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REVIEW



# Emerging drugs for the treatment of attention-deficit hyperactivity disorder (ADHD)

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**ABSTRACT**

**Introduction:** Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting up to 5.3% of children and 2.5% of adults depending on the country considered. Current pharmacological treatments for ADHD are based on stimulant or non-stimulant medications, targeting dopaminergic and noradrenergic systems in the frontal cortex and dopaminergic system in the basal ganglia. These drugs are effective and safe for the majority of patients, whereas about 20% of treated patients do not tolerate current therapies or experience insufficient efficacy. The adequate treatment of ADHD is necessary to allow a proper social placement and prevent the acquisition of additional, more severe, comorbidities.

**Areas covered:** We conducted a review of the scientific literature and of unpublished/ongoing clinical trials to summarize the advances made in the last 10 years (2010–2020) for the pharmacological treatment of ADHD. We found many pharmacological mechanisms beyond dopaminergic and noradrenergic ones have been investigated in patients.

**Expert opinion:** Some emerging drugs for ADHD may be promising as add-on treatment especially in children, amantadine to enhance cognitive functions and tipepidine for hyperactivity/impulsivity. Stand-alone emerging treatments for ADHD include viloxazine and dasotraline, which will soon have more clinical data available to support market access requests.

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ADHD; emerging drugs; innovative drugs; pharmacological therapy

## 1. Background

Attention-Deficit/Hyperactivity disorder (ADHD) is a 'lifespan' neurodevelopmental disorder, which typically manifest early in development, characterized by impairing levels of inattention, disorganization, and/or hyperactivity-impulsivity. These features are displayed in a persistent pattern that is pervasive across multiple settings and causes substantial functional impairment of personal, social, academic, or occupational functioning [1]. Population surveys [2,3] suggest that ADHD occurs in most cultures in about 5.3% of children and about 2.5% of adults aged 19–45 years [4]. Individuals with ADHD are at increased risk for a range of poor social outcomes throughout their lifetime, including substance abuse and addiction, criminality, academic and occupational underachievement, social rejection by peers and family conflicts. Patients with ADHD are also at increased risk for obesity, suicide and premature death compared with the general population. Accordingly, these functional impairments translate to reduced quality of life as measured by psychological, social and health indicators [5]. According to both DSM 5 and ICD-11 criteria [6], ADHD is now considered a chronic condition, with specific criteria for children and adults, and medical treatment is usually provided over several years.

## 2. Medical need

Based on the perspective that ADHD is now considered a life-long disorder, with a high prevalence and a high comorbidity especially in adulthood, the developing of better long-term treatments, not only for children but also for adults, is needed. The development of new treatments must take into account the long-term effectiveness and, at the same time, focus on other issues including low adherence, adverse effects and non-tolerability, especially when comorbid diagnoses are present.

## 3. Existing treatment

Pharmacological treatments for ADHD are classified into stimulants (methylphenidate and amphetamine) and non-stimulants (atomoxetine, guanfacine and clonidine) [7]. Both classes present with limitations and adverse effects with a non-adherence rate ranging between 15 and 87% [8]. Stimulant drugs are the first-line pharmacological treatment for ADHD and their effectiveness has been widely demonstrated, albeit most studies report data only on their short-term use [7,9]. The duration of action is an important limit for these types of drugs. Depending on the active agent and individual variability, stimulants provide coverage of ADHD symptoms for no more than 12–13 hours per dose,

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**Article highlights**

- ADHD is a neurodevelopmental disorder affecting up to 5.3% of children and 2.5% of adults.
- About 20% of treated patients do not tolerate current therapies or experience insufficient efficacy.
- Amantadine to enhance cognitive functions and tipepidine for hyperactivity/impulsivity may be promising as add-on treatment, especially in children.
- Stand-alone emerging treatments for ADHD include viloxazine and dasotraline, both in children and adults.

considering extended-release formulations. Adverse effects are similar for both methylphenidate and amphetamine, presenting more frequently with the use of amphetamine. They include decreased appetite, sleep disturbances, nausea, xerostomia, headache and irritability, seen at all ages but slightly more frequent in young children [8–10]. Moreover, some data suggest that these drugs can affect negatively growth trajectories and increase weight and body-mass index after long-term treatment [7,11]. It has also been speculated that these drugs increase the likelihood of cardiovascular events or induce dependence, but longitudinal research has not confirmed these hypotheses [7]. Finally, it is commonly assumed that children with certain comorbidities should not be prescribed stimulants as they might worsen symptoms, e.g. in children with aggressive behavior, insomnia or tics [7,12].

The efficacy of non-stimulants in the short-term has also been reported [13]. Unlike stimulants Atomoxetine may not exacerbate tics in Tourette's syndrome patients with ADHD [12]. The combination of psychotropic drugs (i.e. polypharmacy) is an increasingly applied strategy in ADHD, especially when comorbidity is present. Many reports suggest that drug–drug interactions are not uncommon in patients on multiple psychotropic treatments [14], raising further concerns.

## 4. Current research goals

The highlighted limitations of current medical treatments underline the importance of the continued search for new and improved drugs. Current research goals include the development of drugs with enhanced long-term effectiveness, higher tolerability and with less adverse effects, mainly when comorbidities are present. Especially in adults, one of the main research focuses is on treating comorbidities and using non-stimulants drugs to avoid risks of misuse.

## 5. Scientific rationale

ADHD core symptoms include inattention, hyperactivity and impulsivity. It is currently hypothesized that all these symptoms are linked to specific malfunctioning in Cortico-Striato-Thalamo-Cortical (CSTC) circuits [15]. Several studies suggest that a dysregulation in the dopaminergic (DA) and noradrenergic (NA) systems, with a minor and unclear role of serotoninergic system, may underlay the disruption of the normal 'tuning' of neurons in prefrontal cortex, while a dopamine system dysfunction may be at the root of cytoarchitecture alterations within one or more basal ganglia nuclei. These findings have been confirmed by Magnetic Resonance Imaging (MRI) studies [15].

Boosting dopamine and/or norepinephrine in the prefrontal cortex and in the basal ganglia nuclei can reduce ADHD symptoms of both inattention and hyperactivity. Inhibition of dopamine reuptake (methylphenidate, amphetamine), and secondarily of noradrenaline reuptake (atomoxetine) are among the most effective mechanisms exploited by the current clinical practice.

