Medicines Adverse Reactions Committee

Meeting date	13/03/2025	Agenda item	3.2.3
Title	**Stimulant medicines used for attention deficit hyperactivity disorder (ADHD) and the risk of Parkinson's disease**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Methylphenidate hydrochloride	Ritalin and Ritalin LA	Novartis New Zealand Ltd
	Rubifen and Rubifen LA	AFT Pharmaceuticals Ltd
	Concerta	Janssen-Cilag (New Zealand) Ltd
	Methylphenidate Extended Release	Teva Pharma (New Zealand) Limited
Dexamfetamine sulfate	Dexamfetamine	Noumed Pharmaceuticals Limited
Lisdexamfetamine dimesylate	Vyvanse	Takeda New Zealand Limited

Not available: Delmosart, Methylphenidate (Teva).

PHARMAC funding	Methylphenidate, dexamfetamine and lisdexamfetamine are funded under Special Authority.
Previous MARC meetings	None.
International action	None.
Prescriber Update	Not applicable.
Classification	Controlled Drug B2 (methylphenidate and lisdexamfetamine) Controlled Drug B1 (dexamfetamine)
Usage data	Funded community dispensings in 2023: • 1.2 million dispensings of methylphenidate. • 75 thousand dispensings of dexamfetamine. • No data for lisdexafetamine – funded as of December 2024.
Advice sought	**The Committee is asked to advise:** • Whether regulatory action is needed at this time in relation to a possible risk of Parkinson's disease with stimulant medicines used for ADHD.

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1 PURPOSE

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by difficulties with attention, hyperactivity and impulsiveness. Central nervous system (CNS) stimulant medicines (methylphenidate, dexamfetamine and lisdexamfetamine) are the first-line pharmacological treatment for ADHD, acting by inhibiting synaptic reuptake of dopamine and noradrenaline.

This memo reviews the available information on a possible association between central nervous system (CNS) stimulant medicines used in (ADHD) and Parkinson's disease. The review was prompted by correspondence received by Medsafe from a psychiatrist expressing concerns about this risk on the basis of possible biological plausibility and the publication of a cohort study that found an increased risk of basal ganglia and cerebellum disorders with stimulant exposure.

2 BACKGROUND

2.1 Stimulant medicines used in the treatment of ADHD

2.1.1 Indications

The stimulant medicines methylphenidate, dexamfetamine and lisdexamfetamine are approved in New Zealand for the treatment of ADHD as part of a comprehensive treatment plan. Dexamfetamine is approved for treatment of children aged three years and older only, while methylphenidate and lisdexamfetamine are indicated for children aged six years and older and adults [1-3].

ADHD is a neurodevelopmental disorder characterised by difficulties with attention, hyperactivity and impulsiveness with onset before 12 years of age. Stimulant medicines are the first-line pharmacological treatment for ADHD [4].

Immediate and sustained release methylphenidate (Rubifen, Rubifen SR, Ritalin and Ritalin SR) and dexamfetamine sulfate are also indicated for the treatment of narcolepsy. Methylphenidate may also be used off-label[1, 2, 5].

Prescribing restrictions

Currently methylphenidate, dexamfetamine sulfate and lisdexamfetamine dimesilate may only be prescribed for ADHD by a practitioner with a vocational scope of practice of paediatrics or psychiatry, or a practitioner acting on their written recommendation [6].

2.1.2 Background on neurotransmitters and ADHD [7]

The pathophysiology of ADHD is complex but is thought to involve lowered synaptic levels of dopamine and noradrenaline. Stimulant medicines are thought to act by inhibiting presynaptic reuptake of dopamine and noradrenaline, thereby increasing extracellular levels. Dexamfetamine and lisdexamfetamine (a longer-acting dexamfetamine prodrug) also inhibit the action of monoamine oxidase (MAO) and facilitate the release of catecholamines [1-4].

The overall effects of stimulants include improved executive functions, decision making, emotion and reward processing.

Dopamine

Dopamine is a monoamine neurotransmitter and catecholamine. Dopamine is synthesised from L-tyrosine, primarily in the substantia nigra pars compacta and ventral tegmental area. Different types of dopamine receptors (D1, D2, D3, D4 and D5) are involved in different functions and are distributed differently throughout the brain. Dopamine is also converted to noradrenaline.

Dopamine reuptake from the synaptic cleft is mediated by dopamine transporters. Dopamine is then degraded by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) to inactive metabolites.

Dopamine acts through several pathways (figure 1). The nigrostriatal pathway extends from the substantia nigra and to the striatum (as part of fronto-striatal circuits) and is involved in regulation of movement. The mesolimbic pathway extends from the ventral tegmental area to the nucleus accumbens and other limbic structures and is involved in reward processing. The mesocortical pathway extends from the ventral tegmental area to the cerebral cortex and is involved in cognition and memory.

Dopamine is involved in many complex functions, such as movement, reward processing, memory, attention, sleep regulation, motivation, and many others [8].

Noradrenaline

Noradrenaline is a monoamine neurotransmitter and catecholamine. It is synthesised from dopamine by dopamine beta-hydroxylase. Noradrenergic pathways are highly distributed throughout the brain. These originate from the locus coeruleus and connect to cortical areas, including the prefrontal cortex, and cerebellum (figure 1). Noradrenaline acts on alpha-1-, alpha-2- and beta-adrenergic receptors. It is removed from the synaptic cleft via reuptake by noradrenaline transporters. In the CNS, noradrenaline is involved in arousal, alertness and attention.

Figure 1: Dopaminergic and noradrenergic pathways [7]

Source: Parlatini V, Bellato A, Murphy D, et al. 2024. From neurons to brain networks, pharmacodynamics of stimulant medication for ADHD. Neuroscience & Biobehavioral Reviews 164: 105841. DOI: doi.org/10.1016/j.neubiorev.2024.105841.

Altered neurotransmission in ADHD [7]

ADHD has been associated with dysfunction in the nigrostriatal, mesocortical and mesolimbic pathways, which are involved in executive functions and affect/behavioural regulation. Noradrenergic dysfunction has also been implicated in ADHD.

Studies of neurotransmission in people with ADHD have focussed on striatal dopamine transporters as a marker of dopamine neuronal integrity. Dopamine transporters modulate the magnitude and duration of dopamine response via reuptake from the synaptic cleft. Studies have found decreased and increased dopamine transporter density in people with ADHD. A meta-analysis found that these differences may be explained by history of stimulant treatment, with lower density being associated with being naïve to stimulant

treatment. Other studies suggest reduced post-synaptic dopamine receptors and dopamine synthesis, supporting altered dopaminergic transmission in ADHD.

In the prefrontal cortex, dopamine transporter density is lower, and reuptake is likely mediated by noradrenaline transporters. Genotype-dependent differences in the noradrenaline transporter binding potential have been observed between adults with ADHD and controls in the thalamus and cerebellum. An epigenetic analysis also found reduced transcriptional activity and noradrenaline transporter binding potential in subcortical regions in ADHD.

