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REVIEW ARTICLE

Beyond the pill: new medication delivery options for ADHD

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Successful treatment of pediatric disorders has necessitated the development of alternative medication formulations, as children may prefer alternative dosage forms to tablets or capsules. This is especially true for attention-deficit/hyperactivity disorder (ADHD), which is one of the most common chronic pediatric conditions and often involves children with a variety of overlapping physical, psychological, or neurodevelopmental disorders. A special challenge for developing alternative dosage forms for ADHD treatment is the incorporation of a once-daily long-acting formulation. Traditional ADHD medication formulations have been limited, and issues surrounding prescribed dosing regimens–including poor medication adherence, difficulty swallowing, and the lack of dosing titration options–persist in ADHD treatment. In other disease areas, the development of alternative formulations has provided options for patients who have issues with consuming solid dosage forms, particularly children and individuals with developmental disorders. In the light of these new developments, several alternative formulations for ADHD medications are under development or have recently become available. This article reviews the various strategies for developing alternative dosage forms in other disease areas and discusses the application of these strategies in ADHD treatment. Alternative dosage forms may increase medication adherence, compliance, and patient preference and, therefore, improve the overall treatment for ADHD.

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Introduction

For the successful treatment of pediatric diseases, delivering medication via formulations that are acceptable to children is a recommended strategy to improve therapeutic outcomes.[1] Given that many medications are formulated as capsules and tablets, the development of alternative formulations is important because children may prefer options other than solid oral dosage forms.[2,3] This is particularly relevant to attention-deficit/hyperactivity disorder (ADHD), one of the most common pediatric conditions, which often involves children with a variety of overlapping physical, psychological, and neurodevelopmental disorders.

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ADHD is a chronic psychiatric disorder characterized by inattention, hyperactivity, and impulsivity.[4–6] In the US, ADHD has been reported to affect ~6–8% of children (in comparison to about a 10% prevalence of asthma in school-aged children[7]) and 4.4% of adults.[8,9] Approximately 95% of ADHD patients are diagnosed before the age of 12, and up to 60% of them continue to meet the diagnostic criteria for ADHD as adults.[9] Selection of an ADHD treatment approach is dependent on a patient's age and the severity of the disease.[5,6,10] Behavioral therapies are the first-line option recommended for preschool-aged children, and pharmacologic agents are often the first-line option for school-aged children and adults, particularly for those with moderate to severe impairment.[10–12] Pharmacotherapy has been proven to be very effective in patients of all ages. Practice guidelines recommend the central nervous system stimulants methylphenidate (MPH) and amphetamine (AMP) as first-line ADHD medications because of their proven efficacy in reducing ADHD core symptoms in both

children and adults.[4,5,13–15] While some patients may preferentially respond to or tolerate one better than the other, both stimulant classes are considered appropriate first-line interventions until efficacy and tolerability can be assessed in an individual patient.[4] Nonstimulant medications are also indicated for treating ADHD, but they are not as effective as stimulants and, therefore, are recommended as a second-line treatment or adjuvant therapy.[5,16]

Most ADHD medications are formulated as solid tablets or capsules that need to be taken daily,[17] which poses a potential challenge for children who experience difficulties swallowing pills or for individuals with autism or other developmental disabilities who may have tactile issues that preclude the use of tablets, capsules, or even sprinkled preparations.[18–20] For example, ~46–89% of children with autism-spectrum disorders have feeding disorders, raising significant concerns for ingesting solid oral formulations.[21,22] Chewing or crushing pills to ease ingestion may alter the pharmacokinetics of the medications and is inadvisable for most stimulants.[23] Although short-acting liquid formulations of stimulants have long existed,[24] long-acting alternative dosage formulations have only recently become available and include liquid suspensions, chewable tablets, and orally disintegrating tablets (ODTs).[25–29] Additionally, the only option for a non-oral route of administration is a transdermal-patch system.[30] Despite their proven effectiveness, adherence to ADHD stimulants is poor across patients of all age groups for various reasons,[31,32] and difficulty swallowing or an aversion to oral tablets may be a barrier to ADHD treatment.[18,19] Alternative oral dosage forms, especially those in long-acting formulations with reduced dosing frequencies, may ease medication delivery and improve outcomes for patients. However, incorporating a once-daily long-acting formulation into alternative dosage forms can be challenging.