Several treatments have been proposed for ADHD in children and adults targeting the same mechanisms of approved drugs (see following section on monoaminergic reuptake inhibitors), while the majority tried to act on mechanisms that have not been addressed yet in the context of ADHD, but are involved with cognition and attention in other disorders (including schizophrenia and Alzheimer's dementia). Some drugs (i.e. N-pantoyl-GABA, a fusion analog of GABA and pantothenic acid) were tested with no underlying specific hypotheses on their involvement with attention or ADHD. Other drugs were tested as add-on therapies to improve efficacy on residual symptoms or to mitigate possible adverse effects.

For instance, the glutamatergic system has an unclear role in the mechanism of attention and hyperactivity [16], even though modulators of AMPA receptor (n-NMDA receptor for glutamate) could reduce hyperactivity in a hydroxydopamine-lesioned rat model, and mGluR5 inhibition promoted hyperactivity in rats [17], thus suggesting a potential therapeutic role for drugs targeting these systems.

The exact mechanisms underlying the effect of melatoninergic agents are currently not completely clarified. Melatonin is an endogenous metabolite of serotonin, produced starting from the amino-acid tryptophan. Melatonin binds to several receptors, currently known only in part, and it is involved with the regulation of circadian rhythms, hormone production. It is antihypertensive, antidepressant, anxiolytic and anti-inflammatory. In addition, melatonin has been shown to reduce manifestations of ADHD in murine models [18]. Aside from acting directly on manifestations of inattention and hyperactivity, melatoninergic agonists may be useful to maintain the sleep-wake cycle in patients using stimulants, known to disrupt the melatonin cycle compromising sleep quality and amount [19].

Dopamine receptors D4 are also tightly linked to glutamatergic signaling. They have been related to a functional regulation of AMPA receptors activity [20]; moreover, specific modulators of D4 receptors could alter the phenotype of hydroxydopamine-lesioned rats and D4 knockout hydroxydopamine-lesioned rats do not display the expected hyperactivity.

Lots of antipsychotic drugs are frequently used for the control of problem behavior that, even though not a core feature of ADHD, is often an element that disrupts the lives of patients and of their families. Their mechanism of action is

predominantly based on D2 dopaminergic and H1 histaminergic antagonism. New drugs were tested according to this hypothesis.

The involvement of the cannabinoid system in ADHD and attention has no clear explanation and the clinical efficacy of phytocannabinoids for ADHD treatment is based on anecdotal evidence and self-administration by patients. Data on the role of phytocannabinoids in enhancing dopaminergic transmission [21–23], which is thought to be the main therapeutic mechanism of ADHD therapies, are still controversial [21–25] but worthy for further study.

Boosting acetylcholine function and enhancing prefrontal cortex activity with histamine are two other precognitive approaches. Nicotinic cholinergic transmissions in the central nervous system are crucial for the regulation of arousal, attention and cognition [26,27]. Nicotinic receptors of the α4β2 subtype (nAChR α4β2) are found only in some regions of the central nervous system (cortex, hippocampus, striatum and thalamus) implicated with attention [28] and specific nAChR α4β2 agonists were demonstrated to improve attention and cognitive performance in healthy adults [29]. Histaminergic transmission is traditionally known to control wakefulness and has been implicated with arousal and attention in animal models, with particular regard to H3 receptors [30]. H3 antagonists have been demonstrated to increase arousal without the adverse impact of stimulants [30] in the cat. H1 receptors are instead responsible of maintaining wakefulness and H1 antagonists are powerful sedatives and hypnotics.

## 6. Competitive environment

We have conducted a systematic review of the literature using PubMed as a source database, including all drugs that have been tested in clinical trials published during the years 2010–2020. This led to the inclusion of novel emerging drugs (not yet fully tested), repurposed emerging drugs (drugs that have been repurposed and systematically tested in clinical trials for ADHD) and drugs with a suspended clinical development (drugs that had negative results at clinical testing and are now on hold). Details of the reviewed drugs are available in Table 1 for drugs that have published trials and in Table 2 for drugs without public results.

### 6.1. Monoamine reuptake inhibitors

#### 6.1.1. Noradrenergic reuptake inhibitors (NRIs)

*6.1.1.1. Viloxazine (novel emerging).* Viloxazine (SPN-812) is a novel NRI that was tested [31] in a parallel arms randomized double blind trial on children. Viloxazine 100, 200, 300, 400 mg/d was compared with placebo over 8 weeks. Tolerability was lower for viloxazine (23–33% drop-outs) than for placebo (12.5%), not dose dependent, and it was not stressed by the Authors. The most frequent adverse events were somnolence, headache, decreased appetite, and the overall incidence of psychiatric adverse events was approximately 20%: irritability was the only psychiatric adverse event listed as it occurred in more than 5% of subjects. Viloxazine was superior to placebo starting from week 4, although at the endpoint only the 300 and 400 mg/d doses retained superiority.

*6.1.1.2. BLI-1008 (novel emerging).* BLI-1008 is an NRI extract derived from a Chinese herbal sedative, currently under phase 2 development by BioLite for the treatment of adult ADHD [32]. BioLite claims BLI-1008 does not reduce appetite, yet in the ongoing clinical trial it is administered after meals.

*6.1.1.3. NRIs on hold.* Reboxetine is a specific NRI [33] suggested as potentially useful for attention and executive functions [34]. Reboxetine was tested in adults [35] and children [36] with suggestions of partial efficacy and with adverse effects including headache, low appetite, sleep disturbances, anxiety and irritability. Edivoxetine is a specific NRI, which has been tested on pediatric patients [37–39]. Edivoxetine had an efficacy and tolerability similar to the ones of methylphenidate; adverse events occurring more frequently with edivoxetine than with methylphenidate were nausea, vomiting and somnolence, while several events occurred less than with methylphenidate, especially sleep disorders and reduced appetite/weight loss. No statistical comparison between edivoxetine and methylphenidate regarding efficacy was published. Ampreloxetine from Theravance was discontinued for the treatment of ADHD after phase 2 trials [40]; it is now being developed for neurogenic orthostatic hypotension. Arbor Pharmaceuticals tested AR08, a noradrenergic functional agonist with unknown mechanism of action, up to phase 2 [41], when it was discontinued.

#### 6.1.2. Serotonin–norepinephrine reuptake inhibitors (SNRIs)

Duloxetine (repurposed emerging) was tested [42] in a single-arm trial on adolescents, lasting 6 weeks. Duloxetine dose was 60 mg/d. A reduction of ADHD symptoms was evident since week 4, with all sub-scores reduced at week 6. We find it worth mentioning that 24% patients dropped out of treatment (18% for adverse events), which was not highlighted in the paper, and the most frequent adverse events were decreased appetite, dry mouth and insomnia, headache, nausea, somnolence, anxiety, and nervousness.