Other neurotransmitter systems may also be involved in the pathophysiology of ADHD. The role of serotonin and altered balance between excitatory and inhibitory (glutamatergic and GABAergic) neurotransmission are emerging areas of interest.

2.1.3 Pharmacology of stimulant medicines used in ADHD [7]

Methylphenidate exists as two enantiomers (d-threo and l-threo-methylphenidate). The therapeutic effects are due to the d-enantiomer. Methylphenidate binds allosterically (at a different site to the endogenous substrate) to dopamine transporters and noradrenaline transporters, inhibiting dopamine and noradrenaline reuptake and increasing their availability (figure 2)..

Amphetamines also exist as d- and l-isomers. The d-isomer binds more potently to dopamine transporters while the d- and l-isomers bind to noradrenaline transporters with equal potency. Amphetamines are competitive inhibitors (bind to the same site as the endogenous substrate). They act in a similar way to methylphenidate to increase availability of dopamine and noradrenaline (figure 2). At supratherapeutic doses (ie, in abuse), amphetamines induce the release of dopamine which is linked to euphoria and addiction.

Dexamphetamine consists of amphetamine d-isomer. Lisdexamfetamine is a dexamfetamine prodrug that is hydrolysed in the blood, resulting in a different pharmacokinetic profile and longer duration of action.

Figure 2: Mechanism of action of stimulants at synaptic level [7]

The function of dopamine (DA) and norepinephrine (NE) transporters (DAT and NET) is to reuptake DA and NE after they have been released in the synaptic cleft (left panel). Methylphenidate (MPH) acts by blocking both DAT and NET through allosteric binding (ie, it binds them on a different site from that of the endogenous neurotransmitter). Conversely, amphetamines (AMP) block DAT and NET by binding on the same site of the endogenous neurotransmitter, thus acting as a competitive inhibitor. As a result, they both inhibit catecholamines reuptake and increase their availability in the synaptic cleft. However, at high doses, AMPs also induce more complex changes within catecholaminergic neurons (right panel).

Source: Parlatini V, Bellato A, Murphy D, et al. 2024. From neurons to brain networks, pharmacodynamics of stimulant medication for ADHD. Neuroscience & Biobehavioral Reviews 164: 105841. DOI: doi.org/10.1016/j.neubiorev.2024.105841

The mechanism of action for stimulants in ADHD is not fully understood. By inhibiting dopamine and noradrenaline reuptake, stimulants increase the endogenous dopamine stimulation of D1-receptors and the noradrenaline-dependent activation of post-synaptic α2A-receptors, enhancing the function of the prefrontal cortex by reducing 'noise' and enhancing 'signal' within glutamatergic circuits. Other complex mechanisms are likely involved, such as optimisation of the balance between tonic and phasic catecholamine release. This may reduce attentional resources needed for cognitive performance, reduce distractibility and increase perception of events as salient.

Stimulant-induced increased availability of dopamine and noradrenaline has been associated with long-term symptomatic improvement in adults with ADHD, with improvements in executive functions, decision making, emotion and reward processing. However, methylphenidate has been shown to produce similar improvements in attention in individuals with or without an ADHD diagnosis.

It has also been hypothesised that methylphenidate may impact serotonergic and GABAergic signalling. Amphetamines may also inhibit the synaptic vesicular amine transporter (VMAT2) and weakly inhibit monoaminoxidase (MAO).

Emerging areas of research into mechanisms of action of stimulants include modulation of brain-derived neurotropic factor (BDNF), effects on cellular processes (eg, genetic transcription, apoptosis, and release of proinflammatory cytokines), effects on brain iron levels, brain regional structural and functional changes, and functional connectivity changes. There is limited evidence on beneficial effects of long-term treatment on brain function and whether changes persist after stopping treatment.

2.1.4 Risks of stimulant treatment [1-3]

The most frequently reported adverse reactions with stimulants include insomnia, gastrointestinal symptoms, anxiety, decreased appetite and headache.

Growth and appetite suppression

Studies have shown reduced appetite and weight reduction in adults and children during treatment with stimulants. Long-term use of stimulants has been associated with growth suppression in children. Weight and appetite should be monitored throughout treatment. Stimulants should be discontinued if the patient is not growing or gaining weight as expected.

Abuse and misuse

Stimulants have a high abuse potential and may cause psychological dependence. Stimulants should not be used in patients with drug or alcohol dependence.

Cardiovascular risks

Stimulant medicines may increase blood pressure and heart rate. These changes are not usually clinically significant but may be significant in individual patients.

Sudden cardiovascular death has been reported in patients with structural cardiac abnormalities or other serious cardiac problems who were taking stimulant medicines. A causal relationship with stimulants has not been established.

Cardiac risk factors and family history should be evaluated before starting treatment with stimulants. Blood pressure and cardiovascular status should be reviewed regularly throughout treatment.

Stimulant medicines are contraindicated in patients with serious cardiovascular conditions, for example, severe hypertension, arterial occlusive disease, congenital heart disease, cardiomyopathies, myocardial infarction, and arrythmias.

Psychiatric disorders

Stimulants may exacerbate pre-existing psychotic disorders and bipolar disorder. Stimulants can precipitate psychotic or manic symptoms, aggression or hostility. Stimulants are contraindicated in severe agitated states.

Psychiatric symptoms and history should be evaluated before commencing treatment. Patients should be monitored for unusual behaviour or thought changes, including suicidality.

Tourette's syndrome

Stimulants may exacerbate tics and Tourette's syndrome. Stimulants are contraindicated in individuals with personal or family history of Tourette's syndrome.

Seizure threshold

Stimulants may decrease seizure threshold in patients with a history of seizures, and rarely in patients without a history of seizure. Stimulants should be discontinued if seizures occur.

Glaucoma

Stimulants are contraindicated in glaucoma. There have been reports of elevation of intraocular pressure and glaucoma associated with methylphenidate treatment.

Interactions

Coadministration of stimulants with serotonergic medicines is not recommended as this may cause serotonin syndrome.

As stimulants inhibit dopamine reuptake, pharmacodynamic interactions may occur with dopaminergic medicines such as tricyclic antidepressants (TCAs) and dopamine antagonists such as antipsychotics. Concomitant use of methylphenidate with antipsychotics may increase the risk of extrapyramidal symptoms when there is a change in dosage of either medicine.

Concomitant use of stimulants and monoamine oxidase (MAO) inhibitors is contraindicated due to the risk of hypertensive crisis, which can be fatal.

Stimulants may oppose the effects of antihypertensives.

2.2 Parkinson's disease [9]

Parkinson's disease is a neurodegenerative condition defined by bradykinesia combined with either rest tremor, rigidity or both, that progressively worsens with increasing disability. Symptoms and disease progression vary widely between individuals.

