Key Words: adverse effects, attention deficit disorder with hyperactivity, drug development, pharmacology, serotonin, serotonin agents

Serotonergic Drugs for the Treatment of Attention-Deficit/Hyperactivity Disorder: A Review of Past Development, Pitfalls and Failures, and a Look to the Future

By Craig Chepke, Elizabeth Brunner, Andrew J. Cutler

ABSTRACT *~ Serotonin has been implicated in the neurobiology of attention-deficit/hyperactivity disorder (ADHD) due to its association with impulsivity, attention, and emotional regulation. Many compounds with serotonergic properties have been evaluated in ADHD, but few have been approved by regulatory authorities. Utilizing a search of public databases, we identified interventions studied in ADHD. Prescribing information and peer-reviewed and gray literature helped us to determine which compounds had an underlying mechanism of action associated with changing serotonin levels. Of the 24 compounds that met the search criteria, 16 had either failed clinical studies in an ADHD population or had been discontinued from future development. The available evidence was assessed to identify the developmental history of drugs with serotonergic activity and the outlook for new ADHD drug candidates targeting serotonin. Several treatment candidates floundered due to an inability to balance effectiveness with safety, underscoring the potential importance of potency, and selectivity. Ongoing drug development includes compounds with multimodal mechanisms of action targeting neurotransmission across serotonin, norepinephrine, and dopamine pathways; it appears likely that treatment which balances competing and complementary monoamine effects may provide improved outcomes for patients. It is hoped that continuing research into ADHD treatment will produce new therapeutic options targeting the serotonergic system, which can positively impact a wide range of symptoms, including mood, anxiety, and sleep as well as attention and hyperactivity.* Psychopharmacology Bulletin. *2024;54(4):45–80.*

Chepke, MD, DFAPA, Excel Psychiatric Associates, Huntersville, NC; Atrium Health, Charlotte, NC. Brunner, MD, Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ. Cutler, MD, SUNY Upstate Medical University, Lakewood Ranch, FL.

To whom correspondence should be addressed: Craig Chepke, MD, DFAPA, Excel Psychiatric Associates, Huntersville, NC, United States. E-mail: craig.chepke@gmail.com; Phone: +1-704-457-9292

Introduction

Serotonin (5-hydroxytryptamine [5-HT]) is a key molecule in human physiology, acting as a neurotransmitter within the brain and as a peripheral hormone.[1] Via binding to its receptors in the central nervous system, serotonin modulates a multitude of functions, including various behaviors, mood, sleep, and cognition/memory; an imbalance or deficit within the serotonergic system can result in a range of neurobehavioral disorders, including depression, anxiety, schizophrenia, and addiction.[2,3] Due to its association with attention and behaviors such as impulsivity, aggression, and behavioral inhibition,[4] serotonin and the 5-HT receptor system are thought to be involved in the neurobiology of attention-deficit/hyperactivity disorder (ADHD).[5] Moreover, the well-recognized link between deficits in serotonin–receptor binding and negative effects in mood disorders[3,6] is consistent with the symptoms of emotional dysregulation observed in patients with ADHD,[7,8] suggesting significant pathophysiological and symptomatic overlap.

ADHD is a chronic disorder characterized by symptoms of inattention and/or hyperactivity and impulsivity; these symptoms can cause significant distress to patients, as well as impaired function and quality of life.[9] Data from the Global Burden of Disease study estimated an age-standardized prevalence of 1.13% in 2019, with higher rates in males (1.61%) than in females (0.63%).[10] Although historically considered to be most common in children, with reported prevalence rates of up to 8.0%,[11,12] recent data have suggested a similarly high prevalence among adults (up to 6.76%).[11,13] There has been a large increase in the recognition, diagnosis, and burden of ADHD in the United States over the past 3 decades,[14] with 10.47% of children diagnosed with ADHD in 2022, up from 6.1% in 1997.[15] However, there is controversy as to whether this is due to increased symptom awareness (particularly among females),[16,17] changes to the diagnostic criteria,[16] recognition of higher persistence rates (>90%) into adulthood than previously supposed,[18] or overmedicalization of children.[19] What is clear is that individuals who are diagnosed with ADHD are at elevated risk of social difficulties,[20,21] impaired academic and occupational function,[22] psychiatric comorbidities,[23] substance abuse,[24] accidental injuries,[25] and premature mortality.[26]

The etiology of ADHD is diverse, encompassing both environmental factors during the period of central nervous system development[27] and significant genetic influences (the estimated heritability rate is approximately 80%)[28]; these result in alterations in brain structure and function, which impact attention, behavior, and impulse control.[27] Although the exact neurobiology of ADHD remains uncertain, the neurotransmitters dopamine and norepinephrine are thought to be the key players[29];

dopamine is known to be involved in impulsive decision-making, motivation/reward, and risk-taking behavior,[30,31] and norepinephrine with attention and arousal.[32] This hypothesis was reinforced when drugs targeting the dopamine and norepinephrine pathways proved to be effective in treating ADHD.[29,33] However, approximately one-quarter to one-third of patients do not respond to such therapies,[34–36] and the side effects associated with these treatments may restrict their use.[37]

Neuroanatomical evidence is consistent with a role for the serotonergic system in ADHD,[38,39] while pharmacological and genetic manipulation of rodent models has implicated the 5-HT system in the hyperactive, impulsive, and mood dimensions of ADHD.[40] There is an abundance of evidence from both humans and animal models relating to the involvement of serotonin receptors in the occurrence of ADHD,[5,41,42] and a serotonergic hypothesis underpinning ADHD is consistent with the known association between reduced serotonin neurotransmission and mood disorders.[43]

Based on the assumption that direct serotonergic regulation of relevant brain development and activity influence the neurobiology of ADHD (including both core and associated symptoms), various compounds with serotonergic properties have been studied in populations with ADHD. Thus, a large selection of drugs from classes including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs)—all of which target the 5-HT system—have been evaluated in clinical studies of ADHD, with varying levels of efficacy and/or safety.[44–48] Notably, despite a large number of clinical trials, few such compounds have been approved by regulatory agencies for the treatment of ADHD, possibly because they have inadequate activity on dopamine and/or norepinephrine.

The objective of this evidence-based narrative review is to examine the published literature to identify the developmental history of drugs with serotonergic activity that have been studied in ADHD. We aim to highlight the mechanisms of action, the highest development status—with a focus on the reasons for termination—and the possible underlying causes of why some compounds with serotonergic activity failed in this indication. We will also look at clinical studies reported to be ongoing in the first half of 2024 and assess the potential for future serotonergic treatments in ADHD.

Methods

Information Search and Data Collation

We performed a search using the ClinicalTrials.gov website to identify clinical trials in the field of ADHD. The search was conducted

on 23 October 2023, using the search terms 'ADD' and 'ADHD'. The resulting list of 1,610 trials was narrowed further by filtering with the term 'interventions'. A total of 1,139 intervention trials were retrieved; these were evaluated to identify the individual drug interventions. In addition, a literature search was performed using the PubMed database, Google Scholar, and Google Patents to identify any additional drug interventions not previously captured. All drug interventions identified are listed in Supplementary Table 1.

Prescribing information as well as peer-reviewed and gray literature were then searched to determine which of these compounds were reported to have an underlying mechanism of action associated with the neurotransmitter serotonin or its receptor and/or transporter or altered serotonin levels via other mechanisms. We determined that 24 compounds met the criteria of being studied in ADHD and having serotonergic activity, of which 16 were found to have either failed clinical studies in an ADHD population or had been discontinued from future development by the sponsor (Table 1).

Failed/Discontinued Compounds

Broadly, the 16 compounds that were found to have failed/been discontinued for ADHD were divided into three categories. These were (i) 5-HT receptor activity: amantadine, brexpiprazole, memantine, molindone, and vortioxetine (also has considerable serotonin transporter [SERT] inhibition); (ii) SERT activity: dasotraline, duloxetine, lobeline, mazindol CR, modafinil, NS2359, SEP-228432, SPD473/BTS 74398, and venlafaxine; and (iii) histamine H_3 receptor inverse agonism, which increases serotonin release[49]: bavisant and MK-0249.

For those agents approved in other indications (vortioxetine, brexpiprazole, venlafaxine, duloxetine, and mazindol CR), the mechanism of action was obtained from the prescribing information. Where no prescribing information was available, the potential mechanism of action was deduced from the published scientific literature or other public domain sources.

5-HT Receptor Agonist/Antagonists

Amantadine

Although the exact mechanism of action of amantadine is unknown, it is thought to be a weak antagonist of the N-methyl-D-aspartate (NMDA) receptor.[50] In addition, it has been shown in vitro to bind to 5-HT_3 receptors.[51]

TABLE 1

Interventions for ADHD with a Serotonergic Mechanism of Action that Failed in the ADHD Indication*

DRUG	SEROTONIN MECHANISM	SEROTONIN ACTIVITY**	HIGHEST DEVELOPMENT STATUS
Amantadine	5-HT_3 receptor ligand	5-HT_3: IC_{50} = ~21–32 μM (Human)[1] SERT: Ki = 100 μM (Human)[2] SERT: Ki = 57–96 μM (Rat)[3]	• US FDA approved as adjunctive therapy for dyskinesia in PD[4]
Bavisant	Inverse agonism associated with H_3-receptor antagonists increases release of serotonin	–	• Failed ADHD in Phase 2[5]
Brexpiprazole	5-HT_{1A} partial agonist 5-HT_{2A} receptor antagonism	5-HT_{1A}: Ki = 0.12–1.1 nM (Human)[6–8] 5-HT_{1A}: Ki = 0.09 nM (Rat)[7] 5-HT_{1B}: Ki = 365 nM (Human)[8] 5-HT_{1D}: Ki = 23 nM (Human)[8] 5-HT_{1E}: Ki = >10,000 nM (Human)[8] 5-HT_{2A}: Ki = 0.47–3.9 nM (Human)[6–8] 5-HT_{2A}: Ki = 3.8 nM (Rat)[7] 5-HT_{2B}: Ki = 1.3–1.9 nM (Human)[6,8] 5-HT_{2C}: Ki = 29 nM (Human)[8] 5-HT_3: Ki = 754 nM (Human)[8] 5-HT_{5A}: Ki = 614 nM (Human)[8] 5-HT_6: Ki = 117 nM (Human)[8] 5-HT_7: Ki = 3.7–6.6 nM (Human)[6,8] SERT: Ki = 247 nM (Human)[8]	• US FDA approved as adjunctive therapy for MDD in adults, for schizophrenia in patients ⩾ 13 years, and Alzheimer's disease dementia in adults[6] • Reached phase 2 clinical trials for ADHD prior to discontinuation
Dasotraline	Dopamine-norepinephrine-serotonin reuptake inhibitor	SERT: IC_{50} = 15 nM (Human)[9] SERT IC_{50} = 19 nM (Rat)[9]	• US FDA rejected NDA for ADHD[10] • Development in ADHD discontinued[11]

(Continued)

TABLE 1 *(Continued)*

Interventions for ADHD with a Serotonergic Mechanism of Action that Failed in the ADHD Indication*

DRUG	SEROTONIN MECHANISM	SEROTONIN ACTIVITY**	HIGHEST DEVELOPMENT STATUS
Duloxetine	Serotonin and norepinephrine reuptake inhibitor	SERT: IC_{50} = 3–10 nM (Human)[12–17] SERT: Ki = 0.07 nM–9.3 μM (Human)[18–24] SERT: Ki = 0.5–8.8 nM (Rat)[18,21,25,26] 5-HT_{1A}: Ki = >5000 nM (Human)[21] 5-HT_{1B}: Ki = 3959 ± 810 nM (Human)[21] 5-HT_{1D}: Ki = >3000 nM (Human)[21] 5-HT_{1E}: Ki = 3733 ± 618 nM (Human)[21] 5-HT_{1F}: Ki = 4447 ± 30 nM (Human)[21] 5-HT_{2A}: Ki = 504 ± 87 nM (Human)[21] 5-HT_{2B}: Ki = 2100 ± 206 nM (Human)[21] 5-HT_{2C}: Ki = 916 ± 190 nM (Human)[21] 5-HT_4: Ki = >1000 nM (Guinea Pig)[21] 5-HT_6: Ki = 419 ± 89 nM (Human)[21] 5-HT_7: Ki = 2261 ± 115 nM (Human)[21]	• US FDA approved for MDD (adults), GAD (adults/pediatric), DPNP (adults), fibromyalgia (adults/pediatric), and CMP (adults)[27] • Development in ADHD discontinued
Lobeline	Serotonin reuptake inhibitor	SERT: Ki = >10 μM (Human)[28] SERT: Ki = ~46.8 μM (Rat)[29,30] 5-HT_{2A}: Ki = 7400 ± 1500 nM (Human)[31]	–
Mazindol CR	Serotonin and norepinephrine reuptake inhibitor	SERT: IC_{50} = 231 nM (Guinea Pig)[2] SERT: Ki = 84–103 nM (Human)[33] SERT: Ki = 49.3–272 nM (Rat)[34,35] SERT: Kd = ~39 nM (Human)[36]	• US FDA approved for appetite suppression/obesity management but not currently available[37] • Development in ADHD discontinued • Currently being studied for narcolepsy[38]
Memantine	5-HT_3 antagonist	$5HT_3$: IC_{50} = ~2.2 μM (Human)[1] $5HT_{3A}$: IC_{50} = 2.29 ± .24 μM (Human)[1]	• US FDA approved for Alzheimer's disease dementia[39] • Development in ADHD discontinued

