivity	44.3 ± 23.4 [43.2]	41.0 ± 20.7 [40.9]	40.9 ± 20.5 [40.9]
Psychological health	37.8 ± 23.3 [33.3]	33.2 ± 20.5 [33.3]	32.5 ± 18.9 [33.3]
Life outlook	57.4 ± 21.8 [57.1]	54.2 ± 22.5 [51.8]	54.2 ± 20.8 [53.6]
Relationships	46.1 ± 25.4 [45.0]	43.2 ± 23.3 [45.0]	41.8 ± 22.6 [40.0]
Employment[a]			
Currently employed, *n* (%)	394 (67.4%)	168 (60.0%)	159 (60.2%)
Worked during the past 7 days[c], *n* (%)	372 (94.4%)	158 (94.0%)	149 (93.7%)
Average number of hours worked per week[c], mean ± SD [median]	26.7 ± 18.8 [30.0]	25.6 ± 15.9 [30.0]	26.7 ± 0.0 [30.0]
Work productivity and activity impairment[a]			
WPAI SHP[d,e], % ± SD [median]			
Activity impairment due to health	58.6 ± 25.2 [60.0]	62.8 ± 22.4 [60.0]	60.3 ± 0.0 [60.0]
Overall work impairment due to health[c]	60.7 ± 26.7 [61.6]	62.5 ± 24.2 [60.0]	59.8 ± 0.0 [60.0]
Absenteeism	19.7 ± 24.2 [7.9]	19.8 ± 23.9 [9.8]	18.6 ± 0.0 [7.8]
Presenteeism	55.1 ± 26.0 [50.0]	57.0 ± 23.9 [60.0]	55.0 ± 0.0 [60.0]

b) Regression analyses

	Overall AAQoL score[f,g]		Probability of being employed[h,i]		WPAI SHP activity impairment due to ADHD[f,j]	
	Estimate (95% CI)	*p* Value	OR (95% CI)	*p* Value	Estimate (95% CI)	*p* Value
Number of symptoms experienced in the past month (continuous)	1.6 (2.0; 1.3)	<.001*	0.94 (0.90; 0.98)	.006*	1.6 (1.1; 2.1)	<.001*

AAQoL, Adult Attention Deficit/Hyperactivity Disorder Quality of Life Scale; ADHD, attention deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio; SD, standard deviation; WPAI SHP, work productivity and activity impairment specific health problem.

*Significant at the 5% level.

Notes:

[a]Outcomes were measured at the time of data collection;

[b]AAQoL scores range from 0 to 100, with higher scores indicating better HRQoL;

[c]Evaluated among those who reported being currently employed;

[d]Questions were asked during the past 7 days;

[e]WPAI SHP outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. The sum of impairment due to the specified problem and other health reasons is considered impairment due to all health problems; the WPAI SHP measures impairment due to the specified problem and all health problems. Activity impairment refers to the impact of health on the ability to complete daily activities. Overall work impairment refers to the impact of health on the ability to work and is equal to absenteeism (work time missed) plus presenteeism (impairment at work/reduced on the job effectiveness).

[f]The estimate, CI, and *p* value were obtained from ordinary least squares regression with stepwise variable selection of demographic variables (i.e. gender, age, education level);

[g]A negative estimate indicates that each additional symptom experienced in the past month is associated with a decrease in AAQoL score (i.e. lower HRQoL);

[h]The OR, CI, and p value were obtained from logistic regression with stepwise variable selection of demographic variables (i.e. gender, age, education level);

[i]An OR less than 1 indicates that each additional symptom experienced in the past month is associated with a decrease in the odds of being employed;

[j]A positive estimate indicates that each additional symptom experienced in the past month is associated with an increase in activity impairment.

past month was associated with a 6% decrease in the likelihood of being employed (odds ratio: 0.94, $p = .006$; Table 3).

Work productivity and activity impairment

Based on the WPAI-SHP scale, the average activity impairment due to health was 58.6% in the overall sample, and participants with insomnia and other sleep disturbances or emotional impulsivity/mood lability had a numerically higher rate of activity impairment (62.8 and 60.3%, respectively) (Table 3).

Among employed participants, average work impairment due to health was 60.7% (Table 3). Participants with insomnia and other sleep disturbances had a numerically higher rate of work impairment (62.5%) than the overall sample, but it was not the case for those with emotional impulsivity/mood lability (59.8%) (Table 3).

The number of symptoms associated with ADHD/treatment-related adverse side effects was significantly correlated with an increase in activity impairment due to ADHD. Specifically, each additional symptom experienced in the past month was associated with a 1.6-point increase in the percentage of activity impairment measured by the WPAI-SPH ($p < .001$; Table 3).

Insomnia and other sleep disturbances—symptom characteristics and impact on quality of life and work productivity

Among the subgroup of participants who experienced insomnia and other sleep disturbances in the past month ($N = 280$), 47.9% had experienced the symptoms for more than 12 months (Table 4). The vast majority (91.4%) of participants experienced symptoms at least three times a week, including not being able to fall asleep within 30 min of going to bed (62.9%), difficulty falling asleep or sleeping through the night due to racing thoughts (54.6%), and waking up throughout the night and/or early morning (51.4%).

Table 4. Characteristics and management of insomnia and other sleep disturbances.

Sleep disturbances[a]	Participants with insomnia and other sleep disturbances
	N 280
Self reported characteristics of insomnia and other sleep disturbances	
Time since started experiencing insomnia and other sleep disturbances, *n* (%)	
<1 month	10 (3.6%)
1 3 months	32 (11.4%)
4 6 months	57 (20.4%)
7 12 months	39 (13.9%)
>12 months	134 (47.9%)
Unknown/prefer not to answer	8 (2.9%)
Frequency of symptoms[b,c]	
Experienced ≥1 symptom ≥3 times a week, *n* (%)	256 (91.4%)
Cannot fall asleep within 30 min of going to bed	176 (62.9%)
Difficulty falling asleep or sleeping through the night due to racing thoughts	153 (54.6%)
Wake up throughout the night and/or early morning	144 (51.4%)
Increased feelings of sleepiness and/or lack of energy during the day	138 (49.3%)
Difficulty waking up and/or getting out of bed in the morning	129 (46.1%)
Feel uncomfortable (e.g. too hot/cold, pain, difficulty breathing, coughing)	123 (43.9%)
Difficulty falling asleep or sleeping through the night due to feeling jittery and/or restless	121 (43.2%)
Difficulty going to bed due to increased energy and/or overstimulation in the evening	98 (35.0%)
Have bad dreams and/or nightmares	90 (32.1%)
Other symptoms of insomnia or sleep disturbances	16 (5.7%)
Average number of hours of sleep per night, mean ± SD [median]	5.6 ± 2.6 [5.0]
Treatment for managing sleep disturbances	
Used ≥1 treatment during the past month, *n* (%)	226 (80.7%)
Type of treatment[c], *n* (%)	
Prescription medication	161 (57.5%)
≥3 times a week	82 (29.3%)
Over the counter medication	183 (65.4%)
≥3 times a week	65 (23.2%)
Non pharmacological treatment	144 (51.4%)
≥3 times a week	36 (12.9%)
Other	91 (32.5%)
≥3 times a week	29 (10.4%)
Self reported impact of insomnia and other sleep disturbances on work productivity among employed patients	*N* 168
Missed ≥1 day of work in the past month as a result of insomnia and other sleep disturbances, *n* (%)	75 (44.6%)
Number of days of work missed in the past month as a result of insomnia and other sleep disturbances, mean ± SD [median][d]	2.5 ± 4.5 [1.0]

