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ATTENTION-DEFICIT DISORDER (R BUSSING, SECTION EDITOR)

Enhancing ADHD Medication Adherence: Challenges and Opportunities

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Abstract Safe and effective medication for attention deficit hyperactivity disorder (ADHD) is available and recommended as first-line treatment for the core symptoms of inattention, overactivity and impulsiveness. Despite impaired functioning during adolescence, many discontinue medication treatment. For children, healthcare decisions are usually made by the parent; older youth make their own decisions. Beliefs and attitudes may differ widely. Some families understand that ADHD is a neurobiological condition and accept that medication is indicated, for others, such treatment is unacceptable. Converging evidence describes negative perceptions of the burden associated with medication use as well as concerns about potential short and long term adverse effects. Indeed experiences of adverse effects are a frequent explanation for discontinuation among youth. Ways to improve shared decision making among practitioners, parents and youth, and to monitor effectiveness, safety and new onset of concurrent difficulties are likely to optimize outcomes.

Keywords Attention deficit hyperactivity disorder · ADHD · Psychostimulants · Atomoxetine · Medication adherence · Patient compliance · Adverse effects · Treatment refusal · Treatment outcome · Childhood · Adolescence · Psychiatry

Introduction

In the following chapter we summarize patterns of medication use for ADHD and describe what is known about factors influencing adherence to ADHD medication. Choices about using medication are complex, with more recent work focusing on beliefs and attitudes that shape patient preferences. In addition, effectiveness and adverse effects are important factors and we review what is known about the differences among commonly used ADHD medications. We end with a discussion of the challenges and related opportunities facing clinicians who work with young people with ADHD. The field remains under-researched with much more to learn about how to assist greater numbers of young people with ADHD to maximize their potential.

This article is part of the Topical Collection on *Attention-Deficit Disorder*

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Background

Attention deficit hyperactivity disorder (ADHD) is a neurobiological disorder, characterized by symptoms of inattention, overactivity and impulsivity [1]. ADHD is estimated to affect 5 % children worldwide and boys are classified with ADHD approximately twice as frequently as girls and primary school age children approximately twice as frequently as adolescents [1].

Throughout childhood and adolescence, clinically significant ADHD is often associated with concurrent oppositional and aggressive behaviors, also anxiety, low self-esteem, and learning disabilities [1]. While ADHD begins before children enter school, it is most commonly identified and treated in primary school, ages 7 to 9 years old [1]. In the preschool age group, ADHD is characterized not only by impairment in attention span, excessive impulsivity, but also is frequently accompanied by additional disruptive behavior symptoms, including severe temper tantrums, demanding, uncooperative behavior and aggressiveness [1]. While levels of symptoms decrease with age, the majority of children with ADHD continue to show impairment relative to same-age peers throughout adolescence and into adulthood [1].

Table 1 Factors associated with ADHD medication adherence

Factor	Predictors of increased adherence	Predictors of decreased adherence
Parent/family	Two-parent families* [12]	Older parents [12]
	Higher socioeconomic status* [12]	Increased parent-child conflict [1, 40]
	Belief that medication is safe [33••]	Belief that symptoms are not a disorder [12, 38]
	Belief that ADHD is neuro-biological disorder [35]	Distrust of the medical system [12, 38]
		Stigma [12, 38]
		Burden of medication regimen [40]
		Concerns about medication safety [33••]
Healthcare system/ professional	Insurance coverage [46]	Cost of medication [46]
	Specialty care [28]	Lack of providers in the community [24, 46]
	Prior history of medication treatment [12, 38]	
	Good relationship with doctor [38]	
Child	Caucasian racial background [20, 21]	Older child age at diagnosis [40]
	Increased symptom severity [12, 38]	Family history of ADHD [1]
	Combined subtype [1]	Severe behavior problems at home [12, 40]
	Comorbidities present (oppositional defiant disorder, depression, social skills, anxiety, developmental delay, learning disabilities) [12, 38]	Child unwilling [12, 40]
Adolescent	Academic benefits [33••]	Negative attitudes toward medication [33••]
	Few adverse effects [33••, 41]	Stigma [12, 33••, 42, 44••]
		Concerns about treatment dependence [16]
		Experience of social withdrawal [16, 42]
Medication	Long-acting formulations [20, 25, 26]	Medication ineffectiveness [1]
		Adverse effects (physiological/psychological) [1, 42]
		Multiple daily doses [40]
		Difficulties adjusting the dose regimen [52]