A subsequent randomized double-blind trial [43] on adults, tested duloxetine 60 mg/d versus placebo for 6 weeks. 40% patients dropped out of the duloxetine arm in the first week of administration, due to adverse events including xerostomia, increased anxiety, nausea, and dizziness, while the placebo arm had no drop-outs. Duloxetine resulted superior to placebo on self-reported ADHD symptoms but not on investigator-reported symptoms, possibly due to underpowerment.

#### 6.1.3. Norepinephrine-dopamine reuptake inhibitor (NDRIs)

Bupropion (repurposed emerging) was tested [44] in pediatric patients. This was a parallel arms randomized double-blind

Table 1. Experimental treatments in ADHD – drugs with published results.

| Molecule | Action | Study | Dose range (mg/day) | No of patients (#) | Age (yrs) | Inclusion criteria | Exclusion criteria | Control | Duration (weeks) | Primary outcome | Efficacy opinion* | Safety opinion** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Viloxazine | NRI | Johnson, 2020 [31] | 100–400 | 222 | 6–12 | ADHD-RS-IV ≥ 26 | comorbidity | placebo | 8 | ADHD-RS-IV | 1 | 0 |
| Reboxetine | NRI | Riahi, 2010 [35] | 16 | 40 | adult | - | comorbidity | placebo | 6 | CAARS | 1 | 0 |
| Reboxetine | NRI | Riahi, 2013 [36] | 4 | 25 | 6–16 | comorbid anxiety disorders | comorbidity | none | 4 | CPRS, HAM-A | + (non-controlled) | N/A |
| Edivoxetine | NRI | Jin, 2013 [37] | 0.05–0.3 mg/kg | 53 | 6–17 | - | comorbidity | none | 22 (avg) | ADHD-RS-IV | + (non-controlled) | N/A |
| Edivoxetine | NRI | Lin, 2014 [38] | 0.1–0.3 mg/kg | 340 | 6–17 | - | comorbidity | LA-methylphenidate, placebo | 8 | ADHD-RS-IV | 1 | 2 |
| Edivoxetine | NRI | Nery, 2017 [39] | 0.1–0.3 mg/kg | 267 | 6–17 | - | comorbidity | none | 5 years | ADHD-RS-IV | - (non-controlled) | N/A |
| Duloxetine | SNRI | Mahmoudi-Gharaei, 2011 [42] | 60 | 17 | 11–18 | - | comorbidity | none | 6 | CPRS | + (non-controlled) | N/A |
| Duloxetine | SNRI | Bilodeau, 2014 [43] | 60 | 30 | adult | CAARS ≥ 20 | comorbidity | placebo | 6 | CAARS | 1 | 0 |
| Bupropion | NDRI | Jafarinia, 2012 [44] | 100–150 | 44 | 6–17 | ADHD-RS-IV 1.5 SD above the norm | comorbidity, substance abuse | methylphenidate | 6 | ADHD-RS-IV | 2 | 2 |
| Bupropion | NDRI | Hamedi, 2014 [45] | 150 | 42 | adult | - | comorbidity, substance abuse | placebo | 6 | CAARS | 1 | 1 |
| Dasotraline | SNDRI | Koblan, 2015 [46] | 4–8 | 341 | adult | ADHD-RS-IV ≥ 26 and previously treated, or 22 and currently treated | comorbidity | placebo | 4 | ADHD-RS-IV | 1 | 0 |
| Dasotraline | SNDRI | Findling, 2019 [47] | 2–4 | 342 | 6–12 | ADHD-RS-IV ≥ 28 | comorbidity, use of psychoactive drugs other than hypnotics | placebo | 6 | ADHD-RS-IV | 1 | 0 |
| Dasotraline | SNDRI | Wigal, 2020 [48] | 4–6 | 112 | 6–12 | ADHD-RS-IV ≥ 26 | comorbidity | placebo | 2 | SKAMP; PERMP | 1 | 0 |
| Venlafaxine | SNRI | Zarinara, 2010 [51] | 50–75 | 37 | 6–13 | - | comorbidity | methylphenidate | 6 | ADHD-RS-IV | 2 (power issues) | 3 |
| Venlafaxine | SNRI | Amiri, 2012 [52] | 225 | 44 | adult | Past ADHD diagnosis or relatives of children with ADHD | comorbidity | placebo | 6 | ADHD-RS-IV | 0 | 0 |
| Tipepidine | GIRK inhibitor | Sasaki, 2014 [55] | 30 | 10 | 9–11 | - | comorbidity | none | 4 | ADHD-RS-IV | + (non-controlled) | N/A |
| Tipepidine | GIRK inhibitor | Tomoda, 2015 [56] | N/A | 12 | 9–11 | - | comorbidity | none | 4 | ADHD-RS-IV | + (non-controlled) | N/A |
| Tipepidine | GIRK inhibitor | Dehbozorghi, 2019 [57] | 15–30 (add-on) | 53 | 6–12 | treatment with methylphenidate | comorbidity | placebo | 8 | ADHD-RS-IV | 1 | 1 |
| Vortioxetine | SSRI/NaSSA | Biederman, 2019 [58] | 10–20 | 227 | adult | AISRS ≥ 24 | comorbidity | placebo | 12 | AISRS | 0 | 0 |
| N-pantoyl-GABA | GABA agonist | Zavadenko, 2017 [33] | 30 mg/kg | 89 | 6–12 | ADHD-RS-IV ≥ 22 (girls) or 25 (boys) | comorbidity | placebo | 16 | ADHD-RS-IV | 0 | 1 |
| N-pantoyl-GABA | GABA agonist | Kupriyanova, 2017 [34] | 500–1250 (add-on) | 24 | 6–11 | inefficacious treatment with atomoxetine | comorbidity | none | 8 | CHIP | + (non-controlled) | N/A |
| Amantadine | NMDA noncompetitive antagonist | Mohammadi, 2010 [59] | 100–150 | 40 | 6–14 | ADHD-RS-IV 1.5 SD above the norm | comorbidity | methylphenidate | 6 | ADHD-RS-IV | 2 | 3 |
| Memantine | NMDA noncompetitive antagonist | Surman, 2013 [60] | 5–20 | 34 | adult | CGI-S ≥ 4 | comorbidity | none | 12 | AISRS | + (non-controlled) | N/A |
| Memantine | NMDA noncompetitive antagonist | Mohammadi, 2015 [61] | 20 | 40 | 6–11 | ADHD-RS-IV 1.5 SD above the norm | comorbidity | methylphenidate | 6 | ADHD-RS-IV | inferior to methylphenidate | 0 |
| Memantine | NMDA noncompetitive antagonist | Mohammadzadeh, 2019 [62] | 20 | 40 | adult | Past ADHD diagnosis or relatives of children with ADHD | comorbidity | placebo | 6 | CAARS | 1 | 0 |
| Memantine | NMDA noncompetitive antagonist | Biederman, 2017 [63] | 5–20 (add-on) | 26 | adult | under stimulant treatment, 2 BRIEF-A subscores > 65 T | comorbidity | placebo | 12 | BRIEF-A | 1 | 1 |