2.2.1 Signs and symptoms

Bradykinesia includes decrement of sequential movements, reduced arm swing, increased stride time variability and freezing of gait. Other motor symptoms include bulbar dysfunction, manifesting as dysarthria and dysphagia, poor balance and falls.

Non-motor symptoms include constipation, urinary dysfunction, sleep disturbances, pain, cognitive decline, fatigue, personality changes, visual dysfunction, depression, anxiety and hallucinations/psychosis.

Onset of Parkinson's disease is preceded by a long prodromal period. Prodromal symptoms include constipation (most common), hyposmia (earliest symptom), sleep disturbances (including REM sleep behaviour disorder), pain (including asymmetric vague shoulder pain), fatigue and depression. Recognition of prodromal symptoms does not currently offer treatment advantages leading to improved prognosis.

2.2.2 Pathophysiology

The pathophysiology of Parkinson's disease involves many complex interacting mechanisms. It appears to involve aggregation of α-synuclein, dysfunction of mitochondria, lysosomes/vesicle transport, synaptic transport issues, and neuroinflammation. This results in accelerated death of dopaminergic neurons. However, other motor and non-motor circuits are also involved. Loss of nigrostriatal dopamine cells causes a gradient of

striatal dopamine depletion producing an imbalance between direct (facilitatory) and indirect (inhibitory) pathways through the basal ganglia, resulting in bradykinesia.

The link between early gut symptoms and later neurodegeneration is not fully understood. The Braak hypothesis remains under debate but proposes that Parkinson's disease is triggered when a foreign agent enters via nasal cavity and gut, initiating Lewy pathology, producing the prodromal gastrointestinal and olfactory symptoms and spreading via olfactory and vagus nerves to the brain. A multimodal imaging study to identify dysfunction of the gut, heart, brainstem, and nigral projections in people with Parkinson's disease conceptualised two types of disease: a body-first type with early gut and cardiac involvement, and a brain-first type with pathology starting in the nigrostriatal system. It is not clear whether Lewy pathology is the cause of neurodegeneration or whether it is a neuroprotective response to neurodegeneration.

2.2.3 Epidemiology

The incidence of Parkinson's disease increases with age. However, age of onset is younger than 65 years in 25% of cases and younger than 50 years in 5-10% of cases. The term young-onset Parkinson's disease is used where age of onset is younger than 40 years, or in some cases, younger than 50 years.

Incidence is increasing rapidly, even after adjustment for population ageing. Advances in accurate diagnosis provide a partial explanation. The increased incidence is disproportionately high in some countries with high income or GDP growth.

In women, the incidence is lower with an older age of onset , compared with men. However, women have a higher risk of developing dyskinesia and treatment response fluctuations. Men have a greater risk of cognitive decline.

2.2.4 Risk factors

Parkinson's disease can be genetic or sporadic. Genetic Parkinson's disease represents a minority of cases (5-10% of cases). Several genetic associations have been identified and are associated with younger onset of disease.

Various environmental and lifestyle factors have been linked with the development of Parkinson's disease but in some cases the literature is conflicting. Toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can produce a clinical picture of Parkinson's disease. Environmental exposure to pesticides is thought to have a plausible relationship. Head injury is also a known risk factor.

Smoking, coffee drinking, anti-inflammatory drug use, high plasma urate levels, and physical activity appear to have negative associations with Parkinson's disease, but causal relationships have not been established.

Comments

There is a suspected association between ADHD and Parkinson's disease. See section 3.1.1 for a description of the review article 'Is attention-deficit/hyperactivity disorder a risk syndrome for Parkinson's disease?'.

2.2.5 Diagnosis

Parkinson's disease is not a single entity. Many different causes can lead to a similar clinical presentation, described as parkinsonism.

Diagnosis is made on the basis of clinical signs and symptoms, as well as exclusion of signs and symptoms that are suggestive of an alternative diagnosis (figure 3). The International Parkinson and Movement Disorder Society diagnostic criteria for Parkinson's disease (MDS-PD) state that parkinsonism (bradykinesia in combination with rest tremor and/or rigidity) is an essential criterion. The balance of supportive criteria (eg, good response to dopaminergic therapy) and red flags for atypical parkinsonism (eg, early bulbar dysfunction) assist the diagnosis. Absolute exclusion criteria rule out a diagnosis of Parkinson's disease (eg, ataxia).

Figure 3: Clinical diagnostic process [9]

Source: Bloem BR, Okun MS and Klein C. 2021. Parkinson's disease. The Lancet 397(10291): 2284-2303. DOI: 10.1016/S0140-6736(21)00218-X (accessed 4 March 2025).

2.2.6 Pharmacological treatments [10]

Several medicines are used in Parkinson's disease to increase the availability of dopamine and reduce motor symptoms (figure 4).

Dopamine-receptor agonists (ropinirole, lisuride, or pramipexole) are often the initial treatment. Dopamine agonists cause fewer motor complications in long-term treatment compared with levodopa, but the overall motor performance improves slightly less. The dopamine-receptor agonists are associated with more adverse effects than levodopa. Apomorphine may be used in advanced disease with unpredictable 'off' periods with levodopa treatment.

Levodopa is the amino acid precursor to dopamine and acts by replenishing striatal dopamine. It is administered in combination with a dopa-decarboxylase inhibitor (carbidopa or benserazide) which reduces peripheral conversion of levodopa to dopamine. This limits gastrointestinal and cardiovascular adverse effects and enables effective levels of dopamine in the brain with lower doses of levodopa.

It was previously thought that levodopa could be toxic and hasten disease progression by promoting oxidative stress. Studies have not found any evidence of this and do not support postponing symptomatic treatment in people who experience disability [9].

Levodopa treatment is associated with potentially troublesome motor complications including response fluctuations and dyskinesias. Response fluctuations are characterised by large variations in motor performance, with normal function during the 'on' period, and slowness and restricted mobility during the 'off' period. 'End-of-dose' deterioration with progressively shorter duration of benefit also occurs.

