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Optimizing outcomes in ADHD treatment: From clinical targets to novel delivery systems

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CNS SPECTRUMS

CME Review Article

Optimizing Outcomes in ADHD Treatment: From Clinical Targets to Novel Delivery Systems

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CME REVIEW ARTICLE

Optimizing outcomes in ADHD treatment: from clinical targets to novel delivery systems

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Our knowledge and understanding of the underlying neurobiology and symptomatic expression of ADHD has advanced dramatically over the past decade. Associated with these advances has been a similar explosion of new treatment options to individualize treatment for our patients.

This article will:

- review strategies to measure ADHD symptoms and functional difficulties while seeking to achieve full symptomatic remission throughout the day
- summarize recent findings regarding the management and prioritization of ADHD and comorbid conditions and
- discuss the various pharmacologic treatment options with a focus on recently developed molecules and novel delivery systems

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Introduction

While once considered a condition of hyperactive boys, our knowledge and understanding of attention deficit hyperactivity disorder (ADHD) and related conditions has dramatically evolved over the last decade. Landmark studies by Biederman, Faraone, and Adler among others have changed and deepened our understanding of ADHD to include a condition that not only affects boys but quite often affects girls.[1–4] The evolution of symptoms across the lifespan and the concomitant neurologic changes that underlie this symptomatic expression have similarly evolved. More recently, landmark studies by Dalsgaard and others have brought to light the significantly increased morbidity and mortality associated with preschoolers, children, and adults struggling with ADHD and associated conditions.[5,6]

This article will provide the following:

1. A more thorough understanding of data relating to the long-term consequences of unrecognized and undertreated ADHD both within an individual and on a global basis
2. Ways to better identify and diagnose the various clinical presentations across the lifespan
3. A better understanding of how to clinically manage and prioritize the treatment of patients with ADHD and comorbid conditions
4. A discussion of various pharmacologic treatment options and newer novel delivery systems
5. Strategies to measure ADHD disorder throughout the day and monitor improvement while seeking to achieve full symptomatic remission

Consequences of ADHD Across the Lifespan

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that affects approximately 8–11% of school aged children, both in the United States and throughout the rest of the developed world.[7] Initially considered primarily a condition of hyperactive boys, it has come to be recognized as a condition that affects both boys and girls and often persists from childhood to adolescence and into adulthood.[8] The classic triad of hyperactivity, impulsivity, and inattention captures many of the core aspects of ADHD but fails to capture some of the difficulties surrounding executive function and emotional reactivity, which collectively account for much of the social, educational, occupational, and

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emotional impairment of the disorder. In early childhood and throughout grade school, ADHD is diagnosed more frequently in boys than girls; this is possibly related to the higher expression of overt hyperactive symptomatology that is found in preadolescent boys.[4] ADHD patients with predominantly inattentive symptoms are often overlooked, misdiagnosed, or diagnosed 2–3 years later in life because the overt outward marker of hyperactivity has often been used to identify this condition.

Our basic understanding of the neurophysiology of ADHD has advanced dramatically with landmark studies by investigators such as Nora Volkow, who highlighted the differences in dopamine transporter activity in children with ADHD; Philip Shaw, who tracked maturation of the prefrontal cortex in children with ADHD, and more recent studies looking at the influence of genetic heritability and environmental factors.[2,8,9] These studies, taken in total, show that ADHD is a highly genetic neurologic condition, and it affects numerous cortical and subcortical pathways that coordinate information processing, impulsivity, emotional modulation, and neurochemical pathways which modulate communication between these cortical regions. ADHD has an overall genetic heritability of approximately 75%, ie, 3 out of 4 times there will be a genetic family history. Environmental factors also influence our genes, with epigenetic changes occurring in a number of our children exposed to environmental stressors, such as prenatal nicotine exposure, lead exposure, or severe psychosocial trauma.[10,11]

Long-term, follow-up, longitudinal studies have shown that ADHD children are at greater risk of academic difficulties, emotional dysregulation with oppositional defiant disorder tendencies, and emotional volatility. Longitudinal imaging studies have shown a 2- to 3-year delay in maturation of the prefrontal cortex and associated pathways in children with ADHD as compared to non-ADHD controls.[9] It is therefore not surprising that ADHD symptomatology continues to evolve throughout childhood, adolescence, and into early adulthood as the underlying neurophysiology of the brain continues to mature and is influenced by outside environmental demands, such as high school, college, employment, and the social demands of adulthood.

By adolescence there is an increased rate of drug and alcohol abuse, an increased rate of motor vehicle and traffic-related difficulties, and a dramatically increased rate of teenage pregnancy for ADHD individuals compared to controls.[12] Followed into adulthood, ADHD individuals have lower occupational and economic performance; have increased difficulty with financial management; and have increased rates of psychiatric comorbidity, such as depression, alcohol and drug abuse, emotional lability, intermittent explosive disorder, and a variety of anxiety disorders.[13] Most importantly for ADHD adults, we find increased rates of marital dysfunction and divorce, dramatically worsened abilities to maintain ongoing friendships and relationships, and significantly lower evaluations of self-esteem and self-worth.[12]

Can Treatment Make a Difference?