Alternative oral formulations that ease ingestion in children have been successfully established for treating conditions that commonly occur in children, such as bacterial infections, pain, and allergies. Some examples include fruit-flavored liquid amoxicillin, loracarbef, and doxycycline solutions;[33] ibuprofen oral liquid suspension, chewable tablets, and ODTs;[34,35] and sublingual formulations for allergy and asthma allergen immunotherapy.[36–38] Other than ease of ingestion, these formulations may possess additional advantages over their capsule or tablet counterparts, such as a more favorable pharmacokinetic profile or improved safety. Beyond pediatric care, alternative oral dosage forms have also demonstrated benefits in many chronic disease areas–including cardiovascular, dyslipidemia, and chronic pain.[39] However, most of the alternative dosage forms are short-acting formulations that require multiple daily doses.[3] With advances in technology, long-acting transdermal patches, oral liquid solutions, and ODTs with reduced dosing frequencies are emerging, such as buprenorphine extended-release (ER) transdermal patches, azithromycin oral suspension, and ketoprofen orally disintegrating/sustained-release tablets,[40–43] which may further facilitate medication administration.

Alternative Dosage Forms for the Management of Psychiatric Disorders

Alternative oral dosage forms, such as chewable tablets, liquid solutions, sublingual tablets, and ODTs have been developed for the treatment of psychiatric disorders.[44,45] Aside from obviating swallowing difficulties, each oral dosage form provides unique benefits.[3,40,44,46] Liquid agents can be accurately split into a flexible dose, enabling gradual dose adjustment.[40] The sublingual route of administration avoids first-pass metabolism, resulting in quicker absorption and onset of effect as compared to other oral delivery methods.[45] The use of ODTs may enhance compliance not only in individuals with swallowing or tactile issues but also in pill-averse patients who willfully refuse medication, as ODTs disintegrate rapidly after administration and prevent surreptitious behaviors, such as cheeking, pouching, or spitting pills out.[47] The ODT formulation may also reduce misuse of psychotic medications (e.g., stimulants) that can have the potential for abuse, misuse, or diversion.[45]

Different dosage forms may also affect patients' adherence to their medications. Like many chronic disease areas in which medication discontinuation is common, such as diabetes (adherence = 31–87%, depending on the study[48]) and hypertension (adherence ~50%[49]), medication adherence in patients with psychiatric disorders is also suboptimal, ranging from 40 to 60%.[50,51] Psychiatric medications in liquid, sublingual, or ODT forms improve adherence compared with standard tablets.[51] In addition, simplifying medication regimens has a positive effect on adherence in patients with psychiatric disorders.[52,53] Long-acting formulations have been shown to enhance medication adherence in the management of depression,[54] Parkinson's disease,[55] and dementia.[56]

The benefits of ODTs in psychiatric treatment have been documented in studies of olanzapine, an antipsychotic medication indicated for the treatment of schizophrenia and bipolar I disorder.[47] Clinical studies indicate that olanzapine formulated as an ODT is as effective as the standard tablet formulation,[57–59] but 61% of patients opted for ODTs versus 27% for standard tablets in a study, suggesting that ODTs are a patient-preferred formulation.[57] Furthermore, olanzapine ODT has significantly improved medication adherence[59] and reduced caregiver burden because of high patient acceptance.[58–60] Other examples of alternative oral

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dosage forms in psychiatric treatment include risperidone and aripiprazole ODTs for treating schizophrenia and bipolar disorder,[45] risperidone oral solution for treating schizophrenia,[61] mirtazapine ODT for treating depression,[62] asenapine sublingual tablets for treating schizophrenia and bipolar mania,[63] and benzodiazepine (e.g., alprazolam, lorazepam, and clonazepam) ODTs for treating anxiety, depression, and panic disorder.[64–66] ODTs have consistently demonstrated advantages of easy ingestion and high patient preference across different classes of medications.[62,64,66]

