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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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Keywords:
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Adverse neuropsychiatric events
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Anxiety
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Bipolar
Psychosis
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; Miake-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 Psychinfo 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 addressed[1]
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).

[1] Including outcomes anticipated in the study to be beneficial.

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

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	Free text
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 years[3] (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).

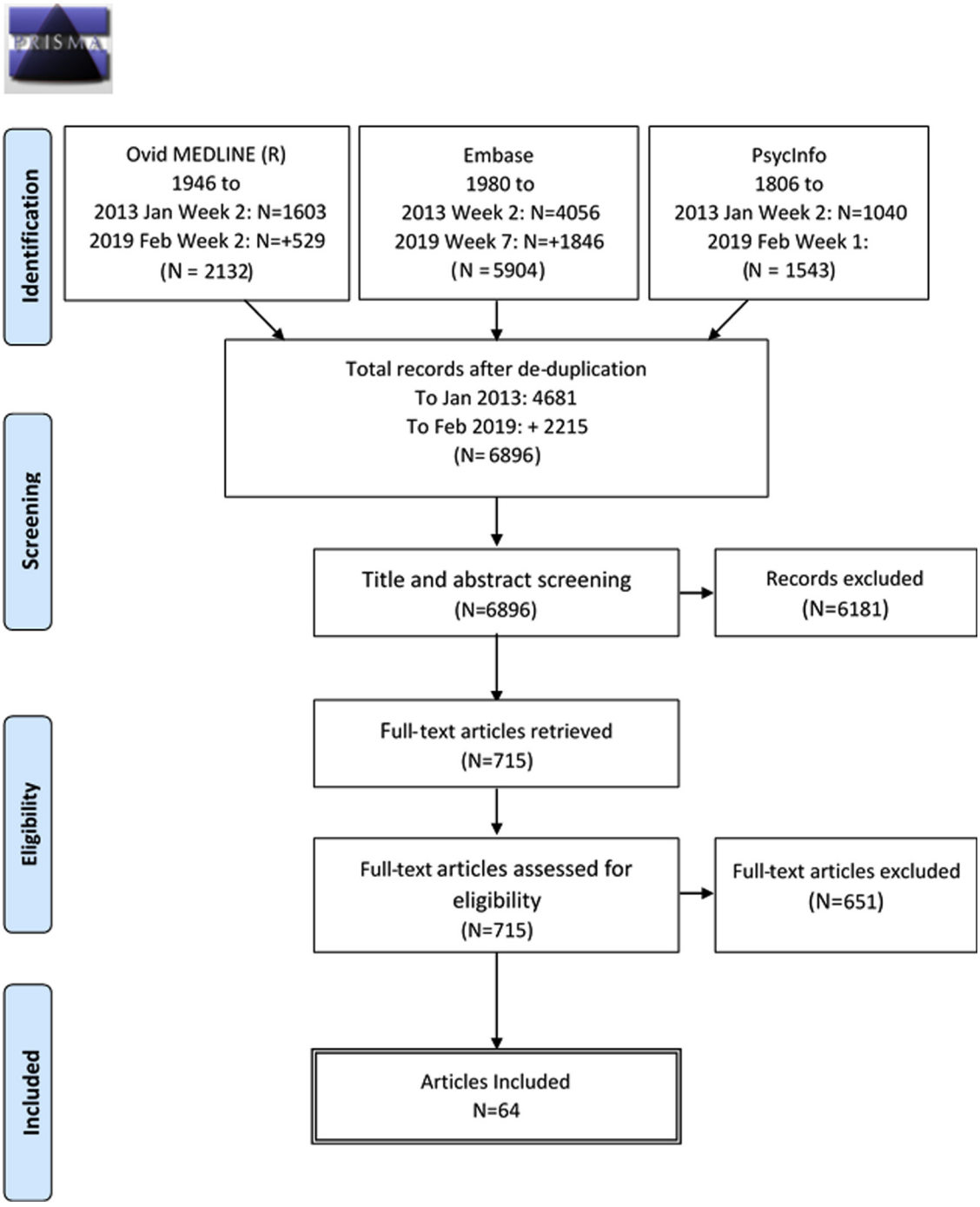


Fig. 1. Prisma flow chart for literature search.

