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Effects of Methylphenidate on Memory and Attention in Healthy Adults

Review

Methylphenidate (MPH) is the most prescribed medicinal drug for people diagnosed with attention deficit/hyperactivity disorder. However, the off-label use by healthy adults has increased over the last year due to the potential beneficial effects on cognitive performance. It causes augmented catecholaminergic neurotransmission by blocking dopamine and norepinephrine's reuptake mainly in prefrontal cortex and striatum. The aim of this review was to examine the effects of MPH on memory and attention in healthy adults. The results were ambiguous, however, MPH's beneficial effects on memory were found more consistently than effects on attention. In addition, individuals whose baseline performance was lower than average benefitted more than others. Optimal dosing seems to be dependent on the task and cognitive domain tested. The controversy about cognitive enhancing drugs arises when taking side effects, as well as ethical aspects, into consideration. Common adverse effects are insomnia and appetite loss. In conclusion, despite the positive effects of MPH on memory and attention, the use of MPH as cognitive enhancer in healthy adults is not recommended based on the lack of longitudinal studies and the risks of adverse effects. MPH self-medication is not recommended.

Keywords: Methylphenidate, attention, memory.

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INTRODUCTION

Methylphenidate (MPH) primarily gets prescribed for attention-deficit/hyperactivity disorder symptoms, such as difficulty concentrating, impulsivity and hyperactivity (Leonard, McCartan, White & King, 2004). However, MPH is increasingly used as cognitive enhancer by healthy individuals, which is the topic of the present review.

The most common way of MPH administration is oral which is delivered in a pill form. This then becomes absorbed through the intestinal tract, where MPH is partially deactivated by first-pass metabolism in the liver. After accessing the systemic blood circulation, the drug crosses the blood-brain barrier enabling its immediate effects on the neural networks. Other ways of administration would be an intravenous injection or inhalation which causes the direct entry of the substance into the brain. Due to a lack of first-pass metabolism and partial deactivation, these methods are considered as more dangerous as they lead to a more rapid onset of the drug's actions and feelings of euphoria (Dubljević & Ryan, 2015).

Dosing of MPH can be either weight-based (e.g. 0.5 mg/kg) or absolute (e.g. 18 mg). It has been estimated that the clinically efficacious dose ranges from 0.3 mg/kg to 1.0 mg/kg in children with ADHD (Leonard et al., 2004).

The action of immediate-release MPH typically lasts for about 4 hours and works by causing a change in catecholaminergic activity of the brain. It is not untypical that children will continue to suffer from this disorder throughout adolescence and later into adulthood, however, symptoms that manifest most in adulthood are difficulties maintaining routines whereas hyperactivity becomes less salient (Leonard et al., 2004).

Until now, the molecular mechanisms by which MPH often succeeds in improving symptoms associated with ADHD are not entirely understood (Urban & Gao, 2012). Early research on its mechanism of action hypothesises that MPH's effect on dopamine (DA) in the brain is likely to be the primary mode for yielding a therapeutic effect in ADHD patients

(Challman & Lipsky, 2000). Positron emission tomography (PET) studies, such as the one conducted by Volkow and colleagues (2005) have identified the possible role of dopamine in MPH's action by monitoring MPH's concentration and its effects in regions of the human brain. It was found that methylphenidate inhibits the reuptake of DA by binding to dopamine transporters (DAT) causing an accumulation of extracellular dopamine which rises proportionally to MPH-induced blocking of transporters and the amount of DA release. Hence, dopaminergic neurotransmission gets magnified with a therapeutic dose of 0.5 mg/kg of MPH occupying about 60% of DAT. As dopamine is a neurotransmitter that stimulates corticostriatal signalling and weakens background signals in striatal cells, augmentation in dopaminergic activity is associated with increased motivation to accomplish the task, as well as enhanced stimuli salience (Volkow, Wang, Fowler & Ding, 2005).

