

Reports of perceived adverse events of stimulant medication on cognition, motivation and mood: Qualitative investigation and the generation of items for the Medication and Cognition (MCQ) rating scale

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Abstract

Objective: There is no questionnaire to specifically monitor perceived adverse events of methylphenidate (MPH) on cognition, motivation and mood. The current study therefore had two goals. First, to harvest accounts of such putative events from transcripts of interviews in samples enriched for such potential experiences. Second, to use the derived data to generate items for a new questionnaire that can be used for monitoring such events in medication trials or routine clinical care.

Method: Following a literature search aimed at identifying associations between MPH and cognition and/or motivation, a qualitative semi-structured interview was designed to focus specifically on the domains of cognition (i.e. reasoning; depth/breadth of thinking; intellectual capacity; creativity) and motivation (i.e. drive, effort; attitudes towards rewards/incentives). Interviews were conducted with 45 participants drawn from four groups; (a) Clinicians; child and adolescent psychiatrists and paediatricians specialising in ADHD (n=15); (2) Teachers, with experience of teaching at least 10 medicated children with ADHD (n=10); (3) Parents of children with ADHD (n=8) treated with MPH; and (4) adolescents/adults with ADHD (n = 12). Purposeful sampling was used to selectively recruit ADHD participants whose histories suggested a degree of vulnerability to MPH adverse events. Data were analysed using a deductive approach to content analysis.

Results: While we probed purposefully for cognitive and motivational adverse events, a third domain, related to mood, emerged from the reports. Therefore 3 domains, each with a number of sub-domains, were identified from the interview accounts: (i) Cognition (six subdomains; attention/concentration, changes in thinking, reduced creativity, sensory overload, memory, slower processing speed); (ii) Motivation (four subdomains; loss of intrinsic motivation for goal directed activities, external locus of control, lack of effort/engagement in daily tasks, increased focus on incentives); and (iii) Mood (three subdomains; dampening of

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spontaneity/flat affect, mood dysregulation, increased anxiety/edginess). On the basis of these reports, 34 items were specified and incorporated into a prototype questionnaire which was piloted and refined on the basis of field-testing.

Conclusions: Items were identified that capture potential/perceived cognitive, motivational and mood-related adverse events of MPH. The items generated will allow us to further develop and psychometrically examine their prevalence, and the extent to which they are associated with medication adherence, treatment outcome, impairment and other reported adverse events (e.g., loss of appetite/cardiovascular effects).

Introduction

Methylphenidate (MPH), along with other stimulant and non-stimulant medications, is recommended for the treatment of attention deficit/hyperactivity disorder (ADHD) based on evidence of efficacy from randomized controlled trials (Graham et al., 2011; NICE, 2008). While generally well tolerated (Faraone & Buitelaar, 2010), MPH has been associated with a range of adverse events/reactions over both the short and medium/long term (Cortese et al., 2013). The most common of these include loss of appetite, restricted growth and weight suppression (Faraone, Biederman, Morley & Spencer, 2008), increases in blood pressure and heart rate (Hammerness, Perrin, Shelley-Abrahamson & Wilens, 2011; Graham & Coghill, 2008), sleep disturbances (Schachter, Pham, King, Langford & Moher, 2001), and possible exacerbation of existing tics (Pringsheim & Steeves, 2011).

Short-term positive effects of MPH on cognition and motivation are well documented in neuropsychological studies (Coghill et al., 2014; Volkow et al., 2004). Stimulant medication may improve some cognitive functions (attention) but there are also reports that it impairs others such as divergent thinking (Douglas, Barr, Desilets & Sherman, 1995) flexibility and planning (Advocat, 2010) or creativity (Farah, Haimm, Sankoorikal & Chatterjee, 2008), at least in some cases. In terms of adverse events, laboratory studies provide some evidence of cognitive rigidity (Solanto, 1984), reward desensitization (Andersen, Napierata, Brenhouse, & Sonntag, 2008), altered attribution style/sense of agency (Carlson, Pelham, Milich, & Hoza, 1993) and/or impaired memory (Sprague & Sleator, 1977) with some of these cognitive changes being dose-dependent such that higher doses lead to more impairing adverse events. Consistent with this notion, there are also reports in the literature of higher doses of MPH being more effective for behavioural management but impacting negatively on executive attention control and working memory (Berridge et al., 2006). Thus, if clinicians and families prioritise behavioural targets in treatment goals, this may limit potential impact of MPH on

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academic achievement more generally, given the lower doses required for cognitive enhancement (c.f., Hale et al., 2011). Finally, there have also been reports of adverse *emotional* events (e.g., Pelham & Hoza, 1996), which are known to play a role in both cognitive ability and motivational style.

