New Drugs to Treat ADHD: Opportunities and Challenges in Research and Development

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Contents

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Abstract Since the landmark MTA (Multimodal Treatment of ADHD) trial unequivocally demonstrated the efficacy of methylphenidate, catecholaminergic drugs, especially stimulants, have been the therapeutic mainstay in treatment of Attention-Deficit Hyperactivity Disorder (ADHD). We review the new drugs which have entered the ADHD formulary. The lessons learned from drug-candidates that have succeeded in clinical trials together with those that have not have also been considered. What emerges confirms and consolidates the hypothesis that clinically effective ADHD drugs indirectly or directly increase catecholaminergic neurotransmission in the prefrontal cortex (PFC). Attempts to enhance catecholaminergic signalling through modulatory neurotransmitter systems or cognitive-enhancing drugs have all failed. New drugs approved for ADHD are catecholaminergic reuptake inhibitors and releasing agents, or selective noradrenaline reuptake inhibitors. Triple reuptake inhibitors with preferential effects on dopamine have not been successful. The substantial number of failures probably accounts for a continued focus on developing novel catecholaminergic and noradrenergic drugs, and a dearth of drug-candidates with novel mechanisms entering clinical development. However, substantial improvements in ADHD pharmacotherapy have been achieved by the almost exclusive use of once-daily medications and prodrugs, e.g. lisdexamfetamine and Azstarys®, which improve compliance, deliver greater efficacy and reduce risks for diversion and abuse.

Keywords Attention-deficit hyperactivity disorder · ADHD drugs · Treatments

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ADHD RS	ADHD Research Scale
AE	Adverse event
AISRS	Adult ADHD Investigator Symptom Rating Scale
BED	Binge-eating disorder
BIS-11	Barratt Impulsiveness Scale, Version 11
BRIEF	Behaviour Rating Inventory of Executive Function
C-II; CIV	Schedule 2; Schedule 4 controlled drug
CGI-S	Clinical Global Impressions Scale
CNS	Central nervous system
DA	Dopamine
DAT	Dopamine reuptake transporter
DBRCT	Double-blind, randomized clinical trials
EDE-Q7	Eating Disorder Examination Questionnaire Brief Version
ER	Extended release
FDA	Food and Drug Administration
IR	Immediate release
LDX	Lisdexamfetamine

MTA	Multimodal treatment of ADHD
NA	Noradrenaline (norepinephrine)
NET	Norepinephrine reuptake transporter
NICE	National Institute for Health and Care Excellence
NSDUH	National Survey on Drug Use and Health
PERMP	Permanent Product Measure of Performance
PFC/FC	Prefrontal cortex/Frontal cortex
SDX	Serdexmethylphenidate
SERT	Serotonin reuptake transporter
SKAMP	Swanson, Kotkin, Agler, M-Flynn and Pelham scale
YBOCS-BE	Yale-Brown Obsessive Compulsive Scale adapted for Binge Eating
XR	Extended release

1 Introduction

The intervening decade between the publication of our previous review (Heal et al. 2012) and this one has been one of contradictions. Several new drugs to treat Attention-Deficit Hyperactivity Disorder (ADHD) have entered the formularies, but the search for new drugs with novel mechanisms to deliver a better balance between clinical benefit and risk has been unsuccessful. Knowledge about ADHD, its neuropathology and the pharmacological mechanisms of drugs that are effective in treating the disorder has substantially increased. On the other hand, the failure of many drug-candidates, with mechanisms different from indirect or direct potentiation of catecholaminergic neurotransmission, has closed off many research avenues. The outcome has been to focus research on enhancing the therapeutic efficacy of catecholaminergic ADHD drugs and diminish their deficiencies, e.g. duration of action, adverse events and potential for abuse.

In the UK, there has been a major shift by NICE (National Institute of Health and Care Excellence) to recommend stimulants as first-line therapy in ADHD in children ($\geq$5-years) and adults (NICE: Guidance NG87, 2018). This contrasts with its previous opinion there was no clinically significant difference between the efficacy of non-stimulants and stimulants in treating ADHD (NICE: Review of Technical Appraisal 13, 2006); a view that was not shared by the British Association of Psychopharmacology Consensus Group on ADHD (Bolea-Alamañac et al. 2014).

For researchers in the field, it has consolidated the link between the catecholaminergic pharmacology of clinically effective ADHD drugs (and now prodrugs), their relative efficacy and relative potential for adverse events.

In this chapter, we will explore these topics, offer an assessment of the prospects for new drugs to treat ADHD and possible directions for future research.

2 Current Status of Drugs to Treat ADHD

The list of currently approved drugs in the USA and UK/Europe for the management of ADHD is reported in Table 1. The number and variety of drugs available to prescribers in the USA is far more extensive than in UK/Europe. As an example, mixed enantiomers/mixed salts amphetamine (Adderall and Adderall-XR), which was for some considerable period the most widely prescribed ADHD drug in the USA, has never been approved in UK/Europe.

New additions to the formulary since writing the last review are the global introduction of the *d*-amphetamine prodrug, lisdexamfetamine (LDX) and an extended-release formulation of the α_2-adrenoceptor agonist, guanfacine. Other medications approved in the USA are clonidine-XR, viloxazine (a selective norepinephrine reuptake inhibitor with some additional serotonergic properties) and Azstarys® (a fixed-dose combination of d-methylphenidate and serdexmethylphenidate [d-methylphenidate prodrug]).

3 Non-clinical and Clinical Pharmacology of Approved Drugs to Treat ADHD

As shown in Fig. 1, all ADHD drugs exert their therapeutic actions by enhancing the signalling of either norepinephrine and dopamine or norepinephrine alone. They accomplish this action by one of four distinct mechanisms: selective inhibition of the norepinephrine reuptake transporter (NET) (atomoxetine), dual inhibition of NET and the dopamine reuptake transporter (DAT) (methylphenidate), catecholamine release by the NET and DAT transporter substrates (*d*- and *l*-amphetamine) or direct activation of postsynaptic α_{2A}-adrenoceptors (guanfacine and clonidine).

It is important to note that these drugs all potentiate norepinephrine neurotransmission (either alone or in combination with dopamine), but none of them selectively enhances dopaminergic neurotransmission.

One of the common misconceptions is dopamine is the primary mediator of the therapeutic effects of ADHD drugs (Volkow et al. 2012; del Campo et al. 2011, 2013; Sharma and Couture 2014; Aarts et al. 2015). The misconception probably derives from the fact that amphetamine and methylphenidate are powerful dopaminergic stimulants and consequently this mechanism underpins their efficacy in ADHD.

It has been demonstrated in multiple studies that the dopamine neuronal systems in the brains of subjects with ADHD are dysregulated (Ernst et al. 1999; Volkow et al. 2007; del Campo et al. 2013; Aarts et al. 2015) and the dopaminergic reward system in the brain is also underactive (Patros et al. 2016; Marx et al. 2021). However, in our view, linking efficacy in ADHD with drug effects in the striatum (e.g., Volkow et al. 2012; del Campo et al. 2011, 2013; Aarts et al. 2015) is misleading because it places excessive emphasis on a secondary therapeutic

Table 1 List of drugs currently approved to treat ADHD

Generic drug name	Trade names	Generic versions	Mode of action	USA		UK/Europe	
				Children adolescents	Adults	Children adolescents	Adults
d-Amphetamine	Adzenys ER, Adzenys XR-ODT, Dexedrine Spansules, Dyanavel XR Evekeo, Evekeo ODT	Yes	Catecholamine (NA +DA) releasing agent[a]	Yes	Yes	Yes	Yes
Mixed salts/mixed enantiomers amphetamines (3:1 mixture of d- and l-isomers)	Adderall, Adderall-XR	Yes	Catecholamine (NA +DA) releasing agent[b]	Yes	Yes	N/A	N/A
Methamphetamine	Desoxyn	Yes	Catecholamine (NA +DA) releasing agent[c]	Yes	Not approved	N/A	N/A
Lisdexamfetamine (d-Amphetamine prodrug)	Vyvanse	No	D-Amphetamine prodrug Catecholamine (NA +DA) releasing agent	Yes	Yes	Yes	Yes
dl-*threo*-Methylphenidate	Aptensio XR, Concerta, Concerta XL, Cotempla XR-ODT, Daytrana, Delmosart, Equasym XL, Jornay PM ER, Matoride XL, Medikinet XL, Metadate CD, Methylin, Quillichew ER, Quillivant XR, Relexxii, Ritalin, Ritalin SR, Xaggitin XL, Xenidate XL	Yes	Psychostimulant catecholamine (NA+DA) reuptake inhibitor	Yes	Yes	Yes	Yes
d-*threo*-Methylphenidate	Focalin, Focalin-XR	Yes	Psychostimulant catecholamine (NA+DA) reuptake inhibitor[d]	Yes	Yes	N/A	N/A

(continued)

Table 1 (continued)

Generic drug name	Trade names	Generic versions	Mode of action	USA		UK/Europe	
				Children adolescents	Adults	Children adolescents	Adults
Serdexmethylphenidate (d-*threo*-methylphenidate prodrug) + d-*threo*-methylphenidate	Azstarys	No	Psychostimulant catecholamine (NA+DA) reuptake inhibitor[d]	Yes	Yes	N/A	N/A
Atomoxetine	Strattera	Yes	NA-selective reuptake inhibitor	Yes	Yes	Yes	Yes
Viloxazine	Qelbree	No	NA-selective reuptake inhibitor/$5HT_{2C}$ agonist/$5HT_{2B}$ antagonist[e]	Yes	No	N/A	N/A
Guanfacine	Intuniv, Tenex	Yes	α_{2A}-Adrenoceptor agonist	Yes[f]	Yes[f]	Yes	Not approved
Clonidine	Kapvay	Yes	α_{2A}-Adrenoceptor agonist	Yes[f]	Yes[f]	N/A	N/A

N/A Not available, *NA* norepinephrine, *DA* dopamine

[a] Profile in vivo DA $\geq$ NA (Heal et al. 2009)

[b] Profile in vivo DA $\approx$ NA (Heal et al. 2008)

[c] Profile in vivo DA $>$ NA with lower potentiating effect on NA transmission in PFC (Kuczenski et al. 1995; Shoblock et al. 2003, 2004)

[d] Profile in vivo almost identical to dl-*threo*-methylphenidate (Heal and Pierce 2006; Heal et al. 2009).

[e] Yu et al. (2020)

[f] Also approved as adjunctive therapy in combination with stimulants

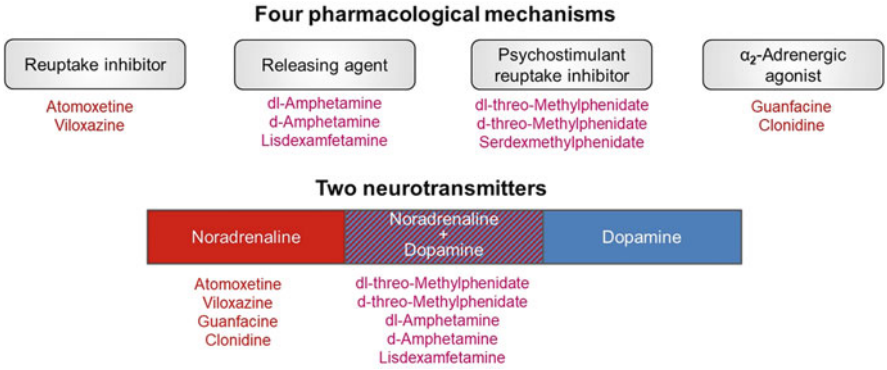

Fig. 1 Mechanism of action of ADHD drugs

mechanism of these drugs. Moreover, it ignores the fact that selective norepinephrine reuptake inhibitors and α_2-adrenoceptor agonists, which are clinically effective in ADHD, do not enhance striatal or limbic dopaminergic signalling (Bymaster et al. 2002; Gresch et al. 1995; Tanda et al. 1996).

