

Advances in **ADHD**

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**Medication Non-Adherence
in Children with ADHD:
Challenges and Strategies**

Raun D Melmed and Laura H Jensen

**Stimulant Pharmacotherapy
in ADHD in Patients with
Co-Occurring Substance
Use Disorders**

John J Mariani and Frances R Levin

**ADHD, Bipolar Disorder,
or a Case of the "Diagnostically
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Dr Melmed receives research grant support from Lilly, Shire, and Pedimed and is a consultant and speaker for Lilly, Shire, Cephalon, UCB, McNeil, and Novartis. Ms Jensen has no relevant financial interests to disclose.

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**Answers should be recorded in the spaces provided overleaf.
One answer is correct for each question.**

Medication Non-Adherence in Children with ADHD: Challenges and Strategies

Raun D Melmed and Laura H Jensen
Advances in ADHD 2006;1(2):42–6.

- In the Multimodal Treatment Study of ADHD (MTA), which treatment group had the least robust outcome?
 - Medication alone
 - Behavioural therapy alone
 - Both of the above
 - Community treatment group
 - None of the above
- What are common factors that need to be considered to enhance treatment adherence?
 - Parental attitudes to medication
 - Cultural expectations
 - Developmental considerations
 - Age of the child
 - All of the above
- What are important factors to be taken into account when prescribing medications for ADHD?
 - Developmental age
 - Dosing regimen
 - Route of administration
 - Parental ambivalence to the use of medication
 - All of the above
- What routes of administration are available for administering ADHD medication?
 - Oral
 - Transdermal
 - Intranasal
 - A and B only
 - A, B, and C
- How does compliance with ADHD compare with that seen in other treatment conditions?
 - Compliance is worse with ADHD treatment regimens
 - Compliance is worse with other chronic treatment regimens
 - Compliance is similar for both treatment groups
- What are common reasons for non-compliance in the use of ADHD medications in 7 year old children?
 - Swallowing difficulties
 - Fear of "drugs"
 - Embarrassment with taking medications at school
 - None of the above
 - All of the above
- What are the common reasons for non-compliance in the use of ADHD medications in adolescents?
 - They want to be in control
 - They want to make decisions for themselves
 - It is developmentally inappropriate to expect them to remember to take their medication
 - All of the above
 - A and B only
- What is the doctor's role in enhancing adherence in ADHD treatment programs?
 - Appropriate discussion of side effects
 - Sounding out families' cultural attitude towards medication
 - Discussing the issues of compliance
 - Providing tools to enhance compliance
 - All of the above
- What factors need to be taken into account when prescribing ADHD medications?
 - Route of administration
 - Duration of action of treatment
 - Need for school time dosing
 - Potential for abuse
 - All of the above
- How does the child's family affect adherence to ADHD medication?
 - Hectic lifestyles can mean complicated dosing regimens are not adhered to
 - As ADHD is inheritable, parents of children with ADHD frequently exhibit disorganization and inattention, meaning that they cannot implement the medication regimen in their household
 - The ongoing expense of medication may be draining for under-insured and low-income families
 - Families do not like to provide medication to their children and seek alternative methods
 - All of the above

Stimulant Pharmacotherapy in ADHD in Patients with Co-Occurring Substance Use Disorders

John J Mariani and Frances R Levin
Advances in ADHD 2006;1(2):47–52.

- The estimated prevalence of ADHD in adults in the US is:
 - 0.3%
 - 3%
 - 8%
 - 12%
 - 16%
- The risk of a substance use disorder in adults with ADHD is:
 - The same as the general population
 - Less than the general population
 - Greater than the general population
 - Not known
- Research findings with regards to the safety of using stimulants in patients with ADHD and co-occurring substance use disorders:
 - Suggest stimulants can be used safely in controlled conditions
 - Suggest stimulants are contraindicated in patients with substance use disorders
 - Are inconclusive
 - Suggest that stimulants are easily diverted and misused under controlled conditions
 - None of the above
- Research findings with regards to the efficacy of stimulants in patients with ADHD and co-occurring substance use disorders:
 - Suggest that stimulants are ineffective in treating ADHD symptoms
 - Suggest that stimulants worsen ADHD symptoms
 - Suggest that stimulants may have benefit in treating ADHD symptoms
 - Suggest that stimulants worsen substance abuse symptoms
- Which of the following are recommended clinical management tools when prescribing stimulants to patients with co-occurring ADHD and substance use disorders?
 - Tamper-proof prescription pads
 - Conservative use of refill authorization
 - Urine toxicology testing
 - Use of delayed-release preparations
 - All of the above
- Signs that a patient may be misusing, abusing, or diverting prescribed psychostimulants include:
 - Frequent requests to replace lost or missing medication or prescriptions
 - Frequent requests for dose increases beyond the recommended dosing range
 - Enquiries from the pharmacist about possible altered prescriptions
 - Refusal to provide a urine toxicology specimen
 - All of the above
- Which of the following are possible diagnostic challenges in patients with ADHD and co-occurring substance use disorders?
 - Inability to identify periods of abstinence when ADHD symptoms were present
 - Similarity of substance-induced attentional and hyperactivity symptoms with ADHD
 - Potential for malingering and drug-seeking behavior
 - Lack of collateral history from family to corroborate the presence of symptoms
 - All of the above
- Which of the following are true regarding individuals with ADHD and comorbid substance use disorders?
 - A later onset of substance abuse than those without ADHD
 - An increased probability of having a remission of the substance use disorder
 - A tendency to take longer to reach remission of the substance use disorder
 - A decreased likelihood of having a persistent substance use disorder
- Which of the following are correct with regards to individuals with ADHD and comorbid substance use disorders?
 - Non-stimulant medications are more effective at treating ADHD symptoms than stimulant medications
 - Stimulant medications are too dangerous to use
 - No effective pharmacotherapy exists
 - Ongoing substance use may lessen the efficacy of pharmacotherapy
- ADHD and substance use disorders have been most closely linked to which neurotransmitter system?
 - Norepinephrine
 - Serotonin
 - Dopamine
 - γ -aminobutyric acid
 - N*-methyl-D-aspartic acid

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Advances in ADHD is designed to bring a critical analysis of the world literature on ADHD, written by clinicians, for clinicians, to an international, multidisciplinary audience. Our mission is to promote better understanding of the treatment of ADHD across the global healthcare system by providing an active forum for the discussion of clinical and healthcare issues.

Leading Articles - These major review articles are chosen to reflect topical clinical and healthcare issues in ADHD. All contributions undergo a strict editorial review process.

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Telephone: +44 (0)20 7759 2999 Fax: +44 (0)20 7759 2951 Email: info@advances-in-adhd.com

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Medication Non-Adherence in Children with ADHD: Challenges and Strategies

Raun D Melmed^{1,2} and Laura H Jensen¹

¹Melmed Center, Scottsdale, AZ, ²Southwest Autism Research and Resource Center, Phoenix, AZ, USA

Medication non-adherence in children and adolescents with ADHD is common and costly. In this article, we review the factors that contribute to medication non-compliance in ADHD. Some of these factors are overt, while others can be more difficult to discern. Socio-cultural factors, therapy that is not child-orientated and family-focused, family structural issues, dosing regimens and schedules, developmental considerations, adolescent concerns, co-occurring disorders, swallowing and sensory sensitivities, lack of efficacy, untoward side-effects, and child and parental ambivalence can all lead to non-adherence. Identifying the factors that lead to non-compliance in our own practices is the first important step in ensuring optimal outcomes for individuals being treated for ADHD. Methods to manage or eliminate these factors altogether are explored. *Advances in ADHD* 2006;1(2):42–46.

Non-adherence to medication in the treatment of ADHD can be either intentional or unintentional, but both situations can lead to ineffective symptom relief and to an unsuccessful experience with medication management. Non-adherence to medication in pediatrics occurs in as many as 50% of cases, even in acute illnesses [1,2]. The cost of medical care increases dramatically for all when non-adherence occurs; the inflation of cost is estimated at US\$200 billion a year in the US [3].

Several factors that affect treatment compliance are outside of the control of prescribing clinicians. With awareness of the contributory factors, clinicians can design treatment strategies that conform to the developmental level of the child, and the culture and capacity of the family, which will result in improved success. This article explores the causes of non-adherence to medication in the treatment of ADHD, and outlines strategies to manage circumstances that lead to non-adherence.

Challenges and strategies

Few studies have explored medication non-adherence in ADHD [4]. Those that have studied this cite numerous causes, including reluctance to take medication and inadequate supervision by the prescribers of the medication regimen [5]. Capone and McDonnell compared prescription data for stimulants with that for antidiabetic medications and statins to lower cholesterol [6]. The study was designed to determine whether medication non-adherence or persistence rates were lower in those with ADHD compared

with those with other chronic conditions. Their results showed that medication compliance declined dramatically from the first to the seventh month for all the medications studied. The compliance rate at month 7 for mixed amphetamine salts-extended release was 22.9%, and for methylphenidate-modified release was 23.5%; in comparison, the rates for the statins and rosiglitazone were 26.0–30.1% and 33.5%, respectively. Thus, as ADHD is a chronic condition, it poses the same challenges as other medical issues. Some of the more common situations that lead to non-adherence, which have been observed in the present authors' clinical experience, are listed in Table 1.

Socio-cultural factors

Health beliefs account for some of the apparent differences that are evident in the identification and treatment of ADHD in various cultural groups. Caucasian children are diagnosed with ADHD more often than Hispanic/Latino, African American, and Native American children [7]. Indeed, the majority of the research published on ADHD in children has been conducted on Caucasian males [8]. Hoagwood et al. showed that Caucasians were more likely than African Americans to receive stimulants, while Zito et al. showed that African American children were less than half as likely as Caucasian children to have their prescriptions for ADHD filled [9,10]. In addition, use of the internet in a family's home cannot be assumed; in these cases, education and learning materials acquire a more important function during the office visit. The clinician must determine the health beliefs and uniqueness of each individual and family situation. Regardless of cultural background or ethnicity,

Address for correspondence: Raun D Melmed, Melmed Center, 5020 East Shea Boulevard, Suite 100, Scottsdale, AZ 85254, USA

Table 1. Factors associated with non-adherence.

Socio-cultural factors
Therapy that is not child-orientated and family-focused
Family structural issues
Dosing regimens and schedules
Developmental considerations
Adolescent concerns
Family history
Child ambivalence
Prescribing practices
Co-occurring disorders
Swallowing and sensory sensitivities
Lack of efficacy
Untoward side-effects
Parental ambivalence

counseling as part of the treatment program has been found to increase patient satisfaction in ethnic minority patient populations [11,12].

Child-orientated, family-focused therapy

Child-orientated and family-focused treatment is crucial to achieving compliance to medication. Even improving eye contact throughout the patient visit can reduce non-adherence [13]. Medication management of ADHD is always only part of an overall treatment plan; the likelihood of treatment compliance is increased by involvement of the individual and the family in their treatment, and by a greater number of intervention modalities [14]. Findings from the National Institute of Mental Health Multimodal Treatment Study of ADHD reveal that successful treatment includes both medication management and behavioral intervention. In addition, major differences were apparent between the medication and the combined medication management and behavioral intervention groups when compared with the results of those receiving community management. These differences were reflected in substantial improvement for ADHD symptoms in particular. Treatment outcomes in the combined medication and behavioral intervention groups were also more successful in areas such as social skills, relationships, and comorbid disorders. These differences may have been due to the medication in the first two groups being administered by experts in a comprehensive fashion, which included monthly visits, careful titration, retitration, and assuring and teaching compliance [15].

Family structural issues

More individuals are involved in the administration of treatment in blended and reconstituted families, thus leading

to greater opportunities for errors and disagreements to occur. Knowledge of and agreement with the use of medication are often at issue between parents. This is especially germane around the time of separation and divorce. Acrimonious divorce situations often result in accusations and blame surrounding child management issues, particularly medication. In these situations, the child is often conflicted as to the need for treatment, for fear of siding with either party. Complicated medication regimens further deter compliance, especially when the child spends time in more than one household.

Even families with the best intentions can be non-compliant due to disorganization, hectic schedules, or general family complexity. Agreement on treatment strategies should be ensured by all parties, and the family must think proactively and realistically about what they can do to ensure that the medication plan is followed.

Dosing regimens and schedules

Successful treatment is characterized by well-thought out dosing, monthly follow-up visits, and communication [15]. Decisions are best made with respect for the family structure and culture. Considerations may include how busy family life is; for example, hectic lifestyles may mean that once daily dosing might prove more appropriate than multiple doses in a day. If the child spends time at more than one household, the scenario that would ease transfer between families needs to be determined. The option of school involvement may not be desirable for the family. However, a noon dose may necessitate a nurse visit at school. Although nurse visits can be viewed negatively, some children appreciate the visit and check-in with a friendly adult. The family will need to decide who will ensure that the child will take the medication with food, and with which foods the child will take their medication.

Developmental considerations

The developmental level of a child affects their willingness and/or motivation to comply with medication regimens. With emotional and physical maturation, the capability of acting in accordance with a prescribed medication routine may change. At any age and stage, eliciting the child's assent through rapport and education ensures greater compliance. In this context, an approach tailored to the child's developmental age is essential. This would include consideration of the child's ability to understand the information and to be able to comply with the prescribed plan. For example, a kindergarten age child cannot be expected to remember to go to the school nurse at noon to take medication without a call from the school nurse; this would clearly be a developmentally inappropriate expectation

that would result in non-compliance. Demystification of the diagnosis through accurate delineation and identification of the problem along with the proposed solutions is required for initiation of the treatment process. Keeping the child engaged in these discussions is crucial, as this will aid parents in understanding the central importance of the child in the treatment process.

For younger children, inquiring about concerns they may have about themselves, their school performance, and their friendships is helpful. Their answers are often diagnostically illuminating and will build rapport. Analogies of how the medication works, for example, likening the use of medication to using glasses or binoculars in order to improve focus, are helpful.