Although classic ADHD studies have shown that both behavioral and medical interventions can improve core ADHD symptoms, there has been debate about the overall long-term functional impact of ADHD interventions. Studies by Biederman, Wilens, and others have shown that consistent ADHD treatment decreased the rate of drug and alcohol abuse later in life.[14] Numerous studies in analog classroom settings have shown improved concentration on task-related activities, such as completing math problems, and improvement on behavioral tasks measured by rating scales such as the Swanson, Kotkin, Atkins, M-Flynn, and Pelham scale (SKAMP).[15]

Studies by Dalsgaard and others have shown that ADHD is associated with significantly increased morbidity and mortality (Figure 1).[5,6] These studies have found increased rates of accidental injury requiring medical treatment and injury requiring emergency room intervention. Utilizing the Danish birth registry, Dalsgaard found that on a nationwide basis, ADHD individuals had dramatically increased mortality rates compared to the general population. ADHD preschoolers had an 86% increased mortality rate, school aged students had a 58% increased mortality rate, and adults with ADHD had a 325% increased mortality rate relative to non-ADHD individuals within the same population.[5] These studies went on to analyze whether ADHD treatment within the overall population of Denmark impacted these adverse outcomes. They found that ADHD treatment was associated with an overall decrease in accidental injury and medical utilization due to accidents and trauma (Figure 2). On a nationwide basis, they found a 25–37% decrease in emergency room utilization among ADHD individuals receiving treatment versus those not receiving treatment.[6]

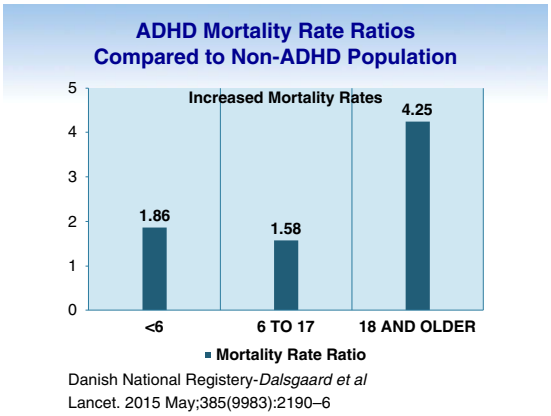

FIGURE 1. ADHD Mortality Rates.[5]

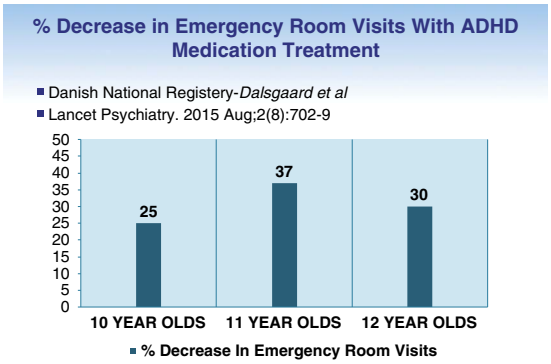

FIGURE 2. Decrease in emergency room visits with ADHD treatment.[6]

Diagnosis and Recognition of Symptoms

ADHD is a pervasive condition with symptoms that start in childhood or adolescence. There are 18 classic symptoms.[7] Nine of these symptoms involve primarily inattentive or cognitive symptomatology, and 9 involve primarily hyperactive or impulsive symptomatology. According to *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-V) criteria, children with ADHD must have a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development with ≥6 inattentive symptoms for an inattentive presentation, ≥6 hyperactive/impulsive symptoms for a hyperactive/impulsive presentation, or ≥ both 6 inattentive and 6 hyperactive/impulsive symptoms to meet criteria for a combined presentation. Longitudinal studies of ADHD children followed into adulthood by Barkley and others have shown that ADHD adults had difficulty remembering symptoms dating back to early childhood and therefore the DSM-V diagnostic criteria have been modified.[12] For a diagnosis in late adolescence or adulthood, several symptoms must have been present before age 12, and there must continue to be ≥5 of 9 symptoms in either the inattentive, hyperactive/impulsive, or in both domains for diagnosis.

Improving the accuracy of ADHD diagnosis and treatment

Clinical data and research evidence have highlighted the need to shift from a subjective to a more objective measure of ADHD diagnosis and treatment. A variety of fairly sensitive and specific ADHD rating scales have been developed to better define and measure ADHD symptoms, both during initial diagnosis and throughout ongoing treatment. While in no way substituting for a thorough clinical evaluation, these scales help to do the following:

- Better quantify and define ADHD impairments during the initial diagnosis
- Measure ADHD symptoms at various time points throughout the day
- Track ADHD symptoms to make sure that overall symptomatic improvement, symptomatic remission, and functional normalization have been optimized for each patient
- Save time by providing an objective measure of symptom severity before meeting with a patient

Why should a clinician use ADHD rating scales?