It is widely accepted that ADHD drugs reduce its core symptoms by potentiating catecholaminergic signalling in the prefrontal cortex (PFC; Arnsten 2009; Arnsten and Pliszka 2011; Berridge and Devilbiss 2011; Sharma and Couture 2014; Heal and Pierce 2006; Heal et al. 2008, 2009, 2012, 2013a) and the major driver of the effect is through a norepinephrine-based mechanism. The PFC has sparse and diffuse dopaminergic innervation, but it is the low density of DAT sites (Hitri et al. 1991; Sesack et al. 1998) and their inefficient clearance of synaptic dopamine (Cass and Gerhardt 1995; Sesack et al. 1998; Mundorf et al. 2001) that results in a substantial proportion of released dopamine being transported into norepinephrine-releasing neuronal terminals via NET sites (Morón et al. 2002; Stahl 2003). Blockade of PFC NET sites by norepinephrine reuptake inhibitors increases extracellular concentrations of both norepinephrine and dopamine (Gresch et al. 1995; Bymaster et al. 2002; Swanson et al. 2006; Yu et al. 2020). In contrast, selective blockade of DAT sites in the PFC has little impact on synaptic dopamine or norepinephrine concentrations (Tanda et al. 1997). Through their inhibitory and autoreceptor actions, α_2-adrenoceptor agonists actually decrease the exocytotic release of norepinephrine and dopamine in the PFC (Gresch et al. 1995; Tanda et al. 1996) and yet are effective in treating the disorder. Clear evidence that DAT is not a critical effector of efficacy in ADHD is illustrated by the weak efficacy of bupropion in clinical trials (see Heal et al. 2012) and discontinuation of several drug-candidates that preferentially enhance dopaminergic neurotransmission (see Table 2).

If one accepts the premise that enhancing norepinephrine or general catecholaminergic neurotransmission in the PFC is a prerequisite in treating ADHD, it does not preclude an important secondary role for dopaminergic actions. Numerous articles have implicated abnormal reward processing in sub-cortical brain regions including the caudate, putamen, ventral striatum and nucleus accumbens (Teicher et al. 2000; Volkow et al. 2012; Paloyelis et al. 2012; Costa Dias et al. 2013; Aarts

Table 2 New drug-candidates evaluated as potential treatments for ADHD

Drug-candidate	Mode of action	Company	Status in ADHD	References
Centanafadine (EB1020)	Noradrenaline + dopamine reuptake inhibitor	Otsuka/ Neurovance	Phase 3 in children Positive findings in Phase 2 and 3 trials in adults	Wigal et al. (2020b)
Mazindol	Noradrenaline + dopamine reuptake inhibitor	NLS Pharmaceutics	Phase 2/3 Positive findings in Phase 2 trials in adults and children	Konofal et al. (2014) Wigal et al. (2018)
Dasotraline	Noradrenaline + dopamine reuptake inhibitor	Sunovion	Positive findings in Phase 3 trials FDA declines approval Discontinued in 2020	Adler et al. (2021) Findling et al. (2019)
Vortioxetine	Serotonin reuptake inhibitor + $5HT_{1A}$ agonist + $5\text{-}HT_3$ antagonist	Lundbeck	Lack of efficacy in Phase 2 trial Discontinued in ADHD	Biederman et al. (2019)
Edivoxetine (LY22166840)	Noradrenaline reuptake inhibitor	Eli Lilly	Positive findings in Phase 2 trials Discontinued in 2013	Lin et al. (2014) Nery et al. (2017)
GSK372475 (NS2359)	Triple monoamine reuptake inhibitor	GSK/ Neurosearch	Lack of efficacy Discontinued	Wilens et al. (2008)
DOV102677	Triple monoamine reuptake inhibitor	Dov Pharmaceuticals	Discontinued Company wound up	No published data
SPD473	Triple monoamine reuptake inhibitor	Shire Pharmaceuticals	Discontinued Shire acquired by Takeda	No published data
Posanicline (ABT089)	Nicotine α_4/β_2 partial agonist	AbbVie/ NeuroSearch	Lack of efficacy Discontinued Neurosearch wound up	Wilens et al. (2011) Bain et al. (2012) Apostol et al. (2012)
AZD1446 (TC6683)	Nicotine α_4/β_2 partial agonist	AstraZeneca/ Targacept	Lack of efficacy Discontinued Targacept acquired by catalyst	Jucaite et al. (2014)

(continued)

Table 2 (continued)

Drug-candidate	Mode of action	Company	Status in ADHD	References
Sofinicline (ABT894)	Nicotine α_4/β_2 agonist	AbbVie/ NeuroSearch	Minimal efficacy Discontinued Neurosearch wound up	Bain et al. (2013)
AZD3480 (TC1734)	Nicotine α_4/β_2 agonist	AstraZeneca/ Targacept	Minimal efficacy Discontinued Targacept acquired by catalyst	Potter et al. (2014)
Bavisant (JNJ31001074)	Histamine H_3 antagonist	Johnson & Johnson	Lack of efficacy Discontinued	Weisler et al. (2012)
Org26576	AMPA modulator	Merck	Lack of efficacy Discontinued	Adler et al. (2012)

et al. 2015) and dysregulated dopaminergic connectivity with the PFC (Paloyelis et al. 2010; Volkow et al. 2012; Costa Dias et al. 2013; Fabio et al. 2020) in the psychopathology of ADHD. Although there is general consensus on these points, there is also considerable disparity between the findings, which probably reflects the complexity and heterogeneity of the disorder.

Delay-discounting is an accepted measure of intolerance of delayed reward and impulsivity. Individuals with ADHD exhibit steeper rates of delay-discounting than individuals without ADHD (Shiels et al. 2009; Paloyelis et al. 2010; Patros et al. 2018; Castrellon et al. 2019; Fabio et al. 2020). A large meta-analysis exploring possible associations between dopaminergic function and reward discounting in adults revealed minimal influence on discounting in healthy individuals (Castrellon et al. 2019). In contrast, impulsivity and intolerance of delayed reward has been linked to the dopamine transporter gene, DAT1 (Paloyelis et al. 2010, 2012; Aarts et al. 2015; Castrellon et al. 2019), the metabolizing enzyme, catecholamine-*O*-methyltransferase $(COMT)_{val158met}$ (Paloyelis et al. 2012) and $D_{2/3}$ receptor availability (Rosa-Neto et al. 2005; Volkow et al. 2012; Castrellon et al. 2019).

The involvement of striatal dopaminergic systems in the therapeutic effect of stimulant ADHD drugs comes from several sources. Methylphenidate reduces delay-discounting in children with ADHD (Shiels et al. 2009). Rosa-Neto et al. (2005) demonstrated a significant correlation between $D_{2/3}$ receptors in the right striatum and the severity of inattention and impulsivity in ADHD. Furthermore, increased synaptic dopamine concentrations produced by methylphenidate correlated with improvements in impulse control, attention, information processing and consistency of attention or variability. Methylphenidate normalized reward processing in adults with ADHD carrying the 9*R* allele on the DAT1 gene (Aarts et al. 2015). Long-term methylphenidate administration to previously treatment-naïve subjects produced increases in synaptic dopamine concentrations in the ventral striatum, prefrontal and temporal cortices that correlated with objective reductions in ratings of inattention and hyperactivity (Volkow et al. 2012).

The synopsis above summarizes the pivotal role which enhanced catecholaminergic neurotransmission in the PFC and dopaminergic neurotransmission in the ventral striatum and limbic regions play in mediating the therapeutic actions of all ADHD drugs. Moreover, as they are generally compounds with no off-target affinity, it creates the situation where the pharmacological effects responsible for efficacy in ADHD are the same as those which produce their adverse effects (see Heal and Pierce 2006; Heal et al. 2008). Therefore, optimizing benefit/risk when using these drugs to treat ADHD is a fine balance between maximizing efficacy and inducing unacceptable levels of side-effects.

Previously, we described how the use of intracerebral microdialysis can provide insights into the efficacy, side effects and abuse potential of ADHD drugs (Heal and Pierce 2006; Heal et al. 2008, 2009, 2012). In this review, we use the same approach to evaluate the latest generation of ADHD drugs and those in clinical development. We discuss the pharmacology of many of the drugs currently used to treat ADHD and the strong link between their pharmacological properties and efficacy, side effects and abuse liability. To avoid repetition, for a general overview of amphetamine, methylphenidate, atomoxetine, modafinil and bupropion, we refer readers to our earlier reviews (Heal et al. 2009, 2012), for the pharmacology of the isomers of amphetamine (Heal et al. 2008) and for methylphenidate (Heal and Pierce 2006), for an in-depth analysis of the pharmacology of amphetamine (Heal et al. 2013a) and the enigmatic, cocaine-like pharmacology of methylphenidate (Heal et al. 2014). Here, we confine ourselves to an analysis of ADHD drugs that have been approved since the publication of Heal et al. (2012) with a revisit on the pharmacology of the α_{2A}-adrenoceptor agonists, which now appear to be differentiated pharmacologically and clinically from the non-stimulants.

3.1 Lisdexamfetamine

Lisdexamfetamine (LDX) is a *d*-amphetamine prodrug comprising *d*-amphetamine covalently bonded to L-lysine. LDX is highly unusual because it is not catabolized to liberate the active drug in the gut or the liver, as are most other prodrugs; instead, it is metabolized by a rate-limited enzymatic hydrolysis in red blood cells (Pennick 2010; Sharman and Pennick 2014). The catabolic products are *d*-amphetamine (active drug) and the naturally occurring amino acid, L-lysine. *d*-Amphetamine is a close analogue of the catecholamine neurotransmitters, dopamine and norepinephrine, it is a competitive substrate for DAT and NET and the vesicular monoamine transporter-2 (VMAT-2) (see review by Heal et al. 2013a). *d*-Amphetamine is translocated into presynaptic terminals by these ATP-driven carrier systems where it displaces dopamine and norepinephrine from the cytosolic (newly synthesized) and vesicular storage pools. These monoamines are expelled into the synaptic cleft by reversal of DAT and NET's direction of transport ("reverse transport") (Heal et al. 2013a).

The pharmacokinetics due to the rate-limited enzymatic catabolism of LDX profoundly influence its pharmacological actions, resulting in more gradual and

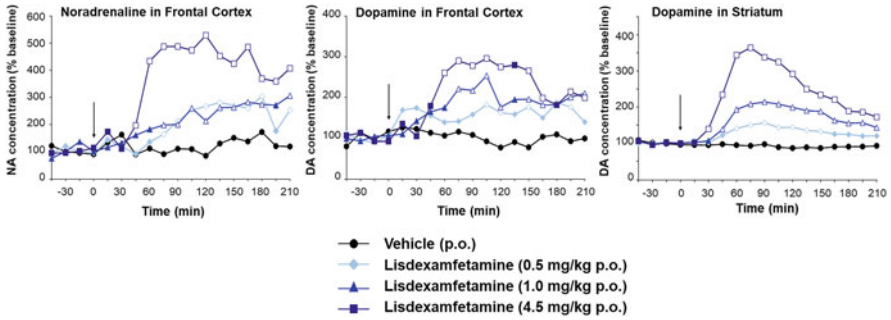

Fig. 2 Profile of LDX on catecholaminergic neurotransmission in the frontal cortex (FC) and striatum. Dual-probe microdialysis experiments in freely-moving rats (Rowley et al. 2014). Results are statistically-adjusted means; $n = 5–8$ rats/group. Doses of LDX are expressed in terms of *d*-amphetamine base. The vertical arrow indicates time of drug administration. Data were analysed by ANCOVA followed by multiple *t*-test (*d*-amphetamine) and Williams' test (lisdexamfetamine). Significant differences are denoted by the open symbols. *NA* norepinephrine [noradrenaline], *DA* dopamine

sustained monoamine increases at the synaptic level with a less stimulant profile than *d*-amphetamine. This point is exemplified when the effects of LDX and immediate-release *d*-amphetamine (IR-*d*-amphetamine) on extracellular dopamine in the striatum and locomotor activity were compared in rats (Rowley et al. 2012). LDX had a much longer duration of action than IR-*d*-amphetamine and, at the same dose, was markedly less stimulant (Fig. 2). LDX also exhibited anticlockwise hysteresis in its pharmacodynamics resulting in reduced activation as extracellular dopamine concentrations increased and longer maintenance of effect when they declined (Rowley et al. 2012). This phenomenon, which is not shared by IR-*d*-amphetamine, may help to explain why LDX has an extended duration of efficacy in the clinic. LDX dose-dependently increased extracellular concentrations of both catecholamines in the PFC and dopamine in the striatum (Rowley et al. 2014). The peak of monoamine efflux occurred ~60 min after LDX was administered and was ~400% of baseline in both brain regions (Fig. 3). Therefore, LDX has the ability to markedly potentiate catecholaminergic neurotransmission in PFC (essential for efficacy) and dopaminergic neurotransmission in the striatal and limbic systems (a secondary driver of efficacy).