Adolescent concerns

Adherence to treatment in adolescents with ADHD is low, necessitating the clinician to spend extra time to address the particular concerns of this age group [16]. Teenagers endeavor to be in control and make decisions for themselves; this is developmentally appropriate for an adolescent [17]. Speaking directly to the adolescent, either alone or in the company of their parents, is essential. At follow-up visits, if the teenager appears reluctant to take the medication or to participate in the treatment process, direct questions are helpful: how do you feel on this medication? Do your friends know? Does this medication change you? Do you like those changes?

In certain situations when the adolescent is resistant to the idea of treatment, participation in a medication trial with outcome measures that are meaningful to them is helpful. In cases where reluctance or outright refusal is apparent, the patient could be monitored and tracked when off the medication, which can be more nurturing and successful than enforcing the continuation of the medication [18].

Regardless of the individual's age and developmental stage, greater participation in the decision-making process increases the likelihood of follow-through and compliance. This includes disclosure of expected impact on symptoms and common side effects.

Family history

ADHD and its symptoms are strongly heritable, and symptoms of inattention, distractibility, and disorganization can be expected to be found in parents [19]. Thus, compliance with complex treatment regimens could be hampered. In these situations, provision of adjunctive interventions and strategies to the family, such as counseling, coaching, or tutoring, is helpful. These can provide the required tools for parents by offering novel options for managing challenges as they occur. Coaching

in ADHD can target the complexities and unique qualities that those with ADHD live with by helping parents and children see their challenges as strengths (e.g. being able to multitask), while at the same time providing practical solutions to the problems at hand. Referral of parents or guardians suspected of having symptoms of ADHD for diagnosis and treatment is often necessary.

Child ambivalence

The child's uncertainty about the prospect of taking medication is also a concern. Social anxieties such as fear of being ostracized by siblings and peers and having to take "drugs" are common. At school, a regimen requiring administration of medication during the day can lead to embarrassment, teasing, and invasion of privacy. This can adversely affect the child's self-esteem, and cause discomfort and dislike for the treatment, and will eventually lead to non-adherence. The use of long-acting medications and alternative routes of administration can certainly avoid some of these pitfalls. In all situations, spending time with the child and allowing for opportunities to voice these concerns is recommended, along with targeted developmental counseling.

Prescribing practices

Certain situations of medication non-adherence are easily avoided; for example, multiple doses in a day can be cumbersome and unrealistic in many situations [20]. In fact, a drug regimen that is complex, inconvenient, or requires lifestyle alterations is known to decrease compliance [1]. Longer-acting stimulants can ensure more consistent drug administration, eliminate midday dosing supervision, and provide better protection of personal privacy [6,21]. Alternative routes of medication administration, e.g. using skin patch technology, might similarly improve compliance. The ongoing expense of medication, especially in underinsured and low-income families, can also be draining and may be awkward for the family to mention.

It must also be considered that compliance is an attention-demanding task that needs to be taught. This underlines the importance for clinicians to ask about it routinely. Compliance can be improved and monitored through the use of a pill box. Parents should be informed that they or their child/adolescent needs to undertake this task or at least check that the pill has been taken. Where compliance is an issue, incorporating the pill into a daily routine can be helpful, e.g. alongside cereal or brushing their teeth in the morning.

Co-occurring disorders

The presence of ADHD without comorbid disorder is rare in any sample [22]. Over half of children (50–65%) with ADHD

have at least one psychiatric disorder, the most common being oppositional defiant disorder (ODD), conduct disorder (CD), anxiety disorders, and depression. Greenberg notes that up to 33% of children will have a depressive episode. Anxiety disorders are comorbid with ADHD in up to 25% of cases, and 25–30% of children with ADHD have a learning disability [22,23].

Non-adherence may be a repercussion of these comorbid disorders. For example, the hallmark symptoms of ODD include non-compliance, emotional over-reactivity, and failure to take responsibility for actions [24]. The challenges in managing ODD are numerous, and indeed the absence of ODD is a positive predictor of successful medication compliance [25].

Swallowing and sensory sensitivities

Physiological barriers such as sensory sensitivities need to be considered. Difficulty in swallowing a tablet or a capsule can impede compliance; for some, even the taste of medication precludes compliance. Solutions to physiological barriers depend on the specific problem encountered. When difficulty with swallowing is present, the choice of a medication that can be sprinkled onto food is helpful. If a tablet or capsule cannot be crushed or sprinkled, the pill can be coated in light olive oil or put in sauce or pudding to ease swallowing. Alternative delivery systems are also becoming available, including pharmacies that can compound certain medications into suspensions with a variety of flavorings. Methylphenidate patch technology is a further option that can circumvent swallowing altogether.

Lack of efficacy

The efficacy and side effects of medication need to be monitored through the use of rating scales. Systematic monitoring with periodic review of diagnostic information is helpful in determining the effectiveness of medication management. Specific diagnostic and target symptoms should be tracked [26]. Various tools utilize the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, such as “often loses things necessary for tasks or activities” [27]. In addition, the family and child need to clearly identify their own targeted symptoms in order to ascertain improvement. When all are comfortable knowing that the clinician has listened to and understands their unique situation, compliance will improve [28]. If targeted symptoms do not improve, diagnostic considerations, including the presence of targeted symptoms, need to be reviewed and alternative treatment strategies must be considered.

Untoward side effects

Attending to the issues of side effects and long-term health warnings are part of the complete educational framework. The best management of many side effects involves full disclosure through an informed consent process. Families armed with this information will have appropriate expectations regarding side effects, and a good understanding of their likelihood, their expected duration, and possible interventions to minimize them. Situations where families learn of negative information in the media, or if the child experiences a side effect without warning, might result in loss of confidence in the professional capability of the clinician. Honesty and reassurance are vital components in establishing rapport and in engendering successful medication management with all ages [28].

Parental ambivalence

A common cause of medication non-adherence is ambivalence by the parents. Family members frequently disagree on the use of medication for children. Alternative treatment approaches are common and are often the initial preferred mode of treatment of ADHD by parents. The family’s choice of medical care needs to be respected.

For medical professionals who see a wide array of children with a variety of developmental and behavioral issues, the option of being able to adopt an integrative approach to practice has become both apparent and valuable [29]. This “integrative” method is a bio-psychosocial model that assimilates complementary therapies with more traditional approaches, along with consideration of the child’s functional developmental capacities, their different environmental influences, and, most importantly, incorporating all of this into the family’s culture. In this context, “alternative” methods can instead become integrative as both approaches can be used together [30].

Conclusion

The causes of medication non-adherence in the medical treatment of ADHD are numerous. With awareness of contributory factors, clinicians can design treatment strategies that match the developmental level of the child and the structure and culture of the family, which will result in effective symptom relief and successful treatment outcomes.

Disclosure

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Stimulant Pharmacotherapy in ADHD in Patients with Co-Occurring Substance Use Disorders

John J Mariani and Frances R Levin

Columbia University College of Physicians and Surgeons, New York, NY, USA

ADHD is the most common mental disorder observed in childhood, with a large proportion of cases persisting into adulthood. Adult ADHD is frequently comorbid with a substance use disorder (SUD). Psychostimulants are the treatment of choice for ADHD treatment, but many clinicians are reluctant to prescribe stimulants to patients who have an SUD. This article presents a review of the evidence regarding the use of stimulant medication in patients with SUDs, and discusses recommendations for clinical practice. *Advances in ADHD* 2006;1(2):47–52.

ADHD is characterized by persistent patterns of inattention, hyperactivity, and/or impulsivity that are more extreme than would be expected in an individual at the same developmental stage or age. It is the most common mental disorder in childhood, with an estimated prevalence of 5–10% in the US [1–3]. Studies suggest that up to 60% of childhood cases of ADHD will continue to have clinically significant symptoms of ADHD as adults, and the prevalence of adult ADHD is estimated to be 2–5% in the US [4–11]. ADHD symptoms result in a large individual and public burden; it is estimated that the consequences of ADHD result in the annual loss of 120 million days of work in the US labor force (approximately 2 weeks per adult with ADHD), which is equivalent to US\$19.5 billion lost human capital [12].

As an individual with ADHD develops into an adult, there is a high risk of developing co-occurring psychiatric disorders, including substance use disorders (SUDs). It is estimated that up to 80% of adults with ADHD have at least one comorbid psychiatric disorder [9]. Conversely, adult ADHD is a common comorbid mental disorder among patients with SUDs. While community-based epidemiological studies have not historically surveyed the rates of adult ADHD, the recently published National Comorbidity Survey Replication (NCS-R) found that, among the 8.1% of respondents retrospectively classified as having had childhood ADHD, 36.3% continued to meet symptoms as adults [6]. Another analysis of the NCS-R data that utilized blinded clinical

follow-up interviews estimated the prevalence of adult ADHD to be 4.4% [8]. Furthermore, the NCS-R study showed that 15.2% of individuals with adult ADHD met the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition criteria for a SUD, compared with 5.6% of individuals without ADHD, resulting in a significant odds ratio of 3.0 [8]. Complementary to this, the NCS-R study found that, among individuals with SUDs, 10.8% met criteria for adult ADHD, compared with a prevalence of 3.8% in individuals without SUDs.

In clinical samples of patients with SUDs seeking treatment, the reported rates of comorbid ADHD are higher than those found with the community-based NCS-R, with the prevalence of adult ADHD found to range from 10–24% [13–15]. In addition, it is estimated that >25% of substance-abusing adolescents meet diagnostic criteria for ADHD [16–18]. This disparity in rates of co-occurring ADHD and SUDs observed in community-based and clinical studies could be due to Berkson's bias, which is the phenomenon that patients in clinical treatment settings are more likely to exhibit a higher degree of association between two disorders [19].

While the exact cause of ADHD is unknown, available evidence suggests that dopamine neurotransmission dysfunction is at least partly responsible for the characteristic symptoms of ADHD. Evidence supporting dopamine involvement in ADHD symptomatology includes pharmacotherapy studies that have shown that stimulant medications that increase dopamine levels can treat ADHD symptoms, genetic studies that have linked dopamine genes to ADHD, and neuroimaging studies of patients with ADHD that have shown anomalies in dopamine function and structural abnormalities in regions of the brain with

Address for correspondence: John J Mariani, The New York State Psychiatric Institute, Columbia University, Division of Substance Abuse, 1051 Riverside Drive, Unit 66, New York, NY 10032, USA.
Email: jm2330@columbia.edu

concentrations of dopamine-producing neurons [20–29]. The development of SUDs is also linked to dopamine, suggesting that there may be common factors that lead to comorbidity of ADHD with SUDs [30].

The primary pharmacotherapies for ADHD are controlled substances with potential for abuse, meaning that the treatment of ADHD in patients with SUDs is both complex and controversial. This article will review the relevant research findings and provide recommendations for clinical management of this issue.

Pharmacology of psychostimulants

The two most commonly used pharmacotherapies for child and adult ADHD are the psychostimulants methylphenidate (MPH) and amphetamine analogues, although non-stimulant medications, including tricyclic antidepressants, bupropion, monoamine oxidase inhibitors, atomoxetine, and venlafaxine, have also received study.

Amphetamine

Amphetamine is a potent central nervous system stimulant whose effects are thought to be due to stimulation of the cortex and the reticular activating system. Its primary mechanism of action is promotion of dopamine release, although it also blocks dopamine reuptake [30]. In the US, amphetamine analogues are used mostly for ADHD, and less commonly for narcolepsy. Commercially available amphetamine analogues include methamphetamine, dextroamphetamine, and mixed amphetamine salts (MAS). Methamphetamine is available only as an immediate-release preparation and is rarely used due to abuse and diversion concerns. Dextroamphetamine is available in immediate- and sustained-release preparations. MAS is a fixed-combination amphetamine composed of equal amounts of dextroamphetamine saccharate, dextroamphetamine sulfate, racemic amphetamine aspartate monohydrate, and racemic amphetamine sulfate. Like dextroamphetamine, immediate- and sustained-release preparations of MAS have been developed. The side effects most commonly associated with amphetamine administration include insomnia, emotional lability, nausea/vomiting, nervousness, palpitations, elevated blood pressure, and rapid heart rate. Rare, but serious, adverse effects include severe hypertension, seizures, psychosis, and myocardial infarction.

MPH

MPH is a classical psychostimulant widely used in the US for the treatment of ADHD. It is a piperidine derivative that is structurally related to amphetamine and functions by blocking dopamine reuptake in the striatum [31]. MPH is available in multiple immediate- and sustained-release preparations, using

a variety of strategies for delaying absorption. The most common side effects of MPH are insomnia, nervousness, tachycardia, and hypertension. Serious adverse effects include severe hypertension, seizures, psychosis, and myocardial infarction, although these occur rarely.

Abuse potential of psychostimulants

Psychostimulants are medications with abuse potential. According to the National Survey on Drug Use and Health (NSDUH), in 2003, 8.8% of Americans aged 12 years or older had used prescription-type stimulants non-medically at least once in their lifetime [32]. Hence, although MPH and amphetamine analogues are widely used in the treatment of ADHD, concern exists with respect to their abuse potential, particularly in patients with SUDs. In a laboratory double-blind choice procedure, individuals with ADHD significantly chose MPH over placebo when assessed, while other measures of abuse potential were not elevated [33]. Laboratory studies of patients with and without SUDs suggest that both MPH and amphetamine analogues demonstrate characteristics that are associated with abuse potential [34,35]. Methamphetamine has been shown to be a positive reinforcer in humans, providing further evidence for its abuse potential [36]. In contrast to the data described above, a laboratory study of cocaine-dependent patients receiving MPH treatment found that cocaine craving or ratings associated with abuse potential were not increased with MPH, suggesting that the context of use, in this case therapeutic, may influence subjective effects and abuse potential [37]. The reinforcing effects of stimulants are associated with rapid changes in serum concentrations. However, sustained-release preparations of MPH slow the rate of onset of the drug's effect, and are associated with less stimulant-like drug effects (e.g. increased ratings of "good effects") in healthy volunteers. Hence, it is likely that delayed-delivery stimulant preparations have lower abuse potential than those that are released immediately [38,39]. An additional characteristic of delayed-release preparations that makes diversion and abuse less likely is that they are more difficult to use via a non-oral route (e.g. injected or insufflated intranasally).