Formulations of Stimulants for Treating ADHD

The success of alternative oral formulations has been well-established in psychiatric treatment, but alternative oral formulations for ADHD medications are still limited. The stimulants for ADHD treatment, methylphenidate and amphetamine, are available in a variety of formulations[67] (Tables 1 and 2). Although methylphenidate and amphetamine have demonstrated similar efficacies at the population level, individual patients may respond better to one or the other.[4,5] Thus, the choice as to which stimulant to prescribe depends on factors such as treatment history and patient and prescriber preference.[13,68] Owing to their short halflives, first-generation stimulants were short-acting (or immediate release) medications.[69] Short-acting methylphenidate and amphetamine typically take effect within 30 minutes after dosing, with durations of action ranging from 3 to 6 hours.[70–72] Thus, they require 2 to 4 doses a day to provide 12-hour symptom control.[70,71] Despite the proven effectiveness of short-acting stimulants,[69,72,73] the need for multiple daily dosing may lead to fragmented treatment coverage, missed doses, and social stigma for school-aged children, along with liability concerns regarding in-school medication storage due to dosing requirements during school hours.[72,74,75]

Long-acting (or ER) methylphenidate and amphetamine formulations have been developed to overcome the issues caused by frequent dosing associated with short-acting stimulants. Some long-acting stimulants contain two compartments or different populations of beads that release medication at different speeds, providing both rapid onset of action and long-lasting treatment effects; while others are prepared in a controlled-release formulation that delivers the active ingredient under osmotic pressure at a controlled rate throughout the day.[76,77] In addition, one long-acting amphetamine formulation is supplied as an inactive prodrug, lisdexamfetamine, which is converted to active amphetamine after being absorbed from the gastrointestinal tract.[78] Long-acting stimulants are designed for patients to take once daily in the morning, with symptom control lasting for 8 to 12 hours.[68,72,76] Clinical studies have demonstrated that once-daily long-acting stimulants are as effective as multiple-dosed short-acting stimulants in reducing ADHD core symptoms and improving cognitive skills in both children and adults.[75,79–81] Insurance claim data suggest that ADHD children who received long-acting stimulants were less likely to visit an emergency department or become hospitalized than those receiving short-acting stimulants.[82] Compared with short-acting stimulants, the advantages of long-acting stimulants include simpler dosing, reduced stigma related to medication use, reduced burden on schools regarding medication storage, and improved adherence.[71,83–85] In addition, long-acting stimulants have a smoother pharmacokinetic profile, with reduced fluctuation in plasma medication concentrations compared with their short-acting counterparts, which may prevent euphoria and rebound effects.[71] Furthermore, stimulants are controlled substances that have the potential for diversion and abuse.[86,87] Long-acting stimulants are associated with lower rates of misuse or abuse than their short-acting counterparts because their use does not correlate as strongly with euphoria and it is more difficult to extract active drug ingredients.[83,87,88] Several long-acting alternative formulations of stimulants have recently become available, including liquid suspensions, chewable tablets, and ODTs.[25,26,29] While the extent to which a formulation affects adherence to ADHD medication regimens remains to be investigated, the potential for better treatment individualization through the development of alternative dosage forms may improve outcomes in patients with ADHD.

Poor medication adherence in ADHD treatment

Analyses of insurance claims have revealed that medication adherence rates among ADHD patients are about 50% in the first year, but the rates decrease considerably over time (32.8% at 2 years; 17.2% at 5 years).[32] On average, children and adults only strictly adhere to their initially prescribed dosing regimens for 34.2 and 49.5 days, respectively, although they may continue with their medications on compromised schedules or doses for approximately 200 days.[31] These studies were based on claim data from 2008 or earlier, when most ADHD medications were likely to be short-acting agents. Later analyses of data, including both short- and long-acting ADHD medications, demonstrated an approximate 24–30% increase in adherence for long-acting medications compared with their short-acting counterparts.[84,85] The reasons for poor medication adherence in ADHD include side effects, ineffectiveness, lack of insight into the disease, dosing inconvenience, social stigma, and costs.[67] Specific reasons for medication nonadherence vary among patients of different age groups. Children often

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TABLE 1. Summary of short-acting and long-acting methylphenidate[24-26,29,76,103,104,106,107,109,111,115–119]