More recent studies have demonstrated that not only MPH's effect on DA accumulation but also on norepinephrine (NE) seem to be important in its pharmacodynamics (i.e. effects on the brain). NE's actions are amplified similarly by MPH inhibiting the transporters required for reuptake respectively. In comparison to the amount of blocked DAT, a standard clinical dose of 0.5 mg/kg MPH was shown to reach up to 20% more occupancy in NE transporters (NET) (i.e. total of approximately 80% NET binding) (Hannestad et al., 2010). As noradrenergic transmission is stimulated by MPH inhibiting NE reuptake, it seems likely that in sensory areas of the brain, synaptic input becomes magnified. This could lead to improvements in ADHD symptoms, in which inaccurate sensory processing may be the cause of easy distractibility and hindered focussing on a target stimulus (Drouin, Wang & Waterhouse, 2007). Moreover, experimenting with MPH infusions in animals, Zhang et al. (2012) have found strong support for the prefrontal cortex (PFC) being one of the major sites MPH acts on. The PFC is known to play a crucial role in the regulation and maintenance of attention and is involved in complex cognition and memory. Hannestad et al. (2010) state that the PFC's pyramidal cells are affected by even slight changes in extracellular norepinephrine and dopamine and that it is possible that

the beneficial effects of MPH occur predominantly there. It became evident that MPH's therapeutic effects are most likely due to excessive amounts of DA binding to D2 receptors and NE binding to ?2 receptors. However, whether a therapeutic effect occurring at a dose of 0.5 mg/kg is more due to 60%-70% DAT blockage or 70%-80% NET occupancy remains speculative (Hannestad et al., 2010).

By boosting motivation and sharpening attention through stimulating dopaminergic and noradrenergic neurotransmission, MPH was proven to be an effective medication for the majority of children and adults suffering from ADHD. In contrast, off-label use by healthy persons has been increasing over the recent years (Sahakian & Morein-Zamir, 2007). In the media, information about the number of people taking MPH non-medically is frequently inaccurate and overemphasized. Studies estimating prevalence rates on healthy people using prescription drugs for cognitive enhancement in general found a broad range from approximately 1% to 20%. A German study assessing prevalence among 1053 university students found that 2.2% have used MPH at least once in their lifetime (Franke, Bagusat, Rust, Engel, & Lieb, 2014). However, determining the true prevalence rates is difficult and existing literature is often vague (Dubljevic & Ryan, 2015).

Taking into consideration the widespread and increasing trend of illicit MPH use, concern is arising regarding the adverse effects users could suffer, as well as other moral issues making enhancement of cognitive functioning with prescription stimulants such as MPH debatable. Cognitive functioning refers to a variety of separate categories including attention, memory, executive functions, perception, language and more (Nehlig, 2010). This review will solely focus on memory and attention, as these areas have been shown to be strongly related to performance in academia (Rabiner, Carrig, & Dogne, 2013; Dehn, 2011). The aim of this thesis is therefore to examine the effects of MPH on memory and attention in healthy adults. Moreover, it will take the disadvantages of MPH usage such as negative side effects on the body and moral

concerns into account before globally evaluating if the use of MPH as cognitive enhancer in healthy adults can be further recommended.

EFFECTS ON COGNITIVE DOMAINS

Attention

Based on MPH's proven enhancing effects on dopaminergic transmission and the assumption that dopamine is essential in goal-directed actions and stimuli salience, many researchers initially expected attention to be one of the cognitive domains MPH would have the greatest effect on (Linssen, Sambeth, Vuurman, & Riedel, 2014).

Attention is "the focusing of our inner resources and state of consciousness" (Cohen, 2014, p.3) and it can be subdivided in various categories including selective-, divided- and sustained attention. Due to the inability of the human brain to process all sensory stimuli we are confronted with at once, our attentional system allows us to narrow processing capacities appropriately to relevant properties of our environment while blending out the irrelevant details. Selective attention refers to the prioritising of some stimuli over others. A stimulus can draw an observer's attention just by being outstanding from competing stimuli through e.g. visual features which refers to bottom-up attention. This can be distinguished from top-down attention which describes the act of willingly directing one's focus on specific items (Katsuki & Constantinidis, 2013). Another subcategory of attention is called divided attention which describes paying attention to multiple items at the same time. Furthermore, vigilance or sustained attention refers to a prolonged reaction to the appropriate cue which is indicative for the participant's maintenance of attention (Repantis, Schlattmann, Laisney & Heuser, 2010).