The efficacy of LDX in ADHD has been demonstrated in several, large-scale, double-blind, randomized clinical trials (DBRCTs) in children (Biederman et al. 2007; Coghill et al. 2013; Dittmann et al. 2013; Ichikawa et al. 2020a, b) and adults (Adler et al. 2008a; Babcock et al. 2012). LDX is approved to treat ADHD in many countries in North and South America, Europe and Asia, and in 2019, it became the first stimulant drug to be approved for use in ADHD in Japan.

LDX's efficacy in ADHD is rapid in onset with significant separation from placebo as early as Week-1 in children (Biederman et al. 2007; Coghill et al. 2013; Ichikawa et al. 2020a) and adults (Adler et al. 2008a) and it reaches a plateau

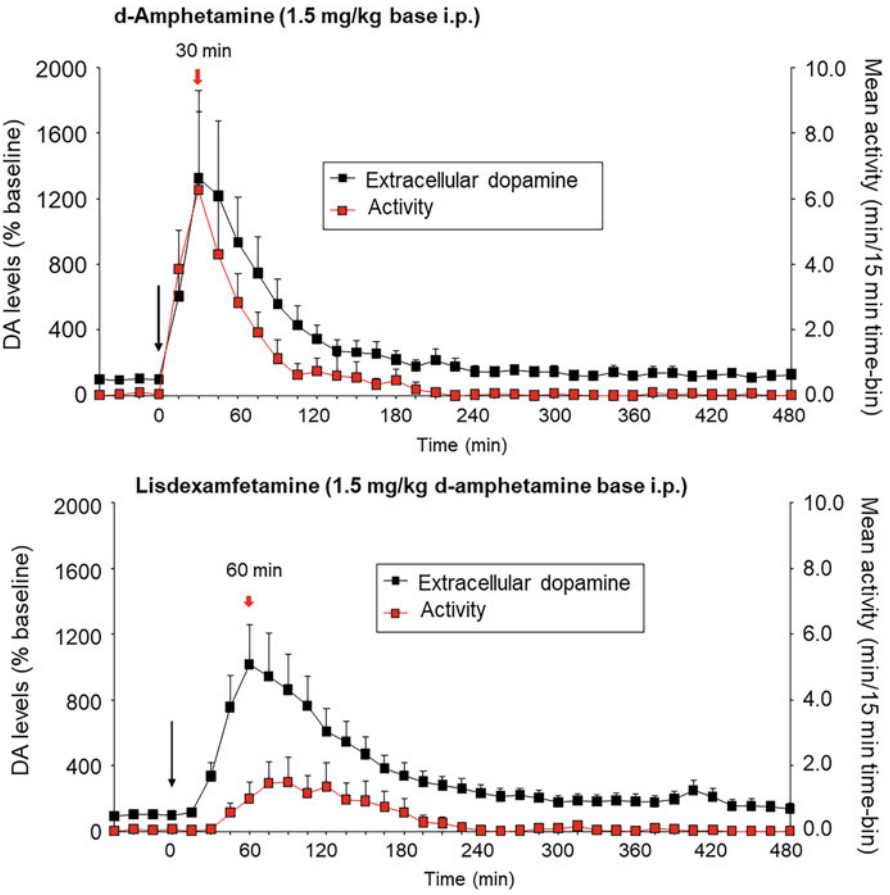

Fig. 3 Comparison by microdialysis of the effects of d-amphetamine and LDX on extracellular dopamine (DA) in the striatum and on locomotor activity of rats. Locomotor activity measured simultaneously with automated microdialysis sampling using the Culex Bambino/Raturn system. The >1000% increase of extracellular DA that occurred very shortly after administration of immediate-release d-amphetamine induced profound locomotor activation, whereas the gradual, >1,000% increase in extracellular dopamine following administration of LDX kept the rats awake and alert with minor effect on locomotor activity. *DA* dopamine

after 5–6 weeks (Dittmann et al. 2013; Adler et al. 2008a; Brams et al. 2012). LDX substantially decreases ADHD symptoms (ADHD-RS-IV Total), including reductions in the inattentive and hyperactivity/impulsiveness sub-scales (Coghill et al. 2013, 2014a; Adler et al. 2008a; Wigal et al. 2011). LDX's efficacy was extremely high and similar across both assessment methods (Wigal et al. 2011; Coghill et al. 2013, 2014a).

LDX's effects are dose-dependent in children and adults, but its magnitude of effect appears to be greater in children than adults across all symptom domains. The

unique rate-limited hydrolysis of LDX gives it a long duration of action with significant improvements for at least 11–14 h (Biederman et al. 2007; Wigal et al. 2011; Martin et al. 2014; Coghill et al. 2014b); however, its onset of action appears somewhat slower than IR-amphetamine (Martin et al. 2014).

No pharmacological tolerance to LDX's therapeutic effect occurs on long-term treatment with efficacy in open-label trials reported at 6 months (Coghill et al. 2014b), 1 year (Mattingly et al. 2013; Ichikawa et al. 2020b) and 2 years (Coghill et al. 2017). Compared with baseline performance, cognitive function in children and adolescents was not impaired after two years on LDX, but it was not generally improved either (Coghill et al. 2018). Interestingly several novel drugs with cognitive-enhancing properties, such as vortioxetine (see Sect. 4.4), have failed in ADHD clinical trials. It exemplifies the point that ADHD is primarily driven by its psychopathology of inattentiveness, impulsivity and hyperactivity and it is reducing these abnormalities not cognitive enhancement which delivers efficacy.

LDX's adverse events (AEs) are typical of powerful catecholaminergic drugs and include decreased appetite, insomnia, abdominal pain, irritability, dizziness, nausea, vomiting, dry mouth and weight loss. The lower efficacy of LDX in treating adults compared with children/adolescents is reflected in the AE profile where frequency increases substantially with dose in children (Biederman et al. 2007) but is relatively stable across doses in adults (Adler et al. 2008a).

The active metabolite of LDX, *d*-amphetamine, is a C-II controlled drug (drugs with a high potential for abuse, but have an accepted medical use) in UK, the USA and many other countries. Microdialysis/behavioural experiments clearly demonstrated due to its rate-limited enzymatic liberation of *d*-amphetamine, LDX was far less stimulant than IR-*d*-amphetamine (Rowley et al. 2012), suggesting poses a lower risk for abuse. This was supported by findings from drug-discrimination and intravenous self-administration studies in rats (Heal et al. 2013b) where LDX failed to generalize to *d*-amphetamine and did not serve as a positive reinforcer. In contrast, methylphenidate generalized to *d*-amphetamine and was self-administered at levels similar to cocaine. Changing the route of administration of methylphenidate or *d*-amphetamine from oral to intraperitoneal increased their potency 2 to 3-fold in the drug-discrimination but had no effect on the potency of LDX. Even when rats were given intravenous access to LDX, the prodrug still did not serve as a reinforcer.

Reduced abuse potential was also observed in human abuse trials where LDX was compared against *d*-amphetamine by both the oral (Jasinski and Krishnan 2009a) and intravenous routes (Jasinski and Krishnan 2009b). When given orally, LDX took 4 h to produce maximum drug-liking compared with 1 h for *d*-amphetamine and, in addition, it was ~50% less potent (Jasinski and Krishnan 2009a). When administered by the intravenous route at the same dose (in terms of *d*-amphetamine base equivalents), *d*-amphetamine produced an unequivocal "drug-liking" signal, but LDX did not differentiate from placebo (Jasinski and Krishnan 2009b).

Another important factor when assessing abuse potential is the feasibility for employing dangerous, non-clinical routes. In this regard, LDX is highly advantaged because its potency is not increased when taken intranasally or intravenously (Heal et al. 2013b; Hutson et al. 2014; Ermer et al. 2016). The US scheduling of LDX in

C-II reflects the vagaries of the Controlled Substances Act whereby prodrugs get placed into the same schedule as their active metabolite. The decision by most other countries to follow this lead does not in our view accurately reflect the lower abuse risk that is posed by LDX, which is a novel chemical entity, compared with *d*-amphetamine.

3.2 Viloxazine

Viloxazine is a weak, selective, norepinephrine reuptake inhibitor that was approved for use as an antidepressant in Europe in the 1970s but is no longer in the formulary. Viloxazine was revived as an extended-release formulation, viloxazine-ER (SPN-812; Qelbree®) to treat ADHD and approved for use in children and adolescents in the USA in April 2021 (Qelbree® FDA Product Label 2021).

Viloxazine has a weak affinity for NET (*K*i=155 nM) with >100-fold selectivity versus the serotonin transporter (SERT: *K*i=17,300 nM) and negligible affinity for DAT (*K*i >100,000 nM) (Yu et al. 2020). In vitro, tritiated monoamine uptake inhibition studies confirmed those transporter affinities (Martin et al. 1978). Yu et al. (2020) have portrayed SPN-812 as having an advantaged pharmacology based on its actions at 5-HT_{2B} and 5-HT_{2C} receptors; since they occur at >10 μM, they are unlikely to be clinically relevant.

In vivo microdialysis experiments showed that SPN-812 increased efflux of norepinephrine and dopamine in the PFC; the effect was reasonably rapid in onset with peaks of ~700% of basal at 60 min (Yu et al. 2020). Unusually for a drug with this pharmacology, SPN-812 increased 5-HT (serotonin) efflux in the PFC by ~500% over basal and significantly enhanced extracellular dopamine, norepinephrine and 5-HT in the nucleus accumbens (Yu et al. 2020). These effects should be viewed with caution because they occurred after intraperitoneal injection at a single dose of 50 mg/kg which is far higher than the pharmacological or clinical dose range (≤400 mg/day; Qelbree® US Product Label).

