Clinical Review of New Medications for Treating Attention-Deficit/Hyperactivity Disorder

Jozef Zelenak, MD, MBA, Alexander Getz, MD

As a busy child and adolescent psychiatry fellow, I appreciate having access to condensed information about new psychopharmacologic treatments available on the market, which helps me remain informed and improves my patients' care. I appreciated when my faculty mentor brought to my attention Daughton's 2009 article[1] that reviews attention-deficit/hyperactivity disorder (ADHD) pharmacotherapies. However, several years have elapsed since that article was published, and there have been new medications released to market. These medications are not novel compounds but rather new preparations of existing compounds that broaden modes of administration and provide additional pharmacokinetic variations. Thus, a brief update is in order.[1]

The objective of this article is to provide for clinicians treating ADHD a brief overview of several new stimulant medications that have recently become available on the market. Specifically, there are seven medications reviewed in this article: Aptensio extended-release (XR), QuilliChew extended-release (ER), Quillivant XR, Adzenys extended-release orally disintegrating tablets (XR-ODT), Dyanavel XR, Evekeo, and Zenzedi. Of note, this article is not intended to be a substitute for referencing recommended prescribing guidelines.

Method

The list of new stimulant medications was obtained from a variety of sources. The Food and Drug Administration (FDA) website was reviewed for methylphenidate- and amphetamine-based medications that had been approved as of November 2016. Press releases from a variety of pharmaceutical companies were reviewed regarding new pharmacotherapeutic treatments for ADHD. Focus was placed on stimulant medications with novel delivery mechanisms. Once new medications of interest were identified, information was obtained primarily from prescribing information sheets and from direct phone or email contact with parent pharmaceutical companies. Information for reporting was selected with anticipated clinical relevance and utility and also brevity in mind. The information presented here for each medication includes information about the structure and delivery mechanism of the medication, unique features of the medication, brief prescribing recommendations, and information about the parent pharmaceutical company. Retail price for each medication is reported for cost comparison.

Methylphenidate-Based Medications

Aptensio XR (methylphenidate hydrochloride extended-release capsules): Aptensio XR is a racemic mixture of methylphenidate hydrochloride provided as a capsule of dextromethylphenidate (D-MPH) and levomethylphenidate (L-MPH) isomers. It contains multilayered beads, composed of an immediate-release layer containing 40% of methylphenidate dose and an extended-release layer containing 60% of methylphenidate dose formulation for once daily dosing.[2]

The unique feature of Aptensio XR is that it currently is one of the longest-acting extended-release stimulant medications for ADHD treatment available on the market, lasting up to 12 hours. It also is available in seven different doses for ease of prescription. This medication may be suitable for children who need longer daytime coverage with stimulants and may provide a single-dose alternative to multiple immediate-release doses or the combination of a shorter-acting extended-release dose in the morning and a booster dose in the afternoon.

Aptensio XR is manufactured by Patheon and marketed by Rhodes Pharmaceuticals LP.[2] It received FDA approval in April 2015 for patients 6 years and above, and was brought to market in June 2015.

QuilliChew ER (methylphenidate hydrochloride extended-release chewable tablets): QuilliChew ER is a chewable tablet that contains a racemic mixture of methylphenidate hydrochloride with a 1:1 proportion of D-MPH to L-MPH isomers. Since L-MPH is extensively metabolized, it represents only about 2% of D-MPH circulating plasma concentration. QuilliChew ER contains methylphenidate in 30% immediate-release and 70% extended-release formulations for once daily dosing.[3] QuilliChew ER contains Tris Pharma's patent-protected OralXR+ technology, which involves a robust aqueous polymer coating of medication particles and provides a controlled and extended release of the medication.

A unique feature of QuilliChew ER is that it is the first and only extended-release methylphenidate chewable tablet for ADHD treatment available in the US. This may be suitable for young children who struggle to swallow pills and would prefer to chew them instead.

QuilliChew ER is manufactured by Tris Pharma and distributed by NextWave Pharmaceuticals, which is a subsidiary of Pfizer Inc.[3] It received FDA approval in December 2015 for patients 6 years and above and was brought to market in February 2016.

