Current and Investigational Medication Delivery Systems for Treating Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: To review currently available formulations and emphasize unmet needs in the pharmacologic management of attention-deficit/hyperactivity disorder (ADHD).

Data Sources: Publications and clinical trials were identified through PubMed and ClinicalTrials.gov, respectively. A Web-based search identified prescribing information for approved agents for treating ADHD, along with relevant guidelines and diagnostic criteria.

Study Selection: The following search terms were used: (1) *ADHD* or *attention-deficit/hyperactivity disorder* or *ADD* or *attention deficit hyperactivity disorder* and/or (2) *amphetamine* or *methylphenidate* or *atomoxetine* or *guanfacine* or *clonidine*. Additional searches were performed using product brand names, and *clinical trial* was applied as a filter. Relevant studies were only included if published in English-language peer-reviewed journals and if involved agents were currently available (or pursuing approval) in the United States. Reviews of literature prior to 2005 and from 2005 to 2008 have been published previously; therefore, the present search focused on studies published from January 2009 through May 2016. In addition, reference lists of review articles and relevant studies were also examined to help identify additional studies.

Data Extraction: A total of 578 publications were identified from the PubMed search, from which 426 publications were initially excluded based on review of the title and abstract. Reasons for exclusion included a focus on comorbid disorders, specific subpopulations, endpoints unrelated to improving ADHD symptomatology (eg, executive function, cognition, substance use), or quality of life measures. A more thorough assessment of the remaining citations, including publications and prescribing information, produced the final 219.

Results: Pharmacotherapy with stimulant and nonstimulant options is the most common approach for treating ADHD in adults and children. Stimulants are mostly formulated as either tablets or capsules; however, the newer generation includes transdermal patches, oral suspensions (liquids), chewable tablets, and orally disintegrating tablets. Nonstimulants are available in oral capsule (atomoxetine) and tablet (guanfacine and clonidine) formulations.

Conclusions: Despite the broad range of treatment options currently available, nonadherence remains a significant problem in ADHD. While evidence is currently lacking, the availability of new formulations may improve adherence.

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Attention-deficit/hyperactivity disorder (ADHD), which is characterized by impairments in maintaining sustained attention, modulating activity level, and exercising impulse control,[1] is the most prevalent neurobehavioral disorder in children.[2] A study[3] conducted in 2011 estimated that 11% of US school-aged children had ever received a diagnosis of ADHD. In addition, although ADHD symptoms tend to decline with age,[4] symptoms and associated impairment persist into adulthood in approximately 50% of cases,[5] affecting at least 4% of the adults in the United States.[6]

While there has been a reported 42% increase in ADHD diagnoses in children since 2003 in the United States, it is unclear if the true prevalence is increasing or if the increased rate reflects overdiagnosis or more disease awareness as a result of the more inclusive guidelines put forth in 2013 with the introduction of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*).[3,7–9] Despite increasing incidence rates, ADHD remains underdiagnosed in some patient populations including children and adults in the United States.[10–12] Additionally, the prevalence of ADHD and its subtypes reportedly varies by the socioeconomic and racial and ethnic composition of the population.[11,12]

ADHD symptoms are often associated with considerable functional impairment. In children and adolescents, symptoms can negatively affect family life, academic achievement, and overall conduct.[13–15] Similarly, adults with ADHD tend to have lower educational attainment and higher rates of arrests, traffic violations, unemployment, and divorce.[16,17] The annual incremental costs of ADHD have been estimated to range from $143 billion to $266 billion in 2010 US dollars.[18]

The primary treatment goals for patients with ADHD are improving symptoms and functionality and removing behavioral obstacles through behavioral therapy and pharmacologic agents.[19] Behavioral therapies are the first-line option recommended for preschool-aged children, while pharmacologic agents are often the first-line option for school-aged children and adults.[2,20] Although most patients exhibit a clinical response to stimulant therapy, some patients respond differently in terms of efficacy or tolerability to the different classes of medication.[21] A priori predictors of treatment response would be invaluable,[22] but few reliable predictors of response are available, and most therapeutic decisions are based on trial-and-error.[23]

Currently, more than 20 different pharmacologic options exist from which providers may choose in everyday clinical practice, and there are numerous other stimulant and nonstimulant options in various stages of clinical development.[24,25] This systematic review summarizes recent phase 2 through 4 clinical trials of pharmacologic ADHD treatments.

Clinical Points

- There are many formulations of stimulants and nonstimulants for treating attention-deficit/hyperactivity disorder (ADHD) that clinicians use in treatment programs for their patients.
- A comprehensive understanding of the efficacy, safety profile, and administration features of each formulation is critical for proper treatment individualization.
- Use of formulations that are acceptable to patients with ADHD may improve adherence in a patient population with significant demonstrated rates of nonadherence.

METHOD

Publications and clinical trials were identified through PubMed and ClinicalTrials.gov, respectively. The following search terms were used: (1) *ADHD* or *attention-deficit/hyperactivity disorder* or *ADD* or *attention deficit hyperactivity disorder* and/or (2) *amphetamine* or *methylphenidate* or *atomoxetine* or *guanfacine* or *clonidine*. Additional searches were performed using product brand names, and *clinical trial* was applied as a filter.