While there are some reports that adverse events of MPH may manifest as changes in cognition and motivation, these may not be mentioned or questioned in the course of routine clinical practice. Regulatory bodies like the European Medicines Agency (EMA, 2010) require the monitoring and collection of pharmacovigilance data, which involves the monitoring of medication effects after licensing for adverse effects not reported or found in clinical trials. These data are required to be collated for potential adverse effects/events during the clinical development of psychotropic compounds and via post-marketing surveillance for up to 2 years in adult and paediatric populations. However, it is not well understood how consistently *cognitive* adverse events are reported once the regulatory monitoring and reporting period for the medication has ended (post 2 years for ADHD medication) as it depends on clinicians and patients spontaneously identifying and reporting these as adverse events or side effects (e.g., through yellow card reporting in the UK – MHRA, 2015).

While typical acute adverse effect scales for stimulant treatments, such as the Safety Monitoring Uniform Report Form (SMURF; Greenhill et al., 2004) or the Side Effects Scale (Barkley et al., 1990) collate information such as ‘stares a lot’, ‘talks less’, ‘prone to crying’, ‘anxious’, or ‘sadness’, detailed standardized assessments of potential adverse events of MPH across broader psychological domains – for instance those relating to cognition, motivation, and mood- are still lacking. Nevertheless, this may be of particular importance as it has been suggested that cognitive, motivational and emotional adverse events are significant reasons

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for lack of adherence with, or discontinuation of, long-term medication use, particularly during adolescence (Charach et al., 2004; 2008; Lindstrom, 1994).

The lack of routine monitoring of cognitive and motivational adverse events in everyday clinical practice could be linked to a more general lack of systematic monitoring of treatment response as many clinicians still rely on spontaneous reporting of adverse events by patients and parents (Kovshoff et al. 2012). It is also likely due to the fact that, compared to other elements of the putative MPH adverse event or effect profile, the concept of cognitive or motivational adverse events remains both poorly defined and articulated with no standardised approach to reporting available. Other potential reasons for the lack of focus on cognitive and motivational adverse events include that (i) they may be more difficult to observe than typical adverse events; (ii) they might be experienced as subtle and/or vague signs that are difficult to describe and self-report, particularly by younger children; (iii) they may be rare; (iv) it may be difficult to establish a causal link (if one exists) between these adverse events and the medication, or to differentiate between concerns specific to MPH and core or secondary symptoms of the ADHD itself; or (v) the benefits of MPH experienced by the patient and families may outweigh any potential cognitive or motivational adverse events experienced and so these adverse events may not be seen as sufficiently significant to warrant reporting.

The current paper represents the first stage in a project to investigate cognitive and motivational adverse events following stimulant medication use as part of the European Commission 7th Framework Programme for research; Attention Deficit/hyperactivity Drugs Use Chronic Effects (ADDUCE; www.adhd-adduce.org - Grant no 260576) (Inglis et al., submitted; Murray et al., 2013). Within this larger programme of research, one subproject involved the development of a questionnaire to systematically measure putative cognitive and motivational adverse events following MPH treatment. This will eventually allow us to estimate the prevalence of such effects in the general population of individuals treated with

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MPH, explore the association with adherence and treatment outcome, and assess their impact on daily functioning.

Aims and Objectives

The goal of this study was to generate items that characterise potential adverse events that may be associated with MPH as perceived by the patient, family, clinicians or teachers that impact on cognition and/or motivation. Our aim was to elicit examples of potential adverse cognitive and motivational events that, at least to our participants, were believed to be associated with MPH treatment so that these accounts could provide candidate items for a questionnaire that could then be validated in a larger representative sample. We first aimed to collect multiple examples and experiences of cognitive and motivational adverse events, including the key stakeholder groups in ADHD management (i.e. children and adults with ADHD, parents of children with ADHD, teachers and clinicians). The views and experiences described were then transformed into items that could be used to elicit quantifiable responses on a questionnaire. The questionnaire was then piloted in a group of children with ADHD, and subsequently refined to ensure acceptability and accessibility of items and concepts.