Table 1. Methylphenidate-Based Medications

	GENERIC	FORMULATION	AVAILABLE DOSES	STARTING DOSE	TITRATION/ ONSET DURATION	MAX DOSE PER DAY	NOTES	PRICE[a]
Aptensio XR	racemic methylphenidate hydrochloride[2]	extended-release capsules[2]	imprint is "APTENSIO XR" on colored cap and dose level on white body of capsule, 10 mg (light turquoise blue cap), 15 mg (orange cap), 20 mg (yellow cap), 30 mg (blue violet cap), 40 mg (pink cap), 50 mg (green cap), 60 mg (gray cap)[2]	10 mg qAM (Age ≥ 6)[2]	10 mg per day at weekly intervals; onset at 60 min; lasted up to 12 hrs post dosing[2]	60 mg[2]	may take with or without food; capsules may be opened and sprinkled on applesauce; no specific flavor indicated[2]	$227
QuilliChew ER	racemic methylphenidate hydrochloride[3]	extended-release chewable tablets[3]	capsule-shaped tablets, 20 mg (scored, speckled off-white colored, debossed "NP 12"), 30 mg (speckled light pink colored, debossed "NP 13"), 40 mg (not scored, speckled dark pink-colored, debossed "NP 14")[3]	20 mg qAM (Age ≥ 6)[3]	10 mg, 15mg, or 20mg per day at weekly intervals; onset at 45 min; lasted up to 8 hrs post dosing[3]	60 mg[3]	may take with or without food; cherry-flavored tablets[3]	$318
Quillivant XR	racemic methylphenidate hydrochloride[4]	extended-release oral suspension[4]	powder is reconstituted with water, product forms the extended-release oral light-beige to tan viscous suspension containing 5 mg methylphenidate base per 1mL of solution[4]	20 mg qAM (Age ≥ 6)[4]	10 mg to 20 mg per day at weekly intervals; onset at 45 min; lasted up to 12 hrs post dosing[4]	60 mg[4]	may take with or without food; solution should be stored at 25°C (77°F) and is stable for up to 4 months after reconstitution; banana-flavored solution[4]	$272

Note: All information reported for each medication in this table, except price, was obtained from the respective "highlights of prescribing information" document. See References for details. ER = extended release; qAM = quaque ante meridiem (every morning); XR = extended release.

[a] Price of medication reported is based on the average retail price of the most common version of medication formulation sold with discount coupons included as reported by GoodRx.[10]

Quillivant XR (methylphenidate hydrochloride extended-release oral suspension): Quillivant XR is an oral suspension containing a racemic mixture of methylphenidate hydrochloride with a 1:1 proportion of D-MPH to L-MPH isomers. Since L-MPH is extensively metabolized, it represents only about 2% of D-MPH circulating plasma concentration. Quillivant XR contains methylphenidate in 20% immediate-release and 80% extended-release formulations for once daily dosing.[4] Quillivant XR contains Tris Pharma's aforementioned patent-protected OralXR+ technology.

A unique feature of Quillivant XR is that it is the first extended-release liquid stimulant for ADHD treatment available in the US. This may be suitable for young children who struggle to swallow pills.

Quillivant XR is manufactured by Tris Pharma, Inc. and distributed by NextWave Pharmaceuticals, which is a subsidiary of Pfizer Inc.[4] It received FDA approval in September 2012 for patients 6 years and above, and was brought to market in January 2013.

Amphetamine-Based Medications

Adzenys XR-ODT (amphetamine extended-release orally disintegrating tablets): Adzenys XR-ODT is an orally disintegrating tablet containing a racemic mixture of amphetamine salt with a 3:1 proportion of dextroamphetamine (D-AMP) to levoamphetamine (L-AMP) isomers. It contains amphetamine in 50% immediate-release and 50% delayed-release formulations for once daily dosing.[5] Adzenys XR-ODT contains Neos Therapeutics's patent-protected Rapidly Disintegrating Ion Masking (RDIM) technology, which involves polymer-coated resin particles that disintegrate orally.

A unique feature of Adzenys XR-ODT is that it is the first and only extended-release amphetamine orally disintegrating tablet for ADHD treatment available in US. This may be suitable for young children who struggle to swallow pills.

Adzenys XR-ODT is manufactured and marketed by Neos Therapeutics Inc.[5] It received FDA approval in January 2016 for patients 6 years and above, and was brought to market in May 2016.

Dyanavel XR (amphetamine extended-release oral suspension): Dyanavel XR is an oral suspension containing a racemic mixture of amphetamine salt with 3.2:1 proportions of dextroamphetamine (D-AMP) to levoamphetamine (L-AMP) isomers.[6] Dyanavel XR contains Tris Pharma's aforementioned patent-protected OralXR+ technology for the extended-release formulation.

A unique feature of Dyanavel XR is that it is the first and only extended-release amphetamine oral suspension for ADHD treatment. This may be suitable for young children who struggle to swallow pills.

Dyanavel XR is manufactured and marketed by Tris Pharma, Inc.[6] It received FDA approval in October 2015 for patients 6 years and above, and was brought to market in April 2016.

Evekeo (amphetamine sulfate tablets): Evekeo is prepared as a tablet with a racemic mixture of amphetamine sulfate with a 1:1 proportion of dextroamphetamine (D-AMP) to levoamphetamine (L-AMP) isomers.[7] Evekeo is provided as immediate-release formulation.