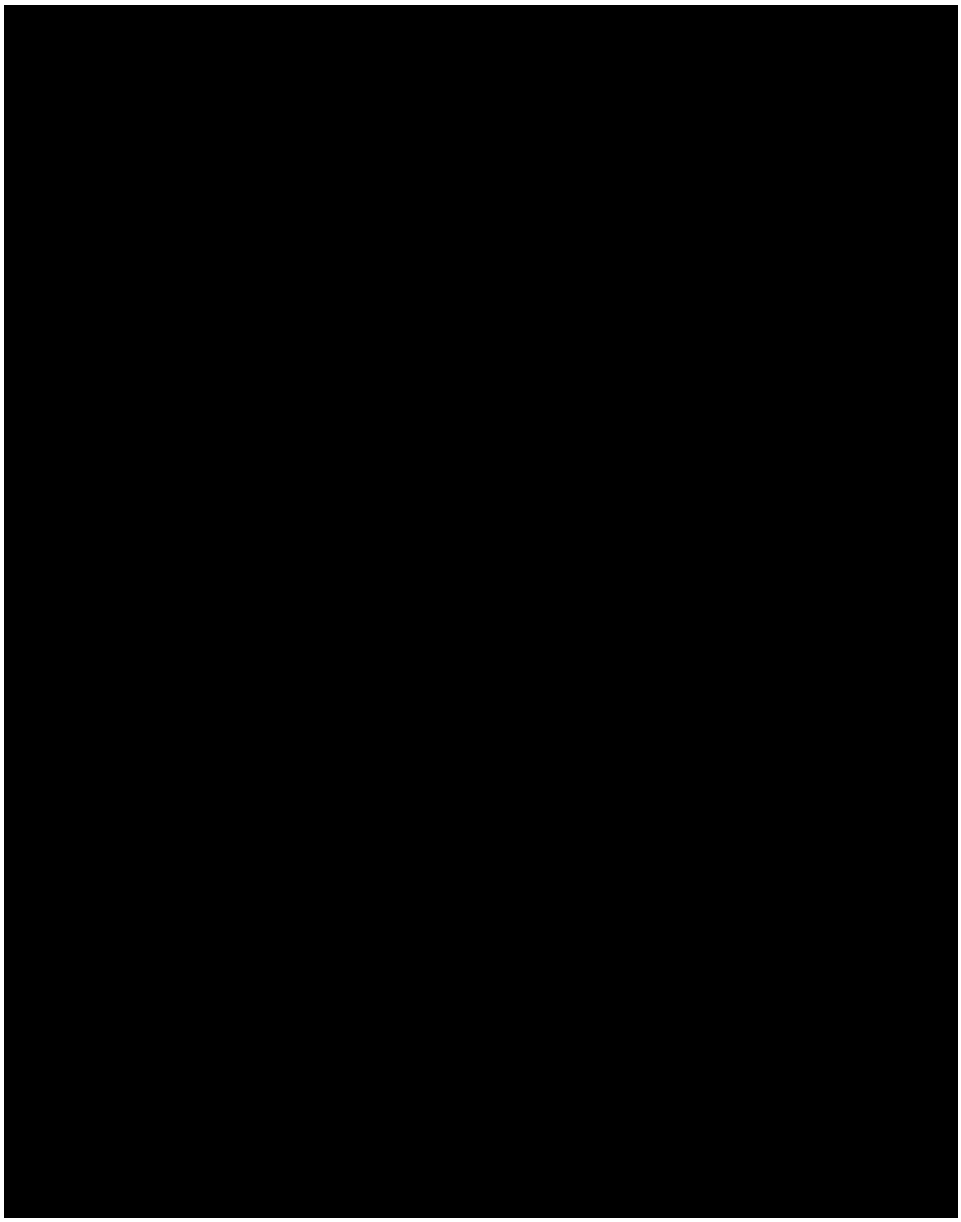
Both dopamine-receptor agonists and levodopa can cause impulse control disorders such as pathological gambling, hypersexuality, excessive buying and binge eating. Hypotensive reactions, excessive daytime sleepiness and sudden onset of sleep can occur at the beginning of treatment.

Monoamine-oxidase B inhibitors (selegiline and rasagiline) are used in conjunction with levodopa to reduce 'end-of-dose' deterioration in advanced Parkinson's disease or in patients with mild motor symptoms.

Catechol-O–methyltransferase (COMT) inhibitors (entacapone and tolcapone) prevent the peripheral breakdown of levodopa. They are also used in 'end-of-dose' deterioration with levodopa.

Amantadine is a weak dopamine agonist that may be useful in reducing levodopa-induced dyskinesia.

Figure 4: Sites of action of medicines for Parkinson's disease [9]



Various neurotransmitters that are involved with their respective working mechanism are described. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. COMT=catechol O-methyltransferase. MAO-B=monoamine oxidase type B. NMDA=N-methyl-D-aspartate. SNRI=serotonin–noradrenaline reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.

Source: Bloem BR, Okun MS and Klein C. 2021. Parkinson's disease. The Lancet 397(10291): 2284-2303. DOI: 10.1016/S0140-6736(21)00218-X (accessed 4 February 2025).

2.2.7 Prognosis

Parkinson's disease is a progressive condition, although the rate of deterioration varies considerably across different individuals. Life expectancy is decreased; however, many people live for decades with Parkinson's disease. Common causes of death include aspiration pneumonia and complications following a hip fracture.

2.3 Data sheets

New Zealand and international product information for methylphenidate, dexamfetamine, lisdexamfetamine and mixed amfetamine salts do not list a risk of Parkinson's disease or parkinsonism.

Dyskinesia, ataxia, tremor, choreoathetoid movements, and tics are listed adverse events in the methylphenidate, dexamfetamine and lisdexafetamine data sheets [1-3]. The methylphenidate data sheet states that concomitant use of methylphenidate with antipsychotics is not recommended due to counteracting mechanisms of actions, and may increase the risk of extrapyramidal symptoms [2].

The Vyvanse (lisdexamfetamine) and Adderall XR (mixed amfetamine salts) United States prescribing information state 'Acute administration of high doses of amphetamine (d- or d, l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fibre damage in rodents. The significance of these findings to humans is unknown' [3, 11].