Product name	Formulation	Daily dosage	T_{max} (mean, hours)	$T_{1/2}$ (mean, hours)
Standard capsules or tablets				
Concerta® (methylphenidate hydrochloride extended-release tablets)	Tablet, ER	1	Initial peak at 1; second peak at 6–10	3.5[a]
Focalin® (dexmethylphenidate hydrochloride tablets)	Tablet	2	1–1.5	2.2
Metadate ER® (methylphenidate hydrochloride extended-release tablets)	Tablets, XR	1	4.7[b]	N/A
Methylin ER™ (methylphenidate hydrochloride extended-release tablets)	Tablet, ER	2–3	Initial peak at about 1; the second peak at 6–10	3.5[a]
Ritalin® (methylphenidate hydrochloride tablets)	Tablet	2–3	1.9[a] or 1.8[b]	3.5[a] or 2.5[b]
Ritalin-SR® (methylphenidate hydrochloride sustained-release tablets)	Tablet, ER	2–3	3.4[a] or 4.7[b]	4.1[a]
Capsules that can be sprinkled on foods				
Aptensio XR™ (methylphenidate hydrochloride extended-release capsules)	Capsule, ER	1	Initial peak at 2; second peak at 8[a]	5.09[a,c] or 5.43[a,d]
Focalin XR® (dexmethylphenidate hydrochloride extended-release capsules)	Capsule, ER	1	Initial peak at 1.5; second peak at 6.5[a]	3[a] or 2–3[b]
Metadate CD® (methylphenidate hydrochloride extended-release capsules)	Capsule, ER	1	Initial peak at 1.5; second peak at 4.5[c,e]	6.8[a]
Ritalin LA® (methylphenidate hydrochloride extended-release capsules)	Capsule, ER	1	Initial peak at 2; second peak at 5.5[a] or 6.6[b]	3.3[a] or 2.4[b]
Transdermal patch				
Daytrana® (methylphenidate transdermal system)	Transdermal patch, ER	1	10[f]	4–5.[b,g] 1.4–2.9[b,h]
Chewable tablets				
Methylin™ (methylphenidate hydrochloride chewable tablets)	Chewable tablet	2–3	1–2	3[a]
Quillichew ER™ (methylphenidate hydrochloride extended-release chewable tablets)	Chewable tablet, ER	1	5[i]	5.2
Oral solutions				
Methylin™ (methylphenidate hydrochloride oral solution)	Oral solution	2–3	1–2	2.7[a]
Quillivant XR® (methylphenidate hydrochloride for extended-release oral suspension)	For suspension, ER	1	4	5.2

ER = extended release; N/A = not applicable; $T_{1/2}$ = halflife; T_{max} = time to peak plasma concentration.

[a] In adults.

[b] In children.

[c] Capsule.

[d] Sprinkle.

[e] 25–30% of subjects had only one observed peak.

[f] 8 after repeat patch applications when worn up to 9 hours.

[g] *d*-methylphenidate.

[h] *l*-methylphenidate.

[i] Median.

TABLE 2. Summary of short- and long-acting amphetamine[27,28,105,116,118,120–122]

Product name	Formulation	Daily dosage	T_{max} (mean, hours)	$T_{1/2}$ (mean, hours)
Standard capsules or tablets				
Adderall (amphetamine mixed salts tablets)[a]	Tablets	1–3	3	10–11.[b] 12–14[c]
Desoxyn® (methamphetamine hydrochloride tablets)	Tablet	1–2	NR	4–5
Dexedrine® (dextroamphetamine sulfate Spansule® sustained-release capsules)	Tablet, ER	1–2	3	12
Evekeo™ (amphetamine sulfate tablets)	Tablet	1–3	NR	10
Capsules that can be sprinkled on foods				
Adderall XR® (amphetamine mixed salts capsules)[a]	Capsule, ER	1	7	10.[b,d] 11.[b,e] or 9,[b,f]; 10.[c,d] 13–14,[c,e] 11[c,f]
Orally disintegrating tablets				
Adzenys XR-ODT™ (amphetamine extended-release orally disintegrating tablets)	ODT, ER	1	5,[b,g] 5.25[c,g]	11,[b,d] 9–10[b,f]; 14,[c,d] 10–11[c,f]
Oral solutions				
Dyanavel™ XR (amphetamine extended-release oral suspension)	Oral suspension, ER	1	4	12,[b] 15[c]
ProCentra® (dextroamphetamine sulfate oral solution)	Oral solution	1–2	NR	11.75
Prodrug capsules				
Vyvanse® (lisdexamfetamine dimesylate capsules)	Capsule	1	1,[f,h] 3,[f,i] 5[b,g]	1,[h] 11.6[b]