Pharmacotherapy for adult ADHD co-occurring with SUDs

As in children, the mainstay of treatment of adult ADHD is pharmacotherapy. MPH and amphetamine analogues are the primary pharmacotherapies studied for adult ADHD, and have been demonstrated to have clinically and statistically significant effects on reducing ADHD symptoms in adults [40–43]. Non-stimulant medications, such as antidepressants, have a moderate effect on ADHD symptoms in adults [44].

Atomoxetine, a non-stimulant agent that recently received approval from the US Food and Drug Administration for the treatment of ADHD in children and adolescents, also has evidence of efficacy in adults [45,46].

The treatment of adult ADHD in patients with SUDs has been controversial; historically there has been reluctance on the part of clinicians to use these psychostimulants in patients with addictive disorders. However, although non-stimulant medications have been shown to have efficacy for adult ADHD, these agents do not seem to have equivalent efficacy when compared with psychostimulants. Some researchers have proposed approaches that emphasize medications with a lower risk of abuse, such as tricyclic antidepressants or bupropion, before using traditional stimulants, such as MPH or amphetamine analogues [47,48]. However, clinical trials of MPH and dextroamphetamine for the treatment of either cocaine dependence or ADHD in patients with co-occurring SUDs suggest that stimulant medications can be used safely in patients with SUDs and have a relatively low risk of abuse under monitored conditions [22,49–55].

MPH has been shown to be effective in uncontrolled trials in reducing ADHD symptoms and cocaine use [51,56]. However, a three-arm, double-blind, placebo-controlled trial of bupropion and MPH for ADHD treatment in cocaine-dependent patients who were receiving methadone maintenance therapy for opioid dependence found no benefit of either bupropion or MPH on ADHD symptoms or cocaine use outcomes [50]. In addition, a double-blind, placebo-controlled trial of MPH in the treatment of adult ADHD patients with comorbid cocaine dependence found that MPH improved ADHD symptoms on some measures, and did not cause a reduction in cocaine use [22]. In contrast, an uncontrolled trial of bupropion for the treatment of cocaine dependence and adult ADHD in 11 patients reported that ADHD and cocaine use symptoms decreased significantly [57]. None of the trials using stimulants reported abuse of prescribed stimulant medication.

Psychostimulants, including amphetamine analogues, MPH, and modafinil, have also been studied for the treatment of cocaine dependence. The results of these studies have been mixed with regard to effects on cocaine use outcomes, with the most consistent effects reported for dextroamphetamine [52,55]. Dextroamphetamine has also been evaluated for the substitution treatment of amphetamine dependence, and this approach has been found to be feasible [54,58]. Despite concerns that psychostimulant use may lead to increased craving and cocaine use, this has not been reported in controlled clinical trials [51,53,55].

While the treatment literature for ADHD in patients with SUDs is not well-developed, the emerging theory is that

medications effective for adult ADHD may have benefit in adults with ADHD and co-occurring SUDs, but the therapeutic benefit may be lower or non-existent if the substance use is ongoing [59]. As in children, the available evidence supports the use of stimulants over non-stimulant medications for adult ADHD. However, it should be expected that a proportion of patients with ADHD and comorbid SUDs will misuse, abuse, or divert stimulant medications, particularly in unstructured treatment settings [60–62]. The hypothesis that stimulant treatment can worsen SUD outcomes is not supported by the results of clinical trials. Most clinicians who are experienced in the treatment of ADHD in patients with SUDs would recommend the use of sustained-release preparations of stimulants to reduce the potential for misuse, although clinical data are lacking to support this approach. Novel delivery systems, such as the crush-resistant shell of Concerta (Alza Corporation, Fort Washington, PA, USA) [63] or the recently approved methylphenidate skin patch, are more resistant to abuse, and may be desirable alternatives in patients with ADHD and comorbid SUDs. As additional non-stimulant medications for ADHD become available (e.g. atomoxetine), they should be studied for potential abuse in patients with SUDs.

Clinical management of ADHD co-occurring with SUDs

The decision to use stimulant pharmacotherapy in a patient with ADHD and co-occurring SUDs requires an individualized risk–benefit assessment. An initial approach to this analysis is to consider the impact of ADHD on individuals who do not have SUDs. Adults with ADHD generally have less educational attainment, greater sociopathy, more traffic accidents, more car license suspensions, and more psychosocial problems with social deficits, and experience a greater frequency of divorce and job dismissals [64].

There is evidence that ADHD affects the development and course of SUDs; individuals with both SUDs and ADHD are more likely to encounter the following setbacks:

- An earlier onset of substance abuse than those without ADHD.
- A greater likelihood of having a continuous problem if they develop substance dependence and a reduced probability of going into remission.
- A tendency to take longer to reach remission [65].

Despite having more treatment exposure, individuals who have ADHD seem to fare less well with substance abuse treatment. Therefore, the diagnosis and treatment of

Table 1. Treatment management recommendations for ADHD patients with comorbid substance use disorders.

<p>Random urine toxicology testing</p> <p>Use delayed-release preparations</p> <p>Use tamper-proof prescriptions</p> <p>Indicate on prescription the amount to be dispensed numerically and alphabetically</p> <p>Avoid providing refills</p> <p>Keep careful records of prescriptions provided</p> <p>Be alert to unusual frequency of “lost” or “missing” prescriptions or medication</p>

ADHD in patients with SUDs is essential to achieve the best possible clinical outcome.

All patients with SUDs should be screened for the presence of ADHD, as failure to treat ADHD symptoms can negatively impact on SUD treatment outcome as well as overall social-occupational functioning. As part of a comprehensive assessment of a patient with an SUD, the presence of symptoms of inattention or hyperactivity should be evaluated. If symptoms have been present during periods of prolonged abstinence or prior to the onset of the SUD, further assessment is indicated.

Diagnosing ADHD in patients who are actively using substances or who recently initiated abstinence is challenging. Substances that are abused have many acute and chronic effects that mimic the symptoms of psychiatric disorders, including ADHD. For example, stimulant use can lead to changes in attentional capacity and activity level during both intoxication and recovery from intoxication; chronic marijuana use can lead to deficits in attention. In addition, many patients are unable to describe recent periods of time when they were not actively using substances, making the distinction between primary and substance-induced symptoms difficult. When patients initially present for substance abuse treatment, other co-occurring psychiatric conditions, such as mood or anxiety disorders, may also require clinical attention.

Ideally, patients should be assessed after a period of prolonged abstinence; however, in many cases this is not possible [66]. Often a careful evaluation of the clinical history of symptoms during past periods of abstinence or prior to the onset of substance use problems is the best available method of assessing whether inattention and hyperactivity symptoms represent a primary disorder or are substance-induced. However, a conservative approach must be maintained as retrospective diagnoses of childhood ADHD in adults made on the basis of self-report tend to overdiagnose ADHD [67,68]. Symptoms that occur during

periods of active substance use are difficult to interpret; if they occur exclusively in the context of active substance use, a diagnosis of ADHD is inappropriate.

Assessment for malingering is an important component of evaluating a patient with an SUD for ADHD, as the principal treatment options for ADHD are potentially abusable stimulants. Inattention symptoms tend to predominate in adults with ADHD and symptom assessment is almost entirely based on self-report, meaning that the potential for patients with SUDs attempting to mislead clinicians in an effort to obtain stimulants is always present.

Prescribing psychostimulants to patients with SUDs carries an inherent risk of misuse or abuse by the patient, as well as a danger of diversion (i.e. medication sold or given to other individuals). The use of psychostimulants in patients with SUDs requires careful monitoring, including urine toxicology testing. Relapse or worsening of substance use may necessitate reassessment of the appropriateness of stimulant pharmacotherapy. Careful documentation of all prescriptions must be maintained in order to monitor the amount and frequency of the drug being prescribed, and use of tamper-proof prescription forms is advised. On the prescription, the amount to be dispensed should be written both numerically and alphabetically (e.g. dispense #30 [thirty]). Refills should not be provided early in treatment and should be avoided until it is clear the patient is clinically stable. Repetitive requests to replace “missing”, “lost”, or “stolen” medication should be cause for concern, as should similar appeals for dose increases when not clinically supported. Delayed-release preparations are preferred to reduce the rate of change of drug blood levels, to decrease reinforcement, and to discourage non-oral use. Despite use of all possible mechanisms that reduce the risk of diversion, misuse, or abuse of stimulants (Table 1), it should be expected that a small percentage of patients with ADHD comorbid with SUDs will do so, and that careful clinical monitoring will detect such non-therapeutic use early and minimize its adverse effects.

Summary

While stimulant medications have the potential for abuse and must be used cautiously in patients with SUDs, the available evidence suggests that stimulants administered under monitored conditions can be safe and effective in such patients. However, ongoing substance use can limit the efficacy of stimulant pharmacotherapy, and careful monitoring can only reduce, not eliminate, the risk of misuse, abuse, and diversion of such medications when used to treat ADHD and comorbid SUDs. The decision regarding administration of stimulant therapy for these patients should be made on the basis of a broad clinical assessment and an

individual risk–benefit analysis. Psychostimulants can be used safely and effectively in many patients; however, careful monitoring during treatment is essential to ensure prescribed stimulants are used in a therapeutic manner. In the case of worsening substance use or evidence of diversion of prescribed medication, treatment should be discontinued.

Disclosure

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ADHD, Bipolar Disorder, or a Case of the “Diagnostically Homeless”?

Case study and discussion of treatment presented by Alice R Mao

Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA

Advances in ADHD 2006;1(2):53–58.

This report describes a 15 year old female who was diagnosed with ADHD at the age of 6 years. Her kindergarten and first-grade teachers had noticed that she appeared unfocused in class, required frequent redirection in order to stay on task, and was disrupting other students with her constant chattering. She lost her pencils, money, and articles of clothing on a near daily basis, requiring time-consuming searches for the misplaced item.

Her mother noticed that she was easily frustrated when attempting to do any school work and generally had a short temper. She argued with her mother constantly, perceiving that she was criticized more frequently than her brother. When outside the home, she had to be supervised closely, as her impulsivity led her into precarious situations. She had a tendency to wander away from her mother in public places leading to frantic searches to locate her. Generally, she had followed her interests and was either in a toy department or peering into a candy machine.

At 7 years of age, she was started on 5 mg methylphenidate (MPH) once daily. After initiation of medication, her mother received fewer complaints about her disruptive school behavior; however, she continued to have difficulty learning and focusing in the classroom, particularly in the afternoon. Consequently, the dose of MPH was increased to 5 mg twice daily (7.00 am and 11.00 am). She tolerated the dose increase without problems and had only mild appetite suppression that did not lead to significant weight loss. No problems with sleep were reported. She continued on this dose until the age of 9 years and her grades were reported to be adequate. Conduct problems were occasional and generally not remarkable.

At the age of 10 years, the dosage of MPH was increased to 10 mg twice daily. Despite the dose increase, the effects of the medication appeared to be wearing off too early in the day and she was noticeably more fidgety in class. The medication increase appeared to be effective in improving both her attention problems and her impulsive tendencies to wander out of the classroom and talk inappropriately.

During the summer after fourth grade, her mother elected to discontinue medications as her daughter was refusing to take the MPH, claiming it was not providing her with any benefit.

For the next 4 years the child received no treatment. Although her school grades were barely passing, she did not have to repeat any school examinations so medications were never restarted. However, her behavioral problems began to worsen. When aged 15 years she was found to be smoking marijuana, abusing benzodiazepines, and drinking alcohol. She also left home during the night to meet boyfriends that her mother deemed unsuitable, and who were at least 4 years older than she was. Conflicts with her mother worsened to the point that they had daily arguments, at times involving threatening gestures; however, no physical contact was ever made. A student accused her of stealing money that was left in a locker, although no charges were filed as there was no evidence that she had stolen the money.

When she failed her last semester examinations in the ninth grade, her mother could no longer ignore the deterioration in both her academic and behavioral functioning. Therefore, she took her daughter for psychiatric evaluation in order to determine whether reinitiation of medication would help to reduce the rapid decline that was occurring. The patient was highly resistant to being evaluated and was visibly angry about being “tricked into coming for an appointment”. The mother stated that she felt that she could barely tolerate living with her daughter due to her frequent volatile mood changes and, at times, irrational behavior.

The patient’s past medical history was notable for a record of recurrent otitis media leading to eventual ear tube placement at the age of 3 years. A mild developmental delay in expressive language resolved when her hearing improved. No allergies were reported, and she was not receiving any other medication. There was no history of gestational problems, fetal distress, head trauma, seizure disorders, or loss of consciousness.

Her family psychiatric history was significant, with her father having a longstanding history of mood instability, cocaine abuse, and multiple incarcerations for drug possession. He did not have a history of treatment for psychiatric illness; however, his brother had been diagnosed with bipolar disorder. The patient's mother had been diagnosed with major depressive disorder and inattentive-type ADHD in the past, but was not receiving any treatment at the time of the evaluation.

The child's social history was significant for the absence of a paternal presence in her life. She had never met her father as her parents divorced when she was an infant. She and her mother lived together with no other family members. Her mother was employed as a sales manager in a large retail store and occasionally had to return home late. Her grandmother who had helped to raise her had passed away when she was 11 years old.

On the mental status examination, the patient was visibly angry and guarded when she entered the examination room with her mother. During the initial history-gathering part of the interview, she refused to answer questions that were asked to her, avoiding eye contact with the examiner. If her mother attempted to answer or describe problematic behaviors, she would interrupt and vehemently defend herself. She repeatedly called her mother a "liar", despite her mother presenting irrefutable evidence of recent drug use with positive drug test results.