Just as it is helpful for an internist to know an individual's blood pressure or hemoglobin A1c when diagnosing and optimizing treatment for a hypertensive or diabetic patient, ADHD rating scales can be similarly useful in managing our patients (Table 1).

The ADHD-Rating Scale (ADHD-RS), the Vanderbilt, and the Conner's are examples of ADHD scales that have been shown to be consistent diagnostic measures of core ADHD symptoms and are sensitive to treatment effect.[16–19] Various ratings of executive function, such as the Behavior Rating Inventory of Executive Function (BRIEF), can be utilized to measure executive function deficits, which frequently cause impairment for ADHD individuals.[20]

Another group of scales has been developed to measure ADHD symptoms and how they fluctuate throughout the day. Analog Classroom and Analog Workplace settings have been developed to measure ADHD symptoms and evaluate how different treatment modalities improve symptoms over the course of the day. In these settings, the 13-item SKAMP is used to measure attention, behavior, and deportment in children, and the Permanent Product Measure of

TABLE 1. ADHD screening and rating scales

Scales	Notes
ADHD Rating Scale (ADHDRS)	Ages 6–12; parent and teacher forms
Adult ADHD Self-Report Scale (ASRS)	Adults; the first part is a screening test, the second part more in-depth questions
Before School Functioning Questionnaire (BSFQ)	Parent form
Behavior Rating Inventory of Executive Function (BRIEF)	Ages 5–18; parent and teacher forms
Conners' Rating Scales	Ages 3–17; parent, teacher, and self-report (ages 12–17) forms
Conners-Well's Adolescent Self-Report Scale	Used for screening, not diagnosis
Conners Adult Attention Deficit/Hyperactivity Disorder Rating Scale	Adult; investigator, observer, and self-report forms
Daily Parent Rating of Evening and Morning Behavior (DREMB)	Parent form
Permanent Product Measure of Performance (PERMP)	Age-adjusted math problems; 10-minute test
Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP)	Ages 7–12; teacher form
SNAP-IV Rating Scale-Revised (SNAP-IV-R)	Ages 6–18; includes parent and teacher forms
Vanderbilt ADHD Rating Scales	Ages 6–12; parent and teacher forms

Performance (PERMP) measures a child's or adult's ability to sit and complete a series of basic math equations during 10 minutes; these tests are then repeated at various time points throughout the day.[15,21] The Daily Parent Rating of Evening and Morning Behavior (DPREMB) evaluates behaviors in the morning and evening.[22] The Before School Functioning Questionnaire (BSFQ) has been developed to help clinicians better evaluate ADHD symptoms and functional impairments, which frequently occur and cause significant disruption during the morning hours.[23]

Goals for Treatment

ADHD medications have some of the highest effect sizes of any medical intervention.[24] Studies also demonstrate, however, that response to specific medications is highly individual. A patient may respond well to a methylphenidate preparation but may fail to respond to or may have significant adverse effects with an amphetamine preparation. Studies show that some patients respond equally well to either class, while other individuals have a preferential response to either a methylphenidate preparation or an amphetamine preparation.[25] Children who have experienced adverse effects or have failed stimulants may go on to either tolerate or preferentially respond to nonstimulants such as atomoxetine, guanfacine XR, or clonidine XR. Finally, studies have shown that combinations of nonstimulants with stimulants can have beneficial effects for patients who were only partial responders to a stimulant alone.[26]

Studies with all 3 classes of medications–methylphenidates, amphetamines, and nonstimulants–have highlighted that it is all too easy for clinicians to settle for partial improvement while still leaving patients with ongoing symptomatology. Clinical response has often been defined as a 25–30% symptom improvement, but this still leaves patients with ongoing and significant symptomatic and functional impairment. Long-term trials with sustained-release stimulants have shown that 90–95% of patients achieve 30% symptomatic improvement. Interestingly, clinicians interpret 30% symptom improvement as "much" or even "very much improved" on global clinical measures.[27–30]

Patients and clinicians may be tempted to be satisfied with 30% improvement, even though the evidence is clear that such minimal improvement almost inevitably means continued functional impairment. For most patients, further improvement is possible. Long-term trials demonstrate that nearly 75–80% of patients can achieve >50% symptom reduction and achieve symptomatic remission with an overall ADHDRS score of less than 18, meaning that ADHDRS scores are mild or less on average (Figure 3).[31,32]