(Continued)

Table 1. (Continued).

| Molecule | Action | Study | Dose range (mg/day) | No of patients (#) | Age (yrs) | Inclusion criteria | Exclusion criteria | Control | Duration (weeks) | Primary outcome | Efficacy opinion* | Safety opinion** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fasoracetam | mGluR agonist | Elia, 2018 [64] | 50–400 | 30 | 12–17 | Vanderbilt ≥ 16, mutations in genes of glutamatergic signaling | comorbidity | placebo | 5 | CGI-S | 1 | 1 |
| Org26576 | AMPA positive allosteric modulator | Adler, 2012 [65] | 200–600 | 68 | adult | CGI-S ≥ 4, AISRS ≥ 22 | comorbidity | placebo | 8 | AISRS | 0 | 0 |
| Melatonin | MTR agonist | Mohammadi, 2012 [67] | 3–6 (add-on) | 60 | 7–12 | treatment with methylphenidate | comorbidity | placebo | 8 | SDSC | 0 | 1 |
| Agomelatine | MTR agonist | Niederhofer, 2012 [68] | 25 (add-on) | 10 | 17–19 | pharmacological treatment | comorbidity | placebo | 4 | Wender-Utah rating scale | 1 | 1 |
| Agomelatine | MTR agonist | Salardini, 2016 [69] | 15–25 | 54 | 6–15 | ADHD-RS-IV 1.5 SD above the norm | comorbidity | methylphenidate | 6 | ADHD-RS-IV | 2 | 2 |
| Molindone | D2/H1 antagonism | Stocks, 2012 [70] | 10–40 | 78 | 6–12 | severe problem behavior | comorbidity | none | 12 | NCBRF behavior subscale | + (non-controlled) | N/A |
| MK-0929 | D4 antagonist | Rivkin, 2012 [71] | 15 | 35 | adult | AISRS ≥ 20 | comorbidity | placebo | 9 | AISRS | 0 | 1 |
| Sativex | THC+CBD | Cooper, 2017 [72] | 10.8 + 10–11.6 + 20 | 30 | adult | CAARS ≥ 24 | comorbidity, substance abuse | placebo | 6 | QbTest | 0 | 1 |
| MK-0249 | H3 inverse agonist | Herring, 2012 [73] | 10 | 72 | adult | CAARS ≥ 24 | comorbidity | LA-methylphenidate, placebo | 10 | AISRS | 0 | 2 |
| Bavisant | H3 antagonist | Weisler, 2012 [74] | 1–10 | 424 | adult | CAARS age-dependent threshold | comorbidity | LA-methylphenidate, atomoxetine, placebo | 6 | ADHD-RS-IV | 0 | 0 |
| 2-pyridylacetic acid | metabolite of betahistine (H3 antagonist, H1 weak antagonist) | Moorthy, 2015 [75] | 50–200 | 16 | adult | CAARS ≥ 20 | comorbidity | placebo | acute | CPT, SSRT | 1 | 1 |
| Pozanicline | nAChR α4β2 partial agonist | Wilens, 2011 [77] | 0.085–0.7 mg/kg | 393 | 6–12 | CGI-S ≥ 4 | comorbidity, previous non-response to stimulants | atomoxetine, placebo | 6 | ADHD-RS-IV | 0 | 1 |
| Pozanicline | nAChR α4β2 partial agonist | Apostol, 2012 [78] | 2–80 | 221 | adult | CGI-S ≥ 4 | comorbidity | placebo | 12 | CAARS | 1 | 1 |
| Pozanicline | nAChR α4β2 partial agonist | Bain, 2012 [79] | 40–80 | 160 | adult | CGI-S ≥ 4 | comorbidity | none | 8 | CAARS | 0 | 0 |
| Sofiniclin | nAChR α4β2 agonist | Bain, 2013 [81] | 1–8 | 243 | adult | CGI-S ≥ 4 | comorbidity | atomoxetine, placebo | 10 | CAARS | 1 | 3 |
| AZD1446 | nAChR α2β2/α4β2 agonist | Jucaite, 2014 [82] | 30–240 | 79 | adult | CGI-S ≥ 4 | comorbidity | placebo | 12 | CAARS | 0 | 1 |
| AZD3480 | nAChR α4β2 agonist | Potter, 2014 [83] | 5–50 | 30 | adult | CGI-S ≥ 4 | comorbidity, smokers | placebo | 12 | CAARS | 1 | 1 |

*Efficacy opinion: 0, not different from placebo; 1, superior to placebo; 2, not different from active treatment; 3, superior to active treatment; +, positive opinion (non-controlled study); -, negative opinion (non-controlled study).
**Safety opinion: 0, worse than placebo; 1, not different from placebo; 2, not different from active treatment; 3, superior to active treatment.

Table 2. Experimental treatments for ADHD – drugs without public results.

| Molecule | Group | Action | Status | Age | Sponsor |
|---|---|---|---|---|---|
| BLI-1008 | noradrenergic | NRI | phase 2 ongoing | adults | BioLite |
| Centanafadine | serotoninergic/dopaminergic/noradrenergic | SNDRI | phase 3 ongoing | adults | Otsuka |
| OPC-64005 | serotoninergic/dopaminergic/noradrenergic | SNDRI | phase 2 completed | adults | Otsuka |
| Oxytocin nasal spray | hormone | OTR agonist | phase 1 ongoing | adults | nonprofit |
| Oxytocin nasal spray | hormone | OTR agonist | phase 2 ongoing | children | nonprofit |
| CX717 | glutamatergic | AMPA positive allosteric modulator | unclear-phase 2 | | |
| Ampreloxetine | noradrenergic | NRI | discontinued-phase 2 | | |
| AR08 | noradrenergic | unknown, functional agonist | discontinued-phase 2 | | |
| Bradanicline | cholinergic | nAChR α7 partial agonist | discontinued-phase 2 | | |
| Brilaroxazine | serotoninergic/dopaminergic | D2, D3, D4, 5-HT1A, 5-HT2A partial agonist and 5-HT2A, 5-HT2B, 5-HT6, 5-HT7 antagonist | discontinued-phase 1 | | |
| Ciforadenant | purinergic | A2A antagonist | discontinued-phase 2 | | |
| GlyTI-M | glycinergic | Glycine transporter I inhibitor | discontinued-phase 2 | | |
| IRL-752 | serotoninergic/noradrenergic | 5-HT7 antagonist and NE α antagonist | discontinued-phase 1 | | |
| Opipramol+nicotine | cholinergic/opioid | σ agonist, nAChR agonist | discontinued-phase 2 | | |
| Vafidemstat | dopaminergic/noradrenergic/other | KDM1A and MAO-B inhibitor | discontinued-phase 2 | | |

