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Neurological and psychiatric adverse effects of long-term methylphenidate treatment in ADHD: A map of the current evidence

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ABSTRACT

Abbreviations: ADD, Attention Deficit Disorder; ADDUCE, attention deficit/hyperactivity disorder drugs use chronic effects study; ADHD, attention deficit/hyperactivity disorder; AE, adverse events; CHMP, committee for medicinal products for human use (European Medicines Agency); DSM, diagnostic and statistical manual of mental disorders (American Psychiatric Association); EEG, electroencephalography; ICD, International Classification of Diseases (World Health Organisation); IR-MPH, Immediate Release methylphenidate; MPH, methylphenidate; MTA, Multimodal Treatment of Attention Deficit Hyperactivity Disorder Study; OROS-MPH, osmotic-controlled release oral delivery system methylphenidate; SUD, Substance Use Disorder; UK, United Kingdom; US, United States

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Bipolar
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Substance use disorder
Tics
Seizures
Sleep disorders

Methylphenidate (MPH), the most common medication for children with Attention Deficit/Hyperactivity Disorder (ADHD) in many countries, is often prescribed for long periods of time. Any long-term psychotropic treatment in childhood raises concerns about possible adverse neurological and psychiatric outcomes.

We aimed to map current evidence regarding neurological and psychiatric outcomes, adverse or beneficial, of long-term MPH (> 1 year) treatment in ADHD. We coded studies using a “traffic light” system: Green: safe/favours MPH; Amber: warrants caution; Red: not safe/not well-tolerated. Un-categorisable study findings were coded as “Unclear”.

Although some evidence suggests an elevated risk of psychosis and tics, case reports describe remission on discontinuation. Several studies suggest that long-term MPH may reduce depression and suicide in ADHD. Evidence suggests caution in specific groups including pre-school children, those with tics, and adolescents at risk for substance misuse.

We identified a need for more studies that make use of large longitudinal databases, focus on specific neuropsychiatric outcomes, and compare outcomes from long-term MPH treatment with outcomes following shorter or no pharmacological intervention.

1. Introduction

Methylphenidate (MPH) is the most commonly prescribed medication for children with Attention Deficit/Hyperactivity Disorder (ADHD) in many countries. As ADHD is a developmental disorder that may persist across the lifespan, MPH is often prescribed over long periods of time: Wang et al. (2016b) found that in Taiwan, over a third of patients with ADHD treated with immediate release MPH (IR-MPH) and nearly a half of those treated with osmotic release oral delivery system MPH (OROS-MPH) were still taking MPH two years after treatment initiation. A follow-up investigation of participants in the United States Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study (Molina et al., 2009) showed that at 8 years after treatment initiation, 32.5% were still taking medication, including MPH, for over 50% of days. Concerns about a broad range of possible adverse effects of long-term stimulant treatments have been highlighted in the media and by some interest groups, scientists and health professionals (Klein-Schwartz, 2002).

In 2009, after reviewing the available research evidence, the Committee for Medicinal Products for Human Use (CHMP) concluded that the ratio of benefit-to-risk for MPH when used for the authorized indications, such as ADHD, was favourable (European Medicines Agency, 2007). However, they also noted that more data were needed on long-term effects in children and young adults, including neurological and psychiatric effects. In particular, CHMP noted a range of psychiatric adverse events, including aggression, psychosis, mania, irritability and suicidality, and suggested that methylphenidate may play a causative role in the development of serious psychiatric disorders.

The objective of the European Union-funded ADDUCE (Attention deficit/hyperactivity disorder drugs use chronic effects) project, was to address this knowledge gap (see www.adhd-adduce.org for more information, grant agreement number 260,576). In the current study, we aimed to map the current evidence base regarding adverse neuropsychiatric effects, including behavioural effects, of long-term MPH treatment (treatment duration of a year or more), including long-term effects of such treatment.

Investigating potential adverse neuropsychiatric effects of any treatment for ADHD is complicated by comorbidity and the symptom overlap between ADHD and other neuropsychiatric conditions. These include mood, anxiety and substance use disorders (SUDs) (Kessler et al., 2006); bipolar disorder (Marangoni et al., 2015); psychotic-like symptoms (Hennig et al., 2017); and sleep disorders (Silvestri et al., 2009). In turn, in children with Tourette Syndrome (TS) (Freeman et al., 2000) and epilepsy (Salpekar and Mishra, 2014) there is a high prevalence of comorbid ADHD. Treatment with MPH to address the symptoms of ADHD may help with some of these comorbid symptoms. However, being a psychotropic drug, it also has the theoretical potential to induce or exacerbate them. Similarly, while effective treatment

with MPH during childhood and adolescence may reduce the risk of adverse neuropsychiatric outcomes, prolonged exposure to any psychoactive drug during development has the theoretical potential to raise the risk of at least some neuropsychiatric disorders.

The question as to whether long-term MPH treatment has adverse neuropsychiatric effects, either during or after prolonged treatment, is therefore not only clinically important, but particularly challenging to answer. For example, ADHD severity may be an important potential confounder as it may be associated with both the need for long-term MPH therapy and high levels of underlying neuropsychiatric comorbidity. The problem of disentangling the elevated risks of adverse outcomes arising from ADHD itself or from the risks posed by exposure to the drugs used to treat it can be approached in a variety of ways and at many units of analysis, from individual longitudinal case studies to nationwide cohort studies. Each approach is likely to contribute relevant information. The purpose of this study was to provide as complete a picture as possible of the evidence base to date.

Our investigation was submitted to Prospero (registration number CRD42013005049). Our initial aim, as documented in the Prospero submission, had been to delineate the adverse neuropsychiatric effects of long-term methylphenidate use, using “group-based analyses separately for each adverse symptom; quantitative versus narrative synthesis depending on number of studies to be entered in the final analyses.” However, our searches revealed a highly heterogeneous evidence base, with a wide range of methodologies, outcomes of interest, treated populations, and comparators, which precluded meaningful quantitative synthesis for many outcomes. It therefore became evident that the priority was to provide an “evidence map” (Hetrick et al., 2010; Miale-Lye et al., 2016) that would help prioritize the research agenda. In this approach, study parameters are systematically extracted from studies that meet eligibility criteria, and tabulated under headings decided *a priori*. This table can then be interrogated to address specific questions of interest.

We set out to produce an evidence map of the research literature relating to the potential adverse neuropsychiatric effects of long-term MPH treatment, defined as treatment for one year or more. Our search embraced investigations designed to investigate both adverse and potentially beneficial long-term outcomes of long-term treatment.

2. Method

2.1. Data sources and selection

We searched the Medline, Embase, and Psycinfo publication databases for terms relating to “ADHD”, “methylphenidate”, “tics”, “self-injury”, “mood disorders”, “psychoses”, “substance use”, “epilepsy”, “sleep disorders”, “dyskinesia” (see Appendix for search strategy details).

2.1.1. Inclusion criteria

A study was included if:

- It was an original full article that provided evidence regarding potential neurological, psychiatric or behavioural adverse effects of MPH in humans of any age. We included studies that investigated any potential neurological, psychiatric or behavioural outcome of MPH treatment (outside the core symptoms of ADHD), irrespective of whether they were hypothesised to be positive or negative.
- The participants had been diagnosed with the disorder variously referred to as: ADHD; Attention Deficit Disorder (ADD) with or without hyperactivity; hyperkinetic reaction of childhood; hyperactive disorder, or hyperkinetic disorder.
- It was clear that the mean, median or modal treatment duration was 12 months or more.

2.1.2. Exclusion criteria

A study was excluded if:

- It was clear that the indication for treatment with MPH was not ADHD.
- The mean or most common duration of treatment was no more than 12 months' duration, and evidence of harm consisted only of adverse events (AEs) recorded during that 12 month exposure. Studies where the most common duration of treatment was 12 months were included if potential adverse outcomes were evaluated at or later than 12 months.
- It was not possible to separate the effects of MPH from other forms of treatment.

2.1.3. Screening

The search was conducted in two waves. The first search included records up to January Week 3, 2013, and returned 4681 unique records. One researcher screened titles and abstracts for relevance, and a random 20% of the exclusions were checked by a second researcher. Full-text copies were obtained for the remaining records (N = 435). These were then screened using our full inclusion and exclusion criteria. Records in languages other than English were assessed by a person with proficient ability in that language. All full-text exclusions were checked by a second investigator.

In the second wave of searches, the same search was iteratively updated using the same search terms, the final search being on 19th February 2019. This process returned a further 2215 unique records. In this wave, only English-language articles were included for full-text review (N = 280). All exclusions at both title and abstract screening stage and at full-text screening stage were checked by a second investigator.

2.2. Data extraction and mapping

Our data extraction tool was developed in Microsoft Excel, with drop-down menus for categorical items, and free-text cells as appropriate. It was piloted on six included studies, after which further refinements were made where necessary. Investigators extracted data from the full texts, highlighting areas of uncertainty for resolution through discussion. Data headings fell into five broad categories:

- 1 Study characteristics, e.g. aims, design, setting
- 2 Sample characteristics, e.g. age range, comorbidities, gender, sample size, diagnostic criteria
- 3 Treatment details, e.g. treatment duration, MPH formulation, concomitant treatments, comparator treatment where relevant
- 4 Potential adverse outcomes addressed¹

5 Study conclusions, categorised using a "Traffic-light" system ("Yes", "Proceed with Caution"; "No"; "Unclear")

- For comparative studies: Does the study overall favour MPH?
- For non-comparative studies: Do the authors conclude that MPH is safe/well-tolerated?²

For the comparative studies, if the comparator was another active treatment, we coded the result as "Yes" if the outcome favoured MPH, or "No" if it favoured an alternative. If there was no clear difference between comparators, we coded the result as "Yes" if the outcome was beneficial for all comparators, and "Proceed with Caution" if the risk associated with all treatments was low. In all other cases, we coded the result as "Unclear". Where the comparator was "no treatment", we coded the result as "Yes" only if the outcome was positively better for MPH. For studies that showed significant adverse effects of MPH, we coded the result as "Proceed with Caution" unless the result clearly contraindicated the use of MPH, in which case it would be coded "No". Any other result was coded as "Unclear".

The full list of headings is given in [Table 1](#): Data map headings. The evidence map file itself is available in Supplementary materials.

Following data extraction, we used pivot tables to generate tabulated summaries of the evidence for each outcome. Narrative summaries made use of study-specific information as appropriate.

3. Results

Sixty-four publications met our criteria for inclusion, with publication years ranging from 1971 to 2018. Numbers of publications included and excluded at each stage of the process are given in the PRISMA diagram in [Fig. 1](#).

Publications consisted of 39 group studies, eight case series studies, and 17 single case studies. We treated each case within a case series as a separate item of evidence, and applied our inclusion and exclusion criteria to each case. In three of the case-series publications ([Kazanci et al., 2015](#); [Schubiner et al., 1995](#); [Sprafkin and Gadow, 1993](#)) two of the individual cases reported met inclusion criteria. The final evidence map therefore consisted of 67 items of evidence: 39 group studies, and 28 individual case reports extracted from 25 publications. Of the 39 group studies, we coded 28 as comparative designs (including both categorical and continuous comparators) and 11 as non-comparative.

3.1. Study characteristics

3.1.1. Study designs

Of the 28 comparative studies, 23 were observational cohort studies, and five were controlled trials. Three of the controlled trials were Randomized Controlled Trials (RCTs), and two were time-series treatment-withdrawal challenge studies (see [Table 2](#) for further details). Of the 11 non-comparative group studies, six were prospective open-label longitudinal studies, and five were retrospective studies ([Table 3](#)). Of the 25 publications contributing to the 28 case reports, eight were case series with a common theme and 17 were single case reports ([Table 4](#)).

Investigating potential harms of MPH treatment was the primary aim in all the non-comparative studies, and all but one of the case studies. However, in 9 (23%) of the comparative studies, investigation of harms was a secondary aim. In most of these (7/9), the primary aim was investigation of long-term neuropsychiatric outcomes in children, adolescents or adults with ADHD, with MPH treatment as a potential modifier of outcome (see [Fig. S1.1](#) for a summary of study designs and aims, broken out by study type).

