



**University of Dundee**

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# 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 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.

**Methods:** Following a literature search aimed at identifying associations between MPH and cognition and/or motivation, a qualitative semistructured interview was designed to focus specifically on the domains of cognition (i.e., reasoning, depth/breadth of thinking, intellectual capacity, and creativity) and motivation (i.e., drive, effort, and attitudes toward rewards/incentives). Interviews were conducted with 45 participants drawn from the following four groups: (a) clinicians, child and adolescent psychiatrists, and pediatricians specializing in attention-deficit/hyperactivity disorder (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 analyzed using a deductive approach to content analysis.

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**Results:** While we probed purposefully for cognitive and motivational adverse events, a third domain, related to mood, emerged from the reports. Therefore, three domains, each with a number of subdomains, 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 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 nonstimulant medications, is recommended for the treatment of attention-deficit/hyperactivity disorder (ADHD) based on evidence of efficacy from randomized controlled trials (NICE 2008; Graham et al. 2011). While generally well tolerated (Faraone and 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 et al. 2008), increases in blood pressure and heart rate (Graham and Coghill 2008; Hammeress et al. 2011), sleep disturbances (Schachter et al. 2001), and possible exacerbation of existing tics (Pringsheim and Steeves 2011).

Short-term positive effects of MPH on cognition and motivation are well documented in neuropsychological studies (Volkow et al. 2004; Coghill et al. 2014). Stimulant medication may improve some cognitive functions (attention), but there are also reports that it impairs others such as divergent thinking (Douglas et al. 1995), flexibility and planning (Advocat 2010), or creativity (Farah et al. 2008), at least in some cases. In terms of adverse events, laboratory studies provide some evidence of cognitive rigidity (Solanto 1984), reward desensitization (Andersen et al. 2008), altered attribution style/sense of agency (Carlson et al. 1993), and/or impaired memory (Sprague et al. 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 behavioral management but impacting negatively on executive attention control and working memory (Berridge et al. 2006). Thus, if clinicians and families prioritize behavioral targets in treatment goals, this may limit the potential impact of MPH on 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 and 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 through postmarketing surveillance for up to 2 years in adult and pediatric 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 for lack of adherence with, or discontinuation of, long-term medication use, particularly during adolescence (Charach et al. 2004, 2008).

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 standardized 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 hence, these adverse events may not be seen as sufficiently significant to warrant reporting.

The current article 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) (Murray et al. 2013; Inglis et al.

submitted). Within this larger program 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 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 characterize 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.

### Methods

#### 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.

To maximize 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 six pediatricians, seven child and adolescent psychiatrists, and two senior nurse prescribers specializing 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 consulta-

tions where they would have had a chance to examine potential adverse effects. The mean length of experience of MPH prescribing was 12.0 years (standard deviation [SD]=6.6). Individuals with ADHD ( $n=12$ ; 7 females, 4 males, 1 preferred not to disclose) included three adolescents (ages 12–17 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 while 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 with medicated children with ADHD. To ensure confidentiality, participants were ascribed unique anonymized 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 the 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 semistructured 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 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 postdoctoral-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 through telephone).

#### Data analysis

A content analysis approach to the data (Ritchie and Spencer 1993) was used as it provides a flexible and deductive method for analyzing text data. For the current study, conventional content analysis was used through which coding categories were derived directly from the text (Hsieh and 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 familiarized 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 the text that described the adverse events of medication in the predetermined areas of cognition and motivation (e.g., memory, attention, and creativity). 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.

While 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 scrutinized by the second. The second researcher independently recoded 10% of the transcripts, effectively retesting all of the codes. Any differences between the codings were discussed until a mutual agreement on the final coding manual was achieved.

## Results

### Categories, domains and subdomains

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 domains and subdomains by category 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 were described cognitive, 80% mood related, and 51% motivational adverse events. A detailed breakdown of these figures by category and participant group is shown in Table 1. Table 2 represents a summary of categories and domains.

**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 the following three

TABLE 1. NUMBER AND PERCENTAGE OF PARTICIPANTS WHO IDENTIFIED ADVERSE EVENTS IN EACH GROUP BY DOMAIN

	<i>Participants with ADHD</i> N (12), (%)	<i>Parents</i> N (8), (%)	<i>Clinicians</i> N (15), (%)	<i>Teachers</i> N (10), (%)
Cognition	11 (92)	5 (62)	13 (87)	9 (90)
Motivation	9 (75)	4 (50)	7 (47)	6 (60)
Mood	9 (75)	5 (62)	12 (80)	8 (80)

ADHD, attention-deficit/hyperactivity disorder.