Figure 1 shows the design for the systematic search strategy that was used to identify relevant studies. Relevant studies involved any age group (children, adolescents, or adults) and agents currently available (or pursuing approval) in the United States. Because similar reviews of literature prior to 2005[26] and from 2005 to 2008[24] have been published, the present search focused only on studies completed or published in English-language peer-reviewed journals between January 2009 and May 2016. In addition, reference lists of review articles and relevant studies were also examined to help identify additional studies.

RESULTS

A total of 578 publications (from January 2009 to May 2016) were identified from the PubMed search, from which 426 publications were initially excluded based on review of the title and abstract. Reasons for exclusion included a focus on comorbid disorders, specific subpopulations, endpoints unrelated to improving ADHD symptomatology (eg, executive function, cognition, substance use), or quality of life measures. We also used a Web-based search to identify prescribing information for approved agents for treating ADHD, along with relevant guidelines and diagnostic criteria. A more thorough assessment of the remaining citations produced the final 219.[1–219]

Stimulants

Stimulants including methylphenidate and dexmethylphenidate and amphetamine derivatives (ie, mixed amphetamine salts, lisdexamfetamine, and dextroamphetamine) are considered first-line therapeutic options for adults and children with ADHD.[27,28] Short-term use of these agents reduces symptoms, including short attention span, distractibility, impulsive behavior, hyperactivity, and restlessness, in addition to improving vigilance, cognition, reaction time, response time, response inhibition, and short-term memory.[29] In general, stimulants offer greater effectiveness than nonstimulant options,[30] and approximately 70% of patients will experience clinical improvement with their initial stimulant treatment.[31,32] Stimulants have been shown to also improve performance in some individuals without ADHD.[33]

Overall, side effects with stimulants tend to be mild to moderate in severity and can be managed by reducing the dose or by modifying the medication administration time.[29] Commonly observed side effects, including insomnia, anorexia, nausea, decreased appetite, weight loss, headache, increased blood pressure, elevated heart rate, abdominal pain, irritability, and mood lability, usually emerge soon after beginning treatment and generally subside over time.[29] Although there is concern that use of stimulants in children may stunt growth, the results of a recent longitudinal study[34] suggest that stimulants do not cause significant changes in growth or adult height. However, in rare instances, stimulants have been associated with more serious side effects including seizures, hypertension, psychosis, and hepatotoxicity.[29] In general, stimulants can be used safely in children and adults.[35,36]

ADHD is thought to result from dopaminergic and noradrenergic imbalances that result in inefficient information processing by pyramidal neurons in the prefrontal cortex.[37] Although the exact mechanisms of the therapeutic action of stimulants in ADHD are incompletely understood, it has been hypothesized that they work by increasing extraneuronal catecholamine concentrations in the prefrontal cortex.[37,38] Both classes of stimulants (methylphenidate and amphetamine derivatives) increase synaptic dopamine and norepinephrine transmission.[38] Dopamine may decrease background noise associated with extraneous input that contributes to inattentive symptoms, and norepinephrine may increase the signal gain associated with task-relevant information.[37]

Most short-acting stimulant formulations have a duration of action ranging from 3 to 6 hours,[29,31,39] which may necessitate multiple doses to manage ADHD symptoms throughout the day. Short-acting formulations are associated with decreased adherence, potential embarrassment or stigma for individuals taking doses during the daytime (eg, during school or work hours), difficulties with storing and handling controlled substances, and increased potential for diversion.[39] In order to help overcome some of these drawbacks, numerous long-acting stimulant formulations have been developed, with durations of effect of up to 12 hours.[30,40,41] Included among the long-acting stimulant options are multiple controlled-release formulations that combine a rapid onset of action with extended coverage throughout the day (ie, multiphasic release).[39] More recent advances with stimulant formulations, including transdermal patches, oral suspensions (liquids), chewable tablets, and orally disintegrating tablets (ODTs), provide patients with alternatives if they cannot or prefer not to swallow tablets