ADHD, attention deficit/hyperactivity disorder; SD, standard deviation.
Notes:
[a]Outcomes were measured at the time of data collection.
[b]Symptoms were adapted from the Pittsburg Sleep Quality Index (PSQI) and asked during the past month.
[c]More than one option could be selected (i.e. not mutually exclusive).
[d]Evaluated among participants who reported the number of workdays missed (i.e. excluding participants who answered unknown [*N* 24]).

Symptoms associated with insomnia and other sleep disturbances led to additional treatment, both pharmacological and non-pharmacological, in 80.7% of the participants, with 29.3% reported taking a prescribed medication at least three times a week (Table 4).

Over half (50.4%) of the participants in this subgroup reported that insomnia and other sleep disturbances had "a lot" or "extremely" negative impact on their overall well-being. Furthermore, the proportion of participants who reported insomnia and other sleep disturbances had "a lot" or "extremely" negative impact on their ability to handle daily activities, interpersonal relationships, ability to obtain and/or maintain a job, and concentration and productivity while working/at school activities ranged from 41.1 to 50.4% (Figure 2).

Among employed participants who experienced insomnia or other sleep disturbances ($N = 168$), 44.6% reported missing at least one day of work in the past month due to these symptoms (Table 4). The mean number of workdays missed in the past month as a result of insomnia and other sleep disturbances was 2.5 days (Table 4).

Emotional impulsivity/mood lability—symptom characteristics and impact on quality of life and work productivity

Among the subgroup of participants who experienced emotional impulsivity/mood lability in the past month ($N = 264$), 43.2% had experienced the symptoms for more than 12 months (Table 5). The majority (80.3%) of participants experienced the symptoms often or very often, including feeling irritable and/or easily frustrated (67.8%), feeling overly emotional and/or agitated (63.6%), and having unpredictable mood and/or increased mood fluctuations (50.8%). Symptoms associated with emotional impulsivity/mood lability led to additional treatment, both pharmacological and non-pharmacological, in 84.1% of the participants, with

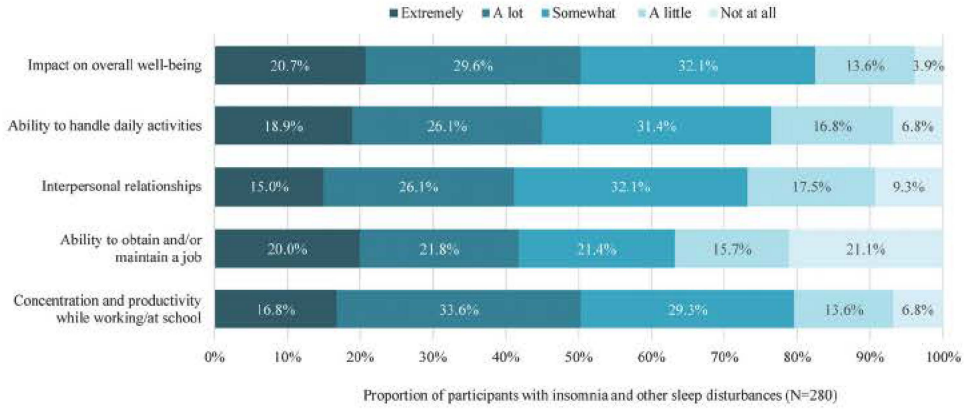

Figure 2. Impact of insomnia and other sleep disturbances on quality of life and work productivity.

Table 5. Characteristics and management of emotional impulsivity/mood lability.

Emotional impulsivity/mood lability[a]	Participants with emotional impulsivity/mood lability *N* 264
Self reported characteristics of emotional impulsivity/mood lability	
Time since started experiencing emotional impulsivity/mood lability, *n* (%)	
<1 month	9 (3.4%)
1 3 months	40 (15.2%)
4 6 months	44 (16.7%)
7 12 months	39 (14.8%)
>12 months	114 (43.2%)
Unknown/prefer not to answer	18 (6.8%)
Frequency of symptoms[b,c]	
Experienced ≥1 symptom often or very often, *n* (%)	212 (80.3%)
Feel irritable and/or easily frustrated	179 (67.8%)
Feel overly emotional and/or agitated	168 (63.6%)
Unpredictable mood and/or increased mood fluctuations	134 (50.8%)
Others have discussed mood fluctuations and/or irritability with respondent	112 (42.4%)
Other symptoms of emotional impulsivity/mood lability	23 (8.7%)
Treatment for managing emotional impulsivity/mood lability	
Used ≥1 treatment during the past month, *n* (%)	222 (84.1%)
Type of treatment[c], *n* (%)	
Prescription medication	175 (66.3%)
≥3 times a week	88 (33.3%)
Over the counter medication	139 (52.7%)
≥3 times a week	45 (17.0%)
Non pharmacological treatment	169 (64.0%)
≥3 times a week	50 (18.9%)
Other	93 (35.2%)
≥3 times a week	25 (9.5%)
Self reported impact of emotional impulsivity/mood lability on work productivity among employed patients	*N* 159
Missed ≥1 day of work in the past month as a result of emotional impulsivity/mood lability, *n* (%)	60 (37.7%)
Number of days of work missed in the past month as a result of emotional impulsivity/mood lability, mean ± SD [median][d]	1.9 ± 0.0 [0.0]

ADHD, attention deficit/hyperactivity disorder; SD, standard deviation.
Notes:
[a]Outcomes were measured at the time of data collection.
[b]Symptoms were adapted from the Wender Reimherr Adult Attention Deficit Disorder Scale (WRAADDS; Emotional Dysregulation Scale) and asked during the past month;
[c]More than one option could be selected (i.e. not mutually exclusive).
[d]Evaluated among participants who reported the number of workdays missed (i.e. excluding participants who answered unknown [*N* 27].

33.3% reported taking a prescribed medication at least three times a week (Table 5).