Method

Participants

The research protocol and all study documents received University of Southampton (ERGO Study ID 681; RGO Ref 8377) and NHS Research Ethics Committee (REC Study ID: 11/SC/0541) approval. Within this protocol, all participants were provided with information sheets describing the aims and objectives of the study, given the opportunity to reflect and ask questions about participation, and signed consent or assent forms describing how their interview data would be used. They were also provided with debrief forms outlining how to withdraw from the study if desired, obtain a copy of the findings when the study was complete, and signposting to additional services if required.

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To maximise the chances of identifying a range of potential cognitive and motivational experiences associated with MPH treatment, and to ensure that we were able to saturate our data, purposeful sampling of four independent groups of approximately 8-12 participants each, were recruited from within the South of England; experienced ADHD clinicians, adults and adolescents with ADHD who self-identified as having experienced unwanted adverse events when taking MPH, parents of children with ADHD who self-reported that their child experienced unwanted adverse events when taking MPH, and experienced teachers of medicated children with ADHD (e.g., from special needs classes, pupil referral units). Thus, all of the participants had personal or professional experience with and/or history of general MPH adverse events. The group of clinicians ($n = 15$; 9 females, 6 males) with professional experience of treating ADHD, consisted of 6 paediatricians, 7 child and adolescent psychiatrists and 2 senior nurse prescribers specialising in ADHD. They were included in the study if they had a minimum of 5 years experience of prescribing MPH to patients with ADHD and opportunities for the follow-up consultations where they would have had a chance to examine potential adverse effects. Mean length of experience of MPH prescribing was 12.0 years ($SD=6.6$). Individuals with ADHD ($n = 12$; 7 females, 4 males, 1 preferred not to disclose) included three adolescents (ages 12 to 17 years, mean age 14.6 years, $SD = 2.5$) and nine adults who had undergone relatively extended treatment (i.e., more than 12 months of consecutive use) with MPH and self-reported experiencing adverse events when taking the medication. For parents of patients/individuals with ADHD ($n = 8$; 7 females, 1 male), inclusion criteria stipulated that they had a child who had experienced evident adverse events whilst taking MPH (either past or present; we included any form of event that was deemed unwanted or adverse in the eyes of patients or families). Teachers ($n = 10$; 6 females, 4 males) who had significant experience of teaching MPH-treated children with ADHD (min. 10 children) were also interviewed. They had a mean duration of 6.4 years ($SD=3.9$) working

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with medicated children with ADHD. To ensure confidentiality, participants were ascribed unique anonymised identifiers. These consisted of a letter referring to the category to which they belonged (C=clinicians, P=parents; T=teachers; AC=individuals with ADHD) and a number (e.g., C1 for Clinician number 1). We recorded interviews and transcribed and coded them immediately after interviewing participants so that we were able to sample to saturation (i.e. the point at which no new codes were returned from the interview transcripts).

Interview Procedure

The semi-structured interview was developed by the research team to include open-ended questions about potential cognitive and motivational adverse events perceived to be directly related to MPH (e.g., could you describe any positive/negative effect of MPH on your thinking). After piloting the original interview schedule with three participants including one medicated adult with ADHD, one clinician, and one parent of an adolescent with ADHD, the final interview schedule comprised of a total of 34 questions focusing on cognitive (n=17) and motivational (n=17) adverse events. Interviewers encouraged participants to describe any potential adverse events in their own words. When describing an experience, interviewers took care to clarify whether the participant believed the experience *only appeared after or worsened since* starting MPH. The participants were informed that the study was exploratory and that the aim was to shed light on any cognitive and/or motivational adverse events which they may have noticed in their professional practice and/or personal experience of MPH. Interviews were conducted by post-doctoral level researchers who had been trained to conduct qualitative interviews and had extensive experience in this technique. Interviews typically lasted for 60 minutes and occurred at a time and place that was convenient for participants (e.g. home, place of work or via telephone).