ER = extended release; NR = not reported; ODT = orally disintegrating tablets; $T_{1/2}$ = halflife; T_{max} = time to peak plasma concentration.
[a] Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, and amphetamine sulfate.
[b] *d*-amphetamine.
[c] *l*-amphetamine.
[d] In adults.
[e] In adolescents.
[f] In children.
[g] Median.
[h] Lisdexamfetamine.
[i] Dextroamphetamine.

discontinue medications under their parents' or caregivers' discretion because of side effects, high medication costs, denial of illness, and difficulty swallowing.[17,67,89] Together, the need for school-aged children, especially those taking short-acting stimulants, to go to the nurse's office for dosing during school hours, which can lead to unwanted social stigma, and liability issues related to school storage of controlled medications may discourage medication adherence.[71,74,75] Parents and caregivers play a critical role in medication adherence.[17] A family history of ADHD (especially parental) is associated with decreased adherence,[17] possibly because of ADHD symptoms in the adult, such as forgetfulness and difficulty managing the child's medication regimen. Fears about the long-term risks or drug abuse associated with stimulant use may be another reason that affects adherence,[17,74,89] although these risks are low when medications are used appropriately. Disagreement between parents about their children's need for medication could also impact medication use.[89] This may be particularly relevant for children with ADHD who split time with their separated or divorced parents, only one of whom supports use of the medication. Additionally, perceiving ADHD as a parenting problem rather than as a disease with biological origins may lead to resistance to medication therapy and inadequate parental supervision of medication adherence.[90,91]

Adolescents are generally less willing to use ADHD medications than children and adults because of their growing autonomy and rebelliousness.[17,19,92,93] According to interviews with ADHD patients between ages 11 and 16 years, some patients felt that medications deprived them of their self-identity and "gained control over them."[19] As adolescents become older and more involved in treatment decision making, they may deliberately stop taking their medications.[19] Other common reasons for medication discontinuation in this population include high medication costs, denial of illness, lack of insight, and forgetfulness.[19,67,92,94]

Among adults with ADHD, side effects, high medication costs, and forgetfulness are the most commonly reported reasons for medication nonadherence.[19,67] Additionally, lack of insight–not viewing ADHD as a disease with a biological basis–and negative attitudes toward pharmacotherapy, such as fear of side effects and loss of authentic self, may also prevent patients from adhering to their medication regimens.[19,67,93]

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Using long-acting stimulants improves medication adherence. Clinical studies based on patient self-reports, pill counts, and claims analyses have shown that long-acting stimulants significantly improve adherence in both children and adult patients with ADHD compared to short-acting stimulants.[17,90,95–97] For nonadherent ADHD patients who have been on short-acting medications, switching to long-acting formulations enhances medication adherence.[16,98] The once-daily long-acting formulations simplify dosing regimens and avoid the social stigma caused by administration in public or at school. The convenience and improved patient acceptance offered by long-acting stimulants may account for the increased adherence.[96]

Difficulty swallowing

Difficulty swallowing represents a significant barrier to pharmacotherapy.[99,100] A wide variety of medical conditions, such as stroke, cancer, neurological disorders, connective tissue diseases, and gastroesophageal reflux disease, can lead to swallowing difficulties.[101] In addition, many adults without conditions affecting their ability to swallow have difficulty swallowing and express a preference for formulations that eliminate swallowing pills or capsules.[2,100]