Almost half (44.7%) of the participants in this subgroup considered emotional impulsivity/mood lability as having "a lot" or "extremely" negative impact on their overall well-being. Furthermore, the proportion of participants who reported insomnia and other sleep disturbances had "a lot" or "extremely" negative impact on their ability to handle daily activities, interpersonal relationships, ability to obtain and/or maintain a job, and concentration and productivity while working/at school activities ranged from 37.9 to 44.7% (Figure 3).

Among employed participants who experienced emotional impulsivity/mood lability (*N* = 159), 37.7% reported missing at least one day of work in the past month due to these symptoms (Table 5). The mean number of workdays missed in the past month as a result of emotional impulsivity/mood lability was 1.9 days (Table 5).

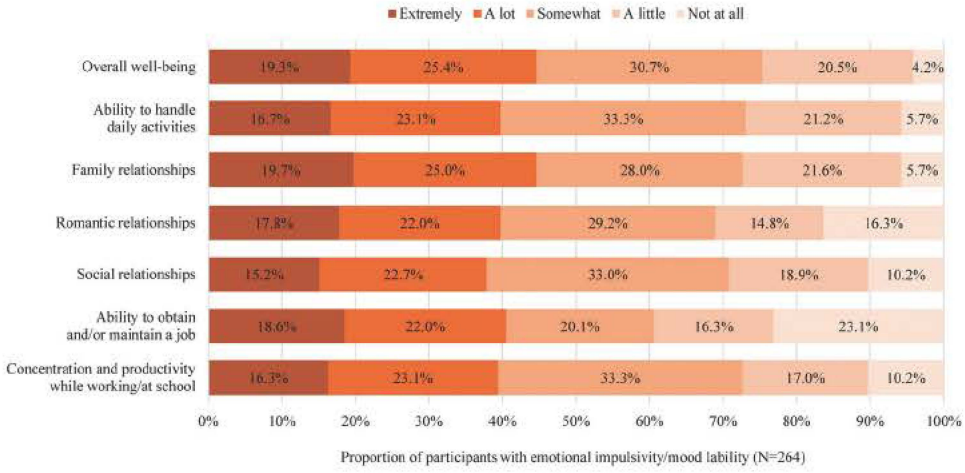

Figure 3. Impact of emotional impulsivity/mood lability on quality of life and work productivity.

Discussion

The current online survey conducted among adults receiving ADHD medications in the US found that over 95% of the participants experienced at least one symptom associated with ADHD/treatment-related adverse side effects in the past month, and these symptoms imposed a substantial impact on the participants' lives. Most participants in the subgroups who experienced insomnia and other sleep disturbances, or emotional impulsivity/mood lability symptoms perceived their symptoms as frequent, persistent, and had a lot or extremely negative impact on their quality of life and work productivity. Previous studies have shown that patients with ADHD experience multiple adverse side effects, some of which may be associated with treatments[1,10]. While existing studies have shown how ADHD/treatment-related adverse side effects attributed to certain observed treatment outcomes (e.g. treatment changes, poor adherence) [24,25], there is scant information on the impact of symptoms associated with ADHD/treatment-related adverse side effects on patients' daily living. The current study quantified the effects of these symptoms and revealed their substantial impact that affected almost all adults with ADHD participating in this study. Specifically, each symptom was associated with a 1.6-point decrease in the overall AAQoL score, implying that the ~8-point clinically important reduction in HRQoL would be reached in the presence of five or more symptoms[23], whereas the average number of symptoms experienced by the participants was 5.8 and was even higher among the subgroups. The number of symptoms was also found to be significantly correlated with a decreased likelihood of being employed and an increased rate of work and activity impairment. Notably, unemployment and productivity loss have previously been shown to constitute the largest proportion of total societal excess cost attributable to ADHD among adults in the US and accounted for US$96 billion in excess economic burden[25]. Considering that not all negative externalities can be translated into dollar amount, the actual burden imposed by these symptoms could be considerable. Meanwhile, it is reasonable to believe that not all symptoms have an equal impact on various outcomes. Although it may be challenging to delineate the effects of specific symptoms from the myriad of symptoms experienced by patients, this study showed that patients with insomnia and other sleep disturbances as well as those with emotional impulsivity/mood lability symptoms tended to have worse outcomes than the overall population, suggesting that the management of these symptoms may be crucial. Collectively, the findings of the current study demonstrate that symptoms associated with ADHD/treatment-related adverse side effects experienced by adults have a substantial impact on the quality of life and work productivity that could be of important clinical and economic consequences.

The frequency of symptoms associated with ADHD/treatment-related adverse side effects reported by participants of the current survey was substantially higher than the 40.3% found in a recent US chart review study among adult patients with ADHD[20]. The apparent discrepancy is likely due to the assessment of these adverse side effects from the physician vs. patient perspective. It is important to note that the documentation of symptoms in medical charts depends largely on patients' initiative to seek medical attention. However, the current survey found that almost a third of participants did not discuss at least one symptom with their healthcare provider for reasons such as decision to self-manage the symptoms, presumption that the healthcare provider could not help with the symptoms, and reluctance to take additional medications. The lack of discussion with physicians may explain the discrepancies between the physician and patient perspectives on patients' experience during treatment and points to the considerable burden borne by patients in real life. The survey also found that patients tended to take additional medications (prescribed or over-the-counter) to manage the ADHD/treatment-related adverse side effects. Polypharmacy not only increases costs and the complexity of the regimens, but also amplifies the risk of complications[26], all of which may lead to negative consequences in patient's quality of life.

Relatively few studies have specifically assessed the impact of symptoms associated with ADHD/treatment-related adverse side effects on the quality of life and work productivity of adults with ADHD. In a post-hoc analysis among 206

adults with ADHD (medication status unknown), those with extreme deficient emotional self-regulation (DESR) symptoms (e.g. temper outbursts, emotional impulsivity) were found to have a lower quality of life, worse social adjustments, and were more likely to have never been married/divorced compared with those without extreme DESR symptoms[27]. In a recent cross-sectional study that included 63 young adults with ADHD (71.4% receiving medication), emotional dysregulation was found to have a negative impact on HRQoL (measured by AAQoL) that was beyond that exerted by core ADHD symptoms[28]. These studies illustrate that emotional symptoms can have a negative impact on the quality of life in adults with ADHD. The current study extends these findings by evaluating the impact of the most common symptoms associated with ADHD/treatment-related adverse side effects on the daily living of adults with ADHD and quantifying the burden exerted by these symptoms.