Data Analysis

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A content analysis approach to the data (Ritchie and Spencer, 1993) was employed as it provides a flexible and deductive method for analysing text data. For the current study, conventional content analysis was employed whereby coding categories were derived directly from the text (Hsieh & Shannon, 2005). While our interview was designed to gather information about positive and negative effects of MPH, given our overall aim was to develop a questionnaire measure of adverse events, only negative/adverse experiences/events of MPH treatment were coded.

In the first phase, two researchers familiarised themselves with the transcripts through a thorough reading from beginning to end. Then, the researcher who performed the main analysis read each transcript carefully again, making notes and highlighting text that described the adverse events of medication in the pre-determined areas of cognition and motivation (e.g., memory, attention, creativity, etc.). The researcher then generated preliminary codes from the first five transcripts from each participant group, and coded the remaining transcripts using these original codes, adding new codes whenever new information was encountered that did not fit in with the existing codes. Whilst coding, the researcher collapsed or combined lower-level codes to form higher-level codes (for instance, 'inability to take in others' point of view' and 'fixation on thoughts/actions' were combined into higher-level code 'rigidity of thought', which then formed part of 'top-level' code 'Changes in thinking'). During this process, a complete detailed coding manual devised by the first coder was scrutinised by the second. The second researcher independently re-coded 10% of the transcripts, effectively re-testing all of the codes. Any differences between the codings were discussed until a mutual agreement on the final coding manual was achieved.

Results

Domains, Themes, and Subthemes

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Overall, at least one cognitive and/or motivational adverse experience of MPH was reported by 89% of participants interviewed in this study (note that this figure does not relate to prevalence rates of adverse events in the general ADHD population treated with stimulants but only in our highly selective purposeful sample). Table 1 provides a summary of themes and subthemes by domain listed in order of frequency of report/nomination by participants (in descending order from the most commonly identified adverse experience/event with the medication), alongside a prototypical statement and illustrative quote for each.

During the analysis stage, a third category of ‘mood’-related adverse events was added although it was not specifically probed in the study. A total of 84% of participants described cognitive; 80% mood-related, and 51% motivational adverse events. A detailed breakdown of these figures by domain and participant group is shown in Table 1. Table 2 represents a summary of domains and sub-domains.

Table 1 and 2 about here

Cognitive. Cognitive AEs were most commonly reported. Six domains emerged, ordered according to frequency; (1) *Poorer Attention/Concentration*, (2) *Changes in Thinking*, (3) *Reduced Creativity*, (4) *Sensory Overload*, (5) *Poorer Memory*, and (6) *Slower Processing Speed*. (1) Negative events on *Attention/Concentration* were most commonly cited and divided into three subdomains; (i) ‘zoning out/staring’ leading patients to experience a lack of clarity of thought and tendency to stare into space for long periods of time, (ii) ‘hyper- or over-focusing’ particularly leading to difficulties transitioning or dividing attention between tasks, and (iii) ‘increased distractibility’. (2) Undesirable *Changes in Thinking* patterns were the second most frequently mentioned domain of cognitive adverse events with MPH treatment, and it included two subdomains; (i) ‘increased fixation on one’s

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thoughts which included the single-minded absorption in one's thoughts and/or preoccupation with doing things in a certain predetermined way and (ii) 'rigid thinking' led users to struggle to consider another's point of view, or alternative ways of doing things.

(3) *Reduced Creativity* was reported by individuals who described a sensation of overly structured thinking experienced at the expense of creativity. (4) The fourth cognitive domain involved *Sensory Overload*. Here, respondents reported that their senses were heightened often to an undesirable degree after taking MPH. This led to a hyper-awareness of surroundings which was perceived as negative and ultimately impacted on thinking, when experienced acutely. (5) *Poorer Memory* was reported by 18% of participants. In particular, individuals described increased forgetfulness and trouble remembering or recalling recent events. (6) The sixth and final cognitive domain mentioned was *Slower Processing Speed*; some participants talked about responding to events more slowly which led to a dampening of their competitive drive, while others spoke of slower thoughts which were particularly problematic for those who wished to be creative. Here, analytic depth was perceived to lead to the negative sensation of a reduction in quick thinking and an increase in the time it takes to process information.

