Innovations in Attention-Deficit/Hyperactivity Disorder Pharmacotherapy: Long-acting Stimulant and Nonstimulant Treatments

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Abstract

This article reviews innovations in attention-deficit/hyperactivity disorder (ADHD) pharmacotherapy and describes research on the newer, long-acting stimulant and nonstimulant treatments for ADHD. Results from peer-reviewed articles comparing the efficacy and safety of longer-acting methylphenidate or amphetamine-based stimulants and the nonstimulant atomoxetine are described. Longer-acting stimulants and nonstimulants provide increased clinical utility compared with short-acting stimulants. Efficacy and safety are similar to 2- or 3-times-a-day treatment with short-acting stimulants. Longer-acting stimulants and nonstimulants provide increased convenience and flexibility for treating youth with ADHD and show considerable promise. Direct head-to-head studies are needed to better inform clinical decision making and to identify moderators and mediators of differential response.

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most common and well characterized child and adolescent psychiatric disorders.[1,2] Longitudinal studies of hyperactive children followed into adulthood indicate that ADHD symptoms continue into adulthood for most individuals, even for those with previous stimulant treatment.[3] These findings, coupled with several popular books on ADHD in adults,[4] have increased awareness of ADHD for all age groups. Individuals with ADHD also exhibit increased psychiatric and psychosocial comorbidity, chronic and acute health conditions, and medical care use when compared with non-ADHD individuals.[5] Consequently, both specialists and primary care physicians should be familiar with the diagnosis of ADHD and innovations in medical management of this disorder.

Stimulant medications have been used to treat the core ADHD symptoms of overactivity, impulsivity, and inattention since 1937.[6,7] The safety and short- and immediate-term efficacy of stimulants have been demonstrated in some studies.[8,9] When given at appropriate doses, a significant percentage of patients are able to obtain normal functioning as evidenced by less severe ADHD symptoms with little or no impairment.[10,11]

ADHD Treatment Before 2000

Until recently, ADHD has been viewed primarily as a childhood disorder. Generally, medication was used to improve school behavior and academic performance. The most common treatment options before 2000 were either immediate-release, short-acting stimulants, such as methylphenidate (MPH) (Ritalin) or dextroamphetamine (Dexedrine) taken twice daily, or first-generation, extended-release (ER), intermediate-acting stimulants, such as mixed amphetamine salts (Adderall [MAS]), sustained-release (SR) MPH (Ritalin SR), dextroamphetamine spansules (Dex Span), or pemoline (Cylert). The efficacy and duration of effects of MAS on behavior and ADHD symptoms is similar to MPH taken twice daily.[12] The pharmacokinetic and pharmacodynamic profile of SR MPH is highly variable and not clearly superior to short-acting stimulants in efficacy.[13,14] Pemoline has a behavioral half-life of 6

to 8 hours.[15] However, its use declined significantly after concerns about hepatotoxicity were reported.[16] Consequently, until recently, immediate-release, short-acting stimulants were the most commonly used pharmacological treatment of ADHD.

Because of an increasing awareness that impairments associated with ADHD extend beyond the school day, as well as concerns about worsening of symptoms as stimulant concentrations decline or rebound, many clinicians had begun adding a third dose of a short-acting stimulant in the late afternoon.[17] Kent et al showed that adding a third dose of MPH improved evening behavior.[18] Similarly, Stein et al conducted a study contrasting MPH given 3 times a day with MPH given 2 times a day and reported increased efficacy and satisfaction with no significant increase in stimulant side effects with the 3-dose regimen.[19] Thus, longer durations of treatment (ie, 10-12 hours) may be optimal for many youth with ADHD.

The landmark National Institute of Mental Health Multimodal Treatment Study of ADHD (MTA) demonstrated that a carefully titrated stimulant medication management regimen typically administered 3 times daily for core ADHD symptoms was superior to behavior modification alone or community-based interventions.[20,21] However, a contrast group of community providers treating youth with ADHD with stimulant medication were found to use lower dosages and less effective treatment regimens than the MTA medication management strategy, which emphasized robust doses, individual titration until significant benefit, and a duration of treatment that extended beyond the school day and weekends.[20,22,23] Thus, despite impressive efficacy data from controlled studies of short-acting stimulants, there was little evidence that empirically developed "best practices" for medication use were being translated to real-life practice settings.