Linssen and colleagues (2014) performed a review of the effects of single dose MPH on healthy participants across several cognitive domains. Of the 27 studies that measured

attention/vigilance, 29% of the studies were able to report significant findings with respect to MPH's beneficial effects in healthy volunteers. This makes attention/vigilance the fourth affected domain of six that were examined. According to the authors, the tasks of this domain are frequently used in MPH studies for control purposes as a result of their presumable MPH sensitivity. Furthermore, these results should be interpreted with care because often, an attention task was not always tested as one but was divided in numerous separate measurements.

Some researchers found the dose-response curve of MPH to have an inverted-U shape. This entails the largest response to the drug occurs with a moderate dose, while a lesser response is associated with minimal and maximal doses (Finke et al., 2010). Linssen and her colleagues stated that this curve possibly differs between the cognitive domains respectively. By examining low, moderate and high doses in separate studies, they were able to gain an understanding of the dose-response relationships for each cognitive domain. The researchers recognised that some studies might not have obtained significant results due to inappropriate dosages (Linssen et al., 2014).

One study (del Campo, 2013) assessed individual differences in responding to MPH. This study distinguished low- and high baseline performers in a double-blind, placebo controlled cross-over design. 16 males with ADHD and 16 males without medical condition participated in two positron emission tomography (PET)- and one magnetic resonance imaging (MRI) scan while performing a sustained attention task under the influence of 0.5 mg/kg MPH or a placebo. Blood samples of the participants were also taken in order to ensure that they were tested within MPH's effective window and to monitor plasma levels of MPH between participants. On the Rapid Visual Information Processing task, participants are instructed to respond to a target sequence of digits among a stream of single digits. Performance on the task was measured by the participant's sensitivity (i.e. rate of correct responses). There was no main- or interaction effect for MPH found, meaning that all participants together, disregarding ADHD diagnosis or

MPH intake performed equally. However, after splitting subjects into low- and high-baseline performers it became evident that all low-performance subjects benefitted from drug intake whereas the high-performance group did not show any improvements. In addition, the researchers detected that the MPH low-baseline performance group exhibited low dopamine receptor availably in their left caudate nucleus before MPH intake. Interestingly, after a single MPH dose they showed an increase in midbrain dopamine levels as well as normalised dopamine levels in the left caudate in contrast to the other participants. Regarding the high-baseline performers, the authors explain that their consistent results may be attributable to the ceiling-effect. This means that high performers already had a superior baseline performance so that there might have been not enough room for large improvements after MPH intake. This result may also be explained by the inverted-U function in which high-performance subjects would already be at the optimum catecholamine level and thus do not perform better under the influence of MPH. From this study, it can be concluded that attentional deficits are likely to stem from deficient dopamine receptor availability in the midbrain and left caudate and that MPH supports compensation for this. Also, MPH effects seem to be identical among all low baseline performers, regardless of the presence of an ADHD diagnosis or not (del Campo et al., 2013).

A study conducted by Agay, Yechiam, Carmel, and Levkowitz (2014) also wanted to test if the baseline-dependent effects of MPH can be considered as normalised performance in which the poor performers become better and the high performers diminish to an average level. Alternatively, they proposed that a MPH evoked normalisation of performance could occur for inferior performers only while superior performers are not affected at all. Twenty adults with ADHD and a control group of 19 healthy individuals underwent two sessions of a rapid Go/No-Go task. In this test the participants had to discriminate between target and non-target stimuli. Reaction time, accuracy over time and response time variability was acquired as an assessment of sustained attention. While some received a placebo on the first trial and approximately 0.28

mg/kg MPH on the second, others received MPH first and the placebo on the second session. In contrast to the outcome of the study by del Campo (2013) it turned out that MPH did have a positive effect on sustained attention in both groups of ADHD and control participants. Moreover, MPH-induced improvements were larger for participants with low-baseline performance, but not lower for people with high-baseline performance. These results add up to previous found evidence that MPH leads to normalisation of performance in attention tasks in people that initially showed low performance, but not in individuals with previous above average. As a possible explanation for this finding, the researchers propose that high performers, in contrast to low performers, may rely more on automatic processes while carrying out the task which then does not demand as much cognitive control. Therefore, dopamine and norepinephrine levels are not as relevant for performance and MPH does not lead to attenuated performance when these levels exceed the optimum (Agay. Yechiam, Carmel & Levkowitz, 2014).