* The evidence regarding direction of influence is not consistent

Many studies have documented increased risk for youth with ADHD for leaving school early, increased contact with the law, early onset substance use, and associated conduct, mood and anxiety disorders [1]. More recently studies have also documented higher risk for dangerous driving, suicidal behavior, problem gambling, eating disorders and early parenthood [2–6]. Over the years, `ADHD interventions have largely targeted children in the primary school age group`, with the hope and expectation that early treatment will diminish such poor psychosocial and mental health outcomes in adolescence. However few studies exist that examine long-term effectiveness of interventions with follow up beyond 12 months [1]. Most of those available evaluate use of medications, primarily psychostimulants [1]. Overall outcomes in adolescence remain less than optimal with many youth continuing to show functional impairment even where stimulant medications have been combined with intensive behavioral interventions [7]. A few studies suggest that continued medication use during adolescence improves academic outcomes and postpones substance initiation [8–10]. However it is difficult to distinguish between medication treatment and other family, socioeconomic and psychosocial factors that may support increased use of healthcare services. Interestingly, a recent population based study from Sweden among persons older than 16 years, shows that periods of medication use are associated with diminished contact with the law, and non-use is associated with a return to illegal activities [11]. This study demonstrates effectiveness of medication interventions for an important functional outcome, but also underlines that the benefits of medication are not maintained when treatment is discontinued. Therefore one important reason for suboptimal outcomes in adolescence may be poor medication adherence [12].

There are primarily two types of pharmacological agent with proven efficacy over 12 months for ADHD: psychostimulants, (e.g., methylphenidate, or amphetamine derivatives such as dextroamphetamine and mixed amphetamine salts) and a norepinephrine reuptake inhibitor, atomoxetine [1]. Psychostimulants continue to provide control of ADHD symptoms and are generally well tolerated for months to years at a time, although adverse effects, most commonly decreased appetite, sleep disturbances, headaches and stomachaches, may continue to be present [13]. Methylphenidate improved ADHD symptoms and overall functioning alone or in combination with psychosocial/behavioral interventions for 14 months and up to

24 months [7, 14]. The benefits and safety of methylphenidate for symptom control and general functioning are most clearly documented, for boys, ages 7 to 9 years at initiation, with ADHD combined type [1]. However the benefits of psychostimulants wear off when the medication is not taken as the pharmacological half life is 3 to 5 hours in immediate release medication [15]. Best practice guidelines recommend that for full benefit both in school and at home, children with ADHD should use these agents all day every day [15]. Children who use psychostimulants, often continue treatment for three years or more, although many discontinue use once they reach adolescence [16, 17].

Patterns of Medication Use

Rates of clinical identification and medication treatment for ADHD have increased over time from the early 1990s to 2005 or later [1]. Rates of medication use have increased due to increased duration of use as well as increased use among girls, preschool children, adolescents and adults [1]. Rates vary by geography, provider type and patient characteristics as well as formulation of pharmacological agent. Diagnosis and treatment is more common in the United States than elsewhere world-wide, with approximately 1/3 of children and youth given a diagnosis of ADHD receiving consistent treatment within the past year [18]. More prescriptions, primarily pscyhostimulants, are given to patients in the south and midwest regions of the United States compared with the northeast [19]. Within the United States, Caucasian children and those from higher income groups are more likely to receive prescriptions and to use medication consistently than children and youth from minority background [20, 21]. The most common age to begin medication is between 5 and 9 years, more among boys than girls [22]. One quarter to one third of patients receive a single prescription [23, 24]. Treatment often is short-term or intermittent, with one half to two thirds discontinuing within one year [22, 23]. Teenagers are less likely to continue taking psychostimulants relative to younger children. Once-daily extended release preparations improve the duration of stimulant use compared with immediate-release agents [20, 25, 26].

Information is available about differences between provider type and subsequent prescribing patterns. Specialists' practice patterns are different from those of primary care physicians. Children diagnosed by psychiatrists are less likely to receive a prescription within the initial six months after diagnosis than those identified by primary care physicians, even after adjustment for comorbid conditions [27]. Psychiatrists are more likely to provide titration of stimulant doses with a lower initial dose, a higher maximal dose, and three or more visits in the first 90 days, suggesting increased monitoring [28]. Presence of comorbid disorders, especially bipolar disorder, schizophrenia, or autism decreased the use of ADHD drug use, but increased the use of other categories of psychotropics, prescribed primarily by psychiatrists and neurologists [27]. The techniques for medication initiation used by specialists may be one reason that specialist care leads to increased duration of use over time [29]. While efficacy and safety of pharmacological agent are important for continued use, the high-rate of non-refill following initial prescription, as well as the variability by geography, provider characteristics and the child's age, ethnicity, and socioeconomic status suggests a nuanced approach to medication adherence is warranted.