TABLE 2. SUMMARY OF DOMAINS

<i>Category</i>	<i>Domain</i>
Cognitive	Slower attention/concentration Changes in thinking Reduced creativity Sensory overload Poorer memory Slower processing speed Dampening of mood/spontaneity
Mood	Mood dysregulation Sense of being different Increased anxiety
Motivation	Loss of intrinsic motivation for goal-directed activities External locus of control Lack of effort/engagement in daily tasks Increased focus on rewards/incentives

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 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 hyperawareness 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) First, 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 behavior regulation to medication rather than to their own ability. (3) Some individuals reported MPH led to a lack of effort/engagement with tasks, for example, MPH was perceived to lead to increased difficulties initiating or participating in everyday tasks such as tidying or homework. (4) Finally, some

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 subdomains. (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 while 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.

**Initial development of the prototype Medication and Cognition Questionnaire.** All of the domains and subdomains described in the coding manual and listed in Table 3 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 paraphrased from participants' own words (Table 4).

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](http://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 years, who did not have diagnosis 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 (United Kingdom, 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 nonrepresentative 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 experi-

ence/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, for example, from controlled clinical trials or postmarket reporting. Determination of prevalence rates of these adverse events is currently being undertaken with the 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 et al. (2014) conducted qualitative interviews with 12 young people aged 12–15 years and their parents to investigate their attitudes toward use of stimulant medication. While most participants noted the 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 et al. (2006, p. 220) 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, behavioral, social, and physiological effects of the drug. In particular, they described feeling like everything was in slow motion, their daily experiences involved feeling flat or monotone, and that the medication made them feel unsociable and killed their personality.

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, p. 24) acknowledges that a “small group of children” felt that stimulant medication “gave them a ‘second personality.’”

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 are 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

TABLE 3. MCQ ITEMS

<i>Over the last 4 weeks have you ...</i>	<i>Not at all</i>	<i>A little</i>	<i>More or less</i>	<i>A lot</i>	<i>Completely</i>	<i>Is this a problem for you?</i>	
1. Over-focused on jobs you had to do	0	1	2	3	4	Yes	No
2. Had trouble remembering recent experiences or events	0	1	2	3	4	Yes	No
3. Had trouble thinking of different ways to do things (e.g., like when you are doing a maths problem)	0	1	2	3	4	Yes	No
4. Felt like you weren't putting much effort into things	0	1	2	3	4	Yes	No
5. Been anxious or worried	0	1	2	3	4	Yes	No
6. Not been interested or excited to achieve your goals	0	1	2	3	4	Yes	No
7. Been distracted	0	1	2	3	4	Yes	No
8. Expected or wanted other people to praise or reward you	0	1	2	3	4	Yes	No
9. Been emotional (e.g., had lots of strong feelings)	0	1	2	3	4	Yes	No
10. Felt more boring and less exciting than usual	0	1	2	3	4	Yes	No
11. Had a very sensitive sense of smell, touch, taste or hearing	0	1	2	3	4	Yes	No
12. Been thinking slowly	0	1	2	3	4	Yes	No
13. Been well behaved	0	1	2	3	4	Yes	No
14. Noticed your thinking was fuzzy or confused	0	1	2	3	4	Yes	No
15. Felt nervous or had butterflies in your stomach	0	1	2	3	4	Yes	No
16. Not been creative	0	1	2	3	4	Yes	No
17. Noticed your mood or temper kept changing	0	1	2	3	4	Yes	No
18. Been sensitive to sights, sounds, or touch	0	1	2	3	4	Yes	No
19. Been focused on doing things in a certain way	0	1	2	3	4	Yes	No
20. Been forgetful	0	1	2	3	4	Yes	No
21. Not been pushing yourself to work as hard or harder than other people	0	1	2	3	4	Yes	No
22. Needed and wanted to be rewarded for work/behaviour	0	1	2	3	4	Yes	No
23. Been focused on your own thoughts (e.g., can't get out of your head)	0	1	2	3	4	Yes	No
24. Not shown creativity	0	1	2	3	4	Yes	No
25. Had trouble trying to understand other people's views or opinions	0	1	2	3	4	Yes	No
26. Had slow reflexes or reacted slowly	0	1	2	3	4	Yes	No
27. Found it difficult to think quickly	0	1	2	3	4	Yes	No
28. Found it really hard to start your normal everyday tasks (e.g., morning work or household chores)	0	1	2	3	4	Yes	No
29. Been "good"	0	1	2	3	4	Yes	No
30. Thought too hard or were lost in your own thoughts	0	1	2	3	4	Yes	No
31. Stared at things or people	0	1	2	3	4	Yes	No
32. Had no personality or "get-up-and-go"	0	1	2	3	4	Yes	No
33. Not been making an effort	0	1	2	3	4	Yes	No
34. Had trouble concentrating	0	1	2	3	4	Yes	No

MCQ, Medication and Cognition Questionnaire.