MK-0249	SERT activity Inverse agonism associated with H_3-receptor antagonists increases release of serotonin	–	• Failed ADHD in Phase 2a[40]
Modafinil	SERT interactions	SERT: IC_{50} = >232 μM (Human)[41,42] SERT: IC_{50} = >300 μM (Rat)[43] SERT: Ki = 31.3 μM (Rat)[44]	• US FDA approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or shift work disorder[45] • US FDA did not recommend approval for children with ADHD due to safety concerns[46]
Molindone	5-HT_{2B} antagonist 5-HT_{2A} antagonist	5-HT_{2B}: IC_{50} = 0.08–0.41 μM (Human)[47] 5-HT_{2A}: IC_{50} = 14 μM (Human)[47] 5-HT_{2A}: Ki = 320 nM (Human)[48] 5-HT_{2A}: Ki = 501 nM (Rat)[49] 5-HT_{2A}: Kd = 5800 nM (Human)[50] 5-HT_{1A}: Ki = 3797 nM (Human)[48] 5-HT_{2C}: Ki = >10000 nM (Human)[48] 5-HT_6: Ki = 1008 nM (Human)[48] 5-HT_6: Ki = >5000 nM (Rat)[49] 5-HT_7: Ki = 265–3053 nM (Human)[48,51] 5-HT_7: Ki = 265 ± 36 (Human)[49]	• Failed ADHD in Phase 3[52]
NS2359	SERT inhibitor Norepinephrine, dopamine, and serotonin reuptake inhibitor	SERT: IC_{50} = 10 nM (Human)[53,54]	• Development in ADHD discontinued[55] • Most recently studied in cocaine-related disorders[55]

(Continued)

TABLE 1 *(Continued)*

Interventions for ADHD with a Serotonergic Mechanism of Action that Failed in the ADHD Indication*

DRUG	SEROTONIN MECHANISM	SEROTONIN ACTIVITY**	HIGHEST DEVELOPMENT STATUS
SEP-228432	Norepinephrine, dopamine, and serotonin reuptake inhibitor	SERT: IC_{50} = 34 nM (Human)[53]	–
SPD473/BTS 74398	Non-selective monoamine uptake inhibitor	SERT: Kd = 19 nM[56]	–
Venlafaxine	Serotonin and norepinephrine reuptake inhibitor	SERT: IC_{50} = 20–145 nM (Human)[20,57] SERT: Ki = 7.8–82 nM (Human)[20,21,58] SERT: Ki = 77 nM (Rat)[21] SERT: ED_{50} = 2.0 mg/kg (Rat)[21] 5-HT_{1A}: Ki = >10000 nM (Human)[21] 5-HT_{1B}: Ki = >10000 nM (Human)[21] 5-HT_{1D}: Ki = >10000 nM (Human)[21] 5-HT_{1E}: Ki = >10000 nM (Human)[21] 5-HT_{1F}: Ki = >10000 nM (Human)[21] 5-HT_{2A}: Ki = 2230 nM (Human)[21] 5-HT_{2B}: Ki = >10000 nM (Human)[21] 5-HT_{2C}: Ki = 2004 nM (Human)[21] 5-HT_4: Ki = >10000 nM (Guinea Pig)[21] 5-HT_6: Ki = 2792 nM (Human)[21] 5-HT_7: Ki = >10000 nM (Human)[21]	• US FDA approved for MDD, GAD, SAD, and panic disorder[59] • Development in ADHD discontinued • Follow-on compound desvenlafaxine used off-label for ADHD[60]

Vortioxetine	5-HT_3 receptor antagonism 5-HT_{1A} receptor agonism 5-HT_7 receptor antagonism 5-HT_{1B} partial agonist 5-HT_{1D} antagonist	5-HT_3: Ki = 3.7–23 nM (Human)[61,62] 5-HT_3: IC_{50} = 12 nM (Human)[62] 5-HT_3: IC_{50} = 0.18 nM (Rat)[62] 5-HT_3: EC_{50} = 2100 nM (Human)[62] 5-HT_{1A}: Ki = 15–39 nM (Human)[61–63] 5-HT_{1A}: EC_{50} = 200 nM (Human)[62] 5-HT_{1B}: Ki = 33 nM (Human)[61,62] 5-HT_{1B}: EC_{50} = 120 nM (Human)[62] 5-HT_{1D}: Ki = 54 nM (Human)[61,62] 5-HT_{2C}: Ki = 180 nM[62] 5-HT_{5A}: Ki = 221 nM[62] 5-HT_7: Ki = 19–450 nM (Human)[61–63] SERT: Ki = 1.6 nM (Human)[61,62] SERT: IC_{50} = 5.4 nM (Human)[61,62] SERT: IC_{50} = 2.9–5.3 nM (Rat)[62,63]	• US FDA approved for MDD[61] • Failed ADHD at Phase 2[64]

*References for this table can be found in the Supplementary Materials.
**Species has been identified as reported.
5-HT, 5-hydroxytryptamine; ADHD, attention-deficit/hyperactivity disorder; CMP, chronic musculoskeletal pain; DPNP, diabetic peripheral neuropathic pain; EC_{50}, half maximal effective concentration; ED_{50}, the dose of a medication that produces a specific effect in 50% of the population that has been administered that dose; GAD, generalized anxiety disorder; IC_{50}, half-maximal inhibitory concentration; Kd, dissociation constant; Ki, inhibition constant; MDD, major depressive disorder; NDA, New Drug Application; OSA, obstructive sleep apnea; PD, Parkinson's disease; PFC, prefrontal cortex; SAD, social anxiety disorder; SERT, serotonin transporter; US FDA, United States Food and Drug Administration.

Several studies evaluating amantadine in ADHD have been published. In an open-label, uncontrolled trial of amantadine given orally to 24 patients aged 5–13 years, symptoms were evaluated at baseline and week 6 using parent and teacher ADHD rating scales (ADHD-IV rating scale).[52] Treatment was titrated from 50 mg/day for 4 days to 100 mg/day for an additional 4 days, and finally to 150 mg/day. At week 6, the parent ADHD score had decreased from 41.04 ± 6.9 at baseline to 28.9 ± 8.7 ($p < 0.001$, effect size $d = 1.5$), and the teacher ADHD score from 35.8 ± 9.6 to 26.2 ± 9.5 ($p < 0.001$, effect size $d = 1.0$). Half of the patients (13/24) reported adverse events (AEs), of whom one discontinued treatment. The most common AEs were transient decrease in appetite (n = 5) and headache (n = 4).[52]

A randomized clinical trial in children treated with amantadine (100–150 mg/day depending on weight) or the stimulant methylphenidate (MPH) for 6 weeks showed similar improvements in ADHD symptoms with both drugs, with no significant differences between treatments on parent ADHD rating scale scores. The two types of AEs that differed significantly between treatment groups were decreased appetite (45% amantadine and 85% MPH) and restlessness (5% amantadine and 40% MPH).[53] In a retrospective study of 297 pediatric patients with psychiatric symptoms, including 251 with ADHD, amantadine (⩽400 mg/day) appeared to be an effective treatment, with a success rate of 64.5% in improving symptoms.[54] In addition, given that 48.1% of amantadine responders were receiving combination therapy with a stimulant (e.g., MPH or amphetamine), these data suggested that amantadine could also serve as a viable adjunct to stimulant treatment. Amantadine was also well-tolerated, with just 17/297 patients (5.7%) discontinuing due to AEs.[54]

Although these studies suggested that amantadine was safe and efficacious for the treatment of ADHD, no consistent dosage or regimen has been determined, and no further clinical development has been identified since 2021. This may be because the drug is available in generic forms, and no manufacturer is willing to sponsor the official clinical trial program that would be necessary to obtain regulatory approval.

Brexpiprazole

Brexpiprazole has high receptor binding affinity to norepinephrine, serotonin, and dopamine receptors. It is an antagonist at norepinephrine α1B and α2C receptors and serotonin 5-HT_{2A} receptors, as well as partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors.[55,56]

Data relating to the use of brexpiprazole in ADHD comes primarily from a randomized placebo-controlled phase 2 trial in

559 stimulant-naïve adults and 174 prior stimulant-nonresponding adults with ADHD, in which all participants received stimulants for 5 weeks.[57] After this period, 168 stimulant-naïve patients and 68 prior stimulant nonresponders who failed treatment were randomized to receive either adjunctive brexpiprazole or placebo. When assessed using scales including the Conners' Adult ADHD Rating Scale (CAARS), Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, Clinical Global Impression (CGI), and the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), stimulant-naïve patients were found to have no improvement with adjunctive brexpiprazole, while prior stimulant nonresponders showed a tendency toward treatment benefit only on the WRAADDS scale. AEs were similar in the brexpiprazole and placebo groups.[57]

Brexpiprazole is indicated for the treatment of other psychiatric disorders; however, development for the treatment of ADHD was terminated by the sponsor following phase 2 clinical study.

Memantine

Like amantadine, memantine is an NMDA receptor antagonist,[58] which in vitro has been shown to have antagonistic actions at 5-HT_3 receptors.[51] In a randomized placebo-controlled clinical trial study of 40 adult patients (18–45 years) with ADHD, 6 weeks of treatment resulted in significant differences in behavior and attention deficit between patients treated with memantine and those receiving placebo ($p < 0.001$). Treatment with memantine was reported to be tolerable, with mild AEs.[59]

Memantine has been approved by the US Food and Drug Administration (FDA) as a treatment for Alzheimer's disease since 2003,[58] with no further clinical development in ADHD.

Molindone

Molindone is an antipsychotic medication used historically for the treatment of schizophrenia,[60] although the original clinical development sponsor (Endo Pharmaceuticals, Inc.) discontinued production in 2010 due to manufacturing/sourcing difficulties.[61] In vitro studies have shown that at therapeutic concentrations molindone is a potent antagonist for dopamine receptors D_{2S} and D_{2L} and the serotonin receptor 5-HT_{2B}.[62]

Data from phase 2 studies in children with ADHD suggested that adjunctive (to MPH or amphetamine) molindone treatment was able to produce improvements in behavior, particularly symptoms of persistent impulsive aggression.[63,64] A new formulation of molindone was utilized by Supernus Pharmaceuticals in the phase 3 studies CHIME

1 (NCT02618408) and 2 (NCT02618434), as well as the open-label extension study CHIME 4 (NCT02691182), for the treatment of impulsive aggression in children in conjunction with standard ADHD treatment. Although the results have not been published in a peer-reviewed journal, data published on the trial registration website indicate that the studies failed to meet the primary endpoints. Despite dropping the lower dose arm (18 mg/day) of the CHIME 1 and 2 studies after interim analyses,[65] no statistical differences were observed between molindone 36 mg/day and placebo in the frequency of impulsive aggression (NCT02618408, NCT02618434, NCT02691182). AEs occurred in up to 19% of patients in the higher dose arm. A further study (NCT03597503) was planned in adolescents but was terminated due to business decisions, which were unrelated to safety. Subsequently, all clinical development activities for molindone in ADHD were halted.[66]

Vortioxetine

Vortioxetine is a serotonin modulator approved for major depressive disorder, which exerts its effects via 5-HT_3, 5-HT_{1A}, and 5-HT_7 receptor antagonism, as well as 5-HT_{1B} partial agonism and 5-HT_{1D} antagonism.[67,68] Vortioxetine has also shown moderate to high affinity for SERT.[67]

A proof-of-concept study was reported in 2019, in which 227 adult patients (18–55 years) with a diagnosis of ADHD received treatment with vortioxetine (10 or 20 mg/day) or placebo for 6 weeks. ADHD symptoms were assessed using the Adult ADHD Investigator Symptom Rating Scale (AISRS); although symptoms improved with both vortioxetine doses, there were no statistically significant differences from placebo. Both doses were well-tolerated.[69] As the drug failed to meet the primary endpoint in this proof-of-concept study, no further development in ADHD was undertaken.

SERT Activity

Dasotraline

Dasotraline is a potent inhibitor of the dopamine and the norepinephrine transporter, and a weak inhibitor of SERT.[70] Dasotraline was evaluated for the treatment of ADHD in an extensive clinical development program, including several late-phase placebo-controlled studies, yet failed to produce data sufficient to obtain regulatory approval.

In a placebo-controlled phase 2/3 study, treatment with dasotraline 4 mg/day was reported to significantly improve the symptoms and behaviors associated with ADHD (specifically attention and hyperactivity)

in children aged 6–12 years.[71] However, 2 mg/day of dasotraline did not differ significantly from placebo on the primary endpoint of ADHD Rating Scale Version IV–Home Version (RS-IV HV) score or secondary efficacy measures. Common dasotraline-related AEs included insomnia, decreased appetite, decreased weight, and irritability, and 12.2% of patients receiving dasotraline 4 mg/day discontinued treatment, compared with 1.7% in the placebo group.[71] Dasotraline 4 mg/day was also found to be efficacious and generally well-tolerated in a phase 3 placebo-controlled, laboratory classroom study of children (aged 6–12) with ADHD.[72] Compared with placebo, dasotraline significantly improved scores on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)–combined score (dasotraline −3.2, placebo +2.0; $p < 0.001$; effect size = 0.85). Children showed improvements in the attention and deportment subscale scores. In line with the prior phase 2/3 study, the most frequent AEs associated with dasotraline were insomnia (19.6%), headache (10.7%), and decreased appetite (10.7%); 5.4% of dasotraline-treated patients discontinued the study compared with 1.8% in the placebo group.[72]

Dasotraline was also evaluated in a phase 3, placebo-controlled study of adults (18–55 years) with ADHD, at doses of 4 or 6 mg/day.[73] However, neither dose was found to be significantly better than placebo in terms of the primary endpoint (reduction in ADHD RS-IV HV total score), although the 6-mg/day dose produced a significant effect at week 8 using unadjusted data. The most frequent AEs occurring with dasotraline (vs placebo) were insomnia, decreased appetite, dry mouth, and anxiety; these appeared to be dose-related.[73]

Based on these clinical trial data, the US FDA rejected a new drug application (NDA) for dasotraline in ADHD, citing the need for additional studies to more fully determine its efficacy and tolerability for this indication.[74] The sponsor subsequently announced the withdrawal of the NDA and stated their intention to discontinue the clinical development program.[75]

Duloxetine

Duloxetine is a member of the SNRI drug class, being a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less-potent inhibitor of dopamine reuptake.[76]

Duloxetine is indicated for the treatment of several psychiatric disorders,[76] and was evaluated in a 6-week double-blind, placebo-controlled trial in 30 adults (18–50 years) with ADHD.[77] Efficacy results were mixed; duloxetine 60 mg/day had greater improvements on CGI-Severity scores (3.00 vs 4.07 for placebo; $p < 0.001$) and CGI-Improvement scores (2.89 vs 4.00; $p < 0.001$), plus greater decreases on

5 of 8 subscales of the CAARS at week 6. However, there was no effect on depression or anxiety. At week 1, 80% (12/15) of participants receiving duloxetine reported AEs, and 6 participants stopped treatment as a result.[77] No additional studies of duloxetine in ADHD were identified, with no further clinical development for duloxetine in this indication.