Patterns of continued medication use for ADHD vary considerably, depending on sample characteristics and method of measurement [12]. In community samples using prescription databases, such as those described in the preceding paragraph, the mean time to discontinuation ranges from 3 to 5 months, however, when single prescriptions are removed, duration of use is considerably longer [17, 29, 30]. Cohort studies following participants enrolled in industry sponsored trials document low rates of discontinuation due to adverse effects, 12 % over 12 months on OROS methylphenidate, 15- 21 % over 24 months on mixed amphetamine salts, 11 % discontinued atomoxetine over more than 2 years [1]. Consistent use was documented for 86 % of participants at 12 months in a cohort study examining effectiveness of OROS methylphenidate [31]. In general, estimates from surveys and clinical samples suggest that 36-68 % of children consistently use ADHD medications once initiated [12]; consistent use declines over time from approximately 50 % at 2 years to 36 % at 5 years [13]. Fluctuations in use are common; some children use medications regularly, others discontinue, and still others stop and restart medications, sometimes more than once [13, 17].

Alongside the multiple patterns of ongoing medication use, there often are multiple changes in dose and formulation [17]. While treatment guidelines may encourage daily use, parent interviews and self report surveys and cohort studies suggest that up to 40 % of families prefer to target behavior and learning at school and do not use medications on weekends and during school vacations [12].

Medication Adherence

Empirically based models of health behavior offer the opportunity to examine social, cognitive, and experiencial factors that influence medication adherence, cognitive behavioral models such as the health beliefs model take into account characteristics of the specific disorder, patient beliefs and attitudes, and the efficacy and safety profile of the medication, while a model such as the trans-theoretical

model of change, describes the importance of experience and associated changes in attitude over time [12]. While the concept of treatment adherence has evolved in the past 20 years, it remains poorly operationalized and measured, leading to a variety of interpretations by patients and providers [32•]. For young children with ADHD, healthcare decisions are usually made by the parent and therefore the parent's perceptions and experiences are of central importance. However, parents often incorporate their understanding of their child's experiences [12].

In general, medication adherence connotes the child's and parent's participation and engagement in using a medication regimen believed to be beneficial by both the family and the clinician who prescribes. The therapeutic partnership maintained by ongoing patient-provider transactions over time is essential for long-term adherence [32•]. For a chronic condition such as ADHD, where successful outcomes are more likely to occur with continued medication use, challenges can arise with development as the young person becomes an adolescent. Ideally the patient-provider relationship also undergoes adjustments as the family transfers healthcare decision-making from the parent to the youth. However, adolescents are less willing to use medications for ADHD than are their parents [33••].

Factors That Influence Use of ADHD Medications

Generally speaking we can organize factors that are associated with use of medication for ADHD into parent or family characteristics, child characteristics, practitioner or health system factors and medication-related factors (Table 1). Parent beliefs about ADHD and attitudes toward treatment are significant determinants of initiation [34]. For example those parents who view the child's difficulties as a medical disorder that requires a biological intervention will agree with using medication and encourage long term use [35]. Many however prefer implementing behavioral strategies and other non-medication strategies, such as dietary changes, exercise or counseling [36, 37]. Families are more accepting of a trial of stimulants when the diagnostic process has been thorough, and included comprehensive psychological testing [36]. Some parents feel that medication is unacceptable as treatment of ADHD behaviors, and do not choose to use it for their child [35]. Many parents have mixed feelings about starting medication, and often weigh concerns about adverse effects and social disapproval against potential behavioral and academic benefits [12, 38]. Increased knowledge about ADHD, and associated attitudes that using medication is safe, effective and socially acceptable increases willingness to use medication [33••]. However while knowledge may increase willingness to try medication treatment, it is not clearly associated with long term use [39].