² This determination was based on our reading of the authors's conclusion. Note that authors' criteria for safety/tolerability may differ between studies.

¹ Including outcomes anticipated in the study to be beneficial.

Table 1
Data map headings. Data map headings. NR = Not Reported.

| Heading | Explanation | Entry |
|---|--|--|
| First author, year | Study identifier in first author-date form | Free text |
| Investigation of harms of long-term MPH use | Was investigation of harms an explicit aim of the study? | Primary aim, Secondary aim, Unclear aim, Post-hoc reporting |
| Study design | What was the study design? | Systematic review, RCT, Cluster RCT, Cross-over RCT, Non-randomized Controlled Trial, Comparative Cohort, Nested Case-control, Case-control, Non-comparative Trial, Non-comparative Cohort, Time Series, Case-series, Case Report, Survey, Other |
| Study design -Other (text) | Study design details if not otherwise specified | Free text |
| Study related to Postmarketing Surveillance Program | Whether or not the study was a post-marketing surveillance study. | Yes/No |
| Centre | How many centres in the study? | Single, Multi, NR |
| Study Funding | How was the study funded? | Industry, Non-Industry, Unclear, NR |
| Study Location | In which geographical region did the study take place? | North America, Central or South America, Africa, Europe, Middle East, South Asia, Asia Pacific, Australia or New Zealand, Multi-region NR |
| Multi-region | Study location details if not otherwise specified | Free text |
| Sample size | Total sample study size, including data not analysed | Integer |
| Does this study report neuropsychiatric harms? | Does this study report neuropsychiatric harms? | Yes, No (stop further data extraction) |
| Study setting | What was the setting for the study? | Community or school, Hospital or clinic, Prison/forensic, NR |
| Data analysis level | Was the relevant data analysis conducted at study level or at subgroup level? | Study level, Subgroup level |
| N analyzed | What was the sample size of the group or subgroup analysed | Integer |
| Duration of most common follow-up time point in years | When was the followup data collected? | Integer |
| Study population description | What was the study population? | Free text |
| Notable eligibility criteria impacting generalisability | What were the eligibility criteria? | Free text |
| Age category | How old were the participants? | < = 5, > 5- < 18, < 5- < 19, Adults only, Adolescents only, Mixed, Other category, Unclear or NR |
| Age category-other | Age of participants if not otherwise specified | Free text |
| Sex/gender | What was the gender composition of the sample? | Females only, Males only, Mixed (predominantly females), Mixed (predominantly males), Mixed, NR |
| ADHD diagnostic criteria | What criteria were used for ADHD diagnosis? | ICD, DSM, ICD or DSM, Other, NR |
| ADHD subtypes | What was the ADHD subtype composition of the sample? | Combined, Inattentive, Hyperactive/impulsive, Mixed, Other, NR |
| Notable ADHD comorbidity 1 (analysis level) | What, if any, notable comorbidities were reported? If more than one, give the most notable. | Anxiety, Autism spectrum/communication, Bipolar disorder, Depression, Dyskinesias, Eating disorder, Intellectual disability (IQ < 70), Obsessive compulsive, ODD/CD, Psychosis/hallucinations, Seizures/EEG abnormalities, Self-injury/suicidal thoughts/behaviours, Sleep disorders, Specific learning impairment/learning disability, Substance use disorder, Tics/Tourette syndrome, Other, NR, None |
| Notable ADHD comorbidity 1 -other | If “other” entered for previous heading, specify the most notable comorbidity here. | Free text |
| Notable ADHD comorbidity 2 (analysis level) | What additional comorbidities, if any, were reported? If more than one, enter “Mixed”. | Anxiety, Autism spectrum/communication, Bipolar disorder, Depression, Dyskinesias, Eating disorder, Intellectual disability (IQ < 70), Obsessive compulsive, ODD/CD, Psychosis/hallucinations, Seizures/EEG abnormalities, Self-injury/suicidal thoughts/behaviours, Sleep disorders, Specific learning impairment/learning disability, Substance use disorder, Tics/Tourette syndrome, Other, Mixed, NR, None |
| Notable ADHD comorbidity 2 -other | If “Other”, or “Mixed” entered for previous heading, enter all other comorbidities reported. | Free text |
| Intervention | Was the MPH intervention investigated combined with another intervention? | MPH, MPH + Other |
| Intervention-Other | If “other” entered for previous heading, specify here. | Free text |
| MPH Release type | What was the MPH release-type? | Immediate release, Modified release, Transdermal, Mixed, Unclear or NR |
| MPH formulation | What was the MPH formulation? | Concerta XL, Equasym XL, Medikinet XL, Ritalin SR, Ritalin LA, Mixed, Unclear or NR |
| MPH dose format | How was the MPH dose quantified? | Mean, Median, Range, One dose, Other, NR |
| MPH dose format – other | MPH dose format if not otherwise specified | Free text |
| MPH dose (numbers only) | What was the MPH dose? | Number |
| Dose Unit | What were the MPH dose units? | Free text |
| Most common treatment duration in months | What was the most common treatment duration in months? | Integer |
| Comparator category | For comparative studies: what was the comparator? | No treatment or placebo, Other stimulant, Other non-stimulant drug, BT, Other treatment, Mixed, Multiple comparators, NA (single group) |
| Specific Comparator(s) – when multiple comparators or “other treatment” | For comparative studies: what was the comparator if not otherwise specified? | Free text |
| Notable concomitant treatment | Specify any notable concomitant treatment. | Bupropion, Clonidine, Guanfacine, Melatonin, Mood stabiliser, Other, Mixed, NR |
| Notable concomitant treatment-Other | Any notable concomitant treatments if not otherwise specified | Free text |

(continued on next page)

Table 1 (continued)

| Heading | Explanation | Entry |
|---|--|---|
| Low Mood/Depression | Was this potential neuropsychiatric outcome investigated or reported in the study? | Yes/No |
| Anxiety | | Yes/No |
| Irritability/emotional reactivity | | Yes/No |
| Suicidal behaviour/ideation | | Yes/No |
| (Non-suicidal) Self harm | | Yes/No |
| Bipolar disorder | | Yes/No |
| Psychosis | | Yes/No |
| Psychotic like symptoms | | Yes/No |
| Substance use disorder | | Yes/No |
| Tics | | Yes/No |
| Other dyskinesias | | Yes/No |
| Seizures or EEG abnormalities | | Yes/No |
| Sleep disorders | | Yes/No |
| Visual disturbances | | Yes/No |
| Other notable neuropsychiatric outcome | | Potential neuropsychiatric outcome investigated but not otherwise specified |
| Favours MPH (comparative studies) | For comparative studies: did the outcome favour MPH? | Yes, No, Proceed with Caution, Unclear, NA |
| Authors judgement of safety (non-comparative studies) | For non-comparative studies: what was the authors' judgement of safety? | Yes, No, Proceed with Caution, Unclear, NA |
| Other comments | Any other comments | Free text |

3.1.2. Sample sizes

Sample sizes in the comparative studies ranged from $N = 5$ to 289,840, the two smallest being within-subject time-series designs. The eight largest studies all made use of national/state-wide databases. For the non-comparative group studies, sample sizes ranged from $N = 18$ to 228. For sample size histograms see Fig. 2.

3.1.3. Participants

3.1.3.1. Age and gender. The majority of studies were of children and/or adolescents, sometimes extending into young adulthood by the time of the reported outcomes. The age and gender composition of the group studies is shown in Fig. S1.2. Twenty-two of the case reports were of children or adolescents (20 male), and six were of adults (four male).

3.1.3.2. Diagnoses

3.1.3.2.1. Diagnostic terms and criteria for ADHD. Diagnostic terms reflected the changing definitions and terminology for ADHD over the extensive range of publication dates (1971–2018) of the included studies. In studies in which the original diagnosis had been made prior to 1980, the diagnostic term reflected the DSM-II label “hyperkinetic reaction of childhood” (“hyperactive”; “hyperactivity”; “hyperkinesis”). Two publications used the term Attention Deficit Disorder (ADD), introduced in the DSM-III in 1980. Studies in which the diagnosis had been made after the introduction of the term ADHD in the DSM-III-R used this term (see Fig. S1.3).

ADHD diagnostic criteria were often unreported; where they were, in all but one study these were either DSM or ICD criteria (see Fig. 5, Panel B). Twenty-four of the group studies used DSM criteria, ranging from DSM-II to DSM-IV-TR, while six studies used ICD codes. Twelve group studies reported ADHD subtypes. Eight case reports referred to DSM criteria (DSM-III to DSM 5). Three case reports specified a subtype.

3.1.3.2.2. Comorbid disorders. Not all 39 group studies reported on the presence or absence of comorbid disorders. Of the 25 that did, only one excluded participants with comorbidities (Hammerness et al., 2017). The remainder reported at least one comorbid disorder in their sample, and 12 reported two or more comorbidities. Seven group studies investigated cases of ADHD with specific comorbidities: three with epilepsy (Fosi et al., 2013; Gucuyener et al., 2003; Mulas et al., 2014); three with a tic disorder (Gadow et al., 1999; Nolan et al., 1999; Riddle et al., 1995); and one by Kutlu et al. (2017), of cases with oppositional defiant disorder (ODD) or comorbid conduct disorder (CD). Thirteen of the case studies reported on comorbidities: one reported that there were no comorbid disorders, eight reported one

comorbid disorder, and four reported more than one.

Either ODD or conduct disorder CD was most commonly reported as the first or most prevalent comorbidity, followed by tic disorder or Tourette Syndrome, and anxiety disorder. These disorders were also the most commonly reported comorbid disorders overall (Table 5).

3.1.4. Predictors of outcome

3.1.4.1. MPH treatment. The type of MPH release formulation (e.g. immediate or modified release) was often unreported, unclear, or reported as mixed (see Fig. S1.4).

In 24 of the 67 studies, the type of MPH delivery was clearly specified, and in 50 studies, dosage was reported. The estimated most common MPH treatment duration in studies ranged from 1 to 6 years³ (See Table 6).

3.1.4.2. Comparators. Comparators were highly varied (see Fig. 3). Fifteen of the comparative studies had multiple comparators. Twelve studies included comparisons or contrasts with other pharmacological treatments including other stimulants (3 studies) and the non-stimulant atomoxetine (6 studies). Many studies compared outcomes after long-term MPH treatment with outcomes after either no, or less, exposure to MPH treatment. Six of these used continuous measures of treatment exposure (MPH and/or other treatment) e.g. duration or dosage as predictors of outcome. The comparators for each comparative study are given in Table 7.

3.1.5. Outcome categories

Our data-extraction tool had 15 headings for potential adverse outcomes, including *other notable neuropsychiatric outcome* (Table 1). We found no studies that investigated *non-suicidal self-harm* as an outcome of long-term MPH treatment. Our heading “visual disturbances” was designed to record studies in which visual disturbances of a neurological origin were investigated. However, the only studies in which visual disturbances were reported were those in which the report suggested that they were better categorised as psychotic-like symptoms. Outcome categories for Comparative Studies are given in Table 7 and for non-Comparative Studies in Table 8.

³ Five studies used Taiwan’s nationwide health insurance database. While a mean duration of MPH treatment was not explicitly given as being over 12 months in these five studies, a study of treatment persistence using the same database indicates that the proportion of cases of ADHD who persist with MPH treatment for over 12 months is over 50% (Wang et al., 2016b).