Another study that aimed at exploring the effects of MPH on sustained attention was conducted by Tomasi et al. (2011) who compared healthy people who received a 20 mg dose of MPH and healthy controls in a blocked visual attention task. In this task, participants had to covertly attend to moving balls on a computer screen until they stop and then compare a new set of balls to the initial set to decide if their positions match. Meanwhile, measurements of the participants' functional MRI blood-oxygen-level dependent (BOLD) signals in the dorsal attention network and the default mode network in the brain were taken. The dorsal attention network is comprised of areas like the PFC and parietal regions and is known to exhibit increased activation in tasks requiring attention, whereas the default mode network (e.g. the post cingulate cortex and insula) is characterised by inhibited activation during these. Hence, the researchers expected that the MPH group (n=16) would show higher activation in the dorsal attention network and stronger deactivation of the default mode network in comparison to the control group (n=16) who did not receive MPH while performing an attention-demanding task. The results reflect their initial hypothesis which clearly demonstrates that MPH promotes

activation in the dorsal attention network. Nonetheless, no significant difference was found for task accuracy between the groups. Moreover, reaction times did not differ significantly. These results, however, must be seen in the light of the limitations that it was not controlled for placebo effects and as every participant yielded almost 100% accuracy, it is difficult to investigate the influence MPH might have had on the experimental group (Tomasi et al., 2011).

But does a general MPH-induced increase in attention reflected by some of the results necessarily lead to increased attention to solely the target or could it also mean that attention is enhanced to the entirety of incoming information without specifically privileging the target? This was examined in a study conducted by ter Huurne et al. (2015). Their aim was to compare the accuracy and reaction time of 20 healthy adults in a visuospatial attention task under the influence of either 20 mg MPH or a placebo. In a computer task, detection of the target stimuli was accompanied by distractors of which some were categorised as "strong" because they had characteristics similar to the target and others as "weak" as they had no similarities with the target. The target stimuli were faces located at a previously cued position, whereas the strong distractors were faces located at the opposing visual hemifield. The weak distractor was a scrambled face in the hemifield that was not cued. Participants were asked to respond by pressing the button that corresponds to the sex of the target face. It was found that strong distractors caused longer reaction times and a decline in accuracy, relative to the weak distractor, in each condition. Moreover, the MPH group was more accurate, but they also had a longer reaction time than the placebo-group suggesting that they had reduced their speed in favour of accuracy. Discussing these results, the researchers asserted that accuracy might have been improved in the MPH group because MPH led to enhanced target-like stimuli processing which, in turn, enabled the subjects to improve in distinguishing the target from the distractor. Existing literature suggests that the PFC, a site which MPH was shown to act on the most, encodes incoming information categorically (Sreenivasan, Curtis, & D'Esposito, 2014). As the strong distractors in this study were comprised of similar features to the target they might have

gotten processed in a preferential way too. This could have provoked a slowed-down decision-making process and accordingly longer reaction times. Alternatively, ter Huurne and co-authors (2015) explained that the longer reaction times might be the result of lowered impulsivity in the healthy subjects, as MPH was proven to reduce impulsivity in people with ADHD. However, as MPH did not appear to have a main effect on reaction time this explanation is regarded as less probable. In conclusion, this study provided support for the enhancing distractibility effect of MPH due to increased processing of environmental stimuli. Nonetheless, there is a possibility that this is only the case if the distractor and target belong to the same category. Also, a further limitation may be that it was not controlled for blood plasma levels of MPH. Therefore, in this manner, it could not be guaranteed that testing occurred during the optimal time window and that variability of MPH blood levels between participants is not too large (ter Huurne et al., 2015).

In sum, the effects of MPH on attention in healthy adults seem to be controversial. While some studies found support for MPH enhancing attention by stimulating DA and NE neurotransmission, most of the empirical work has not found a general improvement in attention induced by MPH, but rather effects that only occur in a baseline- and dose-dependent manner. Thus, the largest improvements could be observed in individuals that showed a low baseline performance initially and it seems to be likely that medium-dosed MPH yields the most positive effects in healthy adults.