study lasting 6 weeks where 100–150 mg/d bupropion were compared with 20–30 mg/d methylphenidate (depending on weight). The Authors concluded that bupropion was not different from methylphenidate regarding efficacy; however, they stated that a vastly larger sample size would have been required to statistically support non-inferiority. Adverse events were similar in quality and frequency.

Bupropion was tested [45] in adults. This 6-weeks parallel arm placebo controlled randomized double-blind trial used bupropion at a fixed 150 mg/d dose. Bupropion was significantly more effective than placebo after 6 weeks of treatment, while it was statistically as safe as placebo. However, we stress that several important adverse events were nominally more frequent with bupropion, including agitation, palpitations and paresthesia. Moreover, the Authors mentioned a sizable number of drop-outs, without clarifying the numbers and prevalence per arm, a fact that would suggest, in our opinion, an unsatisfying tolerability with bupropion.

### 6.1.4. SNDRIs

*6.1.4.1. Dasotraline (novel emerging).* Dasotraline is a triple reuptake inhibitor with a preference for dopamine and norepinephrine and a five-fold weaker affinity for the serotonin transporter. In preclinical tests, dasotraline significantly reduced impulsive and immediate reward choices, similarly to methylphenidate. In humans, dasotraline may be optimal for a once-daily administration, due to slow absorption and long half-life.

Dasotraline was tested in a placebo controlled randomized double-blind trial [46] in adults. Dasotraline 4–8 mg/d was administered for 4. The use of hypnotic Z-drugs (Zaleplon, Zolpidem, Zopiclone) was allowed to manage adverse events. Tolerability was good with dasotraline 4 mg/d (11% drop-outs vs. 9% for placebo) but not 8 mg/d (49% drop-outs). However, only the 8 mg/d arm showed significant reductions of the ADHD symptoms. The adverse events reported most frequently were insomnia, decreased appetite, nausea and dry mouth.

Another placebo controlled randomized double-blind trial [47] was conducted in children. Dasotraline was used at 2 or 4 mg/d for 6 weeks. Drop-out rates were similar across treatment arms (from 20 to 24%); however, in the 4 mg/d arm half of the drop-outs were due to adverse events, as compared to a quarter in the 2 mg/d arm. Treatment with 4 mg/d dasotraline, but not 2 mg/d, was superior to placebo on ADHD symptoms starting with the first week of treatment. The adverse events most frequent were insomnia, decreased appetite and weight, irritability and non-serious psychotic symptoms. Dasotraline 4 mg/d was thus effective, with some safety concerns.

A similar pediatric trial [48] tested dasotraline 4 and 6 mg/d at bedtime against placebo in a randomized double-blind manner, using academic performance scales as primary outcomes. The 6 mg/d arm was discontinued during the trial due to a 15% drop-out rate for adverse events, while the 4 mg/d arm showed a 5% drop-out rate, all due to adverse events, which was better than that of placebo (11%). Dasotraline 4 mg/d resulted in significant improvements on academic performances, sustained throughout the day. Common adverse events occurring significantly more for dasotraline 4 mg/d were insomnia, headache and decreased

appetite. Five percent (three) patients reported hallucinations connected with dasotraline, which resolved in 2/3 cases without altering treatment. Weight reduction was reported without stating its significance. Dasotraline 6 mg/d showed a higher incidence of insomnia, hallucinations, affect lability and larger weight loss, suggesting in our opinion low tolerability at high dose.

#### 6.1.4.2. Centanafadine (novel emerging).

Centanafadine is a triple reuptake inhibitor, with preferential potency for NE and DA and a mild effect on 5-HT in a ratio of 1:6:14, respectively; its sustained-release form is currently being development by Neurovance (Otsuka) in phase 3 for adult ADHD [49].

#### 6.1.4.3. OPC-64005 (novel emerging).

OPC-64005 is a triple reuptake inhibitor by Otsuka, which recently completed a phase 2 trial. Results should be soon published [50].

#### 6.1.4.4. Venlafaxine (repurposed emerging).

Venlafaxine is an inhibitor of monoamines reuptake, with a dose-dependent specificity. At low dose (75 mg) venlafaxine is an SSRI; at higher doses (150–225 mg) it acts as SNRI, while also having a weak effect on dopamine reuptake.

A randomized double-blind trial of venlafaxine [51] was conducted in children. Low-dose venlafaxine (25 mg x2-3/d) was compared with methylphenidate 20–30 mg/d. The trials lasted 6 weeks. Drop-out rates were equal across arms, while headaches and insomnia were more common with methylphenidate. No efficacy difference emerged.

Venlafaxine was tested also in adults [52]. This randomized double-blind trial lasting 6 weeks used venlafaxine 75 mg x3/d versus placebo. Venlafaxine was nominally more effective than placebo, yet reaching no significantly larger effect. Tolerability was similar, as the only adverse effect ascribed to venlafaxine was sexual dysfunction.

### 6.2. Other monoamine-based mechanisms

#### 6.2.1. Tipepidine (novel emerging)

Tipepidine is an inhibitor of G-protein-coupled inwardly rectifying potassium (GIRK)-channel currents. This activity has been associated with an increase in monoamine levels in the brain [53] and tipepidine can suppress experimentally induced hyperactivity in rats [54].

Tipepidine was studied [55] in children, in a single-arm trial lasting 4 weeks. Tipepidine was dosed 10 mg x3/d and 7 among 10 children used tipepidine in adjunct to other psychiatric drugs. ADHD symptoms were reduced and there were no drop-outs nor adverse effects. A similar single-arm trial [56] obtained the same results.

A randomized placebo controlled double-blind trial [57] was conducted in children. Tipepidine 5–10 mg x3/d was added to a preexisting methylphenidate therapy (0.3–1.5 mg/kg/d) over 8 weeks. Tolerability was equal and good across arms, adverse events were also reported indifferently; the most common were anorexia, malaise and headache. Tipepidine add-on resulted in a significant incremental improvement of ADHD symptoms, especially hyperactivity – impulsivity.