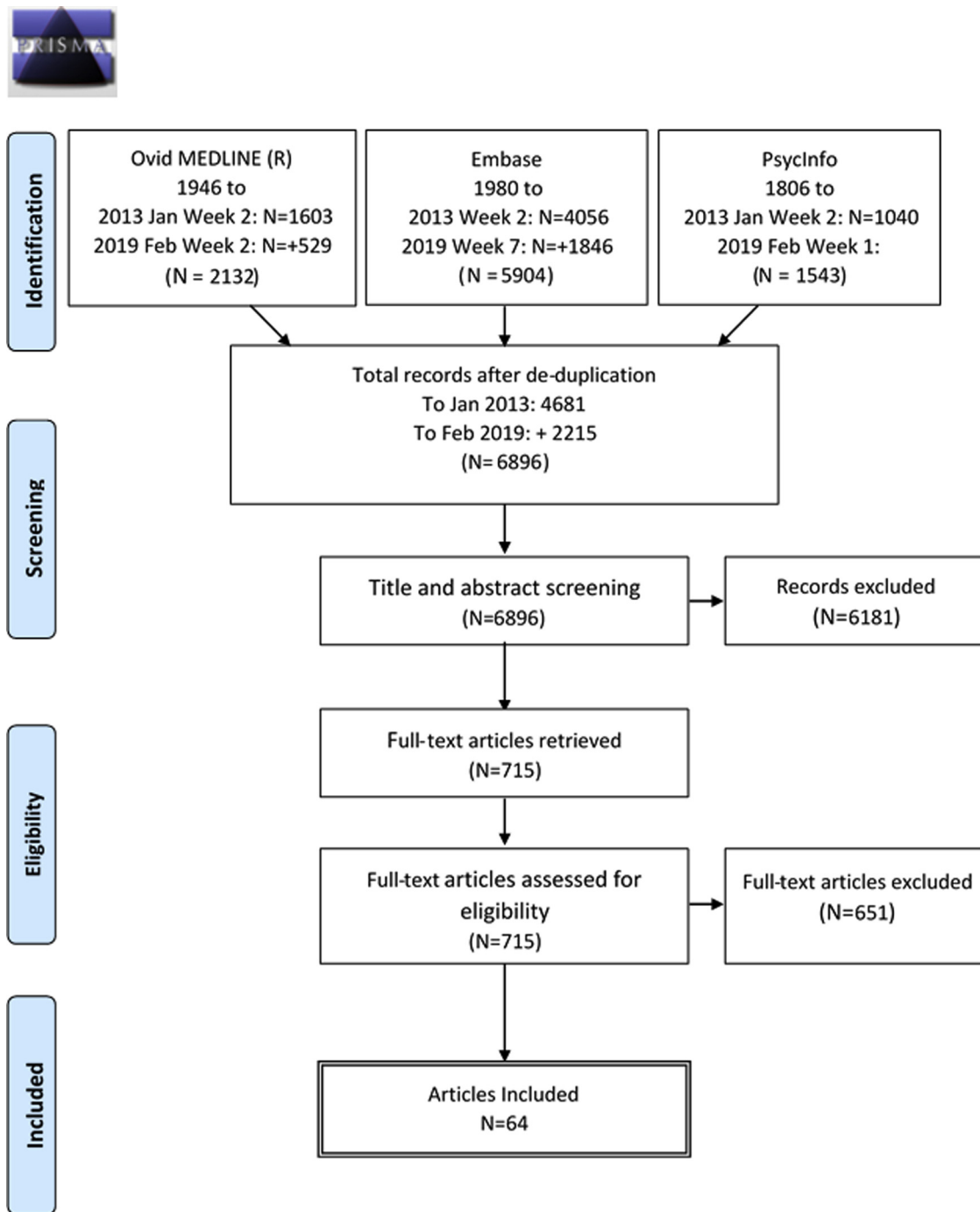


Fig. 1. Prisma flow chart for literature search.

During data extraction, it became apparent that the research questions addressed by the group studies fell into two broad types. The first type comprised questions regarding the safety or tolerability of long-term (> 12 months) MPH treatment by measuring *adverse events/effects* (AEs) during long-term MPH treatment. Included in this group were studies that investigated the risk of *exacerbation* of specific pre-existing conditions or risk factors e.g. a history of tics or seizures. The second type comprised questions regarding long-term outcomes for participants who had received or were still receiving long-term MPH treatment. The primary aim of some of these studies were to investigate potential medium-to-long-term benefits of long-term MPH treatment for these outcomes, while for others it was to establish long-term risk. We therefore added a *post hoc* variable to the evidence map in which we

categorised the group studies into these categories (see Fig. S1.5). Some studies fell into a grey area between the two, being studies of medium-term neuropsychiatric outcome immediately following a period of MPH treatment. In these cases, two investigators conferred on categorisation, and the decision was made on the basis of the nature of the primary study question.

The *AE* studies were a mix of comparative and non-comparative designs, including open-label extensions to clinical trials. In these safety/tolerability studies, the adverse effects recorded or solicited were often diverse, but studies only met our inclusion criteria if the effects included at least one neuropsychiatric effect. In *Outcome* studies, the evidence for potential adverse effects or outcomes was provided by evaluation of neurological, psychiatric or behavioural symptoms. The

Table 2
Comparative studies. Comparative study details. For “Favours MPH”, Y = Yes; C = Proceed with Caution; U = Unclear.

| | Potential adverse outcome question addressed | N analysed | Treatment duration | Outcome measure | Favours MPH? |
|--------------------|--|------------|--------------------|---|--------------|
| N < 1000 | | | | | |
| Cohort | | | | | |
| | Hechtman et al., 1984 | 76 | 36 | Psychiatric assessment | Y |
| | Lipkin et al., 1994 | 122 | 13-23 | Solicited tic reports | U |
| | Corkum et al., 1999 | 172 | 12 | Sleep questionnaires | U |
| | Paternite et al., 1999 | 97 | 30 | Chart Evidence | C |
| | Chuman et al., 2001 | 27 | 24 | AEs | U |
| | Hemmer et al., 2001 | 205 | < 12 | Seizure records | C |
| | Varley et al., 2001 | 517 | 16 | AEs | U |
| | Huss et al., 2008 | 215 | 27 | Diagnostic interview | U |
| | Mannuzza et al., 2008 | 176 | 23 | Follow-up by clinicians | Y |
| | Gau and Chiang, 2009 | 281 | 20 | Sleep questionnaires | U |
| | Ginsberg et al., 2015 | 25 | 36 | SUD rating scales | Y |
| | Haynes et al., 2015 | 704 | 24 | AEs | Y |
| | Kitel-Schneider et al., 2016 | 70 | 12 | Self-rating scale | U |
| | Hammeress et al., 2017 | 211 | 13 | SUD rating scale | Y |
| | Schrantee et al., 2018 | 91 | 72 | Self-rating scales for Depression, Anxiety, SUD | C |
| Time-series | | | | | |
| | Riddle et al., 1995 | 5 | 12 | Tic rating scales | C |
| | Nolan et al., 1999 | 19 | 51 | Tic rating scales | U |
| RCT | | | | | |
| | Quinn and Rapoport, 1975 | 73 | 12 | Rating scales | U |
| | Hechtman et al., 2004 | 103 | 36 | Self-rating scales | Y |
| | Philipsen et al., 2015 | 419 | 12 | Self-rating scale | U |
| N > 1000 | | | | | |
| Cohort | | | | | |
| | Cortese et al., 2015 | 2331 | > 12 | AEs | Y |
| | Jerrell et al., 2014 | 22,797 | 17 | ICD codes | U |
| | Steinhausen and Bisgaard, 2014 | 20,742 | 36 | ICD codes | Y |
| | Shyu et al., 2015 | 146,098 | 12 | ICD codes | C |
| | Lee, 2016 | 142,160 | 12 | ICD codes | Y |
| | Wang et al., 2016a | 289,840 | 12 | ICD codes | Y |
| | Huang et al., 2018 | 20,574 | 12 | ICD codes | Y |
| | Liang et al., 2018 | 84,898 | 12 | ICD codes | Y |

Table 3
Non-comparative studies. Non-comparative study details. For “MPH safe?”: Y = Yes; C = Proceed with Caution; U = Unclear.

| Potential adverse outcome question addressed | N analysed | Treatment duration (months) | Outcome measure | MPH safe? |
|--|------------|-----------------------------|-------------------|-----------|
| RETROSPECTIVE DESIGNS: | | | | |
| Chart review | | | | |
| Cherland and Fitzpatrick, 1999 | 98 | 21 | AEs | C |
| Fosi et al., 2013 | 18 | 12 | Seizure frequency | Y |
| Mulas et al., 2014 | 17 | 24 | EEG | C |
| Weiss et al., 1975 | 22 | 60 | EEG | Y |
| Edvinsson and Ekselius, 2018 | 46 | 72 | AEs | Y |
| PROSPECTIVE DESIGNS: | | | | |
| Open label longitudinal study | | | | |
| Gucuyener et al., 2003 | 119 | 12 | EEG | Y |
| Wilens et al., 2005 | 228 | 21 | AEs | Y |
| Atzori et al., 2009 | 134 | 36 | AEs | Y |
| Torgersen et al., 2012 | 52 | 41 | DSM-IV codes | Y |
| Kutlu et al., 2017 | 118 | 12 | Self-report scale | Y |
| Gadow et al., 1999 | 34 | 24 | Tic rating scales | C |
| Open label trial extension | | | | |
| Rate of psychotic side effects in stimulant-treated children | | | | |
| MPH safety in children with ADHD + severe epilepsy | | | | |
| Pharmacological management of ADHD with MPH and ATX within a context of epilepsy | | | | |
| MPH treatment as a risk factor for seizures | | | | |
| Long-Term Tolerability and Safety of Pharmacological Treatment of Adult Attention-Deficit/Hyperactivity Disorder | | | | |
| MPH treatment as risk factor for seizures | | | | |
| Adverse effects of MPH treatment in children | | | | |
| Adverse events affecting compliance with MPH treatment | | | | |
| Comorbid SUD under long-term stimulant treatment of ADHD | | | | |
| MPH effects on emotional dysregulation | | | | |
| MPH as a risk factor for tic exacerbation in young people with ADHD + tic disorder | | | | |

measures used to evaluate symptoms in these studies included both broad and targeted symptom rating scales; ICD codes; and objective markers (e.g. tic monitoring; EEG).

3.2. Summaries of findings by pharmacological comparators

Below we summarise the findings of studies that compared long-term MPH treatment with other pharmacological treatments.

3.2.1. Atomoxetine

Of the six studies that included a comparison with atomoxetine, two were investigations of adverse effects of treatment. In a large pharmacovigilance study, Cortese et al. (2015) found significantly fewer neuropsychiatric AEs overall for MPH than for Atomoxetine⁴. Haynes et al. (2015) investigated factors predicting worsening ADHD severity, and measured a range of AEs to MPH and atomoxetine treatment; and these included sleep AEs⁵. We coded the result of this study as *Unclear*. The other three studies used large national databases and each considered a specific long-term outcome: Lee et al. (2016) investigated mood disorder⁶; Wang et al. (2016a), considered bipolar disorder⁷ and Liang et al. (2018) considered suicidal behaviour.⁸ For all three outcomes, as neither MPH nor atomoxetine treatment was associated with increased risk, and long-term MPH treatment was associated with reduced risk, we coded these results as *Favours MPH*.

We conclude that further large studies are needed to evaluate the long-term risks and/or benefits of MPH vs atomoxetine with regard to other long-term neuropsychiatric outcomes.

3.2.2. Other stimulants

Three studies compared MPH with other stimulants (e.g. dexamphetamine; pemoline; Adderall). Two investigated emergence of tics (Lipkin et al., 1994; Varley et al., 2001), and compared MPH with dexamphetamine and pemoline. While tic emergence rates were low in both studies, neither study found any significant difference in tic emergence rates between stimulants. We coded the results of Lipkin et al. as *Unclear*. The children in the larger study by Varley et al. excluded children with a history of tics, and we coded the results of Varley et al.'s larger study as *Proceed with Caution* for this population. Ghuman et al. (2001) investigated AEs, including tics, in pre-schoolers (N = 27) treated with MPH, Adderall and dexamphetamine. As AE rate was generally high for all three stimulants, with no significant difference between stimulants, we coded the result for the comparative safety of MPH as *Unclear*. We conclude that the evidence base for the relative safety of MPH vs other stimulants with regard to tics is weak, as is the evidence base for its relative safety in pre-schoolers.