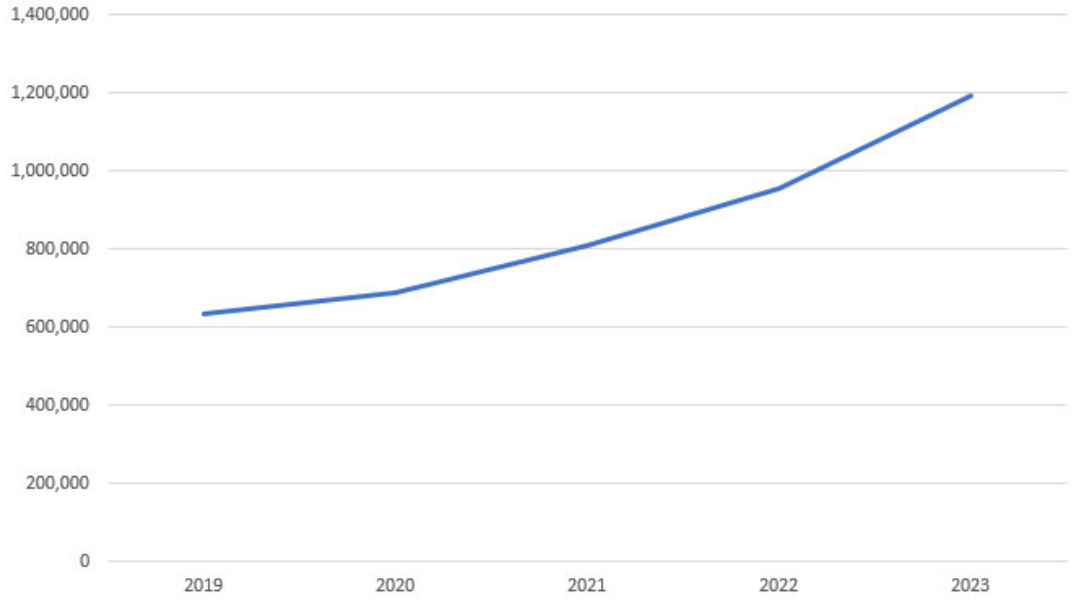
2.4 Usage

The usage of methylphenidate and dexamfetamine has increased between 2019 and 2023 (figure 5 and figure 6). Usage of dexamfetamine is relatively low (~75,000 dispensings in 2023) compared to methylphenidate (~1.2 million dispensings in 2023). No data is available for lisdexamfetamine as it was an unfunded medicine between 2019 and 2023. Lisdexamfetamine has become a funded medicine as of December 2024.

Comments

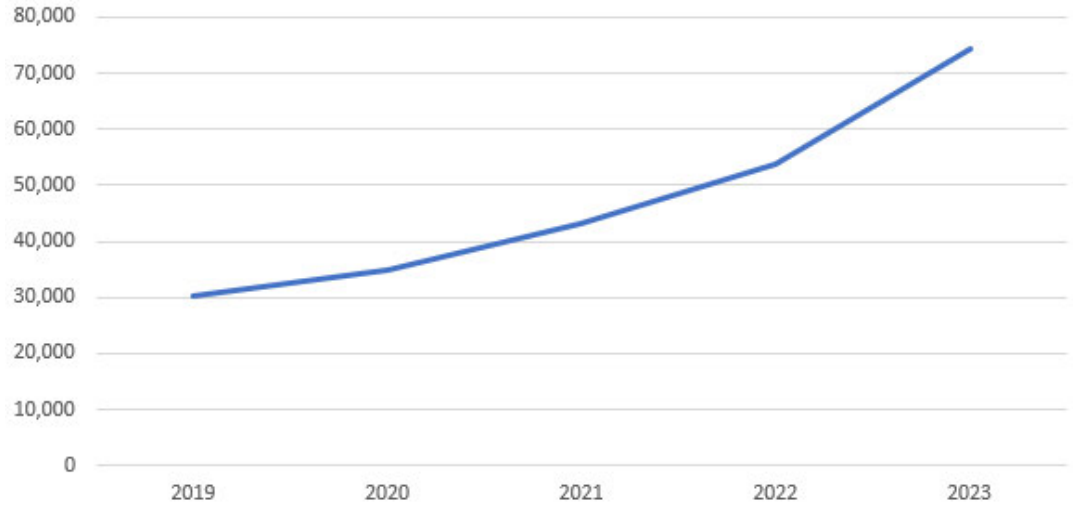
Future usage patterns may be impacted by current methylphenidate supply shortages and the recent funding of lisdexamfetamine.

Figure 5: Total number of funded community dispensings of methylphenidate (all funded strengths and formulations) between 2019 and 2023.



Source: Pharmaceutical Data web tool version 12 September 2024. Data extracted from the Pharmaceutical Collection on 23 July 2024. URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 15 January 2025).

Figure 6: Total number of funded community dispensings of dexamfetamine between 2019 and 2023.



Source: Pharmaceutical Data web tool version 12 September 2024. Data extracted from the Pharmaceutical Collection on 23 July 2024). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 15 January 2025).

According to a published analysis of dispensing patterns in New Zealand, dispensings of ADHD medicines increased from 188 per 100,000 population in 2006 to 819 per 100,000 population in 2022. The dispensing rate for adults increased from 55 per 100,000 in 2006 to 556 per 100,000 in 2022, representing a 10-fold increase (figure 7). The analysis found that despite increases, dispensing rates for ADHD remain lower than prevalence estimates [12].

Figure 7: Dispensing of ADHD medicines in New Zealand per 100,000 population [12].

Source: Beaglehole B, Jarman S and Frampton C. 2024. Dispensing of attention-deficit hyperactivity disorder medications for adults in Aotearoa New Zealand. N Z Med J 137(1594): 23-30. DOI: 10.26635/6965.6392 (accessed 15 January 2025).

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Is attention-deficit/hyperactivity disorder a risk syndrome for Parkinson's disease? Baumeister, 2021. [13]

This review article discusses the evidence around a suspected association between Parkinson's disease and ADHD, including stimulant treatment. The article is attached as **Annex 1.**

Commonalities between ADHD and Parkinson's disease

There is evidence that Parkinson's disease and ADHD share structural, chemical, and functional alterations of mesencephalic dopaminergic neurons.

Hyperechogenicity of the substantia nigra on transcranial sonography is seen in Parkinson's disease and is correlated with increased risk of subsequent development of Parkinson's disease. Hyperechogenicity of the substantia nigra has also been observed in ADHD. Parkinson's disease and ADHD also have similar structural changes in projection regions of mesencephalic dopaminergic neurons.

Striatal dopamine transporters may be increased or decreased in ADHD. A meta-analysis found that dopamine transporter density was higher in previously medicated ADHD patients and lower in stimulant-naïve ADHD patients. Deficits in mesolimbic dopamine transporters have also been observed in ADHD patients. The mesolimbic dopamine pathway is involved in mediating reward processing, which may be impaired in both Parkinson's disease and ADHD.

There may be parallels between the neuropsychological features of Parkinson's disease and ADHD. Both conditions may involve impairments in core domains of executive function, including working memory, cognitive flexibility, inhibitory control, and planning.

Stimulant neurotoxicity

It has been suggested that a relationship between ADHD and Parkinson's disease may be partly explained by toxic effects of stimulants on dopaminergic neurons.

Animal and human research indicates that methamphetamines and other amphetamines are toxic to mesencephalic dopaminergic neurons. In animal studies, prolonged exposure to methamphetamine/amphetamine has shown cell loss in the substantia nigra, degeneration of striatal dopaminergic axon terminals, decreases in striatal dopamine and dopamine transporter, and decreased dopamine transporter function. Most animal data relate to high stimulant doses; however, there is some evidence of this effect with exposures comparable to clinical use.

Illicit use of methamphetamine/amphetamine is associated with increased parkinsonism, and increased risk of later development of Parkinson's disease, including younger onset of disease. Echogenicity of the substantia nigra is increased in abstinent adult users, and the degree of echogenicity is positively correlated with duration of use and cumulative dose. Postmortem studies of methamphetamine/amphetamine users show decreased markers of striatal dopamine function.