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	Young adult psychiatric outcomes in MPH-treated vs untreated ADHD	76	36	Psychiatric assessment	Y
	Lipkin et al., 1994	Medication risks of tic emergence in children with ADHD	122	13-23	Solicited tic reports	U
	Corkum et al., 1999	ADHD and MPH as risk factors for sleep disorder	172	12	Sleep questionnaires	U
	Paternite et al., 1999	Mood, Anxiety, Suicidality, psychosis, SUD in young adulthood	97	30	Chart Evidence	C
	Ghuman et al., 2001	Treatment-associated Adverse Events in MPH vs other stimulants in preschoolers	27	24	AEs	U
	Hemmer et al., 2001	MPH as seizure risk in ADHD	205	< 12	Seizure records	C
	Varley et al., 2001	Tic emergence	517	16	AEs	U
	Huss et al., 2008	Nicotine use in MPH-treated vs untreated ADHD	215	27	Diagnostic interview	U
	Mannuzza et al., 2008	Age at initiation of stimulant treatment and SUD as an outcome in ADHD	176	23	Follow-up by clinicians	Y
	Gau and Chiang, 2009	ADHD and MPH as risk factors for sleep disorder	281	20	Sleep questionnaires	U
	Ginsberg et al., 2015	SUD outcomes in MPH-treated adult male prisoners with ADHD	25	36	SUD rating scales	Y
	Haynes et al., 2015	AEs for MPH vs atomoxetine in ADHD	704	24	AEs	Y
	Kittel-Schneider et al., 2016	ADHD and duration of MPH treatment as predictors of stress in adults with ADHD	70	12	Self-rating scale	U
	Hammerness et al., 2017	SUD risk in youth with ADHD treated with stimulants	211	13	SUD rating scale	Y
	Schrantee et al., 2018	Long-term effects of stimulant exposure on cerebral blood flow response to methylphenidate and behavior in attention-deficit hyperactivity disorder	91	72	Self-rating scales for Depression, Anxiety, SUD	C
Time-series	Riddle et al., 1995	Effects of discontinuation and reinitiation of MPH treatment on tics	5	12	Tic rating scales	C
	Nolan et al., 1999	Stimulant Medication Withdrawal during Long-Term Therapy in Children with Comorbid ADHD and Tic Disorder	19	51	Tic rating scales	U
RCT	Quinn and Rapoport, 1975	Outcomes of MPH vs imipramine and no treatment on anxiety	73	12	Rating scales	U
	Hechtman et al., 2004	MPH-moderation of adjunct nonpharmacological therapy on emotional status	103	36	Self-rating scales	Y
	Philipsen et al., 2015	MPH-moderating effects of adjunct nonpharmacological therapy on mood	419	12	Self-rating scale	U
N > 1000						
Cohort	Cortese et al., 2015	Safety of MPH and atomoxetine	2331	> 12	AEs	Y
	Jerrell et al., 2014	Bipolar disorder as an outcome of ADHD	22,797	17	ICD codes	U
	Steinhausen and Bisgaard, 2014	Medication risk factors for SUD in ADHD	20,742	36	ICD codes	Y
	Shyu et al., 2015	ADHD and MPH as risk factors for later diagnosis of schizophrenia	146,098	12	ICD codes	C
	Lee, 2016	ADHD and medication as risk factors for later diagnosis of depression	142,160	12	ICD codes	Y
	Wang et al., 2016a	ADHD and medication as risk factors for later diagnosis bipolar disorder	289,840	12	ICD codes	Y
	Huang et al., 2018	Risk of suicide attempts in adolescents and young adults with attention-deficit hyperactivity disorder: a nationwide longitudinal study	20,574	12	ICD codes	Y
	Liang et al., 2018	ADHD and MPH as risk factors for suicide	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	Rate of psychotic side effects in stimulant-treated children	98	21	AEs	C
	Fosi et al., 2013	MPH safety in children with ADHD + severe epilepsy	18	12	Seizure frequency	Y
	Mulas et al., 2014	Pharmacological management of ADHD with MPH and ATX within a context of epilepsy	17	24	EEG	C
Follow-up	Weiss et al., 1975	MPH treatment as a risk factor for seizures	22	60	EEG	Y
	Edvinsson and Ekselius, 2018	Long-Term Tolerability and Safety of Pharmacological Treatment of Adult Attention-Deficit/Hyperactivity Disorder	46	72	AEs	Y
PROSPECTIVE DESIGNS:						
Open label longitudinal study	Gucuyener et al., 2003	MPH treatment as risk factor for seizures	119	12	EEG	Y
	Wilens et al., 2005	Adverse effects of MPH treatment in children	228	21	AEs	Y
	Atzori et al., 2009	Adverse events affecting compliance with MPH treatment	134	36	AEs	Y
	Torgersen et al., 2012	Comorbid SUD under long-term stimulant treatment of ADHD	52	41	DSM-IV codes	Y
	Kutlu et al., 2017	MPH effects on emotional dysregulation	118	12	Self-report scale	Y
Open label trial extension	Gadow et al., 1999	MPH as a risk factor for tic exacerbation in young people with ADHD + tic disorder	34	24	Tic rating scales	C

