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2006 AACAP EDUCATIONAL OUTREACH PROGRAM FOR GENERAL RESIDENTS

I was able to attend AACAP for the first time with this award. I still remember the wonderful experience I had in the mentoring program, meeting leaders in our field that have continued to be mentors to me for the past 10 years. I was amazed at the breadth of learning I experienced in the symposia and workshops I attended. It really broadened my training as a psychiatry resident.

2007–08 AACAP PILOT RESEARCH AWARD
Project Title: “Prenatal Stress and Effects on Inhibitory Neurons”

This project allowed me to take the first steps in a field of research, examining the mechanisms by which prenatal stress is a risk factor for child psychiatric disorders. This research is at the heart of my lab’s work now 10 years later. The award funded the first few experiments in a significant paper, the first I published on the topic of prenatal stress in Psychoneuroendocrinology. The project also provided pilot data with which I wrote other grants, including a successful application for an NIMH career development award and a NARSAD Young Investigator Award. The impact of this grant is still very much alive: I received 3 other grants in the past 2 months to fund projects that are offshoots of this first original work. AACAP not only allowed me to start this work but also gave me the support that was necessary for me to gain the confidence of other stakeholders.

2009 AACAP EDUCATIONAL OUTREACH PROGRAM FOR CAP RESIDENTS

I was able to participate in an oral presentation for the first time at a national meeting, leading a session about mentoring using online resources. I continued to network with many senior mentors in the field and other junior physician-scientists in child psychiatry.

2009 AACAP ROBINSON-CUNNINGHAM AWARD

Manuscript: Risk and resilience: early manipulation of macaque social experience and persistent behavioral and neurophysiological outcomes. I learned a great deal about brain and behavior development while writing and publishing this paper. I also appreciated the importance of making science clinically-accessible and continually working to bring science and clinical practice together to inform each other.

2011 AACAP JUNIOR SCHOLARS TRAVEL AWARD

I was able to present updated findings about the prenatal stress animal model project I had started in 2007 through the Pilot award. I participated as a mentor in the AACAP mentoring program for the first time and learned a lot about the perspectives of students and residents considering entering our field. I was grateful to begin learning how to be a mentor at the faculty level from observing the skill of more experienced mentors around me.
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What is JAACAP Connect?
All are invited! JAACAP Connect is an online companion to the Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP), the leading journal focused exclusively on psychiatric research and treatment of children and adolescents. A core mission of JAACAP Connect is to engage trainees and practitioners in the process of lifelong learning via readership, authorship, and publication experiences that emphasize translation of research findings into the clinical practice of child and adolescent psychiatry.

Why do we need JAACAP Connect?
The field of child and adolescent psychiatry is rapidly changing, and translation of scientific literature into clinical practice is a vital skillset that takes years to develop. JAACAP Connect engages clinicians in this process by offering brief articles based on trending observations by peers, and by facilitating development of lifelong learning skills via mentored authorship experiences.

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Motivated by the ACGME/ABPN Psychiatry Milestone Project©, JAACAP Connect aims to promote the development of the skillset necessary for translating scientific research into clinical practice. The process of science-based publication creates a vital set of skills that is rarely acquired elsewhere, and models the real-life thought process of translating scientific findings into clinical care. To bring this experience to more trainees and providers, JAACAP Connect aims to enhance mastery of translating scientific findings into clinical reality by encouraging publishing as education.

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The Coolest Job in the World

Richard Livingston, MD

My class from Little Rock Central High will celebrate our fiftieth reunion this fall. After completing college and a Teacher Corps program, I became a biology teacher at my alma mater. I had considered medical school, but frankly was tired of the student role.

One academic year, “G,” one of my high-achieving sophomores from the last class hour of the day, missed a couple of days of school in the fall. I heard from another teacher that, while on a hunting trip, G had tripped on a root, accidentally discharged his rifle, and killed his best friend. The day he returned to school, he lingered after class and seemed to want to chat, volunteering to help me set up lab for the next day. Thereafter, most days for about a month, he hung around. I listened a lot. The content he shared only got really serious once or twice. He went back to his normal routines, and a couple of weeks later, he left me a note of thanks. It ended, “I know hanging around with you helped me. I have no idea how or why. But, thank you.”

Being a science geek, I tried to read up on the science of helping relationships. What was readily available was kind of interesting, but seemed, well, not very scientific. But, when I decided to apply to medical school, I was already considering child and adolescent psychiatry. (By the way, G is still doing well in the world.)

The first year of medical school included full-immersion laboratories and hundreds of lecture hours. I remember three specific lectures. One was the physiology of flatus; one was the physics of coronary artery narrowing. The third was titled “Multiple Causality,” by John Peters, the first child psychiatrist at the University of Arkansas for Medical Sciences (UAMS). Dr. Peters explained that, when he was trained, every psychiatric
problem was considered to be either a conditioned response (if you were a Pavlovian) or a subconscious reaction to something in the environment (if you were a psychoanalyst). Analysts ran the academic centers of American psychiatry, and the DSM-II listed nearly everything as a “reaction”: “schizophrenic reaction,” “hyperkinetic reaction,” “depressive reaction.” So, Dr. Peters explained, was he taught.

Then, driving one day with his three dogs in the back seat, his car was T-boned by a pickup truck that ran a stop sign. No physical injury resulted to human or dog, but the dogs, who had all had the same experience, reacted behaviorally very differently. The oldest dog showed no change at all. One became irritable and aggressive, snapping and growling readily. The third became nervous, petrified even to see a car. Dr. Peters began contemplating what might account for the differences in responses. Genetics provided a possible contributing factor. (Dr. Peters and his group went on to establish that it was possible to breed a fear of people into a line of pointer dogs, thus proving that a genetic contribution to anxiety is possible.) Similar variety in the responses of three boys who witnessed the same plane crash later that year reinforced his ideas, and he published his theory, “Multiple Causality: Toward Clarification of the Diagnostic Dilemma in Child Guidance,” in Volume 1 of J. Hellmuth’s 1965 edition of Learning Disorders. I was intrigued. Here was a confluence of biology and other facets of life, suggesting some complexity to explain how we are what and who we are.

