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REVIEW

Clinical guidance on pharmacotherapy for the treatment of attention-deficit hyperactivity disorder (ADHD) for people with intellectual disability

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ABSTRACT

Introduction: ADHD causes significant distress and functional impairment in multiple domains of daily life. Therefore, diagnosis and treatment are important to improve the quality of life of people. The pharmacotherapy for ADHD is well established but needs systematic evaluation in Intellectual Disability (ID) populations.

Areas covered: This paper reviews the ADHD pharmacological treatment in people with ID using the PRISMA guidance for scoping reviews to help identify the nature and strength of evidence.

Expert opinion: In the last 20 years, seven randomized controlled trials have evaluated pharmacotherapies for ADHD in people with ID; five looking at methylphenidate. Generally, studies were underpowered; all but two had less than 25 participants. Of the two larger trials one was single blinded and therefore open to bias. Only two used a parallel-group method, the remainder were mostly short crossover trials; not ideal when measuring behavioral and psychological parameters which are long standing. The remaining evidence is made up of observational studies. Methylphenidate and atomoxetine, particularly at higher doses, have shown clear benefits in people with ID. Most people with ID tolerated ADHD medications well. Benefits were seen in behavioral and/or cognitive domains. The evidence base is limited, though promising, for dexamfetamine, clonidine, and guanfacine.

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Attention-deficit hyperactive disorder; hyperkinetic disorder; pharmacotherapy; intellectual disability; learning disability; neurodevelopment

1. Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with an increased prevalence of 6–16% [1,2] in people with intellectual disabilities (ID) compared to people without ID where it is estimated as 1.8–8.4% [3,4].

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines ID as a neurodevelopmental disorder that begins in childhood characterized by intellectual difficulties as well as difficulties in conceptual, social, and practical areas of living [5]. Around 1% of the population is estimated to have ID [6]. There is a high prevalence of psychiatric, neuropsychiatric, and neurodevelopmental disorders in people with ID [7–10].

Attention-deficit hyperactivity disorder (ADHD) is another of the neurodevelopmental disorders that begins during childhood, manifested with symptoms of inattention and/or hyperactivity & impulsivity causing a functional impairment [5]. Diagnosis of ADHD is important as a lack of treatment can lead to a poorer quality of life. Studies have shown that ADHD can increase substance misuse, criminal behavior, foster poor academic achievements, increased convictions, de-stabilize relationships, increase the likelihood of unemployment [11–14]. One of the main functional impairments is reported to be challenging behavior; for example, verbal and physical aggression. [15].

Management of ADHD includes the use of pharmacological and non-pharmacological treatment options [16]. Pharmacological options are mainly divided into stimulant and non-stimulant medications. Methylphenidate and dexamfetamine preparations are the main stimulant medications licensed to treat ADHD [16]. There are three non-stimulant medications used to treat ADHD; atomoxetine, clonidine, and guanfacine. All five medications have a well-established evidence base in the general population [17,18]. Diagnosis and treatment of ADHD in people with ID can be challenging for various reasons. In addition to communication challenges, increased psychiatric and neuropsychiatric comorbidity can make the treatment decisions more challenging.

Missed diagnosis and lack of treatment in people with ID have shown to increase the use of other psychotropic medications such as antipsychotics [8]. Therefore, treatment of ADHD in people with ID is important in order to improve quality of life, reduce functional impairment, and prevent overuse of psychotropic medications. The dearth of suitable studies further limits the treatment of people with ID and ADHD. In this review, we look at the availability and quality of evidence in the pharmacological management of ADHD in people with ID.

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Article highlights

- The available evidence supports the use of methylphenidate and atomoxetine for ADHD management in people with intellectual disability.
- There is evidence to support the use of higher doses of methylphenidate to treat ADHD in people with intellectual disability.
- There is some evidence for dexamfetamine, clonidine, and guanfacine.
- There is evidence suggesting that people with intellectual disability may respond differently to ADHD medications compared to the general population.
- Further research evaluating the evidence for first- and second-line ADHD medications in people with intellectual disability is warranted.

2. Method

2.1. Search strategy

A literature review based on PRISMA scoping guidelines was undertaken [19]. PubMed, Medline/EMBASE, and Psychinfo were used to identify all forms of current evidence on ADHD medications in people with ADHD and ID in peer-reviewed journals between 1 January 2000 and 31 January 2020. Keywords used in this search are provided in Appendix A1. The study selection and screening process of identified studies were completed by JM, full text articles were then reviewed independently by JM and BP. This is illustrated in pathway 1.

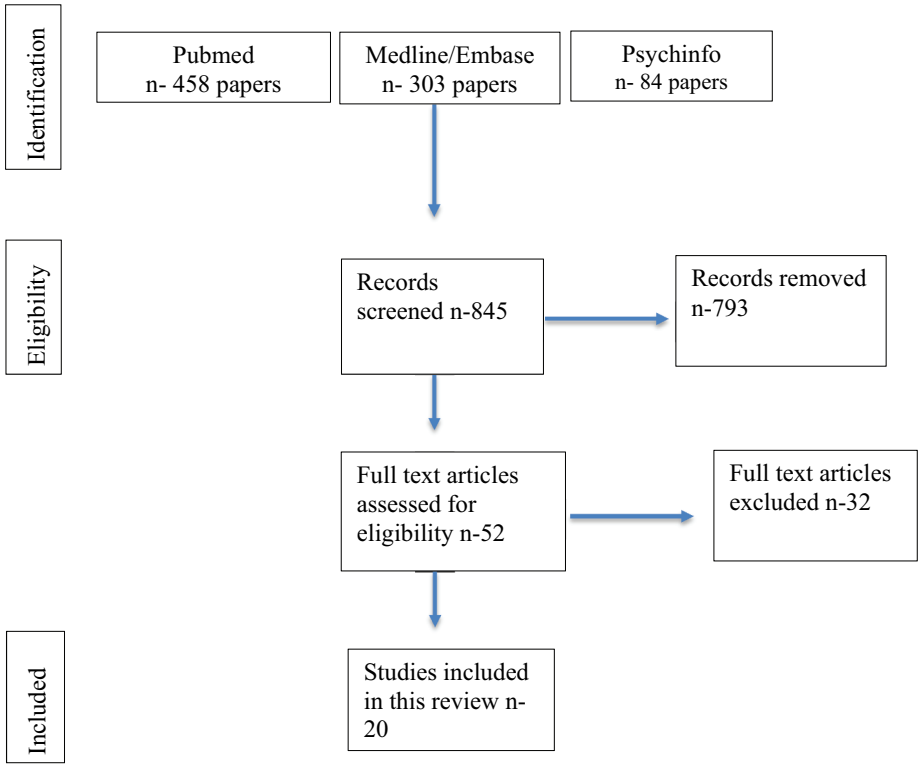
At the first level, titles were reviewed and excluded due to irrelevance to the search criteria, or studies conducted in animals, or in-vitro. At the second stage of the shortlisting process the abstracts were reviewed and papers excluded for the following reasons: no abstract, not in English language, animal studies, in-vitro studies, poster abstracts, articles published prior to the year 2000 and articles which did not look at ADHD medication in people with ID. Full articles were then obtained for all studies accepted post the first and second review levels and full articles were screened for inclusion in the final analysis.

3. Results

A total of 20 studies were found between 1 January 2000 and 31 January 2020. Studies varied from meta-analysis to observational studies. Tables 1-3 provide the result summaries. The sample size for randomized controlled trials varied from ten to 122. All studies but one featured children/young people with ID and ADHD, with an age range of three to 18. One study [20] was done solely in adults (n = 10). Methylphenidate was the most researched drug; covered by 10 papers including two systematic reviews.

3.1. Measures

ADHD diagnosis in the participants of included studies was mainly made by using DSM-4 criteria. Some studies did not explain how the diagnosis was made. The diagnosis of ID was made using IQ in most studies. Several different scales were used in the studies, which are described in Box 1. The most commonly used scales were 'the Aberrant Behavior Checklist (ABC)' [21], 'the ADHD Rating Scale' (ADHD-RS-IV) [22],



Pathway 1: Selection and screening pathway

Box 1. ADHD scales used by studies reviewed.