In addition to stimulants, nonstimulant medications, such as the tricyclic antidepressants, have been extensively evaluated for ADHD.[24] However, because of an unfavorable side-effect profile and concerns about cardiotoxicity, their use for ADHD treatment has declined significantly despite their efficacy.[25] The clinical significance of cardiac risk of these agents to ADHD patients when properly monitored, however, remains controversial.[26]

Development of Long-acting Medications

Within the past few years, several second-generation, extended-release, long-acting stimulants have been developed and evaluated for treating youth with ADHD. The longest acting MPH-based stimulant, osmotic release oral system (OROS) MPH (Concerta), was designed to mimic MPH given 3 times daily.[27] Based on research by Swanson et al,[28] a unique osmotic delivery system with an overcoat of 22% immediate-release MPH was developed to provide increasing MPH concentrations over 6 to 8 hours with clinical effects up to 12 hours. Other long-acting stimulants were soon developed, including Metadate CD (MCD), ER MPH (Ritalin LA), and ER formulation of MAS (Adderall XR). MCD and ER MPH were designed to be similar in duration of effect to twice-daily MPH. MCD contains 30% immediate-release MPH and 70% MPH beads coated with a controlled-release polymer to deliver MPH gradually with clinical effects for a 6- to 8-hour period. Ritalin LA is composed of 50% immediate-release and 50% ER MPH beads to provide a second bolus. Adderall XR, the longest acting amphetamine preparation, is an ER formulation of a racemic mixture of dextro- and leve-isomers of amphetamine salts in a capsule containing microbeads released in 2 pulses, approximately 4 hours apart.[28-30]

Atomoxetine hydrochloride (Strattera) for ADHD is the first nonstimulant to receive an indication for ADHD from the US Food and Drug Administration. Atomoxetine is a selective noradrenergic agent, which was initially developed as an antidepressant. Although efficacy for treating adults with ADHD was first demonstrated in 1998,[31] several short- and intermediate-term efficacy and safety studies were subsequently conducted with children and adolescents with ADHD.[32] Although atomoxetine has a plasma half-life of approximately 4 hours, its clinical effects have been reported to last significantly longer when taken either once or twice daily.[33]

This review will describe what is known about these new agents, particularly the long-acting stimulants and nonstimulants as

compared with short-acting stimulants or placebo. This review searched for controlled studies of efficacy and safety of long-acting stimulant and nonstimulant medications. **Tables 1** through **3** contain summaries of recent studies with these medications.

Methylphenidate-based, Long-acting Medications

The efficacy of OROS MPH in reducing ADHD symptoms has been demonstrated in a multisite study,[34,35] 2 laboratory school settings,[25,28] and in a dose-response study.[36] The effects of OROS MPH were comparable to MPH given 3 times per day on both parent and teacher ratings of ADHD and oppositional defiant disorder (ODD) symptoms, on peer interaction, and on clinician-rated global efficacy.[27] In the Pelham study,[35] there was also a statistically significant difference between OROS MPH and MPH 3 times a day on parent ratings of Inattention/Overactivity and the Abbreviated Conners' scale, favoring OROS MPH. Moreover, slightly more of the parents preferred the week on OROS MPH relative to MPH 3 times a day (47% vs 31%). Because this study employed a "double-dummy" procedure, parent preference was not the result of increased convenience of once-a-day dosing. Further research is needed to identify the specific reasons for parent preference of OROS MPH over MPH 3 times a day (eg, increased or longer efficacy, fewer side effects, smoother wear-off effects).