Lobeline

Lobeline is a potent antagonist at both the α3β2 and α4β2 neuronal nicotinic receptor subtypes, and appears to perturb dopamine storage and release mechanisms.[78] In vitro pharmacological evaluation has also suggested potency and selectivity for SERT inhibition.[79]

The effects of sublingual lobeline (7.5, 15, or 30 mg) was assessed in a proof-of-concept study using cognitive tasks and self-report measures in 9 adult volunteers (21–45 years) with ADHD. The results indicated a modest improvement in working memory but no significant improvement in attention. Patients reported not liking the taste, and nausea appeared to be a dose-related AE.[80] A follow-on phase 2 clinical trial of sublingual lobeline was conducted in 13 adult patients with ADHD (NCT00664703); although the study was completed, no results have been reported to date. It is assumed that the data were not positive and that no further development was warranted.

Mazindol CR

Mazindol is an anorexiant that produces stimulatory effects on the central nervous system similar to those produced by amphetamines.[81] Mazindol has been shown to alter neuronal catecholamines via its activity as an SNRI[81] and was recently reported to be a partial orexin-2 receptor agonist and triple monoamine reuptake inhibitor.[82]

Mazindol controlled release (1–3 mg/day) was evaluated in a randomized, double-blind, placebo-controlled 6-week trial in 85 adults (aged 18–65) with ADHD.[83] Based on ADHD-rating scale (ADHD-RS-DSM5) scores, mazindol improved symptoms to a greater extent than placebo (least squares mean −18.9 vs −5.7; mean difference −13.2 [95% confidence interval {CI} −18.7 to −7.6]; effect size 1.09), with differences observable from day 7. Treatment was reported to be well-tolerated, with no serious AEs, and no discontinuations due to treatment-emergent adverse events. A small effect on heart rate, similar to that produced by class II stimulants, was noted.[83]

Although the study authors noted that phase 3 studies were planned for mazindol in ADHD,[83] according to ClinicalTrials.gov no such studies have been identified. Mazindol is currently being studied for narcolepsy (NCT05055024, NCT04923594, NCT05914194),[84] and

it could be assumed that the lack of clinical developmental progress in ADHD was a business decision.

Modafinil

Modafinil is a compound with wakefulness-promoting properties similar to those of amphetamines and MPH; its exact mechanism of action is unknown but appears to involve dopamine reuptake, as well as release of histamine and orexin.[85,86] Data from animal studies have also indicated a dose-dependent interaction with SERT, thereby increasing dialysate serotonin levels.[87]

A meta-analysis of five clinical trials in a pediatric population with ADHD concluded that modafinil produced greater improvements in ADHD-RS-5 home (standardized mean difference, −0.77 [95% CI −1.11 to −0.44]) and school (−0.71 [95% CI −0.96 to −0.47]) scores compared with placebo. The most common AEs with modafinil were decreased appetite and insomnia. Discontinuation rates due to AEs were similar to the control group.[88] Despite positive trial data, the US FDA advisory committee did not recommend approval of modafinil for children with ADHD because of panel members' concern of modafinil's potential to cause Stevens-Johnson syndrome.[89]

Although development of modafinil in this indication was terminated, it has been used off-label to treat ADHD.[90] In addition, the follow-on drug armodafinil (an R-enantiomer of modafinil) is reported to be in use as a 'smart drug' to improve cognition in healthy individuals and has been used to treat ADHD off-label.[91] However, studies with armodafinil have shown no significant effect on serotonin or its receptor.[92]

NS2359

NS2359 is a mixed monoamine reuptake inhibitor with equipotent effects on norepinephrine and dopamine transporters as well as SERT.[93]

In a phase 2a study in 126 adults with ADHD, no significant differences between NS2359 and placebo in terms of the primary outcome measure (reduction in investigator-rated ADHD-RS total score) were observed (7.8 vs 6.4; $p < 0.45$). Overall, NS2359 had no effect on ADHD symptoms, although subgroup analyses suggested a modest improvement in attention and authors noted a low dose as a potential cause. The most frequent treatment-related AE was insomnia; no serious AEs were reported.[93] Further clinical development of NS2359 in ADHD was discontinued.[94]

SEP-228432

SEP-228432 (also called SEP-432) is a triple reuptake inhibitor of serotonin, norepinephrine, and dopamine.[95] The manufacturer (Sepracor Inc.) reported an interest in developing this compound for ADHD,[96] which was further reported in 2010 with the acquisition of Sepracor Inc. by Sumitomo Pharma.[97]

A phase 1 study in healthy volunteers (NCT01531972) was completed to ascertain the pharmacokinetics, as well as SERT and dopamine transporter (DAT) occupancy, by single-photon emission computed tomography (SPECT).[98] However, by 2012, no further clinical development for SEP-228432 in ADHD had been reported.[99]

SPD-473

SPD-473 (also called BTS 74 398) is a mixed monoamine (serotonin, dopamine, and norepinephrine) reuptake inhibitor.[100] It was reported to have completed phase 1 development in ADHD,[100,101] but it appears that clinical development activities in all indications have subsequently ceased.[100,101]

Venlafaxine

Venlafaxine is an SNRI indicated for the treatment of several psychiatric disorders[102] and has been evaluated for the treatment of ADHD in several controlled and uncontrolled clinical trials.[46,103]

In an open-label study of 9 adult patients (18–65 years), treatment with venlafaxine was associated with significant reductions in ADHD symptomatology at Week 2 (ADHD-RS, $p < 0.02$; CGI, $p < 0.006$), with 7/9 patients being considered responders, and only mild-to-moderate AEs being reported.[104] A subsequent 6-week double-blind trial in 44 adults with ADHD failed to find a significant difference between venlafaxine and placebo in the effect on ADHD symptoms. No serious AEs were reported.[105] A meta-analysis of 10 studies concluded that venlafaxine showed some efficacy in the treatment of ADHD, but was less potent than duloxetine.[46] Despite the lack of official regulatory approval for this indication, venlafaxine has been reported to be used for the treatment of ADHD.[106]

Histamine H_3 Receptor Inverse Agonism

Bavisant

An H_3 receptor antagonist, bavisant was considered a good candidate for potential use in the treatment of attention and cognitive disorders[107] and has been evaluated in several studies in ADHD.

In a randomized, double-blind, placebo- and active-controlled phase 2 study evaluating three dosages of bavisant (1, 3, or 10 mg/day) in adults with ADHD, the mean change in the total ADHD-RS-5 score with bavisant was −9.3 (1 mg), −11.2 (3 mg), and −12.2 (10 mg) versus −8.8 in the placebo group. For the 10-mg/day group, the change was not statistically superior to placebo ($p = 0.161$) and no further hierarchical testing was conducted. The highest dosage of bavisant was poorly tolerated (89.0% experienced AEs and 19.2% discontinued as a result).[107] Three early-stage studies in children (NCT00890240 and NCT00890292) and adults (NCT00566449) with ADHD were also completed, but to date, no results have been published.

MK-0249

MK-0249 was a developmental compound investigated in various cognitive defects, including ADHD,[108] sleepiness associated with obstructive sleep apnea,[109] and Alzheimer's disease.[110] MK-0249 administration acts on the H_3 receptor to increase histamine release,[108] which is pro-cognitive and could assist with ADHD symptoms; the H_3 receptor also acts as a heteroreceptor that regulates the release of neurotransmitters such as serotonin.[108]

In a randomized, double-blind, placebo-controlled, crossover phase 2a study of MK-0249 (5–10 mg/day) versus MPH, MK-0249 did not differ from placebo ($p = 0.341$) in terms of AISRS scores, whereas MPH produced significant improvements ($p < 0.001$). Although MK-0249 was reported to be generally well-tolerated, 5/37 (13.5%) patients discontinued treatment due to AEs, compared with 6.8% in the MPH group and 3.7% in the placebo groups. A greater percentage of patients reported insomnia with MK-0249 treatment compared with placebo (32% vs 11%, respectively).[108] Given the unfavorable outcome in this study, plus failures in the studies for obstructive sleep apnea[109] and Alzheimer's disease,[110] further clinical development of MK-0249 was discontinued.

Discussion

Evaluating the Developmental Failures

Due to the large body of evidence indicating a role for 5-HT in mood disorders,[2,3] and their very high comorbidity in patients with ADHD, many pharmaceutical companies have looked at serotonergic compounds for the treatment of ADHD, with mixed success. For every drug that has been approved in this field, several others have either failed clinical trials or have been withdrawn from development. Some compounds

were assessed in a clinical trial program involving multiple randomized studies yet still failed to generate data that were sufficiently robust to obtain regulatory approval. Other compounds, despite showing promise in early-stage trials, were not investigated further, possibly because there was no sponsor willing to fund the trials likely needed to progress to an NDA or for other business-related reasons. The reasons for discontinuation or non-approval are multifactorial, with study design factors such as patient selection, ADHD diagnostic criteria, and scales and endpoints each playing a part. However, it is also possible that patient selection and appropriate dose selection, including the need to balance effectiveness with safety may underlie at least some of the problems observed during drug development for ADHD.

Potency and selectivity are key attributes when considering efficacy and tolerability. Off-target effects resulting in AEs may reduce the dosage range for a particular compound, thereby decreasing the ability of the prescribing physician to maximize its effectiveness sufficiently to control symptoms. As shown in Table 1, the reported half-maximal inhibitory concentrations (IC_{50}) and inhibition constants (Ki) vary widely among the drugs described here, suggesting that each will have a different benefit-risk profile during ADHD treatment.

Moreover, specific serotonergic efficacy and tolerability effects are likely to be further complicated by AEs elicited in response to the other effects of a given drug, e.g., toxicity driven by binding to/inhibition of noradrenaline and dopamine receptors and transporters. However, this level of information would require a much deeper investigation of the exact mechanism of action than is available for many approved and failed ADHD treatment candidates, several of which remain imperfectly understood. It is likely that there is a 'Goldilocks zone', in which the effects in the brain are sufficient to manage ADHD symptoms without triggering the type and severity of AEs likely to lead to discontinuation. In support of this, we note that several studies of failed drugs (including amantadine, molindone, dasotraline, and bavisant) struggled to determine an optimal dose, and some approved drugs (notably amphetamines and MPH) are routinely titrated by physicians in an attempt to obtain the best outcomes. Patterns of drug administration (for short durations or intermittently) may also limit the therapeutic value of developmental serotonergic drugs.[111] The fact of a particular compound having a known serotonin effect and proven efficacy in other neurobehavioral disorders may not be enough to indicate that it should be tested for effectiveness in ADHD. Instead, a deeper understanding of its potency and selectivity appears necessary before embarking on clinical trials.

Current Treatment Landscape of Serotonergic Drugs Used in ADHD

Several of the best-known and most commonly used pharmacological treatments for ADHD are associated with effects on serotonergic neurotransmission. Amphetamines are non-catecholamine, sympathomimetic amines,[112–114] but have also been shown to have affinity for SERT, thereby increasing extracellular serotonin.[115,116] Amphetamines have been shown to robustly improve the severity of ADHD symptoms but are associated with AEs (e.g., elevated blood pressure, cardiovascular conditions, gastrointestinal symptoms, decreased appetite, long-term suppression of growth, and neuropsychiatric symptoms, such as irritability, mania, and psychosis[117,118]) that can result in high discontinuation rates.[119]

The mechanism of action of MPH in ADHD is not fully understood, but it is thought to block dopamine and norepinephrine reuptake.[120,121] The evidence for a serotonergic role is not as conclusive as for amphetamines; the affinity of MPH for SERT is lower than for dopamine or norepinephrine transporters,[122] although MPH has been reported to have agonist activity at the 5-HT_{1A} receptor.[123] Some researchers have found no indication of an MPH effect on 5-HT pathways,[115] while others have suggested that MPH administration can rebalance serotonin levels in the brain and blood, thereby reducing hyperactivity[124,125] and synchronizing biological rhythms[126] in patients with ADHD. The relative activity on the serotonin system for a given patient could be subject to inter-individual variability. MPH is widely used in ADHD, although studies have shown that dosing and clinical response are variable,[127] likely due to genetic differences in the activity of the carboxylesterase 1 enzyme, which metabolizes MPH,[128] and as a result of titration in an attempt to minimize AEs.[129]

Atomoxetine is reported to be a selective NRI[130] but has also been shown to bind in vitro to SERT.[131] The effectiveness of atomoxetine was established following an extensive development program involving multiple randomized controlled clinical studies in both children (4 studies) and adults (2 studies).[132,133] Viloxazine ER, another selective NRI,[134] has also been shown to increase brain serotonin levels via its actions at 5-HT receptors (5-HT_{2B} and 5-HT_7 antagonist and 5-HT_{2C} agonist).[135] It can be hypothesized that the 5-HT_{2C} agonist activity of viloxazine regulates dopamine signaling in both the midbrain and striatal regions via interactions with gamma-aminobutyric acid interneurons,[136–139] which have been shown to reduce impulsive behavior.[140]

In addition, there are several drugs which have some degree of serotonergic activity that are not approved by the US FDA for the treatment of ADHD but are nonetheless reported to be used for this purpose

(often concomitantly alongside stimulants). Agomelatine is a melatonin agonist and selective serotonin antagonist, with effects at 5-HT_{2C} and 5-HT_{2B} receptors.[141–143] It is currently approved in other countries, but not in the US, for the treatment of adult depression,[141] and has been reported to have psychostimulant activities, with the ability to regulate cognitive activity and circadian rhythms.[143] In a small clinical trial in ADHD, the addition of agomelatine to MPH or atomoxetine suggested clinical efficacy, particularly in terms of the impact on comorbid sleep, anxiety, or oppositional defiance disorder.[144] In another study, agomelatine monotherapy was found to be as effective as MPH on parent and teacher rating scale scores.[145] Across all published studies and indications, agomelatine is considered well-tolerated with high levels of adherence.[143]

The TCA desipramine is indicated for the treatment of depression in the US[146] and has been reported to be used in the treatment of ADHD.[147,148] It appears to exert its effects via blocking norepinephrine and serotonin reuptake,[148] and has been reported to alter 5-HT receptor sensitivity.[149] However, although clinical studies in ADHD have indicated that desipramine can decrease clinical symptoms, there are serious concerns regarding its safety, particularly in children.[150] Imipramine is another TCA indicated in the US for depression[151] and has been linked to the treatment of ADHD,[152] although the clinical data supporting its use are older.[45] It exerts a serotonergic effect via inhibition of SERT and alterations in 5-HT_{1A} receptor sensitivity.[153,154]

Compounds Currently in Development

Several compounds with some degree of serotonergic activity are currently in clinical development for the treatment of ADHD. It will be of future interest to assess the final regulatory outcome in the light of what is known about the serotonergic potency and selectivity of each of these drugs.