Motivation. The motivation category had four domains. (1) Firstly, experiences/events related to *Loss of Intrinsic Motivation for Goal-Directed Activities* referred to patients taking MPH who described themselves as more compliant and more able to complete activities, but experiencing less intrinsic motivation. (2) The second domain in relation to motivation was the development of an *External Locus of Control*. Participants reported that some individuals with ADHD may attribute behaviour regulation to medication rather than to their own ability. (3) Some individuals reported MPH led to a *Lack of Effort/Engagement with Tasks*, e.g., MPH was perceived to lead to increased difficulties initiating or participating in everyday tasks such as tidying or homework. (4) Finally, some

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participants noted that MPH users were more demanding of and required *Increased Focus on Rewards/Incentives* to complete tasks on medication. They also reported that medication led to a greater expectation and need for others to praise or reward them for activities.

Mood. A third domain, described as mood-related, emerged as the second most frequently cited adverse event of MPH. There were three sub-domains. (1) The most commonly cited being *Dampening of Spontaneity*. This included descriptions of individuals ‘losing their spark’ and becoming ‘dull’ or ‘boring’ when medicated. (2) The second most frequently described mood-related adverse event was related to *Mood Dysregulation*. Mood swings, emotional lability, and feelings of depression were reported. Secondary repercussions of this involved individuals being unable to think about and focus on tasks given their experience of negative affect. (3) Events related to *Increased Anxiety* whilst on medication were also mentioned. Here, participants gave the example of subjects choosing not to take MPH on days likely to be stressful (e.g., test days or important meetings) as they felt it would amplify and worsen anxiety.

Table 3 about here

Initial Development of the Prototype Medication and Cognition

Questionnaire. All of the domains and subdomains described in the coding manual and listed in Table 4 were used to develop prototypical questionnaire items for the Medication and Cognition Questionnaire (MCQ). Two items per domain/subdomain were created. Where possible, these were para-phrased from participants' own words (See Table 3).

The first draft of the questionnaire was piloted with 20 children with ADHD aged 7 – 16 years (Mean = 11.2; SD = 2.69) participating in the ADDUCE project (www.adhd-adduce.org) who had been taking MPH for 18 months. Following this pilot phase, it was found that 20/34 items were not consistently understood by some of the younger participants. A focus group of six typically developing children aged 7 who did not have diagnoses of ADHD was formed to help generate age-appropriate phrasing for these items. For example, the item 'Had difficulty considering alternative ways of doing things was changed to 'had trouble thinking of different ways to do things (like when doing a maths problem)'. The final item set is listed in Table 4.

The final questionnaire is being piloted within the larger ADDUCE project trial at the 18 month data collection point across the four European sites (UK, Hungary, Italy and Germany). These data will then be used to investigate the internal consistency and factor loading of the items, and to further refine the items as necessary, for example, to ensure they are developmentally appropriate, and understandable across a wide age range. We will also assess the psychometric properties of the MCQ, including conducting test-retest reliability with a subset of participants, and through tests of concurrent (e.g., looking at the relationship with mood measures) and predictive validity (looking at outcomes and medication adherence across the sample).

Discussion

Our interviews with our purposively selected and non-representative sample of clinicians, teachers, parents, and individuals with ADHD about their negative experiences and reports of MPH use, provided descriptions of potential adverse events of MPH on cognition, motivation, and mood, at least in most cases. The purpose of our qualitative interview was to harvest an in-depth and broad account of any potential cognitive or functional impact (regardless of dose), in a sample of participants enriched for experience/knowledge of adverse events/reactions to MPH. That is to say, participants all had direct (as in the case of patients) or indirect experience of adverse events/reactions more generally. *Crucially*, this was not a survey of adverse events associated with MPH in a representative sample of MPH-treated ADHD patients, and so proportions of individuals reporting events cannot in any way be equated with prevalence rates, e.g., from controlled clinical trials or post-market reporting. Determination of prevalence rates of these adverse events is currently being undertaken with the Medication and Cognition Questionnaire (MCQ) as part of the ADDUCE 2 year longitudinal naturalistic prospective pharmacovigilance study (Inglis et al., submitted) and will be reported separately.

With these caveats in mind, our findings corroborate and extend the conclusions of an emergent body of literature that has sought to examine possible adverse impacts of stimulant medication from patient and practitioner perspectives. Accordingly, Charach, Yeung, Volpe, Goodale and DosReis (2014) conducted qualitative interviews with 12 young people aged 12 to 15 years and their parents to investigate their attitudes towards use of stimulant medication. While most participants noted benefits of stimulants in multiple domains, they also expressed concerns about negative changes in their subjective experience and feelings about

themselves. They reported that their medication caused them to feel less happy, quieter, 'weird', unsociable and less outgoing. They also noted other adverse events including headaches and mood lability, which alongside the undesirable changes in their sense of self, led to a desire to discontinue medication.