Memory

Research shows that dopaminergic neurotransmission in the PFC and striatum are related to working memory (Clatworthy et al., 2009) and dopamine is involved in retaining memories that are motivationally significant (Shohamy, Adcock, 2010). Consequently, it could be hypothesized

that elevated dopamine transmissions evoked by MPH intake could lead to improvement in memory.

In the present, it is assumed that the human memory system consists of distinct, yet interactive systems (Nyberg et al., 2002). The process of creating a memory starts at the level of our sensory memory which receives and briefly stores information about the environment through bottom-up and top-down processes in perception. Sensory information of the stimulus enters our brain (i.e. bottom-up) and is recognised and analysed in the light of our expectations and contextual circumstances (i.e. top-down). In the working memory which has a large role in complex cognitive function, both recently acquired (i.e. short-term) and information retrieved from the long-term memory are held for processing during cognitive tasks (e.g. reasoning) (Baddeley, 1992). Short-term memory is marked by transient neuronal activity and information will eventually fade entirely if it is not given meaning or is rehearsed. This process of rehearsal or association with meaning is called consolidation and involves the strengthening of synapses over time which causes the memory to become a long-term memory (Lieberman, 2012).

Repantis et al. (2010) conducted a systematic review of scientific literature that assessed the effects of MPH on several cognitive domains in a placebo-controlled manner. Memory was the only out of six domains in which performance of healthy subjects was significantly improved compared to the placebo. More specifically, the largest effect of MPH was observed in spatial working memory. For example, Mehta et al. (2000) conducted a within-subject study in which a PET scan was used in order to prove the hypothesis that healthy adults would benefit from 40 mg MPH. In addition, it was hypothesized that, compared to the placebo session, they would exhibit greater changes in regional cerebral blood flow, compared to placebo, in parts of the frontal and parietal lobe which are typically involved in spatial memory. Before the memory task, baseline performance was examined for each participant using a digit span test. Then, participants performed a visual search computer task in which they had to touch multiple circles on the screen in order to see if they revealed a token or not. The aim was to find as many tokens

as possible and it was considered an error when a participant touched the same circle twice or touched a circle that hid a token in a previous trial. As expected, MPH led to a significant higher accuracy compared to placebo in the same participants. Additionally, imaging of the regional cerebral blood flow revealed that the blood flow in left dorsolateral prefrontal cortex and posterior parietal cortex was less in participants after MPH compared to placebo. It is possible that this attenuated blood flow is linked to more efficient activity in these particular brain areas and MPH's known ability to enhance signal to noise ratio. Moreover, this study also found the baseline-dependent effect of MPH that could be observed in the attention studies, too (Mehta et al., 2000). It is important to note that this study recruited only ten male participants which may threaten the external validity of the results. Also, the authors underline that the other studies included in the systematic review by Repantis et al. (2010) disregarded that effects could be contingent upon baseline performances of the participants which may have contributed to inconsistent findings. Moreover, many studies used extremely low doses of MPH (10 mg - 20 mg) which is, under the assumption that the dose response curve follows an inverted-U shape, suboptimal for examining MPH's effects.

There are, however, also studies that found results that conflict with the notion of the inverted-U association between dosage and effects. Linssen et al. (2012) conducted a study in which 19 healthy male participants were tested on two memory related tasks amongst others while comparing the dose dependent effects of MPH in doses of 10, 20 or 40 mg with placebo. The testing phase consisted of four different testing days in which one of the four treatments was given to the participants in a random order. In one task, a word list had to be remembered by the participants and recalled both immediately and at a delayed point in time, followed by a recognition task. It was found that the doses 20 and 40 mg MPH affected the delayed recall of word lists positively while the 10 mg dose and immediate recall did not differ from placebo. Due to the observation that only the late recall was affected, it was concluded that MPH ameliorated memory consolidation. This was an expected finding as similar improvements on memory

consolidation have been found earlier after pharmacologically comparable amphetamine intake. As the observed dose-response relationship in this study was linear, these results pose a challenge for the notion of the inverted-U shaped function which may not be applicable to memory consolidation. A possible limiting factor might have been that the word list was not difficult enough and a ceiling effect occurred. Additionally, the participants performed equally on the spatial working memory task, regardless of the condition. The researchers state that this might be due to the time pressure the subjects experienced in this task which may have combined with the overall arousing effects of MPH to overarousal and, thus, impaired performance (Linssen et al., 2012).