ABC score: Kilincaslan 2016 [58], Simonoff 2013 [35], Aman 2003 [46], Pearson 2003 [42], Capone 2016 [63], Handen 2008 [64].
ADHD-RS-IV: Fernandez-Jaen 2010[55], Kilincaslan 2016 [58], Fernandez-Jaen 2013 [56].
CGI: Fernandez-Jaen 2010[55], Kilincaslan 2016 [58], Fernandez-Jaen 2013 [56], Jou 2005 [57], Mazzone 2011[59], Simonoff 2013 [35], Fosi 2013 [49], Handen 2008 [64], Posey 2004 [62], Agarwal 2001 [61].
Conners': Fernandez-Jaen 2010[55], Fernandez-Jaen 2013 [56], Jou 2005 [57], Simonoff 2013 [35], Aman 2003 [46], Pearson 2003 [42].
ACTeRS; Pearson 2003 [42].
SNAP-IV: Filho 2005 [48].
NCBRF: Filho 2005 [48].
RBPC: Aman 2003 [46], Pearson 2003 [42].
CASQ: Aman 2003 [46].
CATQ: Gothelf 2003 [52].
CCPT: Gothelf 2003 [52].

Conners' Parent and Conners' Teacher Rating scales' [22–24], and the Swanson, Nolan, and Pelham SNAP Rating Scale [25]. Box 2 provides a brief explanation of each of the common scales, i.e. parameters they measure and their validity.

3.2. Evidence for the use of methylphenidate in ADHD in ID

The literature on methylphenidate in ADHD in people with ID is mainly summarized by two major systematic reviews published in 2018 [33] and 2019 [34], covering the relevant randomized controlled trials within the literature. We discuss these two papers first below, followed by other articles found by our search.

Box 2. Scale scoring systems explained.

The ABC score, developed to detect response to treatment is composed of 5 subscales: 1) irritability, 2) social withdrawal, 3) stereotypic behavior, 4) hyperactivity/noncompliance and 5) inappropriate speech [21].
The ADHD-RS-IV records frequency of the 18 DSM-4 symptoms of ADHD [22].
Conners' score (CPRS/CTRS) can be completed by both parents (CPRS) and teachers (CTRS), has multiple versions, generally including a combination of 6 subscales; Oppositional, Cognitive Problems/Inattention, Hyperactivity, Anxious-Shy, Perfectionism, and Social Problems, ± ADHD index, Conners' global index and DSM-4 inattention and hyperactivity scores. Some versions include conduct problems and inattention subscales [22–24] .
The ACTRS is an abbreviated Conner's score – a different ADHD scoring system devised by the same author [22].
The ACTeRS: ADD-H Comprehensive teacher rating scale – the sole scale where higher scores represent a better outcome. It contains measures of hyperactivity, attention, social skills, and oppositional behavior [26].
The SNAP-IV scale screens for nine symptoms of ADHD hyperactive-impulsive type, nine symptoms of ADHD inattentive type, and eight symptoms of oppositional defiant disorder as taken from the DSM-4 [25].
CATQ: Conners' abbreviated teacher questionnaire; scores observable behaviors involving impulsive, inattentive or overactive tendencies, each item rated 0–3 [27].
CASQ: Conners' abbreviated symptom questionnaire. A 10 item scale used related to emotional and ADHD symptoms [28].
CCPT: Conners' continuous performance test: a visual vigilance task, the patient is instructed to press the spacebar every time any letter except X is shown. [29].
RBPC: The revised behavior problem checklist; an 89 item tool with subscales including conduct problems, attention problems, anxiety and motor excess [30].
NCBRF: Nissonger childhood behavior rating form; a 76 item assessement looking at social and problem behaviors, adapted for people with ID and/or autism [31].
CGI: Clinical global impression (is a score determined by clinicians grading a patient using their judgment, can be retrospective based on impression from patient notes or prospective [32].

- CGI-I/CGI-GI: CGI-impression/global impression, the most commonly used CGI score, represents a clinician's overall impression of a patient's progress; 1 represents 'very much improved,' 2 represents 'much improved,' 3 represents 'mild improvement,' 4 'no change,' 5, 6, and 7 representing minimally, much, and very much worsened.

A score of 1 or 2 with CGI is used to define patients being 'responders' i.e. at least much improved following an intervention.

- CGI-S: CGI-severity; clinicians grade the severity of a patient's condition, can then be compared as at baseline and then post-treatment score. Score ranges from 1 (normal) to 7 (severely ill).

Note on interpreting statistic of 'Cohen' g/effect size (ES)'
Where stated by articles we have included effect size in our review; a useful means of interpreting an intervention's effect.
G/ES = difference in means/pooled weighted standard deviations; a G of 1 indicates the two groups differ by 1 standard deviation, 2 means they differ by 2 standard deviations, .
Cohen [3] suggested using the following rule of thumb for interpreting results of effect size:
·Small effect (cannot be discerned by the naked eye) = 0.2
·Medium Effect = 0.5
·Large Effect (can be seen by the naked eye) = 0.8
Definitions:
Commonly papers describe patients as 'responders' – to determine where a drug has had a clinically apparent effect.
Responder with CGI score: achieving a score of 1 (very much improved) or 2 (much improved).
Responder with all other scores: Unless otherwise specified refers to an improvement of 30% or more vs. baseline; an arbitrary measure which has been adopted in the field (34) to detect patients who show a good clinical response to an intervention.
Significance:
Within the body of text, p values are given by asterisk; 1* = $p < 0.05$, 2** = $p < 0.01$, 3*** = $p < 0.001$.
Exact p values are provided in tables.

Table 1. Summary of clinical trials for methylphenidate + ID + ADHD ALL comparisons for outcomes in this table are given as placebo vs maximum dose of MPH.

Study	Sample population	Study design	Outcome	Effect size (standard deviation – if given)
Filho 2005 [48]	46 children mean age 11.4 (SD 2.5) in MPH group & 12.1 (SD 2.0) in Risperidone arm **Diagnoses** 1.ADHD 2.Moderate MR **IQ** Mean 48.4 in MPH & 46.8 in risperidone	Single-blind parallel group RCT over 4 weeks; MPH vs risperidone **Dosing** MPH up to 0.7 mg/kg/day Risperidone 0.5–4 mg/day	Risperidone vs MPH SNAP-IV Total: Risperidone p = 0.05 Inattention: Not significant Hyperactivity: Not significant ODD: Not significant NCBRF Hyperactivity: Not significant *Absolute values are not given in this paper- we are only able to comment on whether there was a significant difference between the two arms*	**Risperidone vs MPH** 1.50 vs 1.11 1.00 vs 1.33 1.07 vs 0.67 0.97 vs 0.73 1.34 vs 0.97
Simonoff 2013 [35]	122 children aged 7–15, mean age 11.2 years (SD 2.3) **Diagnoses** 1.Hyperkinetic disorder 2.LD **IQ** Range 30–69, mean 52 (SD 10.1)	Double-blind placebo parallel group RCT over 16 weeks **Dosing** MPH 0.5/1.0/1.5 mg/kg/thrice daily	**Parents** Connors' index: 19.1 vs 27.8 p = 0.011 Connors' hyperactivity: 7.7 vs 9.2 p = 0.03 ABC hyperactivity score: 20.6 vs 28.7 p < 0.001 **Teachers** Conner's index: 14.5 vs 18.6 p = 0.001 Conners hyperactivity: 6.4 vs 9.0 p < 0.001 ABC hyperactivity: 13.2 vs 18.1 p < 0.001 CGI: 40% achieved a score of 1 or 2 vs 7.1% of patients taking placebo***	0.39 (0.09–0.70) 0.33 (0.03–0.63) 0.56 (0.29–0.83) 0.52 (0.23–0.82) 0.54 (0.25–0.82) 0.54 (0.26–0.81)
Aman 2003 [46]	90 children aggregated over 3 trials, age range 4–17, mean 9.0 (SD2.9) **Diagnoses** 1. Low IQ Mean 58.5 (SD = 16.1) 2. ADD, ADHD, conduct disorder (only 1 patient)	Aggregated 3 x double-blind placebo controlled crossover RCTs 2/3/4 weeks duration respectively **Dosing** MPH 0.4 mg/kg/once daily	**Teachers** Conner's TRS Global: 2.58 vs 2.15 ** Conduct: 1.97 vs 1.64* Inattention: 2.58 vs 2.24 *** Hyperactivity: 2.78 vs 2.26*** CASQ 17.3 vs 13.2*** 45% of children were 'responders' with CASQ ABC Irritability: 12.38 vs 8.39* Hyperactivity: 26.58 vs 18.61*** **Parent** RBPC Conduct: 19.39 vs 17.68* Motor excess: 5.19 vs 4.47** ABC Hyperactivity: 27.69 vs 22.71** Global rating 4.41 vs 5.84** *Exact p values not provided by this paper*	Not stated Not stated 0.46 0.69 0.56 Not stated 0.58 Not stated 0.26 0.35 0.56

(*Continued*)

Table 1. (Continued).