A few years later, after general psychiatry training at Washington University in St. Louis, I was invited to become UAMS’s first fellow in child psychiatry. I plunged in, got trained, and then joined the faculty, where I stayed for ten years. Another academic position followed at the New Jersey Medical School, then some years in private practice, and I am now back at UAMS.

My brain looks for, and is fascinated by, patterns, and the grander, the better. Fortunately, I also tolerate ambiguity well, and have learned to be patient. All these traits serve me well, and forty years later, I assert that I have the coolest job there is.

We may be the only medical specialty in which practitioners can truthfully assert that some of our patients end up better off when we are done than they were before a problem was present. At the very least, the child psychiatrist may help liberate young persons to develop to their fullest potentials. We may improve Inez’s focus so that she can sustain enough attention to master the concept and calculation of electrochemical valence, and embrace the college-level chemistry class she was dreading. Oliver may be able to sit still for the first time and finish his meals, improving his nutrition and his dad’s anxiety. Shanika finally might be able to complete her trauma narrative in therapy, and become able to walk past the neighborhood park where she was assaulted without her heart rate soaring. Jonathan might learn to reject the insults offered by his hallucinatory voice, before Doc finds just the right medication and dose to banish the voice from consciousness. Wolf may catch on to the connections between symbols and sounds, such that learning to read is now possible.

We are not the only people who can help, certainly. But we are the ones who collect the puzzle pieces and put them together; we are the folks who understand best how the biological, psychological, social, and developmental dimensions interact, how attempts at coping can become hard-wired, for better or worse. We are the folks whose extended neurologic exam reveals that Cindy at age ten still has residual tonic neck reflex (TNR). TNR is essential for an infant: the head turns toward whichever arm extends, a reflex substrate upon which hand–eye coordination develops. But if you still do it at age ten, it can cause trouble. Trying to catch a softball, Cindy extends her arm—and her head turns reflexively, and she cannot keep her eye on the ball, and she catches poorly, and she is among the incompetent kids who are rotten at softball, which may lead to her hating sports, having a disadvantage in her social functioning among peers, and seeing herself as incompetent. We are the
folks who know what to prescribe for that problem. Occupational therapy may help her diminish the TNR; a good adaptive PE teacher may help her learn to plant herself squarely in the path of the ball so that no arm extension is required. We are the folks who can anticipate her increased risk, both statistical and logical, for anxiety in adolescence and for possible prevention—maybe even primary prevention.

We are the docs who understand Mel's struggle to sit still during worship, and how a little touch of carefully timed medication may suffice to enable him and his family to participate without the constant vigilance that once stressed them all so thoroughly.

We are the doctors whose specialty training provides us the greatest depth and breadth of understanding of all the lines of human development, how they intertwine and interact with forces both internal and external, and what might work to re-establish the good momentum of development.

An old medical school joke says the following: the surgeon knows nothing and does everything; the internist knows everything and does nothing; the psychiatrist knows nothing and does nothing; the pathologist knows everything and does everything, one day too late.

Okay, I laughed. But, the best is left out. We child and adolescent psychiatrists know important stuff, we do liberating stuff; often, I feel, we have absolutely, positively, beyond doubt, the best of all aspects of doctoring.

Welcome to the coolest job in the world.

About the Author

Richard Livingston, MD, is a professor of Child and Adolescent Psychiatry at the University of Arkansas for Medical Sciences. The department has established an award in his name for excellence in teaching residents, despite his feeble assertion that he is not dead yet.

Disclosure: Dr. Livingston reports no biomedical financial interests or potential conflicts of interest.
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The Default Mode Network: How the Mind Wanders

Florence Levy MD, PhD, FRANZCP

The advent of sophisticated brain mapping techniques (magnetic resonance imaging [MRI], functional MRI [fMRI]) has given rise to the accidental discovery of a “default mode network” (DMN) in the brain, which is activated when individuals at rest are left undisturbed to think to themselves.1 The activity associated with engagement of the DMN has been described as “mind-wandering,” and has received increasing attention in the literature.3 This rest state is involved in the “generation and manipulation of mental images, reminiscence of past experience based on episodic memory and making plans.”2(p295)

A number of studies have revealed a distributed set of regions that make up the DMN. These include the association cortex, but not the sensory and motor cortices. The functioning of the DMN is now thought to be relevant in a number of psychiatric disorders. In this paper, we will begin by defining the DMN, and then explore two key neuroscience concepts that are important to understand its function. We then will consider the DMN in terms of its application to psychiatric disorders, as well as possible clinical applications.

Theme 1: What Is the Default Mode Network?
The DMN may be described as a brain system or network of interacting brain areas that are tightly functionally connected and distinct from other systems in the brain, and is most commonly shown to be active when a person is not focused on the outside world, such as during daydreaming and mind-wandering. According to Buckner et al., DMN functions include internally focused preoccupations such as autobiographical memory retrieval and construction of self-relevant mental simulations, as well as envisioning future events.3 Also included is reflection about one’s own emotional state and the ability to conceive the perspectives of others (theory of mind). It has remained unclear whether the DMN functions as a unitary circuit or as a number of overlapping hubs with related but separate functions, and whether these functions are subject to developmental change.

Theme 2: Key Concepts
A number of concepts are key to understanding the DMN. Functional connectivity (FC) refers to the temporal correlations between the oscillatory firing of neuronal regions—otherwise put, separate brain region neurons that become activated at the same time may be considered functionally connected, even if they are not anatomically connected.3 The DMN is characterized by temporal synchrony between functionally specific and diverse brain regions. FC is believed to increase with age and should be distinguished from frontostriatal circuits, which are anatomically connected neural pathways that connect frontal lobe regions with the basal ganglia and mediate motor, cognitive, and behavioral functions within the brain.