Viloxazine-ER was evaluated in 4 Phase 3, clinical trials in paediatric patients. Studies 812P301 and 812P303 evaluated viloxazine-ER in children and 812P302 and 812P304 in adolescents. Once-daily doses ranged from 100–400 mg in children and 200–600 mg for adolescents (FDA Qelbree® Integrated Review 2021; Johnson et al. 2020; Nasser et al. 2020, 2021). In study 812P301 (Nasser et al. 2020), children had moderate/severe ADHD. Both viloxazine-ER doses separated from placebo at Week-6, but there was no difference in efficacy between 100 and 200 mg/day. The differences from placebo were statistically significant, but the clinical benefit was moderate. Viloxazine-ER decreased scores on the Inattentive and Hyperactivity/impulsivity sub-scales. Separation from placebo was evident at Week-1 on 100 mg/day, but not the higher dose. Results from the second 6-week trial in children and the two trials in adolescents are reported in detail in the FDA Qelbree® Integrated Review (2021). Results from 812P303 mirrored the first trial in children with 200 and 400 mg/day showing moderate efficacy in ADHD, with a slow onset of

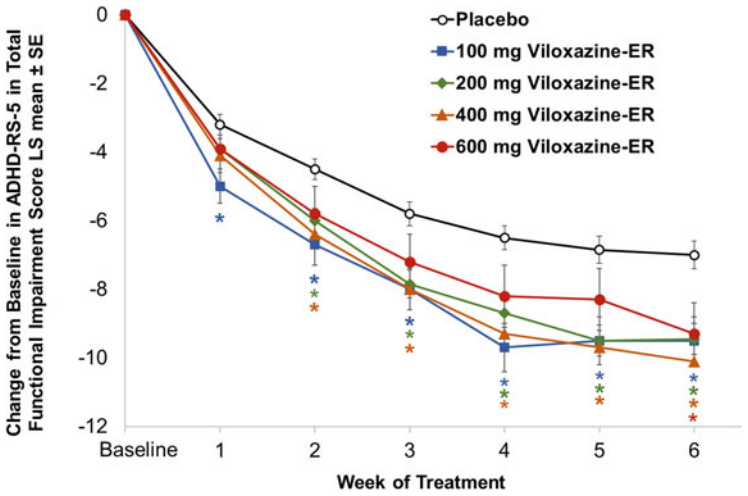

Fig. 4 Efficacy of viloxazine-ER in Phase 3 trials in paediatric ADHD subjects. Results are mean ± SEM change from baseline in the ADHD-RS-5 Total Functional Impairments (ADHD-RS-5 TFI) score by treatment week for 100, 200, 400 and 600 mg/day versus placebo. Significantly different from placebo: $*p < 0.05$. Asterisks colour coded to match each dose of Viloxazine-ER. *P* values obtained from mixed-model, repeated measures change from baseline in ADHD-RS-5 TFI score as function of fixed-effect terms for baseline ADHD-RS-5 Total FI Score, age group, treatment, visit and treatment-by-visit interaction, as fixed independent variables. *TFI* Total Functional Impairment. Data abstracted from Nasser et al. (2021).

action and no difference in efficacy between the two doses. In the two trials in adolescents, the moderate efficacy, slow onset of action and lack of dose-response for viloxazine-ER were confirmed; in fact, neither the 400 or 600 mg/day doses met the primary endpoint in 812P304 (FDA Qelbree® Integrated Review 2021). Nasser et al. (2021) collated the findings from all four trials to produce an overview of the efficacy and tolerability of viloxazine-ER in paediatric subjects. The ADHD-RS-5 results in Fig. 4 illustrate the slow onset of effect, moderate efficacy and lack of a dose-response relationship. Frequently reported AEs associated with viloxazine-ER treatment were somnolence/sedation, headache, fatigue, decreased appetite, abdominal pain, upper respiratory infection, nausea and vomiting (FDA Qelbree® Integrated Review 2021). The FDA noted that somnolence appeared to be dose-related, occurring at rates of 10%, 12%, 14% and 19% at doses of 100, 200, 400 and 600 mg/day, respectively. Sedation, fatigue and nausea also appeared to be dose-dependent.

In summary, viloxazine-ER performs in ADHD like a selective norepinephrine reuptake inhibitor in terms of efficacy, onset of action and AE profile. Based on the clinical evidence, the augmented pharmacology of viloxazine-ER has not differentiated it from atomoxetine.

3.3 Prodrugs for Methylphenidate

The prodrug approach has also been applied to methylphenidate. Dr. Travis Mickle, who discovered LDX, made a prodrug of *d-threo*-methylphenidate (*d*-methylphenidate) (Mickle 2019). Serdexmethylphenidate (SDX) consists of *d*-methylphenidate connected to a nicotinoyl-L-serine molecule via a carboxymethylene linker (Azstarys® FDA Multi-discipline Review 2021). As a prodrug, SDX has no affinity for DAT, NET or SERT and does not bind to any receptor, transporter, modulatory site, ion channel or transporter that mediates the actions of drugs.

The enzymes responsible for catabolizing SDX to liberate *d*-methylphenidate (active moiety) and *d*-ritalinic acid (inactive) are not known. Enzymatic conversion of SDX is believed to take place in the lower gastrointestinal tract (Azstarys® FDA Multi-discipline Review 2021) and, therefore, therapeutic concentrations of *d*-methylphenidate do not appear in patients until several hours after taking the medication. Since the efficacy of drug action correlates with plasma *d*-methylphenidate concentrations (Azstarys® FDA Multi-discipline Review 2021), SDX is unsuitable for treating ADHD as monotherapy. Azstarys® is a combination medication comprising SDX plus *d*-methylphenidate (SDX/d-methylphenidate: 26.1/5.2 mg, 39.2/7.8 mg, 52.3/10.4 mg). Azstarys has been approved based on biological equivalence to Focalin-XR; it has not been evaluated in Phase 3 trials. Azstarys is as effective as other methylphenidate-based medications and has a ~10 h duration of action. The AE burden of Azstarys compared against other methylphenidate ADHD drugs is not known at this stage.

Commave Therapeutics/KemPharm conducted three trials in drug-experienced human volunteers to evaluate the abuse potential of Azstarys via the oral, intranasal and intravenous routes. When tested orally the FDA concluded that Azstarys (120 and 240 mg) showed less abuse potential than Focalin-XR® (80 mg; C-II) or phentermine (60 mg; an amphetamine-like drug in C-IV), but the study failed to show that the prodrug had no abuse potential when compared with placebo (Azstarys® FDA Multi-discipline Review 2021). Intravenously injected Azstarys (30 mg) demonstrated less abuse potential than *d*-methylphenidate (15 mg, i.v.; C-II) and did not have abuse potential compared with placebo (Azstarys® FDA Multi-discipline Review 2021). Although insufflated Azstarys (80 mg) had less abuse potential than *d*-methylphenidate (40 mg intranasal), it unequivocally showed greater abuse potential than placebo (Azstarys® FDA Multi-discipline Review 2021). Its peak "drug-liking" occurred ~15 min after nasal administration, which was similar to *d*-methylphenidate. Moreover, ~25% subjects reported high "overall liking" of the Azstarys session and 20% strongly wanted to take it again. These data reveal that the most likely route of abuse of Azstarys will be intranasal. FDA has classified SDX in C-IV; however, because *d*-methylphenidate is in C-II, Azstarys is classified as a C-II medication (Azstarys® FDA Product Label 2021).

Since Azstarys has been approved, based on biological equivalence to Focalin-XR, it is reasonable to assume that the drug's efficacy, duration of action and safety will also be similar. Dose-for-dose, the human abuse potential of Azstarys was less

than Focalin-XR, which is an advantage. However, Azstarys is a C-II controlled drug and therefore the hurdles to prescribing it have not been reduced. Overall, we do not believe that Azstarys will be a "game changer" in ADHD pharmacotherapy.

3.4 Comment (Summary/Overview)

The last decade has witnessed a consolidation of the position that catecholaminergic drugs are the only effective pharmacological treatment for ADHD. New drugs have refined and varied the offering with the introduction of prodrugs for *d*-amphetamine and *d*-methylphenidate, and by offering a raft of drug delivery systems to provide once-daily medications with an extended duration of action. No drug with a novel pharmacological mechanism has been approved. In the following section, we will discuss the state of play for new pharmacological approaches.

4 Update on the Progress of R&D in the Search for New Drugs to Treat ADHD

Defining the pharmacological, clinical and tolerability/safety characteristics of the "ideal" drug to treat ADHD is a useful measure against which to evaluate existing drugs and assess the progress of research and development when developing new drugs. We propose the following target product-profile for the ideal ADHD drug.

The "ideal" drug should:

- Reduce impulsivity, distractibility, inattention and hyperactivity symptoms of ADHD
- Improve cognitive control and function
- Deliver high levels of efficacy and remission
- It should be suitable for treating ADHD patients with comorbidities: e.g., depression, anxiety, oppositional/defiant disorder, conduct disorder, substance use disorder, tics
- It should have a benign adverse event profile: no insomnia, no effect on sleep, no effect on appetite/weight, normal growth, no necessity for "drug holidays"
- It should be safe when used long-term
- It should be a once-daily medication

The "ideal" drug should not:

- Produce pharmacological tolerance that would result in dose-escalation
- Cause psychological or physical dependence
- Have potential for human abuse
- Be a Controlled Drug

The drug-candidates under evaluation at the time of writing the previous chapter (Heal et al. 2012), together with those that have entered, and in some cases exited, clinical development in the ensuing period, are reported in Table 2. Every drug-candidate has been discontinued for lack of efficacy, except edivoxetine (Eli Lilly). Development compounds seeking to modulate prefrontal function through nicotinic, histaminergic and AMPA receptor mechanisms failed to demonstrate efficacy in clinical trials. Edivoxetine (a selective norepinephrine reuptake inhibitor) was shown to be effective in ADHD trials (Lin et al. 2014; Nery et al. 2017), whereas the triple uptake inhibitors with relatively powerful dopaminergic actions, GSK372475 (NS2359; GSK/Neurosearch), DOV102677 (Dov Pharmaceuticals) and SPD473 (Shire Pharmaceuticals) proved to be ineffective (Table 2). With the downgrading of atomoxetine (Eli Lilly) to third-line therapy in ADHD, due to its perceived lesser efficacy than the stimulants, it is likely that edivoxetine was discontinued in development in ADHD for strategic and marketing reasons.

Four drug-candidates in Table 2, centanafadine (EB-1020), mazindol, dasotraline and vortioxetine entered development after publication of our previous review.

4.1 Centanafadine

Centanafadine (EB-1020), developed by Otsuka, is a monoamine reuptake inhibitor with IC_{50} potencies for norepinephrine, dopamine and 5-HT of 6 nM, 38 nM and 83 nM, respectively (Bymaster et al. 2012). Irrespective of whether the compound is viewed as a catecholamine or triple reuptake inhibitor, its pharmacological profile includes potent norepinephrine reuptake inhibition properties. In microdialysis experiments, centanafadine increased extracellular dopamine and norepinephrine in the PFC with peak increases of 300–400% occurring 40–60 min after intraperitoneal administration of 10 or 20 mg/kg (Bymaster et al. 2012). Centanafadine also produced similar increases of dopamine in the striatum (Bymaster et al. 2012). The compound was effective in preventing hyperactivity in the neonatal 6-hydroxydopamine brain lesion model of ADHD (Bymaster et al. 2012).

Wigal et al. (2020b) published the findings from two Phase 2 clinical trials of centanafadine in adults with ADHD. In the Phase 2A, flexible-dose study, 41 subjects received escalating doses of centanafadine $\leq$500 mg/day. ADHD severity was high at baseline but was significantly reduced by centanafadine at Week-4. All doses (200–300, 400 and 500 mg/day) produced significant improvements in total Adult ADHD Investigator Symptom Rating Scale (AISRS) scores, and inattention and hyperactivity/impulsive sub-scales. The Phase 2B study employed a 2 $\times$ 3-week crossover design with a 1-week washout in between. Of 85 patients, 42 were randomized to a centanafadine-SR/placebo sequence and 43 *vice versa*. Although 400 mg/day formed the largest treatment arm, higher 600 and 800 mg/day doses were also investigated. All doses showed significant efficacy on the primary outcome, but the two higher ones were not well tolerated. Centanafadine 400 mg/day significantly decreased AISRS total, inattention and hyperactivity/impulsive scores

at Week-3. It was efficacious from as early as Week-1. The most common AEs (placebo-subtracted results) were decreased appetite (16%), nausea (13%), insomnia (11%), fatigue (9%) and dry mouth (7%). Discontinuations for AEs were the same as for placebo.

In June 2020, Otsuka posted a press release announcing positive results from two, 6-week, Phase 3 clinical trials to evaluate the efficacy, safety and tolerability of oral centanafadine in adults with ADHD (Otsuka Press Release 2020). In both trials, centanafadine (200 mg and 400 mg/day) produced statistically significant improvement over placebo on the primary efficacy endpoint, which was change from baseline to Day-42 on the AISRS total score. Centanafadine also significantly improved Clinical Global Impressions Scale (CGI-S), the key secondary efficacy outcome measure. The company stated that trials to study the efficacy and safety of centanafadine in paediatric patients with ADHD were underway.