#### 6.2.2. Vortioxetine (repurposed emerging)

Vortioxetine is a SSRI and selective serotonin-norepinephrine modulator. Since it demonstrated some positive effects on cognition, vortioxetine was tested in a parallel arms randomize controlled trial [58] in adults. Vortioxetine 10 or 20 g/d was confronted with placebo for 12 weeks. Tolerability was similar for all arms, with drop-out rates around 10–15%, while adverse events with vortioxetine were nausea and fatigue. Vortioxetine was not superior to placebo on the main outcome.

#### 6.2.3. Brilaroxazine (on hold)

Brilaroxazine is a multifunctional drug with dopaminergic D2, D3, D4 partial agonism, serotoninergic 5-HT1A, 5-HT2A partial agonism and 5-HT2A, 5-HT2B, 5-HT6, 5-HT7 antagonism. Brilaroxazine underwent phase 1 trials for ADHD, but is now being developed by Reviva Pharmaceuticals for pulmonary hypertension and schizophrenia.

### 6.3. GABAergic transmission

N-pantoyl-GABA (NPG) (novel emerging) is a fusion analog of GABA and pantothenic acid, which possesses particular neuropharmacological characteristics. It can act as GABA agonist; moreover, it has a dopaminergic effect and stimulates acetylcholine production. Its involvement with attention or ADHD is not clearly based. NPG was studied [33] on 6 children with ADHD without comorbidity. In this double-blind randomized controlled trial against placebo, NPG was titrated over 4 months up to 30 mg/kg in two daily fractions. Efficacy of NPG was not different from placebo at any time point, on the main outcome. However, a significant improvement in the secondary outcomes from the Weiss Functional Impairment Rating Scale (WFIRS) and Toulouse-Pieron test (TPT) was noted after 4 and 1 months, respectively. There were no serious adverse events and NPG performed similarly to placebo regarding safety. NPG was tested also as add-on [34] at the maximum dose of 1250 mg/d, in a single-arm study lasting 2 months. The additional NPG was efficacious from the second week, on the CHIP subscales school performance and risk aversion. Adverse effects were not investigated.

### 6.4. Glutamatergic transmission

Metabotropic glutamate receptors are functionally different: mGluR1 and 5 have agonistic effects on NMDA receptors while the other mGluRs are antagonists.

#### 6.4.1. Amantadine (repurposed emerging)

Amantadine is a noncompetitive antagonist of NMDA receptors, which increases dopamine release and inhibits dopamine reuptake. It has been used as an antiviral and for Parkinson's dementia. Amantadine was studied [59] in a double-blind randomized controlled trial in children. Amantadine 50 mg, or methylphenidate 10 mg were administered 2 or 3 times per day depending on weight, for 6 weeks. One patient per group dropped out of study and adverse effects were comparable, except for appetite decrease and restlessness, which were more common with methylphenidate. The efficacy of

both treatments was similar at every time-point, with a similar decreasing trend.

#### 6.4.2. Memantine (repurposed emerging)

Memantine is a noncompetitive antagonist of NMDA receptors, licensed for use in dementia, tested for several other psychiatric applications as a stand-alone or adjunct therapy.

Memantine was tested in a single-arm trial [60] on ADHD adults. Memantine doses were individually adjusted up to 10 mg x2/d. The study lasted 12 weeks. A considerable (18%) number of participants did not tolerate memantine, while the others reached the largest dose. The therapeutic effect on ADHD symptoms and neuropsychological parameters was large, to the point that 56% participants were clinically negative at the endpoint. The most common adverse effects included confusion, sedation, dizziness and gastrointestinal and musculoskeletal disturbances.

Memantine was tested also in children [61]. This randomized double-blind parallel arms trial compared memantine 10 mg x2/d versus methylphenidate 10 mg x2 or 3/d depending on weight. The study lasted 6 weeks. A significantly higher proportion of patients dropped out of memantine treatment as compared with methylphenidate (35% vs. 5%), which was not stressed by the Authors. Among study completers, there was no difference between memantine and methylphenidate treatments regarding adverse events, nor ADHD symptoms at any time point. However, there was a significant difference in the change of scores over time, indicating a larger reduction with methylphenidate. Memantine seemed to be less effective than methylphenidate in this study and, in our opinion, also less tolerable.

Memantine was tested again in a double-blind randomized controlled trial versus placebo in adults [62]. Memantine was used at 10 mg x2/d for 6 weeks. A sizable number of patients dropped out of memantine treatment as compared with placebo (30% vs. none), which was again not stressed by the Authors. Among study completers, there was no difference in the occurrence of adverse events, while memantine resulted much superior to placebo in the reduction of ADHD symptoms. Memantine was effective in reducing ADHD symptoms but in our opinion the higher rate of drop-out suggested tolerability issues, not reported by the Authors.

A different group of investigators [63] tried memantine as an add-on treatment to improve executive functions in adults with ADHD. This 12-week double-blind randomized controlled trial used memantine up to 10 mg x2/d versus placebo. Patients treated with additional memantine showed no significant increases in adverse events and similar rates of discontinuation as compared to those who received additional placebo. Inhibition and self-monitoring problems were significantly improved by memantine addition, while organization problems were worsened. No effect of additional memantine treatment was found on core ADHD symptoms.

#### 6.4.3. Glutamatergic drugs on hold

Fasoracetam is a nonselective agonist of all mGluRs, with a non-clarified dose specificity. Fasoracetam was tested [64] in adolescents with ADHD and mutations in genes connected with the glutamatergic signaling, resulting to be tolerated and efficacious in this selected population. Four other clinical trials have been conducted with fasoracetam in the pediatric age, lasting up to summer 2019, but no results have been published and the sponsor does not have fasoracetam anymore in its pipeline. **Org25676** is a positive allosteric modulator of AMPA receptors, tested [65] in adults. Org25676 demonstrated potential efficacy and safety at a low dose, not with higher and flexible doses. **GlyTI-M** is an inhibitor of the glycine transporter I, which should affect the NMDA glutamatergic functioning; it was tested up to phase 2 by a nonprofit sponsor in Taiwan [66]. Its status is unknown.

### 6.5. Melatoninergic transmission

#### 6.5.1. Melatonin (repurposed emerging)

Melatonin has been tested [67] at the prescription dose of 3–6 mg versus placebo in a parallel arms randomized double-blind trial in add-on to methylphenidate, in children. Melatonin had non-significant effect in contrasting the sleep deteriorations due to methylphenidate. In addition to the conclusions of the Authors, we remark that melatonin was more tolerable than placebo, as shown by respective drop-out rates of 7% and 25%. However, in retainers, melatonin caused more sadness than placebo.