A unique feature of Evekeo is that it is a 1:1 racemic mixture of D-AMP to L-AMP (Adderall from Shire contains a 3:1 racemic mixture of D-AMP to L-AMP). Animal studies showed that, in comparable doses, D-AMP is more effective than L-AMP at reducing hyperactivity and impulsivity, while L-AMP is more effective than D-AMP at improving sustained attention.[8] Hence, Evekeo, with a higher proportion of L-AMP to D-AMP as compared to Adderall, may be more effective for patients with the predominantly inattentive type of ADHD. Of note, with regard to potential adverse effects, Evekeo may have a more pronounced effect on the cardiovascular system than Adderall, since L-AMP has greater effect on the cardiovascular system than D-AMP.[8]

Evekeo is manufactured by Mikart, Inc. and marketed by Arbor Pharmaceuticals.[7] It received FDA approval

Table 2. Amphetamine-Based Medications

	GENERIC	FORMULATION	AVAILABLE DOSES	STARTING DOSE	TITRATION/ ONSET DURATION	MAX DOSE PER DAY	NOTES	PRICE[a]
Adzenys XR-ODT	racemic amphetamine salt; 3:1 (D-AMP: L-AMP)[5]	extended-release orally disintegrating tablets[5]	orally disintegrating orange mottled round tablets, 3.1 mg (debossed A1 on one side), 6.3 mg(A2), 9.4 mg(A3), 12.5 mg(A4), 15.7 mg(A5) and 18.8 mg(A6)[5]	6.3 mg qAM (Age 6-17); 12.3 mg qAM (Age ≥ 18)[5]	3.1 mg or 6.3 mg per day at weekly intervals[5]	18.8 mg (Age 6-12); 12.5 mg (Age ≥ 13)[5]	may take with or without food; allow tablet to disintegrate in saliva before swallowing; orange-flavored tablets[5]	$308
Dyanavel XR	racemic amphetamine salt; 3.2:1 (D-AMP: L-AMP)[6]	extended-release oral suspension[6]	light-beige to tan colored viscous suspension containing 2.5 mg amphetamine base per 1mL of solution[6]	2.5 mg or 5 mg qAM (Age ≥ 6)[6]	2.5 mg to 10 mg per day at weekly intervals; onset at 60 min; lasted up to 13 hrs post dosing[6]	20 mg[6]	may take with or without food; solution should be stored at 20-25°C (68-77°F); bubblegum-flavored solution[6]	$268
Evekeo	racemic amphetamine sulfate salt; 1:1 (D-AMP: L-AMP)[7]	immediate-release tablets[7]	colored tablets debossed "EVK" on one side and with dose number on the other side; 5 mg (single-scored, white),10 mg (double-scored, blue)[7]	2.5 mg qd (Age 3-5); 5 mg qd or bid (Age ≥ 6)[7]	2.5 mg per day at weekly intervals for 3–5-year-olds, 5 mg per day at weekly intervals for 6 years and older, divided doses should be given in 4–6-hour intervals; onset at 45 min; lasted up to 10 hrs post dosing[7]	40 mg[7]	may take with or without food; no specific flavor indicated[7]	$397
Zenzedi	dextro-amphetamine sulfate; 1:0 (D-AMP: L-AMP)[9]	immediate-release tablets[9]	colored tablets with different shapes for each dose, debossed on one side with dose number in milligrams and the other with "MIA"; 2.5 mg (white, square), 5 mg (pink, oval), 7.5 mg (light green, triangle), 10 mg (peach, round), 15 mg (light blue, pentagon), 20 mg (purple, capsule-shaped), 30 mg (light yellow, hexagon)[9]	2.5 mg qd (Age 3-5); 5 mg qd or bid (Age ≥ 6)[9]	2.5 mg per day at weekly intervals for 3 –5-year-olds, 5 mg per day at weekly intervals for 6 years and older; divided doses should be given in 4–6-hour intervals[9]	40 mg[9]	may take with or without food; no specific flavor indicated[9]	$70

Note: All information reported for each medication in this table, except price, was obtained from its respective "highlights of prescribing information" document. See References for details. Bid = bis in die (twice a day); D-AMP = dextroamphetamine; L-AMP = levoamphetamine; ODT= orally disintegrating tablets; qAM = quaque ante meridiem (every morning); qd = quaque die (every day).

[a] Price of medication reported is based on the average retail price of the most common version of medication formulation sold with discount coupons included as reported by GoodRx.[10]

in September 2014 for patients 6 years and above, and was brought to market in March 2015. In addition to treatment of ADHD, Evekeo also is indicated for treatment of narcolepsy and exogenous obesity.