When the non-clinical findings (Bymaster et al. 2012 and below) and clinical results are viewed overall, they indicate centanafadine is not a stimulant like methylphenidate, but its ability to enhance striatal dopaminergic neurotransmission also differentiates it from the noradrenergic ADHD drugs, atomoxetine and viloxazine. Centanafadine's effect places it between these two drug classes. The safety profile in clinical trials showed no AE signals to indicate that centanafadine has stimulant effects; on the contrary, fatigue was a commonly reported AE.

We have explored the abuse potential of centanafadine in animals in comparison with methylphenidate and bupropion. Centanafadine generalized to *d*-amphetamine in drug-discrimination testing in rats, but only at the high oral dose of 10 mg/kg (Heal et al. 2020). Methylphenidate and bupropion also dose-dependently generalized to *d*-amphetamine. In an earlier study, we showed that atomoxetine does not generalize to *d*-amphetamine (Gosden et al. 2018). In intravenous self-administration in cocaine-trained rats, methylphenidate and bupropion served as strong reinforcers maintaining self-administration at the same level as cocaine. However, centanafadine served as a reinforcer at only two of four tested doses and maintained self-administration at a significantly lower level than cocaine (Heal et al. 2020). If the non-clinical findings translate to humans, they indicate that centanafadine's potential for human abuse will be low.

4.2 Mazindol

Mazindol is a highly potent norepinephrine reuptake inhibitor: *K*i = 0.65 nM to 0.9 nM (Hyttel 1982; Cheetham et al. 1996). It is also a moderately potent reuptake inhibitor of dopamine (*K*i = 18 nM; Hyttel 1982) and 5-HT (*K*i = 30 nM; Hyttel 1982). Mazindol's potency as a NET inhibitor is similar to atomoxetine (*K*i = 0.7 nM). Recently, there have been claims that mazindol has a unique pharmacological profile based on its affinity for 5-HT_{1A}, 5-HT_7, H_1, μ-opioid and orexin-2 receptors (Wigal et al. 2018). Given that these actions were observed at a screening concentration of 10 μM, their relevance to the actions of mazindol can be discounted.

Mazindol (Mazanor®, Sanorex®) is an old drug that was originally developed in the 1960s as a short-term appetite suppressant for weight loss in obesity. Mazindol is no longer marketed in the USA as an appetite suppressant and its sale in Europe was banned by European Medicines Agency in 2003.

There are no published microdialysis data on the effects of mazindol on extracellular catecholamines in the PFC. In rat striatum, mazindol produced rapid, dose-related increases in dopamine efflux with peak effects at 60 min of ~400% and ~750% of basal concentrations at doses of 10 mg/kg and 25 mg/kg, respectively (Ng et al. 1992). Mazindol's effect on dopamine was sustained for several hours. Nakachi et al. (1995) similarly reported that mazindol (28.5 mg/kg) produced a rapid increase in striatal dopamine efflux with a peak of ~500% of basal at 60 min. The drug produced low level activation and stereotypy as well as some odd behavioural effects, e.g. shaking and skin jerks. Mazindol's activating effects were lower than those produced by nomifensine or GBR12909 (Nakachi et al. 1995).

Although the pharmacological characterization of mazindol is incomplete, it is reasonably safe to assume that, given its potency as a NET inhibitor, it will substantially enhance norepinephrine and dopamine neurotransmission in the PFC in addition to dopaminergic signalling in the striatum. Therefore, the pharmacological properties of mazindol are consistent with those of a clinically effective ADHD drug. The effect of mazindol on brain dopamine signalling has been studied by positron emission tomography (PET) imaging in human subjects (Sakayori et al. 2014). Mazindol 0.5 and 1.5 mg dose-relatedly increased synaptic dopamine concentrations as revealed by the displacement of [^{11}C]-raclopride in the striatum, caudate and putamen. Comparing mazindol's dopamine increase against other CNS-active drugs, Sakayori et al. (2014) concluded that its magnitude of effect was similar to *d*-amphetamine and nicotine.

The efficacy and safety of mazindol in ADHD has been evaluated in children (Konofal et al. 2014) and adults (Wigal et al. 2018). A 1-week, open-label, pilot study was carried out in 24 children who were low responders to methylphenidate (Konofal et al. 2014). Mazindol 1 mg/day produced an impressive decrease from baseline in the children's ADHD-RS-IV score at Week-1, with a highly significant improvement in the CGI-S score. AEs were moderate in 34.8% of subjects and severe in 19.6%. They included decreased appetite (37.0%), drowsiness (17.4%), intestinal distension (8.7%) and upper abdominal pain (6.5%). Mean weight loss was 0.5 kg compared with baseline and 0.8 kg compared with the follow-up.

A controlled-release formulation of mazindol was evaluated in a 6-week, DBRCT in 85 adults (mazindol-CR = 43; placebo = 42). Mazindol-CR (up to 3 mg/day) significantly decreased ADHD-RS-V scores starting at Week-1 with maximum effect occurring at Week-4. The effect size suggested that the efficacy of mazindol-CR was on a par with the stimulants, but this conclusion should be tempered because of the use of a forced-titration design, which favours efficacy over tolerability. Frequently reported AEs (placebo-subtracted) were gastrointestinal disorders (15.4%), dry mouth (8.6%), nausea (8.6%), constipation (5.6%), decreased appetite (4.6%) and fatigue (5.9%). Weight-loss was 1.7 kg overall and probably more in the maximum 3 mg/day mazindol-CR group. Heart rate was increased by

11 bpm, diastolic blood pressure and systolic blood pressure by 5.3 and 5.4 mmHg, respectively. Based on these limited clinical findings, mazindol is unequivocally effective as an ADHD treatment; however, the onerous level of AEs observed with the high dose producing the greatest efficacy indicates that, if the drug is approved, its effectiveness may be reduced by limitations placed on the maximum daily dose.

The controlled drug scheduling of mazindol has already been determined; it is a C-IV drug in the USA and C-III in the UK, setting its risk for human abuse at a lower level than the C-II stimulants. In drug-discrimination studies, mazindol dose-dependently generalized to cocaine (Witkin et al. 1991; Mansbach and Balster 1993; Baker et al. 1993) and *d*-amphetamine (Gosden et al. 1996). Mazindol was more potent than cocaine but less potent than *d*-amphetamine (Witkin et al. 1991; Baker et al. 1993; Gosden et al. 1996). Mazindol has been reported to serve as a positive reinforcer in intravenous self-administration experiments in monkeys (Bergman et al. 1989; Spealman et al. 1989) and dogs (Risner and Silcox 1981), and in conditioned place preference in rats (Kankaanpää et al. 2002). The results from human abuse studies tell a rather different story with mazindol producing dysphoric and aversive effects in normal human volunteers (Holmstrand and Jonsson 1975; Chait et al. 1984) and no positive signals of drug-liking in amphetamine-dependent subjects (Götestam and Gunne 1972) or experienced cocaine users (Preston et al. 1993).

Based on the non-clinical and clinical findings and many years of post-marketing experience as an appetite suppressant, the evidence shows that mazindol has the powerful catecholaminergic properties to make it an effective ADHD treatment. It has greater potency on NET than DAT, which is consistent with the former being the main driver of efficacy. Mazindol is clearly stimulant, but nonetheless poses a relatively low risk for human abuse. The effect size of mazindol at 3 mg/day is impressive, but in our opinion, this efficacy comes with an unacceptably high level of AEs, especially those relating to increases in blood pressure and heart rate, and decreases in appetite and body weight.

4.3 Dasotraline

Dasotraline [(1R,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetra-hydronaphthalen-1-amine] is a potent catecholamine reuptake inhibitor (DAT: $IC_{50} = 3$ nM and NET: $IC_{50} = 4$ nM) with weaker effects on 5 HT (SERT: $IC_{50} = 15$ nM) (Koblan et al. 2016). Dasotraline is slowly absorbed after oral administration in humans with a t_{max} of 10–12 h and a long $t_{1/2}$ (terminal elimination half-life) of 47–77 h (Chen et al. 2016; Hopkins et al. 2016; Koblan et al. 2015). It takes 2 weeks of daily dosing to reach steady-state plasma concentrations (Chen et al. 2016; Koblan et al. 2015).

Microdialysis measurements of nucleus accumbens dopamine efflux were consistent with human pharmacokinetics: small, dose-dependent increases that were slow in onset and sustained for many hours (Fig. 5; Heal et al. 2017; Rowley et al. 2017). Dasotraline is clearly different from the stimulants, *d*-amphetamine and

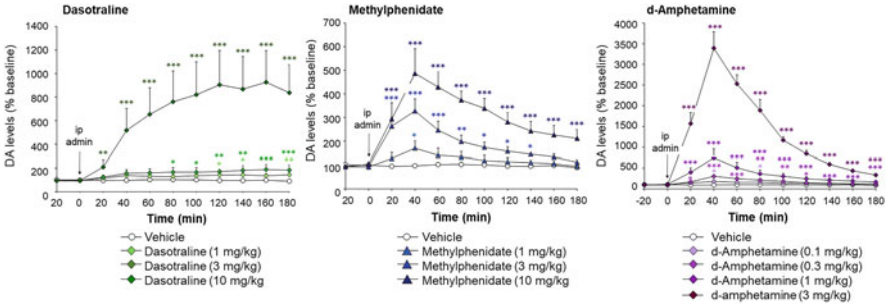

Fig. 5 Comparison of dasotraline, d-amphetamine and methylphenidate on extracellular dopamine concentrations in rat nucleus accumbens. Single probe microdialysis experiments were performed in freely-moving rats with microdialysate dopamine concentrations quantified by HPLC-ECD. Results were back-transformed, adjusted means ± SEM (n = 6–9 rats/dose group). Drug doses are reported as free base and the time of administration is indicated by the vertical arrow. Data were log-transformed and analysed by ANCOVA with log(baseline) as covariate followed by Williams' test. Significant differences versus the vehicle group are denoted by: $*p<0.05$, $**p<0.01$, $***p<0.001$. DA dopamine. N.B. The graphs for dasotraline, methylphenidate and d-amphetamine are plotted using different scales for levels of dopamine efflux

methylphenidate, which produce rapid, large short-lasting increases in dopamine efflux (Fig. 5). One key difference between the mechanisms of releasing agents and reuptake inhibitors is the former are transporter substrates which expel neuronal monoamines by firing-independent reverse transport, while the latter are transport blockers which potentiate and prolong synaptic monoamines after firing-dependent exocytosis (Heal et al. 2013a). Tetrodotoxin blocked neuronal firing and abolished dasotraline's ability to increase synaptic monoamines, showing its actions are exclusively mediated by reuptake inhibition (Heal et al. 2017).

Dasotraline was evaluated in a DBRCT proof-of-concept trial in adults (Koblan et al. 2015). Three hundred and forty-one subjects were randomized in a 1:1:1 ratio to receive 4 weeks of treatment with dasotraline at a fixed dose of 4 or 8 mg/day or placebo (337 received ≥1 treatment). The primary outcome measure was the ADHD RS-IV with CGI-S as one of the secondary measures. Subjects were moderately to severely ill at baseline. At Week-4, the reduction from baseline in ADHD RS-IV score was significant for the higher dose of dasotraline, but not the lower dose. The placebo-subtracted efficacy of dasotraline was relatively modest, and there was no significant effect of the 8 mg/day dose until Week-3. The computerized cognitive assessment battery showed no significant effects for dasotraline on measures of attention, working memory, or episodic memory.