Study	Sample population	Study design	Outcome	Effect size (standard deviation – if given)
Pearson 2003 (Behavioral effects paper) [42]	24 children mean age 10.9 years (SD2.4) **Diagnoses** 1)DSM-3 ADHD 2)LD 3)No other psychiatric diagnosis **IQ** Mean IQ56.5 (SD 10.24) 17 with mild LD 7 moderate LD	Double blind placebo controlled crossover RCT 4 weeks duration **Dosing** MPH 0.15/0.30/0.60 mg/kg/twice daily	**Teacher** ADD-H CTRS (ACTeRS) Attention:15.88 vs 19.75 p = 0.024 Hyperactivity: 17.67 vs 11.08 p < 0.001 Oppositional: 13.08 vs 9.17 p = 0.012 Conners TRS Hyperactivity: 26.75 vs 10.75 p < 0.001 Conduct: 12.42 vs 9.21 p < 0.001 Emotional overindulgent: 8.42 vs 4.04 p = 0.006 Asocial: 3.63 vs 1.67 p = 0.009 Daydream-attention: 3.88 vs 2.17 p = 0.022 Hyperactivity index: 16.29 vs 6.58 p < 0.001 **Parent** Conners PRS Impulsive-hyperactive: 5.96 vs 4.50 p = 0.18 Others NS ABC, RBPC, PIC- all NS	Not given in paper

*Legend: *P < 0.05, **P < 0.01, ***P < 0.001, NS = not significant, SD = standard deviation, ODD = oppositional defiant disorder, MPH = methylphenidate, LD = learning disability, MR = mental retardation. An effect size of 1 indicates the mean is 1 standard deviation away from the group the outcome data is compared to (i.e. the placebo/alternative treatment group).*

Sun and colleagues [34] reviewed eight studies looking at a total sample size of 242 patients, with mean age 9.17, on methylphenidate and 181 on placebo over a period from 1982 to 2013; all but one [35] were published before the year 2000. IQ range for patients was 30–85, hence covering people with both ID and borderline intellectual functioning. The primary outcome was an improvement in overall severity of ADHD symptoms. The authors found a significant improvement in ADHD symptoms with MPH vs placebo; effect size (Hedges' g = 0.878 95% CI 0.612–1.143 p = <0.001) – highly significant, and g of 0.878 representing a 'large' effect size [36]. Meta-regression analysis suggested a significant positive association between ADHD severity and methylphenidate dosage (slope = 1.335, p < 0.001) and did not detect a significant association between IQ (p = 0.119).

Subgroup-analysis showed that 'high-dose' (>0.6 mg/day) patients had a significantly greater improvement in CTRS score (Hedges' g = 1.638; a very large effect size) vs 'low-dose' (<0.6 mg/day) patients (hedges' G = 0.694) p = 0.001 [37]. There were also significant improvements in inattention, hyperactivity, and conduct. There were no significant differences in dropout rates or treatment discontinuation rates between methylphenidate and placebo. This is grade one A evidence that MPH is effective in children with ID and ADHD, in a dose-dependent manner. As the authors state, the data is very heterogeneous, and they do not comment on the prevalence of co-morbidities such as autism which could somewhat influence application to the general population of patients with ID.

A systematic review by Tarrant and colleagues [33] included 13 studies spanning from 1982 to 2013. It included a total of 630 patients aged 4–26 split equally, 315 in each of the placebo and MPH arms, with IQ ranging from unmeasurable to 90. They included all but one [38] of the papers covered by Sun, but also discussed further 7 trials [39–45] omitted from Sun et al. This review reported an average response rate to MPH of 40–50%, at doses ranging between 0.3 and 1.5 mg/kg/day. Five were over 8 weeks (2 of these 12 or more) while the remainder lasted 3–5 weeks. Due to the heterogeneity of the outcome parameters within their search results, the Tarrant paper was unable to conduct a meta-analysis. They conclude that due to poor quality evidence, 'MPH may be effective in some but not all children and adolescents with ID and ADHD'.

Our search found an aggregate analysis [46] by Aman et al., which itself was not included in Tarrant or Sun papers, though two of its three constituent RCTs were part of Sun's meta-analysis. This looked at three double-blind crossover RCTs investigating the effect of 0.40 mg/kg/day methylphenidate in 90 children with low IQ aged 4–17 with either ADHD, ADD, or (in one case only) conduct disorder. Mean IQ was 58.5 (SD = 16.1). They found a significant reduction in mean teacher's Conners' inattention (13%***), hyperactivity (19%***), and global scores (17%**), and CASQ as rated by teachers (24%***). Forty-five percent of children were 'responders' (responder in non-CGI scores defined as improvement in score of 30% or more, unless otherwise specified) in CASQ score. In the ABC hyperactivity score, they found an

improvement of 30%*** as rated by teachers and 18%** by parents. Parent 'Global rating' (32%**), RBPC motor excess (14%**), and conduct problems (9%*) also showed significant improvements compared to placebo. On subgroup analysis of people with IQ above or below 50, only 19.4% of children below 50 were considered to be responders compared to 30% over 50.

In another double-blind placebo-controlled crossover RCT of 24 children with ADHD and ID Pearson et al. found significant improvements in both ACTRS and CTRS scores with increasing doses of MPH up to 0.60 mg/kg/day [42]. With teacher-rated scores there were significant improvements in ACTRS attention (20%*), hyperactivity (37%***), and oppositional behavior (30%*). With Conners' TRS significant improvements of 60%*** in hyperactivity, 44%* in daydream attention, and 60%*** in hyperactivity index were reported. Furthermore, looking into the relationship between dose and efficacy the authors found that MPH had a significant curvilinear dose-related relationship in patients with ID and ADHD in cognitive functions, sustained attention, visual/auditory selective attention, and inhibition/impulsivity suggesting the linearity of the relationship even on a low dose can produce a small improvement compared to placebo [41]. In addition to ADHD symptoms, there were also improvements of 57%** in social behaviors, 26%*** in conduct problems, and 52%** in emotional overindulgence scores. MPH was well tolerated, showed greater efficacy in hyperactivity than inattention.

In a separate publication analyzing the same data set, Pearson and colleagues [47] found that a proportion of these patients when experienced an initial mild cognitive (35%) or behavioral (38%) decline vs placebo in the first week of low dose 0.15/mg/kg MPH. In the fourth week on maximum dose of MPH (0.60 mg/kg), this fell to 9% of patients showing some cognitive or behavioral decline. The authors postulate this represents normal fluctuations in the population; i.e. at any time patient's condition may worsen; though this was less likely to occur when they were on high dose MPH. They also found that improvements in behavioral or cognitive function occurred independently; i.e. the absence of a behavioral response does not mean the patient has failed to exhibit a cognitive benefit and vice versa.