Pediatric patients are more likely to encounter difficulties in swallowing solid dosage forms than adults.[2,100] A survey of 304 parents with children aged 0 to 26 years (less than 1% over age 21) reported that more than 50% of the children were unable to swallow a standard-sized pill or a small capsule.[2,102] In addition to physical inabilities, children may refuse to ingest pills because of conditioned anxiety associated with repeated negative experiences, such as aversive medication taste and fear of gagging.[18] Parents may resort to cajoling, threatening, or crushing and mixing medications in food to improve adherence, potentially altering medication pharmacokinetics and negatively affecting efficacy and safety and causing distress in children.[18] Adults who experience difficulties swallowing often complain about large pill size, sticky pill texture, and bad taste or smell of medications.[99,100] Common approaches used to address this issue include drinking more water, opening capsules, splitting or crushing pills, mixing contents with food, tilting the head backward when swallowing, and switching to a different dosage form.[99,100] However, crushing tablets and capsules may result in inaccurate dosing.[100]

Difficulty swallowing is a common issue in treatment and can affect medication adherence in ADHD patients of all ages;[74] therefore, several techniques have been developed to ease pill ingestion. Some stimulant dosage forms allow patients to open the capsule and sprinkle the contents on applesauce (Metadate CD®, Ritalin LA®, Adderall XR®, Aptensio XR™, Focalin XR®) or in yogurt, water, or orange juice (Vyvanse®).[27,103–107] However, to ensure effectiveness and dosage accuracy, the entire contents of the capsule need to be ingested without being chewed.[103–105] Among children with ADHD or autism, swallowing training by encouraging the swallowing of mock pills of increasing size has resulted in successful pill ingestion.[18] In other pediatric disease areas, such swallowing exercises as modeling-based behavioral intervention, swallowing technique instructions, and coating the back of the mouth and tongue with flavored spray have demonstrated effectiveness.[2] These strategies may also reduce barriers to ADHD treatment.

The need for treatment individualization

Evidence-based ADHD guidelines recommend that medication regimens should be tailored to the individual, as each patient may differ in their response to or tolerability of distinctive medications.[68] In efforts to optimize patient outcomes, clinicians should consider both medication class (stimulants vs. nonstimulants and types of stimulants/nonstimulants) and formulation.[68] The selected formulation should not only provide effective pharmacokinetic and pharmacodynamic profiles but also satisfy the patient's/family's preferences. For example, patients who frequently travel may opt for a dosage form that is easy to carry and can be taken without water.[47] In addition, practice guidelines recommend medication dose titration for individual ADHD patients to achieve an optimal dose with minimal side effects while retaining therapeutic effectiveness.[5]

Overview of New Stimulant Formulations

In ADHD management, multiple medication and formulation options better enable treatment individualization, leading to more favorable responses and increased patient satisfaction. Because the majority of treated ADHD patients are children who may be more sensitive to medication texture and tastes and dislike certain flavors,[3,108] selection of a specific favored dosage form may enhance their adherence to medications.[3] To satisfy the need, several alternative stimulant dosage forms are under development or have become available, including a transdermal system,[30] a long-acting chewable tablet,[25] liquid suspensions,[26] and ODT formulations.[29]

Daytrana® (Noven Therapeutics LLC, Miami, FL) is a long-acting methylphenidate transdermal patch that received FDA (U.S. Food and Drug Administration) approval in 2006.[109] This patch is applied to the hip area 2 hours before the treatment effect is needed and can be worn for up to 9 hours.[30,109] In three randomized,

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double-blind, placebo-controlled studies conducted in children or adolescents, daily 9-hour usage of Daytrana provided significantly better ADHD symptom control than placebo. Most side effects associated with Daytrana are consistent with those of oral methylphenidate, except for application site reactions, which are specifically related to this formulation.[109] Transdermal methylphenidate not only precludes the need for swallowing pills but also provides flexibility in adjusting the duration of drug exposure, as the treatment effect can be discontinued simply by removing the patch.[110] Because transdermal methylphenidate avoids first-pass metabolism and releases the active ingredient continuously, it provides a smoother pharmacokinetic profile than oral dosage forms, including some ER oral formulations that have a biphasic drug release.[110]