Considering that all symptoms in this study were captured over the month prior to data collection, the impact of symptoms described herein may represent only a tip of the iceberg in regard to the real burden experienced by patients over their ADHD journey, which often lasts for several years or even over the entire lifespan for some. Thus, it is imperative to address the unmet needs and alleviate patient burden by improving the current management of adult patients with ADHD. In this regard, enhanced physician–patient communication is crucial. There is a need for increased physician awareness to engage discussion with their patients regarding symptoms associated with ADHD/treatment-related adverse side effects and patient satisfaction during the entire treatment course. Patient education on how physicians can help manage these symptoms may also improve treatment experience and outcomes. This may be particularly important for adult ADHD patients, as they may have developed mechanisms over time to cope with these symptoms without seeking external help. Hence, it is important to foster patients' trust in their physicians so that patients feel more comfortable discussing their problems, which will aid physicians in offering appropriate help. Additionally, even though some patients may not discuss certain symptoms with their physicians because they feel the symptoms are manageable, these adverse side effects are having a substantial impact on their quality of life, which may in turn affect their behavior (e.g. being less adherent) and hence treatment outcome. Thus, educating patients on the importance of discussing these symptoms with their physicians would be essential to maximize the potential benefit of treatment. Furthermore, designating more time for each appointment (which currently lasts for ~15–20 min for primary care visits) to allow sufficient time for patients to raise all their concerns and questions and for physicians to assess all potential symptoms is warranted; this may require system changes in payment structure and healthcare resource allocation[29,30]. Collaborative care approach involving interdisciplinary healthcare teams may also be implemented to help improve outcomes of patients with ADHD[31].

Notably, it was observed in the current study that up to 1 in 5 participants displayed reduced adherence to their ADHD treatments due to symptoms associated with ADHD/treatment-related adverse side effects. Thus, more tolerable ADHD treatments with fewer side effects may help improve treatment adherence for this subset of patients. In fact, it has previously been shown that ADHD/treatment-related adverse side effects were important drivers of treatment changes in adults with ADHD, and that suboptimal improvement of symptoms and undesirable side effects were the among the most common reasons for a lack of satisfaction with current treatment options[20]. Additionally, the number of treatment changes has also been associated with increased healthcare costs[32] Therefore, more effective and tolerable treatment options coupled with better management of ADHD/treatment-related adverse side effects may result in increased patient satisfaction and potentially greater adherence and persistence, which may in turn improve quality of life and word productivity and alleviate the clinical and economic burden of adult ADHD.

Limitations

The findings of the current study should be interpreted in light of certain limitations. Respondents of the survey were those accessible through Dynata's panel and who wished to participate in the study; accordingly, the sample may not be representative of the US population of treated adults with ADHD. A large proportion of participants had comorbid anxiety disorder and depression; hence, the findings may not be generalizable to milder or unselected ADHD cases with different comorbidity profiles. Additionally, data analyzed for this study relied on participants' recollection of past events. Although the survey was designed to ask about events that occurred in the recent past as much as possible, recall bias or errors in the accuracy or completeness of respondents' recalled experiences may have occurred. Furthermore, given it would be difficult for the participants to distinguish treatment-related adverse side effects from other symptoms experienced, this survey collected information on all symptoms experienced that could be associated with ADHD/treatment-related adverse side effects. Thus, the rate of treatment-related adverse side effects experienced in real-world settings could not be accurately captured.

Conclusions

Findings from this study suggest that symptoms associated with ADHD/treatment-related adverse side effects are common among adults treated for ADHD in the US, and these symptoms were significantly correlated with reduced HRQoL, reduced probability of being employed, and increased activity impairment. Furthermore, the subsets of participants with insomnia and other sleep disturbances and emotional impulsivity/mood lability perceived the symptoms as having a substantial negative impact on their quality of life and work productivity. Thus, better management of ADHD/treatment-related adverse side effects and more tolerable treatment options have the potential to improve quality of life and work productivity among adults with ADHD.

Transparency

Declaration of funding

Financial support for this research was provided by Otsuka Pharmaceutical Development & Commercialization, Inc. The study sponsor was involved in several aspects of the research, including the study design, the interpretation of data, the writing of the manuscript, and the decision to submit the manuscript for publication.

Declaration of financial/other relationships

JS is an employee of Otsuka Pharmaceutical Development & Commercialization, Inc. AC received research support from Allergan, Takeda/Shire, Emalex, Akili, Ironshore, Arbor, Aevi Genomic Medicine, Neos Therapeutics, Otsuka, Pfizer, Purdue, Rhodes, Sunovion, Tris, KemPharm, Supernus, and the U.S. Food and Drug Administration; was on the advisory board of Takeda/Shire, Akili, Arbor, Cingulate, Ironshore, Neos Therapeutics, Otsuka, Pfizer, Purdue, Adlon, Rhodes, Sunovion, Tris, Supernus, and Corium; received consulting fees from Arbor, Ironshore, Neos Therapeutics, Purdue, Rhodes, Sunovion, Tris, KemPharm, Supernus, Corium, Jazz, Tulex Pharma, and Lumos Pharma; received speaker fees from Takeda/Shire, Arbor, Ironshore, Neos Therapeutics, Pfizer, Tris, and Supernus; and received writing support from Takeda/Shire, Arbor, Ironshore, Neos Therapeutics, Pfizer, Purdue, Rhodes, Sunovion, and Tris. MC, MGL, RB, and AG are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Otsuka Pharmaceutical Development & Commercialization, Inc. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

MC, MGL, RB, and AG contributed to study conception and design, collection and assembly of data, and data analysis and interpretation. JS and AC contributed to study conception and design, data analysis and interpretation. All authors reviewed and approved the final content of this manuscript.

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Data availability statement

The data analyzed in this study are subject to Health Insurance Portability and Accountability Act privacy restrictions and are not publicly available. De identified data could be made available by the corresponding author upon reasonable request.

Ethics statement

This study was conducted in accordance with the applicable ethical regulations and was exempt from full review by the Western Copernicus Group Institutional Review Board, as the survey did not collect any participant identifying information. Participant consent was collected at the time of participation.