Simonoff et al.'s major double-blind placebo-controlled randomized controlled trial of 122 children with the hyperkinetic disorder and ID found strong evidence that MPH in an optimal-titrated dose of 0.5, 1.0, or 1.5 mg/kg/thrice daily was superior to placebo [35]. In the primary outcomes of parent and teacher's Conners' index; MPH showed significant benefit with effect sizes of 0.39 p = 0.011 (95% CI 0.09 to 0.70) and 0.52 p = 0.001 (95% CI 0.23 to 0.82) respectively, and no correlation between IQ or presence of autistic symptoms. On CGI score, 40% of patients were judged improved or very much improved with MPH vs 7% of the placebo arm. This paper was included in the previously described systematic reviews; however, we describe it further separately here due to it being the largest trial to date in this group by a factor of around three.

Filho and colleagues [48] in a single-blind parallel group 4-week RCT compared risperidone 0.5–4 mg/day vs. MPH up to 0.7 mg/kg/day in 45 children with ADHD and moderate LD. They found a significantly greater improvement (P = 0.05) clinically with risperidone compared to MPH, though the improvement was also seen in the MPH arm. However, there was a significant ($p < 0.05$) weight gain of 1.01 kg in the risperidone group, vs. weight loss of 0.53 kg in the MPH group. Handen and colleague's open-label prospective observational study investigating the impact of ADHD on tests of play skills in children with ID showed that MPH significantly improved scores of directly observed play intensity and global ratings of activity; two areas where the children with ADHD had a deficit at baseline [44].

There have been smaller studies looking at prescribing MPH in people with ADHD and ID and other conditions. Epilepsy is known to be more prevalent in patients with both ADHD and ID. Fosi et al. looked at MPH in patients with ID, ADHD, and severe epilepsy examined in a retrospective open-label observational study in 18 patients with treatment-refractory epilepsy, 67% of whom had severe LD [49]. Sixty-one percent were rated as improved on treatment with MPH in CGI-I scores. ADHD is commonly associated with certain genetic syndromes such as William's syndrome. Green et al.'s retrospective observational study [50] described the response of 18 children with a mean age 6.3 (SD 1.4) with William's syndrome and ADHD, treated with MPH mean dose of 10.5 mg/day (SD5.9), for a mean duration of 4.3 years (SD 3.8). Of all participants, 72.2% of patients were considered as treatment responder according to CGI-I scores [50].

Velocardiofacial syndrome (VCFS) can be associated with ID. No papers looking at solely people with ID and VCFS were identified. However, Green [51] published a trial in 34 patients with VCFS given MPH, which found a clinically significant improvement in 72% of patients, in whom the mean IQ was 82.8 (SD10.5). Gothelf [52] found in a 4 week prospective open-label observation study, in children with VCFS, low dose (0.3 mg/kg/od) MPH was effective in improving ADHD symptoms. The 12 patients treated came from an initial group of 18, in whom the mean IQ was 77.0 SD ± 15; however, for the treated patients, no exact IQ is stated. Mean CATQ score decreased by 49% after treatment; this was highly significant with $p < 0.0001$. Neuropsychological testing in the form of CCPT found significant improvements 1 h after MPH administration in omission errors, variability of reaction time, and 'hits' (all $P < 0.05$). There was a strong negative correlation between MPH improvement in CCPT index and IQ ($r = -0.68$, $p = 0.01$); useful negative evidence that the lower IQ group with VCFS responded sub-maximally.

3.3. Evidence for the use of dexamphetamine in ADHD in ID

Dexamphetamine works by increasing synaptic extracellular dopamine and norepinephrine levels in the prefrontal cortex [53]. Though dexamphetamine are first-line ADHD medications [16], the evidence base in the ID population has been limited. The sole result was a Cochrane review of amphetamine in ADHD in ID published in 2009 [54]. Within this, the only paper meeting inclusion criteria was a double-blind RCT of

amphetamine vs MPH vs placebo [38], in 15 children (mean age 7.9) with fragile x-syndrome and mean IQ of 58. Dexamphetamine 0.2 mg/kg given once daily was found to cause no significant improvement vs placebo in ADHD symptoms as assessed by Conners' parents/teachers questionnaire and ACTRS.

3.4. Evidence for the use of atomoxetine in ADHD in ID

Atomoxetine is a commonly used non-stimulant ADHD medication. It is recommended as a second-line treatment by NICE Guidelines [16]. Despite this, studies have shown that atomoxetine is a commonly prescribed ADHD medication in people with ID and ADHD [10]. Our search produced five papers on the use of atomoxetine in treating ADHD in people with ID (Table 2). All studies were conducted in children with ID and included a total of 185 children with mild to severe ID.

Fernandez-Jaen and colleagues [55] in their open-label prospective observational study investigated the effect of atomoxetine mean dose 1.22 mg/kg/day over a period of 16 weeks, in 48 children ages 5–19, with ID and ADHD. There was a statistically significant improvement of 22%*** in CGI-S, and in ADHD-RS-IV scores; 31%*** as measured by parents, and 33%*** as measured by teachers (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$). This indicates atomoxetine was effective in reducing the severity of ADHD (CGI-S) as assessed by clinicians, and ADHD symptoms as assessed by parents and teachers (ADHD-RS-IV). Forty-nine percent of patients were 'responders' with CGI-I; indicating clinicians judged patients to be either 'much' or 'very much' improved (a score of 1 or 2). Conners' score concurred, with significant improvements in both inattention and hyperactivity subscales, and an improvement of 27%*** and 34%*** in total score with parent and teachers, respectively. This study found no correlation between age or level of ID for any outcome. On follow up, 23 patients continued on treatment at 1 year, with patients discontinuing due to perceived inefficacy/intolerance or cost of treatment.

Fernandez-Jaen and colleagues in a second study [56] conducted a prospective open-label observational study for 24 children with ADHD and pervasive developmental disorders (PDD) for 16 weeks. Nineteen (80%) of the children in this study had ID. Atomoxetine dose ranged from 25 to 60 mg, once daily. There was a statistically significant improvement in all Conners' subscales of attention, hyperactivity/impulsivity, and conduct problems; with an improvement of 28%** in total score, & in ADHD-RS-IV subscales of inattention & hyperactivity; with an improvement of 23%*** in the total score as rated by parents. Similarly, with scores assessed by teachers, a significant improvement in all subscales was demonstrated; total ADHD-RS-IV score improved by 27%** and Conners' 21%*, this was not influenced by the presence of ID. Five patients discontinued due to inefficacy or intolerability, out of the remaining 19, fifteen patients were still on treatment at 1 year – no reason is stipulated for further drop-outs.

Jou and colleagues [57] reported a retrospective open-label observational study of atomoxetine in 20 children between 6

Table 2. Summary of studies that were NOT RCTs, for methylphenidate in LD/ADHD.

Study	Sample population	Study design	Outcome; All values given as at baseline vs after treatment
Gothelf 2003 [52]	12 children mean age 11 (SD5.0) **Diagnoses** 1)VCF syndrome 2)ADHD **IQ** Mean IQ ~77.0 (SD 15)	Prospective open label observational study 4 weeks duration **Dosing** MPH 0.3 mg/kg/once daily only	CATQ: 15.5 (SD 4.2) vs 7.6 (SD 3.0) $p < 0.0001$ K-SADS-P-ADHD Attention: 1.26 (SD 0.37) vs 0.65 (SD 0.38) $p < 0.001$ Hyperactivity: 1.19 (SD 0.49) vs 0.28 (SD 0.34) $p < 0.0001$ Impulsivity: 1.31 (SD 0.52) vs 0.42 (SD 0.46) $p < 0.0001$ Total: 1.25 (SD 0.35) vs 0.48 (SD 0.33) $p < 0.0001$ CCPT Overall index: 16.8 (SD 4.8) vs 5.8 (SD 7.4) $p < 0.001$
Fosi 2013 [49]	18 young people aged 6–18, mean age 11.5. **Diagnoses** 1)LD 2)ADHD 3)refractory epilepsy **IQ** 3 mild LD 3 moderate LD 12 profound LD	Retrospective open label observational study, mean duration 12 months (range 2–108). **Dosing** MPH 0.5–1 mg/kg/day titrated clinically. Median 0.5 mg/kg/day.	CGI-I: 11 achieved a score of 1 or 2 (61%).