3.2.3. Other pharmacological comparators

Two studies compared MPH with medications not primarily indicated for ADHD. In an open-label RCT, Quinn and Rapoport (1975) investigated anxiety in a sample of boys after a year's treatment with MPH, the antidepressant imipramine, or placebo and found no significant differences in anxiety between any treatment.⁹ We coded this result as *Unclear*. Using a large nationwide database, Steinhilber and Bisgaard (2014) investigated SUD as an outcome following treatment with either MPH, antipsychotic treatment, antidepressant treatment or mixed treatment, and found a benefit for MPH but the opposite for

⁴ See section on Low Mood or Depression; Irritability/Emotional reactivity; Suicidal behaviour/ideation; Psychosis and psychotic like symptoms.; Seizures or EEG abnormalities; Sleep disorders.

⁵ See section on Sleep disorders.

⁶ See section on Bipolar disorder.

⁷ See section on Low Mood or Depression.

⁸ See section on Suicidal behaviour/ideation.

⁹ See section on Anxiety.

Table 4
 Case reports and outcomes. Case reports, with the potential adverse outcomes reported. Check marks indicate which of the 10 neuropsychiatric outcome were investigated or reported on in that study. For “MPH safe?”: Y = Yes; C = Proceed with Caution; N = No; U = Unclear.

| | Study | Low Mood/ Depression | Anxiety | Irritability/ emotional reactivity | Suicidal behaviour/ ideation | Bipolar disorder | Psychosis or Psychotic symptoms | Substance use disorder | Tics and other dyskinesias | Seizures or EEG abnormalities | Sleep disorders | MPH safe? |
|---|------------------------------------|-------------------------|---------|--|------------------------------------|---------------------|---------------------------------------|---------------------------|-------------------------------|----------------------------------|--------------------|--------------|
| Children/adolescents | | | | | | | | | | | | |
| 15 year old hyperkinetic girl (Case 3) | Lucas and Weiss, 1971 | | | | | | ✓ | | | | | C |
| Boy with hyperactive behaviour | Weiner et al., 1978 | | | | | | ✓ | | | | | N |
| Boy with ADHD | Rosenfeld, 1979 | ✓ | | ✓ | ✓ | | ✓ | | | | | U |
| Boy with ADHD | Goyer et al., 1979 | | | | | | ✓ | | | | | U |
| Boy with hyperactive behaviour (Case 1) | Young, 1981 | | | | | | ✓ | | | | | N |
| Twin boy with hyperactivity and Tourette syndrome (Case “DV”) | Waserman et al., 1983 | | | | | | | ✓ | | | | U |
| Boy with ADHD + addiction | Jaffe, 1991 | | | | | | ✓ | | | | | C |
| 2 boys with ADHD (Patients A and B) | Sprafkin and Gadow, 1993 | | | | | | ✓ | | | | | C |
| Boy with ADHD | Garland, 1998 | | | | | | ✓ | | | | ✓ | C |
| Boy with ADHD | Ickowicz, 2002 | ✓ | | | ✓ | | | | | ✓ | | Y |
| Boy with ADHD | Gross-Tsur et al., 2004 | | | | | | ✓ | | | | | N |
| Boy with ADHD | Rashid and Mitelman, 2007 | | | | | | ✓ | | | | | N |
| Girl with ADHD | Schertz and Steinberg, 2008 | | | | | | | | ✓ | | | C |
| Boy with ADHD (Case “Matthew”) | Chammas et al., 2014 | | | | | | ✓ | | | | | C |
| Boy with ADHD | Eryilmaz et al., 2014 | | | | ✓ | | | | | | | U |
| 2 boys with ADHD (Cases 2 & 3) | Kazanci et al., 2015 | | | | | | | ✓ | | | | C |
| Boy with ADHD | Erkuran et al., 2016 | | | | ✓ | | | | | | | C |
| Boy with ADHD | Ekinci et al., 2017 | | | | | | ✓ | | | | | C |
| Boy with ADHD | Villafuerte-Trisolini et al., 2017 | | | | | | | | | | ✓ | U |
| Boy with ADHD | Socanski et al., 2018 | | | | | | | | | ✓ | | Y |
| Adults | | | | | | | | | | | | |
| 23 year old man with ADD residual type (Case 3) | Khantzian et al., 1984 | | | | | | | ✓ | | | | Y |
| 2 men with ADHD + alcohol dependency (Cases 1 & 3) | Schubiner et al., 1995 | | | | | | ✓ | | | | | Y |
| Woman with ADHD + bulimia, bipolar | Guerdjikova and McElroy, 2013 | ✓ | ✓ | | | ✓ | ✓ | | | | ✓ | Y |
| Man with ADHD + cocaine addiction | Imbert et al., 2013 | | | | | | ✓ | | | | | Y |
| Woman with ADHD | Lee, 2016 | | | | | | ✓ | ✓ | | | | U |

Sample sizes (N analysed)

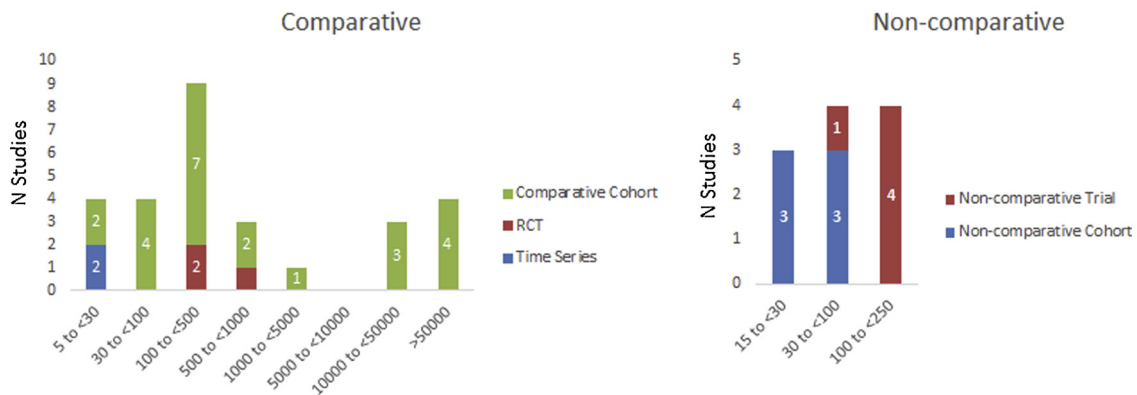


Fig. 2. Histograms of sample sizes for (left) comparative and (right) non-comparative group studies, broken out by study design. Numbers in white indicate number of studies.

Table 5

Comorbidities. Specific comorbidities reported, with 1) the number of studies reporting each comorbid disorder and 2) the number of studies reporting that disorder as the only or most prevalent, comorbid disorder. Comorbid disorders as listed in rank order of the number of studies reporting that disorder.

| Comorbidity | N studies reporting as comorbidity | N studies reporting as only, or most prevalent, comorbidity |
|--|------------------------------------|---|
| ODD/CD | 15 | 11 |
| Tics/Tourette syndrome | 11 | 6 |
| Anxiety | 11 | 3 |
| Substance use disorder | 7 | 4 |
| Depression | 7 | 1 |
| Intellectual disability (IQ < 70) | 7 | 1 |
| Autism spectrum/communication | 6 | 0 |
| Seizures/EEG abnormalities | 5 | 4 |
| Bipolar disorder | 3 | 1 |
| Psychosis/hallucinations | 3 | 1 |
| Specific learning impairment/learning disability | 3 | 1 |
| Obsessive compulsive | 2 | 1 |
| Personality Disorders | 2 | 1 |
| Personality Disorders | 1 | 1 |
| Eating disorder | 1 | 0 |
| Sleep disorders | 1 | 0 |
| Feeding Disorder | 1 | 0 |
| Motor skills disorder | 1 | 0 |
| Mood Disorder | 1 | 0 |

Table 6

Treatment durations. Estimated most common duration of MPH treatment in included studies, rounded down to nearest whole number of years.

| Most common duration of MPH treatment | N total studies | N group studies | N case reports |
|---------------------------------------|-----------------|-----------------|----------------|
| 1 year | 32 | 23 | 9 |
| 2 years | 13 | 7 | 6 |
| 3 years | 8 | 5 | 3 |
| 4 years | 3 | 1 | 2 |
| 5 years | 6 | 1 | 5 |
| 6 years | 5 | 2 | 3 |

antipsychotic and antidepressant treatments. We coded their results as *Favours MPH*.

We conclude that for most neuropsychiatric outcomes, the evidence base is weak regarding relative safety of long-term MPH over medications not primarily indicated for ADHD.

Comparators

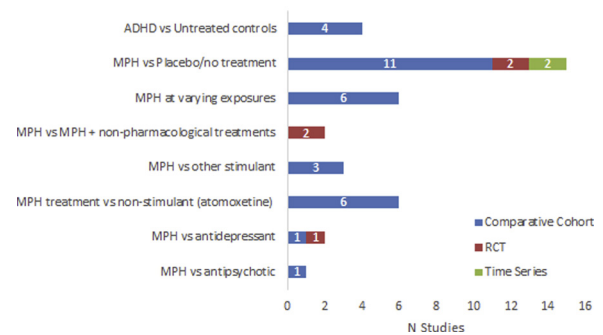


Fig. 3. Comparators used in comparative studies. Numbers refer to number of studies using that comparator. Numbers sum to more the number of comparative studies (N = 28) as 15 studies used multiple comparators.

3.3. Summaries of findings by adverse outcome

The evidence regarding each potential adverse outcome is summarised below. Codes for the results or authors' conclusions for each study are given in the final columns of Tables 2–4. Detailed narrative summaries are given in S2, including details of the rating scales used.

3.3.1. Low mood or depression

Fourteen studies reported on low mood or depression as a potential adverse outcome of long-term MPH treatment: eight comparative studies, three non-comparative studies, and three case reports. The evidence regarding Low Mood/Depression is summarised in Table 9.

Several of the group studies provided evidence in favour of MPH with regard to low mood/depression. These included three comparative studies in children and young adults: two large cohort studies with sample sizes > 1000 (Cortese et al., 2015; Lee et al., 2016) and an RCT (Hechtman et al., 2004). It also included three non-comparative studies (Edvinsson and Ekselius, 2018; Gadow et al., 1999; Kutlu et al., 2017). However, the evidence from five smaller (N < 1000) comparative studies was unclear (Ghuman et al., 2001; Hechtman et al., 1984; Paternite et al., 1999; Philipsen et al., 2015; Schrantee et al., 2018). One case study indicated the need for caution in the case of an MPH-abusing youth (Garland, 1998). We conclude that the evidence base regarding mood outcomes from long-term MPH treatment is relatively strong, includes two well-powered comparative studies (Cortese et al., 2015; Lee et al., 2016), and tends to favour MPH. A detailed narrative summary is given in S2.2.