Cariprazine is an atypical antipsychotic indicated by the US FDA for several psychiatric disorders.[155] It acts as a partial agonist at the dopamine D_2 and D_3 receptors and serotonin 5-HT_{1A} receptors, and as an antagonist at 5-HT_{2A} and 5-HT_{2B} receptors. Its binding affinity is reported to be high at 5-HT_{2B} receptors (Ki = 0.58 nM) and 5-HT_{1A} receptors (Ki = 2.6 nM), moderate at 5-HT_{2A} receptors (Ki = 18.8 nM), and low at 5-HT_{2C} receptors (Ki = 155 nM).[155] A flexible-dose clinical trial in adults with ADHD is currently recruiting (NCT04843423).

Centanafadine is a first-in-class norepinephrine, dopamine, and serotonin reuptake inhibitor (NDSRI) being developed for the treatment

of ADHD in children, adolescents, and adults.[156] It has IC_{50} values of 6 nM for norepinephrine, 38 nM for dopamine, and 83 nM for serotonin transporter reuptake.[157] The NDSRI mechanism may provide a more favorable safety and tolerability profile when compared to the current standard of care. Moreover, the serotonergic activity of centanafadine has been postulated to mitigate treatment-related AEs such as sleep disturbances and changes in appetite.[157] Modulation of serotonin could also assist with associated symptoms of ADHD that are not as well-treated by the current standard of care, including anxiety and depression.[157] To date, the sponsor has completed 9 clinical studies in ADHD, with 2 currently ongoing (NCT05279313 and NCT05428033). Data from two phase 3 studies of the sustained-release formulation conducted in adults with ADHD reported statistically significant improvements in AISRS total scores versus placebo and a low rate of treatment-emergent AEs leading to discontinuation.[158] Two phase 3 studies in pediatric ADHD patients have also been completed, but only topline results have been reported to date; both trials met the primary efficacy endpoint for the higher dose studied, with no new safety concerns identified.[156]

Solriamfetol, a dopamine and norepinephrine reuptake inhibitor (DNRI), is indicated to improve wakefulness in adults with excessive daytime sleepiness that is associated with narcolepsy or obstructive sleep apnea.[159] Preclinical data suggest that solriamfetol exhibits agonist activity at the $5\text{-}HT_{1A}$ receptor[160] as well as trace amine-associated receptor 1 (TAAR1) agonism,[160] which is believed to have several effects on serotonin neurotransmission, including enhancing the potency of $5\text{-}HT_{1A}$ agonists.[161] Agonist activity at TAAR1 was also shown to be involved in serotonergic neurotransmission.[162,163] According to the manufacturer, solriamfetol has low binding affinity for the serotonin transporter (K_i = 81.5 μM) and does not inhibit serotonin reuptake (IC_{50} > 100 μM).[159] Following the publication of positive data from a dose-optimization pilot study of solriamfetol in 60 adults with ADHD,[164] a phase 3 clinical study was initiated and is currently recruiting (NCT05972044).

Clinical Implications and Future Treatment Expectations

Given that ADHD is one of the most common neuropsychiatric disorders,[11–13,165] and places a high burden on individuals and society, there is a great deal of interest in developing safe and effective treatments. Currently approved therapies include stimulant drugs (MPH and amphetamine derivatives) and a handful of non-stimulants, but concerns relating to efficacy and safety remain.[34–37]

The unfavorable outcome rate for drugs intended for ADHD treatment is large, and the bar for evidence robust enough for regulatory approval is set high.[101] Nonetheless, there has been considerable progress in the understanding of ADHD neurobiology, and each failure expands our knowledge base and should enable more rational drug development, improved trial procedures, and better optimized dosing in the future.

While the initial focus of drug development was on the catecholamines, norepinephrine and dopamine,[101,166] there is also a large body of evidence indicating a role for the serotonergic system in ADHD. Given the large number of failed trials, it does not appear that serotonergic modulation alone is likely to produce efficacious treatments for ADHD. Instead, it seems likely that altering the balance between monoamine neurotransmission systems is likely to provide the best outcomes, with serotonergic activity complementing effects on norepinephrine and dopamine. Notably, one of the drugs currently in development, centanafadine, is an NDSRI targeting all three of these neurotransmitter systems; based on clinical trial data to date, centanafadine demonstrated clinically meaningful efficacy with a favorable safety and tolerability profile. The use of this and other multimodal agents is expected to expand the pool of available drugs for ADHD, simultaneously providing robust and consistent efficacy alongside a favorable safety profile and lower potential for abuse, and delivering additional benefits with regard to comorbidities (such as sleep, anxiety, and mood).[166]

Limitations of this Review

This narrative review does not represent an exhaustive analysis of every compound with serotonergic activity ever tested in ADHD. Instead, it is intended to provide a summary of this often-overlooked area of research, to consider the role of 5-HT in the pathology and treatment of ADHD, and to generate discussion regarding the high unfavorable outcome rate to date. As this study was reliant on information available in the public domain, several compounds for which no data have been made publicly available have been omitted and some supporting sources that were not peer-reviewed have been included.

Conclusions

There is an ever-increasing body of evidence suggesting a role for 5-HT in the neurobiology of ADHD and indicating that modulation of serotonergic neurotransmission and rebalancing of monoamines within the brain may provide an avenue of drug development by which outcomes for patients with ADHD can be improved. In this evidence-based narrative review, many compounds with serotonergic activity

that have been studied in ADHD were identified, and pinpointed key reasons for a halt in the developmental process, which include finding the correct dose and selectivity to produce a balance between potency and tolerability. At the current time, clinical studies of several drug candidates with serotonergic activity are ongoing, and it is anticipated that such treatments may positively impact multiple ADHD-associated symptoms, including anxiety and emotional dysregulation, in addition to inattention and hyperactivity. ✤

Acknowledgments

The authors thank Sally-Anne Mitchell, PhD, and Julia L. Jones, PhD, of The Medicine Group for providing medical writing support, which was funded by Otsuka Pharmaceutical Co., Ltd., and in accordance with Good Publication Practice 2022 guidelines (https://www.ismpp.org/gpp-2022). The authors also thank Olesya Taylor for her insight and contributions to this work.

Disclosures

Craig Chepke has served on the advisory boards of AbbVie, Acadia, Alkermes, Axsome, Biogen, Bristol Myers Squibb, Corium, Idorsia, Intra-Cellular, Janssen, Lundbeck, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, and Teva; Advisory Board (spouse): Bristol Myers Squibb, Otsuka; served as a consultant for AbbVie, Acadia, Alkermes, Axsome, Biogen, Boehringer Ingelheim, Corium, Intra-Cellular, Janssen, Lundbeck, MedinCell, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Supernus, and Teva; has received grant or research support from Acadia, Axsome, Harmony, Neurocrine, and Teva; and has been on the speaker's bureau for AbbVie, Acadia, Alkermes, Axsome, Bristol Myers Squibb, Corium, Intra-Cellular, Janssen, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sumitomo, and Teva. **Elizabeth Brunner** is a full-time employee of Otsuka Pharmaceutical Development & Commercialization, Inc. **Andrew J. Cutler** has been a consultant or advisory board member for AbbVie, Acadia, Alfasigma, Alkermes, Anavex Life Sciences, Axsome, Biogen, Biohaven, BioXcel, Boehringer Ingelheim, Brii Biosciences, Bristol Myers Squibb, Cerevel, Chase Therapeutics, Cognitive Research, Corium, Delpor, Evolution Research Group, 4M Therapeutics, Intra-Cellular Therapies, Ironshore Pharmaceuticals, Janssen/J&J, Jazz Pharma, Karuna, LivoNova, Lundbeck, Luye Pharma, Maplight Therapeutics, MedAvante-ProPhase, Mentavi, Neumora, Neurocrine, Neuroscience Education Institute, NeuroSigma, Noven, Otsuka, PaxMedica, PureTech Health,

Relmada, Reviva, Sage Therapeutics, Sumitomo Pharma America, Sunovion, Supernus, Teva, Thynk, Tris Pharma, Vanda Pharmaceuticals, VistaGen, and VivoSense; has been on a speaker bureau for AbbVie, Acadia, Alfasigma, Alkermes, Axsome, BioXcel, Corium, Intra-Cellular Therapies, Ironshore Pharmaceuticals, Janssen/J&J, Lundbeck, Neurocrine, Noven, Otsuka, Sunovion, Supernus, Teva, Tris Pharma, and Vanda Pharmaceuticals; and has stock options in 4M Therapeutics and Relmada.

References

1. Kanova M, Kohout P. Serotonin—Its synthesis and roles in the healthy and the critically ill. *Int J Mol Sci*. 2021;22(9):4837. doi:10.3390/ijms22094837
2. Lin SH, Lee LT, Yang YK. Serotonin and mental disorders: A concise review on molecular neuroimaging evidence. *Clin Psychopharmacol Neurosci*. 2014;12(3):196–202. doi:10.9758/cpn.2014.12.3.196
3. Pourhamzeh M, Moravej FG, Arabi M, et al. The roles of serotonin in neuropsychiatric disorders. *Cell Mol Neurobiol*. 2022;42(6):1671–1692. doi:10.1007/s10571-021-01064-9
4. Lucki I. The spectrum of behaviors influenced by serotonin. *Biol Psychiatry*. 1998;44(3):151–162. doi:10.1016/s0006-3223(98)00139-5
5. Hou YW, Xiong P, Gu X, Huang X, Wang M, Wu J. Association of serotonin receptors with attention deficit hyperactivity disorder: A systematic review and meta-analysis. *Curr Med Sci*. 2018;38(3):538–551. doi:10.1007/s11596-018-1912-3
6. Lin J, Liu W, Guan J, et al. Latest updates on the serotonergic system in depression and anxiety. *Front Synaptic Neurosci*. 2023;15:1124112. doi:10.3389/fnsyn.2023.1124112
7. Hirsch O, Chavanon M, Riechmann E, Christiansen H. Emotional dysregulation is a primary symptom in adult attention-deficit/hyperactivity disorder (ADHD). *J Affect Disord*. 2018;232:41–47. doi:10.1016/j.jad.2018.02.007
8. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. *Am J Psychiatry*. 2014;171(3):276–293. doi:10.1176/appi.ajp.2013.13070966
9. Faraone SV, Banaschewski T, Coghill D, et al. The World Federation of ADHD International Consensus Statement: 208 evidence-based conclusions about the disorder. *Neurosci Biobehav Rev*. 2021;128:789–818. doi:10.1016/j.neubiorev.2021.01.022
10. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry*. 2022;9(2):137–150. doi:10.1016/S2215-0366(21)00395-3
11. Ayano G, Demelash S, Gizachew Y, Tsegay L, Alati R. The global prevalence of attention deficit hyperactivity disorder in children and adolescents: An umbrella review of meta-analyses. *J Affect Disord*. 2023;339:860–866. doi:10.1016/j.jad.2023.07.071
12. Salari N, Ghasemi H, Abdoli N, et al. The global prevalence of ADHD in children and adolescents: A systematic review and meta-analysis. *Ital J Pediatr*. 2023;49(1):48. doi:10.1186/s13052-023-01456-1
13. Song P, Zha M, Yang Q, Zhang Y, Li X, Rudan I. The prevalence of adult attention-deficit hyperactivity disorder: A global systematic review and meta-analysis. *J Glob Health*. 2021;11:04009. doi:10.7189/jogh.11.04009
14. Cortese S, Song M, Farhat LC, et al. Incidence, prevalence, and global burden of ADHD from 1990 to 2019 across 204 countries: Data, with critical re-analysis, from the Global Burden of Disease study. *Mol Psychiatry*. 2023;28(11):4823–4830. doi:10.1038/s41380-023-02228-3
15. Li Y, Yan X, Li Q, et al. Prevalence and trends in diagnosed ADHD among US children and adolescents, 2017–2022. *JAMA Netw Open*. 2023;6(10):e2336872. doi:10.1001/jamanetworkopen.2023.36872
16. Abdelnour E, Jansen MO, Gold JA. ADHD diagnostic trends: Increased recognition or overdiagnosis? *Mo Med*. 2022;119(5):467–473.
17. London AS, Landes SD. Cohort change in the prevalence of ADHD among U.S. adults: Evidence of a gender-specific historical period effect. *J Atten Disord*. 2021;25(6):771–782. doi:10.1177/1087054719855689
18. Sibley MH, Arnold LE, Swanson JM, et al. Variable patterns of remission from ADHD in the multimodal treatment study of ADHD. *Am J Psychiatry*. 2022;179(2):142–151. doi:10.1176/appi.ajp.2021.21010032