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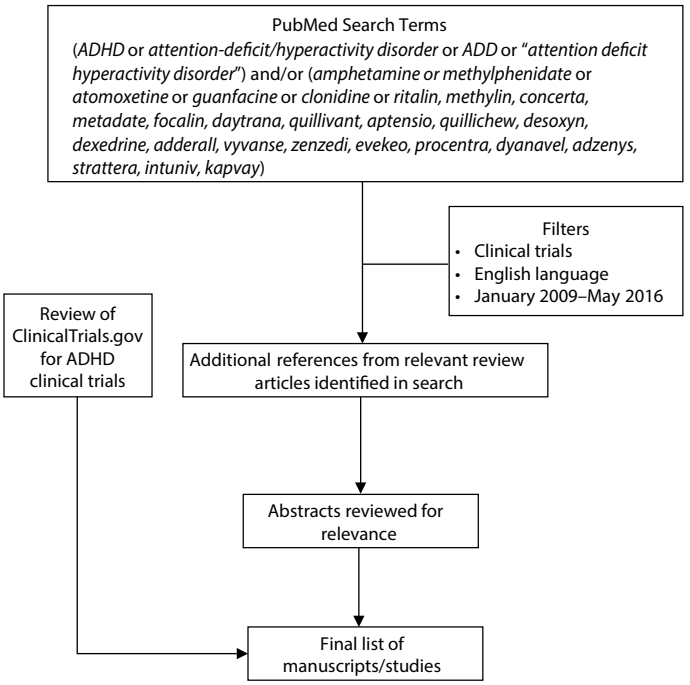
Figure 1. Schematic Diagram of the Search Strategy Employed to Identify Relevant Studies as of May 2016



or capsules (or prefer not to open and sprinkle capsule contents on food) without compromising efficacy or duration of effect.[42]

Although there have been no direct comparisons between the abuse potential of short- and long-acting stimulants, some of the characteristics of long-acting stimulants suggest that they could reduce the likelihood of diversion. For instance, the once-daily administration of long-acting stimulants could reduce the supply of medication at schools needed for intraday dosing.[39] In addition, controlled release of stimulants may result in less euphoria[43,44] because the reinforcing effects of drugs are related to the rate of delivery to the brain.[45] Lastly, the long-acting stimulant lisdexamfetamine is a prodrug that must be metabolized to dextroamphetamine in the bloodstream for a therapeutic effect. There was no difference in the pharmacokinetic (PK) profile of *d*-amphetamine when 50-mg lisdexamfetamine was administered orally or intranasally in a study[46] of healthy adults; these attributes may make lisdexamfetamine less attractive to abusers than immediate-release dextroamphetamine.[46–48]

Methylphenidate. Methylphenidate was first synthesized more than 70 years ago,[49] and its efficacy and safety in patients with ADHD have been studied extensively. Numerous methylphenidate formulations of *d*- isomers (ie, dexmethylphenidate) or racemic mixtures of both *d*- and *l*- isomers, including liquids (both solution and suspension), chewable tablets, oral tablets, capsules, an oral disintegrating tablet, and a transdermal patch, are currently approved or in late stages of development (Table 1).

Short-acting methylphenidate formulations, including oral tablets, chewable tablets, and solutions, require frequent dosing to control symptoms throughout the day and produce large peak/trough effects. Nevertheless, these agents may be useful when an additional dose is needed later in the day to supplement a once-daily dose or for those patients who wish to have greater flexibility in dosing.[29] Long-acting methylphenidate formulations have a duration of action of 8 to 12 hours.[2] The first-generation long-acting methylphenidate formulation (Ritalin SR, Novartis Pharmaceuticals, East Hanover, New Jersey[50]) used a wax matrix as the modified-release technology to provide a duration of up to 8 hours. However, Ritalin SR has a variable duration of action due to an inconsistent absorption profile of methylphenidate from the wax matrix and is not widely used in clinical practice.[113–116]

Subsequently, several controlled-release methylphenidate formulations have been developed with a multiphasic release profile. The osmotically controlled-release (OROS) oral methylphenidate tablet formulation (Concerta, Janssen Pharmaceuticals, Titusville, New Jersey[59]) is designed to deliver methylphenidate in a controlled manner for approximately 10 to 12 hours.[117] The OROS formulation does not allow the pill to be crushed, which may present challenges for patients who have difficulty taking oral medications.[24] However, it may also reduce the risk of diversion and abuse because it cannot be easily manipulated for more rapid absorption.[29,39] Metadate CD (UCB, Smyrna, Georgia[88]) is a capsule formulation that includes a mixture of immediate- and extended-release beads (30% immediate-release to 70% extended-release ratio). Metadate CD delivers methylphenidate through a 2-phase drug release providing symptom control through ~8 hours.[24,88,118] Aptensio XR (Rhodes Pharmaceuticals, Coventry, Rhode Island[107]) is another capsule formulation; however, it contains multilayer beads (40% as immediate- and 60% extended-release). After administration, methylphenidate concentrations reach an initial maximum at ~2 hours, followed by a second peak ~4 to 6 hours after the first, offering a 12-hour duration of action.[108] Other controlled-release capsule formulations (Ritalin LA, Novartis Pharmaceuticals, East Hanover, New Jersey[90]; Focalin XR, Novartis Pharmaceuticals, East Hanover, New Jersey[95]) use the spheroidal oral drug absorption system, which involves 50% immediate-release and 50% extended-release beads covered by a polymer coating.[24] The capsules containing the controlled-release beads may be opened, allowing for the beads to be sprinkled over certain foods.[24] Additionally, 2 new capsule formulations are in clinical development. The first, HLD200, is composed of trilayered DELEXIS microbeads that deliver methylphenidate after an ~8 to 9–hour delay, with a ~17-hour time to maximum plasma concentration, intended for administration in the evening for next-day symptom coverage (ClinicalTrials.gov: NCT02493777, NCT02255513, and NCT01907360, Ironshore [America] Inc, Camana Bay, Cayman Islands, subsidiary of Highland Therapeutics, Berwyn, Pennsylvania.). The second is PRC-063, an extended-release methylphenidate