In addition to overall symptom improvement, our treatments must deliver symptomatic improvement at time points where functional impairment is occurring for our patients. Studies by Sallee, Whalen, Mattingly, and others have shown that clinicians primarily focus on consequences of ADHD during school and work while overlooking impairments that occur at the beginning and end of the day.[33–35] Sallee[33] found that 79% of caregivers have discussed early morning functional impairments, such as getting out of bed, getting dressed, self-hygiene, eating breakfast, packing their backpack, and being able to catch the bus, as being some of the most impairing issues for their children with ADHD. Of these caregivers, 48% indicated they had to wake up early in the morning to administer ADHD medication before their child's normal wake time because of functional difficulties experienced before their child's medication had taken effect.[33]

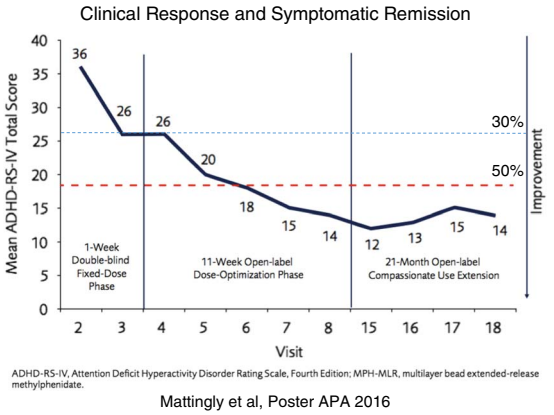

FIGURE 3. Clinical response and symptomatic remission with ADHD treatment.[32]

Comorbid Conditions

Numerous studies in the U.S. and other countries around the world have found that ADHD commonly presents with a constellation of comorbid challenges and disorders.[13,36] Young children with ADHD frequently have associated learning disorders or developmental disabilities, such as difficulties with sensory integration, problems with working memory, speech and language delay, and difficulties with reading comprehension. A baseline battery of neurocognitive testing to detect specific learning challenges should be considered in all school-age children with ADHD. Recognition of specific learning challenges can help to better identify therapeutic interventions and academic accommodations, which can be of great benefit for children struggling with ADHD and associated learning difficulties.

Emotional impulsivity, oppositional behavior, and poor frustration tolerance

Many children, adolescents, and adults with ADHD struggle with symptoms associated with poor frustration

tolerance. These symptoms can present in childhood as difficulty waiting, impatience with delays, or excessive frustration when asked to shift from a preferred to a nonpreferred task. Such frustration often leads to a sequence of escalating emotional and behavioral dyscontrol, "meltdowns" out of proportion to the task at hand, and emotional fragmentation.[37] Meltdowns may last only minutes, but they leave the child, his or her family, and those around them emotionally nonfunctional for far longer periods. At such times, parents and caregivers may unintentionally worsen outcomes by raising the level of negative emotional tone, with angry scolding or excessive disciplining. Such "heat of the moment" tactics usually only cause further fragmentation and decompensation. Caretaker strategies that model calmness, promote emotional modulation, and preemptively forecast transitions while strategically planning for potential frustration have been shown to help minimize the frequency and severity of emotional fragmentation.

Oppositional thoughts and behaviors can trouble ADHD individuals of any age.[12,38] Difficulties shifting from preferred to nonpreferred tasks and impaired recognition of the emotional impact of their behavior on others frequently lead to such oppositional patterns in ADHD individuals.[39] Therapeutic techniques that teach patients to "unstick" when locked into ineffective behavioral or cognitive patterns, that foster abilities to externalize and appreciate the emotional impact of their behavior on others, and that improve the ability to transition from preferred to nonpreferred tasks or thoughts can lessen the tendency toward negative and oppositional patterns and improve the functioning of ADHD children, adolescents, and adults alike.

Comorbid mood and anxiety disorders

ADHD frequently presents with comorbid anxiety disorders, mood disorders, and affective instability. A number of rating scales have been developed to help better ascertain and evaluate the presence of child and adolescent depression, comorbid anxiety conditions, and the possible emergence of bipolarity in preadolescent, adolescent, and young adult patients. Studies by Geller, Biederman, and others have highlighted the diagnostic conundrum of ADHD in the presence of significant mood disorders and mood lability, and give guidance on how to better recognize and diagnose childhood ADHD versus underlying bipolar disorder. Geller *et al*[40] found that when preadolescent children with ADHD were compared to children with bipolar disorder versus non-emotionally impaired controls, 5 screening questions emerged as the best way to help differentiate ADHD children from those with bipolar disorder (Figure 4). The five best discriminating questions were as follows:

1. Racing thoughts
2. Decreased need for sleep
3. Elated mood
4. Grandiosity
5. Hypersexuality and hypersexual behavior

Of note, irritability and episodic, dysphoric mood were not good discriminating items, since these were frequently found both with bipolar children and with children with classic ADHD.