A second concept is the function of “anti-correlation.” The DMN is described as being anti-correlated to a task-positive executive network (comprising the dorsolateral prefrontal cortex [DLPFC], inferior parietal cortex [IPC], and supplementary motor cortex [SMC]). The latter selects and maintains important task-specific information in working memory, contributing to planning and behavioral control,4,5 while the former addresses internal issues. It has been suggested that the brain has a pattern of alternation between the DMN and the task-positive network, such that at any particular point in time there is an exclusivity of function between these two attentional orientations, leading to a pattern of “fluctuating attention, periodic lapses and associated performance variability.”5(p981) The inattentiveness observed in attention-deficit/hyperactivity disorder (ADHD) is postulated as due to inadequate suppression of the DMN. This increased DMN activity was associated with the intrusion of thoughts unrelated to the task or daydreaming with alternation between introspective and exterospec-
The Default Mode Network

tive states. Excess default mode interference in executive functions was suggested as a possible mechanism that explained response variability in ADHD. The regulation of competition between task-positive and DMN networks is not well understood. Cyclical fluctuations of attention are often regarded as pathological, though given their pervasiveness, pathology should be seen as a matter of degree. Excess task positivity (as in obsessive-compulsive disorder) may be just as detrimental as excessive mind-wandering or daydreaming. This distinction can be important in deciding whether and when to treat ADHD and raises the question of whether objective measurement is possible. Currently this decision is largely made on clinical grounds, assisted by parental and teacher rating scales. A more objective approach would be to also use measures that reflect default mode and executive fluctuations.

Theme 3: Default Mode Network and Psychopathology

Autism spectrum disorder (ASD) has also been characterized by deficits in theory of mind and by hypoconnectivity between remote cortical regions with hyper-connectivity locally. Children with ASD showed reduced connectivity between DMN nodes and increased local connectivity within DMN nodes and the visual and motor resting-state networks. There is also an absence of the previously described anti-correlation between the DMN and task-positive networks, which may result in a reduction in introspective thought. In children with ASD, these long-distance connections failed to develop during adolescence, suggesting developmental effects.

Abnormalities in functional connectivity of the DMN have been described in schizophrenia (greater connectivity, with excessive mentalizing and environmental alertness), depression (increased affective connectivity and introspection), and Alzheimer’s disease (pathology appears to form preferentially throughout the default network).

Theme 4: Clinical Applications

DMN activity is most commonly measured by blood oxygen level (BOLD) measures, which reflect changes in blood oxygen levels in distinct anatomical regions. In the future, one could imagine using fMRI in clinical practice to quantify activity in the DMN and using quantified DMN activity as a diagnostic clue and measure of illness severity. Further, this could be a biomarker to track both developmental changes over time and response to treatment in conditions such as ADHD and ASD.

Activity in the DMN can also be measured using less intrusive, indirect methods, such as assessing performance on specific psychometric tests—for example, tests that measure reaction time and how reaction time may be affected by the intrusion of thoughts that are not relevant to the task at hand. If these tasks can be validated as reliable measures of DMN activity, they could prove to be a preferred method for DMN evaluation in clinical settings.

Conclusion

In summary, the DMN is a promising new concept in neuroscience that has implications both for our understanding of certain psychiatric disorders and for potential utility in predicting outcomes, although future research is needed. Clinicians should be familiar with the basic functions of this network and the key concepts outlined in this paper in order to understand and respond to the clinical implications of emerging findings in this area.

Take Home Summary

A set of brain regions is active when the brain is at rest: this is called the “default mode network.” A balance exists between engagement of the default mode network and task-positive brain regions. Future work may allow the assessment of default mode network activity to support diagnoses, measure illness severity, and track improvement over time.
References


About the Author

Florence Levy, MD, PhD, FRANZCP, is the Head, Child and Family East at Prince of Wales Hospital, Sydney, Australia, a conjoint professor at the University of New South Wales, and a staff pediatric psychiatrist at the Avoca Clinic. She has pursued a career-long interest in the phenomena and treatment of ADHD and was awarded the 1997 Norbert and Charlotte Rieger Award for Scientific Achievement for an article published in the Journal of the American Academy of Child and Adolescent Psychiatry, “Attention-Deficit/Hyperactivity Disorder: A Category or a Continuum? Genetic Analysis of a Large-Scale Twin Study.”

Disclosure: Dr. Levy reports no biomedical financial interests or potential conflicts of interest.
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Cutting Edge Psychopharmacology: Fads vs. Facts?
“Holy Psychotherapy, Batman!” Diagnosing Mental Illness in Superheroes

Keith Miller, MD

Superheroes and doctors don’t have the best history. In fact, it was psychiatrist Dr. Frederick Wertham, and not supervillain Dr. Doom, who raised significant concern that comic books were negatively impacting children in his provocative book, Seduction of the Innocent. Although Dr. Wertham nearly destroyed the comic book industry, it thankfully has recovered—as has the relationship between superheroes and the field of medicine. There has been a recent explosion of interest in graphic medicine, the intersection between comics, medical education, and patient care. Comics are now used to deliver public health education,1-3 to communicate diagnostic criteria and informed consent to patients,4,5 and to help patients process their own illnesses.6,7

Most of these medical comic books involve the creation of new characters or stories that are designed only for specific health care purposes. Until recently, few studies focused on popular comics, and those that did seem to have focused on the ways that comic characters may perpetuate negative stereotypes related to illness and health care concerns.8-10 However, medical researchers are starting to examine the inspiring power of established popular culture superheroes such as Batman and Spider-Man, starting with these superheroes’ potential positive impacts on children’s resilience.11

This article asks whether or not some of our favorite superheroes meet DSM-5 criteria for any psychiatric diagnoses and, if so, whether these superheroes might serve both as positive role models for patients with mental illnesses and as exciting examples for educating the public about mental health.

Method

I identified Marvel Comics and DC Comics superheroes who have been featured in films or television shows released within the past 15 years, under the assumption that they would be recognized by and popular with the general public. Taking into account each specific character’s appearances and portrayals in comic books, movies, video games, and television shows, I determined if he/she met DSM-5 criteria for any mental disorder.

Results

Since his first appearance in 1939 in Detective Comics #27, Batman (alias Bruce Wayne) has become one of the most popular superheroes worldwide. However, despite the fact that he keeps the streets of Gotham City safe, even Bruce Wayne himself claims that “a guy who dresses up like a bat clearly has issues.”12 Eccentric though he may be, does Batman meet DSM-5 criteria for any specific disorder?