Table of non-RCT publications of methylphenidate in ID (case reports excluded).

Table 3. Evidence summary for atomoxetine.

Study	Sample population	Study design	Outcome: all scores given as at baseline vs endpoint
Fernandez-Jaen 2010 [55]	48 children aged 5–19, mean age 8.8 (SD 3.38) **Diagnoses** DSM-4 1)LD 2)ADHD 3) Chromosom opathy **IQ** IQ<62	Prospective observational open-label study, 16 weeks duration **Dosing** Increasing dose of ATX, initially approximately 0.4 mg/kg/day in week 1, 0.8 mg week 2, 1.2 mg week 3; mean 1.22 mg (SD 0.19), maximum 60 mg dose/day	CGI-I: 22 achieved a score of 1 or 2 (49%) CGI severity: 5.31 vs 4.13 P < 0.001 **Parent** ADHD-RS-IV Total: 36.22 vs 25.07 p < 0.001 Inattention: 19.5 vs 13.4 p < 0.001 Hyper-impulsive: 16.72 vs 11.67 p < 0.001 Conners' Inattention:11.02 vs 7.94 p < 0.001 Hyperactive: 9.52 vs 6.63 p < 0.001 Conduct: 11.75 vs 8.88 p < 0.001 Total: 32.30 vs 23.47 p < 0.001 **Teachers** ADHD-RS-IV Total: 29.17 vs 19.56 p < 0.001 Inattention: 16.21 vs 11.04 p < 0.001 Hyper-impulsive: 12.95 vs 8.52 p < 0.001 Conners' Inattention: 10.25 vs 6.95 p < 0.001 Hyperactive: 8.15 vs 5.50 p = 0.001 Behavioral issues: 9.45 vs 6.05 p < 0.001 Total: 27.85 vs 18.50 p < 0.001
Kilincaslan 2016 [58]	37 children aged 6–17, mean age 10.16 (SD 3.6) **Diagnoses** DSM-4; 1)ASD or PDD 2)ADHD **IQ**10 mild 10 mild LD 17 moderate LD 10 severe LD	Retrospective observational open label study, 12 weeks duration **Dosing** ATX initially 0.3–0.5 mg/kg/da increased to 1.0–1.4 mg (mean 1.20 mg ± 0.11)	CGI-I: 18 achieved a score of 1or 2 (48.6%) ADHD-RS-IV Total: 38.8 vs 28.8 p < 0.001 effect size (ES) = 0.42 Inattention: 20.9 vs 15.4 p < 0.001 ES = 0.45 Hyperactive: 12.9 vs 10.0 p < 0.003 ES = 0.29 Impulsivity: 4.9 vs 3.5 p = 0.007 ES = 0.25 ABC Hyperactivity: 26.7 vs 20.2 p < 0.001 ES = 0.40 Social withdrawal: 25.3 vs 19.8 p = 0.005 ES = 0.26
Fernandez-Jaen 2013 [56]	24 children aged 5–17 years, mean 8.8 years (SD3.38). **Diagnoses** 1)PDD 2)LD (in 80%) 3)ADHD symptoms **IQ** No data beyond stating 80% of patients had LD	Prospective open-label observational study, 16 week duration **Dosing** Increasing dose of ATX, initially approximately 0.4 mg/kg/day week 1, 0.8 mg week 2, 1.2 mg week 3; mean 1.20 mg (SD 0.20) maximum 60 mg dose/day	CGI:I: 52% were 'responders' CGI-S: 5.3 vs 4.20 p < 0.001 **Parents** ADHD-RS-IV Inattention: 19.77 vs 14.18, p = <0.001 Hyperactivity-impulsivity: 15.54 vs 11.50 p < 0.001 Total: 35.31 vs 25.68 p < 0.001 Conners' Inattention: 10.84 vs 8.10 p = 0.003 Hyperactivity: 9.84 vs 6.68 p = 0.001 Conduct problems: 12.15 vs 8.94 p = 0.005 Total: 32.84 vs 23.73 p = 0.001 **Teachers**ADHD-RS-IV Inattention: 15.53 vs 12.61 p = 0.012 Hyper-impulsivity: 15.23 vs 9.84 p = 0.003 Total: 30.76 vs 22.46 p = 0.003 Conners' Inattention: 9.90 vs 7.72 p = 0.009 Hyperactivity: 8.36 vs 6.45 p = 0.012 Conduct problems: 12.36 vs 10.00 p = 0.035 Total: 30.63 vs 24.18 p = 0.014

(*Continued*)

Table 3. (Continued).

Study	Sample population	Study design	Outcome: all scores given as at baseline vs endpoint
Jou 2005 [57]	20 children, aged 6–19 years, mean age 11.5. **Diagnoses** 1)ASD (80%) 2)Aspergers/PDD-NOS **IQ** 50% had LD; 4 mild 4 moderate 2 severe	Retrospective open label observational study, mean duration 19.5 weeks (SD10.5). **Dosing** ATX initially 18 mg/day, titrated up to 1.2–1.4 mg/kg/day; mean final dose 43.3 mg (SD 18.1).	CGI-I; 60% scored 1 or 2 (12/20) Conners' parent Conduct: 10.5 vs 8.1 p = 0.01 Hyperactivity: 17.1 vs 13.0 p = 0.001 Inattention: 7.5 vs 5.8 p = 0.01 Learning: 7.2 vs 5.6 p = 0.01
Mazzone 2011 [59]	55 children, aged 5–15 years. **Diagnoses** 1)ADHD 2)LD **IQ** Range 43–117, mean 80.6 ± 18.6	Retrospective open label observational study, 2–168 weeks duration; mean 57.3 weeks (SD 39.4). **Dosing** ATX ranging 10–110 mg/day, mean 1.28 mg/kg/day.	Focused on data pertaining to the patients with low range IQ only; CGI-I score of 1 or 2; IQ <85 20.71% vs 76.9% of IQ >_85 P < 0.001 IQ & final CGI-I score was negatively correlated (R = −0.68, p < 0.01).

and 19 years of age (mean 11.5 years). This study assessed the benefit of a mean dose of atomoxetine 43.3 mg (standard deviation (SD) 18.1) for a mean duration of 19.5 weeks (SD 10.5) on ADHD symptoms in patients with PDD, 10 of whom had diagnosed ID, using CGI-GI (clinical global impression – global improvement score),16 had comorbid autism. The initial dose was 18 mg/day, titrated up to 1.2–1.4 mg/kg/day. Twelve patients were deemed 'responders' on CGI-GI; of whom six (50%) had ID; two mild, two moderate, and two severe. Of the eight non-responders, four patients (50%) had ID; two mild, and two moderate.

Kilincaslan [58] described the benefits of atomoxetine for both social withdrawal and ADHD symptoms in a retrospective open-label observation study of 37 children with comorbid ASD and ID. Eighteen (48.6%) of the patients were judged responders by CGI-I, and 16 reached their primary endpoint of CGI-I score 1 or 2 and >_25% reduction in ADHD-RS-IV score. Neither age nor level of ID correlated with the clinical response to atomoxetine. There was a significant improvement with treatment of 25.8%** in ADHD-RS-IV, and ABC parameters of social withdrawal (22%***) and hyperactivity (24%***). The behavior of 'being uninterested in others' was noted to be improved (p 0.008) suggesting that atomoxetine may reduce the intensity of certain autism symptoms.

Mazzone and colleagues [59] retrospective open-label observational study investigated the efficacy of atomoxetine across a spectrum of IQ; from 43 to 117, finding, in contrast to the above papers, a negative correlation between cognitive function and clinical benefit (Pearson's $r = -0.68$, $p < 0.01$). Among patients with IQ 70 or less, only one of 17 patients achieved a CGI-I score of 1 or 2 thus 'responder' status; vs 20 of 26 patients with IQ 85 or greater. There was no difference in tolerability.

None of these observational papers calculate statistical power, though they generally had relatively small sample sizes. The sole paper to show a relatively poor impact of atomoxetine had a small sample size of only 17 patients with ID. Fernandez-Jaen's 2010 paper was perhaps the sole reasonably powered paper, with a population of 48.