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 Atomoxetine[4]. 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 AEs[5]. 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 disorder[6]; Wang et al. (2016a), considered bipolar disorder[7] 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, Steinhausen 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

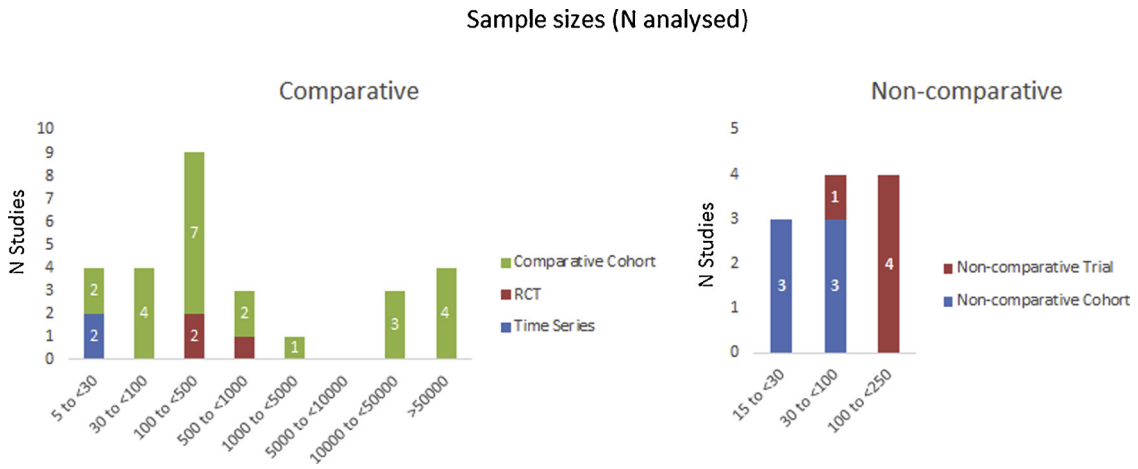


Fig. 2. Histograms of sample sizes for (left) comparative and (right) non-comparative group studies, broken out by study design. Numbers in white indicate number of studies.

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.

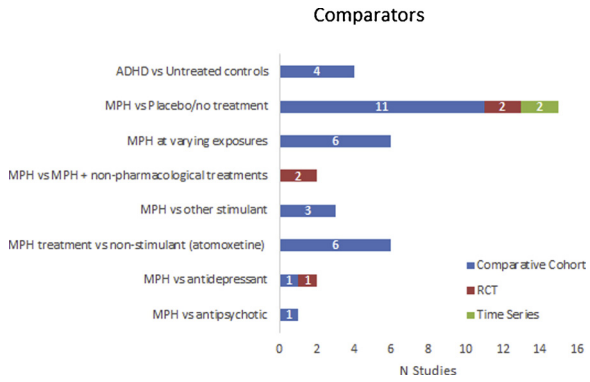


Fig. 3. Comparators used in comparative studies. Numbers refer to number of studies using that comparator. Numbers sum to more the number of comparative studies (N = 28) as 15 studies used multiple comparators.