#### 6.5.2. Agomelatine (repurposed emerging)

Agomelatine is a multifunctional drug that combines melatoninergic agonism with serotoninergic 5-HT2C antagonism, possibly gaining an advantage over melatonin. It is currently used for the treatment of major depression forms with important shifts in the circadian rhythm.

Agomelatine was tested [68] as an add-on. This 4-weeks open-label trial of agomelatine 25 mg/d against placebo lasted 4 months. The authors did not report safety results, claiming agomelatine was similar to placebo in tolerability. In spite of the minimal sample size, agomelatine was superior to placebo in all sub-scores of the main measure. Agomelatine add-on to methylphenidate resulted to be safe and efficacious in increasing the improvement of ADHD core symptoms.

Agomelatine was tested also as a separate treatment [69] in children, in a 6 weeks parallel arms randomized double-blind trial. Agomelatine was used at 15–25 mg/d versus methylphenidate 20–30 mg/d. The two treatments displayed similar results on ADHD symptoms and the trial was adequately powered to claim non-inferiority. The Authors concluded that the treatments were equally safe; however, we noted that agomelatine tended to be safer than methylphenidate: the drop-outs were not different, while methylphenidate caused non-significantly more insomnia (24% vs. 4%, $p = 0.09$) and headache reactions (28% vs. 8%, $p = 0.13$).

### 6.6. Dopaminergic transmission

#### 6.6.1. D2 receptors and molindone (repurposed emerging)

The mechanism of action of antipsychotic is predominantly based on D2 dopaminergic and H1 histaminergic antagonism.

Molindone was tested [70] at 10–40 mg/d on pediatric patients in a parallel arms non-controlled trial lasting 12 weeks. Adverse events were dose dependent in frequency and intensity and were mainly somnolence, weight increase, akathisia, sedation and abdominal pain. ADHD symptoms were reduced around 30% with molindone 10–30 mg/d and around 50% with 40 mg/d. No further trials of molindone were published.

#### 6.6.2. D4 receptors and MK-0929 (on hold)

The D4 antagonist MK-0929 was evaluated [71] in adults, where it showed no efficacy.

### 6.7. Cannabinoid transmission

Sativex (repurposed emerging) is an oromucosal spray composed of equal parts of delta-9-tetrahydrocannabinol and cannabidiol, which has been tested [72] in adults. This double-blind randomized controlled trial against placebo lasted 2 weeks of titration and 4 at fixed dose. Tolerability was good and similar across treatment arms, adverse effects were minimal and those typical of sativex were mainly lightheadedness and diarrhea. No significant effect was found for sativex with respect to placebo, although some distinct sub-scores showed signs of improvement. The Authors concluded that the good effect seen in some participants for some indices, but not all participants and indices, is in keeping with the self-administration pattern frequently seen with ADHD patients.

### 6.8. Histaminergic transmission (drugs on hold)

MK-0249, a H3 inverse agonist, was tested [73] in adults, resulting in no appreciable efficacy and in increased insomnia. Bavisant, a highly selective H3 antagonist was tested [74] in adults, in which it was considered not efficacious. Adverse events occurring more with bavisant were insomnia (dose-dependent), abnormal dreams, dysgeusia, nausea and dizziness. 2-pyridylacetic acid is the major metabolite of betahistine, which is an analogue of histamine known to be a potent antagonist of H3 and weak antagonist of H1 receptors. It was tested [75] in adults, producing promising phase 1–2 results on the acute administration; however, no further trials or publications were found.

### 6.9. Nicotinic cholinergic transmission (drugs on hold)

Several partial and full agonists, for nAChR α4β2, have been tried in patients with ADHD. Pozanicline (ABT-089) [76] is a specific α4β2 partial agonist tested in children and adults [77–79]. It never showed a convincing dose-dependent response over placebo. Sofiniclin (ABT-894) [80] is a nAChR α4β2 full agonist. For this reason, a better efficacy was expected, after the failure of pozanicline. It was tested against atomoxetine [81], finding a similar effect, with possibly less adverse effects; however, sofiniclin was not investigated further. AZD1446 is a full agonist of the nAChR α4β2 and α2β2 tested [82] on adults on which it demonstrated no different efficacy or safety as compared with placebo. AZD3480 is a nAChR α4β2 full agonist tested [83] in adults with good tolerability and significant reduction of inattentive symptoms and memory problems and of emotional lability/impulsivity. Response inhibition was improved greatly. No further publications are available for AZD3480, nor clinical trials, despite a plausible usefulness. Bradanicline is a partial agonist of nAChR α7 cholinergic receptors developed by Targacept; it was discontinued after reaching phase 2 due to a lack of efficacy [84].

### 6.10. Other mechanisms and drugs without published results

CX717 (unclear status) is a positive allosteric modulator of AMPA receptors. Cortex Pharmaceuticals developed it up to phase 2; however, results were not published [85]. RespireRX has acquired it and its development status for ADHD is not clear. Oxytocin (repurposed emerging) in the form of nasal spray is currently undergoing nonprofit trials. Oxytocin is in phase 1 for cognitive aspects of ADHD in adults [86] and phase 2 for social and affective aspects of ADHD in children [87]. ND-0801 (on hold) by Neuroderm is a patch containing a combination of opipramol, which is a σ receptor agonist, and nicotine; it was discontinued after reaching phase 2 [88]. Ciforadenant (on hold) is an antagonist of A2A purinergic receptors, which reached phase 2 for the treatment of ADHD, but was discontinued. It is currently being developed as an anticancer drug by Corvus Pharmaceuticals.

## 7. Conclusion

More than one of the revised studies reported promising results in both children and adults. Most of them require replication studies for the considered drug to be used in clinical practice. All the monoaminergic reuptake inhibitors have a great potential to improve ADHD symptoms as they are active on the same mechanisms exploited by the currently-used drugs. The first tested NRIs, reboxetine and edivoxetine, unfortunately did not show the expected efficacy and all the study reported high level of dropouts mainly for side effects. A novel NRI, viloxazine, emerged to be more effective and with less side effects of the first tested NRIS (i.e. reboxetine and edivoxetine). Although less tolerable than placebo, and with unclear psychiatric adverse effects, it may be a valid option for treating ADHD in children. Following promising phase 2 results, viloxazine phase 3 trials are currently ongoing on both children and adults. Data on SNRI duloxetine are not conclusive and might be investigated further, ideally in larger controlled trials that escalate dose slowly, to minimize the impact of adverse events on therapy retention. Overall, the NDRI bupropion, even though it has been used to treat ADHD symptoms off-label for almost two decades, was only moderately effective and possibly more tolerable than methylphenidate for the treatment of patients with ADHD devoid of addictions. However, adequately powered, actively controlled randomized studies are required to support its use.