Table 1. Current and Investigational Methylphenidate Products for Treating Attention-Deficit/Hyperactivity Disorder

Approval Date	Composition	Formulation	Duration of Effect	Clinical Trials Identified[a]
December 1955	Ritalin (methylphenidate hydrochloride)[50]	Oral tablet; 50:50 racemic mix of *d*- and *l*-methylphenidate[51]	3–5 h[2]	References 52–56
March 1982	Ritalin SR (methylphenidate hydrochloride)[50]	Slow-release oral wax-based matrix tablet; 50:50 racemic mix of *d*- and *l*-methylphenidate[51,57]	2–6 h[2]	None identified
May 2000	Methylin ER (methylphenidate hydrochloride)[58]	Extended-release hydrophilic hydroxypropyl methylcellulose gel-based oral tablet; 50:50 racemic mix of *d*- and *l*-methylphenidate[24,51]	8 h[2]	None identified
August 2000	Concerta (methylphenidate hydrochloride)[59]	Extended-release OROS oral tablet; trilayer core that is surrounded by a semipermeable membrane with an immediate-release layer of methylphenidate on the outside; 50:50 racemic mix of *d*- and *l*-methylphenidate[24,51]	12 h[2]	References 60–87
April 2001	Metadate CD (methylphenidate hydrochloride)[88]	Extended-release oral capsule containing 2 different multilayered beads for bimodal delivery (30% immediate-release and 70% delayed-release); 50:50 racemic mix of *d*- and *l*-methylphenidate[24,51]	6–8 h[2]	None identified
November 2001	Focalin (dexmethylphenidate hydrochloride)[89]	Oral tablet[51]	3–5 h[2]	None identified
June 2002	Ritalin LA (methylphenidate hydrochloride)[90]	Extended-release SODAS oral capsule containing 2 different beads for bimodal delivery (50% immediate-release and 50% delayed-release); 50:50 racemic mix of *d*- and *l*-methylphenidate[24,51]	6–8 h[2]	References 91,92
December 2002	Methylin (methylphenidate hydrochloride)[93]	Oral solution	3–5 h[2]	None identified
April 2003	Methylin (methylphenidate hydrochloride)[94]	Oral chewable tablet; 50:50 racemic mix of *d*- and *l*-methylphenidate[51]	3–5 h[2]	None identified
May 2005	Focalin XR (dexmethylphenidate hydrochloride)[95]	Extended-release SODAS oral capsule containing 2 different beads for bimodal delivery (50% immediate-release and 50% delayed-release)[51]	8–12 h[2]	References 96–100
April 2006	Daytrana (methylphenidate)[101]	Extended-release transdermal patch containing methylphenidate within a multipolymeric adhesive layer attached to a polyester/ethylene acetate laminate film backing[57]	11–12 h[2]	References 102,103
September 2012	Quillivant XR (methylphenidate hydrochloride)[104]	Extended-release oral suspension made up of coated particles containing polymer-matrix–bound methylphenidate (~20% uncoated immediate-release and ~80% coated extended-release particles)[57]	12 h[104]	References 105,106
April 2015	Aptensio XR (methylphenidate hydrochloride)[107]	Extended-release oral capsule containing multilayered beads, each bead contains 40% immediate-release layer and 60% controlled-release methylphenidate[57]	Up to 12 h[107]	References 108,109
December 2015	Quillichew ER (methylphenidate hydrochloride)[110]	Extended-release chewable tablet containing 30% immediate-release and 70% extended-release methylphenidate	< 13 h[110]	NCT01654250
TBD	NT-0102 (methylphenidate)	Orally disintegrating tablet containing 30% immediate-release and 70% delayed-release microparticles; 50:50 racemic mix of *d*- and *l*-methylphenidate[111,112]	12 h[112]	References 111,112
TBD	HLD200 (methylphenidate)	Capsule containing trilayered DELEXIS microbeads for delayed and extended-release delivery, designed for evening administration with release beginning in the morning and throughout the next day	NA	NCT02493777
TBD	PRC-063 (methylphenidate)	Extended-release oral capsule	NA	NCT02225639, NCT02139111, NCT02139124

[a]Clinical trial information for all NCT identifiers can be found at ClinicalTrials.gov, phase II–IV only 2009–May 2016.
Abbreviations: ER = extended-release, LA = long-acting, NA = not available, OROS = osmotic-release oral system, SODAS = Spheroidal Oral Drug Absorption System, SR = sustained-release, TBD = to be determined, XR = extended-release.

formulation currently being evaluated in adolescents and adults. Available clinical trial data indicate that efficacy assessments to 16 hours after administration and doses up to 100 mg have been evaluated (ClinicalTrials.gov: NCT02225639, NCT02139111, NCT02139124, Rhodes Pharmaceuticals, LP, Coventry, Rhode Island).[25,57]