When her mother left the room, she became tearful and described her frustration with her mother for trying to make her sound "crazy". She defended her substance abuse stating that it was "normal for teenagers to experiment" and denied using illicit substances for the past month. Her mood was irritable and labile, with affect congruent. Her thought processes were generally goal-directed when she was willing to answer questions. There was no evidence of loose associations or flight of ideas. Her attention span was poor. She was unable to complete serial 7's, and completed serial 3's with significant prompting after each successive subtraction. Recent and immediate memory were intact, and she appeared to have normal abstractive abilities. Fund of knowledge was appropriate to age, but her judgment was not good. Insight also appeared to be poor as she tended to minimize her negative behaviors and blame others for over-reacting.

She was diagnosed with combined-type ADHD and mood disorder not-otherwise-specified. She was started on a trial of the long-acting MPH medication (18 mg osmotic release oral system [OROS] MPH) as published evidence suggests that it is effective in targeting both attention problems and oppositional defiant behaviors [1]. This led to a partial response with an improved attention span, but the

effects of medication wore off too early; thus, the dosage was increased to 36 mg/day. On this dose, her teachers noted that she was less fidgety in class and appeared to be focusing more appropriately. She still talked too much in class but could be redirected.

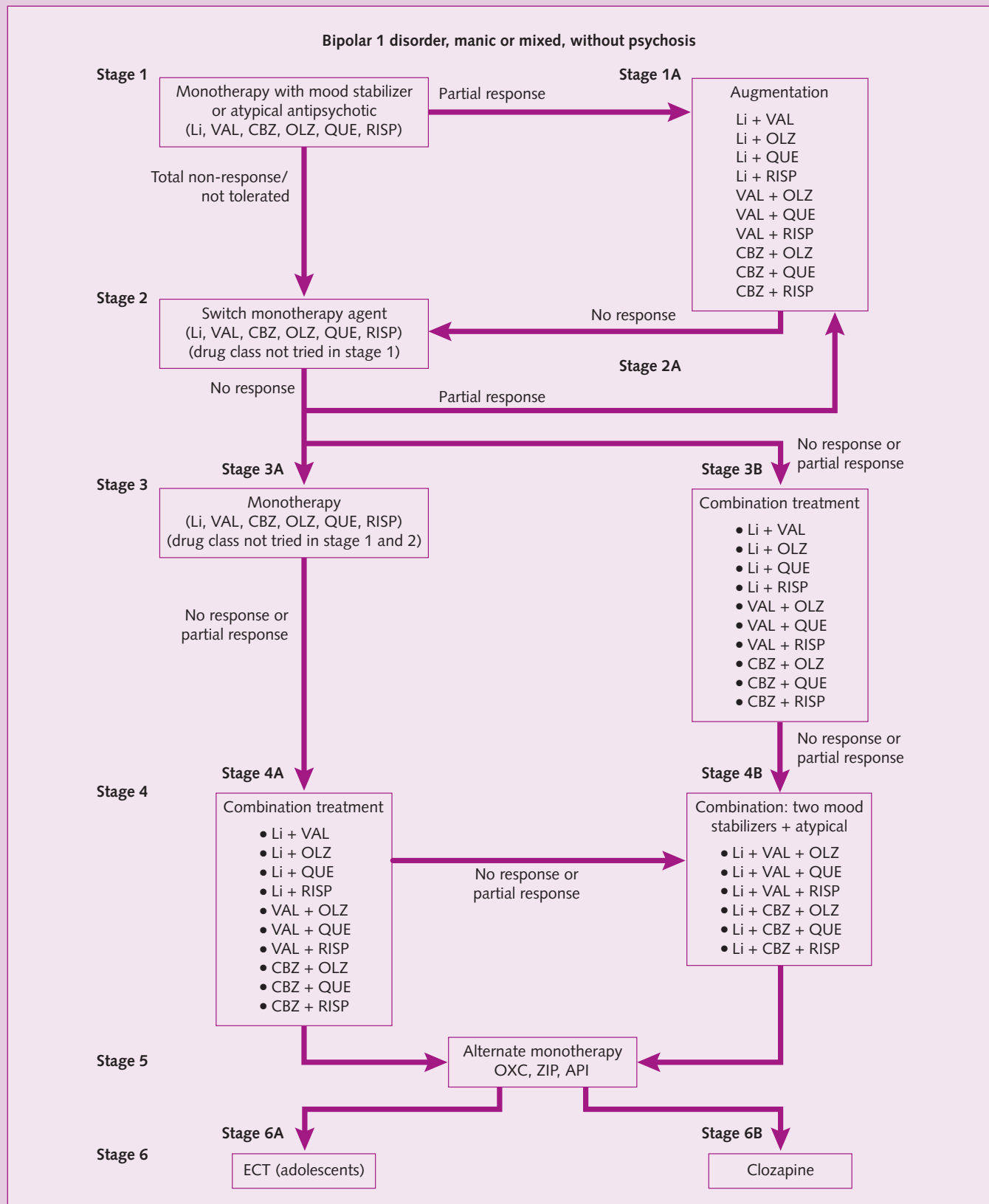
Despite this, her mother continued to express concern that her daughter's irritability was worsening at home and that fighting was persistent. Family and individual counseling were not successful in improving the mother-daughter relationship. She was also having difficulty falling asleep and woke up multiple times during the night. She continued to display reckless and flirtatious behaviors with older classmates. Mood fluctuations occurred so rapidly that her mother stated that she never knew whether her daughter would begin to cry or laugh hysterically. Her reasoning was illogical, stating that she would not mind becoming pregnant as it would help her to "mature faster". She stopped taking oral contraceptives and appeared to be actively pursuing sexual partners by sending out frequent emails with seductive invitations. Despite her increasingly irrational behavior, the patient denied having any hallucinations or suicidal ideation or plans.

At this point, the treatment team raised concerns about the possibility that the diagnosis was actually pediatric bipolar disorder and attempted to differentiate her symptom course from those of ADHD. Pine et al. had noted that the core features of bipolar disorder included marked "state fluctuations" involving switches into depressed, irritable, and extreme positive valence [2]. Specific developmental aspects of the illness exhibited by this patient included marked irritability, in addition to euphoria and depression in very rapid cycles, along with prominent symptoms of ADHD.

Both patient and mother agreed to a trial of medications to treat her marked irritability and rapid alteration of mood states. The risks and benefits of a trial of anticonvulsants versus atypical antipsychotics were discussed based on algorithms presented by the American Academy of Child and Adolescent Psychiatry Workgroup on Bipolar Disorder: Guidelines for Treatment of Child and Adolescent Bipolar Disorder (Fig. 1) [3].

Of the six potential medication options presented (valproate, carbamazepine, lithium, olanzapine, risperidone, and quetiapine), quetiapine was selected due to the potential for reduction of agitation, lower risk for akathisia, and decreased risk for development of diabetes and weight gain [4,5]. Although quetiapine has been studied as an adjunctive treatment for adolescents with bipolar disorder in the inpatient setting, there have been no placebo-controlled, double-blind studies of quetiapine monotherapy treatment in this population. However, evidence exists that this medication is effective in treating adults with bipolar disorder,

Figure 1. Algorithm of treatment options for bipolar 1 disorder, manic or mixed, acute, without psychosis.



ARI: aripiprazole; CBZ: carbamazepine; ECT: electroconvulsive therapy; Li: lithium; OLZ: olanzapine; OXC: oxcarbazepine; QUE: quetiapine; RISP: risperidone; VAL: valproate; ZIP: ziprasidone. Adapted with permission from [3].

and further research is necessary to provide evidence-based treatment options for clinicians treating patients with this symptom presentation. Anticonvulsants and lithium were not selected as the patient's rapidly deteriorating mental health required treatment with a medication that had the potential for rapid onset of symptom reduction.

A trial of 50 mg per day of quetiapine was initiated and gradually increased to an oral dose of 200 mg at night-time to target the mood instability, irritability, increased sexual behaviors, and sleep disturbances. She continued on 36 mg/day OROS MPH as it helped to decrease distractibility and improve ability to focus, but her mother commented that the distractibility during the current episode was far worse than it had been during her earlier episodes between the ages of 9 and 10 years. After 4 days she was able to fall asleep within a few minutes of lying down, and also began to have noticeable personality changes. She was observed to be "calmer" and more "laid back". The frequency of agitation and angry outbursts decreased dramatically. The mother reported that trivial situations that would normally provoke a violent reaction no longer caused her distress. Gradually, her academic grades improved as she was able to sustain attention in class and actually remember to hand in her homework. Her judgment improved and she no longer had a desire to experiment with drugs or "sneak" out of the home to meet boys. Her mother declined to increase the dose of quetiapine as she was satisfied with her daughter's current behavior, and the patient has been maintained on this dose without relapse of rapidly shifting mood states.

Discussion

ADHD is a highly comorbid condition. In the multi-site MTA (Multimodal Treatment Study of Children with ADHD), only 31% of the 576 ADHD children studied had ADHD alone [6]. Most had another comorbid condition, with 40% found to have oppositional defiant disorders, 34% had anxiety disorders, 4% had an affective disorder, 14% had a conduct disorder, 10% had tic disorders, and 16% had learning disabilities. Generally, the rate of comorbidity in children with ADHD increases with age [7]. One of the predictors of increased comorbidity is the persistence of ADHD [7,8]. Thus, adults with ADHD may be particularly vulnerable to high rates of comorbid conditions.

The differentiation of ADHD and bipolar disorder in children and adolescents has historically been extremely difficult due to overlap of symptoms such as impulsivity, rapid mood swings, temper outbursts, attention deficits, and irritability. In addition, lack of consensus regarding the key diagnostic features of bipolar disorder in children and adolescents lead to perceptions of either over- or under-

diagnosis of bipolar disorder in clinical settings. In the current case, the family history of bipolar disorder and major depressive disorder suggested a strong possibility of comorbid mood disorder with ADHD. Lifetime prevalence of bipolar disorder in adolescents has been estimated at 0.90–1.41% [9]. Research has demonstrated that 50% of the offspring of bipolar parents meet criteria for Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) psychiatric disorders, with 14–50% of this group meeting criteria for bipolar I, II, or cyclothymia [10]. Retrospective research also highlights the frequency of early onset, including one study that found that over half of the 494 adult bipolar disorder patients had experienced prodromal symptoms such as mood lability or episodic depression prior to the age of 19 years, with 5% of those surveyed recalling symptoms occurring before the age of 5 years [11]. Evidence shows that some form of bipolar disorder can present in youth; however, there is disagreement in the literature over the precise nature of the disease process. It is unclear whether childhood onset bipolar disorder is a separate entity from an adult diagnosis or whether it is a more severe form of the disorder predicting a worse prognosis.

Children with this constellation of symptoms (hyperactivity, "volcanic rages", extreme anxiety, and mood shifts) have been described as "diagnostically homeless", as they manifest with symptoms that potentially meet criteria for multiple DSM-IV diagnoses, such as bipolar disorder, oppositional defiant disorder, conduct disorder, disruptive behavior disorder not-otherwise-specified, and ADHD, to name a few. When clinicians are overwhelmed by the presentation of multiple, complex, non-pathognomonic symptoms, assessment and treatment that address the following four domains of dysfunction have been suggested as a way to systematically develop a comprehensive treatment strategy [13]:

- Mood/anxiety problems.
- Possible psychosis.
- Language/thought disorder.
- Relationships/socialization problems.

In addition, the FIND (Frequency, Intensity, Number, and Duration) guidelines have been a useful assessment tool for the diagnosis of bipolar disorder in children and adolescents:

- Frequency: symptoms occur most days in a week.
- Intensity: symptoms are severe enough to cause extreme disturbance in one domain or moderate disturbance in two or more domains.
- Number: symptoms occur 3–4 times a day.
- Duration: symptoms occur ≥ 4 h a day, total, not necessarily contiguous.

The clarification of manifestations of euphoria and grandiosity, informant variance, diagnostic implications of medication-induced behavioral toxicity, and treatment implications of family history are all issues that clinicians need to consider as they make the diagnosis of bipolar disorder in children and adolescents [12]. Pediatric bipolar disorder is distinct from the adult form in terms of level of chronicity and rapidity of cycling. In one study of pediatric patients with DSM-IV bipolar disorder, 83.3% of participants were identified as having “any rapid cycling”, defined as the following:

- Rapid: four or more episodes per year.
- Ultra-rapid: episodes lasting a few days to a few weeks.
- Ultradian: cycling within a 24-h period.

The majority (86.7%) of the bipolar subjects in this study reported mixed mania symptoms, rated when mania or hypomania overlapped with the occurrence of major depression or dysthymia [14]. In contrast, adults typically have fewer mixed episodes, with more discrete onsets and offsets [15].

Atypical antipsychotic medications are widely used for the treatment of bipolar disorder. Most empirical data suggest that these medications are efficacious in the treatment of acute mania, and there is developing evidence for the utility of these drugs in other phases of bipolar disorder (depressed phase) and for relapse prevention. The atypical antipsychotics offer different side effect profiles from mood stabilizers (e.g. lithium), or anticonvulsants (e.g. valproate and carbamazepine), and have a faster onset of action. Consequently, atypical antipsychotics provide an important treatment option for child and adolescent patients with bipolar disorder.

The general professional consensus is that, if a child or adolescent patient is diagnosed with bipolar disorder and comorbid ADHD, the bipolar disorder should be treated first as stimulant treatment could possibly exacerbate the mood symptoms. However, as this case illustrates, the time course and sequence of presentation of symptoms can make it extraordinarily difficult to differentiate between the two disorders. Frequently, the ADHD symptoms are treated initially as clinicians may be more focused on the behavioral problems in school, and are reluctant to label a child with the diagnosis of bipolar disorder and the characteristic dramatic mood swings and extreme temper outbursts that may present later in life.