Similarly, Meaux, Hester, Smith and Shoptaw (2006) interviewed 15 college students with ADHD about their experience of stimulant medication. While all participants agreed that stimulants improved their concentration and focus, many also recounted that taking stimulants involved a trade-off between any benefits of the medication and undesirable cognitive, behavioural, social, and physiological effects of the drug. In particular, they described feeling like everything was in slow motion, that their daily experiences involved feeling flat or 'monotone', and that the medication made them feel unsociable and "killed their personality" (p. 220).

As part of the ADHD VOICES Study, Singh et al., (2010) conducted focus groups and 1:1 interviews with 16 young people with ADHD on medication to gather information about their experiences of stimulant treatment. Generally, the participants in their study did not report any specific adverse events of stimulant medication. However in their final report of this study, Singh (2012) acknowledges that a "small group of children" (p. 24) felt that stimulant medication "gave them a 'second personality'" (p. 24).

When taking into account the perspectives of not only patients with ADHD but also parents, experienced clinicians, and teachers, the participants in our study identified adverse events that they perceived to be associated with MPH treatment and related to or associated with cognition, motivational style, and mood. Interestingly, participants in the current study also reported that individuals with MPH treatment developed strategies to manage any unwanted effects of the medication. For example,

those who believed that MPH exacerbated their anxiety would avoid taking their medication on days in which they were worried the impact of the medication might impede performance. However, failure to take prescribed medication may have other important costs to the individual where enhanced attention and concentration is required. Others were able to manage their medication use so that they chose when was most suitable for them to take their medication. For example, those who were required to be risk-taking or creative as part of their jobs or sporting activities avoided taking the medication for key events, and took it only when they felt it would be desirable to slow down thinking, and some of our participants only took it for tasks where creativity was not required. Still others expressed uncertainty about whether the adverse events they experienced could be directly attributed to the medication or to other causes such as puberty or co-morbid mental illnesses, or simply to a greater understanding or awareness of their ADHD symptoms. Management and identification of these sorts of adverse events require further attention and a more systematic and standardised approach to disentangle some of the issues raised. Moreover, further systematic study of these possible adverse events is also important in order to clarify their relationship with predictive/moderating variables (e.g., comorbid conditions, personality traits, genetic variance and potential relationships with physiological side effects). It would also be of clinical importance to identify which children are most likely to develop adverse cognitive, motivational or mood-related adverse events (e.g., with co-occurring anxiety symptoms, for example).

Limitations

While the participants in this study have introduced several interesting avenues for future research and consideration, it is important to note the caveats with which these data must be interpreted. This research represents a specific and goal-

oriented exercise in gathering examples of adverse events associated with MPH treatment. For this purpose, a comparison group of individuals who did not experience negative effects of MPH were not required as the ultimate goal was to collate only the adverse events described during our interview study to develop a measure of adverse events related to/associated with MPH. This measure will now require testing in large, representative samples of ADHD patients both on *and* off MPH medication, with *and* without a positive adverse effect profile, to control for bias effects. Additional testing and refinement may also be required to ensure that the measure has good validity and developmental sensitivity for both younger children and adult populations. Without this test of the data, the adverse events reported here cannot and should not be directly attributed to MPH.

Implications

The limitations above notwithstanding, our tentative findings extend some of the recent reports of adverse events of MPH in the literature by specifically addressing the putative negative impact of MPH treatment on the specific domains of cognitive, motivational and mood functioning with a broader range of participant groups. Despite the more common experience of positive effects of MPH therapy, for some individuals at least, the perceived negative impact of MPH use on their thinking, mood, and motivation has potential implications for treatment. Many clinicians interviewed in this study noted that they did not routinely screen for these types of adverse events and only recorded them if the patient spontaneously reported them. Accordingly, the use of a standardised tool to gather information about cognitive, motivational and mood effects of MPH in clinical practice may help to focus psycho-educational approaches on respective findings, and thus, hopefully contribute to medication adherence and treatment alliance (Adler & Nierenberg, 2010). Moreover,

a greater understanding of the potential adverse events of medication on these important, but often overlooked areas, will ultimately improve individualized patient care.