Two years later, the same research group collected data of more than 50 studies assessing the effects of MPH on memory in healthy adults (Linssen et al., 2014). It was found that, after MPH intake, working memory performance increased in 65% of all studies making it the cognitive domain MPH had the most effects on out of six domains examined. Out of all articles reviewed, performance increased in those studies employing a medium dose (10 mg – 20 mg or 0.15 mg/kg –0.3 mg/kg), which adds to evidence of the existence of the inverted-U dose-response relationship in the domain working memory.

The same review (Linssen et al., 2014) also looked at two other domains related to memory. These domains are “verbal learning and memory” and “visual learning and memory”. Verbal learning and memory deals with declarative memory and includes tasks like memorizing and recalling a pair of associated stimuli or word list learning. Interestingly, even within this category, the optimal dose seems to vary for different tasks as the performance on word list learning appears to improve with larger doses whereas the optimum in verbal paired associates tests is assumed to be medium. Significant results were found in 31% of the studies which supports the use of MPH in its positive effects in healthy adults. In contrast, none of the studies on visual learning and memory that were considered in this review reported a significant effect.

However, there was only a small number of studies integrated in this review which may explain the lack of evidence for effects in this category (Linssen et al., 2014).

Another study brought further insight in the mechanism how MPH improves subjects' performance on memory (Clatworthy et al., 2009). The authors described that the brain processes that are associated with working memory are dopaminergic transmissions from the midbrain to the striatum and PFC. Hence, the researchers expected that MPH induced a decreased dopamine receptor availability in these areas and that, based on this, it is possible to predict enhanced performance on a spatial working memory task in healthy volunteers. To test this, a double-blind placebo controlled study was carried out in which ten male subjects received either 60 mg MPH at the first occasion and a placebo at the second occasion or vice versa. Following the administration of MPH, their dopamine receptor availability was measured by the intravenous injection of [11C]-raclopride and a subsequent PET scan. [11C]-raclopride is a selective antagonist that acts at D2 receptors and can be labeled with a radioisotope for in-vitro imaging of the receptor blocking. This scan exhibits that the less receptors are occupied by [11C]-raclopride the more extracellular dopamine must be bound to dopamine receptors. The results were in line with the expectations. MPH caused a decreased dopamine receptor availability in the ventral striatum during the working memory task and performance was simultaneously improved. A limitation in this study was the small number of participants which may threaten the generalizability of the findings. Furthermore, next to the placebo, only one dose of MPH could be tested. Therefore, the relationship between the response and different dosing could not be investigated (Clatworthy, 2009).

According to the current literature, memory performance can be more improved by methylphenidate in healthy adults. Similar to attention, baseline performance plays an important role in so far as low baseline capacity individuals appear to profit more from MPH intake than others. Furthermore, it was observed that different dosages can have varying effects on the individual. While some studies found evidence for an inverted-U dose-response

relationship, others found contradictory evidence. The review by Linssen et al. (2014) showed that the ideal dosage seems to be highly task-specific and not necessarily equal within a certain cognitive category.

DISCUSSION

The aim of this review was to investigate the effects of MPH on attention and memory in healthy adults. The evidence on the effects MPH has on both attention and memory, that was analyzed further, is controversial. For both cognitive domains, there are articles that support beneficial effects and others that did not.

Studies on the drug's effects on memory seem to be slightly more successful than studies on attention. MPH was shown to have positive effects on spatial working memory. These effects were also reflected in changes in regional blood flow that were associated with more efficient signal processing (Repantis, 2010; Clatworthy). Also, memory consolidation, as well as verbal learning and memory was improved by MPH intake (Linssen et al., 2012; Linssen et al., 2014).