Some researchers have suggested that the ADHD symptoms are a precursor of later development of bipolar disorder when there is a positive family history of mood

disorder. Multiple studies reflect that children and adolescents with bipolar disorder have high rates of comorbid ADHD, ranging from 75–87% (using DSM-IV mania criteria) [16]. Other researchers have found ADHD comorbid with bipolar disorder in 57% of subjects who had mania onset in adolescence, in contrast to only 13% of those studied with adult-onset bipolar disorder [19]. Tillman’s study also found that the onset of ADHD preceded that of manic symptoms by an average of 2 years, raising the question of whether ADHD is possibly an early symptom presentation in the progression of the disease state towards full-blown bipolar disorder [16]. Wozniak et al. demonstrated that 91% of children with mania or a history of mania met ADHD criteria, while only 19% of subjects with a pre-existing ADHD diagnosis also met criteria for mania [17].

Frequently, monotherapy with atypical antipsychotic medications may not be sufficient to improve the full spectrum of the presenting comorbid symptoms, and stimulant or non-stimulant medications for ADHD may need to be co-administered to improve cognitive functioning for optimal re-integration into the school setting. Combination therapy has been posed as an effective treatment for pediatric and adolescent bipolar disorder patients. Kowatch et al. reported that, of the 20 subjects requiring combination treatment (one or two mood stabilizers plus either a stimulant, atypical antipsychotic, or antidepressant), 80% responded with >50% improvement on the Young Mania Rating Scale assessment after experiencing a less favorable response with monotherapy intervention. Investigators recognized the need for addressing the comorbid ADHD that occurred in 28 of the 35 subjects, and found good results from addition of a stimulant only after the patient’s bipolar disorder was stabilized [18].

Hopefully, future research will determine the exact nature of the relationship between the two disorders. Questions remain as to whether ADHD is merely an early presentation of a pre-existing vulnerability that later puts one at risk for bipolar disorder or whether both conditions are actually manifestations of pathology in neurological processes involving attention and emotional regulation. The last hypothesis, although less thought provoking but perhaps equally probable, is that the coincidence of bipolar and ADHD symptoms in childhood, with diminishing hyperactivity of the latter as maturation occurs, indicates the existence of separate disease processes that happen to have similar phenotypic presentations.

Disclosure

Dr Mao has had financial relationships with AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, McNeil, Novartis, and Shire.

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CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Julia Noland and Angelita Sanchez

DIAGNOSIS AND ASSESSMENT

Who receives a diagnosis of attention-deficit/hyperactivity disorder in the United States elementary school population?

Schneider H, Eisenberg D.
Pediatrics 2006;**117**:e601–9.

In a large (n=9278) nationally representative sample of children aged 7–11 years, 5.4% had been diagnosed with ADHD. Characteristics of the children, families, schools, and regions were presented in relation to odds of ADHD diagnosis. Among the independent associations reported was a relationship between higher odds of ADHD and stricter state-level school accountability laws.

The perception that ADHD is diagnosed as a result of a child's environment (e.g. class size and structure) rather than the child's actual condition has caused controversy. The ambiguity of current criteria for ADHD diagnosis means that there are several influences in diagnosis (e.g. parents, teachers, clinicians, and cultural attitudes). The current study aimed to answer whether the diagnosis and treatment of ADHD was comparable throughout the US. It also aimed to clarify whether the diagnosis was a reflection of a problem with the child, or whether it was a consequence of the child's everyday environment.

This study analyzed the results of the 2002 follow-up of the Early Childhood Longitudinal Survey – Kindergarten Cohort. This cohort was representative of US children and contains information from the study children, parents, and teachers. Class size was not independently associated with a higher likelihood of ADHD diagnosis. However, other classroom factors were found to increase the odds of ADHD, including having an older or non-Caucasian teacher. City/suburb/town sizes were not significant factors. The relationship of income with ADHD changed as macro-environmental factors were added to the model. In the final model, only membership in the lowest income quintile was

associated with increased odds of ADHD diagnosis. Child-based factors were also related to the probability of ADHD, including teacher ratings of externalized behavior problems and summer birth. Summer birth often leads to a relatively young age at school-entry, and consequent behavioral competence lower than the child's peers.

The study is limited by its reliance on parent report of ADHD diagnosis, and lack of information on whether the ADHD diagnosis status was appropriate for each individual. Thus, it remains unclear whether the contextual factors identified here are bringing the diagnosis rate closer to or further from the "true" rate in the population.

Address for reprints: H Schneider, Department of Economics,
University of Texas at Austin, BRB 3.116, Austin, TX 78712, USA.
Email: h.schneider@eco.utexas.edu

Validation of population-based ADHD subtypes and identification of three clinically impaired subtypes

Volk HE, Henderson C, Neuman RJ et al.
Am J Med Genet B Neuropsychiatr Genet 2006;**141**:312–8.

In the current study, validation for statistically-derived ADHD nosology was found in the rate of problem behaviors reported on a standardized questionnaire. More attention problems were reported for the children in the severe-combined and severe-inattentive subtypes, as well as the mild-combined subtype.

The current ADHD subtypes used to classify patients are predominantly inattentive, predominantly hyperactive-impulsive, and combined. In this study, a statistical process was used by the authors to classify subjects into subtypes based on ADHD symptoms reported in structured interviews of parents of a sub-sample (n=1342 individuals) of school-age twins. The ADHD categories derived in this manner were severe-and-mild combined, severe-and-mild inattentive, talkative/impulsive, hyperactive, and few symptoms. This population-derived classification system has some overlap with traditional Diagnostic and Statistical

Manual of Mental Disorders-IV (DSM-IV) classification; moreover, this method can also classify subjects who would not have a DSM-IV diagnosis.

Problem behavior frequencies were assessed using the Child Behavior Checklist (CBCL), which parents completed prior to the interview session. Each of the population-derived categories had distinct problem behavior profiles on the CBCL, thereby adding clinical validity to this classification system. Attention and aggression syndrome scores on the CBCL suggested that the severe-and-mild combined and severe-inattentive subtypes were distinct and clinically relevant. More than half of the subjects in the population-derived mild combined subtype met ADHD criteria for an ADHD diagnosis. In addition to this increased sensitivity, the current study supports the suggestion that these ADHD relevant classifications are not affected by the presence of comorbidity (e.g. conduct disorder or major depression) with other externalizing disorders.

Address for reprints: RD Todd, Department of Psychiatry, Box 8134, Washington University School of Medicine, 660 South Euclid Avenue, Saint Louis, MO 63110, USA. Email: toddr@psychiatry.wustl.edu

ATTENTION

Effects of methylphenidate on multiple components of attention in children with attention deficit hyperactivity disorder

Tucha O, Prell S, Mecklinger L et al.

Psychopharmacology 2006;**185**:315–26.

This study examined the efficacy of methylphenidate (MPH) in improving attention in children with ADHD. MPH was found to improve some, but not all, aspects of attention.

This study evaluated the effects of methylphenidate (MPH) on several components of attention in children with ADHD. It was a double-blind, placebo-controlled trial with a crossover design, and children were assessed both while they received their usual MPH dose and following withdrawal of the drug. Participants consisted of 58 children with ADHD (nine girls and 49 boys; mean age 10.81 years, standard error 0.30 years; mean intelligence quotient 98.09, standard error 1.50) and were randomly assigned to their starting treatment. Half of the children with ADHD had initial assessments of their attention while on MPH and then when the drug was withdrawn (placebo). The remaining half started in the reverse order. Children with ADHD were receiving individually customized doses of MPH to ensure effective medication and this clinically appropriate regimen

was continued. The mean total dose was 19 mg/day. The control group contained 58 healthy children, matched for age and sex.

The computerized test battery consisted of eight tasks measuring various aspects of attention, which included measures of alertness, vigilance, divided attention, and flexibility, and aspects of selective attention such as focused attention, inhibition, and integration of sensory information.

Compared with the control group, the children with ADHD had marked impairments of divided attention, vigilance, flexibility, and aspects of selective attention. These children showed significantly improved task accuracies in similar tasks while receiving MPH treatment. Although improvements in attention were seen in these children, they continued to exhibit some deficits in various components of attention, similar to those seen when they were not receiving MPH.

Clinicians should be aware of the need to optimize medication dosage to adequately control ADHD symptoms, while simultaneously keeping in mind the limitations of medication. Clinicians may find that supportive treatment (i.e. educational programs and behavioral treatment) can help to address the problems of ADHD.

Address for reprints: KW Lange, Department of Experimental Psychology, University of Regensburg, 93040 Regensburg, Germany. Email: klaus.lange@psychologie.uni-regensburg.de

TREATMENT STRATEGIES

Stimulant treatment over 5 years: effects on growth

Charach A, Figueroa M, Chen S et al.

J Am Acad Child Adolesc Psychiatry 2006;**45**:415–21.

In a five-year study of children receiving stimulant treatment for ADHD, there was a dose–response relationship between stimulant use and growth in height and weight. Slowed weight gain was estimated to occur at lower levels (1.5 mg/kg/day methylphenidate [MPH] ≥ 1 year) than slowed height gain (2.5 mg/kg/day MPH > 4 years). The data suggest that these effects are reversible.

Stimulants used to treat ADHD have been shown to reduce children's appetite, which could consequently diminish growth. The effects of stimulant use on growth have been reported during a 2-year period of use. In the current study, the effects of stimulant medication were assessed in a moderate sized (n=79) cohort of school-age children who were followed-up for 5 years. Using hierarchical linear

modeling, a typical dose of methylphenidate (MPH) in a 9-year old boy was estimated to produce a 1.4 kg slowing in weight gain over a single year. A higher than typical dose (2.5 kg/mg/day) taken over a longer-than-typical period (4 years) by a 13-year-old boy was estimated to diminish height gains by 1.9 cm. According to the model, breaks in usage led to reversion of the z score to baseline, suggesting that any impact of stimulant use on growth was likely to be reversible. The usage patterns presented suggest such breaks are typical in practice.

The authors suggest that the findings have clinical significance, but only at an individual level. They recommend that clinical management decisions should integrate this evidence of the growth-slowing effects of MPH treatment with information about an individual's growth status, as well as their behavioral and treatment history.

Address for reprints: A Charach, Department of Psychiatry, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, M5G 1X8, Canada. Email: alice.charach@sickkids.ca

Effect of methylphenidate on Stroop Color-Word task performance in children with attention deficit hyperactivity disorder

Langleben DD, Monterosso J, Elman I et al. *Psychiatry Res* 2006;**141**:315–20.

Stroop interference, a measure of poor attentional control, was reduced with stimulant exposure in both children with ADHD (n=18) and drug-naïve, non-ADHD control participants (n=6). Both "on" and "off" the stimulant, the children with ADHD experienced more interference in the Stroop Color-Word task than the controls. The Stroop task may have value in monitoring stimulant treatment responsiveness.

The Stroop Color-Word task is a commercially available test that has some sensitivity to ADHD, and is widely used due to its convenience and familiarity in the clinical setting. The current study investigated the use of the Stroop task in assessing response to methylphenidate (MPH). Interference on the Stroop task is determined by the rate of naming the ink color that a word is printed in. Attentional control is required as the ink that the word is written in is one color (e.g. yellow) but the word will be the name of another color (e.g. red). The correct naming response (i.e. yellow) requires managing attention to the lexical identity of the word that would produce the incorrect response (i.e. red).

MPH was given to 18 prepubescent boys with ADHD and six demographically similar controls. The children with ADHD had already displayed a positive response to MPH

treatment during a MPH trial that lasted ≥ 12 weeks. As the Stroop task has not consistently been shown to be sensitive to untreated ADHD, non-ADHD controls were tested as well as the children with ADHD. The test was conducted when "on" and "off" MPH medication. MPH reduced interference with the Stroop task across the groups. The children with ADHD showed more interference in both treatment conditions than children without ADHD.

As discussed by the authors, the interpretation of these findings is significantly complicated by two prior studies that found no improvement on interference scores in children with ADHD given MPH.

Address for reprints: DD Langleben, Department of Psychiatry, University of Pennsylvania School of Medicine, 3900 Chestnut Street, Philadelphia, PA 19104, USA. Email: langlebe@mail.med.upenn.edu

1. ADHD drugs and cardiovascular risk

Nissen S.

N Engl J Med 2006;**354**:1445–8.

2. ADHD drugs and cardiovascular risk – Letter to the Editor

Anders T, Sharfstein S.

N Engl J Med 2006;**354**:2296–8.

The cardiovascular risks associated with stimulant medications have led to a US Food and Drug Administration recommendation that a black box warning should be placed on stimulants prescribed for ADHD treatment. However, this has caused concern among some clinicians who fear that such a warning may deter patients from taking such medications, despite their proven efficacy in the alleviation of ADHD symptoms.

The US Food and Drug Administration (FDA) Drug Safety and Risk Management Advisory Committee voted (eight votes for versus seven votes against, with one abstention) to recommend a black-box warning describing the cardiovascular risks of stimulants used to treat ADHD. A consultant to this committee, S Nissen (Cleveland Clinic, Cleveland, OH, USA), stated that stimulants could substantially increase the heart rate and blood pressure, which can increase morbidity and mortality rates (1). Ephedra and phenylpropanolamine, both members of this class of drugs, have previously been implicated with unexplained death and serious adverse effects. Dr Nissen further argued that there has been a significant increase in the illicit use of stimulants, particularly among adults.

Review of the data from the Adverse Event Reporting System of the FDA showed that there were 25 cases of drug-related sudden death in children and adults, 19 of

whom were <8 years of age. Amphetamines were implicated in 17 cases (12 children and adolescents and five adults) and methylphenidate was involved in eight cases (seven children and adolescents and one adult). Autopsies showed some cases had congenital cardiac structural abnormalities, arrhythmias, and syncope.