19. Gascon A, Gamache D, St-Laurent D, Stipanicic A. Do we over-diagnose ADHD in North America? A critical review and clinical recommendations. *J Clin Psychol*. 2022;78(12):2363–2380. doi:10.1002/jclp.23348
20. Berchiatti M, Ferrer A, Badenes-Ribera L, Longobardi C. School adjustments in children with attention deficit hyperactivity disorder (ADHD): Peer relationships, the quality of the student-teacher relationship, and children's academic and behavioral competencies. *Journal of Applied School Psychology*. 2022;38(3):241–261. doi:10.1080/15377903.2021.1941471
21. Pawaskar M, Fridman M, Grebla R, Madhoo M. Comparison of quality of life, productivity, functioning and self-esteem in adults diagnosed with ADHD and with symptomatic ADHD. *J Atten Disord*. 2020;24(1):136–144. doi:10.1177/1087054719841129
22. Varrasi S, Boccaccio FM, Guerrera CS, Platania GA, Pirrone C, Castellano S. Schooling and occupational outcomes in adults with ADHD: Predictors of success and support strategies for effective learning. *Educ Sci*. 2023;13(1):37. doi:10.3390/educsci13010037
23. Choi WS, Woo YS, Wang SM, Lim HK, Bahk WM. The prevalence of psychiatric comorbidities in adult ADHD compared with non-ADHD populations: A systematic literature review. *PLoS One*. 2022;17(11):e0277175. doi:10.1371/journal.pone.0277175
24. Van de Glind G, Brynte C, Skutle A, et al. The International Collaboration on ADHD and Substance Abuse (ICASA): Mission, results, and future activities. *Eur Addict Res*. 2020;26(4–5):173–178. doi:10.1159/000508870
25. Brunkhorst-Kanaan N, Libutzki B, Reif A, Larsson H, McNeill RV, Kittel-Schneider S. ADHD and accidents over the life span - A systematic review. *Neurosci Biobehav Rev*. 2021;125:582–591. doi:10.1016/j.neubiorev.2021.02.002
26. Dalsgaard S, Ostergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: A nationwide cohort study. *Lancet*. 2015;385(9983):2190–2196. doi:10.1016/S0140-6736(14)61684-6
27. Nunez-Jaramillo L, Herrera-Solis A, Herrera-Morales WV. ADHD: Reviewing the causes and evaluating solutions. *J Pers Med*. 2021;11(3):166. doi:10.3390/jpm11030166
28. Grimm O, Kranz TM, Reif A. Genetics of ADHD: What should the clinician know? *Curr Psychiatry Rep*. 2020;22(4):18. doi:10.1007/s11920-020-1141-x
29. Curatolo P, D'Agati E, Moavero R. The neurobiological basis of ADHD. *Ital J Pediatr*. 2010;36(1):79. doi:10.1186/1824-7288-36-79
30. van Gaalen MM, van Koten R, Schoffelmeer AN, Vanderschuren LJ. Critical involvement of dopaminergic neurotransmission in impulsive decision making. *Biol Psychiatry*. 2006;60(1):66–73. doi:10.1016/j.biopsych.2005.06.005
31. Franca TFA, Pompeia S. Reappraising the role of dopamine in adolescent risk-taking behavior. *Neurosci Biobehav Rev*. 2023;147:105085. doi:10.1016/j.neubiorev.2023.105085
32. Zhang Y, Chen Y, Xin Y, Peng B, Liu S. Norepinephrine system at the interface of attention and reward. *Prog Neuropsychopharmacol Biol Psychiatry*. 2023;125:110751. doi:10.1016/j.pnpbp.2023.110751
33. Stuhec M, Munda B, Svab V, Locatelli I. Comparative efficacy and acceptability of atomoxetine, lisdexamfetamine, bupropion and methylphenidate in treatment of attention deficit hyperactivity disorder in children and adolescents: A meta-analysis with focus on bupropion. *J Affect Disord*. 2015;178:149–159. doi:10.1016/j.jad.2015.03.006
34. Spencer T, Biederman J, Wilens T, et al. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005;57(5):456–463. doi:10.1016/j.biopsych.2004.11.043
35. Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adolesc Psychiatry*. 1996;35(4):409–432. doi:10.1097/00004583-199604000-00008
36. Childress AC, Sallee FR. Attention-deficit/hyperactivity disorder with inadequate response to stimulants: approaches to management. *CNS Drugs*. 2014;28(2):121–129. doi:10.1007/s40263-013-0130-6
37. Schneider BN, Enenbach M. Managing the risks of ADHD treatments. *Curr Psychiatry Rep*. 2014;16(10):479. doi:10.1007/s11920-014-0479-3
38. Oades RD. Role of the serotonin system in ADHD: Treatment implications. *Expert Rev Neurother*. Oct 2007;7(10):1357–1374. doi:10.1586/14737175.7.10.1357
39. Vanicek T, Kutzelnigg A, Philippe C, et al. Altered interregional molecular associations of the serotonin transporter in attention deficit/hyperactivity disorder assessed with PET. *Hum Brain Mapp*. 2017;38(2):792–802. doi:10.1002/hbm.23418
40. Banerjee E, Nandagopal K. Does serotonin deficit mediate susceptibility to ADHD? *Neurochem Int*. 2015;82:52–68. doi:10.1016/j.neuint.2015.02.001

41. Ruocco LA, Treno C, Gironi Carnevale UA, et al. Prepuberal stimulation of 5-HT7-R by LP-211 in a rat model of hyper-activity and attention-deficit: Permanent effects on attention, brain amino acids and synaptic markers in the fronto-striatal interface. *PLoS One*. 2014;9(4):e83003. doi:10.1371/journal.pone.0083003
42. Sharp T, Barnes NM. Central 5-HT receptors and their function; Present and future. *Neuropharmacology*. 2020;177:108155. doi:10.1016/j.neuropharm.2020.108155
43. Dunn GA, Nigg JT, Sullivan EL. Neuroinflammation as a risk factor for attention deficit hyperactivity disorder. *Pharmacol Biochem Behav*. 2019;182:22–34. doi:10.1016/j.pbb.2019.05.005
44. Park P, Caballero J, Omidian H. Use of serotonin norepinephrine reuptake inhibitors in the treatment of attention-deficit hyperactivity disorder in pediatrics. *Ann Pharmacother*. 2014;48(1):86–92. doi:10.1177/1060028013506561
45. Otasowie J, Castells X, Ehimare UP, Smith CH. Tricyclic antidepressants for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev*. 2014;(9):CD006997. doi:10.1002/14651858.CD006997.pub2
46. Dezfouli RA, Hosseinpour A, Ketabforoush S, Daneshzad E. Efficacy, safety, and tolerability of serotonin-norepinephrine reuptake inhibitors in controlling ADHD symptoms: A systematic review and meta-analysis. *Middle East Current Psychiatry*. 2024;31(1):8. doi:10.1186/s43045-024-00400-1
47. Barrickman L, Noyes R, Kuperman S, Schumacher E, Verda M. Treatment of ADHD with fluoxetine: A preliminary trial. *J Am Acad Child Adolesc Psychiatry*. 1991;30(5):762–767.
48. Padilha S, Virtuoso S, Tonin FS, Borba HHL, Pontarolo R. Efficacy and safety of drugs for attention deficit hyperactivity disorder in children and adolescents: a network meta-analysis. *Eur Child Adolesc Psychiatry*. 2018;27(10):1335–1345. doi:10.1007/s00787-018-1125-0
49. Esbenshade TA, Browman KE, Bitner RS, Strakhova M, Cowart MD, Brioni JD. The histamine H3 receptor: An attractive target for the treatment of cognitive disorders. *Br J Pharmacol*. 2008;154(6):1166–81. doi:10.1038/bjp.2008.147
50. GOCOVRI (amantadine) extended release capsules, for oral use [prescribing information]. Revised 8/2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208944lbl.pdf.
51. Rammes G, Rupprecht R, Ferrari U, Zieglgansberger W, Parsons CG. The N-methyl-D-aspartate receptor channel blockers memantine, MRZ 2/579 and other amino-alkyl-cyclohexanes antagonise 5-HT(3) receptor currents in cultured HEK-293 and N1E-115 cell systems in a non-competitive manner. *Neurosci Lett*. 2001;306(1–2):81–84. doi:10.1016/s0304-3940(01)01872-9
52. Donfrancesco R, Calderoni D, Vitiello B. Open-label amantadine in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2007;17(5):657–664. doi:10.1089/cap.2006.0128
53. Mohammadi MR, Kazemi MR, Zia E, Rezazadeh SA, Tabrizi M, Akhondzadeh S. Amantadine versus methylphenidate in children and adolescents with attention deficit/hyperactivity disorder: A randomized, double-blind trial. *Hum Psychopharmacol*. 2010;25(7–8):560–565. doi:10.1002/hup.1154
54. Morrow K, Choi S, Young K, Haidar M, Boduch C, Bourgeois JA. Amantadine for the treatment of childhood and adolescent psychiatric symptoms. *Proc (Bayl Univ Med Cent)*. 2021;34(5):566–570. doi:10.1080/08998280.2021.1925827
55. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *J Pharmacol Exp Ther*. 2014;350(3):589–604. doi:10.1124/jpet.114.213793
56. REXULTI® (brexpiprazole) tablets, for oral use [prescribing information]. Revised 5/2023. https://www.otsuka-us.com/sites/g/files/qhldwo8366/files/media/static/Rexulti-PI.pdf.
57. Reimherr FW, Gift TE, Steans TA, et al. The use of brexpiprazole combined with a stimulant in adults with treatment-resistant attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol*. 2022;42(5):445–453. doi:10.1097/JCP.0000000000001592
58. NAMENDA® (memantine hydrochloride) tablets, for oral use [prescribing information]. Revised 11/2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021487s025lbl.pdf.
59. Mohammadzadeh S, Ahangari TK, Yousefi F. The effect of memantine in adult patients with attention deficit hyperactivity disorder. *Hum Psychopharmacol*. 2019;34(1):e2687. doi:10.1002/hup.2687
60. MOBAN® (molindone hydrochloride tablets, USP) [prescribing information]. Revised 6/2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017111s066lbl.pdf.
61. US Food and Drug Administration. Determination that MOBAN (Molindone Hydrochloride) Tablets (5 milligrams, 10 milligrams, 25 milligrams, 50 milligrams, and 100 milligrams) and capsules (5 milligrams, 10 milligrams, and 25 milligrams) were not withdrawn from sale for reasons of safety or effectiveness. *Federal Register*. 2013;78(215):66742–66743.
62. Yu C, Gopalakrishnan G. In vitro pharmacological characterization of SPN-810M (molindone). *J Exp Pharmacol*. 2018;10:65–73. doi:10.2147/JEP.S180777
63. Stocks JD, Taneja BK, Baroldi P, Findling RL. A phase 2a randomized, parallel group, dose-ranging study of molindone in children with attention-deficit/hyperactivity disorder and persistent, serious conduct problems. *J Child Adolesc Psychopharmacol*. 2012;22(2):102–11. doi:10.1089/cap.2011.0087