Since his crusade against crime began at age 8 when he witnessed the murder of his parents during a robbery gone wrong, it would be fair to ask whether Batman suffers from posttraumatic stress disorder (PTSD). After all, his trauma did negatively alter his mood and thoughts, as he blames himself for endangering his parents. He has limited interest in activities unrelated to crime-fighting, only forms close relationships with his sidekicks, and is unable to experience happiness as long as crime exists. He also has intrusive memories and flashbacks to his parents’ murders that plague him when he comes in contact with certain enemies (i.e., Scarecrow and his fear gas) or when he feels that he is failing in his mission to fight crime. However, it is unclear if Batman meets any of the other PTSD criteria. Rather than avoiding criminals, guns, and violence, he seeks them out. And his hypervigilance, aggressiveness, and recklessness actually enhance his war against crime. Lastly, Batman still runs Wayne Enterprises and leads the Justice League, proving that he can thrive despite childhood trauma and symptoms associated with PTSD.
While Batman does not meet full DSM-5 criteria for PTSD, a different picture emerges when we examine Iron Man (alias Tony Stark) of the Marvel Cinematic Universe. After nearly dying while battling space aliens in The Avengers, he is portrayed in the film Iron Man 3 as having recurrent intrusive dreams and dissociative flashbacks of the attack, refusing to even mention “the events of New York,” experiencing persistent negative emotions, and isolating himself in his robotics laboratory away from his girlfriend. He also becomes a hyper-vigilant, irritable insomniac. He eventually leaves control of Stark Industries to his girlfriend and struggles to fight crime as Iron Man as a direct consequence of these symptoms, proving that they are quite impairing.13

However, these are far from the only popular culture heroes who struggle with psychiatric symptomatology (Table 1). Characters from both DC and Marvel Comics seemingly demonstrate symptomatology that suggests potential diagnoses as varied as mood disorders, anxiety disorders, substance use disorders, personality disorders, and psychotic disorders. Of note, many of them experienced significantly traumatic upbringings.

<table>
<thead>
<tr>
<th>SUPERHERO</th>
<th>MISSION</th>
<th>POTENTIAL DSM-5 DIAGNOSES</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ant-Man</td>
<td>Scientist Hank Pym shrinks to a microscopic level and controls ants to fight crime</td>
<td>Bipolar disorder</td>
<td>Manic episodes with decreased sleep, grandiosity, increased crime fighting, distractibility, and more experiments than normal</td>
</tr>
<tr>
<td>Batman</td>
<td>Billionaire Bruce Wayne strikes fear into criminals and solves mysteries by night</td>
<td>PTSD</td>
<td>See above</td>
</tr>
<tr>
<td>Daredevil</td>
<td>Blind defense attorney Matt Murdock uses circus acrobatics to prove that “justice is blind”</td>
<td>Major depressive disorder</td>
<td>Anhedonia, depressed mood, excessive (Catholic) guilt, fatigue, and thoughts of self-harm by placing self in harm’s way</td>
</tr>
<tr>
<td>The Hulk</td>
<td>Mild-mannered scientist Bruce Banner mutates into a giant green beast when he gets angry</td>
<td>Dissociative identity disorder, intermittent explosive disorder</td>
<td>Dissociation with an inability to remember actions of the Hulk. Numerous behavioral outbursts that result in extreme destruction when angered</td>
</tr>
<tr>
<td>Iron Man</td>
<td>Billionaire Tony Stark fights crime in a weaponized mechanical suit of armor</td>
<td>PTSD, alcohol use disorder, narcissistic personality disorder</td>
<td>See above. Severe alcohol use led to his loss of the Iron Man suit, and becoming homeless. Grandiose, arrogant, preoccupied by his own success</td>
</tr>
<tr>
<td>Jessica Jones</td>
<td>Jessica Jones works as a private investigator after retiring from the superhero life</td>
<td>PTSD</td>
<td>Recurrent flashbacks to sexual assault by a supervillain; avoidance of memories of him, self-blame, and placement of self in deliberate danger when fighting crime</td>
</tr>
<tr>
<td>Moon Knight</td>
<td>Marc Spector is the embodiment of an Egyptian god of the night</td>
<td>Schizophrenia</td>
<td>Hallucinations of other superheroes, incoherent speech</td>
</tr>
<tr>
<td>The Punisher</td>
<td>Frank Castle embarks on a violent war on crime after his family is killed by mobsters</td>
<td>PTSD</td>
<td>Recurrent flashbacks and self-blame for the death of his family; social isolation with abandonment of friends if they do not follow his murderous fight against criminals</td>
</tr>
<tr>
<td>Spider-Man</td>
<td>Peter Parker fights crime with the strength and web-spinning abilities of a spider</td>
<td>Generalized anxiety disorder</td>
<td>Spider-sense normally alerts him to real danger, but can become hypervigilant and excessive</td>
</tr>
</tbody>
</table>

Note: PTSD = posttraumatic stress disorder.
Discussion
Even though Batman does not meet every DSM-5 criterion for PTSD, Iron Man certainly seems to. In addition, there are a number of other superheroes who might provide novel opportunities by which to introduce and discuss particular mental illnesses, life circumstances, or psychosocial stressors with patients, colleagues, and the public. Comic books recently reached their highest circulation in almost 20 years, and superheroes star in some of the most popular films, TV shows, and video games. Given their recent popular resurgence, these imaginary characters have the opportunity to transcend page and screen and improve the lives of real-world populations.

Comic superheroes with mental illnesses can serve as positive role models for patients and the public. The stigma of mental illness is well documented, and the comic book industry unfortunately has long contributed to the negative perception of the mentally ill. Batman’s and Spider-Man’s foes are incarcerated in Arkham Asylum and the Raven-croft Institute for the Criminally Insane, respectively, and a number of villains, including The Joker (arguably the most famous comic book villain of all time), are described as psychotic despite never demonstrating delusions, hallucinations, or disorganized speech or behavior. However, as highlighted in this review, those with psychiatric symptoms and mental illness do not have to be the villain, but can be heroes and save the world.