3.5. Evidence for the use of clonidine and guanfacine in ADHD in ID

Pharmacotherapies for ADHD have gone beyond stimulant medications to include alpha 2 agonists. There are two main second-line medications used in ADHD: clonidine and guanfacine. Clonidine works through alpha 2A, 2B, and 2C receptors, whilst guanfacine acts mainly through alpha 2A receptors. They mimic norepinephrine actions in the prefrontal cortex through the stimulation of alpha 2A receptors [60].

We found one double-blind placebo-controlled trial by Agarwal et al., looking at the efficacy of clonidine in ADHD and ID [61]. This crossover study was conducted on 10 children with hyperkinetic disorder and ID, given successive 4-, 6- and 8-µg/kg/day dosing of clonidine. There were statistically significant improvements in conduct and impulsive-hyperactive symptom scores. In terms of CGI-GI, 7/10 children on

Table 4. Guanfacine/clonidine/dexamfetamine paper evidence.

Drug/Paper	Sample population	Study design	Outcome
Guanfacine Capone 2016[63]	23 children aged 4–12 years, mean age 7.4 (SD 4.1). **Diagnoses** 1)Down syndrome 2)DSM-4 ADHD **IQ** Mild LD: 7 Moderate: 12 Severe: 3	Open label prospective observational study, duration of mean 146 days (SD 43.1). **Dosing** Guanfacine mean 1.1 mg/day (SD 0.5)	**Guanfacine vs placebo** ABC Irritability: 13.0 vs 9.5 p = <0.0001 Effect size (ES) = 0.47 Hyperactivity: 29.0 vs 21.2 p = <0.0001 ES = 0.9 ABC composite: 49.9 vs 37.7 p = <0.0001 ES = 0.69
Guanfacine Handen 2008[64]	11 children aged 5–9 years, mean 7.25 years. **Diagnoses** 1)ADHD 2)ID (in 8/11) and/or ASD **IQ** Severe ID: 2 Moderate: 3 Mild: 2 Borderline: 1	Double blind placebo-controlled crossover RCT, 6 weeks duration **Dosing** Guanfacine mean 2.68 mg/day	**Guanfacine vs placebo** CGI-GI: 3.82 vs 2.82 p = 0.005 ABC Hyperactivity Parent: 30.91 vs 19.91 p = 0.025 Teacher: 31.91 vs 17.18 p = 0.005
Guanfacine Posey 2004*[62]	80 children mean age of 7.7 years (SD3.5), range 3–18 years, of whom 56 had ID (70%). **Diagnoses** 1)PDD 2)ID **IQ** Mild, n = 25; Moderate, n = 25; Severe, n = 6	Retrospective open label observational study, mean duration of 334 days (SD 374). **Dosing** Guanfacine mean dose 2.6 mg/day (SD1.7)	CGI-GI: Patients with ID (n = 56); 10 of this group scored 1 or 2 (17.9%).
Clonidine Agarwal 2001[61]	10 children age range 6–15 years. **Dosing** 1)Hyperkinetic disorder 2)ID **IQ** Mean IQ 48.2, range 30–69.	Double blind placebo-controlled crossover RCT 12 weeks duration. **Dosing** Clonidine 4/6/8microgram/kg/day	Parents PSQ Conduct: 6.8 vs 4.1 p < 0.05 Impulsive hyperactive: 15.6 vs 7.9 p < 0.01 Total: 78.7 vs 51.8 p < 0.01 HBRS Gross-motor: 5.1 vs 2.4 p < 0.01 Distractibility-concentration: 3.5 vs 2.1 p < 0.01 Cooperation: 3.5 vs 2.4 p < 0.02 Interest in task: 3.5 vs 2.5 p < 0.02 Impulsivity: 3.5 vs 2.1 p < 0.01 CGI-S: 4.6 vs 2.7 p < 0.01
Dextro-amfetamine Cochrane review 2009 (single paper included)[54]	15 children mean age 7.9 years, age range 3.8–11.8 years. **Diagnoses** 1)Fragile X syndrome 2) Low IQ 3)Attentional problems **IQ** Mean IQ 58, range 29–77.	Double blind placebo-controlled crossover RCT **Dosing** Dextroamfetamine 0.2 mg/kg/day vs MPH 0.3 mg/kg/twice daily	No significant difference between dextro-amfetamine and placebo for any measures

Posey 2004 [62] analyzed ID patients separately from entire group; therefore, we have only included data on ID patients
The Agarwal 2001 [61] clonidine study does not report p values for clonidine vs placebo, so values for ADHD scales are given as baseline vs max. dose clonidine

maximal dose were rated as responders, of the remaining three, one achieved remission on a lower dose.

With regards to guanfacine, we found three studies looking at its role in treating ADHD in people with ID. Posey and colleagues [62] conducted a retrospective open-label observational study of guanfacine in 80 children with a mean age of 7.7 years (range 3–18). Fifty-six (70%) of the patient group had a diagnosis of ID (mental retardation). Guanfacine doses ranged from 0.25 to 9 mg/day. There was a trend ($p = 0.06$) for patients without comorbid ID to respond more frequently with CGI-GI score (37.5%) following treatment vs those with ID (17.9%).

Capone and colleagues [63] published an open-label observational prospective study on the efficacy of a mean dose of 1.1 mg/day guanfacine in 23 children aged 4–12, with Down syndrome and ADHD. Statistically significant differences were found in scores of irritability (reducing from 13 to 9.5), hyperactivity (reduced from 29.0 to 21.2), and ABC overall composite score (improved from 49.7 to 37.7). They identified a number of specific questions on the ABC scales which were related to disruptive behavior, aggression, inattention, and hyperactivity and combined them to create a novel subscale for each behavior; finding significant improvements in each area.

Handen and colleagues [64] in their double-blind placebo-controlled crossover RCT investigated the role of guanfacine up to 3 mg/day in 11 children aged 5–9 years, with ADHD and ID and/or ASD. They found significant symptomatic improvements in ABC hyperactivity score only, with both parents (36%*) and teachers (56%**). Three out of five patients who were defined as 'responders' (Handen used a different definition of 'responder' vs the other papers; a >_50% decrease in ABC hyperactivity vs placebo) had mild-moderate ID. Of the six non-responders, four had moderate-severe ID.

3.6. Safety and tolerability

Studies looking at MPH, amphetamine/dexamfetamine, atomoxetine, clonidine, and guanfacine have reported side effects which are summarized in Table 5. Methylphenidate was most commonly associated with anorexia/weight loss, sleep disturbance, and also minor increases in heart rate, irritability, and anxiety. Amphetamine similarly was associated with irritability & mood lability.

Guanfacine and clonidine were commonly associated with transient sedation/somnolence. GI upset, somnolence, and irritability were most commonly reported in atomoxetine. All of the above have been commonly reported in the general population with ADHD [17]. No study found any major difference in type, nature, frequency, and intensity of side effects between the general and ID populations.

4. Conclusion

There is evidence to support the use of MPH and atomoxetine in people with ID. This sits well in real-world practice for people with ID. However, there is a need for focused research possible as real-world studies to look at the specific impact of these drugs, particularly, the improvement it brings in issues such as challenging behavior, reduction in other psychotropic medication, and improved quality of life. A lack of awareness of the significant co-morbidity and the erosive impact of ADHD to the individual even to clinical experts working with people with ID has prevented till date suitable mainstream adoption of ADHD diagnosis and treatment.

It is imperative along with fostering further research attempts be made to share the already present evidence especially the over-representation of ADHD in people with ID, the need to treat it proactively, and the role of MPH and atomoxetine. Future research while consolidating on the evidence of the first-line agents specific for people with ID with regard to effectiveness, titration, and dosing could also explore and investigate the role of other agents and combination therapy. Research into impact on social wellbeing and quality of life outcomes could help influence the economic debate.

There could be a developing role in pharmacogenomics and personalized medicine. Identification of particular genetic disorders or people with ID with certain genotypes might enable swifter and better response from ADHD medication while limiting adverse effects. It is hoped that the findings of this paper provide a starting conversation of how to incorporate current good evidence into mainstream practice while evolving patterns of research to enumerate better current gray areas.