Two liquid dosage forms of long-acting stimulants have recently become available, including a methylphenidate oral suspension, Quillivant XR® (Pfizer Inc., New York), approved in 2012, and an amphetamine oral suspension, Dyanavel™ XR (Tris Pharma Inc., Monmouth Junction, NJ), approved in 2015.[26,28] Quillivant XR is supplied as a powder that needs to be reconstituted with water prior to dispensing. This agent is dosed once daily in the morning, with the treatment effect taking place within 45 minutes and lasting for 12 hours. In a laboratory classroom study, Quillivant XR demonstrated superior efficacy in controlling ADHD symptoms compared with placebo.[26] Dyanavel XR is supplied as a ready-for-use oral suspension dosed once daily in the morning.[28] The efficacy of Dyanavel XR has been demonstrated in a laboratory classroom study in which Dyanavel XR provided a significant improvement in ADHD symptoms compared with placebo.[28] Liquid dosage forms of long-acting stimulants may represent an appealing option for patients who experience difficulties swallowing pills and who require gradual dose titration or precise doses in between the doses available in solid formulations to achieve optimal treatment effect and tolerability.

Although a short-acting methylphenidate chewable tablet (Methylin® chewable tablet, Shionogi Inc., Florham Park, NJ) has been on the market for years,[111] long-acting methylphenidate chewable tablets were unavailable until very recently.[25] Quillichew ER™ (Pfizer Inc., New York) is an ER chewable tablet that is dosed once daily in the morning.[25] While the prescribing information recommends an initial dose for Quillichew ER, patients receiving this medication may undergo dose titration based on their treatment requirements or responses. To satisfy this need, Quillichew ER tablets are functionally scored and supplied in multiple strengths, which facilitates splitting tablets with accurate doses. In a laboratory classroom study, a single dose of Quillichew ER in the morning significantly improved ADHD symptoms over placebo, with the treatment effect lasting for over 8 hours.[25] This formulation not only circumvents the need for swallowing intact pills but also appeals to patients who prefer to chew their medications.

The first approved long-acting ODT stimulant formulation is an amphetamine medication, Adzenys XR-ODT™ (Neos Therapeutics Inc., Grand Prairie, TX).[29] Adzenys XR-ODT is dosed once daily in the morning by placing the ODT on the patient's tongue, where it disintegrates in saliva and can be swallowed without chewing or crushing. In several clinical studies conducted in pediatric or adult patients, Adzenys XR-ODT provided significantly better control of ADHD symptoms than placebo.[29] In addition, a long-acting methylphenidate XR-ODT is under development. In clinical studies, methylphenidate XR-ODT has shown favorable pharmacokinetics and provided effective ADHD symptom relief relative to placebo without causing serious safety concerns.[112,113] Long-acting ODTs not only ease ingestion but also offer the convenience of once-daily-dosing. Stimulants in chewable pills and ODTs are also portable options, as they are more compact and have no risk of leaking or spilling compared with liquid agents and do not require water or other liquids for ingestion.

Conclusions

ADHD is a common psychiatric disorder that typically develops in childhood and usually persists into adulthood.[9,114] For most ADHD patients, the primary treatment is pharmacotherapy using stimulants, which are commonly formulated as tablets or capsules.[4–6,13] Solid oral formulations may negatively affect medication adherence in ADHD treatment because of dosing inconvenience, patient discomfort, or difficulty swallowing. Therefore, efforts to refine stimulant formulations can potentially enhance adherence.[31,32] Among ADHD patients, long-acting stimulants have shown proven effectiveness in improving medication adherence compared with their short-acting counterparts.[17,90,95–97] Alternative oral dosage forms, such as chewable tablets, liquid solutions, and ODTs, may also increase adherence rates, as shown in other disease areas.[39] Among various oral dosage forms, ODTs represent a particularly portable and convenient option to ease ingestion as they obviate the need for carrying liquids. To fulfill the need for alternative oral dosage forms in ADHD treatment, several new ER formulations of stimulants have recently become available, including a methylphenidate ER liquid suspension,[26] an amphetamine ER liquid suspension,[28] a methylphenidate ER chewable tablet,[25] and an amphetamine ER-ODT.[29] Furthermore, a methylphenidate ER-ODT is under

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development.[112,113] The long-acting alternative oral dosage forms have combined advantages of dosing convenience and easy ingestion, thereby potentially improving medication adherence in ADHD patients. However, ER formulations of amphetamine chewable tablets and transdermal patches are still lacking. Future development is directed toward creating more long-acting alternative dosage forms for amphetamine and nonstimulant medications. As more medication formulations become available, clinicians will have more tools to individualize treatment and improve the effectiveness of pharmacotherapy for ADHD.

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