Superheroes also can serve as accessible and familiar “safe spaces” for individuals to use in processing their troubles. For example, while it may be difficult for a patient to discuss the deaths of his or her own parents, he or she might more easily talk about the grief that Batman might feel every day. In this way, superheroes and their narratives would act as scaffolds upon which children and adolescents could build their own stories and through which they could explore their own relationships with psychiatric symptoms and illness. Youth could hold the heroes up as perfect examples of how to respond to trauma or manage mental illness or could critique them and offer alternative opinions and perspectives. For example, some may think that Batman is coping with the loss of his parents in a healthy way by devoting his life to fighting crime, while others may think that his constant anger is a sign that he hasn’t yet fully processed his grief. Comic superheroes provide comfortable characters and stories for patients to explore their own thoughts and emotions.

The use of comic superheroes for therapeutic or clinical benefit has been explored by some. One research group asked if heroes experienced fictional troubles similar to the real-life adversities faced by vulnerable children. Of the 20 film superheroes that they profiled, a vast majority had experienced significant trauma prior to becoming a hero, with most (86%, actually) being orphaned or abandoned. From this finding, the authors extrapolated that children might not feel alone upon learning that they share a common history with a certain hero. This group also suggested that shared aspects of superheroes’ and patients’ histories could be used by providers to build rapport with younger patients.

Conclusion
While most current graphic medicine has focused on specially created “medical comics,” our hope is that popular superheroes can provide positive depictions for individuals with mental illnesses and help patients discuss their own struggles. I have identified a number of heroes with mental illnesses at this time, but to see the results of the rest of this research, you will have to check back. Same Bat-time. Same Bat-channel.

Take Home Summary
- Graphic Medicine is a rapidly expanding field, but most of its research has focused on specially created “medical comics,” with few studies focusing on popular superheroes (Batman, Superman, Spider-Man, the Avengers, etc.).
- There are a number of superheroes who provide novel opportunities by which to introduce and discuss with young patients particular mental illnesses or psychosocial stressors.
- These heroes could provide positive depictions for individuals with mental illnesses and help patients discuss their own struggles.
Dignosing Mental Illness in Superheroes

References


About the Author

Keith Miller, MD, is currently a second-year general psychiatry resident at the Mayo Clinic. He fell in love with superheroes when he first picked up a comic book in his neighborhood grocery store at 6 years old. His favorite superhero is Spider-Man.

Disclosure: Dr. Miller reports no biomedical financial interests or potential conflicts of interest.

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Aggression in Attention-Deficit/Hyperactivity Disorder: When Do Psychotropics Backfire?

Janet Charoensook, MD, Takesha Cooper, MD, MS

Case: A healthy 9-year-old girl who is taking dexmethylphenidate extended-release (ER) (Focalin XR) 10 mg daily presents with residual attention-deficit/hyperactivity disorder (ADHD) symptoms and 1-2 episodes per month of aggressive tantrums. To treat the residual ADHD symptoms, dexmethylphenidate ER is increased to 15 mg daily. The family instantly notices an improvement in the girl’s concentration, but also an increase in the severity, frequency, and duration of aggressive outbursts in the afternoon. These outbursts remit on weekends, when the medication is not administered. The possibility of stimulant rebound is considered, and a booster dose is added, resulting in worsening episodes of severe aggression throughout the evening. Guanfacine is added with little improvement. Dexmethylphenidate ER is tapered off successfully, and dextroamphetamine/amphetamine ER (Adderall XR) is started. Her ADHD symptoms improve, and her aggressive tantrums resolve.

The 2007 American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder states that “controlled trials of stimulants do not support the widespread belief that stimulant medications induce aggression.”1(p910) Indeed, on the whole, aggression in young patients with ADHD tends to decline when they are treated with stimulants.1,2 Yet for a proportion of patients, aggression can worsen with pharmacotherapy for ADHD. Recognizing this phenomenon, the Parameter advises physicians to distinguish between aggression as a true adverse event and aggression as the result of stimulant medication wearing off, or “rebound phenomena.” If it is determined that the patient’s aggression and/or emotional lability is clearly secondary to the ADHD medication, the Parameter recommends the medication be discontinued and a new medication begun.1

Such a recommendation, while seemingly straight-forward, belies the difficulty of determining the cause of new or worsening aggression in ADHD. Aggression, defined by Patel and Barzman as “age inappropriate verbal or physical acts that are reactive or impulsive in nature,”3(p408) and by Saylor and Amann as “behavior with the immediate intent to cause harm – whether to self, others, objects, or property,”4(p19) is difficult to evaluate because of inconsistent usage of imprecise terms to describe the behavior. One parent might label a child’s behavior “violent,” another parent witnessing the exact same behavior might call it “aggressive,” and another parent might label the behavior “hostile.” Because of our varied and imprecise usage of terms to describe similar behaviors, it is difficult to study and to address the already complex relationship between ADHD treatment and aggression. The inconsistent use of terminology can lead to unnecessary pharmacotherapy and an overall underreporting and underappreciation of aggression related to ADHD medications. In this article, we attempt to untangle the possible causes of aggression in the context of ADHD medication treatment, and offer suggestions for providers facing this challenge.

A Connection Between Aggression and ADHD Medications?

Given that there are medical causes of new-onset aggressive behaviors in children and adolescents, providers should always consider whether a primary medical condition could be causing the behavior change. Among such medical causes of aggression are hypothalamic hamartoma, gelastic seizures,5 limbic encephalitis,6 and other epileptic and neurological disorders involving the frontal and temporal lobes.7 Also, children and adolescents who are nonverbal and/or have communication...
difficulties may be less able to express their feelings of pain, infection, or other concerns and, as a result, may demonstrate aggressive behaviors and irritability due to these physical symptoms.8

**Aggression as Part of Rebound Phenomena**

One possible cause of increased aggression in those treated with stimulants is rebound phenomena, also described as “transient behavioral deterioration,”9 which can occur when an ADHD stimulant medication wears off during the day. It can present as irritability, loss of patience, and worsening of core ADHD symptoms, such as increasing hyperactivity and impulsivity.10 But it does not mean that a medication is failing—rather, that its efficacy has worn off by the end of the day. According to the AACAP Practice Parameter on ADHD, clinicians need not seek out a new medication to treat aggression attributable to rebound phenomena. In order to determine if the phenomenon is present, the clinician can ask the patient’s caregiver to keep a diary, tracking the behavior throughout the day. Once it is determined that the behavior is secondary to rebound phenomena, prescribing an immediate release stimulant in the late afternoon may be helpful.