Table 7
 Comparative study designs and outcomes. Comparators with MPH used in comparative study design, and the potential adverse neuropsychiatric outcomes investigated. Upper panel: studies comparing effect of treatments that include MPH with alternative non-MPH treatments. Lower panel: studies that include comparisons between different treatments, all of which include treatment with MPH. Abbreviations: RCT = Randomized Control Trial; nRCT = non-Randomized Control Trial; CC = Comparative Cohort; BT = Behavioural Therapy; MPT = multimodal psychosocial therapy; ACT = Attentional Control Therapy. *Studies that included more than one comparator. Check marks indicate which of the 10 neuropsychiatric outcome were investigated or reported on in that study.

| COMPARATIVE STUDIES | | Number of Studies | Study | Design | Low Mood/Depression | Anxiety | Irritability/emotional reactivity | Suicidal behaviour/ideation | Bipolar disorder | Psychosis or Psychotic symptoms | Substance use disorder | Movement disorders | Seizures or EEG abnormalities | Sleep disorders | |
|--|----|---------------------------------|-------|--------|---------------------|---------|-----------------------------------|-----------------------------|------------------|---------------------------------|------------------------|--------------------|-------------------------------|-----------------|--|
| MPH vs Placebo/no treatment | 15 | Quinn and Rapoport, 1975* | RCT | ✓ | | | | | | | | | | | |
| | | Hechtman et al., 1984* | CC | ✓ | | | ✓ | | | | ✓ | | | | |
| | | Riddle et al., 1995 | TS | | | | | | | | | ✓ | | | |
| | | Corkum et al., 1999 | CC | | | | | | | | | | ✓ | | |
| | | Nolan et al., 1999 | TS | | | | | | | | | ✓ | | | |
| | | Hemmer et al., 2001 | CC | | | | | | | | | | | ✓ | |
| | | Gau and Chiang, 2009* | CC | | | | | | | | | | | | |
| | | Huss et al., 2008 | CC | | | | | | | | | ✓ | | | |
| | | Jerrell et al., 2014 | CC | | | | | | | ✓ | | | | | |
| | | Steinhausen and Bisgaard, 2014* | CC | | | | | | | | | ✓ | | | |
| | | Ginsberg et al., 2015 | CC | | | | | | | | | ✓ | | | |
| | | Philipsen et al., 2015* | RCT | | | | | | | | | | | | |
| | | Shyu et al., 2015 | CC | | | | | | | | | | | | |
| | | Wang et al., 2016a,* | CC | | | | | | | | | | | | |
| | | Schranter et al., 2018 | CC | | | | | | | | | | | | |
| MPH vs MPH in combination with non-pharmacological treatments | 2 | Hechtman et al., 2004 | RCT | ✓ | | | | | | | | | | | |
| | | Philipsen et al., 2015* | RCT | ✓ | | | | | | | | | | | |
| | | Paternite et al., 1999 | CC | ✓ | | | | | | | | | | | |
| | | Mannuzza et al., 2008 | CC | ✓ | | | | | | | | | | | |
| | | Kittel-Schneider et al., 2016 | CC | ✓ | | | | | | | | | | | |
| | | Schranter et al., 2018 | CC | ✓ | | | | | | | | | | | |
| MPH at varying exposures (age at initiation of treatment; duration of treatment; dosage; treatment response) | 6 | Liang et al., 2018 | CC | ✓ | | | | | | | | | | | |
| | | Huang et al., 2018 | CC | ✓ | | | | | | | | | | | |
| | | Lipkin et al., 1994 | CC | ✓ | | | | | | | | | | | |
| | | Ghuman et al., 2001 | CC | ✓ | | | | | | | | | | | |
| | | Varley et al., 2001 | CC | ✓ | | | | | | | | | | | |
| | | | CC | ✓ | | | | | | | | | | | |
| MPH vs other stimulant (dexamphetamine, pemoline, adderall) | 3 | | CC | ✓ | | | | | | | | | | | |
| | | | CC | ✓ | | | | | | | | | | | |
| | | | CC | ✓ | | | | | | | | | | | |

(continued on next page)

Table 7 (continued)

| COMPARATIVE STUDIES | | | | | | | | | | | | | |
|--|-------------------|--|----------------------------------|----------------------------|--------------------------|-----------------------------------|-----------------------------|---------------------------|---------------------------------|--------------------------|--------------------------|-------------------------------|---------------------------|
| | Number of Studies | Study | Design | Low Mood/Depression | Anxiety | Irritability/emotional reactivity | Suicidal behaviour/ideation | Bipolar disorder | Psychosis or Psychotic symptoms | Substance use disorder | Movement disorders | Seizures or EEG abnormalities | Sleep disorders |
| MPH treatment vs non-stimulant (atomoxetine) | 6 | Cortese et al., 2015 Haynes et al., 2015 Lee, 2016 Wang et al., 2016a,* Liang et al., 2018 Huang et al., 2018 | CC CC CC CC CC CC | ✓ ✓ | | ✓ | ✓ ✓ | ✓ | ✓ | | | ✓ | ✓ |
| MPH vs antidepressant | 2 | Quinn and Rapoport, 1975* Steinhausen and Bisgaard, 2014* | RCT CC | | ✓ | | | | | | | | |
| MPH vs antipsychotic | 1 | Steinhausen and Bisgaard, 2014* | CC | | | | | | | ✓ | | | |
| ADHD vs Untreated controls | 4 | Hechtman et al., 1984* Gau and Chiang, 2009* Huang et al., 2018 Hammerness et al., 2017 | CC CC CC CC | ✓ | ✓ | | ✓ | | ✓ | ✓ | | | ✓ |

Table 8 Non-comparative studies and outcomes. Comparative study designs and adverse outcomes reported on. Check marks indicate which of the 10 neuropsychiatric outcome were investigated or reported on in that study.

| Study | Low Mood/ Depression | Anxiety | Irritability/ emotional reactivity | Suicidal behaviour/ ideation | Bipolar disorder | Psychosis or Psychotic symptoms | Substance use disorder | Movement disorders | Seizures or EEG abnormalities | Sleep disorders |
|--|-------------------------|---------|--|------------------------------------|---------------------|---------------------------------------|---------------------------|-----------------------|----------------------------------|--------------------|
| NON-COMPARATIVE STUDIES | | | | | | | | | | |
| Retrospective Designs | | | | | | | | | | |
| retrospective chart review | | | | | ✓ | ✓ | | | ✓ | |
| retrospective follow-up | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ |
| Prospective Designs | | | | | | | | | | |
| Prospective open label longitudinal study | | | ✓ | | | | | ✓ | | ✓ |
| Prospective open label RCT extension | ✓ | | ✓ | | | | | ✓ | | ✓ |

3.3.2. Anxiety

Eleven studies reported on anxiety as a potential adverse outcome: seven comparative studies, three non-comparative studies, and one case report. The evidence regarding anxiety is summarised in Table 10.

Sample sizes for anxiety as an outcome were fairly small. Five group studies (N < = 118), including two comparative (Hechtman et al., 1984; Kittel-Schneider et al., 2016) and three non-comparative (Edvinsson and Ekselius, 2018; Gadow et al., 1999; Kutlu et al., 2017) studies, provided evidence in favour of MPH, but the remaining five (N < = 103) comparative studies (Ghuman et al., 2001; Hechtman et al., 2004; Quinn and Rapoport, 1975; Paternite et al., 1999; Schrantee et al., 2018) were unclear. The single case study indicated that MPH was safe/tolerated for this outcome (Guerdjikova and McElroy, 2013). We conclude that while the evidence with regard to anxiety as an outcome of long-term MPH treatment tends to favour MPH, the evidence base is relatively weak. A detailed narrative summary is given in S2.2.

3.3.3. Irritability/Emotional reactivity

Seven studies reported on irritability or emotional reactivity as a potential adverse outcome: two comparative studies, four non-comparative and one case report. The evidence regarding irritability/emotional reactivity is summarised in Table 11.

One large comparative study (Cortese et al., 2015) and all four smaller non-comparative studies (Atzori et al., 2009; Edvinsson and Ekselius, 2018; Kutlu et al., 2017; Wilens et al., 2005) provided evidence in favour of MPH regarding irritability/emotional reactivity. A small comparative study of pre-schoolers (Ghuman et al., 2001) and a case report (Rosenfeld, 1979) were unclear. We conclude that the evidence base regarding irritability/emotional reactivity outcomes of long-term MPH treatment is limited, although it includes one well-powered study (Cortese et al., 2015) that found in favour of MPH over atomoxetine. A detailed narrative summary is given in S2.3.

3.3.4. Suicidal behaviour/ideation

Nine studies reported on suicidal behaviour/ideation as a potential adverse outcome: five comparative group studies and four case reports. The evidence regarding suicidal behaviour/ideation is summarised in Table 12. None of the included studies reported non-suicidal self-harm as a potential adverse outcome.

All five comparative studies, including three large comparative cohorts (Cortese et al., 2015; Huang et al., 2018; Liang et al., 2018) and two smaller studies (Hechtman et al., 1984; Paternite et al., 1999) provided evidence in favour of MPH regarding suicidal behaviour. Two of the four case reports include cases where MPH had been used in unsuccessful suicide attempts (Erkuran et al., 2016; Eryilmaz et al., 2014), and two were of cases with suicidal ideation (Garland, 1998; Rosenfeld, 1979). We conclude that the evidence base regarding suicidal behaviour and long-term MPH treatment is relatively strong, and tends to favour MPH. A detailed narrative summary is given in S2.4.

3.3.5. Bipolar disorder

Four studies reported on bipolar disorder as a potential adverse outcome: Two large comparative studies, one non-comparative study, and one case report. The evidence regarding bipolar disorder is summarised in Table 13.

One large (N > 1000) comparative cohort provided evidence in favour of MPH regarding bipolar disorder (Wang et al., 2016a). The other (Jerrell et al., 2014) found slightly elevated risk, although in this study, risk was also elevated by comorbid psychiatric diagnoses, suggesting that treatment propensity may have been a confound. The only two other studies for bipolar disorder as an outcome were a small non-comparative retrospective chart review by Cherland and Fitzpatrick (1999) that suggested a need for caution, and a case report of a complex adult case (Guerdjikova and McElroy, 2013). We conclude that the evidence base regarding bipolar disorder and long-term MPH treatment

Table 9
Low Mood/Depression. Studies reporting Low Mood or Depression as a potential adverse outcome.

| Study | N | Study Design | Comparison | Sample description | Measure |
|---------------------------------|---------|---|--|--|------------------------|
| Comparative Studies: | | | | | |
| Favours MPH | 142,160 | Cohort | Atomoxetine | Children and young adults with ADHD diagnosed before age 20 and matched controls | ICD-9-CM codes for MDD |
| Unclear | 2331 | Cohort | Atomoxetine | Children and youth with ADHD, mostly male | AEs* |
| | 103 | RCT | MPH + BT and MPH + attentional control | Children and youth with ADHD | CDI |
| | 76 | Cohort | ADHD untreated and controls untreated | Adults with ADHD | SADS, SCL-90 |
| | 97 | Cohort | MPH dosage, duration, response | Young adult men with ADHD | SADS-L, MMPI |
| | 27 | Cohort | Dexamphetamine and Adderall | Pre-schoolers with ADHD, mostly male | SERF (AEs) |
| | 91 | Cohort | No treatment; late vs early onset of treatment | Adults with a history of ADHD | BDI |
| | 419 | RCT | MPH + Therapy, MPH + Clinical management, Placebo + Therapy, Placebo + Clinical management | Adults with ADHD | BDI |
| Non-comparative studies: | | | | | |
| MPH safe | 118 | Prospective open label longitudinal study | - | Boys with ADHD + CD/ODD | CBCL |
| | 112 | Retrospective cohort | - | Adults with ADHD | AEs |
| | 34 | Prospective open label extension | - | Children and youth with ADHD + tics/TTS, mostly male | CSI-3R |
| Case reports: | | | | | |
| MPH safe | 1 | Case Report | - | Woman with bulimia, ADHD, bipolar | |
| Cautious | 1 | Case Report | - | Boy with ADHD and intranasal MPH abuse | |
| Unclear | 1 | Case Report | - | Boy with ADHD | |

* denotes statistically significant difference against comparator.