The safety and efficacy of MCD was evaluated in a multisite study of 321 children aged 6 to 16 who were treated for 3 weeks with either MCD (20-60 mg) or placebo.[37] At the end of the study, 64% of those receiving MCD were moderately or markedly improved versus 27% of those receiving placebo using symptom ratings on the teacher version of the 10-item Conners' Global Index. Teacher ratings for mornings were similar to afternoons. Effect sizes were moderate for teacher ratings, but small to moderate for parent ratings, which is consistent with the duration of effect of approximately 8 hours. Subjects with more severe ADHD requiring longer duration of treatment were excluded. The most common adverse events in the MCD group were: appetite loss (47%), irritability (45%), trouble sleeping (32%), and listlessness, tired (31%), however, only decreased appetite was rated higher in the MCD versus the placebo group.

Two studies have compared fixed dosages of an intermediate- and long-acting MPH stimulant. A recent multisite study compared MCD with OROS MPH and placebo in a sample of 184 children who were previously taking MPH.[29] In general, the time course of response was related to predicted plasma concentrations of MPH. Thus, MCD, which delivers more MPH earlier than OROS MPH, was superior to OROS MPH in the morning but similar to OROS MPH in the afternoon. OROS MPH was associated with superior outcomes 12 hours postdose. Both active medications were superior to placebo at all time periods except immediately after dosing. There were no statistically significant differences in ratings of stimulant side effects and no severe adverse events. It is unclear how these findings based on fixed doses would translate to broader outcome measures in real-world settings, where the optimal dose is individually titrated until there is significant benefit with reduction in impairment.

In another study of 36 stimulant responders, ER MPH, which was designed to mimic twice-daily MPH, was compared with starting doses of OROS MPH (18 or 36 mg).[38] Children taking 18 or 36 mg of OROS MPH or 20 mg of ER MPH displayed more improvements in teacher ratings of sustained attention and in completed math problems than children taking placebo. In addition, during the first 4 hours of treatment, statistically significant differences favoring ER MPH over OROS MPH were reported in deportment, attention, and math problems completed correctly. Surprisingly, in this study no dose-response differences were reported between 18 and 36 mg of OROS MPH. In addition, the external validity of the study is limited because children were not titrated to optimal dose, and parent or teacher measures of ADHD symptoms, impairment, or satisfaction were not reported. Consequently, it is unclear how the measures obtained during the first 4 hours at fixed dosages generalize to clinical treatment where dosages are titrated until improvement occurs on multiple measures, including reduction in impairment.

Table 1. Methylphenidate-based Stimulants

Study	Subjects	Mean or Fixed-Dose Range	Active Comparator	Placebo	Results	Comments
Wolraich et al[34]	282, 6–12-year-olds with ADHD	34.3 mg OROS MPH	TID MPH (29.5 mg)	Yes	OROS MPH similar to TID in efficacy on core ADHD and ODD symptoms.	Sample contained both ADHD subtypes.
Pelham et al[35]	68, 6–12-year-olds	35 mg OROS MPH	TID MPH (29 mg)	Yes	OROS MPH, MPH TID>placebo in ADHD and ODD, OROS MPH>MPH on parent Abbreviated Conners' and Inattention/Overactivity.	OROS MPH similar or superior to TID in efficacy, similar in safety.
Swanson et al[23]	64, 8–12-year-olds	OROS MPH	TID MPH	Yes	OROS MPH similar to TID MPH on teacher ratings, parent ratings, and lab school measures. Minimal headache and stomachache were most common AEs.	All who entered trial were stimulant responders limiting extrapolations to stimulant-naive samples.
Stein et al[36]	47, 5–16-year-olds (70% stimulant naive)	18-54 mg OROS MPH	Dose response	Yes	Linear dose response for ADHD symptoms in ADHD combined type, insomnia and decreased appetite dose dependent.	Crossover study of dose response. 70% stimulant naive.
Greenhill et al[37]	321, 6–16-year-olds	4-7 mg/day MCD	No	Yes	MCD>placebo in reducing ADHD symptoms.	Sample selected for milder cases. Anorexia more common in MCD group.
Swanson et al[27]	184, 6–12-year-olds	20-60 mg MCD, 18-54 mg OROS MPH	OROS MPH vs ER MPH	Yes	MCD>OROS MPH >placebo in AM, MCD similar to OROS>placebo during afternoon; OROS>MCD in early evening. No difference in AEs.	All stimulant responders.
Biederman et al[30]	134, 6–14-year-olds	10-40 mg ER MPH	No	Yes	ER MPH>placebo on teacher and parent ADHD symptoms, 70% much or very much improved on ER MPH; 90% much or very much improved; placebo 60% much or very much improved.	Only stimulant responders participated in 2-week double-blind trial.