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 comorbid mental illnesses, or simply to a greater understanding or awareness of their ADHD symptoms.

### 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.

### Conclusions

Management and identification of these sorts of adverse events require further attention and a more systematic and standardized approach to disentangle some of the issues raised. Moreover, further systematic study of these possible adverse events is also important 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

TABLE 4. DETAILED INFORMATION ABOUT EACH DOMAIN AND SUBDOMAIN IN ORDER OF FREQUENCY (%) OF REPORTING

<i>Dom</i>	<i>Subdomain</i>	<i>N (%) of participants reporting</i>	<i>Statement</i>	<i>Detailed illustrative quote</i>
Mood	Dampening of mood/spontaneity	31 (69%)	Feel like I'd lost spark  Personality dull	Actually some of the teenage boys complain that they are not interesting when they are on MPH, they'll say "I am really chatty and girls like me when I am not on my MPH, and when I take it yes I get more work done but I am too quiet, I am dull and I don't like it." I've had a couple that asked to be taken off it because girls find them boring (C1) I have an ADHD and that is the only way I know of myself, that's how I know I am being me, like you know you are being you, and when I take meds I feel different which is why I don't like to think of it. With ADHD I feel like quite an exceptional person and when I am off my meds I can think of things creatively and people -when they see me off my medication they know it's me. When I am on my meds [...] my personality, me is shut off (AC2)
Mood	Mood dysregulation	21 (47%)	Emotional  Mood swings	I did cry more when I was on medication I think I was so tired, I was tired and frustrated that I was tired so I got bit emotional about things probably a week or so after I started taking it (AC2) We have seen changes in mood, unexplained crying, screaming, agitation, even on small doses of methylphenidate (C9)
Cog	Attention/concentration (zoning out/staring)	21 (47%)	Thoughts foggy or spacey  Stare at things for long periods	It's like you've been asleep and you just woke up and your head is all foggy. It's like that it puts you in that sort of mode ... in a way like you smoked too many spliffs ... so it's ... fogs your head. it's like you just feel like a zombie. there's much you can physically do, things that are in front of you. I was off my head "oh what's going on with my concentration" (AC4) In some cases not only staring for a long period but they look really withdrawn and non-reactive on very rare occasion (C3)
Mot	Loss of intrinsic motivation	16 (36%)	Less motivated to achieve goals  Less motivated than usual	I think I can attain something when I am on it, but the desire to attain it is greater when I am off it [...] I find it easier to attain a goal when on meds but to be honest I am personally not that bothered about it then (AC3) They sit down in a desk writing in a book, holding a pen, listen to a teacher, describe what they are going to do is much easier when they are medicated because they are not...it sounds awful, but they are not necessarily inspired they know they just need to sit down and do it if that makes sense (T2)
Cog	Changes in thinking (Increased fixation on thoughts)	15 (33%)	Preoccupied by doing things in certain way  Fixated with own thoughts	We have children who did a lot of...more collecting [things] and sorting and ordering. And we had children who had pre-occupation with thought -you know, repeating obsessional thoughts (C9) When you think... you feel like you think over and too much on it... (AC4)
Cog	Reduced creativity	13 (29%)	Less creative  Overly logical	If I've been shooting a film we've got lots of stuff going on and it's the kind of film that I know how to make very well, you know, the kind of thing we do a lot, then I won't take the drugs at all. And while we're doing all the editing and post production I generally won't take the drugs either because the drugs are very, very good if you've got to do loads of different meetings with clients and things like that, but they are not that great if you want to think very creatively (AC5) I am not as creative with my thinking as I am without it [...]When I am off my medication, I can be quite creative especially solving things and looking at things in different ways and when I am on medication it's harder to do that; I get quite logical and I come to that point where I am too logical (AC3)

(continued)



TABLE 4. (CONTINUED)