Table 10
Anxiety. Studies reporting Anxiety as a potential adverse outcome.

| Study | N | Design | Comparison | Sample description | Measure |
|---------------------------------|-----|---|--|---|-----------------|
| Comparative Studies: | | | | | |
| Favours MPH | | | | | |
| Hechtman et al., 1984 | 76 | Cohort | ADHD untreated and controls untreated | Adults with ADHD | SADS, SCL-90 |
| Kittel-Schneider et al., 2016 | 70 | Cohort | MPH treatment < 12 months or none | Adults with ADHD | TICS |
| Paternite et al., 1999 | 97 | Cohort | MPH dosage, duration, response | Young adult men with ADHD | SADS-L, MMPI |
| Unclear | | | | | |
| Hechtman et al., 2004 | 103 | RCT | MPH + BT and MPH + attentional control | Children and youth with ADHD | PH |
| Ghuman et al., 2001 | 27 | Cohort | Dexamphetamine, Adderall | Pre-schoolers with ADHD, mostly male | SERF (AEs) |
| Quinn and Rappoport, 1975 | 73 | RCT | Imipramine, placebo | Hyperactive boys at 1 year follow-up from RCT | Conners PSQ:TSS |
| Schirante et al., 2018 | 91 | Cohort | No treatment; late vs early onset of treatment | Adults with a history of ADHD | BAI |
| Non-comparative studies: | | | | | |
| MPH safe | | | | | |
| Kutlu et al., 2017 | 118 | Prospective open label longitudinal study | - | Boys with ADHD + CD/ODD | CBCL |
| Edvinsson and Ekselius, 2018 | 112 | Retrospective cohort | - | Adults with ADHD | AEs |
| Gadow et al., 1999 | 34 | Prospective open label extension | - | Children and youth with ADHD + tics/Ts, mostly male | CSI-3R |
| Case reports: | | | | | |
| MPH safe | | | | | |
| Guerdjikova and McElroy, 2013 | 1 | Case Report | - | Woman with ADHD + bulimia, bipolar | |

is limited and unclear, although it includes two well-powered studies. A detailed narrative summary is given in S2.5.

3.3.6. Psychosis and psychotic like symptoms

Fourteen studies reported on psychosis and/or psychotic-like symptoms as a potential adverse outcome: four comparative studies, one non-comparative study, and nine case reports. Studies that reported visual disturbances have been included under this heading, as all were of psychotic-like visual experiences, rather than neurological signs. The evidence regarding Psychosis and Psychotic-like symptoms is summarised in Table 14.

Three comparative studies provided evidence in favour of MPH: two studies (Cortese et al., 2015; Paternite et al., 1999) provided evidence that MPH reduces risk of psychotic-like symptoms, and one study (Hechtman et al., 2004) that it reduces the risk hospitalisation for psychosis. However, two comparative studies (Cherland and Fitzpatrick, 1999; Shyu et al., 2015) indicate a need for caution. One of these (Shyu et al., 2015) was a large cohort study that specifically studied psychotic disorders as a potential adverse outcome of MPH treatment. The authors found an elevated risk associated with MPH, although they also found that ADHD itself was a significant risk factor for psychosis. In addition, the authors of four case reports (Gross-Tsur et al., 2004; Lee, 2016; Rashid and Mitelman, 2007; Young, 1981) concluded that psychosis may have resulted from MPH treatment. We conclude that these findings indicate that more research is needed into the relationship between ADHD and psychosis, and into whether MPH moderates that risk, as well as research into individual risk-factors for MPH-related psychosis in young people with ADHD. A detailed narrative summary is given in S2.6.

3.3.7. Substance use disorders

Sixteen studies reported on SUD as a potential adverse outcome: seven comparative studies, one non-comparative study, and eight case reports including 2 cases from one case series. The evidence regarding SUD is summarised in Table 15.

Six of the comparative studies (Ginsberg et al., 2015, Hammerness et al., 2017; Hechtman et al., 1984; Mannuzza et al., 2008; Paternite et al., 1999; Steinhausen and Bisgaard, 2014), including one large comparative cohort (Steinhausen and Bisgaard, 2014), provide evidence in favour of MPH regarding SUD, as do five case reports of adults with comorbid SUD (Guerdjikova and McElroy, 2013; Imbert et al., 2013; Khantzian et al., 1984; both cases reported by Schubiner et al., 1995). In addition, one non-comparative study suggests that long-term MPH treatment in adults without prior SUD does not present a risk for new SUD (Torgersen et al., 2012). However, three case reports of abuse of prescribed MPH suggest that caution is warranted in this regard (Garland, 1998; Goyer et al., 1979; Jaffe, 1991). We conclude that the evidence base for SUD outcomes and long-term MPH treatment is relatively strong, includes one well-powered study that compared MPH with antipsychotic and antidepressant treatment, and tends to favour MPH. A detailed narrative summary is given in S2.7.

3.3.8. Tics and other dyskinesias

Fourteen studies reported on tics and/or other dyskinesias as a potential adverse outcome of MPH treatment: five comparative studies, four non-comparative studies and five case reports. The evidence regarding tics and other dyskinesias is summarised in Table 16.

Several of the group studies were of children with a history of tics or tic disorder. These included two withdrawal-challenge studies (Riddle et al., 1995; Nolan et al., 1999) a comparative cohort (Varley et al., 2001), and a noncomparative study (Gadow et al., 1999). Three of these indicated a need for caution (Gadow et al., 1999; Riddle et al., 1995; Varley et al., 2001), while one (Nolan et al., 1999) was unclear.

Of the group studies in which participants with tics or tic disorder were either excluded or not specifically recruited, three non-comparative studies (Atzori et al., 2009; Edvinsson and Ekselius, 2018; Wilens

Table 11
Irritability/Emotional reactivity. Studies reporting Irritability/Emotional reactivity as a potential adverse outcome.

| IRRITABILITY/EMOTIONAL REACTIVITY | | | | | | |
|-----------------------------------|------------------------------|--------|---|--------------------------|---|------------|
| Study | N | Design | Comparison | Sample description | Measures | |
| <i>Comparative Studies:</i> | | | | | | |
| Favours MPH | Cortese et al., 2015 | 2331 | Cohort | Atomoxetine | Children and youth with ADHD, mostly male | AEs* |
| Unclear | Ghuman et al., 2001 | 27 | Cohort | Dexamphetamine, Adderall | Pre-schoolers with ADHD, mostly male | SERF (AEs) |
| <i>Non comparative studies:</i> | | | | | | |
| MPH safe | Wilens et al., 2005 | 228 | Prospective open label longitudinal study | – | Children and youth with ADHD, mostly male: tics, seizures, psychosis excluded | AEs |
| | Atzori et al., 2009 | 134 | Prospective open label longitudinal study | – | Children with ADHD, mostly male | AEs |
| | Kutlu et al., 2017 | 118 | Prospective open label longitudinal study | – | Boys with ADHD + CD/ODD | CBCL |
| | Edvinsson and Ekselius, 2018 | 112 | Retrospective cohort | – | Adults with ADHD | AEs |
| <i>Case report:</i> | | | | | | |
| Unclear | Rosenfeld, 1979 | 1 | Case Report | – | Boy with ADHD | |

et al., 2005) concluded that MPH was safe/well-tolerated with regard to tics, while two comparative studies (Ghuman et al., 2001; Lipkin et al., 1994), including one of pre-schoolers (Ghuman et al., 2001) were unclear.

The five case reports (Kazanci et al., 2015; Lee, 2016; Sprafkin and Gadow, 1993; Wasserman et al., 1983; Weiner et al., 1978) include three cases with pre-existing tics (Sprafkin and Gadow, 1993; Wasserman et al., 1983). We conclude that more research is needed regarding the safety and management of long-term MPH in those with comorbid tics or tic disorder. A detailed narrative summary is given in S2.8.

3.3.9. Seizures or EEG abnormalities

Nine studies reported on seizures or EEG abnormalities as a potential adverse outcome of MPH treatment: two comparative studies, four non-comparative group studies, and three case reports. The evidence regarding seizures or EEG abnormalities is summarised in Table 17.

Evidence for the safety of MPH treatment in children with ADHD and a history of seizures or abnormal EEG is provided by four group studies (Fosi et al., 2013; Gucuyener et al., 2003; Hemmer et al., 2001; Mulas et al., 2014) as well as two case studies of children with a history of seizures (Ickowicz, 2002; Socanski et al., 2018). The authors of two of the group studies (Hemmer et al., 2001; Mulas et al., 2014) suggest proceeding with caution nonetheless. Evidence regarding emergence of seizures or EEG abnormalities in children with no prior history of seizures was provided by two group studies (Cortese et al.,

2015; Weiss et al., 1975) and a case study (Schertz and Steinberg, 2008). We conclude that while the evidence is limited and unclear, the studies do not indicate evidence for seizures as an AE of MPH treatment in children with no prior history. We conclude that more research is needed into the safety of long-term MPH in children and young people at risk of seizures. A detailed narrative summary is given in S2.9.

3.3.10. Sleep disorders

Eleven studies reported on sleep disorders as a potential adverse outcome of long-term MPH treatment: five comparative studies, three non-comparative studies and three case reports. The evidence regarding sleep disorders is summarised in Table 18.

One large comparative study (Cortese et al., 2015) indicates that atomoxetine may cause fewer sleep AEs than MPH. The results of the other four comparative studies (Corkum et al., 1999; Gau and Chiang, 2009; Ghuman et al., 2001; Haynes et al., 2015), using a range of comparators, are unclear. However, all three non-comparative studies of AEs indicate that MPH is safe/well-tolerated in this regard (Atzori et al., 2009; Edvinsson and Ekselius, 2018; Wilens et al., 2005), as does one of the two case studies (Guerdjikova and McElroy, 2013). Two studies concluded that the relationship between sleep disorders and ADHD is complex (Corkum et al., 1999; Gau and Chiang, 2009). We conclude that more research is needed into the relationship between ADHD, sleep, and long-term MPH treatment. A detailed narrative summary is given in S2.10.

Table 12
Suicidal behaviour/ideation. Studies reporting Suicidal behaviour/ideation as a potential adverse outcome.

| SUICIDAL BEHAVIOUR/IDEATION | | | | | | |
|-----------------------------|------------------------|--------|-------------|---|---|---------------------------------|
| Study | N | Design | Comparison | Sample description | Measure | |
| <i>Comparative Studies:</i> | | | | | | |
| Favours MPH | Hechtman et al., 1984 | 76 | Cohort | MPH v untreated ADHD, controls | Adults with ADHD | SADS, SCL-90 |
| | Paternite et al., 1999 | 97 | Cohort | Different dosages; treatment duration | Young adult men with ADHD | SADS-L, MMPI |
| | Cortese et al., 2015 | 2331 | Cohort | MPH v atomoxetine | Children and youth with ADHD, mostly male | AEs |
| | Liang et al., 2018 | 84,898 | Cohort | Different durations of treatment, no treatment, atomoxetine | Youth under 18 with ADHD | ICD-9 codes: E950–E959 |
| | Huang et al., 2018 | 20,574 | Cohort | No treatment; treatment < 1 year; atomoxetine | Adolescents and young adults with ADHD | ICD9-codes for suicide attempts |
| <i>Case Reports</i> | | | | | | |
| Caution | Garland, 1998 | 1 | Case Report | – | Boy with ADHD and intranasal MPH abuse | |
| | Erkuran et al., 2016 | 1 | Case Report | – | Boy with ADHD | |
| Unclear | Rosenfeld, 1979 | 1 | Case Report | – | Boy with ADHD | |
| | Eryilmaz et al., 2014 | 1 | Case Report | – | Boy with ADHD | |

Table 13
Bipolar Disorder. Studies reporting Bipolar Disorder as a potential adverse outcome.

| BIPOLAR DISORDER | | | | | | |
|---------------------------------|--------------------------------|---------|----------------------------|------------------------------------|------------------------------------|-----------------------|
| Study | N | Design | Comparison | Sample description | Measure | |
| <i>Comparative Studies:</i> | | | | | | |
| Favours MPH | Wang et al., 2016a, | 289,840 | Cohort | Atomoxetine, no treatment | Children with ADHD, mostly male | ICD-9-CM codes for BD |
| Caution | Jerrell et al., 2014 | 22,797 | Cohort | Atomoxetine, duration of treatment | Children and adolescents with ADHD | ICD-9-CM codes for BD |
| <i>Non comparative studies:</i> | | | | | | |
| Caution | Cherland and Fitzpatrick, 1999 | 98 | Retrospective chart review | – | Children with ADHD, mostly male | AEs |
| <i>Case Reports:</i> | | | | | | |
| MPH safe | Guerdjikova and McElroy, 2013 | 1 | Case Report | – | Woman with bulimia, ADHD, bipolar | |

Table 14
Psychosis/Psychotic-like Symptoms. Studies reporting psychosis or psychotic-like symptoms as a potential adverse outcome.