In the letter to the editor, T Anders and S Sharfstein of the American Psychiatric Association acknowledged that patient safety is very important (2). However, they expressed concern that a black-box warning will result in patients and their families being discouraged in availing themselves of effective treatment.

In children, the reported stimulant-related rate of sudden death is not greater than the population base rate. The population base rate of 1.3 sudden deaths/100 000 patient years would be comparable to the rate of approximately 1 per million prescriptions (with 12 prescriptions written per year per patient). The reported sudden death rate associated with stimulants is 0.2–0.5/100 000 patient years.

When prescribing stimulants, it is important to consider medical pathology, in addition to a behavioral presentation during the visit. A thorough medical history and physical examination should be part of the evaluation, with focus on history of unexplained syncope, arrhythmias, cardiac structural abnormalities, hypertension (particularly in adults), and family history of sudden death. A cardiac evaluation may be warranted if there are any suspicions. Patients should be started at the lowest suitable dose; the dose, side effects, and vital signs should all be monitored closely. Parents and patients should be educated about risks and side effects, and recommended to contact the doctor if the need arises. The use of behavioral treatment and educational plans to maximize outcome needs to be considered with lower doses of stimulants.

Address for reprints: SE Nissen, Cleveland Clinic, Cleveland, OH 44195, USA.

Sleep-disordered breathing, behavior and cognition in children before and after adenotonsillectomy

Chervin RD, Ruzicka D, Giordani BJ et al.

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Adenotonsillectomy to correct sleep-disordered breathing improves behavioral problems in children diagnosed with ADHD.

Behavioral disturbances and cognitive impairment are believed to be the main morbidities experienced by children with mild sleep-disordered breathing (SDB). Despite the American Academy of Pediatrics' recommendation, only 10% of children in North America undergo

polysomnography (PSG) to confirm the diagnosis or need for surgery. However, standard PSG may fail to detect the mild forms of SDB that are associated with neurobehavioral morbidities. Limited studies exist describing the extent to which morbidity may respond to treatment in these cases. Moreover, long-term outcomes and gold-standard assessments have not been investigated in mild SDB.

This prospective, non-randomized, follow-up study examined long-term neurobehavioral outcomes and PSG findings in children who underwent clinically indicated adenotonsillectomy (AT). Of 105 children (aged 5–12.9 years), 78 were scheduled for AT and 27 for unrelated surgical care (control group). PSG and neurobehavioral assessments including Multiple Sleep Latency Test (MSLT), neuropsychological testing, and parental behavioral ratings were performed at baseline and at 1 year.

Behavioral rating scales included the Conner's Parent Rating Scales-Revised (L), which is an 80-item instrument often used when comprehensive Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)-consistent data are required, and the Children Symptom Inventory-4 Parent Checklist, which is a 108-item behavior-rating test that screens for a variety of DSM-IV-based childhood emotional and behavioral disorders in children aged 5–12 years. The ADHD index T scores of both instruments were used to construct the behavioral hyperactivity indices. The cognitive-attention index was determined with the Integrated Visual and Auditory Continuous Performance Test, which assessed attention or vigilance, and the Children's Memory Scale attention/concentration subscale. To determine diagnosis, the well-validated Diagnostic Interview Schedule for Children–Parent Interview was administered.

Children in the AT group were more hyperactive, sleepy, and inattentive, and more were diagnosed with ADHD at baseline compared with the control group. At the 1-year follow-up, these same measures were not significantly different between the experimental and control groups. Each outcome measure improved significantly with time for the patients who had AT, but not in those in the control group. Neurobehavioral outcomes could not be predicted by common laboratory measures of SDB severity either at baseline or after 1 year, with the exception of daytime sleepiness.

Children with mild-to-moderate SDB are at risk of significant reversible neurobehavioral complications. In the absence of outcome measures with better ability to predict these complications, it is imperative that clinicians perform a thorough assessment and follow-up of these children.

Address for reprints: RD Chervin, Michael S. Aldrich Sleep Disorders Laboratory, 8D8702 University Hospital, 1500E Medical Center Drive, Ann Arbor, MI 48109-0117, USA. Email: chervin@umich.edu

EPIDEMIOLOGY

Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications

Wilens TE, Gignac M, Swezey A et al.

J Am Acad Child Adolesc Psychiatry 2006;**45**:408–14.

The extent to which stimulant medications are diverted or misused by adolescents and young adults with ADHD has not been sufficiently researched. In the current study, 11% of 98 patients either diverted or sold their medication, compared with none of the control group. Immediate-release methylphenidate was the medication that was most commonly diverted.

Limited information exists on the scale and nature of the inappropriate use of stimulant medications that are prescribed for ADHD. The authors evaluated the prevalence and correlates of stimulant diversion and misuse in adolescents and young adults with ADHD during the most recent follow-up visit of a 10-year longitudinal study of youths with ADHD. Patients (n=260) were enrolled from an ongoing case-control family study of ADHD [1]. A three-stage ascertainment procedure that included a structured interview was used to select the subjects. A self-report medication questionnaire was employed to determine the usage pattern in relation to diversion or misuse (e.g. changes in dose or use with other psychoactive medications).

Of the 98 medicated patients (mean age 20.9±5.1 years), 55 (56%) were receiving ADHD medications, and 43 (44%) were taking psychotropic medications for other indications (control group). There were 46 subjects (48%) who met diagnostic criteria for a substance use disorder (SUD), and 21 (22%) who could be described as having a conduct disorder (CD).

The authors report that 11% of subjects with ADHD (compared with none in the control group) diverted or sold their medications ($z=0.00$; $p<0.05$). They also found that 22% of the ADHD patients took too much or misused their prescribed medication compared with 5% of the control group ($z=1.70$; $p=0.09$). Of the subjects with ADHD who diverted or misused their medications, 83% had comorbid CD and 83% had a SUD. Immediate-release methylphenidate was the medication type that was most often diverted (five of six; 83%) or misused (nine of 12; 75%) by patients, followed by immediate-release mixed amphetamine salts (two of six [33%] diverted; four of 12 [33%] misused).

The study highlights that the majority of adolescents and young adults with ADHD use their medications appropriately.

The existence of comorbid CD or SUD and the use of immediate-release stimulants increase the risk of diversion and misuse. Clinicians need to closely monitor the appropriate use of stimulants and be vigilant with regard to concerns of potential diversion of stimulants by ADHD patients.

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Address for reprints: TE Wilens, Pediatric Psychopharmacology Unit, Massachusetts General Hospital, YAW 6A, 32 Fruit Street, Boston, MA 02114, USA. Email: twilens@partners.org

Recent trends in stimulant medication use among U.S. children

Zuvekas SH, Vitiello B, Norquist GS.

Am J Psychiatry 2006;**163**:579–85.

This US national survey of prescription rates, conducted from 1997–2002, addresses concerns regarding increases in prescription stimulant use among children. In contrast to the previous decade, there were no large increases in stimulant use, and usage by children aged <6 years remained stable.

Stimulants such as methylphenidate and amphetamines have been used to treat ADHD symptoms for >30 years. However, the potential for misuse of such medications has led to concerns over their prescription in children, particularly in those of pre-school age. A survey conducted from 1987–96 found that stimulant use had increased four-fold in children (defined as patients aged <18 years) in the US [1]. This study aimed to establish whether stimulant use continued to increase from 1997–2002.

In the Medical Expenditure Panel Survey (MEPS), a nationally representative sample of civilian families was interviewed five times over 2 years, and follow-back surveys to their pharmacies were conducted. The sample was post-stratified and representative of the population each year. The geographical breadth of the survey is an additional strength. Although sufficiently powered to detect increases in stimulant use, none were detected from 1997–2002 in any age category. Of particular note, after a 1.7- to 3.1-fold increase in stimulant use by young children (<6 years of age) from 1991–95, this did not continue to rise from 1997–2002. Across age categories, prescription rates (2.9%) were below ADHD point estimates. Type of health insurance (public versus private) did not influence stimulant use rates, although those without insurance had lower utilization.

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Address for reprints: B Vitiello, Division of Services and Intervention Research, NIMH, 6001 Executive Blvd, Bethesda, MD 20892-9633, USA. Email: bvitiell@mail.nih.gov

The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication

Kessler RC, Adler L, Barkley R et al.
Am J Psychiatry 2006;**163**:716–23.

To date, adult ADHD has received limited clinical study and acknowledgement. This article reports on a survey that was conducted to more accurately characterize the prevalence, comorbidity, and impairments associated with adult ADHD in the US. Male gender, non-Hispanic white ethnic origin, previous marriage, unemployment, and disability were found to correlate significantly with adult ADHD.

ADHD in adults has only recently been given clinical attention. The first case report of adult ADHD was in 1972 [1]. Non-inclusion of adult ADHD in the two major psychiatric epidemiological surveys of the past 20 years (Epidemiologic Catchment Area Study and the National Comorbidity Survey) highlights this issue.

A screen for adult ADHD was included in the National Comorbidity Survey Replication (NCSR) to obtain more accurate estimates of prevalence, comorbidity, and impairments of adult ADHD in the US. NCSR is a nationally representative household survey that appraises a variety of Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnoses.

ADHD was assessed among 3199 respondents aged 18–44 years. The sample was weighted to be representative of the US population in this age range. Childhood ADHD was retrospectively assessed using the Diagnostic Interview Schedule for DSM-IV. Blinded follow-up interviews were conducted with 154 respondents. The clinical reappraisal interview used the Adult ADHD Clinical Diagnostic Scale, which has been utilized in clinical trials of patients with adult ADHD. The World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) is a fully structured lay-administered diagnostic interview that was used to assess other DSM-IV disorders. The WHO Disability Assessment Schedule evaluated the frequency and intensity of difficulties in basic (mobility, self-care, and cognition) and instrumental (time out of role, productive role performance, and social performance) functioning. The prevalence and correlates of adult ADHD were estimated with multiple imputation.

The estimated prevalence of clinician-assessed adult ADHD was 4.4% (standard error 0.6). Male gender, non-Hispanic white ethnic origin, previous marriage, unemployment, and disability were significantly associated with adult ADHD (odds ratio 1.6–3.3). It was also significantly comorbid with other DSM-IV disorders, such as mood, anxiety, and substance

abuse disorders. Only 10.9% of the respondents had received treatment for ADHD in the year before interview.

Diagnosing adult ADHD utilizing DSM-IV criteria that were initially formulated for children continues to be part of the clinical challenge. Public and physician education on the impact of adult ADHD on daily functioning, and the need for appropriate and timely assessment and treatment, can substantially reduce the burden of an illness that has just recently become the focus of clinical attention.

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Address for reprints: RC Kessler, Department of Health Care Policy, Harvard Medical School, 180 Longwood Avenue, Boston, MA 02115, USA. Email: kessler@hcp.med.harvard.edu

COGNITION

Characterizing cognition in ADHD: beyond executive dysfunction

Castellanos FX, Sonuga-Barke EJ, Milham MP et al.
Trends Cogn Sci 2006;**10**:117–23.

This study reviewed evidence against a single core deficit in ADHD and for deficits in a broad range of executive functioning and motivational tasks, as well as increased reaction time variability. The authors account for the range of these deficits in an adaptation of the "hot" and "cool" executive dysfunction model with a complementary neurophysiological paradigm.

The authors offer a timely model integrating cognitive, motivational, and neuroscientific research in ADHD that will facilitate an important paradigm shift. In the past decade, specific executive functioning deficits associated with ADHD (particularly response inhibition and working memory) have relied heavily on linking genetic, neurobiological, and phenotypic research. However, clinical research suggests that executive functioning deficits are neither necessary nor sufficient for ADHD. Developmental models of distinct motivational deficits and response inhibition pathways in ADHD are gaining attention. Intra-individual variability in reaction time is also of increasing interest. The study authors have presented compatible cognitive and neurophysiological models that can provide a translational framework for integrating research in all of these domains. The cognitive model they highlight describes "hot" and "cool" executive functioning. The cool executive functioning abilities are the traditional cognitive abilities. The hot executive functioning abilities are characterized by the involvement of affective processes or require flexible assessment of affective stimuli. The authors present a neurophysiological

model of spiraling cortico-striato-thalamo-cortical circuits. The article concludes with five suggestions for future directions that are tightly focused on translational research with the aim of discovering neurobiological markers to reflect a more comprehensive understanding of ADHD.

Address for reprints: FX Castellanos, Institute for Pediatric Neuroscience, NYU Child Study Center, 215 Lexington Avenue, New York, NY 10016, USA. Email: castef01@med.nyu.edu

ASSOCIATED BEHAVIORS

Prediction of early-onset deviant peer group affiliation: a 12-year longitudinal study

Lacourse E, Nagin DS, Vitaro F et al.
Arch Gen Psychiatry 2006;**63**:562–8.

The hyperactivity, fearlessness, and lack of prosociality of kindergarten boys in inner-city schools were rated by their teachers. The sample was large and limited to one ethnic subgroup. Boys exhibiting all three behavioral risks were more likely to become involved in deviant peer groups during early adolescence, but only in the context of high-family adversity.

Belonging to a deviant peer-group is associated with the start, persistence, and worsening of conduct problem symptoms during adolescence. This study aimed to identify the childhood behavioral profiles that correlate with association with a deviant peer-group during adolescence. This 12-year longitudinal study was initiated in 1037 boys from low socioeconomic neighborhoods who attended kindergartens in Montreal (QC, Canada).

To determine deviant peer-group involvement, adolescents declared their own affiliation with a group or gang that engaged in “reprehensible acts”. The youths were repeatedly questioned on their involvement with such groups, and outcomes were categorized as early-onset involvement, adolescent involvement, or no involvement. As previously found, individual temperamental characteristics predicted the early-involvement trajectory associated with the most frequent violent acts and criminal misconduct. Family adversity was defined based on relative income, education of both parents, and marital intactness; this factor did not have a main effect on outcomes. However, within the group of children (12.7%) with the high-risk kindergarten profile (above median hyperactivity and below median fearfulness and pro-sociality), those with above median family adversity were more frequently on the problematic early-involvement trajectory (55%) than those with below median family

adversity (26%). For children in the lowest risk behavioral profile (inverse of high-risk profile, 11.4% of the sample), approximately 95% of those in both the low and high family adversity groups were assigned to the never-involved category.

