



MYTH OR SCIENCE? A PILL OF RITALIN A DAY KEEPS THE RESITS AWAY

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Critical Appraisal

Joep, reporter for Vox magazine, tested Ritalin in a personal 2-day experiment. Beforehand, he consulted a psychiatrist to get informed on which dosage to take. He tried to learn as many French words as possible, one day with Ritalin and one day without Ritalin. Both days he managed to learn 3 pages of French words and he made four to five mistakes during his tests. Even though the results are almost identical, his experience was not. The day he took Ritalin he felt more focused; no nail biting, no looking at the clock. However, he felt time was flying by as well and he caught himself staring aimlessly at words sometimes. He concludes that he would rather just drink coffee and eat wine gums [1]. 22-year-old student Ruben, who shared his story with NWSbeat magazine, claims that methylphenidate (MP) directly improved his study results and that he did not experience any adverse effects in the two years he has been using it. He would recommend it to everyone [2]. Koen Burgerhout from Addiction Institute Bouman of GGZ has a very different opinion on the topic. He describes the increase in MP use amongst students as frightening. He questions the effect of MP on healthy individuals and warns of serious side effects including cardiovascular disease and depression [3].

Introduction

Do you know the feeling that you have to study for an important exam, but you keep scrolling on Facebook or watching Youtube videos? Maybe you have tried natural supplements before such as fish oil, to enhance your concentration [4]. Maybe you have even tried something stronger, such as Ritalin, or its substance name: Methylphenidate (MP). If so, you are not the only one. The Dutch Institute for Responsible Drug Use (Instituut voor Verantwoord Medicijngebruik (IVM)) held a survey in 2017 amongst 400 university and university of applied sciences students and found that 1 in 4 students have used MP to improve concentration while studying. A shocking increase in comparison to 2015, when “only” 1 in 10 students admitted to having used MP [5]. Students obtain this drug from friends who are diagnosed with ADHD, or buy it online for a few bucks. Different opinions exist with regard to the consequences of the use of such drugs. Some argue that, in some ways, MP resembles hard drugs such as cocaine and amphetamine. In contrast, other people compare using MP with drinking coffee [6]. We aimed at figuring out the science behind the use of MP as a cognitive enhancer, by people in doubt of their academic performance.

Medical use of methylphenidate

Attention deficit and hyperactivity disorder (ADHD) is the most common indication for prescribing MP, which is the drug of preference for this disorder. In ADHD there is supposedly a shortage of dopamine in the frontal cortex and the striatum [7]. Dopamine is a chemical that belongs to the catecholamine and phenethylamine families. It plays several important roles in- and outside the central nervous system. One of these roles is as the motivational component in reward-motivation behaviour. Another role is as a local chemical messenger in blood vessels and certain organs, such as the heart. Therefore, dopamine plays a role in dilating the blood vessels of the kidneys, which consequently increases kidney filtration and cardiac output due to a positive-inotropic effect [8]. A shortage in the central nervous system results in decreased concentration, distractibility and impulse control [9]. Consequently, dopamine is one of the most investigated neurotransmitters in the treatment of attention deficit disorders. MP blocks the reuptake of dopamine and norepinephrine. This has a stimulatory effect on the central nervous system, relieves ADHD symptoms on short-term, and increases the activity of the sympathetic autonomic nervous system [8].

MP falls under strict legislation in The Netherlands, which is known as the ‘opiumwet’. This law prohibits listed drugs to be smuggled, cultivated, transported, carried or manufactured amongst others [10]. In The United States, the Food and Drug Administration gave MP a ‘black box warning’. This is the strongest warning they hand out and it signifies that studies have found a significant risk of serious adverse effects [11]. It must be noted, however, that there are key differences between Ritalin and amphetamine. Amphetamine does not only block the reuptake of dopamine, similar to MP, it also promotes the release of dopamine from vesicles. This release is thought to underlie the strong addictive potential of amphetamine and other hard drugs such as cocaine. Therefore, one can ask themselves whether previously mentioned measures for MP are indeed justified.

Cognitive enhancement

MP is the most used psychostimulant drug for extending the capacity of alertness and cognition in healthy individuals [12]. Several factors increasing its non-medical use (NMU) have been identified. Higher NMU has been reported among males, Caucasians, students engaged in recreational substance use and students in sororities and fraternities. Other factors predicting the use of MP include a history of risky behaviour (like driving under influence) and symptoms of inattention, depression, anxiety, stress, impulsivity and internal restlessness [13]. Perhaps not surprising, since these behaviours are more prevalent in ADHD patients and could be remediated by MP. It thus may be the case that statements of increased academic performance with MP are partly due to underdiagnosed or subclinical ADHD [14]. The same could be hypothesised for depression or anxiety disorders [15]. Anyway, let us look at a recent meta-analysis on this topic, as we are not going to bust or confirm this myth by hypothesis alone.

In 2015, Ilieva et al. obtained a quantitative estimate on the cognitive effects of MP focussing on inhibitory control, working memory, episodic memory as a primary outcome and dosage required to reach an effect as a secondary outcome. Their meta-analysis included 48 studies and 1409 participants. A significant but small positive effect was found with MP regarding inhibitory control/cognitive focus (i.e. looking less out of the window and less slow strolls to the fridge followed by eating food you do not even feel like eating). Also, a small positive effect was found

in the performance of working memory (lasts 30 minutes after learning). This would give you 15 minutes to race through your notes and then your answers in the first 15 minutes of the exam would be slightly better. Not really satisfying, is it? Episodic memory (lasts one hour to one week after learning) performance showed a medium increase with MP. However, both findings for working and episodic memory qualified for possible publication bias. In other words, it is likely that studies that would cancel out these positive results stayed in file drawers [15]. Interestingly, the best stimulatory effect (though questionable) was reached with a low dosage of MP. Unfortunately, this secondary outcome was also confounded (i.e. no firm conclusions can be drawn) in the studies analysed.