Drop-out rates for AEs on dasotraline were high compared with placebo (4 mg/day = 10.3%; 8 mg/day = 27.8%: placebo = 1.8%). Reasons for discontinuation from dasotraline included insomnia, anxiety, panic attack and a psychotic disorder. Placebo-subtracted AEs included insomnia, decreased appetite, dry mouth, anxiety, nausea, palpitations, weight decrease and panic attack. Heart rate and blood pressure were also dose-dependently increased.

Adler et al. (2021) reported data from a second DBRCT of dasotraline in adults with ADHD. Subjects received 8 weeks of double-blind, once-daily, fixed-dose treatment with dasotraline 4 mg/day, 6 mg/day, or placebo. Neither dose of dasotraline reduced the ADHD RS-IV score from baseline to Week-8 to a significantly greater level than placebo. On the lower hurdle of using uncorrected data, the higher, but not the lower, dose of dasotraline significantly reduced ADHD-RS-IV total score and CGI-S relative to placebo.

The efficacy and safety of dasotraline was also investigated in two studies in children with ADHD (Findling et al. 2019; Wigal et al. 2020a). Findling et al. (2019) conducted a 6-week DBRCT at fixed daily dose of 2 and 4 mg in 336 children. Only the higher dose of dasotraline met the primary endpoint (change from baseline in the ADHD RS-IV total score) and it was also significantly superior to placebo on the inattentive and hyperactive/impulsive sub-scales.

Frequent AEs in the dasotraline (4 mg) group (placebo-subtracted) were insomnia (17.4%), decreased appetite (16.5%), weight decreased (8.7%), affect lability (3.5%), anxiety (3.5%), tachycardia (3.4%) and nausea (3.4%). Seven patients (6.3%) discontinued due to AEs in the 2 mg/day group for insomnia, phobia, decreased appetite, aggression, syncope and EEG changes and 14 patients discontinued in the 4 mg/day group due to insomnia, irritability, abnormal behaviour, ADHD, emotional poverty, visual, mixed or hypnopompic hallucinations, chest pain, costochondritis and pruritus. Psychosis-related symptoms (e.g., hallucinations, illusions) were reported as AEs by seven subjects treated with dasotraline. Although the authors claimed that this incidence was similar to those reported for other ADHD drugs, this conclusion was strongly disputed by Mosholder et al. (2019).

Dasotraline 4 and 6 mg/day has also been investigated in a DBRCT in a 14-day laboratory classroom setting in children (Wigal et al. 2020a). Eligibility for enrolment was established responsiveness to methylphenidate and a $\geq$30% worsening in ADHD during the methylphenidate washout period. Although the protocol was designed to evaluate fixed doses of 4 and 6 mg/day, the 6 mg/day arm was terminated early because of the appearance of unacceptable neuropsychiatric AEs. Thus, a total of 112 subjects were randomized equally to dasotraline 4 mg/day or placebo and comprised both the intention to treat (ITT) and safety populations. Compared with placebo, dasotraline 4 mg/day produced a significantly greater improvement from baseline to Day 15 in the primary SKAMP-combined score (Swanson, Kotkin, Agler, M-Flynn and Pelham) and SKAMP-deportment sub-scale scores. The onset of effect was rapid. Dasotraline also produced significant improvements in the Permanent Product Measure of Performance (PERMP) scores (a skill-adjusted maths test).

The most frequent AEs (placebo-subtracted) in the dasotraline 4 mg/day group were insomnia (16%), decreased appetite (7.1%), perceptual disturbances (5.4%) and orthostatic tachycardia (5.4%). Discontinuation rates were 5.4% (all due to AEs) compared with 10.7% in the placebo group (1.8% for AEs). AEs leading to withdrawal in the dasotraline 4 mg/day group were insomnia, hallucination and rash. In

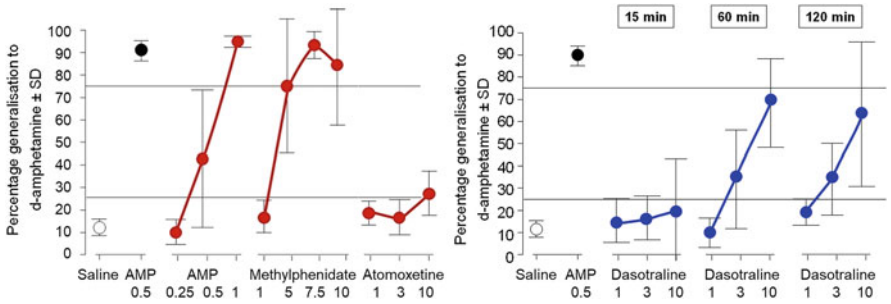

Fig. 6 Comparison of dasotraline and various reference ADHD drugs in d-amphetamine-cued drug-discrimination testing. Freely-fed, female, Lister hooded rats were trained to discriminate between d-amphetamine [AMP] (0.5 mg/kg i.p.) and saline (1 ml/kg i.p.) using a sweetened milk reward in a 2-choice lever-pressing model on a fixed ratio-5 (FR-5) schedule of reinforcement. Test compounds including d-amphetamine for study validation purposes were administered by the oral route. Test sessions were 10 min duration. Rats were not rewarded for operant responses made during the first 2.5 min of the test session. In the remaining 7.5 min, rats were rewarded for presses on either lever on an FR-5 schedule. Results from the non-rewarded 2.5 min part of the 10 min test sessions were used. Results are mean percentage generalization to d-amphetamine ± SD. Total cohort: $N = 26$. Individual drug doses: $N \geq 6$

addition, three patients in this group reported hallucinations (tactile, auditory, visual).

We investigated the abuse potential of dasotraline in *d*-amphetamine-cued drug-discrimination in rats (Gosden et al. 2018). The C-II stimulants, methylphenidate and *d*-amphetamine, both dose-dependently generalized to the *d*-amphetamine training cue, whereas the selective norepinephrine reuptake inhibitor, atomoxetine, generalized to saline. None of the doses of dasotraline generalized to *d*-amphetamine; the greatest effect was ~70% generalization with a dose-test interval of 60 min (Fig. 6).

In stimulant-using, human volunteers, the abuse potential of dasotraline (8, 16 and 36 mg) was compared against methylphenidate (40 and 80 mg) or placebo in a crossover DBRCT (Koblan et al. 2016). Both doses of methylphenidate produced significantly increased "drug-liking" (primary endpoint), "overall drug-liking" and "take drug again" scores relative to placebo. Dasotraline did not separate from placebo on the first two scales but, at the highest dose, marginally did so on the third. Dasotraline (36 mg) produced statistically significant but clinically marginal effects on several other abuse scales and also produced significant negative effects on the "bad drug" and "LSD (dysphoria)" scales. Overall, the non-clinical and clinical evidence demonstrate that dasotraline was clearly differentiated from the C-II stimulant ADHD drugs and posed a minimal risk for human abuse.

Viewing the data overall, dasotraline is a potent DAT and NET inhibitor, but its pharmacological effects are profoundly influenced by its slow rate of brain penetration and extremely persistent inhibition of NET and DAT. There are no published microdialysis data to reveal the magnitude dasotraline's action on extracellular norepinephrine and dopamine in the PFC, and therefore, estimates must be made

based on data from microdialysis experiments in the nucleus accumbens (Fig. 5). These results suggest that dasotraline is likely to produce relatively small, but persistent, increases in norepinephrine and dopamine efflux which would accord with the moderate efficacy of dasotraline in ADHD clinical trials.

The pharmacodynamics of dasotraline on synaptic dopamine concentrations in the nucleus accumbens predict minimal potential for abuse as a stimulant and that prediction has been confirmed by findings in drug-discrimination and human abuse studies. On the other hand, dasotraline's sustained potentiation of mesolimbic dopaminergic transmission accounts for the emergence of psychotic adverse events which limited the tolerable dose range for clinical use. A New Drug Application for the use of dasotraline to treat ADHD was declined by the FDA in August 2018 (Sunovion Press Release 2018). The FDA stated that additional clinical data were needed to further evaluate the efficacy and tolerability of dasotraline. Sunovion continued clinical development of dasotraline for binge-eating disorder (BED) in adults, but in 2020 the company discontinued development of dasotraline in both indications (Sunovion Press Release 2020).

4.4 Vortioxetine

Vortioxetine (Trintellix®) is approved for treatment of major depressive disorder in adults. It has agonist actions at 5-HT_{1A} receptors, partial agonist actions at 5-HT_{1B} and antagonist actions at 5-HT_{3A} and 5-HT_7 receptors (Mørk et al. 2012). Vortioxetine is a potent 5-HT reuptake inhibitor ($IC_{50} = 5.3$ nM) with 26-fold and 170-fold selectivity versus norepinephrine and dopamine reuptake, respectively (Bang-Andersen et al. 2011). Consistent with a reuptake inhibition profile that is potent on 5-HT and weak on norepinephrine, in microdialysis experiments in rats, vortioxetine substantially increased the extracellular concentration of 5-HT in the PFC with marginal increases in dopamine and norepinephrine (Mørk et al. 2012). Vortioxetine showed cognitive-enhancing effects in various animal models including novel object recognition, Y-maze spontaneous alternation and reversal of phencyclidine-induced deficits in attentional set-shifting (Sanchez et al. 2015).

Vortioxetine was evaluated in a DBRCT, proof-of-concept study in 227 adults (Biederman et al. 2019). The study employed an enrichment strategy by including a second stage in which non-responders to placebo were re-randomized to active treatment or placebo. The objective was to minimize the impact of high placebo response rates, thereby increasing the statistical power of the study. Subjects were initially randomized 1:1:3 to vortioxetine, 10 mg/day or 20 mg/day, or to placebo for 6 weeks (Stage 1). Non-responders on placebo were then randomized 1:1:1 to vortioxetine, 10 mg/day or 20 mg/day, or placebo for the following 6 weeks (Stage 2). The subjects were composed of the hyperactive/impulsive (79%) and inattentive (21%) ADHD presentations. In Stage 1, Stage 2 and the pooled analysis set, neither dose of vortioxetine separated from placebo on the primary AISRS scale nor on any of the secondary outcome measures except the Sheehan Disability Scale.

On the specific scales included to measure the effect of vortioxetine on cognitive function (Behaviour Rating Inventory of Executive Function [BRIEF]; BRIEF-A and BRIEF-B), the drug showed no beneficial effects. This large and well-powered clinical trial unequivocally demonstrated vortioxetine's lack of efficacy in ADHD. From a pharmacological perspective, it provides yet another incidence of a serotonergic drug being ineffective in ADHD. We have previously hypothesized that all clinically effective ADHD drugs, with the exception the α_{2A}-adrenoceptor agonists, produce substantial increases in extracellular norepinephrine and dopamine in the PFC (Heal and Pierce 2006; Heal et al. 2008, 2009, 2012, 2013a), the minimal effect of vortioxetine (Mørk et al. 2012) provides further confirmation of the validity of the hypothesis. The final implication of the evidence is that enhancing cognitive function *per se* is of no therapeutic benefit in ADHD unless it is accompanied by a drug-induced reduction of inattentiveness, distractibility, impulsivity and hyperactivity.

4.5 Droxidopa

Droxidopa is a CNS-penetrant norepinephrine prodrug that is metabolized by DOPA decarboxylase to liberate noradrenaline (Goldstein 2006). Droxidopa (Northera®) is approved for adults with symptomatic neurogenic orthostatic hypotension. Adler and Gorny (2019) reported based on an ADHD trial in 20 adult subjects (open-label phase) and 11 subjects (double-blind phase to assess the effect of adjunctive carbidopa) that Droxidopa (3× daily at doses of 200–600 mg for 3 weeks) produced a moderate decrease in the ADHD-RS-Total score. Efficacy was not substantially greater after 6 weeks of treatment. Co-administration of carbidopa did not augment the therapeutic effect of droxidopa. Adverse events appear burdensome with 25% occurrence of headache and somnolence, 20% depressed mood, 15% suicidal ideation, myalgia, hyperhidrosis, and 10% insomnia, musculoskeletal stiffness, nausea, sedation, abnormal dreams and cough (Adler and Gorny 2019).