In a crossover study where 47 youth with ADHD were given placebo and 3 different OROS MPH dosages, Stein et al reported linear dose-response effects on ADHD symptoms and impairment with OROS MPH.[36] There was a difference between ADHD subtypes, with children with ADHD inattentive type responding better to lower doses than children with combined type who required higher dosage levels to achieve normalization. Normalization of ADHD symptoms occurred in half to two thirds of subjects. Using a questionnaire, stimulant side effects were found to be common, but generally mild. Of note, 70% of the sample was stimulant naive. The most frequent significant side effects were insomnia (9%-25%), decreased appetite (5%-27%), and irritability (5%-17%). Decreased appetite and reports of insomnia were more common at the higher dose levels.

A recent trend in ADHD treatment research is to identify more meaningful outcomes other than reductions in ADHD symptoms, such as quality-of-life measures or functional impairments, including family functioning.[39] Another important outcome for adolescents and young adults is developing driving skills, as individuals with ADHD are at increased risk for involvement in motor vehicle accidents and have poor driving records relative to individuals without ADHD.[40] A recent study of driving skills in adolescents with ADHD conducted on a driving stimulator demonstrated significant deterioration at 8:00 PM in 6 adolescents taking MPH 3 times a day versus OROS MPH taken once in the morning. This study suggests that OROS MPH may have a prolonged beneficial effect relative to MPH 3 times daily that extends well beyond the 12 hours OROS MPH is presumed to be effective.[41]

Amphetamine-based Stimulants

The short-term efficacy and safety of the ER formulation of MAS versus placebo was evaluated in a multicenter home and laboratory school study of 509 children.[42] More than 90% of the sample had ADHD combined type and 30% to 38% were treatment naive. Children were randomized to 3 weeks of placebo or 10, 20, or 30 mg of the ER formulation of MAS. Improvement was dose related based on late afternoon parent ratings of ADHD symptoms and morning and afternoon teacher ratings. Loss of appetite

Table 1. (continued) Methylphenidate-based Stimulants

Study	Subjects	Mean or Fixed-Dose Range	Active Comparator	Placebo	Results	Comments
Lopez et al[38]	36, 6–12-year-olds	20 mg ER MPH	Modified-release MPH vs OROS MPH; 18 or 36 mg OROS MPH	Yes	OROS (18 and 36 mg) and ER MPH, ER MPH> placebo, ER MPH> OROS MPH at 11 AM on attention and deportment ratings and arithmetic problems completed.	No titration or optimization of dose.
Cox et al[41]	6 males, aged 16-19	18-144 mg OROS MPH, 30-120 mg MPH	OROS vs TID MPH	No	Driving skills worsened in evening for MPH TID, OROS MPH associated with less variability throughout the day.	4/6 has inattentive subtype.

ADHD indicates attention-deficit/hyperactivity disorder; OROS, osmotic release oral system; MPH, methylphenidate (Concerta); TID, 3 times daily; ODD, oppositional defiant disorder; AEs, adverse events; MCD, long-acting methylphenidate (Metadate CD); ER MPH, extended-release methylphenidate (Ritalin LA).

Table 2. Amphetamine-based Stimulants

Study	Subjects	Mean or Fixed-Dose Range	Active Comparator	Placebo	Results	Comments
McCracken et al McGough et al	51, 6–12-year-olds	10, 20, 30 mg extended-release MAS	10 mg MAS	Yes	Dose-dependent induration for 20 and 30 mg. Substantial intersubject variability in response reported.	
Biederman et al[30]	509, 6–12-year-olds	10, 20, 30 mg extended-release MAS	Dose response	Yes	Dose-dependent improvement in AM and PM. AEs similar to MAS.	AEs occurred in 57% of those taking placebo and in 70.3% taking MAS salts (69% mild, 28% moderate, 4% severe). Anorexia was dose related.