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Symptoms associated with ADHD/treatment-related adverse side effects and their impact on quality of life and work productivity in adults with ADHD

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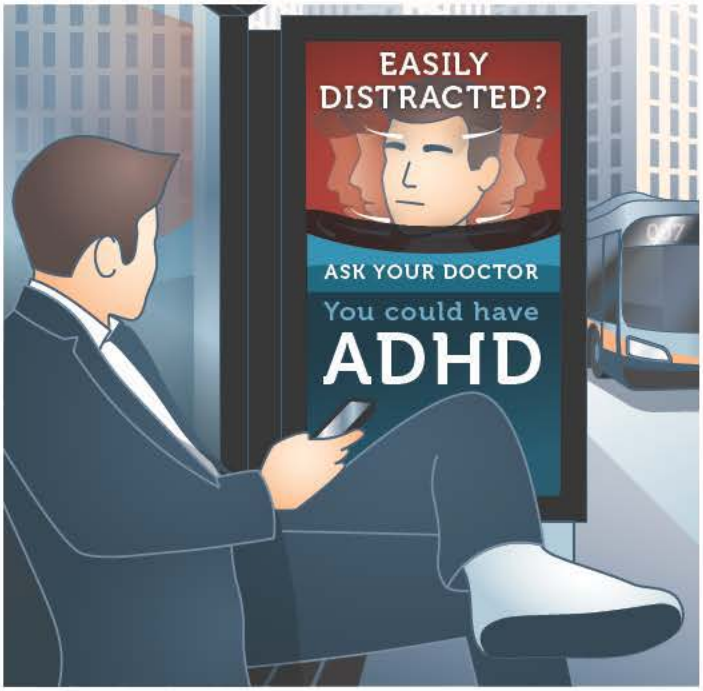
ADHD in adults



Vignette: *Your 23-year-old male primary care patient went to a walk-in clinic after watching a TikTok video about ADHD. He was referred to a family physician with a special interest in ADHD. Now in your office, he presents a letter recommending treatment with lisdexamfetamine (Vyvanse) - mainly on the basis of his score on the Adult ADHD Self-Report Scale. Although you did not request this opinion, your patient would like you to prescribe medication. You are aware of intense promotion for Vyvanse.*[1,2] ***How should you respond?***

Summary and Conclusions

- **Overdiagnosis of adult ADHD and promotion of drug treatments are driving a concerning prescribing epidemic for stimulant drugs and atomoxetine.**
- **Reliable diagnosis is complex and requires documentation of childhood symptoms. ADHD rating scales cannot substitute for detailed clinical assessment.**
- **Evidence from randomized controlled trials about drug efficacy and safety is derived mostly from industry-funded studies lasting ≤ 12 weeks that measured subjective symptom scales. We know little about important functional outcomes such as social and employment success and overall health.**
- **Amphetamines and methylphenidate do not enhance or normalize ability to learn or apply knowledge in everyday life.**
- **Many adults experience adverse effects from ADHD medications. Stimulants can induce pharmacological tolerance, dependence, and problems with withdrawal and misuse.**
- **If you prescribe for adult ADHD, monitor patients within 1-2 weeks for initial assessment of safety and improvement in functions important to success in family life and work. Then reassess regularly.**
- **Lisdexamfetamine (Vyvanse) is substantially more expensive than other stimulants, but has no proven advantage.**

Attention deficit hyperactivity disorder (ADHD) is a cognitive and behavioural neurodevelopmental condition, originally recognized and treated only in children. It is a highly heritable but heterogeneous phenotype, rather than a categorical distinction of "disorder" versus "health."[3] As for all psychiatric conditions, no simple diagnostic test is available. Competent diagnosis requires a comprehensive family, gestational, and developmental history, and observation over time. **To diagnose adult ADHD, documented symptoms must have occurred during childhood.** While questionnaires are necessary and psychometric tests are ancillary, alone they are insufficient bases for valid diagnosis.

Since 2008, the Therapeutics Initiative has released three Therapeutics Letters and a drug assessment on ADHD pharmacotherapy for children and adolescents.[4-7] In 2012, we highlighted the rising trend of ADHD diagnoses in younger children starting primary school.[8] This Letter examines evidence on adult ADHD, with an emphasis on drug treatments.

Although most evidence is short-term and of questionable quality, it surpasses what's available for alternatives like cognitive behavioural therapy. **We find that challenges in diagnosis and limited long-term evidence continue to hinder evidence-based decision-making and patient safety.**

A July 2023 multidisciplinary webinar available with open access from the British Medical Journal explores what we know and do not know about ADHD and its treatment.[9] Presentations cover challenges in appropriate medical diagnosis and treatment, including the weak precision of diagnostic scales and rapidly increasing non-clinical "diagnosis" via social media – especially TikTok.

Overdiagnosis and overtreatment in children

Increasing medication of children and suspected overdiagnosis was first reported from the USA in 1999, but is now well recognized.[10-13] In British Columbia, we demonstrated in 2012 a potent birth-month effect for diagnosis and treatment of pediatric ADHD.[8] Compared with children born in January (earlier in a calendar year) boys born from September through December were 41% more likely, and girls 77% more likely to be prescribed a stimulant. Related to age at first school entry, Quebec investigators term this phenomenon the "medicalization of immaturity."[14] Also reported in France and the United States,[15,16] it was confirmed from 12 countries by a 2019 systematic review that noted only a weak relative age effect in Denmark, where school entry is often delayed for relatively young children.[17] During the Covid-19 pandemic, reported ADHD symptoms increased in children.[18]

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This relative age effect can result in a life-long diagnosis of a mental disorder attributable solely to age, rather than true illness. A Dutch analysis of methylphenidate prescriptions from 1995-2015 concluded that dramatically increased incidence was not related to new evidence, and that starting doses often exceeded Dutch guidelines.[19]