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 neurospsychiatric 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					✓					
		Schrantee et al., 2018	CC	✓	✓								
MPH vs MPH in combination with non-pharmacological treatments	2	Hechtman et al., 2004	RCT	✓	✓								
		Philipsen et al., 2015*	RCT	✓									
MPH at varying exposures (age at initiation of treatment; duration of treatment; dosage; treatment response)	6	Paternite et al., 1999	CC	✓	✓		✓		✓	✓			
		Mannuzza et al., 2008	CC							✓			
		Kittel-Schneider et al., 2016	CC		✓								
		Schrantee et al., 2018	CC	✓	✓					✓			
		Liang et al., 2018	CC				✓						
		Huang et al., 2018	CC					✓					
MPH vs other stimulant (dexamphetamine, pemoline, adderall)	3	Lipkin et al., 1994	CC								✓		
		Ghuman et al., 2001	CC	✓	✓	✓					✓		✓
		Varley et al., 2001	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	CC	✓		✓	✓		✓			✓	✓
		Haynes et al., 2015	CC										✓
		Lee, 2016	CC	✓									
		Wang et al., 2016a, *	CC					✓					
		Liang et al., 2018	CC				✓						
		Huang et al., 2018	CC					✓					
MPH vs antidepressant	2	Quinn and Rapoport, 1975*	RCT		✓								
		Steinhausen and Bisgaard, 2014*	CC							✓			
MPH vs antipsychotic	1	Steinhausen and Bisgaard, 2014*	CC							✓			
ADHD vs Untreated controls	4	Hechtman et al., 1984*	CC	✓	✓		✓		✓	✓			
		Gau and Chiang, 2009*	CC										✓
		Huang et al., 2018	CC					✓					
		Hammerness et al., 2017	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.

NON-COMPARATIVE STUDIES	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
Retrospective Designs											
retrospective chart review	Cherland and Fitzpatrick, 1999					✓	✓				
	Fosi et al., 2013									✓	
	Mulas et al., 2014									✓	
retrospective follow-up	Weiss et al., 1975									✓	
	Edvinsson and Ekselius, 2018	✓	✓	✓						✓	✓
Prospective Designs											
Prospective open label longitudinal study	Gucuyener et al., 2003									✓	
	Wilens et al., 2005			✓					✓		✓
	Atzori et al., 2009			✓					✓		✓
	Torgersen et al., 2012							✓			
	Kutlu et al., 2017	✓	✓	✓							
Prospective open label RCT extension	Gadow et al., 1999	✓	✓						✓		

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 the 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.

LOW MOOD/DEPRESSION						
	Study	N	Study Design	Comparison	Sample description	Measure
Comparative Studies:						
Favours MPH	Lee, 2016	142,160	Cohort	Atomoxetine	Children and young adults with ADHD diagnosed before age 20 and matched controls	ICD-9-CM codes for MDD
	Cortese et al., 2015	2331	Cohort	Atomoxetine	Children and youth with ADHD, mostly male	AEs*
	Hechtman et al., 2004	103	RCT	MPH + BT and MPH + attentional control	Children and youth with ADHD	CDI
Unclear	Hechtman et al., 1984	76	Cohort	ADHD untreated and controls untreated	Adults with ADHD	SADS, SCL-90
	Paternite et al., 1999	97	Cohort	MPH dosage, duration, response	Young adult men with ADHD	SADS-L, MMPI
	Ghuman et al., 2001	27	Cohort	Dexamphetamine and Adderall	Pre-schoolers with ADHD, mostly male	SERF (AEs)
	Schrantee et al., 2018	91	Cohort	No treatment; late vs early onset of treatment	Adults with a history of ADHD	BDI
	Philipsen et al., 2015	419	RCT	MPH + Therapy, MPH + Clinical management, Placebo + Therapy, Placebo + Clinical management	Adults with ADHD	BDI
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 bulimia, ADHD, bipolar	
Caution	Garland, 1998	1	Case Report	–	Boy with ADHD and intranasal MPH abuse	
Unclear	Rosenfeld, 1979	1	Case Report	–	Boy with ADHD	

* denotes statistically significant difference against comparator.