64. Ceresoli-Borroni G, Nasser A, Adewole T, et al. A double-blind, randomized study of extended-release molindone for impulsive aggression in ADHD. *J Atten Disord*. 2021;25(11):1564–1577. doi:10.1177/1087054720909084
65. Supernus Pharmaceuticals. News Release Details September 18, 2017. https://ir.supernus.com/news-releases/news-release-details/supernus-provides-update-spn-810-phase-iii-clinical-trials-0?ReleaseID=1040834
66. Surran C. Supernus Pharma's SPN-810 trial did not meet primary endpoint. Seeking Alpha. Accessed June 11, 2024. https://seekingalpha.com/news/3545617-supernus-pharmas-spnminus-810-trial-not-meet-primary-endpoint
67. TRINTELLIX (vortioxetine) tablets, for oral use [prescribing information]. Revised 8/2023. https://content.takeda.com/?contenttype=PI&product=TRI&language=ENG&country=GBL&documentnumber=1
68. D'Agostino A, English CD, Rey JA. Vortioxetine (brintellix): A new serotonergic antidepressant. *P T*. 2015;40(1):36–40.
69. Biederman J, Lindsten A, Sluth LB, et al. Vortioxetine for attention deficit hyperactivity disorder in adults: A randomized, double-blind, placebo-controlled, proof-of-concept study. *J Psychopharmacol*. 2019;33(4):511–521. doi:10.1177/0269881119832538
70. Hopkins SC, Sunkaraneni S, Skende E, et al. Pharmacokinetics and exposure-response relationships of dasotraline in the treatment of attention-deficit/hyperactivity disorder in adults. *Clin Drug Investig*. 2016;36(2):137–146. doi:10.1007/s40261-015-0358-7
71. Findling RL, Adler LA, Spencer TJ, et al. Dasotraline in children with attention-deficit/hyperactivity disorder: A six-week, placebo-controlled, fixed-dose trial. *J Child Adolesc Psychopharmacol*. 2019;29(2):80–89. doi:10.1089/cap.2018.0083
72. Wigal S, Tsai J, Bates JA, et al. A randomized, placebo-controlled laboratory classroom study of the efficacy and safety of dasotraline in children with ADHD. *J Atten Disord*. 2020;26(10):1357–1368. doi:10.1177/10870547211073477
73. Adler LA, Goldman R, Hopkins SC, et al. Dasotraline in adults with attention deficit hyperactivity disorder: A placebo-controlled, fixed-dose trial. *Int Clin Psychopharmacol*. 2021;36(3):117–125. doi:10.1097/YIC.0000000000000333
74. Sunovion. FDA issues a complete response letter for new drug application for dasotraline for the treatment of ADHD. August 31, 2018. https://news.sunovion.com/press-releases/press-releases-details/2018/FDA-Issues-a-Complete-Response-Letter-for-New-Drug-Application-for-Dasotraline-for-the-Treatment-of-ADHD/default.aspx#:~:text=Upon%20completion%20of%20their%20review,for%20the%20treatment%20of%20ADHD
75. Sunovion. Sunovion discontinues dasotraline program. May 13 2020. https://news.sunovion.com/press-releases/press-releases-details/2020/Sunovion-Discontinues-Dasotraline-Program/default.aspx.
76. CYMBALTA (duloxetine delayed-release capsules), for oral use [prescribing information]. Revised 8/2023. https://pi.lilly.com/us/cymbalta-pi.pdf
77. Bilodeau M, Simon T, Beauchamp MH, et al. Duloxetine in adults with ADHD: A randomized, placebo-controlled pilot study. *J Atten Disord*. 2014;18(2):169–175. doi:10.1177/1087054712443157
78. Dwoskin LP, Crooks PA. A novel mechanism of action and potential use for lobeline as a treatment for psychostimulant abuse. *Biochem Pharmacol*. 2002;63(2):89–98. doi:10.1016/s0006-2952(01)00899-1
79. Zheng G, Horton DB, Deaciuc AG, Dwoskin LP, Crooks PA. Des-keto lobeline analogs with increased potency and selectivity at dopamine and serotonin transporters. *Bioorg Med Chem Lett*. 2006;16(19):5018–5021. doi:10.1016/j.bmcl.2006.07.070
80. Martin CA, Nuzzo PA, Ranseen JD, et al. Lobeline effects on cognitive performance in adult ADHD. *J Atten Disord*. 2018;22(14):1361–1366. doi:10.1177/1087054713497791
81. SANOREX® (mazindol) 1 and 2 mg tablets [product monograph]. Revised 7/2015. https://pdf.hres.ca/dpd_pm/00031211.PDF
82. Corser B, Stern T, Bogan R, et al. 0585 A four-week randomized, double-blind, placebo-controlled, phase 2 study of mazindol ER in the treatment of narcolepsy. *Sleep*. 2023;46(Supplement_1):A257–A257. doi:10.1093/sleep/zsad077.0585
83. Wigal TL, Newcorn JH, Handal N, et al. A double-blind, placebo-controlled, phase II study to determine the efficacy, safety, tolerability and pharmacokinetics of a controlled release (CR) formulation of mazindol in adults with DSM-5 attention-deficit/hyperactivity disorder (ADHD). *CNS Drugs*. 2018;32(3):289–301. doi:10.1007/s40263-018-0503-y
84. NLS Pharmaceutics news release. NLS Pharmaceutics to proceed with phase 3 clinical program (AMAZE) for mazindol ER for the treatment of narcolepsy following FDA review and IRB approval of the full study protocol. July 3, 2023. https://feeds.issuerdirect.com/news-release.html?newsid=5667709303839703
85. PROVIGIL® (modafinil) tablets, for oral use [prescribing information]. Revised 1/2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf

86. Ishizuka T, Murotani T, Yamatodani A. Action of modafinil through histaminergic and orexinergic neurons. *Vitam Horm*. 2012;89:259–278. doi:10.1016/B978-0-12-394623-2.00014-7
87. Ferraro L, Fuxe K, Tanganelli S, Tomasini MC, Rambert FA, Antonelli T. Differential enhancement of dialysate serotonin levels in distinct brain regions of the awake rat by modafinil: Possible relevance for wakefulness and depression. *J Neurosci Res*. 2002;68(1):107–112. doi:10.1002/jnr.10196
88. Wang SM, Han C, Lee SJ, et al. Modafinil for the treatment of attention-deficit/hyperactivity disorder: A meta-analysis. *J Psychiatr Res*. 2017;84:292–300. doi:10.1016/j.jpsychires.2016.09.034
89. NPR. FDA committee rejects ADHD use for modafinil. March 24, 2006. https://www.npr.org/2006/03/24/5298885/fda-committee-rejects-adhd-use-for-modafinil
90. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. *J Clin Psychiatry*. 2006;67(4):554–566. doi:10.4088/jcp.v67n0406
91. Esposito M, Cocimano G, Ministrieri F, et al. Smart drugs and neuroenhancement: What do we know? *Front Biosci (Landmark Ed)*. 2021;26(8):347–359. doi:10.52586/4948
92. Loland CJ, Mereu M, Okunola OM, et al. R-modafinil (armodafinil): A unique dopamine uptake inhibitor and potential medication for psychostimulant abuse. *Biol Psychiatry*. 2012;72(5):405–413. doi:10.1016/j.biopsych.2012.03.022
93. Wilens TE, Klint T, Adler L, et al. A randomized controlled trial of a novel mixed monoamine reuptake inhibitor in adults with ADHD. *Behav Brain Funct*. 2008;4:24. doi:10.1186/1744-9081-4-24
94. NS 2359. Adis Inight. Accessed June 11, 2024. https://adisinsight.springer.com/drugs/800010231
95. Heal DJ, Smith SL, Findling RL. ADHD: current and future therapeutics. *Curr Top Behav Neurosci*. 2012;9:361–390. doi:10.1007/7854_2011_125
96. Sepracor Inc. Annual report. December 31, 2008. https://www.sec.gov/Archives/edgar/data/877357/000104746909001949/a2190020z10-k.htm
97. Supplementary Financial Data for the Third Quarter of the Year Ending March 31, 2010 Dainippon Sumitomo Pharma Co., Ltd. https://www.sumitomo-pharma.com/ir/library/financial_results_summary/assets/pdf/ebr20100203_4.pdf
98. Sramek JJ, Hardy LW, Bieck P, et al. Exploratory biomarker study of the triple reuptake inhibitor SEP-432 compared to the dual reuptake inhibitor duloxetine in healthy normal subjects. *CNS Neurosci Ther*. 2016;22(5):404–412. doi:10.1111/cns.12513
99. Supplementary Financial Data for the Second Quarter of the Year Ending March 31, 2013. Accessed July 17, 2024. https://www.sumitomo-pharma.com/ir/library/financial_results_summary/assets/pdf/ebr20121031_4.pdf
100. Shire Pharmaceuticals Group PLC. Annual report. December 31, 2002. http://getfilings.com/o0000950162-03-000641.html
101. Heal DJ, Gosden J, Smith SL. New drugs to treat ADHD: Opportunities and challenges in research and development. *Curr Top Behav Neurosci*. 2022;57:79–126. doi:10.1007/7854_2022_332
102. EFFEXOR XR® (venlafaxine extended-release) capsules [prescribing information]. Revised 1/2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020699s107lbl.pdf.
103. Ghanizadeh A, Freeman RD, Berk M. Efficacy and adverse effects of venlafaxine in children and adolescents with ADHD: A systematic review of non-controlled and controlled trials. *Rev Recent Clin Trials*. 2013;8(1):2–8. doi:10.2174/1574887111308010002
104. Findling RL, Schwartz MA, Flannery DJ, Manos MJ. Venlafaxine in adults with attention-deficit/hyperactivity disorder: An open clinical trial. *J Clin Psychiatry*. 1996;57(5):184–189.
105. Amiri S, Farhang S, Ghoreishizadeh MA, Malek A, Mohammadzadeh S. Double-blind controlled trial of venlafaxine for treatment of adults with attention deficit/hyperactivity disorder. *Hum Psychopharmacol*. 2012;27(1):76–81. doi:10.1002/hup.1274
106. Ninan PT. Use of venlafaxine in other psychiatric disorders. *Depress Anxiety*. 2000;12(Suppl 1):90–4. doi:10.1002/1520-6394(2000)12:1+<90::AID-DA13>3.0.CO;2-B
107. Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C, Investigators ATTS. Randomized clinical study of a histamine H3 receptor antagonist for the treatment of adults with attention-deficit hyperactivity disorder. *CNS Drugs*. 2012;26(5):421–434. doi:10.2165/11631990-000000000-00000
108. Herring WJ, Wilens TE, Adler LA, et al. Randomized controlled study of the histamine H3 inverse agonist MK-0249 in adult attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2012;73(7):e891–e898. doi:10.4088/JCP.11m07178
109. Herring WJ, Liu K, Hutzelmann J, et al. Alertness and psychomotor performance effects of the histamine-3 inverse agonist MK-0249 in obstructive sleep apnea patients on continuous positive airway pressure therapy with excessive daytime sleepiness: A randomized adaptive crossover study. *Sleep Med*. 2013;14(10):955–963. doi:10.1016/j.sleep.2013.04.010
110. Egan M, Yaari R, Liu L, et al. Pilot randomized controlled study of a histamine receptor inverse agonist in the symptomatic treatment of AD. *Curr Alzheimer Res*. 2012;9(4):481–490. doi:10.2174/156720512800492530

111. Riley TB, Overton PG. Enhancing the efficacy of 5-HT uptake inhibitors in the treatment of attention deficit hyperactivity disorder. *Med Hypotheses*. 2019;133:109407. doi:10.1016/j.mehy.2019.109407
112. ADDERALL® CII (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate and amphetamine sulfate tablets) [prescribing information]. Revised 1/2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/011522s043lbl.pdf
113. EVEKEO® (amphetamine sulfate tablets, USP) [prescribing information]. Revised 4/2019. https://www.evekeo.com/pdfs/evekeo-pi.pdf
114. ZENZEDI® (dextroamphetamine sulfate tablets, USP) [prescribing information]. Revised 2/2017. https://zenzedi.com/docs/PIandMedicationGuide.pdf
115. Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *J Neurochem*. 1997;68(5):2032–2037. doi:10.1046/j.1471-4159.1997.68052032.x
116. Jones S, Kauer JA. Amphetamine depresses excitatory synaptic transmission via serotonin receptors in the ventral tegmental area. *J Neurosci*. 1999;19(22):9780–9787. doi:10.1523/JNEUROSCI.19-22-09780.1999
117. Berman SM, Kuczenski R, McCracken JT, London ED. Potential adverse effects of amphetamine treatment on brain and behavior: a review. *Mol Psychiatry*. 2009;14(2):123–142. doi:10.1038/mp.2008.90
118. Torres-Acosta N, O'Keefe JH, O'Keefe CL, Lavie CJ. Cardiovascular effects of ADHD therapies: JACC review topic of the week. *J Am Coll Cardiol*. 2020;76(7):858–866. doi:10.1016/j.jacc.2020.05.081
119. Castells X, Blanco-Silvente L, Cunill R. Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults. *Cochrane Database Syst Rev*. 2018;8(8):CD007813. doi:10.1002/14651858.CD007813.pub3
120. CONCERTA® (methylphenidate HCl) Extended-Release Tablets CII [prescribing information]. Revised 10/2023. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/CONCERTA-pi.pdf
121. RITALIN® hydrochloride (methylphenidate hydrochloride USP) tablets and sustained-release tablets [prescribing information]. Revised 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/010187s077lbl.pdf
122. Gatley SJ, Pan D, Chen R, Chaturvedi G, Ding YS. Affinities of methylphenidate derivatives for dopamine, norepinephrine and serotonin transporters. *Life Sci*. 1996;58(12):231–239. doi:10.1016/0024-3205(96)00052-5
123. Markowitz JS, DeVane CL, Ramamoorthy S, Zhu HJ. The psychostimulant d-threo-(R,R)-methylphenidate binds as an agonist to the 5HT(1A) receptor. *Pharmazie*. 2009;64(2):123–125.
124. Berger A. Ritalin may influence serotonin balance in hyperactive children. *BMJ*. 1999;318(7178):212B. doi:10.1136/bmj.318.7178.212b
125. Gainetdinov RR, Wetsel WC, Jones SR, Levin ED, Jaber M, Caron MG. Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. *Science*. 1999;283(5400):397–401. doi:10.1126/science.283.5400.397
126. Molina-Carballo A, Naranjo-Gomez A, Uberos J, et al. Methylphenidate effects on blood serotonin and melatonin levels may help to synchronise biological rhythms in children with ADHD. *J Psychiatr Res*. 2013;47(3):377–383. doi:10.1016/j.jpsychires.2012.09.020
127. Ching C, Eslick GD, Poulton AS. Evaluation of methylphenidate safety and maximum-dose titration rationale in attention-deficit/hyperactivity disorder: A meta-analysis. *JAMA Pediatr*. 2019;173(7):630–639. doi:10.1001/jamapediatrics.2019.0905
128. Nemoda Z, Angyal N, Tarnok Z, Gadoros J, Sasvari-Szekely M. Carboxylesterase 1 gene polymorphism and methylphenidate response in ADHD. *Neuropharmacology*. 2009;57(7–8):731–733. doi:10.1016/j.neuropharm.2009.08.014
129. Gajria K, Lu M, Sikirica V, et al. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder—a systematic literature review. *Neuropsychiatr Dis Treat*. 2014;10:1543–1569. doi:10.2147/NDT.S65721
130. STRATTERA® (atomoxetine) capsules, for oral use [prescribing information]. Revised 1/2022. https://pi.lilly.com/us/strattera-pi.pdf
131. Ding YS, Naganawa M, Gallezot JD, et al. Clinical doses of atomoxetine significantly occupy both norepinephrine and serotonin transports: Implications on treatment of depression and ADHD. *Neuroimage*. 2014;86:164–171. doi:10.1016/j.neuroimage.2013.08.001
132. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: Two randomized, placebo-controlled studies. *Biol Psychiatry*. 2003;53(2):112–120. doi:10.1016/s0006-3223(02)01671-2
133. Purper-Ouakil D, Fourneret P, Wohl M, Reneric JP. Atomoxetine: A new treatment for attention deficit/hyperactivity disorder (ADHD) in children and adolescents. *Encephale*. 2005;31(3):337–348. L'atomoxetine: un nouveau traitement du trouble deficitaire de l'attention/hyperactivite de l'enfant et de l'adolescent. doi:10.1016/s0013-7006(05)82399-1