Although there are numerous long-acting methylphenidate formulations, most are available only in oral capsule or tablet formulations, which, as previously stated, can present problems for children and adults who prefer not to swallow or have reported difficulty swallowing tablets.[119] To that end, many alternative formulations have been developed (eg, transdermal patch, oral solution, oral suspension, chewable tablet) or are in clinical development (eg, long-acting chewable tablet [NWP09, ClinicalTrials.gov: NCT01654250] and a methylphenidate extended-release

ODT [XR-ODT] formulation [NT-0102, ClinicalTrials.gov: NCT01835548]).[25,111,112]

With the methylphenidate transdermal patch system (Daytrana, Shire, Wayne, Pennsylvania[101]), absorption is unaffected by meals or first-pass metabolism.[120] However, considerable intraindividual variability in absorption has been observed.[121] Nevertheless, the transdermal patch may offer a lower risk for abuse and diversion[120] and allow for greater flexibility in the length of dosing.[122] The patch is intended to be worn for 9 hours; it is applied 2 hours before the effects are needed, and the effects persist for up to 3 hours after the patch is removed.

The extended-release oral suspension of methylphenidate (Quillivant XR, NextWave Pharmaceuticals, Inc, Cupertino, California) offers once-daily dosing[104] with a liquid formulation, which may be especially suitable for those who have difficulty swallowing tablets or capsules. However, because this product is a suspension, vigorous shaking of the bottle is recommended before each dose to ensure that the proper amount is administered.[104] Recently, clinical studies have evaluated the safety and efficacy of the extended-release chewable tablet formulation (Quillichew ER [NWP09], Pfizer Inc, New York, New York; ClinicalTrials.gov: NCT01654250). This formulation was approved by the US Food and Drug Administration (FDA) in December 2015.

NT-0102 is composed of a racemic mixture of *d*-:*l*- methylphenidate and is the first extended-release methylphenidate ODT. The XR-ODT formulation is made possible through ion exchange resin technology. When the methylphenidate salt is dissolved in the presence of the exchange resin during the manufacturing process, the positively charged mobile Na^+ ion of the exchange resin is replaced by the positively charged methylphenidate molecule, resulting in stable methylphenidate microparticles. Methylphenidate microparticles are either coated (extended-release) or uncoated (immediate-release) and compressed into ODTs containing ~30% immediate-release methylphenidate and ~70% extended-release methylphenidate. This methylphenidate XR-ODT formulation remains under regulatory review; however, it has demonstrated a PK profile consistent with once-daily dosing and has shown efficacy in controlling symptoms in children with ADHD through 12 hours in a laboratory classroom setting.[25,57,111,112]

Amphetamine derivatives. Amphetamine was discovered more than 100 years ago and has been used effectively to treat ADHD for nearly 80 years.[48] Some amphetamine formulations currently available or in development are comprised solely of the *d*- isomer (ie, dextroamphetamine), and others are comprised of the racemic mixture of both *d*- and *l*- isomers, along with other formulations containing methamphetamine (Desoxyn, Recordati Rare Diseases Inc, Lebanon, New Jersey[123]) or a mixture of various amphetamine salts (both *d*- and *l*- isomers) (Table 2). Short-acting amphetamine derivative products are available as oral tablets or as an oral solution, whereas long-acting products currently available or in late stages of clinical development include oral capsules, an oral suspension, a transdermal patch, and an ODT.

Dextroamphetamine is available in a longer-acting capsule formulation containing sustained-release beads (Dexedrine Spansule, Amedra Pharmaceuticals, Horsham, Pennsylvania[124]) with an 8-hour duration of action.[24] Lisdexamfetamine (Vyvanse, Shire, Wayne, Pennsylvania[129]), a prodrug of *d*-amphetamine,[159] is another long-acting agent formulated as an oral capsule with a duration of action of up to 13 hours in children and 14 hours in adults with ADHD. Lisdexamfetamine capsules can be opened and the contents dissolved in yogurt, water, or orange juice if a patient has difficulty swallowing the capsules.[129] The extended-release oral suspension formulation (Dyanavel XR, Tris Pharma, Monmouth Junction, New Jersey[156]), approved in October 2015, contains a mixture of *d*- and *l*-amphetamine and has a duration of effect of up to 13 hours. The XR-ODT amphetamine formulation tablet (Adzenys XR-ODT [NT-0202], Neos Therapeutics, Grand Prairie, Texas[157]), which contains a mixture of *d*- and *l*-amphetamine and disintegrates in the mouth without water, contains ~50% immediate-release microparticles and ~50% extended-release microparticles, and received approval in January 2016.[25] This extended-release ODT formulation of amphetamine has a PK profile consistent with once-daily dosing and is bioequivalent to Adderall XR (Shire, Wayne, PA[128]).[25,157] A new long-acting liquid formulation (NT-0201) containing a mixture of *d*- and *l*-amphetamine is also in development and relies on similar technology as NT-0202.[25] The transdermal patch (SPD487) long-acting amphetamine formulation is currently in late stages of clinical development. Additionally, a new capsule formulation similar to HLD200 is in development. HLD100 is also composed of trilayered DELEXIS microbeads and is intended for administration in the evening for next-day symptom coverage; however, this formulation contains delayed- and extended-release amphetamine (ClinicalTrials.gov: NCT01886469, Ironshore Pharmaceuticals and Development, Inc).[25] The mixed amphetamine salt products are available in a short-acting tablet formulation (Adderall, Teva Pharmaceuticals, Horsham, Pennsylvania[125]) and a long-acting capsule formulation (Adderall XR). The long-acting capsule formulation contains an equal number of immediate-release and extended-release beads.[24] The duration of action of the long-acting formulation is 10 to 12 hours.[24] A triple-bead mixed amphetamine salts formulation SPD465/SHP465 (now referred to as SHP465), with a duration of action of up to 16 hours, is under consideration by the FDA for an indication in adults with ADHD.[25,158]