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

ANXIETY						
	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
Unclear	Paternite et al., 1999	97	Cohort	MPH dosage, duration, response	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	PH
	Ghuman et al., 2001	27	Cohort	Dexamphetamine, Adderall	Pre-schoolers with ADHD, mostly male	SERF (AEs)
	Quinn and Rapoport, 1975	73	RCT	Imipramine, placebo	Hyperactive boys at 1 year follow-up from RCT	Conners PSQ,TRS
	Schrantee 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
Comparative Studies:						
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)
Non comparative studies:						
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
Case report:						
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; Waserman et al., 1983; Weiner et al., 1978) include three cases with pre-existing tics (Sprafkin and Gadow, 1993; Waserman 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 cases 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
Comparative Studies:						
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
Case Reports						
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
Comparative Studies:						
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
Non comparative studies:						
Caution	Cherland and Fitzpatrick, 1999	98	Retrospective chart review	–	Children with ADHD, mostly male	AEs
Case Reports:						
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
Comparative Studies:						
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
Non-comparative studies:						
Caution	Cherland and Fitzpatrick, 1999	98	Retrospective chart review	–	Children with ADHD, mostly male	AEs
Case studies:						
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	
	Ekinci 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
Comparative Studies:						
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
	Paternite 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
Non-comparative studies:						
MPH safe	Torgersen et al., 2012	52	Trial	–	Adults with no prior history of SUD, treated with MPH	DSM-IV criteria for SUD
Case reports:						
MPH safe	Khantzian 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	
	Imbert et al., 2013	1	Case Report	–	Man with ADHD and cocaine addiction	
Caution	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.