134. QELBREE® (viloxazine extended-release capsules), for oral use [prescribing information]. Revised 4/2022. https://www.supernus.com/sites/default/files/Qelbree-Prescribing-Info.pdf
135. Yu C, Garcia-Olivares J, Candler S, Schwabe S, Maletic V. New insights into the mechanism of action of viloxazine: Serotonin and norepinephrine modulating properties. *J Exp Pharmacol*. 2020;12: 285–300. doi:10.2147/JEP.S256586
136. Bubar MJ, Stutz SJ, Cunningham KA. 5-HT_{2C} receptors localize to dopamine and GABA neurons in the rat mesoaccumbens pathway. *PLoS One*. 2011;6(6):e20508. doi:10.1371/journal.pone.0020508
137. De Deurwaerdere P, Chagraoui A, Di Giovanni G. Serotonin/dopamine interaction: Electrophysiological and neurochemical evidence. *Prog Brain Res*. 2021;261:161–264. doi:10.1016/bs.pbr.2021.02.001
138. Garcia-Olivares J, Yegla B, Earnest J, Yu C, Rubin J. P175. Unraveling the mechanism of action of viloxazine ER in ADHD. Poster presented at the American College of Neuropsychopharmacology 62nd Annual Meeting (Dec 03–06, 2023; Tampa, Florida). *Neuropsychopharmacol*. 2023; 48(Suppl 1):166.
139. Robinson ES, Dalley JW, Theobald DE, et al. Opposing roles for 5-HT2A and 5-HT2C receptors in the nucleus accumbens on inhibitory response control in the 5-choice serial reaction time task. *Neuropsychopharmacology*. 2008;33(10):2398–2406. doi:10.1038/sj.npp.1301636
140. Pisansky MT, Lefevre EM, Retzlaff CL, Trieu BH, Leipold DW, Rothwell PE. Nucleus accumbens fast-spiking interneurons constrain impulsive action. *Biol Psychiatry*. 2019;86(11):836–847. doi:10.1016/j.biopsych.2019.07.002
141. VALDOXAN (agomelatine) 25 mg film-coated tablets [summary of product characteristics]. Revised 12/2018. https://www.ema.europa.eu/en/documents/product-information/valdoxan-epar-product-information_en.pdf
142. Millan MJ, Gobert A, Lejeune F, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J Pharmacol Exp Ther*. 2003;306(3):954–964. doi:10.1124/jpet.103.051797
143. Savino R, Polito AN, Marsala G, et al. Agomelatine: A potential multitarget compound for neurodevelopmental disorders. *Brain Sci*. 2023;13(5):734. doi:10.3390/brainsci13050734
144. Niederhofer H. Agomelatine treatment with adolescents with ADHD. *J Atten Disord*. 2012;16(6): 530–2. doi:10.1177/1087054711423631
145. Salardini E, Zeinoddini A, Kohi A, et al. Agomelatine as a treatment for attention-deficit/hyperactivity disorder in children and adolescents: A double-blind, randomized clinical trial. *J Child Adolesc Psychopharmacol*. 2016;26(6):513–519. doi:10.1089/cap.2016.0024
146. NORPRAMIN® (desipramine hydrochloride tablets) [prescribing information]. Revised 6/2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/014399s069lbl.pdf.
147. Chung B, Suzuki AR, McGough JJ. New drugs for treatment of attention-deficit/hyperactivity disorder. *Expert Opin Emerg Drugs*. 2002;7(2):269–276. doi:10.1517/14728214.7.2.269
148. Maan JS, Rosani A, Saadabadi A. Desipramine. *StatPearls*. 2024.
149. Cowen PJ, Geaney DP, Schachter M, Green AR, Elliott JM. Desipramine treatment in normal subjects. Effects on neuroendocrine responses to tryptophan and on platelet serotonin (5-HT)-related receptors. *Arch Gen Psychiatry*. 1986;43(1):61–67. doi:10.1001/archpsyc.1986.01800010063008
150. Ghanizadeh A. A systematic review of the efficacy and safety of desipramine for treating ADHD. *Curr Drug Saf*. 2013;8(3):169–174. doi:10.2174/15748863113089990029
151. Imipramine hydrochloride tablet [prescribing information]. Revised 10/2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/040903lbl.pdf
152. Budur K, Mathews M, Adetunji B, Mathews M, Mahmud J. Non-stimulant treatment for attention deficit hyperactivity disorder. *Psychiatry (Edgmont)*. 2005;2(7):44–48.
153. Fayez R, Gupta V. Imipramine. *StatPearls*. 2024. https://www.ncbi.nlm.nih.gov/books/NBK557656/.
154. Bijak M, Tokarski K, Czyrak A, Mackowiak M, Wedzony K. Imipramine increases the 5-HT1A receptor-mediated inhibition of hippocampal neurons without changing the 5-HT1A receptor binding. *Eur J Pharmacol*. 1996;305(1–3):79–85. doi:10.1016/0014-2999(96)00151-3
155. VRAYLAR® (cariprazine) capsules, for oral use [prescribing information]. Revised 2/2024. https://www.rxabbvie.com/pdf/vraylar_pi.pdf
156. Otsuka. Press release. Otsuka pharmaceutical announces positive topline results from two pivotal phase 3 trials of centanafadine as a treatment for adolescents and children with attention-deficit/hyperactivity disorder (ADHD). October 27, 2023. https://www.otsuka-us.com/news/otsuka-pharmaceutical-announces-positive-topline-results-two-pivotal-phase-3-trials#:~:text=Phase%203%20Program-,Centanafadine%20is%20a%20first%2Din%2Dclass%20norepinephrine%2C%20dopamine%2C,children%2C%20adolescents%2C%20and%20adults

157. Wigal SB, Wigal T, Hobart M, et al. Safety and efficacy of centanafadine sustained-release in adults with attention-deficit hyperactivity disorder: Results of phase 2 studies. *Neuropsychiatr Dis Treat*. 2020;16:1411–1426. doi:10.2147/NDT.S242084
158. Adler LA, Adams J, Madera-McDonough J, et al. Efficacy, safety, and tolerability of centanafadine sustained-release tablets in adults with attention-deficit/hyperactivity disorder: Results of 2 phase 3, randomized, double-blind, multicenter, placebo-controlled trials. *J Clin Psychopharmacol*. 2022;42(5):429–439. doi:10.1097/JCP.0000000000001575
159. SUNOSI (solriamfetol) tablets, for oral use [prescribing information]. Revised 3/2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211230s000lbl.pdf
160. Gursahani H, Jolas T, Martin M, et al. Preclinical pharmacology of solriamfetol: Potential mechanisms for wake promotion (P4-13.005). *Neurology*. 2023;100(suppl 2) doi:10.1212/WNL.0000000000204178
161. Revel FG, Moreau JL, Gainetdinov RR, et al. TAAR1 activation modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypoglutamatergic activity. *Proc Natl Acad Sci U S A*. 2011;108(20):8485–8490. doi:10.1073/pnas.1103029108
162. Underhill S, Amara S. MDMA and TAAR1-mediated RhoA activation in serotonin neurons. *FASEB J*. 2020;34(S1):1–1. doi:10.1096/fasebj.2020.34.s1.05856
163. Zhukov IS, Karpova IV, Krotova NA, et al. Enhanced aggression, reduced self-grooming behavior and altered 5-HT regulation in the frontal cortex in mice lacking trace amine-associated receptor 1 (TAAR1). *Int J Mol Sci*. 2022;23(22):14066. doi:10.3390/ijms232214066
164. Surman CBH, Walsh DM, Horick N, DiSalvo M, Vater CH, Kaufman D. Solriamfetol for attention-deficit/hyperactivity disorder in adults: A double-blind placebo-controlled pilot study. *J Clin Psychiatry*. 2023;84(6):23m14934. doi:10.4088/JCP.23m14934
165. Ayano G, Tsegay L, Gizachew Y, et al. Prevalence of attention deficit hyperactivity disorder in adults: Umbrella review of evidence generated across the globe. *Psychiatry Res*. 2023;328:115449. doi:10.1016/j.psychres.2023.115449
166. Cutler AJ, Mattingly GW, Jain R, O'Neal W. Current and future nonstimulants in the treatment of pediatric ADHD: Monoamine reuptake inhibitors, receptor modulators, and multimodal agents. *CNS Spectr*. 2022;27(2):199–207. doi:10.1017/S1092852920001984

References for Table 1. Interventions for ADHD with a Serotonergic Mechanism of Action That Failed in the ADHD Indication

1. Rammes G, Rupprecht R, Ferrari U, Zieglgansberger W, Parsons CG. The N-methyl-D-aspartate receptor channel blockers memantine, MRZ 2/579 and other amino-alkyl-cyclohexanes antagonise 5-HT(3) receptor currents in cultured HEK-293 and N1E-115 cell systems in a non-competitive manner. *Neurosci Lett*. 2001;306(1–2):81–84. doi:10.1016/s0304-3940(01)01872-9
2. Lemmer B. Effects of amantadine and amphetamine on serotonin uptake and release by human blood platelets. *Eur J Pharmacol*. 1973;21(2):183–188. doi:10.1016/0014-2999(73)90224-0
3. Wesemann W, Dette-Wildenhahn G, Fellehner H. In vitro studies on the possible effects of 1-aminoadamantanes on the serotonergic system in M. Parkinson. *J Neural Transm*. 1979;44(4):263–285. doi:10.1007/bf01250322
4. GOCOVRI™ (amantadine) extended release capsules, for oral use [prescribing information]. Revised 8/2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208944lbl.pdf
5. Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C, Investigators ATTS. Randomized clinical study of a histamine H3 receptor antagonist for the treatment of adults with attention-deficit hyperactivity disorder. *CNS Drugs*. 2012;26(5):421–434. doi:10.2165/11631990-000000000-00000
6. REXULTI® (brexpiprazole) tablets, for oral use [prescribing information]. Revised 5/2023. https://www.otsuka-us.com/sites/g/files/qhldwo8366/files/media/static/Rexulti-PI.pdf
7. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *J Pharmacol Exp Ther*. 2014;350(3):589–604. doi:10.1124/jpet.114.213793
8. Psychoactive Drug Screening Program. PDSP Ki Database. 2024. https://pdsp.unc.edu/databases/kidb.php
9. Schreiber R, Campbell U, Quinton MS, Hardy LW, Fang QK, Lew R. In vitro and in vivo pharmacological characterization of dasotraline, a dual dopamine and norepinephrine transporter inhibitor in vivo. *Biomed Pharmacother*. 2022;153:113359. doi:10.1016/j.biopha.2022.113359

10. FDA rejects dasotraline NDA for ADHD, calling for more data. ThePharmaLetter. Accessed June 7, 2024. https://www.thepharmaletter.com/article/fda-rejects-dasotraline-nda-for-adhd-calling-for-more-data
11. Sunovion. Sunovion discontinues dasotraline program. May 13 2020. https://news.sunovion.com/press-releases/press-releases-details/2020/Sunovion-Discontinues-Dasotraline-Program/default.aspx
12. Han M, Song C, Jeong N, Hahn HG. Exploration of 3-Aminoazetidines as Triple Reuptake Inhibitors by Bioisosteric Modification of 3-α-Oxyazetidine. *ACS Med Chem Lett*. 2014;5(9):999–1004. doi:10.1021/ml500187a
13. Fish PV, Fray MJ, Stobie A, Wakenhut F, Whitlock GA. N-Benzyl-N-(tetrahydro-2H-pyran-4-yl) pyrrolidin-3-amines as selective dual serotonin/noradrenaline reuptake inhibitors. *Bioorg Med Chem Lett*. 2007;17(7):2022–2025. doi:10.1016/j.bmcl.2007.01.020
14. Sabatucci JP, Mahaney PE, Leiter J, et al. Heterocyclic cycloalkanol ethylamines as norepinephrine reuptake inhibitors. *Bioorg Med Chem Lett*. 2010;20(9):2809–2812. doi:10.1016/j.bmcl.2010.03.059
15. McComas CC, Vu AT, Mahaney PE, et al. Synthesis and activity of 1-(3-amino-1-phenylpropyl) indolin-2-ones: a new class of selective norepinephrine reuptake inhibitors. *Bioorg Med Chem Lett*. 2008;18(18):4929–4931. doi:10.1016/j.bmcl.2008.08.060
16. Vu AT, Cohn ST, Terefenko EA, et al. 3-(Arylamino)-3-phenylpropan-2-olamines as a new series of dual norepinephrine and serotonin reuptake inhibitors. *Bioorg Med Chem Lett*. 2009;19(9):2464–2467. doi:10.1016/j.bmcl.2009.03.054
17. Dyck B, Tamiya J, Jovic F, et al. Characterization of thien-2-yl 1S,2R-milnacipran analogues as potent norepinephrine/serotonin transporter inhibitors for the treatment of neuropathic pain. *J Med Chem*. 2008;51(22):7265–7272. doi:10.1021/jm8009537
18. Wong DT, Bymaster FP, Mayle DA, Reid LR, Krushinski JH, Robertson DW. LY248686, a new inhibitor of serotonin and norepinephrine uptake. *Neuropsychopharmacology*. 1993;8(1):23–33. doi:10.1038/npp.1993.4
19. Lucas MC, Carter DS, Cai HY, et al. Novel, achiral aminoheterocycles as selective monoamine reuptake inhibitors. *Bioorg Med Chem Lett*. 2009;19(16):4630–4633. doi:10.1016/j.bmcl.2009.06.076
20. Vaishnavi SN, Nemeroff CB, Plott SJ, Rao SG, Kranzler J, Owens MJ. Milnacipran: A comparative analysis of human monoamine uptake and transporter binding affinity. *Biol Psychiatry*. 2004;55(3):320–322. doi:10.1016/j.biopsych.2003.07.006
21. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology*. 2001;25(6):871–880. doi:10.1016/s0893-133x(01)00298-6
22. Kuo F, Gillespie TA, Kulanthaivel P, et al. Synthesis and biological activity of some known and putative duloxetine metabolites. *Bioorg Med Chem Lett*. 2004;14(13):3481–3486. doi:10.1016/j.bmcl.2004.04.066
23. Fish PV, Deur C, Gan X, et al. Design and synthesis of morpholine derivatives. SAR for dual serotonin & noradrenaline reuptake inhibition. *Bioorg Med Chem Lett*. 2008;18(8):2562–2566. doi:10.1016/j.bmcl.2008.03.050
24. Auclair AL, Martel JC, Assié MB, et al. Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety. *Neuropharmacology*. 2013;70:338–347. doi:10.1016/j.neuropharm.2013.02.024
25. Béïque JC, Lavoie N, de Montigny C, Debonnel G. Affinities of venlafaxine and various reuptake inhibitors for the serotonin and norepinephrine transporters. *Eur J Pharmacol*. 1998;349(1):129–132. doi:10.1016/s0014-2999(98)00241-6
26. Manning JR, Sexton T, Childers SR, Davies HM. 1-Naphthyl and 4-indolyl arylalkylamines as selective monoamine reuptake inhibitors. *Bioorg Med Chem Lett*. 2009;19(1):58–61. doi:10.1016/j.bmcl.2008.11.022
27. CYMBALTA (duloxetine delayed-release capsules), for oral use [prescribing information]. Revised 8/2023. https://pi.lilly.com/us/cymbalta-pi.pdf
28. Miller DK, Crooks PA, Zheng G, Grinevich VP, Norrholm SD, Dwoskin LP. Lobeline analogs with enhanced affinity and selectivity for plasmalemma and vesicular monoamine transporters. *J Pharmacol Exp Ther*. 2004;310(3):1035–1045. doi:10.1124/jpet.104.068098
29. Zheng G, Horton DB, Deaciuc AG, Dwoskin LP, Crooks PA. Des-keto lobeline analogs with increased potency and selectivity at dopamine and serotonin transporters. *Bioorg Med Chem Lett*. 2006;16(19):5018–5021. doi:10.1016/j.bmcl.2006.07.070
30. Hojahmat M, Horton DB, Norrholm SD, et al. Lobeline esters as novel ligands for neuronal nicotinic acetylcholine receptors and neurotransmitter transporters. *Bioorg Med Chem*. 2010;18(2):640–649. doi:10.1016/j.bmc.2009.12.002