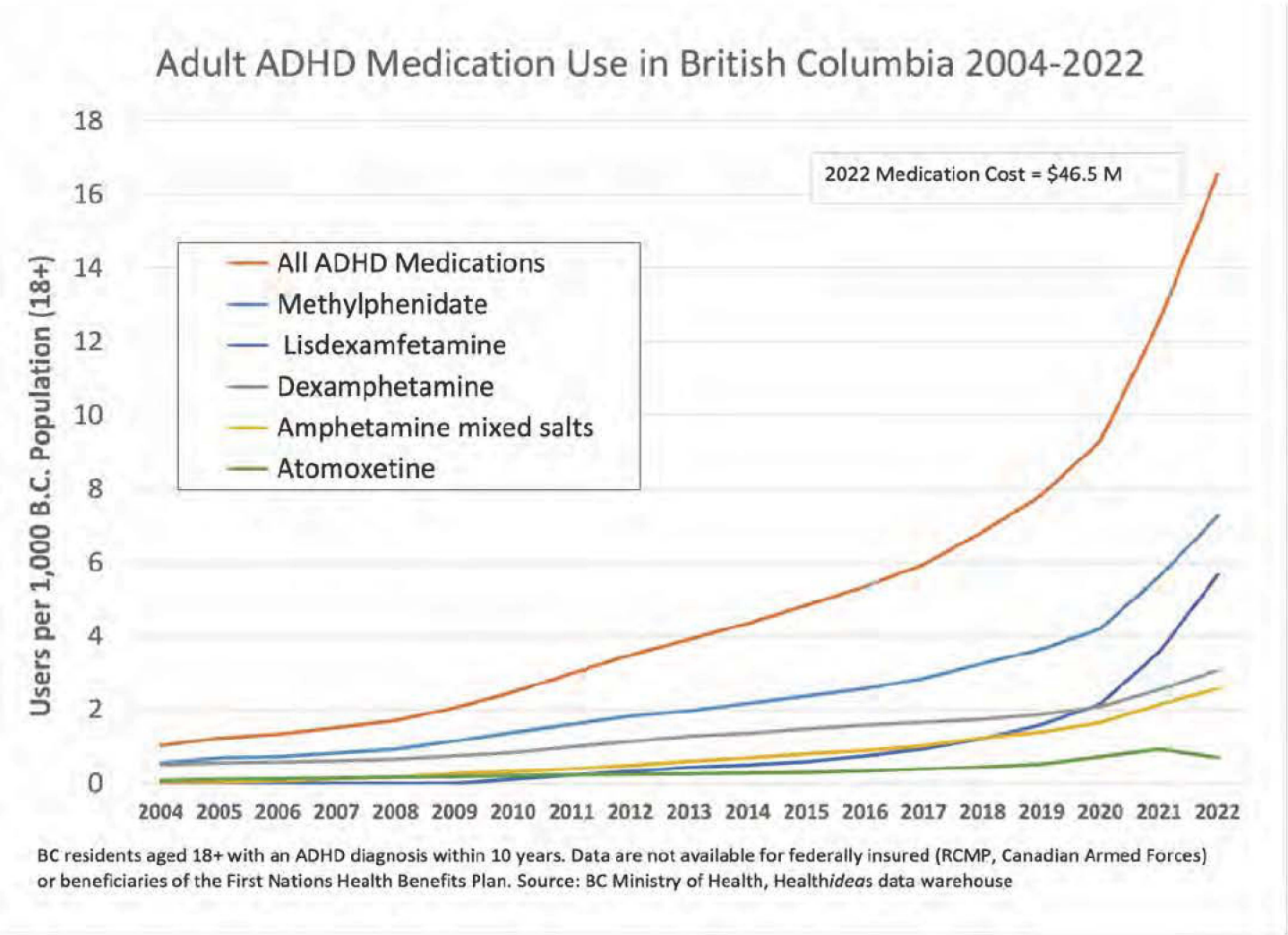
How common is adult ADHD?

In children diagnosed with ADHD, some symptoms are known to persist for up to 16 years into young adulthood.[20] Estimates of persistence vary widely from 4 to 77%, depending on the assessment method.[21] In 2022, Canadian adult prevalence was estimated at 2.9%.[22]

By 2010, adult ADHD drug treatment rates ranged from 0.03%-0.5% in western Europe, Asia and Australia, and reached 1.42% in North America.[23] A Lancet Psychiatry editorial highlighted frequent overdiagnosis and stimulant overuse in wealthy countries, but also noted potential undertreatment.[24] Prescriptions for Canadian adults, primarily methylphenidate and amphetamines, quadrupled between 2005 and 2015, especially among young adult males.[25]

From 2015 to 2019, ADHD drug sales data from 64 countries showed a **10% yearly increase in per capita consumption; in Canada the annual increase was over 11%.**[26] About one in nine children and adolescents in Canada and the USA used ADHD medication, mostly methylphenidate and amphetamines, far higher than in other countries. If this trend persists, adult stimulant treatment rates will also increase.

Our analysis of utilization data (Figure) shows a dramatic increase in adult ADHD medication use in British Columbia from 2004 through 2022. Data are for prescription drugs with a Health Canada indication for treatment of adult ADHD, dispensed to BC residents aged 18+ with a diagnosis code for ADHD in the prior 10 years. Total ADHD medication use in adults has increased at an annual compounded rate of 17% since 2004, from 1 user per 1000 adult population in 2004 to 16.5 users per 1000 adult population in 2022. Combined public and private expenditures for these medications in British Columbia reached a total of $46.5 million in 2022.



BC residents aged 18+ with an ADHD diagnosis within 10 years. Data are not available for federally insured (RCMP, Canadian Armed Forces) or beneficiaries of the First Nations Health Benefits Plan. Source: BC Ministry of Health, Health*ideas* data warehouse

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How reliable is diagnosis?

Current diagnosis of ADHD depends partly on subjective rating scales and questionnaires that are subject to cognitive bias. Questionnaires can result in false "diagnoses," especially when the questions reflect typical daily human experiences and challenges, or reported symptoms overlap with other conditions like anxiety or major depression or different learning disabilities.[21,24,27] Self-scoring tools cannot substitute for careful clinical diagnosis based on comprehensive history and observation in multiple contexts including home, school, and work. Establishing the presence of characteristic symptoms by age 12 may require a search for documentation such as old school report cards, or at least completion of a retrospective rating scale by people who knew the patient during childhood.

The Adult ADHD Self-Report Scale (ASRS-V1.1) is a symptom checklist consisting of the 18 DSM-IV-TR criteria, considered valid for congruence between self-rating and clinician-rating and recommended by the Canadian ADHD Resource Alliance (CADDRA) Guidelines 2021.[28] Toronto's Centre for Addiction and Mental Health (CAMH) recommends the American Psychiatric Association's Diagnostic and Statistical Manual V (DSM-V) criteria for adult ADHD diagnosis[29] and the Weiss Functional Impairment Rating Scale (WFIRS) which has been validated psychometrically.[30]

ADHD symptom rating scales may be useful to suggest a detailed clinical assessment. But patients and practitioners should not confuse them with diagnostic tools, especially because **ADHD does not require urgent diagnosis**. Like CADDRA Guidelines, a *"This Changed My Practice"* article by an experienced British Columbia psychiatrist suggests that a positive screen warrants 3-4 follow-up visits before diagnosis.[31]

Overlap between ADHD and substance use disorders is well recognized.[28] For successful treatment and to avoid creating new problems, it is crucial to evaluate for alcohol, cannabis, opioid, stimulant and other substance use disorders before prescribing medication with potential for misuse.