**Aggression and Non-Stimulant Medications**

To date, there is limited and conflicting literature regarding the relationship between non-stimulant medications and aggression as an adverse event. A retrospective review found that 51 out of 153 (33%) children with a mean age of 10.5 years exhibited “extreme irritability, aggression, mania, or hypomania induction” after receiving the non-stimulant atomoxetine.11 However, the authors of the retrospective review did not indicate the statistical significance of their findings. A meta-analysis focusing specifically on the role of atomoxetine in aggression suggests that less than 2% of patients who took atomoxetine had events related to hostility or aggression.12 These findings were not statistically significant when compared to the occurrence of aggression in patients taking placebo or methylphenidate. Finally, another meta-analysis of the safety of atomoxetine reported that there is no statistically significant increase in the occurrence of aggression among youth who take atomoxetine.13 However, the authors of that meta-analysis note that concurrent use of an antipsychotic to manage the aggression may have masked the potential link between atomoxetine and aggression.13 In one study mentioned in the meta-analysis,13 17% of children and adolescents carrying a diagnosis of ADHD were taking antipsychotic medications despite not having a Food and Drug Administration (FDA) indication for the antipsychotic.14

Another non-stimulant ADHD medication may be linked to aggression as an adverse event. According to an FDA safety review of 676,000 prescriptions (between September 2009 and 2010) for extended-release guanfacine (Intuniv), there were 45 total cases of serious non-fatal adverse events, including four cases of agitation, one case of irritability, and two cases of aggression (categorized as unlabeled adverse effects).15

**Aggression and Methylphenidate-Based Stimulant Medications**

Despite the AACAP Practice Parameter statement to the contrary, studies examining the efficacy and safety of methylphenidate-based stimulants raise concerns about aggression as a possible adverse event. Wilens et al. reported that hostility leading to early treatment discontinuation occurred in 0.5% of patients taking OROS methylphenidate (Concerta; \( n = 2 \)); there was no placebo comparison as the individuals in this study had previously participated in an efficacy or pharmacokinetic study of OROS methylphenidate.16 Wigal et al.17 reported that, among patients treated with dextmethylphenidate, 3 patients out of a total of 44 exhibited emotional lability compared to 1 out of 42 on placebo. FDA safety reviews, which are observational and do not include a placebo comparison group, report aggressive behaviors as adverse events for the methylphenidate transdermal system (Daytrana; aggression, \( n = 5 \) out of 143 nonfatal serious adverse events reported to the FDA between 2006 and 2011),18 dextmethylphenidate hydrochloride (Focalin; aggression, agitation, irritability, \( n = 4 \) out of 164 nonfatal serious adverse events
reported to the FDA between 2005 and 2011), and methylphenidate hydrochloride (Quilivant XR; anger, \( n = 1 \) out of 11 serious nonfatal unlabeled adverse events reported to the FDA). In June 2005, the FDA released postmarketing reports that cautioned that methylphenidate (Concerta) and other methylphenidate-based medications could cause potential aggression or violent behavior. In March 2006 and following a review of available clinical trial data, the FDA Pediatric Advisory Committee reported elevated rates, relative to placebo, of aggression events associated with methylphenidate hydrochloride (Daytrana, Ritalin LA) and atomoxetine (Strattera), but not with other ADHD medications.

**Aggression and Amphetamine-Based Stimulant Medications**

FDA medication guides report hostility as an adverse event associated with amphetamine-based stimulant medications, as well as with methylphenidate-based stimulant medications. In a study by McGough et al., hostility following the administration of extended-release mixed amphetamine salts (Adderall XR) was observed in 3 of 568 participants. Of note, the authors concluded that the hostility was unrelated to the medication. In a pediatric case series reviewed by the FDA, among 135 participants who received lisdexamfetamine (Vyvanse), 45 reported psychiatric adverse events. Of particular relevance to this discussion are the psychiatric adverse events categorized and listed as agitation (\( n = 1 \)), irritability (\( n = 1 \)), affect lability (\( n = 2 \)), anger (\( n = 9 \)), homicidal ideation/violence-related thinking (\( n = 6 \)), and head-banging (\( n = 1 \)). Considering the aforementioned definition of aggression as behavior with immediate intent to cause harm, this review’s classification of adverse effects highlights both (1) the manner in which numerous terms seem to capture various distinct and overlapping aspects of the broader phenomenon of aggression and (2) the possibility that the use of these and other related terms has made and may continue to make more difficult the detection of any true existing relationship between ADHD medications and aggression.

**Summary of the Literature Regarding Aggression and ADHD Medications**

Based on extant literature, the current consensus is that aggression is not a significant adverse event associated with psychopharmacological treatment of ADHD and that ADHD medications generally are well tolerated. However, the existing literature does suggest that aggression is observed among youth receiving psychopharmacological treatment for ADHD. Furthermore, the authors of this article suspect that the literature does not adequately account for the possibilities that (1) observed aggression may reflect rebound phenomena (which, if unrecognized, would lead to an over-attribution of aggression to ADHD psychopharmacological treatment) and (2) the inconsistent use of varied terminology to describe adverse events may make more challenging the identification of a true relation between aggression and medications used in the treatment of ADHD (which would lead to an under-attribution of aggression to ADHD psychopharmacological treatment).

**Understanding New-Onset Aggression in the Context of Psychopharmacological Treatment of ADHD**

To determine whether new-onset aggression in the context of psychopharmacological treatment for ADHD is the result of rebound phenomena or a direct medication adverse event, it is important for clinicians to obtain a detailed history and to carefully establish a timeline. Table 1 offers possible questions a clinician can ask to elucidate a potential relation between the medication and the observed behaviors. Questioning when the patient first began demonstrating the aggressive episodes helps clarify whether the aggressive behavior predated the start of medication or whether the onset of the aggressive behaviors coincides either with the initiation of medication treatment or any dose increases. The temporal relation between the aggressive episodes and the time of administration of a medication dose and, relatedly, between the aggressive episodes and the time of effect onset (based on pharc-
Aggression in Attention-Deficit/Hyperactivity Disorder

Table 1. Possible Questions to Ask About New-Onset Aggression After Psychopharmacological Treatment

- When did these aggressive episodes start?
- How do these episodes relate temporally to the time of medication dosing?
  - When is the medication given?
  - When do the episodes of aggression occur? Soon after the medication is given? Throughout the day? When the medicine is wearing off? After the medicine has worn off?
- Are triggers evident prior to the episodes of aggression?
- Do these episodes occur in multiple settings or contexts, or do they occur consistently and almost exclusively in specific settings or contexts?
- Are there any other medications (including non-psychotropics, like antihistamines or steroids) that could be contributing directly or through interactions?
- Are there any non-medication issues potentially at play (either medical or psychosocial)?