MAS indicates mixed amphetamine salts; AEs, adverse events.
Sources: McCracken JT, et al. *J Am Acad Child Adolesc Psychiatry*. 2003;42:673-683; McGough JJ, et al. *J Am Acad Child Adolesc Psychiatry*. 2003;42:684-691.

(reported in 21.9%) was also dose related. Other adverse events more common in the active treatment group than the placebo group were: insomnia (16.6% vs 1.9%), abdominal pain (14.4% vs 9.5%), vomiting (7.2% vs 3.8%), and nervousness (5.6% vs 1.9%). Spontaneously reported adverse events occurred in 70% of those taking the ER formulation of MAS: 69% rated mild, 28% moderate, and 4% were rated severe.

In a laboratory school study of 51 children, 3 doses of the ER formulation of MAS were compared with placebo and with 10 mg of MAS. More than 90% of the sample was previous stimulant responders. Efficacy in reducing ADHD symptoms relative to placebo was dose dependent. Duration of effect was also related to dose, with 20- and 30-mg doses of the ER preparation associated with effects on classroom behavior and math test performance 10 to 12 hours after administration. Parents commonly reported adverse events, but were not judged to be serious and were described as comparable with side effects seen with MAS. The most common adverse events were nervousness (42%-56%), insomnia (12%-32%), anxiety (12%-27%), emotional lability (12%-27%), and loss of appetite (27%-55%). In this 5-week study, duration of effect, efficacy in reducing ADHD symptoms, and loss of appetite were dose dependent.

Nonstimulants

Several studies of atomoxetine clearly demonstrate short-term efficacy relative to placebo in reducing both inattentive and hyperactive/impulsive ADHD symptoms and improving family and social functioning.[33,43,44] The effect sizes of atomoxetine treatment versus placebo were similar for dosing once or twice daily.[32] Controlled studies suggest that atomoxetine is generally well tolerated in youth with ADHD with few spontaneously reported adverse events. In 2 studies of children and adolescents, loss of appetite occurred more often in those treated with atomoxetine versus those treated with placebo.[44]

Only one published study was found comparing atomoxetine to a stimulant medication. A preliminary, 9-week, open-label study was reported by Kratochvil and colleagues.[45] Both atomoxetine and MPH were associated with reductions in ADHD symptoms and improved global ratings in children

Table 3. Nonstimulants

Study	Subjects	Mean or Fixed-Dose Range	Active Comparator	Placebo	Results	Comments
Michelson et al[43]	297, 8–18-year-olds	1.5, 1.2, 1.8 mg/kg/day	Dose response	Yes	Graded dose-response relationship with ADHD symptoms and social and family functioning, with 1.2-mg/kg dose as effective as 1.8 on ADHD symptoms. All doses well tolerated.	70% of sample previously treated with stimulants.
Spencer et al[44]	Total of 291, 7–13-year-olds for 2 studies	1.5-1.7 mg/kg/day atomoxetine, < 60 mg/day for MPH group	No	Yes	Atomoxetine resulted in improvement in ADHD symptoms vs placebo (eg, 64% vs 25%). Both inattention and hyperactivity reduced. Well tolerated.	No direct comparisons with MPH group, wasn't adequately powered and analysis not included. MPH administered 2 times daily.
Kratochvil et al[45]	228 children, boys aged 7-15, girls aged 7-9 (44 in MPH group)	For extensive metabolizers, 1.4 mg/kg/day atomoxetine, 0.48 for poor metabolizers	31.3 mg/day MPH	No	Both treatments were effective in reducing ADHD symptoms and well tolerated. Vomiting, somnolence, and weight loss occurred more often in the atomoxetine group.	Open-label study, MPH was administered either 2 or 3 times daily, 43% of MPH subjects withdrew early from study vs 36% in atomoxetine group.