Most of the research MPH's effects on attention concerned sustained attention. While some studies reported performance improvements under MPH, the review by Linssen et al. (2014) showed that the majority of studies assessing attention did not find significant results. In one study, MPH induced increased activation of the dorsal attention network as well as decreased activation in the default mode network. While it is established that activity in the former network is related to attention tasks, the latter is commonly less activated during tasks requiring attention. However, on the behavioral level, no differences between accuracy or reaction times between the MPH and the control condition were found in the visual attention task (Tomasi et al., 2011). Possible reasons for the lack of significant results in some studies can be attributed to the fact that they did not consider different dose-response relationships nor the baseline capacity of the individual. Many studies taking this into account were able to report a

significant performance improvement under MPH compared to placebo (e.g. Linssen et al., 2013; Agay et al., 2014).

Literature suggests that the off-label use of cognitive enhancers like MPH is rising, especially among students who believe in the drugs ability to improve concentration, alertness and academic performance (Cakic, 2009). Against this background, it is important to touch upon some implications the non-medical use of methylphenidate as cognitive enhancer has.

Although MPH can have positive effects on memory and attention in healthy adults, it should be mentioned that MPH can also have negative adverse effects. These can be divided into multiple categories. First, cardiovascular problem, such as hypertension and tachycardia and angina can arise from methylphenidate intake (Freese, Signor, Machado, Ferigolo, & Barros, 2012). The central nervous system may also be negatively affected, for example, it was discovered that MPH frequently causes insomnia and nervousness. In contrast to that, headache, dizziness and dyskinesia are considered to be less frequent side effects. As for the gastrointestinal (GI) system, it has been observed that there is a risk for anorexia and that this is one of the most prevailing adverse effects. Nausea, abdominal pain and weight loss depict less severe GI symptoms caused by the consumption of MPH. Dermatologic problems induced by MPH administration are rather uncommon and include rash and urticaria (Challman & Lipsky, 2000). Moreover, it was detected that mental illnesses and behavioral tics are likely to become worse. However, Outram (2010) postulated that MPH's side effects are rather mild and that most of them were not statistically significant in many studies. Additionally, the side effects that were significant were all of shorter and medium term and included primarily loss of appetite, dry mouth and moodiness and slight moodiness. Nonetheless, there is a lack of evidence on long-term usage of MPH which might induce side effects in increased severity and number (Cakic, 2009). As a result, the risks that are associated with MPH intake, as well as the missing information about adverse effects over a longer time period, do not outweigh possible positive effects healthy adults could experience.

Another issue regarding the use of MPH is the risk of dependence. Similar to cocaine which is a well-known addictive substance, MPH causes an accumulation of dopamine to build up by blocking DAT. Some researchers, like Heinz and colleagues (2012) argued that the increase in extracellular dopamine is a factor contributing to the addictive potential MPH has. Activities triggering a rewarding feeling like eating food or sex induce a DA increase of 50 – 100 %, compared to stimulants like MPH that lead to a 175 – 1000% rise (Heinz, Kipke, Heimann & Wiesing, 2012). Others argue that the speed at which DA concentration in the brain rises is more important in the development of an addiction. Compared to oral intake, MPH only creates a 'rush' or a reinforcing feeling when its injected intravenously or inhaled, as research shows (Challman & Lipsky, 2000). Volkow et al. (1995) compared the effects of intravenously injected MPH to cocaine and found that both drugs act on the same brain areas. However, cocaine's peak uptake was slightly quicker than MPH's and cocaine's clearance was faster. Two years later, Volkow and colleagues found a difference between the reinforcing effects of cocaine compared to MPH and that this difference emerges from the speed by which dopamine transporters are blocked instead of the time the blockage lasts for (Volkow et al., 1998). Thus, it can be said that MPH and cocaine differ in their pharmacokinetics. Nonetheless, Kroutil et al. (2006) stated that, in the United States 3.1% of people between 18 and 25 years of age taking ADHD drugs off-label are considered dependent, according to the criteria. The use of MPH is considered as especially dangerous if a family or history regarding substance abuse exists and its risk in inducing addiction should not be underestimated (Challmann & Lipsky, 2000).

MPH as creating inequality?