5. Expert opinion

People with ID should be actively examined for ADHD, and if found should be treated proactively with pharmacological agents irrespective of the level or nature of the ID. While physical and psychological co-morbidity, if present, needs to be weighed against the potential of drug side effects, consideration needs to be also given to the ADHD symptom alleviation and improvements in behavior and quality of life.

With increasing evidence for functional impairment and treatment effectiveness in untreated ADHD in people without ID, there is an improved focus on diagnosis and treatment in people with ID. ADHD medications used in people with ID are similar to those used in the population without ID. The majority of studies found investigated MPH, with few covering atomoxetine, guanfacine, dexamfetamine, and clonidine. Study samples were very small for all studies and focused on children with ID – there were no specific studies looking at ADHD in ID in adults which represented one major weakness. The use of open-label studies and lack of double-blind placebo-controlled trials were other limitations when using results from these studies. Multiple papers published in previous decades, particularly with MPH, mention treatments for ADHD in ID. This review also includes systematic reviews for both methylphenidate & amphetamine. This gives some confidence to our opinions for the two most commonly prescribed pharmacotherapies for ADHD in ID.

Table 5. Side effects.

Study	Side effects (SE) & number discontinued due to adverse events
MPH randomized controlled trials	
Filho 2005 [48]	45 patients, MPH up to 0.7 mg/kg/day vs risperidone 0.5–4 mg/day. **Significantly increased SE:** insomnia, loss of appetite, weight loss loss of 0.53 kg with MPH vs gain of 1.01 kg with risperidone $p < 0.05$. The risperidone group exhibited a significant increase in somnolence and a trend (p0.06) to extrapyramidal symptoms. **Discontinuations:** MPH: 1 (vomiting), risperidone 1 (galactorrhea).
Simonoff 2013 [35]	122 patients, MPH 0.5/1.0/1.5 mg/kg/thrice daily vs placebo. **Significantly increased SE:** sleep disturbance, anorexia, weight loss. Non-significant: looking anxious or sad, crying, meaningless repetitive behaviors, and reduced interaction with other children. No significant change in pulse or blood pressure. **Discontinuations:** 5 due to adverse events: irritability, poor appetite and aggression; nausea and diarrhea; blurred vision; urticaria; and irritability combined with social withdrawal.
Aman 2003 [46]	90 patients, MPH 0.4/mg/kg/once daily vs placebo. **Significantly increased SE:** increase in heart rate (3.9 bpm). No significant change in blood pressure. No other side effects analyzed. **Discontinuations:** Does not specify discontinuations.
Pearson 2003 [42]	24 patients, MPH 0.15/0.30/0.60 mg/kg/bd vs placebo. **Significantly increased SE:** parent reported loss of appetite in 7/24 on MPH vs 0 on placebo*, sleep disturbance in 4/24 on MPH vs 1 on placebo*. No significant change in teacher reported side effects; anxiety in fact decreased (improved) in a dose related manner. Staring behaviors were commonly reported in both MPH and placebo arms; non-significant. 2 teachers reported unresponsive 'zombie-like' behavior at the maximum dose. **Discontinuations:** No discontinuations due to adverse events.
MPH studies other than RCTs	
Green 2012 [50]	18 children with William's syndrome, MPH 0.3–0.5 mg/kg/day. **Side effects:** Common side effects were transient post-treatment episodes of sadness (61.1%), anorexia (33.3%), and irritability (5.6%). **Discontinuations:** In 4 patients due to excess sadness.
Gothelf 2003 [52]	12 children with velocardiofacial syndrome, MPH 0.3/mg/kg/od. **Side effects:** poor appetite (92%), irritability (50%) sadness, stomachaches, talks little with others (all 42%) prone to crying (33%). No derangement to heart rate/BP/ECG. **Discontinuations:** no discontinuations due to adverse events.
Fosi 2013 [49]	18 children with severe epilepsy, MPH 0.5–1 mg/kg/day Discontinuations: 1/18 due to increased seizures. Discontinued in 3 due to side effects; anorexia n = 1, severe withdrawal n = 2, worsened anxiety and ODD n = 1.
Drug/study	**Side effects reported & number discontinued due to adverse events**
Clonidine/guanfacine/dextro-amfetamine papers	
Clonidine	10 children, clonidine 4/6/8ug/kg/day.
Agarwal et al 2001 [61]	**Side effects:** 5 developed drowsiness; however, by the end of the 6 week trial this had abated in all but one child. Dryness of mouth and anorexia occured in one child. All children developed an asymptomatic drop in systolic bp on maximum dose, of mean 8.9% vs baseline. **Discontinuations:** no discontinuations due to adverse events.
Guanfacine	80 children with PDD, guanfacine mean 2.6 mg/day.
Posey 2004 [62]	**Side effects:** 31.3% of patients experienced transient sedation, other side effects; irritability 6.3%, constipation 3.8%, headache and nocturnal enuresis (both 2.5%). 55% experienced changes in blood pressure and heart rate however this was not significant. No change in seizure frequency. **Discontinuations:** no discontinuations due to adverse events.
Guanfacine	23 children with Down syndrome, guanfacine mean dose 1.1 mg/day.
Capone 2016 [63]	**Side effects:** exact frequency of side effects is not specified, other than stating that night time somnolence was prevalent, and otherwise patients experienced only small reductions in blood pressure which were not clinically significant. **Discontinuations:** discontinuations not specified.
Guanfacine	11 children, guanfacine mean dose 2.68 mg/day
Handen 2008 [64]	**Side effects:** no significant difference in side effects vs placebo. Drowsiness, irritability, and enuresis prevented 1 patient each reaching maximum dose. **Discontinuations:** no discontinuations due to adverse events.
Dextro-amphetamine	15 patients with fragile X, amphetamine (0.2 mg/kg/day) vs MPH (0.3 mg/kg/bd) vs placebo.
Cochrane review 2009 [54]	**Side effects:** significant increase in side effects vs placebo with amphetamine, most commonly of mood lability and irritability.
Atomoxetine papers	
Atomoxetine	48 children, ATX mean dose 1.22 mg/kg/day.
Fernandez-jaen 2010 [55]	**Side effects:** 15 (31.25%) experienced side effects; irritability, gastrointestinal side effects and sleepiness.
N = 48	This trial was noted to compare favorably with the side effect profile described by Jou et al [57], where dosing was initially higher, and up-titrated quicker. **Discontinuations:** In 9 (18.75%) due to side effects described above.

(*Continued*)

Table 5. (Continued).

Study	Side effects (SE) & number discontinued due to adverse events
Atomoxetine Fernandez-jaen 2013 [56]	24 children with PDD, ATX titrated up to mean dose 1.20 mg/kg/day. **Side effects:** 5 (20.8%) patients reported side effects; somnolence, GI malaise, irritability occuring in 2 patients each. **Discontinuations:** in 3 patients due to the above side effects.
Atomoxetine Kilincaslan 2016 [58]	37 children with ASD/PDD, ATX mean dose 1.20 mg/kg/day. **Side effects:** there was no significant increase in side effects as rated by BSERS scale. The most prevalent side effect was irritability, n = 4. There was a significant increase in systolic BP. Weight and diastolic BP showed no significant change. The side effect behavior of 'being uninterested in others' was noted to be improved. **Discontinuations:** 5 (13.5%) children at 4 weeks due to increased motor activity n = 1, irritability n = 2, temper outbursts n = 2, increased BP n = 1, and ineffectiveness n = 2.
Atomoxetine Jou 2005 [57]	20 children, ATX 1.2–1.4 mg/kg/day. **Side effects:** constipation, decreased appetite, ear ringing, mood swings, and sedation were reported in 6 patients. Mean weight change was + 0.36 ± 2.41 kg. **Discontinuations:** 1 patient due to severe mood swings.
Atomoxetine Mazzone 2011 [59]	55 children, ATX mean dose 1.28 mg/kg/day **Side effects:** loss of appetite n = 13, abdominal pain n = 12, nausea n = 7, sleepiness n = 2, paresthesia n = 1, mydriasis n = 1. No difference in tolerability between patients with IQ _<70 and of higher IQ. **Discontinuations:** no discontinuations due to adverse events.