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References

- Abikoff, Howard, Hechtman, Lily, Klein, Rachel G., Weiss, Gabrielle, Fleiss, Karen, Etcovitch, Joy, . . . Pollack, Simcha. (2004). Symptomatic improvement in children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. *Journal of the American Academy of Child & Adolescent Psychiatry*, 43(7), 802-811. doi: 10.1097/01.chi.0000128791.10014.ac
- Adler, L.D., & Nierenberg, A. A. (2010). Review of medication adherence in children and adults with ADHD. *Postgraduate Medicine Journal*, 122(1) 184-191. doi: 10.3810/pgm.2010.01.2112.
- Andersen, Susan L., Napierata, Lee, Brenhouse, Heather C., & Sonntag, Kai C. (2008). Juvenile methylphenidate modulates reward-related behaviors and cerebral blood flow by decreasing cortical D3 receptors. *European Journal of Neuroscience*, 27(11), 2962-2972. doi: 10.1111/j.1460-9568.2008.06254.x
- Berridge, C. W., Devibiss, D. M., Andrzejewski, M. E., Arnsten, A.F.T., Kelley, A., E., Schmeichel, B., Hamilton, C., & Spencer, R. C. (2006). Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biological Psychiatry*, 60 (10), 1111-1120. doi: <http://dx.doi.org/10.1016/j.biopsych.2006.04.022>
- Carlson, Caryn L., Pelham, William E., Milich, Richard, & Hoza, Betsy. (1993). ADHD boys' performance and attributions following success and failure: Drug effects and individual differences. *Cognitive Therapy and Research*, 17(3), 269-287. doi: 10.1007/bf01172950
- Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, Graham, J Taylor E, Sergeant J and the European ADHD

- Guidelines Group (2013). Practitioner review: Current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *Journal of Child Psychology & Psychiatry*, 54, 227-246.
- Charach, A., Ickowicz, A., & Schachar, R. (2004). Stimulant treatment over five years: Adherence, effectiveness, and adverse effects. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(5), 559-567. doi: 10.1097/00004583-200405000-00009
- Charach, A., Yeung, E., Volpe, T., Goodale, T., & dosReis, S. (2014). Exploring stimulant treatment in ADHD: narratives of young adolescents and their parents. *Bmc Psychiatry*, 14, 110-110.
- European Medicines Agency (2010). Guideline on clinical investigation of medicinal products for the treatment of attentional deficit hyperactivity disorder (adhd). Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/08/WC500095686.pdf
- Faraone, S. V., Biederman, J., Morley, C. P., & Spencer, T. J. (2008). Effect of stimulants on height and weight: a review of the literature. *J Am Acad Child Adolesc Psychiatry*, 47(9), 994-1009. doi: 10.1097/CHI.ObO13e31817eOea7
- Faraone, S. V., & Buitelaar, J. (2010). Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *Eur Child Adolesc Psychiatry*, 19(4), 353-364. doi: 10.1007/s00787-009-0054-3
- Hale, J. B., Reddy, L. A., Semrud-Clikeman, M., Hain, L. A., Whitaker, J., Morley, J., Lawrence, K., Smith, A., & Jones, N. Executive impairment determines ADHD medication response: Implications for academic achievement. *Journal*

- of Learning Disabilities, 44 (2), 196-212. doi: 10.1177/0022219410391191
- Hammerness, P. G., Perrin, J. M., Shelley-Abrahamson, R., & Wilens, T. E. (2011). Cardiovascular risk of stimulant treatment in pediatric attention-deficit/hyperactivity disorder: update and clinical recommendations. *J Am Acad Child Adolesc Psychiatry, 50*(10), 978-990. doi: 10.1016/j.jaac.2011.07.018
- Hsieh, H. F., & Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qual Health Res, 15*(9), 1277-1288. doi: 10.1177/1049732305276687
- Kovshoff, H., Williams, S., Vrijens, M., Danckaerts, M., Thompson, M., Yardley, L., . . . Sonuga-Barke, E. J. S. (2012). The decisions regarding ADHD management (DRAMA) study: uncertainties and complexities in assessment, diagnosis and treatment, from the clinician's point of view. *European Child & Adolescent Psychiatry, 21*(2), 87-99. doi: 10.1007/s00787-011-0235-8
- Graham, J., & Coghill, D. (2008). Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. *CNS Drugs, 22*(3), 213-237.
- Greenhill, L. L., Vitiello, B., Fisher, P., Levine, J., Davies, M., Abikoff, H., Chrisman, A. K., Chuang, S., Findling, R. L., March, M., Scahill, L., Walkup, J., & Riddle, M. A. (2004). Comparison of increasingly detailed elicitation methods for the assessment of adverse events in pediatric psychopharmacology. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(12), 1488-1496.
- Meaux, J. B., Hester, C., Smith, B., & Shoptaw, A. (2006). Stimulant medications: A trade-off? The lived experience of adolescents with ADHD. *Journal for*