Child characteristics that increase long term use of medication are younger age when starting, more severe ADHD symptoms, additional learning and behavior conditions, and past experiences that medication is effective with few adverse effects [12, 38]. In general children are less likely to use medication when there are severe behavior problems at home and the child is unwilling [12, 40]. Many children and youth on medication do recognize benefits for improved schoolwork and peer relationships [41–43]. Among adolescents, the belief that medication is effective, in combination with few experiences of adverse effects, increases willingness to use medication [33••]. The young person's evaluation of how peers perceive them is very important. Some youth feel ostracized socially due to ADHD behaviors and therefore find taking medications helpful while others may avoid treatment because of fears medication use will create stigma [33••, 42, 44••]. University-aged young people with ADHD described greater medication use when they made the treatment decision themselves, often with the goal to increase academic success [16]. Not surprisingly, as adolescents mature, their ADHD symptoms become less obvious, and their priorities change, patterns of medication use for their ADHD symptoms are likely to change.

Parents describe that a good relationship with their healthcare provider helped in the decision of starting treatment in their children [38]. Those who trust their health care provider and in general trust the health care system are more likely to accept ADHD medication treatment [35]. Parents and pediatricians have a similar, but not identical, understanding of what ADHD is, and the treatment priorities [45]. Families often consult with friends and relatives about the advice doctors provide; where these informal consultations concur with the provider's advice to use medication, it is more likely to happen [45]. Barriers to ongoing medication use include the cost of prescriptions, while limited insurance coverage and taking time off work can interfere with ongoing monitoring and care [46]. Pediatricians note that providing care for children with special needs can be time-consuming, with additional phone calls to schools and mental health professionals outside of usual office hours [47]. The physician's ability to clarify treatment preferences, discuss available options and maintain a treatment alliance with the family is crucial to success.

Medication Effects

The most important medication factors influencing adherence are effectiveness and tolerability. Ease of use, simplified dose regimen, and cost are also important [33••]. The range of formulations for psychostimulants has burgeoned over the last decade, especially in the United States compared with other jurisdictions. A recent review of ADHD

treatment studies examined ADHD medication use greater than 12 months, and found studies of four psychostimulant preparations (methylphenidate immediate release, amphetamine, OROS methylphenidate, and mixed amphetamine salts) and a discontinuation trial evaluating atomoxetine [1]. While best evidence suggests that psychostimulants preparations are all efficacious compared to placebo, very few head-to-head trials among stimulant preparations have been done. However, the once daily formulation of OROS methylphenidate is more likely to be taken consistently than immediate release methylphenidate which requires multiple doses daily for efficacy [25, 26]. While the psychostimulants and atomoxetine both reduce ADHD symptoms, and improve social and academic functioning in placebo controlled trials, not all children benefit equally well. Another comparison of two agents examined OROS methylphenidate and atomoxetine over several weeks, with the conclusion that OROS methylphenidate is more efficacious for core ADHD symptoms [48].

Overall a substantial proportion of treatment discontinuation in the first few months is due to adverse effects of medication [1]. While families often may tolerate some adverse effects over months to years, such as decreased appetite or mild insomnia, other symptoms such as stomach aches, or headaches may be less tolerable [13]. A long-term comparison of dextroamphetamine with methylphenidate formulations, suggests dextroamphetamine agents are less well tolerated by girls than boys [17]. In particular, psychological side effect such as mood changes, irritability, depression and subdued personality are frequent reasons for discontinuation [43]. Increased moodiness and irritability appears to be more common among preschool children than older ones [49]. Other reasons for changing or discontinuing medications are slowing of the child's growth, development of tics, rashes and other concerns the young person or family attribute to the medication. Psychotic symptoms, are estimated to occur ADHD medications at a rate of 1.5 events / 100 person years [50] and suicidal ideation is estimated to occur 5/1357 (0.37 %) in pediatric patients taking atomoxetine [51].

The most frequently cited reasons for discontinuing medication are the family's experience that the medications are not effective or the child is experiencing intolerable adverse effects. The clinician should help the family have realistic expectations for how ADHD medication can help, and provide frequent monitoring in the initial stages to address emerging adverse effects, as two important methods to improve medication adherence [52].