...macokinetics) may also be important. If the aggression occurs almost exclusively after a medication is administered and/or during the time when the medication is expected to be active, the aggression may represent an adverse event. If, based on a medication's pharmacokinetics, the aggression happens at a time of day when the effects of the medication are likely wearing off, the aggression may reflect rebound phenomena. If, based on pharmacokinetics, the aggression occurs during periods during which the medication is no longer active (the effects having worn off), the aggression may reflect baseline symptomatology for which treatment was initiated. In the case of aggression related to either rebound phenomena or the absence of medication effect, the aggression may seem particularly prominent given its presence relative to its prior absence during periods of active medication effect.

The environmental settings and/or contexts in which aggressive episodes occur also may help clarify if the aggression is a medication-related adverse event, reflective of rebound phenomena, or neither. For example, if the episodes occur almost exclusively in a specific setting or context and that setting/context does not coincide with the period of time during which the effects of the medication are wearing off, the behavior is less likely to be an adverse event or a sign of rebound phenomena and is more likely reflective of the specific setting/context itself.

A thorough assessment of new-onset aggression, including the examination of the timeline and circumstances around the behaviors, will increase the likelihood of identifying accurately contributors to the aggression. Doing so will help the clinician distinguish between aggression related to medication adverse effects, rebound phenomena, baseline symptomatology, and/or treatment-resistant symptomatology and, as a result, will also help the clinician avoid potentially ineffective, unnecessary, or even harmful interventions, such as polypharmacological treatment.

Conclusion

The literature exploring the relation between aggression and ADHD is marked by imprecision in how aggression is described and accounted for, and offers inconsistent conclusions regarding any relation between aggression and ADHD medications. As such, for these authors, the question of whether ADHD medications lead to an increased likelihood of aggressive behaviors presently remains unanswered. More research is needed to fully explore the relation between the two. In the meantime, we suggest that clinicians consider whether aggression occurring in the context of psychopharmacological treatment of ADHD reflects adverse medication events. We also suggest that if, based on a comprehensive history and established timeline, the suspicion of medication-related aggression is high, clinicians consider switching to a different medication to treat ADHD. As in the case vignette at the outset of this article, the timeline was assessed carefully and then the medication, dexamethylphenidate ER, was removed. The aggressive
behaviors remitted, and the patient responded positively to a different ADHD medication.

**Take Home Summary**

- It remains unclear whether both classes of stimulant medications as well as non-stimulant medications used in the treatment of ADHD may cause aggression as an adverse event.
- Before switching to or adding on an additional medication, the onset of aggressive behaviors, their temporal relationship to medication administration, and the settings/contexts in which these behaviors occur should be carefully evaluated to determine any potential contributing role of the medication to the aggression.

**References**

20. US Food and Drug Administration. Statement on Concerta and methylphenidate for the June 30 PAC. Available at: http://www.fda.gov/ohrms/dockets/ac/05/


About the Authors
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Disclosure: Drs. Charoensook and Cooper report no biomedical financial interests or potential conflicts of interest.
Member Service Forum: Legislative Program and Congressional Visits

Monday, October 23, 2017
9:00 am-5:00 pm

Please note that this MSF is limited to the first 150 AACAP members with Association membership.

To take full advantage of meeting in our nation’s capital, and to sustain member’s enthusiasm for advocacy following the record-breaking 2017 AACAP Legislative Conference, AACAP members who are U.S. residents are invited to participate in this legislative program to advance children’s mental health through legislation.

The program will begin at 9:00 am on Monday, October 23, and be followed by Congressional Hill visits. This program will help equip members with the necessary know-how and offer the advocacy material needed to successfully lobby your own U.S. Representative and Senators on AACAP’s policy priorities.

This event requires you to make a short trip across D.C., and meetings with your Congressional Representative and Senators will take place on Capitol Hill, immediately after the legislative program. All Congressional meetings should conclude by 5:00 pm.

Prior advocacy and lobbying experience is not required, but seasoned advocates are encouraged to attend. Please note that a volunteer state leader or regional captain assigned to your area will coordinate all appointments with Congressional offices. Individual attendees will receive more details, once registered for this event.

Coordinated by AACAP’s Advocacy Committee, AACAP’s Advocacy Liaison Network, and AACAP’s Government Affairs & Clinical Practice Department.

American Association of Child & Adolescent Psychiatry
Clinical Review of New Medications for Treating Attention-Deficit/Hyperactivity Disorder

Jozef Zelenak, MD, MBA, Alexander Getz, MD

A s 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. 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. It received FDA approval in December 2015 for patients 6 years and above and was brought to market in February 2016.

<table>
<thead>
<tr>
<th>Table 1. Methylphenidate-Based Medications</th>
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<tr>
<th>GENERIC</th>
<th>FORMULATION</th>
<th>AVAILABLE DOSES</th>
<th>STARTING DOSE</th>
<th>TITRATION/ONSET DURATION</th>
<th>MAX DOSE PER DAY</th>
<th>NOTES</th>
<th>PRICEa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aptensio XR</strong></td>
<td>racemic methylphenidate hydrochloride®</td>
<td>extended-release capsules®</td>
<td>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)</td>
<td>10 mg qAM (Age ≥ 6)</td>
<td>10 mg per day at weekly intervals; onset at 60 min; lasted up to 12 hrs post dosing</td>
<td>60 mg</td>
<td>may take with or without food; capsules may be opened and sprinkled on applesauce; no specific flavor indicated</td>
</tr>
<tr>
<td><strong>QuilliChew ER</strong></td>
<td>racemic methylphenidate hydrochloride®</td>
<td>extended-release chewable tablets®</td>
<td>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”®)</td>
<td>20 mg qAM (Age ≥ 6)</td>
<td>10 mg, 15 mg, or 20 mg per day at weekly intervals; onset at 45 min; lasted up to 8 hrs post dosing</td>
<td>60 mg</td>
<td>may take with or without food; cherry-flavored tablets</td>
</tr>
<tr>
<td><strong>Quillivant XR</strong></td>
<td>racemic methylphenidate hydrochloride®</td>
<td>extended-release oral suspension®</td>
<td>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</td>
<td>20 mg qAM (Age ≥ 6)</td>
<td>10 mg to 20 mg per day at weekly intervals; onset at 45 min; lasted up to 12 hrs post dosing</td>
<td>60 mg</td>
<td>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</td>
</tr>
</tbody>
</table>

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. It 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. 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. 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. 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. 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. 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. 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. 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.