All the participants were sons of French-speaking Canadian mothers; non-inclusion of other cultural and ethnic groups limits generalization of these data. However, the early developmental effects implied by the findings, i.e. behavioral problems in schoolchildren increase their risk of involvement with deviant peer groups, are likely to be replicated in other cultures.

Address for reprints: E Lacourse, Department of Sociology, University of Montreal, CP 6128, Succursale Centre-Ville, Montréal, Québec, Canada H3C 3J7. Email: eric.lacourse@umontreal.ca

Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents at risk for alcoholism and other substance use disorders

Nigg JT, Wong MM, Martel MM et al.
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The response inhibition component of executive functioning was able to predict alcohol and drug misuse in at-risk boys. This relationship was independent of the child’s intelligence quotient and conduct disorder symptoms, as well as paternal alcoholism and antisocial personality traits. The effect size was small, accounting for 1–9% of outcome variance.

Alcohol and drug misuse in late adolescence represents a major public health problem. At present, it is unclear whether changes in brain-behavior functioning can lead to alcohol use disorders. Executive functioning is associated with impulsivity and poorly-thought out behavior. Response inhibition is a component of executive functioning that has been linked with behaviors that require self-regulation, and is associated with ADHD and conduct disorders.

This longitudinal study recruited sons (aged 3–5 years) of men who had come to the attention of authorities as a result of alcohol misuse. Other siblings were also enrolled, as well as neighborhood controls. The generalizability of the findings was enhanced by this community-based design. Parents and children were assessed in five waves:

- Wave 1: children aged 3–5 years.
- Wave 2: children aged 6–8 years.
- Wave 3: children aged 9–11 years.
- Wave 4: children aged 12–14 years.
- Wave 5: children aged 15–17 years.

Child behavioral problems and intelligence quotients (IQs) were assessed across the five waves, while substance misuse

(alcohol and drug) and executive function were assessed at waves 4 and 5 only. This study replicated previous findings that showed the child's IQ and symptoms of conduct disorder were able to predict alcohol and substance misuse, and the executive functioning measure did not predict outcomes.

The unique contribution of this investigation is the finding that response inhibition has predictive value. After controlling for IQ and conduct disorder traits in the child, and alcoholism and antisocial personality symptoms in the father, lower response inhibition predicted more alcohol and drug misuse in adolescence. However, the effect size was small, which may limit the relevance of the findings for clinicians. With failure to control for a broader range of potential pre- and post-natal confounding variables, it is difficult to evaluate the relevance of the findings for the genetic-causal hypothesis that is of interest to neuroscientists.

Address for reprints: JT Nigg, Psychology Department, Michigan State University, East Lansing, MI 48824-1116, USA. Email: nigg@msu.edu

Fine motor skills and effects of methylphenidate in children with attention-deficit-hyperactivity disorder and developmental coordination disorder

Flapper B, Houwen S, Schoemaker M.

Developmental Medicine and Child Neurology 2006;**48**:165–9.

Physicians should consider the presence of a developmental coordination disorder in children with ADHD who have fine motor control problems. Medication can improve fine motor control, but additional support may be required to ameliorate handwriting and drawing.

Children with ADHD and developmental coordination disorder (ADHD-DCD) have been shown to perform worse in fine motor activities than children with ADHD alone. This study investigated the fine motor performance and the

effect of methylphenidate (MPH) on these tasks among children with ADHD-DCD.

Twelve children with ADHD-DCD (mean age 9 years, 8 months \pm 1 year, 7 months; 11 boys and one girl) were included in the study. Initially, 36 children were enrolled in a double-blind, placebo-controlled trial to assess the effects of MPH. Patients received weekly switches at three dosage levels (0.5, 0.75, and 1 mg/kg/day) or placebo for 4 weeks with a random assignment to order. Those children that were determined to be MPH-sensitive (improvement of ADHD checklist by >25% on medication) were asked to enroll in the current study. These children were assessed against a control group of 12 children that was matched for sex and age. They were firstly examined without MPH, and then after 4–5 weeks on MPH.

The Movement Assessment Battery for Children (MABC) consists of eight items that measure different aspects of motor ability, and was one of the methods used to diagnose DCD. Its manual dexterity item (flower trail) assessed fine motor skills. The Concise Assessment Method for Children's Handwriting is a measure of quality and speed of handwriting. Handwriting quality is rated according to 13 dysgraphic features.

Compared with the control group, children with ADHD-DCD performed worse on manual dexterity, had poorer performance on handwriting quality, and drew more rapidly and more fluently but less accurately on the graphomotor task. MPH administration resulted in an improvement in handwriting quality and less fluent but more accurate movements on the graphomotor task.

Clinicians should consider the existence of a comorbid DCD in children with ADHD who have residual fine motor problems despite medication-related improvements in inattention and hyperactivity. These children may need further support in school to address the functional problems in handwriting and drawing.

Address for reprints: BCT Flapper, Department of Paediatrics, University Medical Centre Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands. Email: b.flapper@bbk.umcg.nl

Highlights from the American Psychiatric Association (APA) Annual Meeting

May 20–25, 2006, Toronto, ON, Canada

Paul Hammerness

Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

A sample of the research presented at this year's meeting of the American Psychiatric Association (APA) in Toronto (ON, Canada) reflects the state of our current understanding of the efficacy, safety, and impact of treatments for children, adolescents, and adults with ADHD.

ADHD treatment in children and adolescents

Meta-analysis of ADHD treatment studies

Few ADHD treatment studies directly compare agents, and methodological differences limit possible comparisons between monotherapy trials. A recent meta-analysis addressed this issue by examining 29 double-blind, placebo-controlled trials, including 15 agents and multiple outcome measures (n=17) of ADHD or oppositional behavior.

The large sample of children (n=4464) had an age range of 8–15 years and was predominantly male. Studies of non-stimulant agents were more likely than those that investigated stimulants to use a crossover design rather than parallel groups, and change from baseline outcome scores instead of endpoint scores. The average effect size of non-stimulant and other medication types (e.g. bupropion) was 0.62, compared with the average effect size of short- (0.90; $p < 0.002$) or long-acting stimulants (0.83; $p < 0.004$). Beyond the differences observed between stimulant and non-stimulant therapies, this analysis highlights the importance of considering differences in study design when comparing outcomes [1].

Combination pharmacotherapy

There has been little study of the efficacy or safety of combining pharmacological treatments for ADHD. In a 7-week pilot study, children aged 6–17 years were firstly given atomoxetine over a 4-week period. Subjects with mild residual ADHD symptoms were subsequently given osmotic release oral system-methylphenidate (OROS-MPH) in addition to atomoxetine. In total, 33 subjects were exposed to atomoxetine, and 22 patients completed combination treatment.

The addition of OROS-MPH was associated with an additional 32% drop in ADHD symptoms by the end of the study. There were no severe adverse events, but additional side effects were seen when the medications were combined, with headache, nausea, insomnia, and appetite loss being the most commonly reported [2].

Clinical characteristics of treatment response

Ethnic background

There has been little study of whether different racial or ethnic groups have distinct responses to ADHD treatments. Genetic differences may influence an identifiable response by a subpopulation to certain treatments. A *post hoc* analysis was performed of two double-blind, multicenter classroom studies of D-MPH and placebo in 122 children aged 6–12 years, and included 67 Caucasian children, 22 black children, and 32 children of Hispanic or other racial background. The Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale score and a mathematics test were administered pre- and post-treatment. As a group, the black children demonstrated the greatest improvement in the mathematics test performance compared with Caucasian or Hispanic/other category children, but there were no significant differences between the groups on SKAMP ratings [3].

Comorbidity with anxiety disorders

While approximately 30% of children with ADHD or anxiety disorders will experience comorbidity of both conditions, the relationship between specific anxiety disorders and ADHD has not been studied extensively. To explore this relationship further, researchers examined a large sample of referred youth; 509 children in the study had ADHD, 251 presented with anxiety disorders, and 704 had both ADHD and ≥ 1 anxiety disorder. Analyses controlled for differences in age, gender, and socioeconomic status between the three study groups. Overall, there appeared to be minimal bi-directional moderating effects of ADHD and anxiety

disorders, when the level of significance was set at $p < 0.01$ [4]. However, the presence of comorbidity significantly increased rates of mental health treatment; 80% of the comorbid sample received either counseling or directed pharmacotherapy. Moreover, the presence of comorbidity significantly increased rates of the combination of directed pharmacotherapy and counseling for all children. ADHD children with comorbid anxiety were more likely to have received ADHD-targeted counseling, and children with anxiety who had comorbid ADHD were more likely to have received anxiety-targeted pharmacotherapy.

Although a common clinical challenge, there are few clinical trials for ADHD in the context of comorbid anxiety. A multicenter, 12-week, placebo-controlled study explored atomoxetine treatment for children aged 8–17 years who met criteria for both ADHD and either generalized anxiety, separation anxiety, or social phobia. The atomoxetine target and modal dose was 1.2 mg/kg/day. A previous analysis of this study had demonstrated greater benefit for subjects receiving atomoxetine than for those who received placebo, as measured using the Pediatric Anxiety Rating Scale and the ADHD Rating Scale (ADHD-RS). Outcome measures in this subsequent analysis included the self-report Multidimensional Anxiety Scale for Children that assesses symptoms of anxiety, the parent-rated Life Participation Scale for ADHD-Revised, which captures functional improvement related to ADHD-treatment, and the parent-rated Child Health Questionnaire.

Significantly greater improvement for all three outcome measures was observed in patients who received atomoxetine treatment than in those administered placebo. The effect of atomoxetine on the Multidimensional Anxiety Rating Scale was moderate [5].

Novel ADHD treatments in children and adolescents

Methylphenidate transdermal system

The US Food and Drug Administration (FDA) recently approved the MPH transdermal system (MTS), a skin patch delivery form of MPH. Bukstein et al. described an interim report on data collected up to 8 months into a long-term safety study of the MTS. Subjects included in this study had tolerated and benefited from MTS in previous studies of this system. The dose was optimized either prior to or during this long-term study. Of enrolled subjects ($n=326$), 39.9% of patients ended participation 8 months into the study. A small proportion of study subjects (7.7%) discontinued due to adverse events of types typical of MPH treatment studies. Additionally, 6.1% of subjects discontinued due to an application site reaction. Skin reaction was monitored on a scale during the study, and on average was no worse than minimal erythema [6].

In another trial, MTS and OROS forms of MPH delivery were compared with placebo in a 7-week dose-optimization study involving children aged 6–12 years. This large-scale, randomized, parallel-arm study involved 38 centers and 282 patients; however, the study was not designed to allow conclusive comparison between OROS-MPH and MTS treatments. Efficacy was rated by the ADHD-RS-IV, as well as Conner's parent and teacher rating scales.

Subjects were randomized to receive either MTS and a placebo capsule, OROS-MPH and a placebo patch, or placebo capsule and patch. MTS patches were prescribed for 9 h of wear time, and the dose was titrated over 5 weeks to a maximum dose of approximately 30 mg. OROS-MPH was titrated to a maximum dose of 54 mg over 5 weeks. Subjects who exhibited a $\geq 25\%$ reduction in their ADHD-RS-IV scores were maintained in the study for the final 2 weeks.

In the intention-to-treat (ITT) population ($n=270$), subjects who received either MTS or OROS-MPH had similar significant reductions in all efficacy measures compared with the observed placebo response. Clinicians and parents were more likely to rate subjects who received MTS or OROS-MPH as being much or very much improved than patients administered with placebo. The effect size was 0.99 for MTS vs. placebo and 0.83 for OROS-MPH vs. placebo. The majority of side effects experienced on both active treatments were mild, and typical of side effects seen in studies of stimulant treatment [7].

This study also looked closely at the adhesion of the MTS. After 9 h of wear, $>75\%$ of the MTS remained adhered to skin for most subjects. The majority of the study group experienced no or mild discomfort from wearing the MTS patch. The rate of "minimal" or "definite" erythema was slightly greater in individuals receiving MTS than in individuals receiving placebo patches. More significant skin reactions involved a papular response and/or edema. Two individuals, both of whom were in the MTS patch group, required discontinuation of the treatment due to application site reactions [8].

In another study that compared MTS with placebo, 79 children (ITT population) were monitored in a laboratory classroom format. Following a 5-week dose optimization involving active treatment with MTS, subjects participated in a practice classroom, followed by a study classroom 1 and 2 weeks later. In the first study classroom, half the children received active patch; the other half received the active patch on the second classroom day. During titration, subjects were optimized at doses ranging from 10–30 mg/day, and patches were worn for 9 h during the study day. In the classroom, subjects participated in several half-hour "class" sessions, and were rated at several points during the day. Measures included SKAMP-D, ADHD-RS-IV, clinical global

improvement (CGI) ratings, Conner's parent ratings, and mathematics test performance.

Subjects receiving the MTS demonstrated greater improvement in all classroom outcome measures compared with placebo. Notably, although plasma MPH concentration declines with patch discontinuation at hour 9, some measures, including SKAMP-D and mathematical performance, remained improved through to hour 12 of the study.

Side effects were similar to those observed with stimulant treatments. Minimal erythema was reported by 20–30% of patients, and two subjects discontinued the study due to reactions at the site of MTS patch application [9].

Modafinil

Modafinil has not been approved by the FDA for the treatment of ADHD. To explore the long-term impact of modafinil, 533 children aged 6–17 years were enrolled in a 12-month, open-label extension study. Subjects were titrated over 2-week intervals to doses of 170–425 mg daily; 55% of subjects were at the highest planned dose of 410 mg daily. Efficacy was evaluated at 1, 2, 3, 6, 9, and 12 months; over half of the subjects (56%) discontinued the study, with 12% of enrollees lost to follow-up and 7% leaving the study due to adverse events.