A more recent small RCT of 36 students also assessed the students' feeling of well-being during cognitive testing. This was improved by MP, but without significantly improving their cognitive functions. The author's guess is that healthy people do not actually perform better, but they could feel cognitively enhanced, establishing its current popularity [12]. Cropsey et al. continued along this path. They hypothesise that small effects of cognitive enhancers are due to people's expectations of being cognitively enhanced [14]. Therefore, they used a balanced placebo design, using Adderall (an amphetamine, much alike MP). This design has four groups, consisting of two groups who are told the truth (given Adderall/given placebo) and two groups who are deceived (told the opposite of what they receive). Their results showed that the expectation of receiving a stimulant has a positive effect on simple tasks, even more than actual medication, though both effect sizes were small. This might implicate that cognitive enhancement is also moderated by belief (a placebo effect) instead and not entirely by pharmacodynamics.

As stated above, it seems that small positive effects on cognition can be achieved by alternation of dopamine levels in the groups of students that were studied. However, a vital key point is not yet discussed; baseline dopamine levels. This entails that individuals with low dopamine levels can benefit from MP on certain cognitive tasks, while others with high levels of dopamine at baseline will perform worse at the given cognitive tasks. Thus, dopamine has a so-called U-shaped mode of action [16]. Furthermore, it seems that the dopamine level of optimal performance differs amongst the various cognitive functions. For instance, MP increases cognitive focus but this goes at the expense of updating (adapting to potentially changing circumstances) [17].

Negative effects

Considering the results stated in the previous paragraph, the beneficial effects of MP are perhaps somewhat mild. However, the negative effects for occasional MP use are not as well studied and are also depending on usage frequency and dosage. Extensive research has been done on the negative effects of chronic MP use. Lareb, a Dutch center that registers side effects of medication, reported that 75% of patients with ADHD who use MP claim to experience side effects. This results in discontinuation of treatment in 10% of ADHD patients. In general, negative consequences of MP use both prescribed and unprescribed, can be divided into four groups: side effects, abuse, reactions to high doses and complications [18,19].

Side-effects have many different manifestations. Most common (>10%) are insomnia, nervousness, headache, loss of appetite, nausea, and a dry mouth. Furthermore, the side-effects can be aggravated by alcohol and there are interactions with other drugs such as antipsychotics, tricyclic antidepressants, antiepileptics and antihypertensive drugs. It is not indicated after which period of use and at which dose these side-effects occur [18].

Kollins et al. reviewed the abuse potential of MP including 60 studies. They concluded that there is definite abuse potential, since tolerance develops and characteristic stimulant withdrawal symptoms are seen after discontinuation of the drug. These symptoms included insomnia, irritability and depression. However, these effects were minimal or not present in most patients who quit MP by means of a reduction schedule. This study was also conducted with chronic MP users, which questioned if the same applies to occasional users [20].

A high dosage of MP can lead to symptoms such as depression, or anxiety, aggression, emotional lability and headaches. It might also lead to hallucinations and bizarre delusions which could result in dramatic consequences. It must be noted, however, that these effects rarely occur [21]. Complications include raised blood pressure, which possibly places long-term users at risk of heart attacks and stroke. Lareb registered over 1.200 notifications of mild to serious complications after the use of MP [19]. Moreover, stimulant use can also worsen anxiety, depression, psychotic conditions and seizure disorder [18]. Before prescribing MP, a doctor evaluates the patient for these risk factors. If MP is used unprescribed, this evaluation obviously has not taken place. NMU of MP can therefore potentially lead to worsening of psychiatric disorders [11]. Furthermore, there are some studies that suggest that stimulants could influence the user's personality [11,22]. For example, greater focus gained through stimulants could plausibly lead to a loss in creativity, which requires a loosening of mental boundaries [22].

Conclusion

This proclaimed wonder pill seems to influence certain cognitive functions positively, but only in a select group of individuals and possibly at the expense of other cognitive functions. A meta-analysis shows a significant but small positive effect on inhibitory control. Also, it might positively affect working and episodic memory, but these results classified for publication bias. Although confounded, the best effects of MP on cognition were achieved with a low dosage. 10% of ADHD patients discontinue with treatment due to experienced side effects. However, the number of negative effects of unprescribed MP use in students is not known. Nevertheless, these students did not consult a doctor before using MP. Consequently, this could aggravate already existing psychiatric disorders and increase the risk of overdose. The chance of this is questionable when used occasionally however. Overall, the negative effects seem to be predominant, for the average student, when we look at the current knowledge on this topic. On the individual level this could still mean that some people notice a positive effect. A recent RCT suggests that most of the positive effects felt are moderated by belief of being cognitively enhanced instead of true pharmacodynamics. On the other hand, baseline dopamine levels and the level of dopamine required for a specific cognitive task seem to play an important role, complicating the interpretation of study results. It could also be hypothesised that students performing a lot better with MP, indicates underdiagnosed ADHD or personality characteristics within the spectrum.

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