Nonstimulants

Nonstimulant treatments currently available for ADHD are available in oral capsule (atomoxetine) and tablet (guanfacine and clonidine) formulations, although additional agents are being investigated (Table 3). Along with stimulants, atomoxetine is considered appropriate first-line therapy for adults; however, there is insufficient evidence to recommend the use of clonidine or guanfacine for routine treatment in adults.[20] For children, nonstimulants are generally second-line options, unless there are

Table 2. Current and Investigational Amphetamine Products for Treating Attention-Deficit/Hyperactivity Disorder

Approval Date	Product/Composition	Formulation	Duration of Effect	Clinical Trials Identified[a]
December 1943	Desoxyn (methamphetamine hydrochloride)[123]	Oral tablet	NA	None identified
August 1976	Dexedrine (dextroamphetamine sulfate spansules)[124]	Extended-release oral capsule containing 2 different beads; 50% short and 50% delayed absorption[51]	≥ 6 h[2]	None identified
February 1994	Adderall (mixed salts of a single-entity amphetamine product) dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate tablets[125]	Oral tablet; 3:1 *d*-:*l*-amphetamine[51]	6 h[2]	References 126,127
October 2001	Adderall XR (mixed salts of a single-entity amphetamine product) dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate capsules[128]	Extended-release oral capsule containing 2 different beads for bimodal delivery (50% immediate-release and 50% delayed-release); 3:1 *d*-:*l*-amphetamine[25,51]	10 h[2]	Reference 126
February 2007	Vyvanse (lisdexamfetamine dimesylate)[129]	Oral capsules containing *l*-lysine covalently bound to *d*-amphetamine requiring rate-limited hydrolysis to release *d*-amphetamine	10–12h[2]	References 72,73,127, 130–151
October 2011	Zenzedi (dextroamphetamine sulfate)[152]	Oral tablet	NA	None identified
August 2012	Evekeo (amphetamine sulfate)[153]	Oral tablet; 3:1 *d*-:*l*-amphetamine[154]	10 h[154]	Reference 154
May 2014	Procentra (dextroamphetamine sulfate)[155]	Oral solution	NA	None identified
October 2015	Dyanavel XR (amphetamine)[156]	Extended-release oral suspension of coated fine particles via LiquiXR technology; 3.2:1 *d*-:*l*-amphetamine[25]	13 h[156]	None identified
January 2016	Adzenys XR-ODT (amphetamine)[157]	Orally disintegrating tablet containing 50% immediate-release and 50% delayed-release amphetamine microparticles; 3:1 *d*-:*l*-amphetamine[25,157]	Bioequivalent to Adderall XR[157]	None identified
TBD	SHP465 (mixed salts of a single-entity amphetamine product)	Extended-release oral capsule containing 3 different beads for trimodal pulsed amphetamine delivery; 3:1 *d*-:*l*-amphetamine[25]	16 h[158]	Reference 158
TBD	SPD487 (dextroamphetamine)	Transdermal system	NA	NCT01711021
TBD	HLD100 (*d*-amphetamine)	Capsule containing trilayered DELEXIS microbeads for delayed and extended-release designed for evening administration with release beginning in the morning and throughout the next day	NA	NCT01886469
TBD	NT-0201 (amphetamine)	Extended-release liquid suspension of 2 different coated microparticles for immediate- and extended-release 3:1 *d*-:*l*-amphetamine[25]	NA	None identified

[a]Clinical trial information for all NCT identifiers can be found at ClinicalTrials.gov, phase II–IV only 2009–May 2016.
Abbreviations: NA = not available, TBD = to be determined, XR = extended-release, XR-ODT = extended-release orally disintegrating tablet.

circumstances that warrant their consideration.[2] Extended-release formulations of guanfacine and clonidine are also approved for use as monotherapy and as adjunctive therapy to stimulants in children and adolescents with ADHD.[2,182,192]