Evekeo is manufactured by Mikart, Inc. and marketed by Arbor Pharmaceuticals. It received FDA approval...
### Table 2. Amphetamine-Based Medications

<table>
<thead>
<tr>
<th>GENERIC</th>
<th>FORMULATION</th>
<th>AVAILABLE DOSES</th>
<th>STARTING DOSE</th>
<th>TITRATION/ONSET DURATION</th>
<th>MAX DOSE PER DAY</th>
<th>NOTES</th>
<th>PRICE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adzenys XR-ODT</td>
<td>racemic amphetamine salt; 3:1 (D-AMP: L-AMP)(^5)</td>
<td>extended-release orally disintegrating tablets(^5)</td>
<td>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)</td>
<td>6.3 mg qAM (Age 6-17); 12.3 mg qAM (Age ≥ 18)(^5)</td>
<td>3.1 mg or 6.3 mg per day at weekly intervals(^5)</td>
<td>18.8 mg (Age 6-12); 12.5 mg (Age ≥ 13)(^6)</td>
<td>may take with or without food; allow tablet to disintegrate in saliva before swallowing; orange-flavored tablets(^5)</td>
</tr>
<tr>
<td>Dyanavel XR</td>
<td>racemic amphetamine salt; 3.2:1 (D-AMP: L-AMP)(^6)</td>
<td>extended-release oral suspension(^6)</td>
<td>light-beige to tan colored viscous suspension containing 2.5 mg amphetamine base per 1mL of solution(^6)</td>
<td>2.5 mg or 5 mg qAM (Age ≥ 6)(^6)</td>
<td>2.5 mg to 10 mg per day at weekly intervals; onset at 60 min; lasted up to 13 hrs post dosing(^6)</td>
<td>20 mg(^6)</td>
<td>may take with or without food; solution should be stored at 20-25°C (68-77°F); bubblegum-flavored solution(^6)</td>
</tr>
<tr>
<td>Evekeo</td>
<td>racemic amphetamine sulfate salt; 1:1 (D-AMP: L-AMP)(^7)</td>
<td>immediate-release tablets(^7)</td>
<td>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)</td>
<td>2.5 mg qd (Age 3-5); 5 mg qd or bid (Age ≥ 6)(^7)</td>
<td>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)</td>
<td>40 mg(^7)</td>
<td>may take with or without food; no specific flavor indicated(^7)</td>
</tr>
<tr>
<td>Zenedi</td>
<td>dextro-amphetamine sulfate; 1:0 (D-AMP: L-AMP)(^9)</td>
<td>immediate-release tablets(^9)</td>
<td>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)</td>
<td>2.5 mg qd (Age 3-5); 5 mg qd or bid (Age ≥ 6)(^9)</td>
<td>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)</td>
<td>40 mg(^9)</td>
<td>may take with or without food; no specific flavor indicated(^9)</td>
</tr>
</tbody>
</table>

**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).

* 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. 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; 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. 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**

About the Authors

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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.
AACAP’s Legislative Conference and Assembly Meeting

April 8-9, 2018

AACAP’s Legislative Conference and Assembly Meeting will take place in Washington, DC, from April 8-9, 2018. Join us for both events to advocate for children’s mental health.

AACAP Legislative Conference

On April 8 and 9, 2018, learn about the legislative process and public policy issues impacting child and adolescent psychiatry. AACAP’s Government Affairs team will provide you with advocacy materials to help develop and deliver the most effective message. Once again, family advocates will be invited to join AACAP members on Capitol Hill. Join us and make your voice heard as we advocate for children’s mental health.

Visit [www.aacap.org/LegislativeConference](http://www.aacap.org/LegislativeConference) for more information or contact Zachary Kahan, Advocacy & PAC Manager, at zkahan@aacap.org or 202.587.9669.

AACAP Assembly Meeting

On April 8, AACAP’s Assembly of Regional Organizations will meet to discuss the issues facing your state and region. The Assembly consists of AACAP member representatives from across the nation and is always looking for more voices and advocates like you to join the discussion.

Visit [www.aacap.org/Assembly](http://www.aacap.org/Assembly) for more information or contact Megan Levy, Executive Office Manager, at mlevy@aacap.org or 202.966.1994.
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Authors are strongly encouraged to submit an initial outline to the editors, so that early feedback and guidance can be provided prior to the development of a full manuscript. An invitation to submit does not ultimately assure acceptance of the manuscript.

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<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
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<tbody>
<tr>
<td>13%</td>
<td>13% of youth ages 8-15 have a mental illness severe enough to cause significant impairment in day-to-day living</td>
</tr>
<tr>
<td>79%</td>
<td>79% of children ages 6-17 with mental illnesses do not receive treatment</td>
</tr>
<tr>
<td>50%</td>
<td>Nearly 50% of students age 14+ with mental illness drop out of high school (the highest rate of any disability group)</td>
</tr>
<tr>
<td>4,600</td>
<td>More than 4,600 youth die by suicide annually, yet experts believe nearly 80% are preventable</td>
</tr>
<tr>
<td>8-10</td>
<td>Studies indicate on average the delay between first onset of symptoms and treatment is 8 to 10 years</td>
</tr>
<tr>
<td>50%</td>
<td>50% of all lifetime cases of mental illness are diagnosed by age 14</td>
</tr>
</tbody>
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