When people enhance their cognitive abilities with the help of pharmaceuticals like MPH they seem to have an advantage over people that do not, especially in competitive situations as examinations at university. According to a recent survey that asked over 3000 students in

Switzerland about their attitudes towards pharmaceutical cognitive enhancement, 80% of the people say it is unacceptable and unfair (Maier et. al, 2015). As cognitive enhancing drugs like MPH are not very cheap, they may be obtainable primarily for people with greater financial resources. Greely and colleagues (2008) pointed out this ethical concern using the analogy: cognitive enhancing is similar to "allowing some students taking a maths test to use a calculator while others must go without" (p.703), which most people would consider an unfair precondition. However, inequalities, that are due to genetic or environmental preconditions, in educational success already exist. Some individuals have the privilege to be able to go to a private school or a university with high tuition fees, while others do not. Also, genes play a role and may create favoured positions for some individuals. This way, academic success is not determined solely by how hard-working the student may be, but is also influenced by several other factors. But would taking MPH for enhancing cognitive abilities create even more inequality? Many studies that analyzed the effects of MPH on performance at cognitive task found a baseline-dependent effect. If it holds true that MPH benefits low ability individuals the most while not affecting high capacity individuals significantly, it would help students performing worse keeping up with others (Cakic, 2009). Nevertheless, there is still more research needed concerning which groups in particular show beneficial effects of MPH.

Should use of MPH be encouraged or discouraged based on scientific evidence?

The use of MPH holds potential to enhance cognitive performance in the fields of memory and attention. Some studies show that attention can be positively affected (del Campo et al, 2013; Agay et al., 2014, even though many studies could not support this (Linssen, 2014; Tomasi et al., 2011). A positive effect was most prominent when studies differentiated between low- and high- baseline performers and was mostly observed in low performers. Effects on memory were more consistent

as is reflected in the reviews by Repantis et al. (2010) and Linssen (2014) which found memory to be the most enhanced cognitive domain by MPH out of six. Furthermore, medium and high doses of MPH had positive effects on memory consolidation (Linssen et al., 2012). Risking MPH's adverse effects and facing potential addictiveness for the purpose of self-enhancement instead of medical purposes may seem unacceptable for many. This in conjunction with numerous ethical questions one can debate about raises the question whether or not it should be encouraged for use outside of the medical domain. A libertarian perspective could be that, given a person is well aware of all potential harmful effects, they can decide freely if they want to use MPH for cognitive enhancement or not. On the other hand, possible adverse effects should be taken seriously. As MPH's beneficial effects seem to be, to a great extent, limited to low-baseline performance individuals, it is difficult to estimate the degree of improvement, if any, that administration of the drug could lead to. In light of the negative implications associated with MPH including the conflicting scientific evidence, controversial ethical dilemmas and adverse effects, the use of MPH should be limited to use in a medical setting.

Future research and Conclusion

Future research is needed regarding the effects of MPH on healthy people's cognition. More data have to be obtained on the effects of MPH on several cognitive domains such as attention, reasoning, problem solving and others while gaining more insight in individual differences, such as the baseline performance. Also, more research needs to be done on repeated doses MPH on cognition as most of the existing literature deals with single dose studies only. Research on long-term effects after years of usage is still lacking. In addition to that, more research has to be done on the adverse effects and how they might be avoided or eliminated in the drug.

Evidence on beneficial effects of MPH on cognitive abilities, like attention and memory are still somewhat ambiguous. Even if there is a considerable amount of studies showing

significant effects, they seem to depend highly on specifics of the task, individual differences and dosages most of the time. As appealing as the beneficial effects of MPH appear, potential adverse effects, like cerebrovascular-, sleep- and appetite problems should be taken seriously. Moreover, illicit stimulant abuse is also accompanied by ethical concerns. Two opposing positions are that MPH intake in competitive situations is seen as cheating and unfair while the other position postulates MPH is able to decrease inequalities. The beneficial effects of methylphenidate were shown to be greatest for underperforming participants which would mean that MPH intake could contribute to more equal opportunities among competing individuals. If the development of a cognitive enhancing drug that is safe and effective succeeds in the future, the debate about the legitimacy of using these drugs can be revisited. Awareness of the adverse effects should be raised and media should provide more deliberate information about MPH and other cognitive enhancers.

In conclusion, MPH has the potential to increase performance in memory and attention. However, it has been shown that its positive effects are greatest when individuals have a low baseline performance. Against the background of side effects, potential for dependence and ethical conflicts, the use of MPH self-medication for cognitive enhancement is not recommended. Instead, medication intake should be supervised by clinical experts in order to safely handle appropriate doses and timing.

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