The effect of droxidopa is exclusively mediated via increased extracellular concentrations of norepinephrine in the brain, and therefore, its efficacy would be predicted to be similar to the α_{2A}-adrenoceptor agonists. Without concomitant norepinephrine reuptake inhibition and/or monoamine oxidase inhibition, inactivation due to neuronal uptake and catabolism would be very rapid making once-daily dosing difficult to achieve. The observation that droxidopa is efficacious in ADHD is interesting from a clinical and mechanistic perspective, but the probability of droxidopa becoming an addition to the ADHD treatment formulary is probably remote.

4.6 Baicalin

Baicalin (or baicalein) is a flavonoid extracted from the plant *Scutellaria baicalensis Georgi* that is used in Chinese traditional medicine. This compound appears to interact with DAT because it is protective against a number of neurotoxins which employ this transporter system (Gao et al. 2015; Hung et al. 2016). Zhou et al. (2019) proposed baicalin as an interesting compound for the treatment for ADHD based on the observations that it decreased hyperactivity in the spontaneously hypertensive rat model and increased markers of striatal dopamine function. This proposal was based on the erroneous hypothesis by Zhou et al. (2019) that ADHD is a dopamine deficit disorder and ADHD drugs produce efficacy by increasing striatal dopaminergic transmission. Whether baicalin will be efficacious in ADHD will only be answered in clinical trials.

4.7 Summary

A search of the literature revealed relatively few novel pharmacological approaches or compounds being proposed for the treatment of ADHD. Kim et al. (2018) proposed H_3-receptor antagonists as potential ADHD treatments based on the effects of three commercially available compounds in their neonatal habenula lesioned, rat model of ADHD. No drug-candidates with this mechanism are currently in development. An earlier attempt by the company, Johnson and Johnson, to develop the H_3-receptor antagonist, bavisant (JNJ31001074), in ADHD was discontinued due to a lack of efficacy in clinical trials (Weisler et al. 2012).

This overview of new approaches to treat ADHD has confirmed and consolidated the hypothesis that clinically effective ADHD drugs indirectly or directly increase catecholaminergic neurotransmission in the PFC. Attempts to enhance catecholaminergic signalling through modulatory neurotransmitter systems have all been discontinued; most for lack of efficacy. Treatment of ADHD with cognitive-enhancing drugs has similarly failed. New drugs that have been approved for ADHD are either catecholamine or selective norepinephrine reuptake inhibitors. Triple reuptake inhibitors with preferential effects on dopamine reuptake have not been a success. The substantial number of failures in the last decade probably accounts for the focus on developing novel catecholaminergic and noradrenergic (norepinephrine) drugs and the dearth of drug-candidates entering clinical development.

5 Progress in the Pharmacological Management of ADHD

In the previous section, we outlined the profile of the ideal drug to treat ADHD. In this section we will review progress in achieving those objectives.

5.1 Efficacy in ADHD

Results from clinical trials (e.g., Wigal et al. 2005; Wang et al. 2007; Newcorn et al. 2006, 2017; Dittmann et al. 2013; Martin et al. 2014; Soutullo et al. 2013; Nagy et al. 2016) and meta-analyses (e.g., Faraone et al. 2002; Cunill et al. 2016; Bushe et al. 2016; Cortese et al. 2017; Stuhec et al. 2019; Elliott et al. 2020) clearly demonstrate that the effect levels in children, adolescents and adults with ADHD and the proportion of patients that are effectively treated by the current portfolio of drugs are very high. It is often assumed that evidence from these sources also supports the hypothesis that stimulant drugs are more effective than non-stimulants (Dittmann et al. 2013; Cunill et al. 2016; Liu et al. 2017; Riera et al. 2017; Cortese et al. 2018) which has resulted in drugs like atomoxetine being relegated from first-line therapy in the UK (NICE: Guidance NG87 2018). However, the situation is rather more complex. For example, although OROS-methylphenidate (Concerta®) has been reported to be superior to atomoxetine in efficacy in some ADHD trials (Kemner et al. 2005; Starr and Kemner. 2005), it showed no substantial advantage over atomoxetine in others (Kratochvil et al. 2002; Wang et al. 2007). Hanwella et al. (2011) and Rezaei et al. (2016) conducted meta-analyses which revealed that OROS-methylphenidate, which has highly predictable pharmacokinetics, was more clinically effective than atomoxetine, whereas IR-methylphenidate which is less consistently efficacious because it has to be taken 3× daily was not superior. Clinical trial design may also distort the outcomes. Many trials are of short duration, e.g. 6 or 8 weeks, which favours drugs with a rapid trajectory of efficacy. A significant proportion of patients prescribed atomoxetine show a gradual improvement (Sobanski et al. 2015) and meta-analyses of clinical trials of at least 12-week duration showed no efficacy advantage of OROS-methylphenidate over atomoxetine (Bushe et al. 2016; Elliott et al. 2020). Forced-titration protocols are another potential source of bias because they maximize efficacy at the expense of increased AEs. LDX was significantly more efficacious than OROS-methylphenidate in a forced upward-titration trial, but not in a flexible-dose regimen, which balances efficacy against tolerability (Newcorn et al. 2017).

With these caveats in mind, the balance of evidence from clinical trials (Faraone et al. 2002; Soutullo et al. 2013; Martin et al. 2014; Coghill et al. 2013, 2014a; Nagy et al. 2016) or meta-analyses (Faraone and Buitelaar 2010; Stuhec et al. 2015; Cortese et al. 2018) supports the view that LDX and other amphetamine-based medications are the most effective in treating ADHD.

The pharmacology of effective ADHD drugs is highly restricted, which begs the question what happens when patients are unresponsive to their prescribed medication. Hodgkins et al. (2012) analysed data from crossover trials with methylphenidate and amphetamine and observed that 41% of subjects responded well to either medication, but 28% of the group preferentially responded to amphetamine and 16% preferentially to methylphenidate. There is also evidence to demonstrate that switching not only between stimulants, but also to non-stimulant drugs can improve outcomes in poor responders (e.g., Quintana et al. 2007; Newcorn et al. 2008; Jain et al. 2013). The use of guanfacine as an adjunctive treatment is an emerging strategy which is being employed for patients with comorbid disorders (e.g., Findling et al. 2014) and in patients who have troubling residual disability when maintained on stimulants (Wilens et al. 2012; Cutler et al. 2014; Butterfield et al. 2016; McCracken et al. 2016).

Since all effective ADHD drugs have catecholaminergic mechanisms, a logical question is what benefit derives from medication switches or combination therapy? ADHD results from dysregulation in norepinephrine and dopamine signalling; the system is not broken, merely out of balance. The probable explanation is the appropriate balance between norepinephrine and dopamine neurotransmission is needed to optimize drug effect, which is why even subtle changes in medication can have a profound clinical impact.

It is important to appreciate that relative efficacy estimates from head-to-head trials or meta-analyses are based on population data. However, for the prescriber and the ADHD patient, benefit is measured by the clinical outcome for the individual. It all comes down to which drug best meets the patient's needs.

5.2 Once-Daily Medication

All pharmacotherapies for ADHD are available as once-daily medications (see Table 1) including the new introductions, LDX, viloxazine-ER, Azstarys and clonidine-XR. Once-daily pharmacotherapy in ADHD is now regarded as essential. For a disorder that is characterized by inattention and distractibility, expecting a child or adult to self-medicate several times a day is inappropriate and inevitably produces gaps in therapeutic effect. Moreover, all medications with the exception of the α_2-adrenoceptor agonists are C-II controlled drugs. Patients taking them into schools creates opportunities for diversion and places a burden on school authorities. This point has now been accepted in clinical practice guidance documents where once-daily drugs, rather than cheaper immediate-release, are now recommended (Bolea-Alamañac et al. 2014; NICE 2018 Guidance).

Some children are resistant to swallowing pills or capsules and another compliance advantage offered by several drugs is the ability to break the capsule and mix the medication with food or drinks or provide it as a liquid formulation.

5.3 Relapse on Withdrawal

ADHD is now accepted to be a disorder that spans childhood and, for a substantial number of individuals, persists into adulthood. Although clinical trials have shown the efficacy of ADHD medications in all of the relevant age cohorts, most pivotal trials in ADHD are relatively short duration: e.g., 6–12 weeks. The question of whether drugs are effective when taken long-term (>12 weeks) has been answered adequately for the stimulants (Buitelaar et al. 2012; Mattingly et al. 2013; Coghill et al. 2018; Matthijssen et al. 2019) and non-stimulants (Kratochvil et al. 2006; Wilens et al. 2006; Adler et al. 2008b; Fuentes et al. 2013), but perhaps less satisfactorily for the sedative α_2-adrenoceptor agonists (Sallee et al. 2009; Newcorn et al. 2016). If the premise that long-term treatment of ADHD is beneficial, one of the major challenges is to maintain medication compliance. Discontinuation rates in open-label extension trials can exceed 50% (e.g., Sallee et al. 2009; Newcorn et al. 2016). Ahmed and Aslani (2013) indicated non-adherence rates to ADHD medication ranging from 15 to 87%. In the landmark Multimodal Treatment of ADHD (MTA) study, ~25% were found to be non-compliant with drug treatment in ≥50% saliva assays with only 54% of subjects drug-adherent at every time-point (Pappadopulos et al. 2009). There is agreement that although compliance is reasonably good early in treatment during childhood, it declines quite substantially after about a year (Efron et al. 2020) and as the patients enter late adolescence (Ahmed and Aslani. 2013; Efron et al. 2020; Rao et al. 2021), with a particular problem occurring in the transition from home to college (Schaefer et al. 2017). Discontinuation of treatment often results in a regression of the disorder (e.g., Coghill et al. 2014b; Matthijssen et al. 2019) with serious adverse outcomes for a significant proportion of individuals with ADHD (Rao et al. 2021).

As medication compliance is far from ideal, it raises the question of the consequences of discontinuation. Discontinuing amphetamine- or methylphenidate-based stimulants leads to a rapid deterioration of symptoms and rapid relapse to pre-medication status (e.g., Coghill et al. 2014a, b; Brams et al. 2012; Arnold et al. 2004; Matthijssen et al. 2019). Relatively rapid relapse has also been reported after discontinuation of guanfacine-XR (Newcorn et al. 2016). In contrast, efficacy after discontinuing atomoxetine is maintained at high levels for many weeks or months (Michelson et al. 2004; Upadhyaya et al. 2013; Buitelaar et al. 2015; Tanaka et al. 2017). Following 6 months open-label treatment, adults randomized to placebo showed >90% maintenance of efficacy for the following 6 months (Upadhyaya et al. 2013).

This is an interesting and potentially important finding. As discussed earlier in this review, atomoxetine has a relatively slow onset of action compared with the stimulants and often takes 2–3 months to produce its maximum effect. In this respect, the therapeutic effect of atomoxetine resembles the time-course of effect of monoamine reuptake inhibitors in treating depression. This contrasts with the almost instantaneous efficacy produced by the stimulants, and it is well established their effects are directly driven by the concentration of drug in plasma and brain.

Clearly, there are two very different therapeutic mechanisms at work. The intriguing possibility is that atomoxetine may be effecting a more permanent resetting of catecholaminergic function in the brain, leading to remission in patients for substantial periods. The stimulants merely provide daily symptom relief that rapidly dissipates when treatment is discontinued.