<i>Dom</i>	<i>Subdomain</i>	<i>N (%) of participants reporting</i>	<i>Statement</i>	<i>Detailed illustrative quote</i>
Cog	Sensory overload	13 (29%)	Senses overpowering	Sometimes he is saying when you are not even shouting or not shouting very loudly, he'll say you are shouting at him. So I don't know, it may have an impact there. He says "you are shouting, shouting all the time" and yet he'll be shouting. He'll shout when he wants to. It's okay for him to do that but he doesn't like anyone to raise their voice (P5)
			Hypersensitive to sight/sound/taste	Yeah your touch and your smell and everything else is more heightened, the taste buds ... It messes up all your senses really. The colours are more brighter. Yeah things are more brighter... kinda strange (AC2)
Cog	Attention/concentration (hyperfocusing on tasks)	12 (27%)	Focus too much on tasks	My husband had to deal with everything cos I couldn't put my attention on all sorts of different things that I normally would do. Normally I got all 4 [children] of them spinning around me and now I deal with it to some degree, but on meds I wasn't dealing with it at all. Just didn't wanna know [...] I'd spend 15 hours putting together a presentation for my MD (AC2)
			Over-focus on jobs	I'll just sit there and do what I enjoy and get really fixed on that, much more than I would normally do without my medication. Things like eating, washing up, I seem to focus a lot more on them than I would without my medication (AC3).
Mood	Increased anxiety	9 (20%)	Anxious	There's this inner nag, it makes me feel like I am wasting my time but I also feel like I can't ... Like I don't want to stop. I feel like there is some anxious feeling (AC6)
			Feel on edge	I can get more anxious at times. I have good days and bad days. I think I suffer with anxiety anyway but there are days when I think "I'm not going to take one today" because I just know it will make me slightly worse. So if I'm having a really off day then I would leave it because I know that it can have an effect on anxiety (AC8)
Cog	Memory	8 (18%)	Forgetful	Yes, I think he has probably got more forgetful. I have to tell him more than once to do something... more like five times sometimes... (P2)
			Trouble remembering recent events	I will forget things all the time... I forget where my shoes are, I forgot what lessons I need to go to on the day, what time it is (AC1)
Cog	Slower processing speed (MPH slow reaction time)	7 (16%)	Loss of competitive edge	I have had a couple of young people, one of them was sporting champion who didn't take Ritalin before competition because he felt it just dampened his competitive edge and that he needed to be more "devil may care" to be able to compete C2)
			Became slower to react	I find my reactions are a lot slower on tablets then off tablets. I do kickboxing and I find it very hard to do the quick fighting on tablets that I do off tablets[...] For your reactions to be quick it has to be a natural thing that you do. Off a tablet I see everything I see all the little things I hear all the little things I am really supersensitive. On a tablet it dims it all down, it puts a blanket over everything (AC4)
Mot	External locus of control (being good attributed to medication)	7 (16%)	Became good	Interestingly you sometimes get children who will say things like "oh I haven't had my tablet today so I am not going to be good" or "I can't be good today cos I haven't had my tablet" which obviously sounds rather horrifying to us. Either they got that message from school or home or perhaps they have come up with it themselves where they believe they are only good because they are taking the tablet[...] I give them MPH and they get the message that they are only good and only acceptable and only likeable because they are on MPH which is pretty horrific (C1)

(continued)

TABLE 4. (CONTINUED)