TICS & OTHER DYSKINESIAS						
	Study	N	Design	Comparator	Sample description	Measures
Comparative Studies:						
Caution	Riddle et al., 1995	5	nRCT	No active treatment	Boys in tic disorder clinic with ADHD	Video monitoring + C-YGTSS
	Varley et al., 2001	517	Cohort	Dexampetamine, Pemoline	Children with ADHD, history of family history of tics	
Unclear	Lipkin et al., 1994	122	Cohort	Dexampetamine, Pemoline	Children with ADHD	Parent reports
	Nolan et al., 1999	19	nRCT	No active treatment	Children and youth with ADHD + Tics/Tourettes, mostly male	Multiple, including YGTSS
	Ghuman et al., 2001	27	Cohort	Dexamphetamine, Adderall	Outpatient pre-schoolers with ADHD prescribed psychostimulants	SERF (AEs)
Non-comparative studies:						
MPH safe	Wilens et al., 2005	228	Prospective open-label trial	–	Children and youth with ADHD, mostly male: tics, seizures, psychosis excluded	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
Caution	Gadow et al., 1999	34	Prospective open-label trial	–	Children and youth with ADHD + tics/TS, mostly male	Multiple
Case reports:						
Caution	Sprafkin and Gadow, 1993	2	Case Series	–	Boy with ADHD (Patients A & B)	
	Kazanci et al., 2015	2	Case Series	–	Boy with ADHD (Cases 2 & 3)	
Not safe	Weiner et al., 1978	1	Case Report	–	Boy with hyperactive behaviour	
Unclear	Waserman et al., 1983	1	Case Report	–	Twin boy with Tourette syndrome and hyperactivity	
	Lee, 2016	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
Comparative Studies:						
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
Non-comparative studies:						
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
Case reports:						
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
Comparative studies:						
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
Non-comparative studies:						
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
Case reports:						
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
Comparative studies:							
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
Non-comparative studies:							
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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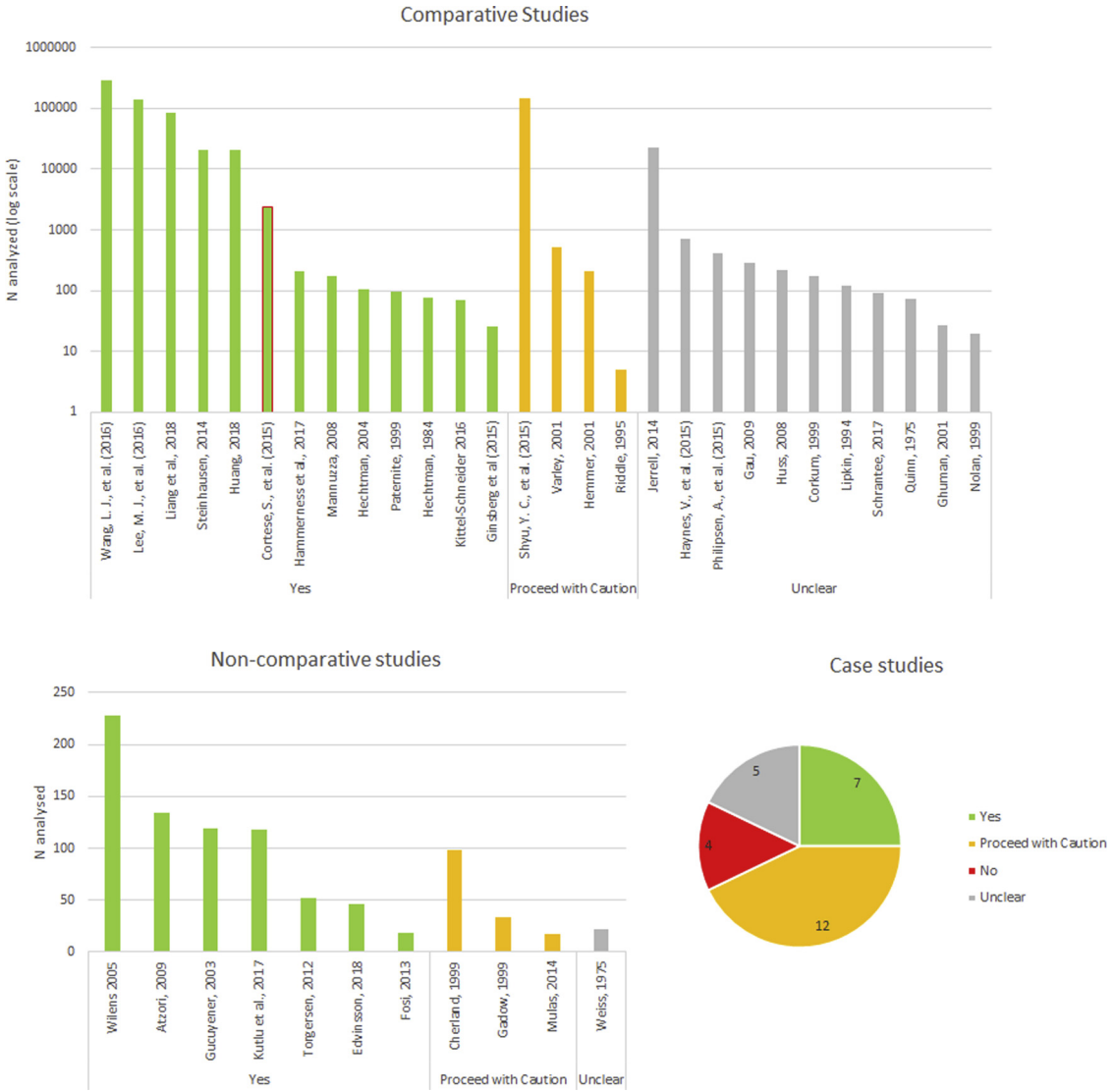


Fig. 4. Studies by overall "traffic light" coding. Sample sizes are shown for group studies; for case studies, the number of studies coded in each category is shown. Note that one group study, Cortese et al. (2015) (shown with red outline) was coded Favours Comparator for one outcome (sleep disorders),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

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Prof. Ralf W. Dittmann has received compensation for serving as consultant or speaker, or he or the institution he works for have received research support or royalties from the organizations or companies indicated: EU (FP7 Programme), US National Institute of Mental Health (NIMH), German Federal Ministry of Health/Regulatory Agency (BMG/BfArM), German Federal Ministry of Education and Research (BMBF), German Research Foundation (DFG), Volkswagen Foundation; Boehringer Ingelheim, Ferring, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Servier, Shire, Sunovion/Takeda and Theravance. He owns Eli Lilly stock. Prof. Kapil Sayal reports grants from the National Institute for Health Research (NIHR) during the conduct of the study. He is a member of the NICE ADHD Guideline Committee.