31. Provencher BA, Eshleman AJ, Johnson RA, et al. Synthesis and Discovery of Arylpiperidinylquinazolines: New Inhibitors of the Vesicular Monoamine Transporter. *J Med Chem*. 2018;61(20):9121–9131. doi:10.1021/acs.jmedchem.8b00542
32. Houlihan WJ, Boja JW, Parrino VA, Kopajtic TA, Kuhar MJ. Halogenated mazindol analogs as potential inhibitors of the cocaine binding site at the dopamine transporter. *J Med Chem*. 1996;39(25): 4935–4941. doi:10.1021/jm960288w
33. Barker EL, Perlman MA, Adkins EM, et al. High affinity recognition of serotonin transporter antagonists defined by species-scanning mutagenesis. An aromatic residue in transmembrane domain I dictates species-selective recognition of citalopram and mazindol. *J Biol Chem*. 1998;273(31): 19459–19468. doi:10.1074/jbc.273.31.19459
34. Kung MP, Essman WD, Frederick D, et al. IPT: a novel iodinated ligand for the CNS dopamine transporter. *Synapse*. 1995;20(4):316–324. doi:10.1002/syn.890200405
35. Rothman RB, Baumann MH, Dersch CM, et al. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*. 2001;39(1):32–41. doi:10.1002/1098-2396(20010101)39:1<32::Aid-syn5>3.0.Co;2-3
36. Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol*. 1997;340(2–3):249–258. doi:10.1016/s0014-2999(97)01393-9
37. SANOREX® (mazindol) 1 and 2 mg tablets [product monograph]. Revised 7/2015. https://pdf.hres.ca/dpd_pm/00031211.PDF
38. NLS Pharmaceutics to Proceed with Phase 3 Clinical Program (AMAZE) for Mazindol ER for the Treatment of Narcolepsy Following FDA Review and IRB Approval of the Full Study Protocol. Accessed June 7, 2024. https://www.sec.gov/Archives/edgar/data/1783036/000121390023053971/ea181301ex99-3_nlspharma.htm
39. NAMENDA® (memantine hydrochloride) tablets, for oral use [prescribing information]. Revised 11/2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021487s025lbl.pdf
40. Herring WJ, Wilens TE, Adler LA, et al. Randomized controlled study of the histamine H3 inverse agonist MK-0249 in adult attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2012;73(7):e891–e898. doi:10.4088/JCP.11m07178
41. Kalaba P, Ilić M, Aher NY, et al. Structure-activity relationships of novel thiazole-based modafinil analogues acting at monoamine transporters. *J Med Chem*. 2020;63(1):391–417. doi:10.1021/acs.jmedchem.9b01938
42. Madras BK, Xie Z, Lin Z, et al. Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. *J Pharmacol Exp Ther*. 2006;319(2):561–569. doi:10.1124/jpet.106.106583
43. Louvet P, Schweizer D, Gourdel ME, et al. Wake-promoting agents: search for next generation modafinil: part IV. *Eur J Med Chem*. 2012;54:949–951. doi:10.1016/j.ejmech.2012.05.038
44. Slack RD, Ku TC, Cao J, et al. Structure-activity relationships for a series of (Bis(4-fluorophenyl) methyl)sulfinyl alkyl alicyclic amines at the dopamine transporter: Functionalizing the terminal nitrogen affects affinity, selectivity, and metabolic stability. *J Med Chem*. 12 2020;63(5):2343–2357. doi:10.1021/acs.jmedchem.9b01188
45. PROVIGIL® (modafinil) tablets, for oral use [prescribing information]. Revised 1/2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf
46. NPR. FDA committee rejects ADHD use for modafinil. March 24, 2006. https://www.npr.org/2006/03/24/5298885/fda-committee-rejects-adhd-use-for-modafinil
47. Yu C, Gopalakrishnan G. In vitro pharmacological characterization of SPN-810M (molindone). *J Exp Pharmacol*. 2018;10:65–73. doi:10.2147/JEP.S180777
48. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology*. 2003;28(3):519–526. doi:10.1038/sj.npp.1300027
49. Roth BL, Craigo SC, Choudhary MS, et al. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. *J Pharmacol Exp Ther*. 1994;268(3):1403–1410.
50. Seeman P, Tallerico T. Antipsychotic drugs which elicit little or no parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. *Mol Psychiatry*. 1998;3(2):123–134. doi:10.1038/sj.mp.4000336
51. Glennon RA. Higher-end serotonin receptors: 5-HT(5), 5-HT(6), and 5-HT(7). *J Med Chem*. 2003;46(14):2795–2812. doi:10.1021/jm030030n
52. Supernus Pharma's SPN-810 trial did not meet primary endpoint. Seeking Alpa. Accessed June 7, 2024. https://seekingalpha.com/news/3545617-supernus-pharmas-spnminus-810-trial-not-meet-primary-endpoint

53. Subbaiah MAM. Triple reuptake inhibitors as potential therapeutics for depression and other disorders: Design paradigm and developmental challenges. *J Med Chem*. 22 2018;61(6):2133–2165. doi:10.1021/acs.jmedchem.6b01827
54. Tu G, Fu T, Yang F, et al. Understanding the polypharmacological profiles of triple reuptake inhibitors by molecular simulation. *ACS Chem Neurosci*. 2021;12(11):2013–2026. doi:10.1021/acschemneuro.1c00127
55. NS 2359. AdisInsight. Accessed June 7, 2024. https://adisinsight.springer.com/drugs/800010231
56. Huot P, Fox SH, Brotchie JM. Monoamine reuptake inhibitors in Parkinson's disease. *Parkinsons Dis*. 2015;2015:609428. doi:10.1155/2015/609428
57. Aggarwal S, Mortensen OV. Discovery and development of monoamine transporter ligands. *Adv Neurobiol*. 2023;30:101–129. doi:10.1007/978-3-031-21054-9_4
58. Franz AK, Wilson SO. Organosilicon molecules with medicinal applications. *J Med Chem*. 2013;56(2):388–405. doi:10.1021/jm3010114
59. EFFEXOR XR® (venlafaxine extended-release) capsules [prescribing information]. Revised 1/2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020699s107lbl.pdf
60. PRISTIQ® (desvenlafaxine) Prescribing Information. Pfizer.; 2023. https://labeling.pfizer.com/showlabeling.aspx?id=497
61. TRINTELLIX (vortioxetine) tablets, for oral use [prescribing information]. Revised 8/2023. https://content.takeda.com/?contenttype=PI&product=TRI&language=ENG&country=GBL&documentnumber=1
62. Bang-Andersen B, Ruhland T, Jørgensen M, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl) phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. *J Med Chem*. May 12 2011;54(9):3206–3221. doi:10.1021/jm101459g
63. Gu ZS, Xiao Y, Zhang QW, Li JQ. Synthesis and antidepressant activity of a series of arylalkanol and aralkyl piperazine derivatives targeting SSRI/5-HT(1A)/5-HT(7). *Bioorg Med Chem Lett*. 2017;27(24):5420–5423. doi:10.1016/j.bmcl.2017.11.007
64. Biederman J, Lindsten A, Sluth LB, et al. Vortioxetine for attention deficit hyperactivity disorder in adults: A randomized, double-blind, placebo-controlled, proof-of-concept study. *J Psychopharmacol*. 2019;33(4):511–521. doi:10.1177/0269881119832538

Supplementary Material

SUPPLEMENTARY TABLE 1

Initial Interventions Identified for the Treatment of ADHD

GENERIC NAME(S)	BRAND NAME(S)
2-pyridylacetic acid	–
Agomelatine	Valdoxan, Thymanax
Amantadine	Gocovri, Osmolex ER, Symmetrel
Amphetamine, dextroamphetamine sulfate, dextroamphetamine-amphetamine	Adderall, Adderall XR, Mydayis, Adzenys XR-ODT, Evekeo, Dezedrine, Zenzedi, Xelstrym
Ampreloxetine, TD-9855	–
AR08	–
Atomoxetine	Strattera
AZD1446	–
AZD3480	–
Bavisant, JNJ-31001074	–
Betahistine HCL	Serc
BLI-1008	–
BP22042013	–
Bradanicline, TC-5619	–
Brexpiprazole	Rexulti
Bupropion	Wellbutrin XL, Wellbutrin SR, Aplenzin, Forfivo XL, Zyban
Cariprazine	Vraylar, Reagila
Centanafadine	–
Clonidine HCl	Clonicel
CX717	–
Dasotraline, SEP-225289	–
Desipramine	Norpramin
Dexmethylphenidate	Focalin
Dimethoxybenzylidene anabaseine, GTS-21, DMXBA	–
Divalproex	Depakote
Duloxetine	Cymbalta
Edivoxetine, LY2216684	n/a
Eszopiclone	Lunesta
Fasoracetam, AEVI-001, LAM 105, MDGN-001, NFC 1, NS 105	–
Galantamine	Razadyne, Reminyl
GlyTI-M	–
Guanfacine HCl, Guanfacine ER, SPD503, TAK-503	Tenex
Imipramine	Tofranil
Lipirinen	Vayarin
Lisdexamfetamine, SPD489, NRP104	Vyvanse
L-methylfolate, 5-MTHF	–
Lobeline	–

(Continued)

SUPPLEMENTARY TABLE 1 ***(Continued)***

Initial Interventions Identified for the Treatment of ADHD

GENERIC NAME(S)	BRAND NAME(S)
L-threonic acid magnesium salt (L-TAMS), MMFS302, MMFS202	–
Mazindol CR	Sanorex, Mazanor
Memantine	Namenda
Metadoxine	Abrixone
Methamphetamine HCl	Desoxyn
Methylphenidate	Ritalin, Aptensio, Concerta, Contempla (NT0102), Daytrana, Jornay PM, Metadate, Quillichew, Quillivant, Rilatine, Medikinet, Adaphen, Addwize, Inspiral, Methmild, Artige, Attenta, Cognil, Equasym, Foquest, Methylin, Penid, Phenida, Prohiper, Tradea, Methylin, Adhansia
MK-0249	–
MK-0929	–
MK-8777, Org 26576, SCH 900777	–
Modafinil	Provigil
Molindone, molindone XR, SPN-810, SPN-810M, AFX-2201, EN-1733A	Moban, Zalvari
Nabiximols	Sativex
Naltrexone	Revia, Depade, Trexan
ND0801	–
Nortriptyline HCl	Pamelor
NS2359, GSK372475	–
Oxytocin nasal spray	–
PDC-1421	–
PF-03654746	–
Pozanicline, ABT-089	–
Reboxetine	Edronax
SEP-228432	–
Serdexmethylphenidate and dexmethylphenidate	Azstarys
Sofinicline, ABT-894	–
Solriamfetol	–
SPD473/BTS 74398	–
TAK-137	–
Tipepidine, tipepidine hibenzate (in Japan)	Asverin, Antupex, Asvelik, Asvex, Bitiodin, Cofdenin A, Hustel, Nodal, Sotal
Tolcapone	Tasmar
Vafidemstat, ORY-2001	–
Varenicline	Chantix
Venlafaxine	Effexor, Vensir, Vencarm, Venlalix, Venlablue
Viloxazine ER, SPN-812	Qelbree
Vortioxetine	Trintellix, Brintellix
Zolpidem	Edluar, Ambien CR, Ambien, Intermezzo, Zolpimist

ADHD, attention-deficit/hyperactivity disorder.