Challenges and Opportunities

The primary reason to examine ADHD medication adherence is to provide the best care possible for children and youth with ADHD so that long-term mental health, psychosocial, and economic outcomes are optimized. However despite extensive examination, solid evidence that medication interventions provide lasting long-term benefits remains elusive. This conundrum is now being addressed using large-scale population-based administrative databases, linking data about prescription renewal rates with health care and educational services information. Using complex statistical methods, these studies show promise for describing community patterns of health care use and associated outcomes. On the other hand, the specifics of individual child characteristics, including clinical diagnosis, interpersonal relationships of families and providers, and co-interventions received are rarely captured, offering little practical guidance to front-line practitioners. The details required to inform day-to-day practice require alternative research methods. For example, studies using mixed qualitative and quantitative methods have begun to answer complex questions about treatment adherence relevant for front line practitioners. Converging evidence from multiple samples offers surprisingly similar descriptions of parent attitudes and beliefs about childhood ADHD and its treatment with medication. Indeed, one very important challenge for physicians arising from this body of evidence is to acknowledge the limitations of medication as a sole treatment for ADHD. Parents, even those who rely on medication to assist their children, identify areas of burden, have ongoing concerns associated with its use, and articulate the need to investigate additional ways to help their child reach their full potential.

Another significant challenge to current practice is to include children as active participants in treatment decisions. This is not only good ethical practice but also the best way to engage them in treatment. The opinions and preferences of children and youth about their ADHD treatment are not yet widely described, but progress is being made. Young children certainly have less involvement in their treatment decisions than adolescents, but when they are unwilling to take medication, their parents experience the burden of conflict and in turn, medication is likely to be discontinued. Developing a thorough understanding of young people's concerns about their mental health treatment, identifying and responding to their priorities and addressing their concerns is important for optimizing outcomes. Over time inattention and overactivity may become less of a focus for intervention and other issues may emerge as more significant. Maintaining the treatment alliance remains key as medication use may once again become a useful option at a later point in time.

When thinking about the long-term course of mental health interventions for a young person with ADHD, it can be important to recognize that early ADHD symptoms are a risk marker for concurrent and subsequent difficulties. The

literature about combining interventions with medication for optimized outcomes remains sparse. The initial psychoeducation about what is ADHD and options for treatment is a crucial first step in providing care, but one that is not yet standardized. The process of seeking help for the behavior and learning problems associated with ADHD is complex and families often depend on informal as well as formal sources of information within their community. Therefore examining the best content to provide and the best ways to communicate it remains important. Widely disseminated, accurate general knowledge about ADHD may also diminish stigma and misconceptions about potential long-term consequences of medication. The general need for such mental health literacy extends to educators as well as health care workers and to other trusted persons to whom parents and youth go for answers.

Primary care practitioners play an important role as educators and gatekeepers in the process of identification and treatment of ADHD. ADHD medication treatment needs to be initiated in a way that encourages adherence and ongoing monitoring should be provided to maximize benefit and minimize adverse effects. As technology is integrated into the provision of healthcare services in general, it will also become useful for those with ADHD. Prior to technical development however, development and evaluation of standardized methods will be required. These may include decision aids to assist in informing parents and youth about options and enhance shared decision making, and monitoring algorithms with reminders to collect key information, address psychological as well as physiological adverse effects and evaluate for potential emergent concurrent disorders. Pharmacies already use automated prescription renewal systems and these could be adapted for daily use by the parent or by the young person.

Experiences of adverse effects remain a significant and frequent reason for discontinuation of medications. As in other areas where personalized medicine is under discussion, there may be genetic biomarkers on the horizon to assist in identifying which agents are likely to be most effective and easier to tolerate for individual persons. Increased understanding about how the brain changes with development and with prolonged treatment will bring new knowledge about how to ensure brain health over many years. Such information may also inform the most effective way to use ADHD medications.

Conclusion

Medication is a key component of evidence-based care for children with ADHD, and patterns of treatment adherence are complex. Despite the fact that many young people show impaired functioning well into adolescence, many who begin medication treatment either stop and start medications over several years or discontinue use altogether. Explanations for poor adherence to ADHD medication treatment include patient perceptions expressing many negative responses to the recommendation of medication use. In addition, the healthcare provider often is working with more than one person in the family who contributes to decisions. Not infrequently, patients and families perceive less than optimum effectiveness and tolerance of adverse effects, both of which lead to discontinuation. In this context, the clinician's ability to maintain a positive working alliance is crucial. Also important is monitoring for concurrent or emergent difficulties; these problems may become the priority rather than the ADHD symptoms, perhaps requiring alternative or additional interventions. As we learn more about brain health and development, additional ways to help young people care for themselves will emerge; we may see an increased focus on sleep hygiene, stress management, diet and exercise, factors known to support positive mental health. Overall increased awareness of the need for shared decision making, with the young person as well as the parents and enhanced monitoring will remain key to enhancing ADHD medication adherence and optimizing long-term outcomes.

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- •• Of major importance

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