5.1. Methylphenidate

Due to the volume, history, and nature of studies, MPH can be regarded as the first-line treatment for ADHD and ID. The evidence base for the use of MPH in people with ID was stronger as compared to other ADHD medications. There were more studies overall, with larger sample sizes and more double-blind placebo-controlled trials. Clear improvement in core symptoms of ADHD in children with ID and ADHD has been demonstrated compared to placebo [34]. A positive association between ADHD severity and MPH dosage exists, highlighting the importance of titrating the dose up, depending on the symptom improvement. There is a reluctance among psychiatrists working with people with ID to prescribe higher stimulant doses in people with ID; a possible cause for iatrogenic harm, as it can lead to partial or no response to treatment.

No significant differences in dropout rates or treatment discontinuation between children with ID on MPH and placebo have been noted. The associations of initial cognition and behavioral worsening are interesting. This can prompt clinicians and carers/parents to assume that ADHD medications are not tolerated or not effective in a person with ID and ADHD, and prevent the full realization of the drug's positive potential. It is worth considering a more gradual titration regime to help build confidence for drug retention, to give the medication its best chance to be effective.

MPH effectiveness, while clear in the ID population in some studies, has been suggested to be lower than that in the general population. However, the above-mentioned bias and confounders could play a role, thus requiring more robust studies to establish this suitably.

In terms of improvements in symptoms, non – ID specific MPH studies have shown an improvement in the core symptoms of ADHD (hyperactivity and inattention), along with other areas, such as improvement in conduct problems and social behavior. There is no evidence to the contrary for ID populations; thus, MPH could be considered for certain aspects of challenging behavior linked to social issues; especially if there are other features of ADHD.

MPH studies also reported overall longitudinal improvements in behavior and cognition, as two independent areas. Some people improved in cognition; without an improvement in behavior; or vice versa. This needs to be taken into consideration when the effectiveness of MPH, in particular, and medication, in general, are assessed in clinical practice – particularly in ID populations.

5.2. Atomoxetine

Even though atomoxetine does not have the same volume of studies as MPH, a good argument to use atomoxetine in managing ADHD in people with ID as a first-line medication exists. All studies reviewed identified definite improvement in ADHD symptoms with atomoxetine. All studies save one showed that there was no relationship between treatment outcome and IQ. Improvement was seen in a range of symptoms from core ADHD features to the improvement of co-morbid autism-related symptoms reduction in social

withdrawal. Though limited evidence suggests there is no difference in response to atomoxetine between ID and non-ID populations.

Of the particular benefit of atomoxetine is its bioavailability and dosing which lends itself to a single dose a day and provides 24-h cover. This is valuable in people with ID who can be distressed by having to take medication multiple times a day. It could in theory also benefit by providing consistent levels for those who have sporadic behavioral fluctuations during the day, whether atomoxetine is a more suitable ADHD medication for people with ID with challenging behavior needs to be explored using future research.

Commonly reported side effects included irritability, somnolence, and reduced appetite. Twenty to thirty percent of children treated with atomoxetine developed above adverse effects. Side effects were temporary in about half of these children. Clinical experience has shown that side effects can be minimized when atomoxetine is started on doses smaller than what is recommended in BNF. Most studies increased the dose of atomoxetine from 18 mg to 60 mg within 3 weeks which is a faster dose increment compared to what happens in clinical practice. However, very low discontinuation rates were seen in studies where doses were titrated slowly. Available evidence suggests caution in using atomoxetine if there are underlying genetic disorders, particularly those associated with psychiatric symptoms (Fragile X, Tuberous Sclerosis, etc.). An exacerbation of anxiety has been observed.

5.3. Other medication

The evidence base for guanfacine, clonidine, and dexamfetamine remains poor for use in people with ID. The only study done in dexamfetamine-based medications showed no clear benefits [38]; however, the study used low doses of amphetamines. Therefore, further studies are needed with a higher dose of amphetamine to assess the efficacy. These cannot presently be advocated as first-line medication for people with ID and ADHD.

5.4. Other considerations

Multi-stakeholder feedback particularly from neutral informed sources such as schools is important when evaluating the effectiveness of ADHD medications. Due consideration needs to be given to the presence of other comorbid physical, psychiatric, and neuropsychiatric conditions. Epilepsy is highly prevalent in people with ID. Similarly, a high prevalence rate of ADHD is reported in people with ID. Clinicians are naturally cautious when treating ADHD in people with epilepsy. However, available evidence though limited suggests that drugs such as MPH are safe and can afford over 60% improvement in ADHD symptoms in people with refractory epilepsy [49]. Larger scale studies are needed to further establish the safety of ADHD medications in people with ID, ADHD, and epilepsy.

Genetic disorders are common among people with ID. Certain genetic syndromes such as Downs' syndrome, William's syndrome, and Smith Magenis syndrome are strongly associated with ADHD. While the evidence is limited especially for specific disorders, it is likely that treating ADHD with MPH will show a positive response. Importantly the dosing needs to be slow and go low.

Evidence base for the combination of ADHD medication is scarce though MPH and atomoxetine have been recognized to be prescribed together especially in general populations. Combining ADHD medications to further improve target symptoms of ADHD and associated symptoms needs further exploration particularly in people with ID where there is no evidence. Any such attempts in people with ID need to consider the possibility of drug sensitivities, best interest, documented rationale, potential short-term and long-term harm, why monotherapy is not suitable and the impact of out of license prescribing.

6. Limitations

This study looked at papers published in the last 20 years and in English only. However, the search in key paper references would identify any important study thus this is not a major bias. Some studies done on people ID and ADHD did not refer to the diagnosis of ADHD in their papers; instead, they described symptoms of ADHD. Such papers could have been missed in the search. However, this confounder has been mitigated by examining references in papers to find out any studies which could be related to the topic inspected. Low-grade evidence papers were included in this review but have been identified and represented clearly in order not to disproportionately affect the final expert opinion.

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Declaration of interest

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Appendix A1:

Search terms were as follows:

((('ADHD medication*' OR 'ADHD drug*' OR 'methylphenidate' OR 'concerta xl' OR 'Ritalin' OR 'dexamfetamine' OR 'dexamphetamine' OR 'dextroamphetamine' OR 'Dexedrine' OR 'Adderall' OR 'amfexa' OR 'lisdexamfetamine' OR 'Vyvanse' OR 'elvanse' OR 'Tyvense' OR 'clonidine' OR 'Catapres' OR 'guanfacine' OR 'Tenex' OR 'Atomoxetine' OR 'Strattera')) AND ('ADHD' OR 'ADD' OR 'Attention Deficit Hyperactivity Disorder*' OR 'hyperkinetic disorder*' OR 'attention deficit disorder*')) AND ('Intellectual* disab*' OR 'Intellectual* impair*' OR 'Intellectual* retard*' OR 'Intellectual* handicap*' OR 'Intellectual* subnormal*' OR 'Intellectual* deficien*' OR 'Learning disab*' OR 'Learning impair*' OR 'Learning retard*' OR 'Learning handicap*' OR 'Learning subnormal*' OR 'Learning deficien*' OR 'Mental* disab*' OR 'Mental* impair*' OR 'Mental* retard*' OR 'Mental* handicap*' OR 'Mental* subnormal*' OR 'Mental* deficien*' OR 'Developmental* disab*' OR 'Developmental* impair*' OR 'Developmental* retard*' OR 'Developmental* handicap*' OR 'Developmental* subnormal*' OR 'Developmental* deficien*' OR 'Neurodevelopmental* disab*' OR 'Neurodevelopmental* impair*' OR 'Neurodevelopmental* retard*' OR 'Neurodevelopmental* handicap*')

We also added MeSH terms:

(1) Exp 'Learning disabilities'
(2) Exp 'Learning disorders'
(3) Exp 'attention deficit disorder'
(4) Exp 'intellectual development disorder'
(5) Exp 'developmental disabilities'