There is less evidence of neurotoxicity with methylphenidate. Studies of high doses of methylphenidate in rats and rhesus monkeys showed no effect on striatal dopamine. However, a study in adult mice found a short-term decrease in striatal dopamine. Studies in young rats and mice have shown changes in dopamine function, raising the possibility that methylphenidate may be more neurotoxic during brain development. However, studies in rhesus monkeys designed to mimic prolonged developmental exposure in children found no effect on dopamine transporters or receptors.

The reasons for differential toxicity between methamphetamine/amphetamine and methylphenidate are unclear. Stimulant neurotoxicity may involve oxidative stress, excitotoxicity, and mitochondrial dysfunction and protein misfolding. Misfolding of α-synuclein is involved in the pathogenesis of Parkinson's disease.

Amphetamine binds preferentially to the N-terminus of α-synuclein and enhances misfolding, whereas MPH binds to both the N- and C-termini, resulting in a loop structure that inhibits misfolding.

Possible linkage mechanisms for an association between ADHD and Parkinson's disease

It is possible that both ADHD and Parkinson's disease can be causally related to a common exposure, such as traumatic brain injury, antipsychotic use, tobacco, or exposure to environmental toxins.

Genetic factors are another possible link. An analysis of nine ADHD candidate genes involved in regulation of monoamine transmitters showed no association with Parkinson's disease. However, ADHD is associated with copy-number variations in PARK2. PARK2 mutations are present in around 10 to 20% of cases of young-onset, sporadic Parkinson's disease.

A relationship with Lewy body pathology has also been explored. Antecedent ADHD symptoms may be increased in Lewy body dementia. Experimental models of traumatic brain injury show increased α-synuclein expression. However, the nature of the relationship between Lewy pathology and neurodegeneration is unclear.

Finally, it has been hypothesised that stimulant medicines damage dopaminergic neurons, directly causing parkinsonism or exacerbating damage caused by other factors. The review discussed the study by Curtin et al (see section 3.1.2 below) found that any use of stimulant medicines was associated with a six to eight-fold increase in the risk for basal ganglia and cerebellar diseases. A possible alternative explanation to exposure-related neurotoxicity is a relationship between stimulant use and more severe ADHD.

The risk was also significantly increased in ADHD patients without stimulant exposure, although misclassification bias was noted as a possible factor in this finding. The risk was increased eight-fold in patients exposed to methylphenidate only, despite the fact methylphenidate appears to be less neurotoxic than methamphetamine/amphetamine.

The outcome of basal ganglia and cerebellar diseases included Parkinson's disease, secondary Parkinson's disease, other basal ganglia diseases and essential tremor. This was intended to increase sensitivity but may have decreased specificity. The association was not statistically significant when limited to diagnoses of Parkinson's disease.

3.1.2 Increased risk of diseases of the basal ganglia and cerebellum in patients with a history of attention-deficit/hyperactivity disorder. Curtin et al (2018) [14]

This retrospective cohort study aimed to determine whether ADHD or dopaminergic ADHD treatments alter the risk of diseases of the basal ganglia and cerebellum, including Parkinson's disease. This article is attached as **Annex 2.**

Methods

Statewide medical records from 1996 to 2016 were retrieved from the Utah Population Database (UPDB). Study inclusion criteria were: (1) at least 20 years of age on 31 December 2011 or date of last follow-up, if earlier and (2) resident of Utah on or after 1 January 1996 (baseline) as determined by vital records and other demographic data in the UPDB. Individuals with HIV or a history of substance use disorders were excluded.

Individuals with ADHD or other hyperactivity disorders were assigned to the ADHD cohort based on ICD-9 codes. A non-ADHD cohort was created at a ratio of 5:1 and matched based on sex and birth year. Non-ADHD subjects were required to have follow-up in Utah from baseline until at least the index diagnosis date of their respective matched ADHD patient.

The authors measured time from baseline to an index diagnosis on or before 31 December 2016 of any adult-onset basal ganglia and cerebellum (BG&C) diseases including Parkinson's disease, secondary parkinsonism, other degenerative diseases of the basal ganglia, and essential or other forms of tremor. Study subjects with no diagnosis of BG&C diseases who died on or before 31 December 2016 were treated as having a competing

cause of death and right censored at their death date. Subjects alive on 31 December 2016 (or at last follow-up, if earlier) who did not develop BG&C diseases were right censored.

A Cox proportional hazards model was used to calculate a hazard ratio (HR) estimate of the risk of an incident diagnosis of BG&C diseases in ADHD patients compared with non-ADHD subjects. To account for matching of non-ADHD to ADHD individuals, separate hazard functions (ie, stratified Cox regressions) were specified for each matched group. A competing risk of death was incorporated. The model included covariate adjustment for race/ethnicity, psychotic conditions and smoking.

Results

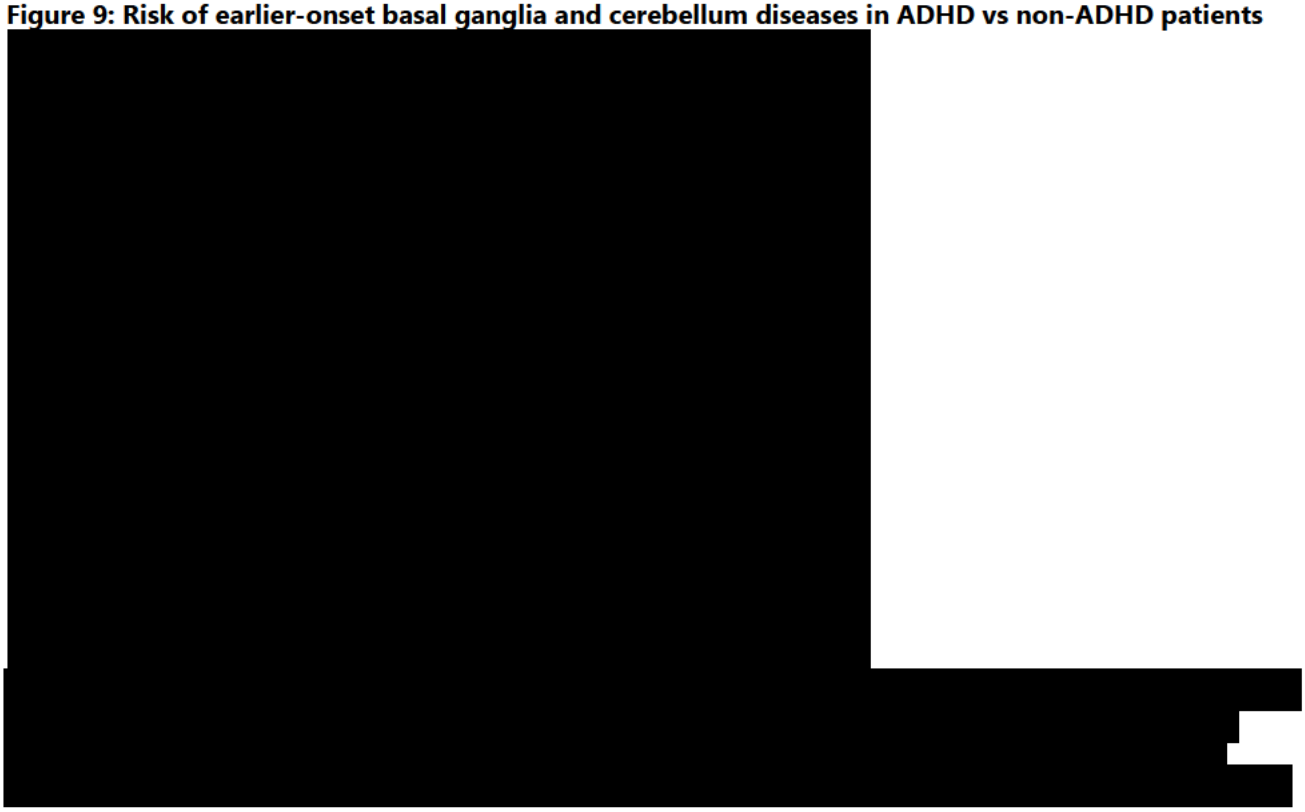
The ADHD cohort consisted of 31,769 patients, of which 4,960 (15.6%) had known stimulant treatment (55% mixed amphetamine salts, 39% methylphenidate, 9% both) who were individually matched to 24,792 non-ADHD subjects. The overall matched non-ADHD cohort consisted of 158,790 people. ADHD was diagnosed more often in men than in women. The median index age at which a diagnosis of ADHD first appeared in the EMR was 26 years. It is likely that many patients had ADHD onset at a much younger age. A similar majority of patients in both cohorts were white, consistent with the Utah population. ADHD patients were more likely to have died during the study and were more likely to have had a psychotic condition diagnosed.