Zenzedi (dextroamphetamine sulfate tablets): Zenzedi is dextroamphetamine sulfate provided as a tablet that contains only the dextroamphetamine (D-AMP) isomer.[9] Zenzedi is provided as an immediate-release formulation.

Two unique features of Zenzedi are that it is pure D-AMP, and is available in seven different doses for ease of prescription. Animal studies showed that, in comparable doses, D-AMP is more effective than L-AMP at reducing hyperactivity and impulsivity, and has less pronounced effect than L-AMP on the cardiovascular system;[8] hence Zenzedi, as compared to Adderall, may be more effective for patients with the predominantly hyperactive-impulsive type of ADHD, and may have fewer adverse cardiac effects.

Zenzedi is manufactured by Mikart, Inc. and marketed by Arbor Pharmaceuticals.[9] The dextroamphetamine sulfate received FDA approval as abbreviated new drug application (ANDA) in October 2011 by Mikart, Inc. It was later acquired by Arbor Pharmaceuticals, which brought it to market in June 2013 under the brand name Zenzedi. In addition to treatment of ADHD, Zenzedi also is indicated for treatment of narcolepsy.

Conclusion

The above-discussed medications offer a variety of ADHD treatment options for addressing unique patients' needs. The choice of which medication to select for treatment should be based on patient-specific factors, such as the predominant type of ADHD with which the patient presents, whether or not the patient is able to swallow pills, prior medication trials, and the desired duration of stimulant coverage.

Take Home Summary

New preparations of stimulants used for treatment of ADHD have been produced that give clinicians additional options to customize treatment to patients' needs. These additional options include expanded modes of medication administration, expanded dose preparations, medication customization for ADHD subtypes, and others. This article provides a concise summary of these latest medication treatment options for clinicians.

References

1. Daughton JM, Kratochvil CJ. Review of ADHD pharmacotherapies: advantages, disadvantages, and clinical pearls. *J Am Acad Child Adolesc Psychiatry.* 2009;48:240-248.
2. Aptensio XR: Highlights of prescribing information. Rhodes Pharmaceuticals LP. http://www.aptensioxr.com/resources/full-prescribing-information.pdf. April 2015. Accessed November 2016.
3. QuilliChew ER: Highlights of prescribing information. Pfizer Inc. http://labeling.pfizer.com/ShowLabeling.aspx?id=2577. February 2016. Accessed November 2016.
4. Quillivant XR: Highlights of prescribing information. Pfizer Inc. http://labeling.pfizer.com/ShowLabeling.aspx?id=965. May 2016. Accessed November 2016.
5. Adzenys XR-ODT: Highlights of prescribing information. Neos Therapeutics Inc. http://www.neostxcontent.com/Labeling/Adzenys/Adzenys_PI.pdf. October 2016. Accessed November 2016.
6. Dyanavel XR: Highlights of prescribing information. Tris Pharma, Inc. http://www.dyanavelxr.com/pdfs/pi.pdf. November 2015. Accessed November 2016.
7. Evekeo: Prescribing information. Arbor Pharmaceuticals LLC. https://www.evekeo.com/pdfs/evekeo-pi.pdf. November 2015. Accessed November 2016.
8. Sagvolden T, Xu T. l-Amphetamine improves poor sustained attention while d-amphetamine reduces overactivity and impulsiveness as well as improves sustained attention in an animal model of Attention-Deficit/Hyperactivity Disorder (ADHD). *Behav Brain Funct.* 2008;4:3.
9. Zenzedi: Prescribing information. Arbor Pharmaceuticals LLC. http://zenzedi.com/docs/PIandMedicationGuide.pdf. June 2014. Accessed November 2016.
10. GoodRx: ADHD Medications. https://www.goodrx.com/adhd/drugs. Accessed June 2017.

About the Authors

Jozef Zelenak, MD, MBA, is a Child and Adolescent Psychiatry fellow at Palmetto Health and University of South Carolina School of Medicine, Columbia, SC.

Alexander Getz, MD, is associate program director of Child and Adolescent Psychiatry at Palmetto Health and University of South Carolina School of Medicine, Columbia, SC.

Dr. Zelenak would like to thank Alexander Getz, MD, from Palmetto Health/University of South Carolina for his mentorship and editing of this article from a prescribing clinician's perspective, and Kenneth Phelps, PhD, also from Palmetto Health/University of South Carolina, for reviewing this article for readability from a non-prescribing clinician's perspective. He would also like to thank Kristine Pumphrey, BA, assistant managing editor of the *Journal of the American Academy of Child and Adolescent Psychiatry*, for assistance during the submission process and Oliver M. Stroeh, MD, and the editorial staff from *JAACAP Connect* for help with editing this manuscript.

Disclosure: Drs. Zelenak and Getz report no biomedical financial interests or potential conflicts of interest.