| PSYCHOSIS/PSYCHOTIC-LIKE SYMPTOMS | | | | | | |
|-----------------------------------|--------------------------------|---------|----------------------------|--|---|----------------|
| Study | N | Design | Comparator | Sample description | Measure | |
| <i>Comparative Studies:</i> | | | | | | |
| Favours MPH | Paternite et al., 1999 | 97 | Cohort | Different dosages and duration | Young adult men with ADHD | SADS-L, MMPI |
| | Hechtman et al., 2004 | 103 | RCT | MPH + BT and MPH + attentional control | Children and youth with ADHD | CDI |
| | Cortese et al., 2015 | 2331 | Cohort | Atomoxetine | Children and youth with ADHD, mostly male | AEs |
| Caution | Shyu et al., 2015 | 146,098 | Cohort | No treatment | Children and youth with ADHD, mostly male | ICD-9-CM codes |
| <i>Non-comparative studies:</i> | | | | | | |
| Caution | Cherland and Fitzpatrick, 1999 | 98 | Retrospective chart review | – | Children with ADHD, mostly male | AEs |
| <i>Case studies:</i> | | | | | | |
| Caution | Lucas and Weiss, 1971 | 1 | Case Report | – | 15 year old hyperkinetic girl | |
| | Weiner et al., 1978 | 1 | Case Report | – | Boy with hyperactive behaviour | |
| | Chammas et al., 2014 | 1 | Case Report | – | Boy with ADHD | |
| | Ekinici et al., 2017 | 1 | Case Report | – | Boy with ADHD | |
| MPH not safe | Young, 1981 | 1 | Case Report | – | Boy with hyperactive behaviour | |
| | Gross-Tsur et al., 2004 | 1 | Case Report | – | Boy with ADHD (Case 1 of 3) | |
| | Rashid and Mitelman, 2007 | 1 | Case Report | – | Boy with ADHD | |
| | Lee, 2016 | 1 | Case Report | – | Woman with ADHD | |
| Unclear | Rosenfeld, 1979 | 1 | Case Report | – | Boy with ADHD | |

3.3.11. Other notable neuropsychiatric outcomes

Three studies reported on “aggression” or “hostility” as an adverse effect, and one reported on “personality changes”. The evidence regarding these outcomes is summarised in Table 19.

Two non-comparative studies (Kutlu et al., 2017; Wilens et al., 2005) provide evidence that MPH is safe/well-tolerated with regard to aggression or hostility as an AE, while the evidence from one comparative study of pre-schoolers (Ghuman et al., 2001) is unclear. Only one study reported on personality changes (Haynes et al., 2015), with no clear conclusion. We conclude that there is limited evidence regarding long-term MPH treatment and other neuropsychiatric outcomes and that further research may be needed into the relationship between long-term MPH treatment and aggression/hostility. A detailed narrative summary is given in S2.11. No other notable neuropsychiatric effects were reported specifically as potential adverse outcomes of treatment.

3.4. Overall result summary

Of the comparative studies, only one (Cortese et al., 2015) reported an outcome (sleep disorders) that we coded as *Favours Comparator* (atomoxetine). Of the seven comparative studies with a sample size > 1000, we coded six, including Cortese et al.’s, 2015 study, as *Favours*

MPH overall, and one, the study by Shyu et al. (2015) of schizophrenia spectrum and other psychotic disorders, as *Proceed with Caution*. Of the smaller studies (N < 1000) we coded eight as *Favours MPH* overall, three as *Proceed with Caution*, and nine as *Unclear*.

The non-comparative group studies were all relatively small studies (N < 1000), and we coded six as *Safe/well-tolerated*, two as *Proceed with Caution* and one as *Unclear*. Of the case-studies, we coded seven as *Safe/well-tolerated*, eleven as *Proceed with Caution*, four as *Not Safe/well-tolerated* and four as *Unclear*.

These codings, with sample sizes where relevant, are shown graphically in Fig. 4.

4. Discussion

This evidence map of studies addressing the potential adverse neuropsychiatric effects of long-term MPH treatment for ADHD reveals a great deal of between-study methodological variability. Comparative studies spanned a wide range of comparators: placebo/no treatment; other pharmacological and non-pharmacological treatments; and different MPH treatment regimens, treatment durations or age of onset of treatment. The heterogeneity also extends to the range of populations studied, from pre-schoolers to adults, as well as to specific at-risk

Table 15
Substance Use Disorders. Studies reporting SUD as a potential adverse outcome.

| SUBSTANCE USE DISORDERS | | | | | | |
|---------------------------------|--------------------------------|--------|-------------|--|--|--|
| | Study | N | Design | Comparator | Sample description | Measures |
| <i>Comparative Studies:</i> | | | | | | |
| Favours MPH | Hechtman et al., 1984 | 76 | Cohort | MPH v untreated ADHD, controls | Adults with ADHD | Psychiatric assessment of past and current nonmedical drug use |
| | Patemite et al., 1999 | 97 | Cohort | Different dosages; duration; treatment response | Young adult men with ADHD | SADS-L |
| | Mannuzza et al., 2008 | 176 | Cohort | Age at MPH treatment initiation | Boys with ADHD | CHAMPS |
| | Steinhausen and Bisgaard, 2014 | 20,742 | Cohort | MPH only v Anti-depressants, anti-psychotics, mixed, no medication | Danish psychiatric central register of ADHD cases | ICD-8 and ICD-10 codes for SUD |
| | Ginsberg et al., 2015 | 25 | Cohort | MPH vs No active treatment | Adult prisoners with ADHD | AUDIT & DUDIT |
| | Hammerness et al., 2017 | 211 | Cohort | No medication or “naturalistic” medicated ADHD; healthy controls | Adolescents with ADHD | DUSI-R |
| Unclear | Huss et al., 2008 | 215 | Cohort | MPH vs No active treatment | Youth and young adults diagnosed with childhood diagnosis of ADHD, mostly male | CIDI |
| <i>Non-comparative studies:</i> | | | | | | |
| MPH safe | Torgersen et al., 2012 | 52 | Trial | - | Adults with no prior history of SUD, treated with MPH | DSM-IV criteria for SUD |
| <i>Case reports:</i> | | | | | | |
| MPH safe | Khantizian et al., 1984 | 1 | Case-series | - | Case 3: 23 year old man with ADD residual type | |
| | Schubiner et al., 1995 | 1 | Case-series | - | Case 1: man with ADHD + alcohol dependency | |
| | Schubiner et al., 1995 | 1 | Case-series | - | Case 3: man with ADHD + alcohol dependency | |
| | Guerdjikova and McElroy, 2013 | 1 | Case Report | - | Woman with ADHD + bulimia, bipolar | |
| Caution | Imbert et al., 2013 | 1 | Case Report | - | Man with ADHD and cocaine addiction | |
| | Jaffe, 1991 | 1 | Case Report | - | Boy with ADHD + addiction | |
| | Garland, 1998 | 1 | Case Report | - | Boy with ADHD and intranasal MPH abuse | |
| Unclear | Goyer et al., 1979 | 1 | Case Report | - | 13 year old hyperactive boy with MPH abuse | |

Table 16
Tics & other dyskinesias. Studies reporting tics and other dyskinesias as a potential adverse outcome.

| Study | N | Design | Comparator | Sample description | Measures |
|---------------------------------|-----|------------------------------|--------------------------|---|----------------------------|
| Comparative Studies: | | | | | |
| Cautious | 5 | nRCT | No active treatment | Boys in tic disorder clinic with ADHD | Video monitoring + C-YGTSS |
| | 517 | Cohort | Dexamphetamine, Pemoline | Children with ADHD, history of family history of tics | Parent reports |
| Unclear | 122 | Cohort | Dexampetamine, Pemoline | Children with ADHD | Multiple, including YGTSS |
| | 19 | nRCT | No active treatment | Children and youth with ADHD + Tics/Tourettes, mostly male | SERF (AEs) |
| | 27 | Cohort | Dexamphetamine, Adderall | Outpatient pre-schoolers with ADHD prescribed psychostimulants | |
| Non-comparative studies: | | | | | |
| MPH safe | 228 | Prospective open-label trial | - | Children and youth with ADHD, mostly male: tics, seizures, psychosis excluded | AEs |
| | 134 | Prospective open label study | - | Children with ADHD, mostly male | AEs |
| | 112 | retrospective cohort design | - | Adults with ADHD | AEs |
| Cautious | 34 | Prospective open-label trial | - | Children and youth with ADHD + tics/TS, mostly male | Multiple |
| Case reports: | | | | | |
| Cautious | 2 | Case Series | - | Boy with ADHD (Patients A & B) | |
| | 2 | Case Series | - | Boy with ADHD (Cases 2 & 3) | |
| Not safe | 1 | Case Report | - | Boy with hyperactive behaviour | |
| Unclear | 1 | Case Report | - | Twin boy with Tourette syndrome and hyperactivity | |
| | 1 | Case Report | - | Woman with ADHD | |

groups, such as pre-schoolers, children with comorbid neurological disorders, and offenders.

The study questions themselves were also heterogeneous: some studies set out specifically to monitor adverse outcomes, either open-endedly as in pharmacovigilance designs, or targeted at specific adverse outcomes, (e.g. tics, psychosis, or EEG abnormalities). In others, the study question is framed as investigating a potential long-term benefit, (e.g. potential reduced risk of adverse adult psychiatric outcomes).

Studies also varied as to whether the primary purpose of the study was to determine the effects of long-term treatment or long-term effects of treatment. In this review, we only included studies in which the most common treatment duration was over one year; however, there may be important long-term effects, both adverse and beneficial, of shorter MPH treatment durations. Future investigators may want to make the potentially important distinction between adverse neuropsychiatric effects of prolonged treatment during the treatment period (e.g. tic emergence; sleep disturbance), and long-term neuropsychiatric outcomes of MPH treatment that lie outside the core deficits of ADHD (e.g. risk elevation or reduction of neuropsychiatric disorders in adulthood). These could include long-term effects of relatively short treatment durations, as well as effects that persist after cessation of treatment.

The evidence map highlights the potential confound between neuropsychiatric and behavioural outcomes of long-term treatment and neuropsychiatric symptoms that may increase the probability of long-term treatment (neuropsychiatric and behavioural treatment propensity factors). Many of the studies included were of patients with comorbid symptoms that were also listed as our potential adverse outcomes of interest; moreover, these comorbid symptoms may themselves sometimes be adverse outcomes resulting from the stresses of living with ADHD. This confound underscores the importance of self-controlled case-series approaches using large databases e.g. Man et al. (2017, 2016), and for large long-term prospective studies.

However, the evidence map also highlights the importance of single case-level studies, study discontinuation data, and details from retrospective chart reviews. While large studies can provide confidence that a treatment is generally beneficial, and/or AEs generally mild and infrequent, these individual-level studies underscore the need for recommendations for caution in specific cases, even for neuropsychiatric outcomes for which evidence indicates overall lowering of long-term risk by long-term MPH treatment. Further research is needed into the predictors of serious, if rare, adverse outcomes, for example in the presence of particular comorbid disorders, such as seizures, psychotic symptoms or tics. Again, studies using large databases, particularly those using self-controlled case series methodology may shed light on these risks.

4.1. Clinical summary

Despite the heterogeneity of the studies, a provisional clinical summary can be made. For depressive symptoms, overall, the studies suggest that long-term MPH treatment has favourable outcomes, including reduced suicide in ADHD. As depression is one of the commonest mental health conditions and suicide is a major public health concern, this is important. Moreover, most of the studies suggest that long-term MPH is safe with regards to anxiety and irritability, at least in those above preschool age. The evidence from studies looking at substance abuse risk generally indicates that long-term MPH use is safe and predicts good long-term outcomes, although caution is indicated with regard to the abuse of prescribed MPH in high risk adolescents.