Atomoxetine inhibits presynaptic norepinephrine reuptake, thereby increasing synaptic concentrations of this neurotransmitter.[38] Atomoxetine has minimal effects on other neurotransmitters.[38] However, stimulation of norepinephrine increases synaptic dopamine concentrations in the prefrontal cortex, which may help explain the effects of atomoxetine in controlling ADHD symptoms.[38] Atomoxetine's onset of action is slower than that of stimulants; several weeks of treatment are typically needed to observe maximal treatment effect.[29] Side effects in adults include dry mouth, insomnia, nausea, decreased appetite, constipation, decreased libido, dizziness, erectile dysfunction, sweating, and dysuria.[200] In children, side effects include somnolence, gastrointestinal upset/nausea, and reduced appetite.[19] Like stimulants, atomoxetine increases heart rate and blood pressure in the short term; however, it has not been associated with sudden cardiac death.[201]

Guanfacine and clonidine are α-2 adrenergic agonists that modulate presynaptic and postsynaptic noradrenergic activity, producing physiologic effects on the prefrontal cortex that affect the pathophysiology of ADHD.[38] Guanfacine may be helpful if risk for abuse/diversion is high,[29] whereas clonidine may be particularly useful in patients with comorbid Tourette's syndrome or other tic disorders.[202,203] The most common side effects of guanfacine include somnolence, fatigue, bradycardia, and hypotension. Although they tend to diminish over time,[204] somnolence and sedation are the leading causes of discontinuing guanfacine treatment[205]; however, guanfacine is less sedating than clonidine.[29] Common side effects of clonidine include dry mouth, sedation, somnolence, dizziness, and constipation.[29]

Extended-release guanfacine and clonidine formulations preclude some side effects associated with plasma-concentration fluctuations inherent to the immediate-release

Table 3. Current and Investigational Nonstimulant Products for Treating Attention-Deficit/Hyperactivity Disorder

Approval Date	Product/Composition	Formulation/Mechanism of Action	Duration of Effect	Clinical Trials Identified[a]
November 2002	Strattera (atomoxetine hydrochloride)[160]	Oral capsule; monoamine reuptake inhibitor targeting norepinephrine[161]	At least 10–12 h[2]	References 52,64, 85,86,138, 162–181
September 2009	Intuniv (guanfacine hydrochloride)[182]	Extended-release oral tablet; α2-agonist[183]	At least 8 h[182]	References 184–191
September 2009	Kapvay (clonidine hydrochloride)[192]	Extended-release oral tablet; α2-agonist[192]	NA; labeled for twice-daily dosing[51]	Reference 193
TBD	Edivoxetine hydrochloride (LY2216684)	Oral tablet; selective norepinephrine reuptake inhibitor[25]	NA	NCT00922636
TBD	Dasotraline (SEP-225289)	Oral capsule/solution; dopamine, norepinephrine, and serotonin triple-reuptake inhibitor[25]	NA	References 194, 195
TBD	Centanafadine (EB-1020 SR)	Sustained-release oral tablet: triple monoamine reuptake inhibitor targeting norepinephrine, dopamine and serotonin[25]	NA	NCT01939353
TBD	Metadoxine	Extended-release oral tablet[25]	NA	References 196–198
TBD	Tipepidine (tipepidine hibenzate)	Oral tablet; inhibitor of G protein-coupled inwardly-rectifying potassium channels[25,199]	NA	Reference 199
TBD	V81444	Oral capsule; adenosine A_{2A} receptor antagonist[25]	NA	NCT02253745
TBD	NS2359	Oral tablet; monoamine reuptake blocker that inhibits norepinephrine, dopamine, and serotonin transporters while also increasing levels of acetylcholine[25]	NA	NCT00467428

[a]Clinical trial information for all NCT identifiers can be found at ClinicalTrials.gov, phase II–IV only, 2009–May 2016.
Abbreviations: NA = not available, TBD = to be determined.

formulations.[193] Extended-release (long-acting) guanfacine hydrochloride (Intuniv, Shire USA, Inc, Wayne, Pennsylvania[182]) has a ≥8-hour duration of effect based on the Conners' Parent Rating Scale–Revised: Short Form and the Conners' Teacher Rating Scale–Revised: Short Form.[206,207] This matrix tablet formulation may help control symptoms of ADHD in patients 6 to 17 years of age but has not been approved for adults with ADHD.[184–191,207] Extended-release clonidine hydrochloride (Kapvay, Shionogi Pharma, Inc, Atlanta, Georgia[192]) was designed to delay active drug absorption in order to decrease peak-to-trough plasma concentration differences, and can be dosed up to twice daily.[193] A significant reduction in ADHD-Rating Scale-IV total score was observed in a study of children and adolescents with ADHD taking extended-release clonidine hydrochloride versus placebo. The effect size was 0.71 for 0.2 mg/d and 0.77 for 0.4 mg/d.[193] Additionally, 0.1 to 0.4 mg/d extended-release clonidine as an adjuvant therapy to a stimulant has shown increased efficacy versus stimulant alone in children and adolescents who had an inadequate response to their baseline stimulant treatment.[208] The potential advantages of guanfacine over clonidine include fewer hypotensive and sedative effects and a longer half-life. Both agents have been suggested to be useful for ADHD patients taking stimulants and with comorbid sleep problems, tics, or Tourette's syndrome.[19]