Pharmacotherapy with stimulants and atomoxetine

Most adults treated for ADHD receive amphetamines or methylphenidate; far fewer take atomoxetine (Figure). This Letter does not discuss guanfacine or bupropion, which are not approved in Canada for adult ADHD. Amphetamines and methylphenidate enhance the central norepinephrine and dopamine systems and can induce pharmacological tolerance and dependence during long-term use. Product monographs include black box warnings about the potential requirement for increasing doses, physical and psychological dependence, and possible misuse, including "diversion" for non-medical use as "recreational" or "performance enhancing" drugs.[32-34] **The home page of Vyvanse drug manufacturer Takeda's US promotional website shows this prominently**, stating: *"Vyvanse has a high chance for abuse and may cause physical and psychological dependence. Your healthcare provider should check you for signs of abuse and dependence before and during treatment."*[2] Compared with stimulants, the selective norepinephrine uptake inhibitor atomoxetine is believed to have a lower risk of diversion, but also increases blood pressure and heart rate, and more frequently causes anorexia, nausea, vomiting or somnolence.[35] The manufacturer warns about the potential for suicidal thinking or attempts.[36]

Harms demonstrated in clinical trials that are significantly more common with methylphenidate than with placebo, but similar to amphetamines, include appetite suppression, dry mouth, headache, palpitations, insomnia, sexual dysfunction, anxiety, feeling jittery, irritable or agitated, and aggression.[37] Apart from sudden cardiac death, acute psychosis may be the most serious potential complication. United Kingdom drug regulators noted an increased reporting of "psychosis/mania" in 3 trials of methylphenidate vs placebo (methylphenidate 3% vs placebo 1%).[37] In a large database study of people ages 13-25 treated with prescription stimulants in the US between 2014-2015, new psychosis was estimated to affect about 1 in 660 patients. Amphetamine prescriptions appeared more likely than methylphenidate to precede a new diagnostic code for psychosis (HR 1.64; 95% CI 1.31 to 2.09).[38] This type of evidence does not establish causation, and the psychosis is usually self-limited.[39] However, a new study of the World Health Organization pharmacovigilance database also raises concern about stimulant-induced psychotic delusions.[40] Misuse of stimulants for sports performance can cause seizures, myocardial infarction, cardiomyopathy, and even sudden death.[41]

BC's Provincial Academic Detailing Service summarized pharmacology, formulations and clinical considerations for drugs licensed for ADHD in Canada.[35] A table of interactions illustrates potential pharmacokinetic and pharmacodynamic issues.

Why treat adult ADHD?

Treatment goals should focus on reasonable expectations for functional improvement and quality of life. For example, improved academic and work performance, stable employment, interpersonal relationships, and overall health outrank the surrogate outcome of rating scale scores. Prescribing decisions should involve informed patient consent, including a clear understanding of potential harms and the paucity of evidence about long-term effects. Patients should appreciate, as for other drugs affecting the brain, that stimulant dependence and withdrawal symptoms are possible.[32-34,42,43]

Amphetamines and methylphenidate do not enhance or normalize ability to learn or apply knowledge in everyday life. They do not improve – but may impair – short-term acquisition of information and "cognitive flexibility" in adults with ADHD compared with control subjects.[44,45] For example, in a complex simulation problem intended to mimic tasks of daily life (optimizing the value of items placed in a knapsack) stimulants increased efforts made by volunteers aged 18 to 35 (N=40), but significantly decreased the quality of results.[46] The 2022 systematic review of extended-release methylphenidate summarizes some uncertainties about its cognitive effects.[37]

Evidence for pharmacotherapy from short-term RCTs in adults

Evidence about drug therapy in children and adolescents remains controversial. For example, a recent unconflicted review of systematic reviews (SRs) and meta-analyses (MAs) concluded that "the evidence claiming that methylphenidate is beneficial in treating children and adolescents with ADHD was of very low certainty."[47] The uncertainty of evidence is reflected in the absence of stimulants from the World Health Organization's 2023 Model Lists of Essential Medicines for Children or

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Adults.[48] WHO twice rejected an application to include methylphenidate, most recently after review in 2021.[49]

Evidence for pharmacotherapy of adult ADHD is derived almost exclusively from randomized controlled trials (RCTs) lasting ≤ 12 weeks. Most systematic reviews and meta-analyses (SR/MAs) conclude that evidence for efficacy and safety from short-term treatment is weak, and limited mostly to rating scale scores. They all conclude that we know very little about long-term drug treatment. Meta-analytic results from different measurement scales are often reported as standardized mean differences (SMD, Cohen's d), which cannot be translated into a likelihood or magnitude of success for clinically important functional outcomes.

A 2022 Cochrane SR/MA of **methylphenidate extended-release (ER) formulations** that includes unpublished information identified 24 relevant RCTs (N=5,066, median age 36, median treatment duration 8 weeks).[37] Most trials excluded people with psychiatric co-morbidity; 90% of participants were enrolled in industry-funded trials. A single trial (N=419) followed patients for 52 weeks, and 2 short trials (N=314) used active comparators (atomoxetine, bupropion). The Cochrane reviewers assessed evidence as "very low-certainty" for "small-to-moderate" effects of methylphenidate vs. placebo for ADHD symptoms rated by participants, investigators, and family. There was no effect on days missed from work. Methylphenidate increased the risk for all adverse effects (RR 1.27, 95% CI 1.19 to 1.37) and increased the point estimate for serious adverse events (RR 1.43, 95% CI 0.85 to 2.43). A 2021 Cochrane SR/MA of **immediate-release (IR) methylphenidate** vs placebo identified 10 RCTs, N=497 adults. The authors concluded there was at best "very low-certainty evidence" for improvements on rating scales.[50]

In 2020, Canadian reviewers published a SR and network MA (SR/NMA) of **any drug treatment** of adult ADHD. This included 81 RCTs, mostly industry funded, total N=12,423.[51] Trial durations were 2-52 weeks, mostly of methylphenidate (36 RCTs), amphetamines (21 RCTs), and atomoxetine (20 RCTs). Reviewers assessed only 5 of 81 RCTs as at low risk of bias, and ¾ of the RCTs lasted < 12 weeks. Many participants had previously received prescription stimulants. From trials lasting > 12 weeks, the reviewers assessed clinical scale responses and (when reported) functional outcomes, including quality of life, executive function, driving behaviour, and a broad range of safety outcomes. Differences in symptom scores were small, subject to bias from treatment unblinding, and when limited to studies at low risk of bias, the authors found "no significant difference between ADHD pharmacotherapy and placebo." They considered certainty of evidence for all outcomes "very low to low." No trial > 12 weeks assessed executive function.

A 2018 Cochrane SR/MA of **dexamphetamine**, **lisdexamfetamine**, and **mixed amphetamine salts** for adult ADHD identified 19 RCTs (N=2,521, mean age 35, mean duration 5.3 weeks).[52] Only 3/19 RCTs exceeded 8 weeks, and only one trial was publicly funded. This review found "low- to very low-quality evidence" that amphetamines reduced patient and clinician-rated ADHD symptoms, compared with placebo, but they were not better for retention in treatment. It found no evidence for a beneficial dose response. Amphetamines increased treatment withdrawal due to adverse effects (RR 2.69, 95% CI 1.63 to 4.45). The review also found no difference between IR and ER formulations for any outcome.