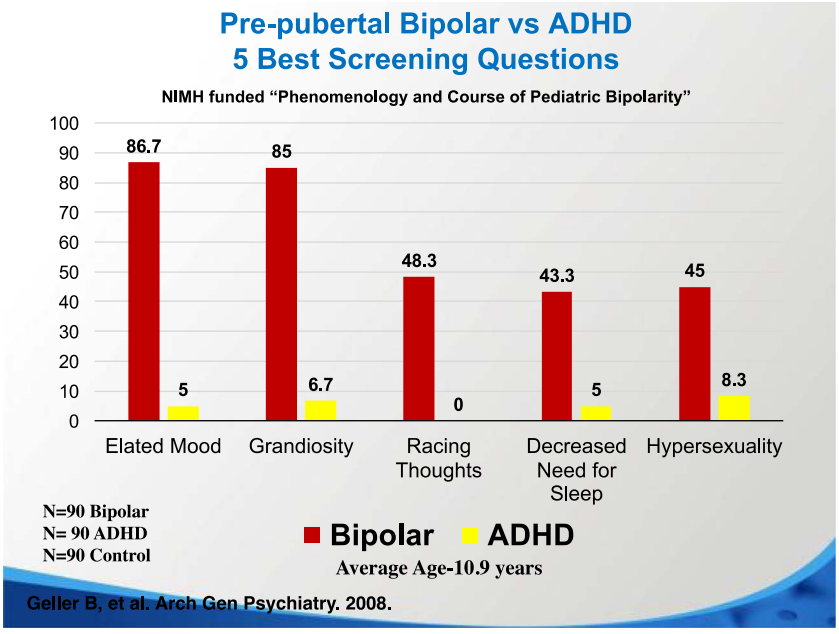

FIGURE 4. Symptoms which differentiate Pre-pubertal Bipolar and ADHD.[40]

Studies looking at children who have ADHD plus significant major depression are at increased chance of eventually evolving into a bipolar spectrum illness, with approximately with 25% of preadolescent ADHD comorbid depression patients eventually developing bipolar disorder.[41] Signs of bipolarity, including the aforementioned 5 symptoms, along with family loading and discreet cycling of mood out of proportion to environmental stimulus should be watched for as children with ADHD plus depression progress throughout the life span. In adulthood, the National Comorbidity Survey Replication Study showed that 47% of adults with ADHD will have a comorbid anxiety disorder, with nearly 1 in 3 ADHD adults also meeting criteria for social phobia and between 5–10% meeting criteria for generalized anxiety disorder, panic disorder, and posttraumatic stress disorder. In the mood disorder spectrum, the National Comorbidity Study found that 38% of ADHD adults meet criteria for a major mood disorder, with 15–-20% meeting lifetime criteria for bipolar disorder, 15–20% meeting criteria for comorbid major depression, and 12% meeting criteria for chronic dysthymia.[13]

In the childhood arena, 2 more recent DSM-V diagnostic dilemmas involve the co-occurrence of autism spectrum disorders and ADHD and the newly established diagnosis of "disruptive mood dysregulation disorder."[7,41] In DSM-IV, the comorbidity of autism and ADHD could not officially be diagnosed concurrently.[39] With changes to DSM-V, it has now been recognized that approximately 50% of children in the autism spectrum will have a comorbid diagnosis of ADHD. Such children tend to be exceptionally sensitive to adverse effects of traditional ADHD medications, and these individuals should be started on extremely low doses of medications that are as smoothly released as possible to minimize emotional lability, tics, twitches, insomnia, agitation, or emotional fragmentation, which frequently occur in these comorbid autism spectrum individuals. In addition to poorly tolerating adverse effects of traditional ADHD medication, these individuals also frequently have tactile and swallowing difficulties. Alternative formulations of ADHD medications may be desired in this population due to difficulties with sensory, tactile, and swallowing issues. Such preparations include medications that can be sprinkled, dissolved in liquid, come in liquid form, or orally disintegrating formulation. DSM-V defines "disruptive mood dysregulation disorder" as a childhood condition where the children are "irritable or angry most of the day nearly every day, have severe temper outbursts an average of 3 or more times per week and have trouble functioning due to irritability in more than one environment" with symptoms occurring consistently for a minimum of 12 months.