SUMMARY DISCUSSION: SELECTING THERAPY FOR INDIVIDUALS WITH ADHD

Management of ADHD should be individualized whenever possible.[22] Although certain patients may respond preferentially to either methylphenidate or amphetamine derivatives,[209] the overall response rate to stimulants is high. Approximately two-thirds of patients will respond to either methylphenidate or amphetamine derivatives; this rate increases to ~90% after trying agents from both stimulant classes.[31,209] The high response rate to stimulants bodes well for patients, considering that onset of the therapeutic effect is essentially immediate.[2] Doses can be titrated frequently (every 3–7 days),[2] and usually treatment can be optimized within a few weeks. For the 10% to 30% of patients who do not respond to stimulant treatment or experience intolerable side effects, treatment with nonstimulant options may be warranted as monotherapy or adjunctive therapy in combination with stimulants.[2,29,210] Factors to consider when selecting therapy include the patient's age, comorbid symptoms, treatment history (and response), and the patient or parental/caregiver attitudes.[31,211] In addition, on the basis of different patient lifestyles, different formulations may be preferential. For instance, individuals with ADHD, especially adults with ADHD, who require extended symptom control later in the day (eg, at the end of an 8-hour work day) may benefit from a long-acting formulation.[2,24] Similarly, ensuring coverage for > 12 hours may be helpful for patients requiring symptom control for afternoon and evening activities.[2,200]

Poor adherence to ADHD treatments is common, which is a considerable unmet need in this therapeutic area, given that ADHD persists for life in many patients. Despite the broad range of treatment options currently available, nonadherence rates range from 13% to 64%.[212] Ineffectiveness and unwanted side effects are the most common reasons for discontinuing treatment, and dosing convenience may be another significant factor in adherence.[213] Other approaches

to dosage administration (eg, opening certain formulations and sprinkling the contents on food or dissolving in water) may improve acceptance. Many novel formulations that circumvent problems associated with swallowing tablets or capsules are currently available (eg, transdermal patch, oral solution, oral suspension, and chewable tablet), while others are in late stages of clinical development or have recently received FDA approval (eg, long-acting chewable tablet and long-acting XR-ODTs). Interestingly, recent evidence suggests that adherence and persistence improve when using long-acting agents (vs short-acting) and stimulants (vs nonstimulants).[213,214] However, a majority of extended-release stimulants are formulated as solid tablets or capsules, and difficulty swallowing tablets or capsules is known to affect adults as well as children.[215] In one survey, fewer than 50% of parents reported that their children could easily swallow a large pill or a small or large capsule.[216] Similarly, in a survey of adult patients, roughly 37% of adults reported difficulty swallowing pills or capsules of which the majority reported always or sometimes experiencing these difficulties.[217] Studies also estimate that 3% of children and adolescents with ADHD discontinue their medication due to swallowing difficulties, and expert opinions report that this rate may be even higher (8%–9%).[213] These results warrant future efforts to fully determine the role of formulations on treatment adherence in ADHD patients of all ages. The development of formulations that are acceptable to both pediatric and adult patients will be crucial to improving adherence.[2,31]

Another challenge with the development of new ADHD formulations (particularly controlled-release formulations) pertains to the criteria defining bioequivalence for generic products. According to the FDA, regulatory bioequivalence is established if the 90% confidence intervals for the ratios (test product to reference product) of various PK parameters fall between 80% and 125%.[218] Therapeutic substitution is permitted for products that are both pharmaceutically equivalent and bioequivalent.[219] However, experience with certain generic versions of Concerta shows that bioequivalence may not universally translate to therapeutic equivalence. These generic versions of Concerta do not use the OROS technology, and after reviewing data, the FDA changed their rating from AB (therapeutically equivalent) to BX (insufficient data to confirm bioequivalence).[219]

In conclusion, long-acting stimulants are a first-line treatment option for adults and children with ADHD, and a variety of distinct formulations are currently available. Many long-acting stimulant agents were initially formulated as oral tablets or capsules, whereas more recently approved agents (and those in late stages of clinical development) include long-acting liquid, long-acting chewable tablets, and long-acting ODTs. Despite the current landscape, which includes more than 20 options (stimulants and nonstimulants), adherence and patient outcomes in ADHD remain far from optimal. New formulations enabling further treatment individualization may improve adherence and overall treatment outcomes.

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Drug names: amphetamine (Dyanavel and Adzenys), atomoxetine (Strattera and others), clonidine (Catapres and others), dexmethylphenidate (Focalin and others), dextroamphetamine (Dexedrine and others), guanfacine (Tenex and others), lisdexamfetamine (Vyvanse), methamphetamine (Desoxyn and others), methylphenidate (Ritalin and others), mixed amphetamine salts (Adderall).

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