Both SNDRIs venlafaxine and, dasotraline might be a useful treatment option for childhood ADHD. However the number, size and reliability of studies on Venlafaxine need to be

increased, despite the frequent off-label use to treat ADHD especially in the U.S.

Dasotraline appears as a potentially valid treatment for pediatric ADHD, mainly due to its slow pharmacokinetics that allow bedtime administration and guarantee sustained performance through the following day. Its safety profile seems to be heavily dose-dependent and the therapeutic index may be narrow. An application for dasotraline was evaluated by the FDA and provisionally denied authorization for ADHD [52], pending further studies on safety. Other SNDRIs are on phase 2 and on phase 3 in adults with initially promising results.

Of the other monoamine active drugs, the only with promising results emerged to be Tipepidine, an inhibitor of G-protein-coupled inwardly rectifying potassium (GIRK)-channel currents. This new drug showed promising results as add-on therapy to methylphenidate, with a good tolerability profile. More studies are required.

The SSRI/NaSSA Vortioxetine might be further investigated for adult ADHD as provisional results are not convincing.

Moderation of glutamatergic system using drugs that seems to improve problems in cognitive function in other disorders like Parkinson's Disorders brought to some interesting results also in ADHD patients. Both amantadine in children and memantine in adults showed to be effective especially as add-on therapy at lower dosage to improve residual problems in executive functions. At higher dosages memantine raised some safety concerns, its use was associated with sizable dropout rates (around 30%). Also fasoracetam showed some promising results in a genetic selected adolescent population, as well as Org25676 in adults, but no replication studies are currently available.

The only study on melatonin as add-on therapy on side effect of methylphenidate showed limited evidence for efficacy; theoretically, melatonin may not be a good add-on choice for patients who have a drug-induced sympathetic activation, due to the susceptibility of melatonin to degradation.

On the contrary agomelatine would not be subjected to the physiological destruction of melatonin, and it seems to be a safe and potentially efficacious treatment for ADHD core symptoms. Whether this depends on the regularization of circadian rhythms or on direct effects, is yet to be clarified. The role of add-on or stand-alone therapy should be clarified by further studies, as agomelatine seems a promising option.

Boosting acetylcholine function through nicotinic receptor modulators may be a promising strategy especially for selected patient populations, without nicotinic addition. Full agonists (sofiniclin and AZD3480) showed higher efficacy than partial agonists (pozanicline). Sofiniclin could be suitable especially for patients who are intolerant to atomoxetine side effects. However, more data are needed but at present no ongoing studies are available.

Compounds active on GABAergic and histaminergic systems showed inconclusive results. Similarly, compounds blocking dopaminergic transmission did not show any efficacy on the core symptoms of ADHD. The use of cannabinoids in ADHD has no clear rationale and the only study available reported unclear results. Future studies need to focus on the different ratios of THC and CBD.

Future clinical studies on treatments for ADHD should include, aside clinical scoring tools, outcomes involving brain imaging. The effectiveness of stimulant drugs has been associated with the attenuation of ADHD-related abnormalities in brain structure, connectivity and function, in particular in the prefrontal cortex, basal ganglia, right amygdala, corpus callosum and cerebellum [89,90]. The use of structural/functional-MRI and/or Magnetic Resonance Spectroscopy (MRS) in combination with pharmacological trials, can help to identify the neural targets and mechanisms of action of new treatments in order to develop targeted therapies and to meet the needs of individual patients (precision medicine). The functional Near Infrared Spectroscopy (fNIRS) is another promising technique for studying metabolic alterations in the cerebral cortex and the effects of pharmacotherapies [91,92]. For instance, this tool has highlighted a frontal-cortical hypo-metabolism in children with ADHD performing neuropsychological tasks and an increase in the concentration of oxygenated hemoglobin in the same brain areas of patients receiving methylphenidate/atomoxetine. Techniques such as these may be particularly helpful when investigating novel drugs and mechanisms of action.

## 8. Expert opinion

In children and adolescents, stimulants are very effective. Concern is about their safety and potential for abuse or misuse, especially for amphetamine. The commonest adverse effects of stimulants include decreased appetite, including increased risk of growth retardation in weight and height, insomnia, stomachache, and headache, tics, increases in blood pressure [8–10]. Atomoxetine is recommended as monotherapy for the treatment of ADHD for individuals with ADHD and comorbidities including tics, mania, and suicidal ideation [7,13] even though the effect of atomoxetine on mania and suicidal ideation has not yet been clarified [93,94].

According to this perspective, innovative drugs for pediatric ADHD should be as effective as stimulants but with less adverse effects, sparing appetite, growth and sleep. Only a few drugs seem to fulfil these requirements.

The most promising innovative drugs seem to be agomelatine, both as an add-on or standalone therapy, and the glutamatergic ones: especially Amantadine and Fasoracetam, which would deserve more studies.

Among drugs active on noradrenergic and dopaminergic systems dasotraline showed comparable efficacy and less adverse effects then methylphenidate, but more data are needed to identify the correct dose range to support market access request.

Also, the NRI edivoxetine showed quite good efficacy, but the safety profile was similar to that of atomoxetine (including nausea vomiting and somnolence), even though better than methylphenidate (including sleep disorder, reduced appetite-weight loss).

Tipepidine, a GIRK inhibitor, deserves special attention for its potential efficacy as add-on treatment on symptoms of hyperactivity and impulsivity not completely responding to methylphenidate.

In adults, innovative drugs should treat comorbidities and avoid risks of misuse.

None of the numerous studies revised seemed to address directly the problem of comorbidity, except for the comorbidity with nicotine abuse. Nevertheless, some studies could be interesting, especially those using drugs that have proven to be effective in depressive and anxiety disorders.

Memantine, both as add-on or stand-alone has good potential, especially for inattentive symptoms and memory problems, and may reduce significantly emotional lability and impulsivity, even though more studies are needed. Both SNDRIs venlafaxine and dasotraline showed good efficacy, but dasotraline has some safety concerns that require further verification.

Imaging techniques such as MRI, fMRI, MRS, fNIRS should be implemented in future clinical trials to be probed as markers of drug efficacy.

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