<i>Dom</i>	<i>Subdomain</i>	<i>N (%) of participants reporting</i>	<i>Statement</i>	<i>Detailed illustrative quote</i>
			Well behaved	They sort of come in and said “I am so much happier now I’m a good boy everyone likes me” but [...] are they just more compliant with people or is there a fundamental shift in cognition (C2)
Cog	Changes in thinking (increased rigidity of thought)	7 (16%)	Trouble considering others’ viewpoints	No...not able to take it in, other people’s point of view. I was trying to listen to people, I was asking people for advice [...] but now I think it’s more because I thought my decision was right...like if they’d say “I think you should do this” I’d be like “Well actually no I think we should do that” (AC2)
			Unable to consider different ways of doing things	There is less negotiating and they do have very strong ideas that can’t be changed [...] Those that are on it [MPH] do seem to be the ones that do have the more sort of unwavering ideas (T3)
Mot	Lack of effort/engagement in daily tasks	7 (16%)	Difficult to start routine or daily tasks	Everyday tasks are more hard to get motivated about to start on my medication than without. I find them easier to do without MPH. I find it easier to finish them but I can’t start them. I: What tasks do you find harder to start? AC3::just everyday tasks that I find boring, like tidying up, cleaning up, things that I have no interest in [...]I’ve got to plan to do hard stuff when I am off my medication cos it’s easier to start (AC3)
			Put less effort into things	Things like going to the toilet. Lad in my class, when he is medicated we have to remind him to do things like that. Which is really strange, you have to say “it’s break time, you need to go to the toilet, its lunch time you need to go to the toilet, it’s home time, you need to go to the toilet.” It’s not something I would have to do if he wasn’t medicated (T2)
Cog	Processing speed (slower thinking)	6 (13%)	Difficult to think quickly	What the young person is saying is that I don’t want to have that boring, detailed ... I don’t want to have the analytical depth; I want to have the free-thinking, whizzy brain stuff, which is ideal for entrepreneurial thinking (C13)
			Thinking more slowly than usual	It’s like they are sitting in honey, it becomes such a tedious, slow process for them and you know that they would’ve got yesterday in an instant, takes a really long time for them to process that information. I find that if they are that way out, they don’t retain their information at all. If they are at a point where they are just repressed by that drug, they don’t retain the information that they’ve just learnt (T2)
Mot	Increased focus on rewards/incentives/external praise	6 (13%)	Need to be rewarded for doing work	Q1: If he’s like “If I do this dad or do this mum will I get that at the end of the week?” and you say “Yeah,” so he thinks a lot about rewards. Interviewer: and was he like that before Ritalin? P1: Not as much (P1)
			Expect others to praise or reward me	For example, if they join a reading group, we have got the treasure chest out to choose a present once they have achieved a certain level of reading or whatever, but they seem to be quite needy and ask right from the beginning “what will my prize be?” So it seems to be a longing to already know what is going to happen, what the outcome is going to be (T5)
Cog	Attention/concentration (increased distraction)	5 (11%)	Distracted	Basically I think normally what might happen is I’ll be doing something complex and another thought will come into my head and it might be something like ... oh how long have I got to do this left? It might be something related to the task, but something will come in and that will distract you just enough to let you forget it (AC6)
			Trouble concentrating	There are ones who have said they can’t concentrate, they can’t pay attention[to a task] (C7)

AC, adult/child with ADHD; ADHD, attention-deficit/hyperactivity disorder; C, clinician; Cog, cognitive; I, Interviewer; Mot, motivation; P, parent, T, teacher; number, participant number (e.g., P1, parent 1).

children are most likely to develop adverse cognitive, motivational, or mood-related adverse events (e.g., with co-occurring anxiety symptoms).

### Clinical Significance

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 standardized tool to gather information about cognitive, motivational, and mood effects of MPH in clinical practice may help to focus psychoeducational approaches on respective findings and, thus, hopefully contribute to medication adherence and treatment alliance (Adler and 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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In the last 3 years, E.J.S.S.-B.—fees for speaking, consultancy, research funding, and conference support from Shire Pharma. Speaker fees from Janssen Cilag, Medice & Qbtech. Book royalties from OUP and Jessica Kingsley. Consultancy from Neurotech solutions.

In the last 3 years, D.C. served in an advisory or consultancy role for Flynn Pharma, Lilly, Novartis, Shire and Vifor Pharma. He received speaker's fee from Lilly, Novartis, and Shire. He is/has been involved in research sponsored by Shire and Vifor Pharma. He has received royalties from Oxford University Press. The present work is unrelated to the above grants and relationships.

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R.W.D. is a former employee of Eli Lilly & Co. and owner of Lilly stock. He has served in an advisory or consultancy role for Boehringer Ingelheim, Janssen-Cilag, Lilly, Lundbeck, Servier, and Shire. He has received conference attendance support and received speaker's fees from Boehringer Ingelheim, Lilly, and Shire. He has been involved in clinical trials conducted by Ferring, Janssen-Cilag, Lilly, Otsuka, Shire, and Sunovion. He has received research funding from the US National Institute of Mental Health (NIMH), the European Union (EU FP7), the German Research Foundation (DFG), the German Ministries of Research and Education (BMBF) and Health (BMG/BfArM), and the Volkswagen Foundation

J.K.B. has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly,

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S.C. within the last 3 years received conference attendance support by Shire. She has been involved in clinical trials conducted by Shire. She is participating in EU FP7 funded project.

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