Prioritization for treatment among comorbid conditions

The old adage of "treat mood and anxiety first" before treating ADHD has long been considered the recommended standard of care when confronted with patients with ADHD and significant mood or anxiety symptoms. Recent findings by Chen *et al*[42] from a nationwide longitudinal study of ADHD and comorbid major depression (MDD/ADHD) may cause clinicians to rethink this strategy. Their study identified 1,891 patients with MDD/ADHD and compared them with 1,891 age- and sex-matched patients with major depression only. Patients with MDD/ADHD had a 232% increased risk of treatment resistance to multiple antidepressants compared with patients with major depression without ADHD. Their study went on to find that individuals receiving regular treatment for ADHD had a significantly lower risk for antidepressant treatment resistance. They concluded that patients who had dual diagnoses of major depression and attention deficit hyperactivity disorder were more likely to have treatment resistance to antidepressants, and that prompt and regular treatment for attention deficit hyperactivity disorder would reduce this risk.[42] This study highlights the fact that when ADHD symptomatology is driving functional impairments and exacerbating underlying mood disorders, anxiety disorders, or substance abuse, concomitant treatment of ADHD and these associated conditions often yields the best overall therapeutic response. Imagine the case scenario of a mother overwhelmed with difficulties due to forgetfulness, distractibility, and poor time management who develops significant anxiety symptoms as a result of her underlying functional difficulties due to ADHD. Similarly imagine a depressed college student struggling with underlying ADHD who has difficulty staying focused and remembering what is discussed in the lecture hall, then returning to his or her dorm room and struggling with cognitive processing and information processing while studying for an upcoming exam. Finally imagine an adult with ADHD with comorbid substance abuse who is struggling with issues surrounding emotional impulsivity and poor frustration tolerance trying to maintain a path to sobriety while struggling with underlying symptoms of ADHD. Careful, judicious treatment of all of these conditions may improve not only the underlying ADHD symptomatology, but may also provide a path to stability for treatment of the associated comorbidities. In the aforementioned cases, attempts should be made to minimize emotional side effects of ADHD treatment while monitoring for potential abuse or misuse of stimulant medications. Numerous studies have shown that long-lasting stimulants and nonstimulant medications will often stabilize emotional impulsivity and can be used carefully in such populations. Slightly more controversial would be the use of low doses of psychostimulants for children and adolescents struggling with bipolar disorder and ADHD. Pediatric and adolescent bipolar studies have shown that low-dose

stimulants used in combination with bipolar medications can be combined when needed to stabilize children and adolescents struggling with comorbid ADHD and bipolar disorder.

Immediate-Release, Sustained-Release, Delayed-Release: Choosing Between Medication Options

The last several years have seen an explosion in stimulant delivery systems available for ADHD treatment (Tables 2–5). Stimulants are now considered the first line pharmacologic treatment option for individuals with ADHD.[43,44] ADHD treatment has progressed from what was initially a decision between short-acting methylphenidate versus short-acting amphetamine, each of which required dosing several times per day in order to maintain therapeutic efficacy. Various strategies have been developed by pharmaceutical manufacturers to avoid the mid-day and intraday dosing. Early modifications involved slow-release wax matrix technologies, which, while extending the duration of action, continued to have difficulties with variable release patterns from day to day and from patient to patient depending on pH-related factors, gastric motility, and meal effects. The next set of sustained-release medications involved beaded technologies, where a certain percentage of medication was released in short-acting, immediate-release beads while another percentage of beads was coated with a pH-dependent layer that would begin to release approximately 4 hours later in the less acidic small intestine, providing clinical efficacy for approximately 8–10 hours. These beaded technologies allowed for adjustment of what percent of beads would be

TABLE 2. Amphetamine formulations

Formulations	Brand names	Duration	Dosing	Approval
Immediate-release d-amphetamine tablet	Zenzedi	4–5-hr	2nd dose at lunch	Ages 3–16
Immediate-release d-amphetamine oral solution	ProCentra (previously Liquadd)	4–6-hr	2nd dose at lunch	Ages 3–16
Extended-release d-amphetamine capsule	Dexedrine	6–8-hr	Once-daily in the morning	Ages 3–16
Lisdexamfetamine dimesylate capsule	Vyvanse	Up to 12-hr Peak at 3.5-hr	Once-daily in the morning	Ages 6–17 and adults
Immediate-release d,l-amphetamine tablet	Adderall	4–6-hr	2nd dose at lunch	Ages 3–12
Immediate-release d,l-amphetamine tablet	Evekeo	6–hr	2nd dose at lunch	Ages 3–12, ages 13–17, and adults
Extended-release d,l-amphetamine orally disintegrating tablets	Adzenys XR-ODT	8–12-hr Peak at 5-hr	Once-daily in the morning	Ages 6–12, ages 13–17, and adults
Extended-release d,l-amphetamine oral suspension	Dyanavel XR	10–12-hr Peak at 4-hr	Once-daily in the morning	Ages 6–17
Extended-release d,l-amphetamine tablet	Adderall XR	8–12-hr Peak at 6–8-hr	Once-daily in the morning	Ages 6–12, ages 13–17, and adults