Several of the studies looking at either psychosis or tics suggest that long-term MPH use is generally safe, although case reports do indicate that MPH should be used with caution in those prone to psychosis or tics. Some evidence suggests that both psychosis and tics remitted after withdrawal of methylphenidate indicating these AEs may be short term. More studies are needed in bipolar disorder and seizures as the evidence is currently sparse and unclear on these outcomes. Sleep

Table 17
Seizures or EEG abnormalities. Studies reporting seizures or EEG abnormalities as a potential adverse outcome.

| SEIZURES OR EEG ABNORMALITIES | | | | | | |
|---------------------------------|-----------------------------|------|------------------------------|-------------------------|---|-------------------------|
| | Study | N | Design | Comparison | Sample description | Measures |
| <i>Comparative Studies:</i> | | | | | | |
| Caution | Hemmer et al., 2001 | 205 | Cohort | No treatment or placebo | Children with ADHD assessed for EEG abnormalities prior to starting stimulant medication, mostly male | EEG, seizures |
| Unclear | Cortese et al., 2015 | 2331 | Cohort | MPH v atomoxetine | Children with ADHD | AEs |
| <i>Non-comparative studies:</i> | | | | | | |
| MPH safe | Gucuyener et al., 2003 | 119 | Prospective open-label trial | – | Children and youth with ADHD + epilepsy or EEG abnormalities, mostly male | EEG |
| | Fosi et al., 2013 | 18 | Retrospective chart review | – | Children and youth with ADHD + epilepsy, mostly male | Seizure Frequency |
| Caution | Mulas et al., 2014 | 17 | Retrospective chart review | – | Children and youth with ADHD + epilepsy | EEG and seizure history |
| Unclear | Weiss et al., 1975 | 22 | retrospective cohort design | – | Hyperactive children | EEG |
| <i>Case reports:</i> | | | | | | |
| Safe | Ickowicz, 2002 | 1 | Case Report | – | Boy with ADHD | |
| | Socanski et al., 2018 | 1 | Case Report | – | Boy with ADHD | |
| Caution | Schertz and Steinberg, 2008 | 1 | Case Report | – | Girl with ADHD | |

disorders, MPH and ADHD appear to have a complex interaction and most studies available are unclear regarding long term outcomes. Studies exploring dosing and timing of MPH are warranted in this area.

Overall, these findings do not suggest that long-term MPH is unsafe with regard to neuropsychiatric outcomes, and several studies suggest that long-term MPH may reduce depression and suicide in ADHD. Although the evidence suggests an elevated risk of psychosis and tics, case reports describe remission on discontinuation. Caution is advised in specialist groups such as pre-school children, those with tics, and adolescents at risk for substance misuse. Given the evidence for positive neuropsychiatric outcomes versus the evidence for risks, long-term MPH use in ADHD would appear to be justified. However, the evidence also highlights the need for careful and regular monitoring of long-term MPH in ADHD by a specialist.

4.2. Limitations

A limitation of this review is that as we only included studies in which it was possible to isolate long-term MPH treatment from long-

term pharmacological treatment more generally, some important studies of long-term medication, were omitted. Notable exclusions resulting from this inclusion criterion are the case-controlled 10-year longitudinal study by Biederman et al. (2009) on the effects of stimulant medication on adult psychiatric outcomes, and studies by Chang et al. on SUD (2014) and depression (2016), as well as the findings from the MTA study (Molina et al., 2009; MTA Cooperative Group, 2004). However, these omissions serve to underscore the importance of both investigations into the potential neuropsychiatric harms of long-term exposure to specific pharmacological treatments for ADHD, and investigations into the potential long-term neuropsychiatric harms of unsuccessfully treated ADHD.

We also note as a limitation that the second wave of the search (articles published after January 2013) only included articles written in English. While only one non-English study from the first wave met our inclusion criteria, it remains possible that later non-English publications may meet these criteria.

Table 18
Sleep disorders. Studies reporting sleep disorders as a potential adverse outcome.

| SLEEP DISORDERS | | | | | | |
|---------------------------------|------------------------------------|------|------------------------------|--|---|---------------------------------|
| | Study | N | Design | Comparator | Sample description | Measures |
| <i>Comparative studies:</i> | | | | | | |
| Favours comparator | Cortese et al., 2015 | 2331 | Cohort | Atomoxetine | Children with ADHD | AEs |
| Unclear | Corkum et al., 1999 | 172 | Cohort | No active treatment | Children | SLQ |
| | Ghuman et al., 2001 | 27 | Cohort | Dexamphetamine, Adderall | Pre-schoolers with ADHD, mostly male | SERF (AEs) |
| | Gau and Chiang, 2009 | 281 | Cohort | No current MPH treatment; healthy controls | Children with ADHD | Sleep Disturbance Questionnaire |
| | Haynes et al., 2015 | 704 | Cohort | Atomoxetine | Children and youth with ADHD, mostly male | AEs |
| <i>Non-comparative studies:</i> | | | | | | |
| MPH safe | Wilens et al., 2005 | 228 | Prospective open-label trial | – | Follow-up from Wilens et al., 2005 | AEs |
| | Atzori et al., 2009 | 134 | Prospective open label study | – | Children with ADHD, mostly male | AEs |
| | Edvinsson and Ekselius, 2018 | 112 | retrospective cohort design | – | Adults with ADHD | AEs |
| <i>Case reports:</i> | | | | | | |
| MPH safe | Guerdjikova and McElroy, 2013 | 1 | Case Report | – | Woman with ADHD + bulimia, bipolar | |
| Caution | Garland, 1998 | 1 | Case Report | – | Boy with ADHD and intranasal MPH abuse | |
| Unclear | Villafuerte-Trisolini et al., 2017 | 1 | Case Report | – | 10 year old boy with catathrenia (sleep disorder) | Somnogram |

Table 19
Other notable neuropsychiatric outcomes. Studies reporting any other notable potential neuropsychiatric adverse outcome.

| OTHER NOTABLE NEUROPSYCHIATRIC OUTCOMES | | | | | | | |
|---|---------------------|--------|---|--------------------------|---|----------------------------------|------------|
| Study | N | Design | Comparator | Sample description | Outcome | Measure | |
| <i>Comparative studies:</i> | | | | | | | |
| Unclear | Ghuman et al., 2001 | 27 | Cohort | Dexamphetamine, Adderall | Pre-schoolers with ADHD, mostly male | Agitation/aggression | SERF (AEs) |
| | Haynes et al., 2015 | 704 | Cohort | Atomoxetine | Children and youth with ADHD, mostly male | Personality changes | AEs |
| <i>Non-comparative studies:</i> | | | | | | | |
| MPH Safe | Kutlu et al., 2017 | 118 | Prospective open label longitudinal study | - | Boys with ADHD + CD/ODD | Aggression, aggressive behaviour | CBCL |
| | Wilens et al., 2005 | 289 | Prospective open-label trial | - | Follow-up from Wilens et al., 2005 | Hostility | AEs |

4.3. Conclusion

We conclude that the evidence base regarding both adverse and beneficial neuropsychiatric effects of long-term MPH treatment would be improved by more studies that make use of large longitudinal databases, focus on specific neuropsychiatric outcomes, and compare outcomes from long-term MPH treatment not only with outcomes from

other treatments but also with outcomes following no pharmacological intervention.

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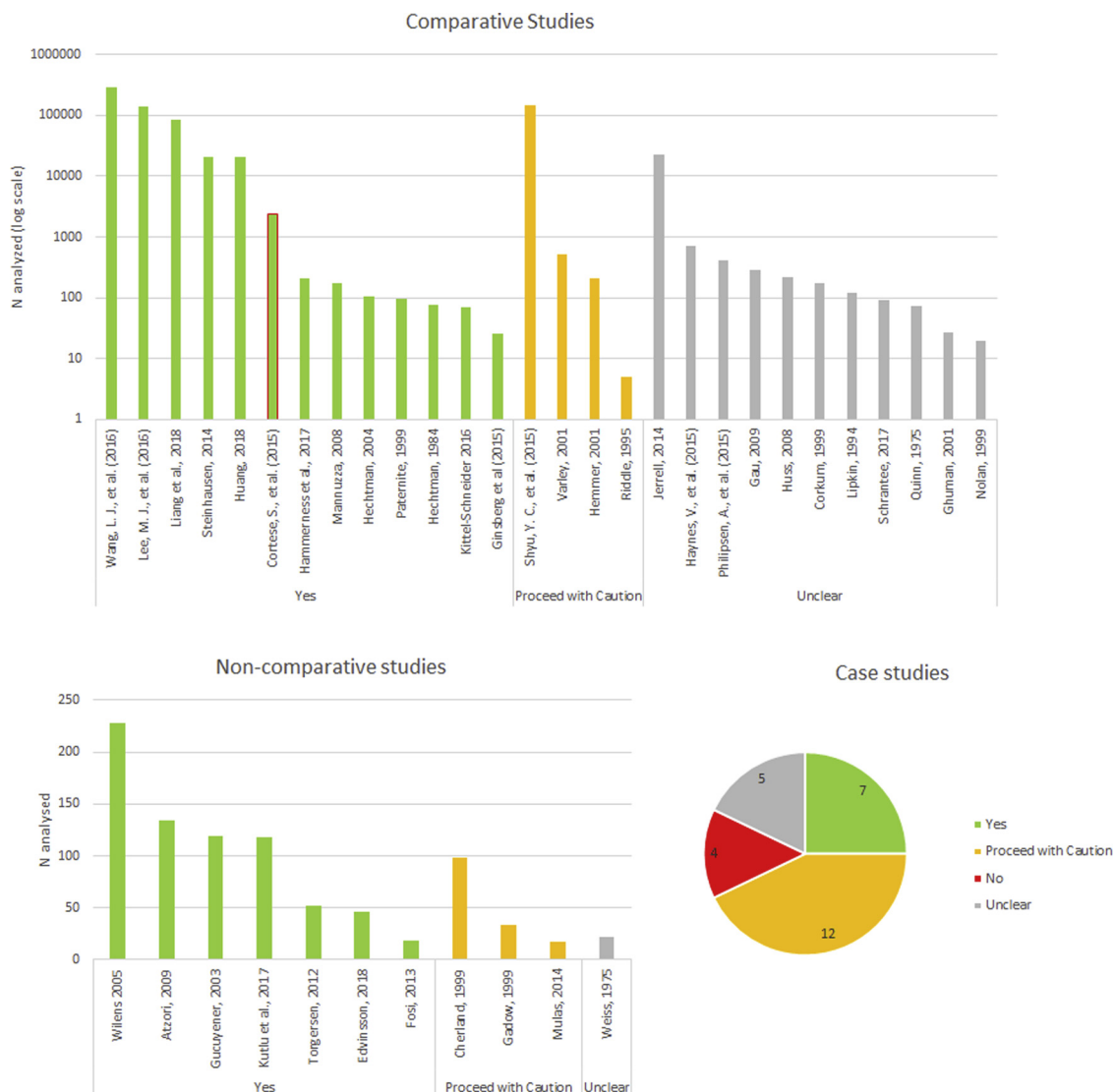


Fig. 4. Studies by overall "traffic light" coding. Sample sizes are shown for group studies; for case studies, the number of studies coded in each category is shown. Note that one group study, Cortese et al. (2015) (shown with red outline) was coded Favours Comparator for one outcome (sleep disorders), but Favours MPH overall.

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Declaration of Competing Interest

Dr Helga Krinzinger; Dr Charlotte Hall; Dr Maddie Groom; Dr Mohammed Ansari; Prof. Bruno Falissard; Dr. Peter Garas; Dr. Sara Inglis; Dr. Hanna Kovshoff; Dr Puja Kochhar; Dr. Peter Nagy; Dr. Antje Neubert; Ms Samantha Roberts; Dr. Jun Xia: none.

Prof. Tobias Banaschewski served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Shire. He received conference support or speaker's fee by Lilly, Medice, Novartis and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships

Prof. Jan K Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Lundbeck, Shire, Roche, Medice, Novartis, and Servier. He has received research support from Roche and Vifor. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

Dr. Sara Carucci has collaboration within projects from the European Union (7th Framework Program) and collaboration as sub-investigator in sponsored clinical trials by Shire Pharmaceutical Company, Lundbeck, Otsuka and Janssen Cilag. Travel support from Shire Pharmaceutical Company and Fidia Farmaceutici.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neubiorev.2019.09.023>.

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