In non-ADHD subjects and ADHD patients, the rates of incident BG&C diseases were 0.19% and 0.52%, respectively. Onset was between ages 21 and 66 years. Overall, ADHD was associated with a 2.4-fold increased risk of BG&C diseases (aHR 2.4, 95% CI: 2.0–3.0; P < 0.0001). Compared to non-ADHD patients, ADHD patients treated with stimulants had a greater risk (aHR = 6.0, 95% CI: 3.9–9.1; P < 0.0001) than those without known stimulant treatment (aHR = 1.8, 95% CI: 1.4–2.3; P < 0.0001). ADHD patients who were only prescribed methylphenidate had an eightfold increased risk of BG&C diseases compared to their corresponding non-ADHD subjects (aHR = 8.0, 95% CI: 4.2–15.1; P < 0.0001) (figure 8).

Figure 8: Risk of basal ganglia and cerebellum diseases in ADHD vs non-ADHD patients.

Risk of younger-onset BC&G disease was similar between ADHD patients without known stimulant treatment and ADHD patients overall. The risk of BC&G diseases was increased in the stimulant-treated group (aHR = 8.6, 95% CI: 4.8–15.6; P < 0.0001) (figure 9).

Figure 9: Risk of earlier-onset basal ganglia and cerebellum diseases in ADHD vs non-ADHD patients



There were 96 non-ADHD (32.3%) and 56 ADHD patients (33.7%) with an ICD-9 diagnosis of Parkinson's disease. In ADHD patients prescribed stimulants, the risk of Parkinson's disease was around four times greater than that of non-ADHD subjects (aHR 3.9, 95% CI: 1.9–8.3). However, the confidence intervals overlapped with that of patients without known stimulant treatment (aHR 2.3, 95% CI: 1.5–3.5) (figure 10).

Figure 10: Risk of Parkinson's disease in ADHD vs non-ADHD patients.

[redacted]

Discussion

The authors observed a two-fold increased risk for expression of BG&C diseases in persons with a history of ADHD compared to individuals with no ADHD history. A similar magnitude of risk was observed when the analysis was restricted to Parkinson's disease. These results are consistent with the hypothesis that an increase in expression of BG&C diseases, including Parkinson's disease, is associated with a history of ADHD, after controlling psychotic comorbidities (as a proxy for antipsychotic use) or tobacco use.

A pattern of significantly increased risk of BG&C diseases in this subset of stimulant-treated patients was detected. Possible explanations include: (1) treatment with psychostimulants may enhance the mechanism(s) responsible for the linkage between earlier-onset ADHD and BG&C diseases expression, (2) a history of ADHD with psychostimulant use may accelerate the temporal related degeneration of the relevant neuronal pathways primarily in those patients who eventually, with age, will manifest this disorder regardless of an ADHD history, or (3) psychostimulant treatment is a marker for a more severe ADHD phenotype, which in turn increases the risk of earlier BG&C diseases expression. Due to limited evidence of methylphenidate neurotoxicity, the latter explanation of confounding by indication may be the most plausible.

Limitations include bias from potential misclassification of non-ADHD subjects who did not have an ADHD history in the database, but who may have been diagnosed outside of Utah or have undiagnosed ADHD, and patients who may have been misdiagnosed as having ADHD.

Administrative claims data may be limited in their ability to identify BG&C diseases and the codes used may have resulted in misclassification. Other potential confounders such as head trauma were not accounted for. The prevalence of ADHD in the study population was low compared to the estimated incidence in the general population. As ADHD was added to the DSM in 1968 and is usually identified in children, the analysis was limited to those who developed onset of these neurological conditions before age 66 years.

Comments

Treatment with stimulants may be indicative of more severe ADHD, which in itself may be associated with subsequent development of Parkinson's disease. The incidence of ADHD in this study was low compared with population estimates. Misclassification of individuals with ADHD is possible due to the limitations of medical claims databases. Exposures/confounders may also not be accurately captured. Conditions such as illicit drug use may not be disclosed by patients. The study didn't account for traumatic brain injury or environmental exposure to toxins.

The analysis of BG&C diseases included secondary Parkinson's and essential tremor. This may increase sensitivity but decrease specificity.

In the analysis of Parkinson's disease, the aHR confidence intervals overlapped for ADHD patients treated with stimulants and those who weren't. The study did not quantify exposure to stimulants and examine a potential dose-response relationship.

3.1.3 Do prescription stimulants increase risk of Parkinson's disease among adults with attention-deficit hyperactivity disorder? A retrospective cohort study. Kindt et al, 2024. [15]

This retrospective cohort study aimed to determine if prescription stimulants influence risk of Parkinson's disease (PD) among older adults with ADHD. This article is attached as **Annex 3.**

Methods

This study used the TriNetX research database to identify adults over 50 years of age with a diagnosis of ADHD. Individuals were excluded if they had a diagnosis of PD prior to turning 50 years of age or if they were never diagnosed with ADHD. They were included if they were 50 years of age or older, did not have a diagnosis of PD, and their diagnosis of ADHD occurred at any point prior to 31 December 2021. The exposed cohort consisted of adults with one or more prescriptions for stimulants. Individuals with ADHD that did not have stimulant medicines were included in the control cohort.