Outcome improvements persisted over this 12-month study, and included decreases in ADHD-RS (home version) scores (38.1 at baseline vs. 15.1 at final visit) and CGI-severity ratings (93% of patients had at least a 1-point reduction at final visit in comparison with baseline). There were also increases in multiple domains of quality of life, as measured by the Child Health Questionnaire.

There were no serious adverse events in this study, and the most commonly reported side effects were insomnia, decreased appetite, and headache (24%, 12%, and 9%, respectively) [10].

Lisdexamfetamine

Lisdexamfetamine is an amphetamine prodrug composed of L-lysine conjugated with D-amphetamine, which becomes active when it is hydrolyzed by the digestive system. Currently, this agent has not received FDA approval for clinical use. A multicenter, analogue classroom study that recruited 50 participants compared 30, 50, or 70 mg of lisdexamfetamine with 10, 20, or 30 mg of extended release mixed amphetamine salts (MAS-XR), or placebo [11]. After dose optimization on MAS-XR, subjects participated in a 3-week, three-way crossover study such that they sequentially received both of the study treatments and placebo, each for a duration of 1 week. During the week-long exposure, MAS-XR were administered at the optimized dose deduced earlier in the study, and lisdexamfetamine was

provided at doses that were estimated to be equivalent to the optimal MAS-XR dose.

Significant and comparable improvements were seen in the mean SKAMP deportment and mathematics test scores with both active treatments in comparison with placebo. The treatments were well tolerated, and the most common adverse events associated with lisdexamfetamine were insomnia (8%), decreased appetite (6%), and anorexia (4%). This study offers initial evidence that lisdexamfetamine may effect equivalent functional improvements when compared with MAS-XR.

Another recent study into lisdexamfetamine was a multicenter, double-blind investigation in which children aged 6–12 years were randomized to one of three doses of lisdexamfetamine (30 mg, 50 mg or 70 mg) or placebo for 4 weeks. The trial was completed by 260 of 290 subjects [12]. ADHD RS score improvements over the 4-week trial were –6.2, –21.8, –23.4, and –26.7 for placebo, lisdexamfetamine 30 mg, 50 mg, and 70 mg, respectively. The study was discontinued by 17% of the placebo subjects due to lack of effect, and 14% of patients receiving 70 mg lisdexamfetamine due to adverse events. The most common adverse events were anorexia, insomnia, headache, and abdominal discomfort.

ADHD in adults

Clinical assessment and treatment adherence

A Harris Interactive online survey that explored comfort in ADHD diagnosis and treatment in adults was completed by 400 primary care physicians during 2 weeks of May 2003 [13]. Two-thirds (65%) of primary care physicians were found to be uncomfortable with making a diagnosis of ADHD without referral to a specialist. Only 5% of survey respondents reported that they would make the final decision to treat ADHD with medication. Although these data are already several years old, they highlight the need for improved mechanisms of ADHD identification and treatment in the primary care setting.

The Adult Symptom Rating Scale (ASRS) is a publicly available self-report survey that clinicians can administer to identify adults who are likely to have ADHD [14,15]. New York University (NY, USA) reported on a 2-year follow-up of adults identified as likely to have ADHD during an ADHD Screening Day conducted in May 2004. At that time, 85% of the small sample screened positive for ADHD (n=33), and discussed these results and referral options with trained clinicians. Of 51 subjects who completed a follow-up survey 2 years later, 47% had sought ADHD diagnosis or treatment, 74% of whom were diagnosed by a specialist, and 4% who were diagnosed by a primary care physician. The 53% of individuals who did not seek diagnosis of

ADHD reported that ADHD symptoms contributed to not obtaining a diagnosis [16]. These symptoms included procrastination as well as accompanying organizational deficits, which can interfere with an individual's ability to follow through, even on personal health related tasks. This study, consistent with larger epidemiological surveys, suggests that a large percentage of adults with ADHD remain untreated.

There is evidence from pharmacy claim records that adherence to prescriptions for ADHD treatment is low. An analysis of pharmacy database records documented filled prescriptions for psychostimulant treatment, diabetes agents, and hypercholesterolemia treatments from autumn 2003 to autumn 2004. Subjects entering the observation period had filled a prescription for the first time in 90 days. Subjects were considered to be continuously taking medication at a time point if the current fill date was within 2 months of the prior one. By month 2 of the observation period, adherence rates were similar for psychostimulants, antidiabetic agents, and statins. By month 7, adherence levels for MAS-XR (22.9%) and MPH-modified release (23.5%) were low. In comparison, slightly higher rates of adherence were seen for the antidiabetic agent rosiglitazone (33.4%) and the statins (26.0–30.1%) at month 7, and similar or slightly lower rates of adherence were seen for insulin treatments (17.6% for insulin glargine) [17].

Treatment studies of adult ADHD

An emerging body of research demonstrates the efficacy and safety of agents used to treat ADHD in adults. However, to date, the only ADHD treatments approved by the FDA for use in adults are D-MPH extended release, MAS-XR, and atomoxetine.

There has been little investigation into the longer-term effects of MPH treatment in adults with ADHD. A recent double-blind study followed 65 adults with ADHD treated with MPH administered three times per day (n=59), or placebo (n=6), for up to 30 weeks. Participants on active medication experienced ADHD improvement ($\geq 30\%$ decrease in ADHD RS) during a 6-week short-term efficacy study. In the 24-week maintenance phase, responders were assessed every 4 weeks.

The mean dose remained at 1.0–1.1 mg/kg/day for MPH and 1.2–1.3 mg/kg/day for placebo during the 24-week study. Mean improvements in ADHD-RS and clinician-rated Global Assessment of Functioning remained stable for all study subjects, as the majority of those who remained in the study were MPH responders. Worsening of ADHD symptoms, defined as loss of $\geq 25\%$ improvement in ADHD RS score from baseline, occurred in 15% of MPH-treated subjects and 43% of placebo-treated patients by the

end of the 24-week maintenance period. Adverse effects of MPH were typical of stimulant treatments, and there were no significant changes in vital signs or blood pressure during this maintenance study [18].

While longer-acting stimulants have been designed to mimic daytime coverage by multiple doses of shorter-acting formulations, few studies have compared the relative safety and efficacy of short- and long-term treatments. Two forms of MPH were compared in a recent analysis of pooled data from two independently conducted 6-week, placebo-controlled, randomized MPH adult clinical trials.

In one trial, daily OROS-MPH was titrated to a maximum of 1.3 mg/kg/day for optimal effect. The second trial assessed immediate-release MPH (IR-MPH) titrated up to a maximum of 1.0 mg/kg/day and administered three times per day. By pooling data, three treatment groups could be analyzed: placebo (n=116), IR-MPH (n=102), and OROS-MPH (n=67). The adult ADHD Investigator Symptom Report Scale (AISRS) was the main outcome measure. At the end of 6 weeks of treatment, AISRS scores were significantly higher in the placebo group than in both the IR-MPH (<0.001) and the OROS-MPH (<0.001) groups. Any differences in AISRS scores between the OROS-MPH and IR-MPH groups were not statistically significant; 66% of subjects receiving OROS-MPH, 70% of subjects receiving IR-MPH, and 31% of subjects receiving placebo were much or very much improved on the CGI scale.

Both MPH treatments were well tolerated, with adverse events typical of stimulant studies and no serious adverse events. Subjects receiving OROS-MPH did report dry mouth, decreased appetite, and gastrointestinal complaints slightly, but significantly, more often than subjects treated with IR-MPH. Small but statistically significant increases in diastolic blood pressure and heart rate were noted for both of the MPH treatments [19].

Combination pharmacotherapy

Some clinicians prescribe more than one agent to manage ADHD symptoms in particular patients, but this practice has not been systematically studied. Two chart review reports offer a preliminary perspective on such treatment combination approaches.

As adults may often have activities that span beyond 8–12 h, short-acting stimulants are sometimes prescribed to cover the hours following the wear-off of a long-acting agent. In a recent chart review, the efficacy of prescribing afternoon D-MPH to 27 individuals aged 8–51 years (mean 18 years) to augment a morning dose of OROS-MPH or MAS-XR was assessed. While all subjects were given extended-release stimulants, eight of the subjects also received D-MPH in the morning as well as the afternoon,

and nine were administered atomoxetine. Subjects who received D-MPH in the afternoon reported benefits lasting 3–6 h (4 h on average), and tolerated the drug well. Two subjects had dose-limiting side effects (agitation and early insomnia) [20].

The second review of an augmentation strategy assessed treatment records of 29 ADHD patients aged 10–60 years (mean age 32 years) who received atomoxetine concurrently with a stimulant. This was a heterogeneous sample, with 11 subjects having comorbid dysthymia or depression, seven with anxiety disorders, and one subject who suffered from bipolar disorder. The majority (76%) of the study sample tolerated the combination of atomoxetine and stimulant, and the rate of discontinuation appeared similar for subgroups with and without comorbidity [21]. Structured measures were not used to assess effect or tolerability.

Therapy for adult ADHD

Patients with ADHD often have residual challenges, such as organizational-functional deficits, despite optimization of medication regimens, yet there is little science to guide clinicians in making recommendations for non-medication approaches to such challenges. However, some studies have suggested that there may be forms of non-pharmacological therapy that are supportive for ADHD patients [22,23].

Recently, 48 patients at five sites were randomized to receive a manualized problem-focused therapy (PFT) and either D-amphetamine (up to 20 mg twice a day) or placebo. Subjects were assessed 10 and 20 weeks into the interventions. The PFT included education about ADHD, training in coping strategies for deficits associated with ADHD, and were also flexible in that some modules were selected to address the particular challenges faced by a subject (e.g. substance use or financial management).

Both groups showed improvement in ADHD-RS scores. By week 20, subjects receiving both PFT and D-amphetamine showed greater maintenance of gains in CGI of ADHD Improvement and Global Assessment of Functioning scores than subjects receiving PFT alone. Significant improvements in the Sheehan Disability Scale for both treatment groups ($p < 0.05$) were not statistically different. Overall, individuals who received PFT and stimulant showed a greater and more persistent benefit than subjects receiving PFT and placebo treatment [24].

Quality of life

As ADHD can have a broad impact on quality of life, there is great interest in capturing change in this impact over the course of a clinical trial. At this year's APA meeting, researchers reported on measurements from the first 10 weeks of a large open-label trial of MAS-XR treatment

using two different instruments, designed to capture changes in quality of life [25,26].

Analyses were conducted on an intent-to-treat population consisting of 702 adults from 81 community practice sites in North America, with a mean age of 37 years. Subjects were given 10–60 mg of MAS-XR daily and were asked to complete the 36-item Short Form Health Survey Version 2. Compared with 1998 US normative data, adults with untreated ADHD had lower scores at baseline pre-treatment for the Mental Health Component summary score by one standard deviation, but similar scores for components reflected in the Physical Component summary score.

After 10 weeks of MAS-XR treatment, scores for mental health sub-domains improved significantly, such that the Mental Health Component summary score became comparable to the US norms [25]. Subjects in the same study also completed the ADHD Impact Module, a quality of life measure that was developed to capture more ADHD-specific aspects of functioning. This self-report instrument was developed based on literature review as well as clinician and patient interviews. It asks subjects to rate overall quality of life, and to complete subscales entitled "Living with ADHD", "General Well-Being", "Performance and Daily Functioning", "Relationships and Communication", "Bothersomeness and Concern", and "Daily Interference". By week 10 of the study, statistically significant improvements occurred in self-rating of overall quality of life as well as in self-rating on all six subscales (all $p < 0.001$) compared with baseline. Strongest improvements were reported for the Performance and Daily Functioning, Bothersomeness and Concern, and Daily Interference subscales [26]. More extensive study will reveal the full relevance of such instruments for use in research and clinical practice.

Conclusion

The 2006 meeting of the APA in Toronto (ON, Canada) demonstrated the wealth of ongoing scientific efforts aimed at advancing treatment for children, adolescents, and adults with ADHD. During this past year, clinical options for the treatment of ADHD have continued to expand, including novel stimulant formulations, further investigations into new drug classes, FDA approval for adult indications, and increased efforts to capture functional outcomes, in addition to clinical symptom-based rating assessments.

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Record your answers here by filling in the blank with the correct letter for the corresponding question:

Medication Non-Adherence in Children with ADHD: Challenges and Strategies. Raun D Melmed and Laura H Jensen
Advances in ADHD 2006;1(2):42-6.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____ 9. ____ 10. ____

Stimulant Pharmacotherapy in ADHD in Patients with Co-Occurring Substance Use Disorders. John J Mariani and Frances R Levin
Advances in ADHD 2006;1(2):47-52.

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____ 9. ____ 10. ____

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4. The activity content met its objectives.	1	2	3	4	5
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LEARNING OBJECTIVES

Medication Non-Adherence in Children with ADHD: Challenges and Strategies

Raun D Melmed and Laura H Jensen.
Advances in ADHD 2006;1(2):42-6.

Goal: To review factors contributing to medication non-compliance in children with ADHD and methods to avoid or eliminate non-adherence.

Objectives: After reading this article, the reader should be able to:

- Identify possible or actual cases of non-compliance in their practice
- Describe methods to manage or eliminate these causes before they occur

Stimulant Pharmacotherapy in ADHD in Patients with Co-Occurring Substance Use Disorders

John J Mariani and Frances R Levin.
Advances in ADHD 2006;1(2):47-52.

Goal: To review the evidence regarding administration of stimulant medication to ADHD patients with comorbid substance use disorders.

Objectives: After reading this article, the reader should be able to:

- Recognize when patients with ADHD and substance use disorders can be safely administered stimulant medication
- Identify potential treatment management strategies that can aid in reducing the risk of substance use in ADHD patients with a co-occurring substance use disorder

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