5.4 Drug-Induced Side Effects

This topic has been extensively discussed in previous reviews (Heal and Pierce 2006, Heal et al. 2009, 2012, 2013a, b). ADHD drugs are generally selective monoamine transporter ligands that are devoid of off-target actions. Viloxazine-ER might be an exception because it is also proposed to interact with various other drug targets (Yu et al. 2020). Overall, recent drug introductions and the failure of all drug-candidates with non-catecholaminergic mechanisms have consolidated the earlier position. Identical pharmacology mediates the therapeutic effect and side-effects of these drugs and, therefore, optimizing treatment will be a balance between maximizing efficacy whilst maintaining side-effects at tolerated levels. This point is clearly illustrated by the head-to-head comparison trial between LDX and OROS-methylphenidate (Newcorn et al. 2017). LDX was significantly more efficacious than OROS-methylphenidate in a forced upward-titration [a design which maximizes efficacy] but not in a flexible-dose regimen [a design which balances efficacy against tolerability] (Newcorn et al. 2017). The advice to prescribers is to avoid over-medicating patients; each incremental dose of the chosen ADHD medication should be given sufficient time to deliver efficacy and for AEs to ameliorate before increasing the dose if the response is inadequate.

As described in earlier sections of this review, many, but not all, AEs are common across all catecholaminergic ADHD drugs. ADHD drugs are usually referred to as "stimulants" and "non-stimulants". Based on pharmacology, therapeutic and AE profile, we propose that the α_2-adrenoceptor agonists should be classified as "sedative" ADHD drugs.

5.5 Abuse Liability

Abuse liability is a major issue for ADHD drugs. Expert opinion and clinical guidance now agree that the stimulants should be first-line treatment in paediatric and adult ADHD (Bolea-Alamañac et al. 2014; [NICE 2018 Guidance]). The current stimulants are all in C-II, which is the most restrictive category for controlled drugs. It creates administrative and logistical challenges for prescribers and remains a barrier to treatment for many parents and some prescribers. Discovering a novel ADHD drug with efficacy equal to *d*-amphetamine or methylphenidate combined with a reduced potential for abuse is a long-standing aspiration in the pharmaceutical

industry and one that has not yet been fully realized. Whilst not downplaying the seriousness of stimulant abuse, the situation for ADHD drugs has improved substantially over the years, but much of the progress does not receive the recognition it deserves because of the rigidity of controlled drug legislation.

Once-daily formulations and prodrugs administered in the home give parents control over drug compliance and removes the need for controlled drugs to be carried by children and adolescents creating risks of theft, diversion and abuse.

Many of these once-daily medications have abuse-deterrent and/or tamper-resistant properties, which makes extracting and abusing the active ingredient extremely difficult. Examples are the Eudragit® polymer beads in Adderall-XR which expand to form a sticky gel if attempts are made to liquid extract amphetamine, rendering the product unusable for insufflation or injection. LDX is a prodrug that is virtually impossible to cleave to yield *d*-amphetamine even under extreme chemical conditions (Alda et al. 2014).

Prodrugs like LDX and Azstarys also reduce the risk of abuse because: (1) they are by definition pharmacologically inactive; (2) they have a delayed onset of effect eliminating the immediate "high" sought by stimulant abusers; (3) at pharmacologically equivalent doses, they produce less drug-liking than the active moiety when taken orally; and (4) their potency is not enhanced when taken by insufflation or intravenous injection (Heal et al. 2013b; Hutson et al. 2014; Ermer et al. 2016; Azstarys FDA Multi-discipline Review 2021).

The greatly reduced risk of abuse compared with illicit cocaine and methamphetamine is reflected in the results from the National Survey on Drug Use and Health (NSDUH) in an annual, household-based national survey on the use of illicit drugs, alcohol and tobacco by Americans aged 12+ years (National Survey on Drug Use and Health [NSDUH], 2015–2019). However, with the exception of the classification of SDX as a C-IV controlled drug, none of these risk-reduction measures is reflected either by the abuse warnings in the product labels or less restrictive scheduling.

6 The Link Between ADHD and Binge-Eating Disorder

There are now established links between ADHD and binge-eating disorder (BED). Many of the mental health problems prevalent and commonly comorbid with ADHD including conduct problems, negative affect, anxiety and impulse control and substance abuse disorders (De Alwis et al. 2014; Eme 2012; Ishii et al. 2003; Pliszka 1998) are also risk factors for the development of BED (Hilbert et al. 2011, 2014; Hudson et al. 2007; Kessler et al. 2013; McCuen-Wurst et al. 2018). ADHD is also associated with higher rates of eating disorders and behavioural addictions (gambling, compulsive buying disorder and internet addiction) (Romo et al. 2018), and anxiety and depression are frequently comorbid with ADHD (Chen et al. 2018; Polyzoi et al. 2018). Impulsivity and intolerance of delayed reward are core

symptoms of BED. McElroy et al. (2016b) reported that subjects with BED exhibited deficits in motor and non-planning impulsiveness, but not attentional impulsiveness.

Mole et al. (2015) studied delay-discounting in obese subjects with/without BED and showed both groups exhibited greater delay-discounting: i.e., increased cognitive impulsivity, compared with normal, healthy volunteers. Increased delay-discounting as an indicator of impulsive choice in binge-eating disorder sufferers has been observed by other investigators (Davis et al. 2010; Stojek et al. 2014). The overlap between the psychopathology of BED and ADHD led to the hypothesis that binge-eating is also an impulse control disorder (Heal and Smith 2021; Kessler et al. 2016; Reinblatt 2015; Ural et al. 2017). This conclusion is further supported by the observation that two catecholaminergic medications, LDX and dasotraline, have proven efficacy in treating BED (Citrome et al. 2019; McElroy et al. 2015; McElroy et al. 2016a; Navia et al. 2017). Beneficial effects of LDX included significant decreases on the obsessional and compulsive scores of the Yale-Brown Obsessive Compulsive Scale adapted for Binge Eating (YBOCS-BE) and the Barratt Impulsiveness Scale, version 11 (BIS-11) self-reported questionnaire scores for non-planning and motor impulsivity (McElroy et al. 2016b). Dasotraline also significantly reduced scores on the YBOCS-BE obsession and compulsion scales (Navia et al. 2018) and although impulsivity scores were not reported, dasotraline-treated subjects showed a marked and significant increase in the dietary restraint score on the Eating Disorder Examination Questionnaire Brief Version (EDE-Q7) scale (Navia et al. 2018). LDX is the only medication that has been approved to treat binge-eating disorder. Dasotraline was recently discontinued in the USA as a treatment for BED (Sunovion Press Release 2020).

7 Concluding Remarks

The intervening decade since we wrote our last review on the pharmacotherapy of ADHD has produced no evidence to question the hypothesis that ADHD is a catecholaminergic disorder which responds to drugs that potentiate noradrenergic and/or dopaminergic signalling in the brain.

Attempts to treat this disorder successfully through neurotransmitter systems that modulate catecholaminergic function or with cognitive enhancers all failed in clinical trials. All of the recently approved drugs and those currently in late-stage clinical development broadly remain within the same pharmacological confines as existing medications. Nonetheless, considerable progress in ADHD therapy has been achieved, particularly in the areas of once-daily treatment, greater levels of efficacy and reduced risks of diversion and abuse.

In our view, the current stratification of ADHD medications as non-stimulants and stimulants does not adequately reflect either their pharmacological or clinical profiles. As illustrated in Fig. 7, we recommend that a third classification of "sedative ADHD drugs" should be added to non-stimulants and stimulants. α_2-Adrenoceptor

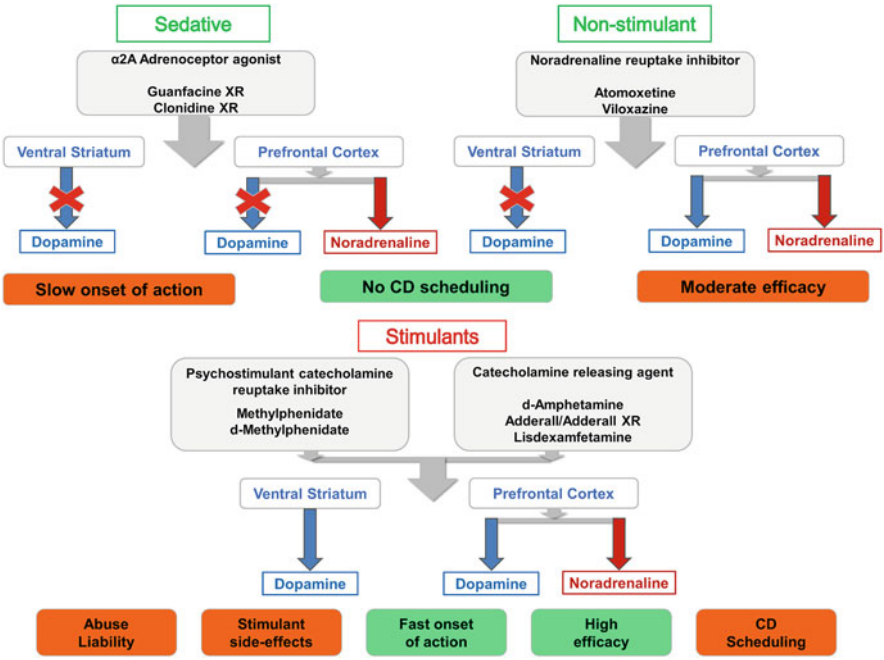

Fig. 7 Revised classification of ADHD drugs. Previous knowledge on the pharmacology of ADHD drugs supplemented by the successes and failures in clinical development of various new drug-candidates supports classification of ADHD drugs into three broad categories based on their actions on catecholaminergic neurotransmission in the PFC, striatum and mesolimbic system. Guanfacine and clonidine which make up the "Sedative" ADHD drugs enhance noradrenergic transmission via α_{2A}-adrenoceptor receptors. These drugs decrease noradrenergic signalling via other adrenoceptor subtypes and either attenuate or are inactive on dopaminergic neurotransmission. The selective noradrenaline reuptake inhibitors comprise the "Non-stimulant" ADHD drugs. They increase noradrenergic and dopaminergic neurotransmission in the PFC, but do not potentiate dopaminergic signalling in the striatum and accumbens. The amphetamines and methylphenidate make up the "Stimulant" ADHD drugs. Although the former are releasing agents and the latter are cocaine-like stimulants, both types of stimulant simultaneously increase noradrenergic and dopaminergic neurotransmission in the PFC and dopaminergic signalling in the striatum and nucleus accumbens. The strengths (in the green boxes) and weakness (in the amber boxes) are shown for the Sedatives, Non-stimulants and Stimulants. The absence of a secondary action on striatal and limbic dopamine function is in our view the main reason why these drugs are less efficacious than the Stimulants and have a slower onset of action. On the other hand, they pose no risk for abuse and they are not Controlled Drugs

agonists, which comprise the sedative category, have an exclusively norepinephrine- and PFC-based therapeutic mechanism which delivers moderate efficacy with a gradual onset of action. With no dopaminergic component to their pharmacology, they pose no risk for human abuse and are not controlled drugs. The non-stimulants comprising the selective norepinephrine reuptake inhibitors deliver noradrenergic and dopaminergic therapeutic effects in the PFC but have no secondary action

dopaminergic neurotransmission in the ventral striatum. The non-stimulants have moderate efficacy with a gradual onset of action and are not abused or controlled drugs. The amphetamine- and methylphenidate-based drugs comprise the stimulant ADHD medications. These powerful drugs markedly increase catecholaminergic neurotransmission in the PFC and dopaminergic neurotransmission in the ventral striatum and carry a significant abuse risk. Although this risk has been considerably reduced through formulation, tamper-resistance and prodrug strategies, they still remain as C-II controlled drugs.

There are few new compounds in early or late-stage development in ADHD. This situation may reflect the failure of drug-candidates with novel pharmacological mechanisms in clinical trials, the high bar for efficacy that has been set by the current generation of ADHD medications, or a belief that when all of these drugs lose patent protection the marketing opportunities for new entries will be relatively modest. Our view is pharmacotherapy for ADHD would be greatly improved by the introduction of new drugs that will offer the efficacy equivalent to the stimulants with a significantly reduced risk of abuse; the latter resulting in less restrictive controlled drug scheduling. Given the experience of LDX and dasotraline, such novel ADHD drugs could also be of considerable benefit in treating binge-eating disorder.

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