The outcome of interest was PD and parkinsonism with a follow-up period of 30 years after the first stimulant prescription. Matching variables were age, sex, race/ethnicity, obesity, type 2 diabetes, statin use and glycolysis-enhancing alpha-1 antagonists, vitamin D deficiency, traumatic brain injury, influenza, melanoma, and prostate cancer.

Propensity score matching (PSM) was used to balance the baseline characteristics between the exposed and the control cohorts. Cox proportional hazard ratios (HRs) were computed to represent differences in outcome incidence between the exposed and control cohorts across the 30-year follow-up period.

Results

A total of 145,369 adults met the study criteria, including 73,725 individuals in the exposed cohort and 71,644 individuals in the control cohort. After PSM, there were 59,471 individuals with ADHD in each cohort. Prior to matching, there was a higher proportion of people in the exposed group who were female, white, overweight, and diabetic. There were also higher levels of melanoma, prostate cancer, use of statins, and documented influenza infections in those prescribed stimulants. After matching, the groups were balanced on all demographics and comorbid conditions.

Of 59,471 individuals treated with prescription stimulants, 131 developed PD while there were 272 individuals who developed PD that were not prescribed stimulant medicines. This analysis yielded a HR of 0.419 (95% CI 0.34, 0.516, P = 0.0013).

Discussion

The authors state that these data suggest that individuals aged 50 years and older with a diagnosis of ADHD and exposure to prescription stimulants have reduced risk for development of PD when compared with individuals with ADHD who are not prescribed stimulant medicines.

A decreased risk for PD in this population could be explained by a variety of mechanisms but most likely centres on reduced oxidative stress. Studies that explored illicit stimulant use suggest that oxidative stress from substance use leads to mitochondrial dysfunction, cellular apoptosis, and neurodegeneration. It has been suggested that prescription stimulants may reduce neurotoxicity associated with illicit stimulants.

The authors note that the study by Curtin et al (see section 3.1.2 above) found increased risk of basal ganglia and cerebellum disorders among all individuals with ADHD, and those who were prescribed stimulants. Similarly to the Curtin et al study, the ADHD population in this study also had a higher incidence of PD than general population estimates. In contrast to the Curtin et al study, this study found a reduced risk for PD among people prescribed stimulants. This study included people with substance use disorders, used different matching variables and did not control for tobacco or antipsychotic use.

Limitations included the use of ICD-10 codes and electronic health record data that may lead to misclassification. The study was unable to quantify stimulant exposure and did not examine a dose-response relationship.

Comments

This study examined the risk of Parkinson's disease in people aged 50 years and older with a diagnosis of ADHD who were treated with stimulant medicines . The reasons for lower incidence in the stimulant-exposed group are unclear. Unmeasured confounders include tobacco use, antipsychotic use and illicit drug use. It is possible that people with a history of substance use disorders or comorbid psychiatric disorders were less likely to receive treatment with prescription stimulants.

3.2 CARM data

There have been no reports to CARM of diagnosed Parkinson's disease or parkinsonism in association with methylphenidate, dexamfetamine or lisdexamfetamine.

A search of the adverse reactions report database for the substances methylphenidate, dexamfetamine and lisdexamfetamine using the standardised MedDRA query (SMQ) 'parkinson-like events' retrieved 4 reports where methylphenidate was a suspect medicine. The reported reaction terms included tremor, shaking, paralysis and musculoskeletal stiffness. The reports do not include information suggesting that the reported reactions were related to Parkinson's disease or parkinsonism.

4 DISCUSSION AND CONCLUSIONS

The biological plausibility of a relationship between stimulant treatment in ADHD and later development of Parkinson's disease is unclear. It is hypothesised that stimulant medicines may have a direct neurotoxic effect. Animal studies show that amphetamines are toxic to mesencephalic dopaminergic neurons at high doses. Illicit use of methamphetamines/amphetamines has been linked with increased parkinsonism and increased risk of later development of Parkinson's disease, including younger onset of disease. Conversely, there is limited evidence of methylphenidate neurotoxicity in animal studies.

A cohort study by Curtin et al found a substantially increased risk of cerebellar and basal ganglia disorders in people with ADHD who were treated with stimulants, compared to people without ADHD. The outcome of 'cerebellar and basal ganglia diseases' was broad, and included conditions such as secondary parkinsonism and essential tremor. The subanalysis of Parkinson's disease found an increased risk in both ADHD patients overall and ADHD patients treated with stimulants. However, the confidence intervals were overlapping for the exposed and unexposed groups.

The risk of cerebellar and basal ganglia disorders was higher in people treated with methylphenidate compared to amphetamines. This is surprising given the lack of evidence that methylphenidate is neurotoxic relative to amphetamines, as outlined in the Baumeister review article. The risk was also increased in people with ADHD with no record of treatment with stimulants, although there is possible misclassification in this group as the average age when ADHD diagnosis first appeared in the records database was 26 years.

Unmeasured confounders include traumatic head injury and exposure to environmental toxins. A limitation of studies using health claims databases is that confounding exposures (eg, illicit drugs, tobacco, antipsychotics) may not be accurately characterised. Stimulant exposure was not quantified and a dose-response relationship was not examined.

Another study by Kindt et al found that people aged 50 years and older with a diagnosis of ADHD who were treated with prescription stimulants had a reduced risk for development of Parkinson's disease when compared with those who were not prescribed stimulant medicines. The reasons for this finding are not clear. Unmeasured confounders include tobacco use, antipsychotic use and illicit drug use. It is possible that people with ADHD who had a history of substance use disorders or comorbid psychiatric disorders were less likely to receive treatment with prescription stimulants. Examination of an epidemiological link between stimulant medicines and Parkinson's disease is complicated by a long latency between exposure and outcome and difficulties in quantifying exposure. There is possible confounding by the underlying condition of ADHD, which involves dysregulation of dopamine pathways, and in itself is associated with confounding conditions such as comorbid psychiatric conditions and illicit drug use.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether regulatory action is needed at this time in relation to a possible risk of Parkinson's disease with stimulant medicines used for ADHD.

6 ANNEXES

Annex 1 – Is Attention-Deficit/Hyperactivity Disorder a Risk Syndrome for Parkinson's Disease? Baumeister, 2021.

Annex 2 – Increased risk of diseases of the basal ganglia and cerebellum in patients with a history of attention-deficit/hyperactivity disorder. Curtin et al, 2018.

Annex 3 – Do prescription stimulants increase risk of Parkinson's disease among adults with attention-deficit hyperactivity disorder? A retrospective cohort study. Kindt et al, 2023.

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