In 2018 Lancet Psychiatry published a very detailed SR/NMA of 133 RCTs of stimulants and non-stimulants in children, adolescents and adults.[53] The authors also sought unpublished trials and information. For people ≥ 18, they assessed efficacy based on clinician ratings at 12 weeks. Reviewers identified 51 RCTs in adults (N=8,131 for efficacy analyses). Data were insufficient to assess treatment for > 12 weeks, and the authors identified very frequent risks of bias. The underlying RCTs assessed efficacy using heterogeneous symptom scales, but the meta-analysis did not include functional outcomes beyond the clinician's subjective impression of improvement. For "tolerability" (withdrawal due to adverse effects), placebo was better tolerated than drug treatment. In contrast, at 12 weeks "acceptability" was better for amphetamines than placebo: the proportion who withdrew for any reason was lower (OR 0.68, 95% CI 0.49 to 0.95).

Overall, we find the available RCT results impossible to translate to clear estimates of harms and benefits that a clinician could find helpful during shared decision making with a patient. Systematic reviews generally find low certainty of evidence about benefits, a broad range of potential harms from drug therapy, and low external validity – the relation of results from RCTs to everyday clinical practice.

Evidence from observational studies

A population based study of Swedish national registries found that in people treated during 2006 with prescription stimulants, criminality was reduced during 2009.[54] Using the same data sources, these authors also reported that medication appeared to reduce the increased risk of serious transport accidents associated with ADHD in males.[55] **Cochrane review authors pointed to contradictory evidence from observational studies, leaving uncertainty about the true effects of medications.**[37]

Less reassuring is a recent meta-analysis of observational studies investigating the association between ADHD medications and risk of any cardiovascular disease (CVD).[56] The authors identified 7 studies including adults. They estimated relative risk of CVD in children and adolescents (RR 1.18; 95% CI 0.91-1.53), in younger and middle-aged adults (RR, 1.04; 95% CI 0.43-2.48) and in older adults (RR 1.59, 95% CI 0.62-4.05). Increased CVD risk appears limited to people with a prior CVD history. The investigators interpret their findings as suggesting "no statistically significant association between ADHD medication use and the risk of any cardiovascular events" but caution that "a modest risk increase could not be excluded, especially for the risk of cardiac arrest or tachyarrhythmias" and note limited information about long-term use.

Do ADHD medications affect substance use disorders?

Authors of the landmark Multimodal Treatment Study of ADHD in 579 children (MTA) followed participants recruited in 1994-1996 for up to 16 years to assess adult substance use (by confidential self-reporting) at a mean age of 25.[57] They found no evidence that prescription stim-

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ulant treatment in childhood either increased or decreased frequent use of alcohol, cigarettes, marijuana, or other substance use in young adulthood. An earlier MA reached similar conclusions.[58] The Swedish national registry study of people treated with stimulants in 2006 found no association with increased substance abuse in 2009, but a possible decrease.[59] A study of US health care claims from 2005-2014 also found evidence that while patients were taking ADHD medications (compared with periods when they were not), concurrent substance-related events such as emergency department visits were less frequent: for males (OR 0.65; 95% CI, 0.64-0.67), and females (OR 0.69, 95% CI 0.67-0.71).[60]

Evidence also limited for non-drug treatments

Evidence for non-pharmacological treatments such as cognitive behavioural therapy (CBT) is derived from very small RCTs. A 2020 SR/MA of 9 RCTs of CBT (N=386) claims superiority for ADHD symptoms of CBT vs no treatment or vs active control treatments.[61] However there was extensive bias. Authors of the 2018 Lancet Psychiatry SR/NMA consider the lack of reliable evidence for non-drug treatments "highly problematic, in particular for those patients who do not opt for, or are unable to tolerate a pharmacologic treatment."[62] **Their 2022 protocol for a new SR/NMA of drug and non-drug treatments for adult ADHD promises results as early as 2024**. But it notes that unavailability of individual patient data and other data quality issues may preclude learning about effects on outcomes such as clear functional improvement.

In British Columbia, the Cognitive Behaviour Therapy (CBT) Skills Group Program provides publicly funded 8-week CBT sessions, including for adults with ADHD.[63] Accredited CBT training is also available for physicians.

Is lisdexamfetamine better than other stimulants?

Health Canada approved lisdexamfetamine (Vyvanse) in 2013 to treat ADHD in adults. It is a prodrug, converted to d-amphetamine in the bloodstream by a red blood cell enzyme.[64] The putative efficacy advantage of a smoother d-amphetamine concentration profile in blood has not been demonstrated, although it can be simulated by delaying an equivalent dose of IR d-amphetamine by 1 hour.[65] Compared with ER mixed amphetamine salts (Adderall XR), unpublished experiments demonstrated by 2006 a similar (1-2 hour) delay in T_{max}.[66-67]

The patent holder (Shire) sponsored a 2010 publication suggesting that as a prodrug requiring activation in the bloodstream, lisdexamfetamine might be less liable to intravenous or intra-nasal ("snorted") abuse.[68] However, Shire terminated prematurely in 2009 after enrolment of only 3 participants a more definitive experiment to compare subjective "drug liking" of the prodrug vs mixed amphetamine salts (Adderall XR). The experiment was halted "based on a non-safety related business priority decision."[69]

Health Canada's 2009 Summary Basis of Decision for approving lisdexamfetamine for children indicates no evidence of a therapeutic advantage over ER mixed amphetamine salts, and no dose response above 30mg/d for efficacy assessed by rating scales. No evidence was then available for treatment longer than 4 weeks.[70] The 2023 product monograph refers to a 6-week withdrawal RCT (lisdexamfetamine vs placebo, N=116) sponsored, designed, analyzed, and written by the manufacturer (Shire).[33,71] Amongst responders who had taken lisdexamfetamine for at least 6 months, people randomized to amphetamine withdrawal (placebo) rated their symptoms worse. Another Shire-controlled 10 week RCT claims slight improvement on a **self-rated** executive function scale in adults taking lisdexamfetamine vs placebo (N assessed = 154/161 randomized).[72] Adverse events such as anorexia, dry mouth, headache, feeling jittery or irritable and insomnia were much higher in the lisdexamfetamine group, so that patient blinding is likely impossible.

There is no evidence for an efficacy or safety advantage of lisdexamfetamine over other amphetamine formulations. However, Vyvanse costs up to 5-fold more than generic ER methylphenidate, and more than amphetamines.[35]

Vignette resolution: *After discussion, you advise your patient that before proposing any diagnosis or considering alternative treatments, you require follow-up visits to obtain a detailed history and collateral information. Surprised by the "Important Safety Information" you showed him on the vyvanse.com website[2] - including the possibility of physical and psychological dependence - he accepts your cautious approach. Colleagues report similar experiences, and agree that your Division of Family Practice should arrange continuing education to facilitate careful diagnosis and responsible treatment of ADHD in your community.*

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Multiple experts and primary care clinicians reviewed the draft of this Therapeutics Letter for factual accuracy, and to ensure it is relevant to clinicians.

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