TABLE 3. Methylphenidate formulations

Formulations	Brand names	Duration	Dosing	Approval
Immediate-release d-methylphenidate tablet	Focalin	Early peak, 4–6-hr duration	2nd dose at lunch	Ages 6–17
Extended-release d-methylphenidate capsule	Focalin XR	Two peaks (after 1.5 and 6.5 hrs), 8–10-hr duration	Once-daily in the morning	Ages 6–17 and adults
Immediate-release d,l-methylphenidate tablet	Ritalin	Early peak, 3–4-hr duration	2nd dose at lunch	Ages 6–12 and adults
Immediate-release d,l-methylphenidate oral solution	Methylin	Early peak, 3–4-hr duration	2nd dose at lunch	Ages 6 to 12
Extended-release d,l-methylphenidate tablet	Ritalin SR Methylin ER Metadate ER	Early peak, 3–8-hr duration	Lunch dosing may be needed	Ages 6–17 and adults
Extended-release d,l-methylphenidate tablet	Concerta	Small early peak, 12-hr duration	Once-daily in the morning	Ages 6–17 and adults
Extended-release d,l-methylphenidate chewable tablet	QuilliChew ER	Peak at 5-hr, 8-hr duration	Once-daily in the morning	Ages 6–17 and adults
Extended-release d,l-methylphenidate capsule	Metadate CD	Strong early peak, 8-hr duration	Once-daily in the morning	Ages 6–17
Extended-release d,l-methylphenidate capsule	Ritalin LA	Two strong peaks (early and at 4 hrs), 6–8-hr duration	Once-daily in the morning	Age 6–12
Extended-release d,l-methylphenidate (capsule)	Aptensio XR	Up to 12-hr duration	Once-daily in the morning	Ages 6–17 and adults
Extended-release d,l-methylphenidate oral suspension	Quillivant XR	Peak at 5-hr, 12-hr duration	Once-daily in the morning	Ages 6–17 and adults
Extended-release d,l-methylphenidate transdermal patch	Daytrana	One peak at 7–10-hr, 12-hr duration	Once-daily in the morning	Ages 6–17

TABLE 4. Nonstimulant ADHD formulations

Formulations	Brand names	Duration	Dosing	Approval
Atomoxetine	Strattera	~5-hour half-life	Once or twice-daily; morning and late afternoon	Ages 6–17 and adults
Guanfacine extended-release	Intuniv	~14–18-hour half-life	Once-daily in the morning	Ages 6–17
Clonidine extended-release	Kapvay	12–16-hour half-life	Morning and night dosing	Ages 6–17

TABLE 5. Drugs in development

Compound	Mechanism/formulation	Company	Stage
SHP465	Amphetamine triple-beaded	Shire	Phase III complete
HLD-200	Methylphenidate Delexis technology—bedtime dosing	Ironshore	Phase III complete
NT0102	Oral dissolving mPH	Neos Therapeutics	Phase III complete
Dasotraline	DA and NE reuptake inhibitor	Sunovion	Phase III
Centanafidine	Triple reuptake inhibitor	Neurovance	Phase IIb complete
d-ATS	Amphetamine transdermal system	Noven	Phase II complete
HLD-100	Amphetamine Delexis technology—bedtime dosing	Ironshore	Phase II
Edivoxetine	NE reuptake inhibitor	Lilly	Phase II
Mazindol	DA and NE reuptake inhibitor	NLS Pharma	Phase II
SPN810 (molindone)	D2 antagonist	Supernus Pharmaceuticals	Phase II
SPN812	NE reuptake inhibitor	Supernus Pharmaceuticals	Phase II

mPH: methylphenidate, DA: dopamine, NE: norepinephrine.

immediate-release versus sustained-release (30/70, 40/60, or 50/50) in order to have greater delivery in the morning or increased medication delivery in the afternoon. Several triple-bead-release preparations are in development, one of which will be a triple-release methylphenidate formulation and one of which will be a triple-beaded amphetamine salt preparation. Each of these formulations will involve a percentage of beads that is immediate-release in the stomach, another percentage of beads that is released 4 hours later in the small intestine, and another percentage of beads that is released 8 hours later in the large intestine. These formulations are designed with the intent to extend duration of clinical efficacy for up to 16 hours.

A more recent adaptation of the beaded technology involves a multilayered release technology, where each bead has a 40% immediate-release outer coating with the inner 60% of each bead composed of multiple pH-dependent coatings, which dissolve as each bead passes through various points in the intestinal tract. This multilayered release profile results in a biphasic pharmacokinetic curve, with an immediate first peak 2 hours post-dose and a second peak 8 hours post-dose.[45] A new multilayered release formulation is being developed to extend the clinical duration from 12 to 16 hours.

Beyond beads

The OROS capsule provides a novel delivery system with ongoing continuous release over 10–12 hours. After ingestion, stomach fluid is absorbed through osmotic pores in one end of the capsule, causing medication to be excreted through a laser-drilled hole at the other end of the capsule.[46]

A prodrug version of amphetamine was developed by binding lysine to amphetamine.[47] Lisdexamfetamine is a hydrophilic, "biologically inactive" prodrug that is not able to cross the bilipid blood–brain barrier. Lisdexamfetamine is enzymatically cleaved into free amphetamine and free lysine by enzymes in the cytosol of the human red blood cells, which provides sustained symptomatic improvement for 13 hours in children and 14 hours in adults. Lisdexamfetamine can be dissolved in fluid such as juice and administered as a liquid dose.