Prof. Edmund Sonuga-Barke's financial declarations are: Speaker fees, consultancy, research funding and conference support from Shire Pharma. Speaker fees from American University of Beirut, Janssen Cilag, Consultancy from Neurotech solutions, Copenhagen University and Berhanderling, Skolerne, KU Leuven. Book royalties from OUP and Jessica Kingsley. Financial support received from Arrhus Univeristy and Ghent University for visiting Professorship. Grants awarded from MRC, ESRC, Wellcome Trust, Solent NHS Trust, European Union, Child Health Research Foundation New Zealand, NIHR, Nuffield Foundation, Fonds Wetenschappelijk Onderzoek-Vlaanderen (FWO), MQ – Transforming Mental health. Editor-in-Chief JCPP – supported by a buy-out of time to University of Southampton and personal Honorarium. Non-financial declarations are: Member of the European ADHD Guidelines Group.

Prof. Ian Wong reports grants from European Union FP7 programme, during the conduct of the study; grants from Shire, grants from Janssen-Cilag, grants from Eli-Lily, grants from Pfizer, outside the submitted work; and Prof Wong was a member of the National Institute for Health and Clinical Excellence (NICE) ADHD Guideline Group and the British Association for Psychopharmacology ADHD guideline group and acted as an advisor to Shire.

Prof. Chris Hollis reports grants from European Union FP7 programme, H2020, National Institute of Health Research (NIHR) and Medical Research Council (MRC) during the conduct of the study; He is a member of the European ADHD Guideline Group (EAGG) and NICE ADHD Guideline Committee.

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 royalities 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.

Prof. David Coghill reports grants from European Commission, during the conduct of the study; grants and personal fees from Shire, personal fees from Eli Lilly, grants from Vifor, personal fees from Novartis, personal fees from Oxford University Press, other than the EC grants these are all outside the submitted work.

Prof. Marina Dankaerts is a member of the European ADHD Guideline Group (EAGG) and holds grants from the European Union FP7 programme.

Prof. Ralf W. Dittmann has received compensation for serving as consultant or speaker, or he or the institution he works for have received research support or royalties from the organizations or companies indicated: EU (FP7 Programme), US National Institute of Mental Health (NIMH), German Federal Ministry of Health/Regulatory Agency (BMG/BfArM), German Federal Ministry of Education and Research (BMBF), German Research Foundation (DFG), Volkswagen Foundation; Boehringer Ingelheim, Ferring, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Servier, Shire, Sunovion/Takeda and Theravance. He owns Eli Lilly stock. Prof. Kapil Sayal reports grants from the National Institute for Health Research (NIHR) during the conduct of the study. He is a member of the NICE ADHD Guideline Committee.

Prof. Edmund Sonuga-Barke's financial declarations are: Speaker fees, consultancy, research funding and conference support from Shire Pharma. Speaker fees from American University of Beirut, Janssen Cilag, Consultancy from Neurotech solutions, Copenhagen University and Berhanderling, Skolerne, KU Leuven. Book royalties from OUP and Jessica Kingsley. Financial support received from Arrhus Univeristy and Ghent University for visiting Professorship. Grants awarded from MRC, ESRC, Wellcome Trust, Solent NHS Trust, European Union, Child Health Research Foundation New Zealand, NIHR, Nuffield Foundation, Fonds Wetenschappelijk Onderzoek-Vlaanderen (FWO), MQ – Transforming Mental health. Editor-in-Chief JCPP – supported by a buy-out of time to University of Southampton and personal Honorarium. Non-financial declarations are: Member of the European ADHD Guidelines Group.

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Prof. Alessandro Zuddas served in an advisory or consultancy role for Angelini, Lundbeck, Otsuka, EduPharma, Shire and Viforpharma. He received conference support or speaker's fee by Angelini and EduPharma. He is/has been involved in clinical trials conducted by Roche, Lundbeck, Jannssen, Servier, Shire & Viforpharma. He received royalities from Oxford University Press and Giunti OS. The present work is unrelated to the above grants and relationships.

Prof. Chris Hollis reports grants from European Union FP7 programme, H2020, National Institute of Health Research (NIHR) and Medical Research Council (MRC) during the conduct of the study; He is a member of the European ADHD Guideline Group (EAGG) and NICE ADHD Guideline Committee.

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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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