Specialists in Pediatric Nursing, 11(4), 214-226. doi: 10.1111/j.1744-6155.2006.00063.x

Murray ML1, Insuk S, Banaschewski T, Neubert AC, McCarthy S, Buitelaar JK, Coghill D, Dittmann RW, Konrad K, Panei P, Rosenthal E, Sonuga-Barke EJ, Wong IC. An inventory of European data sources for the long-term safety evaluation of methylphenidate. *Eur Child Adolesc Psychiatry*. 2013 Oct;22(10):605-18. doi: 10.1007/s00787-013-0386-x. Epub 2013 Mar 19.

MTA Cooperative Group. (1999). Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: The multimodal treatment study of children with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 56(12), 1088-1096. doi: 10.1001/archpsyc.56.12.1088

M. T. A. Cooperative Group. (2004). National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. *Pediatrics*, 113(4), 754-761.

Pelham, W.E. & Hoza, B. (1996). Intensive treatment: A summer treatment program for children with ADHD. In E. Hibbs & P. Jensen (Eds.) *Psychosocial treatments for child and adolescent disorders: Empirically based strategies for clinical practice* (pp. 311-340). New York : APA Press.

Pringsheim, T., & Steeves, T. (2011). Pharmacological treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children with comorbid tic disorders. *Cochrane Database Syst Rev*(4), CD007990. doi: 10.1002/14651858.CD007990.pub2

Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman

- A, Burgess R, editors. *Analysing qualitative data*. London: Routledge; 1993. pp. 173–194.
- Rotter, J. B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs: General and Applied*, 609, 1-28.
- Schachter, H. M., Pham, B., King, J., Langford, S., & Moher, D. (2001). How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *CMAJ*, 165(11), 1475-1488.
- Singh, I. (2012). *VOICES Study. Final Report*. London, UK.
- Singh, I., Kendall, T., Taylor, C., Hollis, C., Batty, M., Mears, A. Keenan, S. (2010). The experience of children and young people with ADHD and stimulant medication: A qualitative study for the NICE guideline. *Child and Adolescent Mental Health*. doi: 10.1111/j.1475-3588.2010.00565.x
- Solanto, Mary V. (1984). Neuropharmacological basis of stimulant drug action in attention deficit disorder with hyperactivity: A review and synthesis. *Psychological Bulletin*, 95(3), 387-409. doi: 10.1037/0033-2909.95.3.387
- Sprague, Robert L., & Sleator, Esther K. (1977). Methylphenidate in hyperkinetic children: Differences in dose effects on learning and social behavior. *Science*, 198(4323), 1274-1276. doi: 10.1126/science.337493
- Swanson, James, & Volkow, Nora. (2001). Pharmacokinetic and pharmacodynamic properties of methylphenidate in humans. In M. V. Solanto, A. F. T. Arnsten & F. X. Castellanos (Eds.), *Stimulant drugs and ADHD: Basic and clinical neuroscience*. (pp. 259-282). New York, NY US: Oxford University Press.
- Volkow, Nora D., Wang, Gene-Jack, Fowler, Joanna S., Telang, Frank, Maynard, Laurence, Logan, Jean, . . . Swanson, James M. (2004). Evidence that

methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. *The American Journal of Psychiatry*, 161(7), 1173-1180. doi: 10.1176/appi.ajp.161.7.1173

Weber, R.P. (1990). *Basic Content Analysis*. Newbury Park, CA: Sage Publications.