The ADHD field has one transdermal methylphenidate option, which provides continuous transdermal release of methylphenidate from the moment the patch is applied with continued efficacy until approximately 2 hours after the patch is removed.[48] This allows flexibility of daytime dosing, with shorter or longer wear times depending on the individual needs of the patient (it can be worn as short as several hours and as long as 9 to 12 hours). Unfortunately, adverse effects such as rash and skin discomfort often hinder the use of this transdermal technology, although it should be noted that a transdermal amphetamine-based patch currently in development may minimize some of the associated skin reactions.

Microparticles

A variety of pH-based ion exchange polymers have been developed to allow ion exchange of stimulant molecules with underlying microparticle polymers.[44] These pH-based

microparticle polymer technologies have allowed the development of sustained-release liquid methylphenidate and amphetamine preparations. The underlying micro particles will not release the bound stimulant until the microparticles absorb ions in the gastric lumen. These liquid formulations offer sustained-release preparations that can be titrated in small increments for children who are especially sensitive to side effects.[49]

An orally disintegrating tablet with a microparticle-based, sustained-release amphetamine has recently been developed. Each orally disintegrating tablet has amphetamine molecules ionically bound to between 100,000 and 200,000 microparticles.[50] A portion of these microparticles begins to release stimulant immediately when they encounter ions in gastric lumen; some of these micorparticles are pH coated so that they will not release the stimulant until they have passed into the small intestine. A similar orally disintegrating methylphenidate preparation is in development.

Two unique microparticle ADHD compounds in development seek to provide both delayed onset and sustained release. These delayed-onset, sustained-release preparations of methylphenidate and amphetamine are dosed in the evening with therapeutic onset upon awakening to avoid the typical 1- to 2-hour therapeutic delay encountered with morning administration of other ADHD stimulants.

Nonstimulants

Three nonstimulants are approved in the U.S. for ADHD treatment. These options either block reuptake of norepinephrine transporters (atomoxetine) or directly stimulate the norepinephrine alpha 2a receptor (guanfacine-XR and clonidine-XR). These options may be utilized for individuals who cannot tolerate the dopaminergic side effects of stimulants, require 24 hour symptomatic coverage, or who have significant concerns about abuse or diversion of stimulants. In addition, both guanfacine-XR and clonidine-XR are approved for use in combination with a stimulant for children who have break-through symptoms on a stimulant alone.

In the pipeline

In addition to novel delivery systems, a number of new molecules–both stimulant and nonstimulant–are in development. A partial list would include the nonstimulants dasotraline, viloxazone, centanafadine, and edivoxetine; molindone-XR for aggression associated with ADHD; and the long half-life stimulant mazindol.[44]

Summary

Our knowledge and understanding of the underlying neurobiology and symptomatic expression of ADHD has advanced dramatically within the U.S. and around the world over the past decade. Associated with these advances has been a similar explosion of new treatment options to individualize treatment for our patients. Optimal treatment today begins with measuring and tracking ADHD symptoms with the goal of treating to symptomatic remission with minimal functional impairment. Individual clinical presentation and patient response guide a clinician's choice between chemical classes of medications: methylphenidate, amphetamine, or nonstimulant. Within both classes of stimulants, we now have delivery systems that tailor the release kinetics to optimize outcomes for each individual patient with immediate-release, 8-hour sustained-release, 12- to 14-hour sustained-release, and, in the near future, 16-hour sustained-release options. In addition, 2 delayed-onset, sustained-release ADHD medications are currently in development, which offer the prospect of improving early-morning symptoms. A deeper understanding of the functional difficulties encountered by ADHD patients throughout their lives, coupled with more consistent use of ADHD rating scales, enable clinicians to choose between a wide variety of medication delivery systems in order to optimize the outcome for each of their patients.

Disclosures

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1. ADHD treatment is associated with:
   A. Decrease in accidental injury and medical utilization due to accidents and trauma
   B. Increase in accidental injury and medical utilization due to accidents and trauma
   C. No change in accidental injury and medical utilization due to accidents and trauma

2. Studies have shown that combinations of non-stimulants with stimulants:
   A. Can have beneficial effects for patients that were only partial responders to stimulant alone
   B. Do not have any synergistic effect for patients that were only partial responders to stimulants alone

3. Research into the best ways to help differentiate between ADHD and bipolar disorder in children identified five questions that best discriminate between the two disorders. Which of the following was NOT one of those questions?
   A. Decreased need for sleep
   B. Elated mood
   C. Grandiosity
   D. Hypersexuality and hypersexual behavior
   E. Irritability
   F. Racing thoughts

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