Therapeutics Initiative
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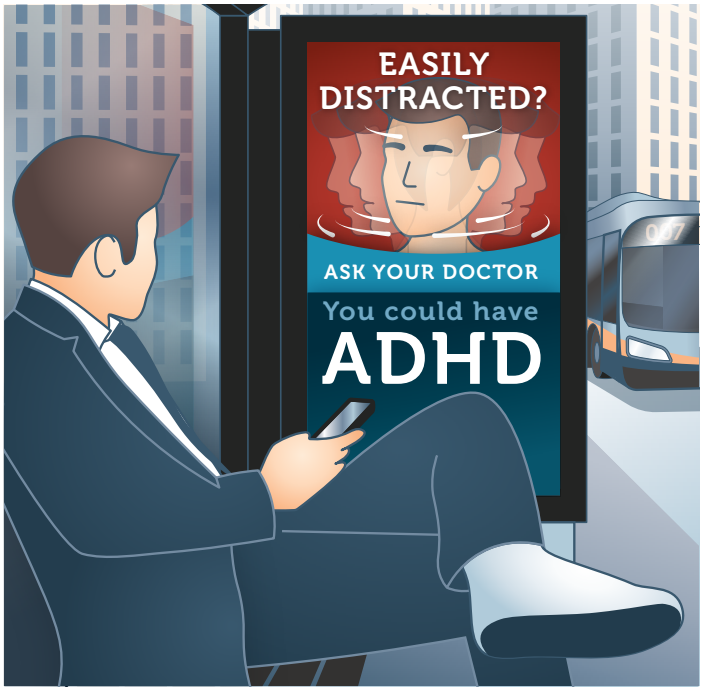
ADHD in adults



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]

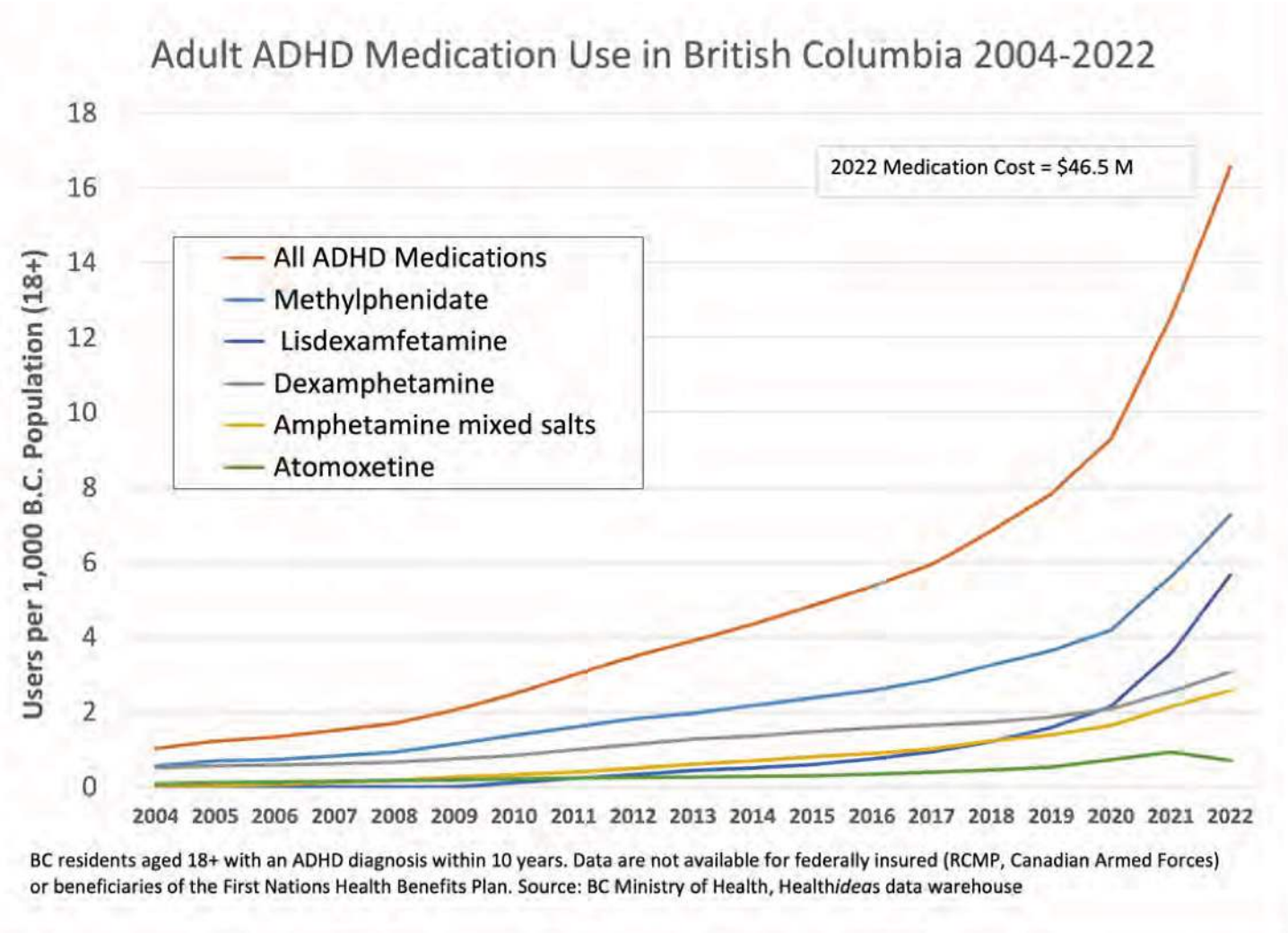
How common is adult ADHD?

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.*

Disclaimer

All inferences, opinions and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the data stewards.

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