ADHD indicates attention-deficit/hyperactivity disorder; MPH, methylphenidate.

aged 7 to 15, according to parent and clinician ratings. Atomoxetine (administered twice daily) and MPH (administered either 2 or 3 times daily) were both well tolerated, with vomiting, insomnia, and weight loss reported more often for the group receiving atomoxetine. Clinical implications of the study are quite limited, however, because of the open-label nature of the study, the lack of objective or blinded assessment of ADHD symptoms, and differential attrition between treatment groups. In addition, it is unclear if children in the MPH arm were receiving optimal MPH treatment, as the dose and dosing regimen (eg, 2 vs 3 times daily) were not standardized or reported.

Summary and Discussion

The landscape of ADHD treatment has changed significantly over the past few years and since the MTA study. Long-acting, often once-a-day medications have largely replaced the short-acting stimulants as the most common pharmacological treatment for children and adolescents because of their significant clinical utility. For an often long-term disorder such as ADHD, long-acting medications provide increased conven-

ience, less embarrassment because of home versus school administration, and represent an easier therapeutic regimen for individuals, schools, and families than treatments that require multiple doses throughout the day. With administration and supervision at home, there is also less concern about potential diversion or stimulant abuse.

A variety of available medications provide different durations of effects and increased flexibility in customizing the treatment to fit the patient. Early studies have established the duration of medication effects on ADHD symptoms, short-term efficacy and safety, and dose-response effects. MPH-based treatments and atomoxetine have been the most studied of the new treatments. In general, studies of long-acting stimulants in childhood ADHD uniformly demonstrated equivalence in efficacy and side effects to short-acting stimulants administered 2 to 3 times per day with increased preference and adherence. In addition to reducing ADHD symptoms, stimulant medications also reduce symptoms of ODD.[23,35,46]

Because of their safety record, stimulants have few absolute contraindications for treatment of ADHD, which presents with a wide range of comorbid psychiatric and neurological disorders.[47] According to the American Academy of Child and Adolescent Psychiatry most recent practice parameters,[48] contraindications for stimulants include: individuals with a previous sensitivity to stimulant medications, glaucoma, symptomatic cardiovascular disease, hyperthyroidism, hypertension, or active psychotic disorder. Recent studies suggest that individuals with a variety of conditions previously assumed to be contraindications can be successfully treated with stimulants, including individuals with comorbid seizure disorders,[49] tics and Tourette's syndrome,[9,50,51] and manic[52] or anxiety symptoms.[46] Use in individuals or families with comorbid substance disorders requires considerable caution and safeguards and remains controversial.

Adverse events associated with long-acting MPH and amphetamine-based stimulants appear to be comparable in severity and prevalence with that of short-acting MPH and amphetamine-based stimulants. However, it should be noted, that with the exception of the Stein et al study,[36] most study samples have consisted primarily of stimulant responders. Thus, the absolute rates of adverse events or side effects may be an underestimate when applied to nonselected clinical populations. A second issue is whether there are differences in specific side effects between MPH and amphetamine-based stimulants. Stimulant side effects are highly correlated with treatment adherence.[53] Although there is some anecdotal evidence of differential response[54] (eg, several treatment reviews),[55,56] well-controlled, adequately powered comparator studies using clinically relevant dosages are needed to inform clinical practice, in addition to studies of moderators and mediators of response, and longer-term safety studies. Nonetheless, it is reassuring that to date adverse events have been generally mild and no new side effects have been associated with the longer-acting stimulants. In the majority of cases, side effects associated with long-acting stimulants and atomoxetine are not severe and respond to dose adjustments or alternative medications.

Atomoxetine, with its different mechanism of action, is associated with a slightly different side-effect profile than stimulant medications, particularly increased somnolence and gastrointestinal symptoms in children. For individuals at risk of stimulant abuse,[57] or who display stimulant-related side effects, which are not transitory, or insignificant (eg, severe stimulant-induced insomnia or tics), atomoxetine and other nonstimulants provide a welcome alternative. Ongoing research is being conducted to determine if there are distinct clinical subgroups that respond optimally to atomoxetine (eg, ADHD and tics, or ADHD and insomnia). It should be noted that efficacy and safety data are not available for children under age 6.

Currently, the field is in great need of effectiveness studies using active comparators with state-of-the-art treatments to evaluate differential effects that would assist clinicians and families in making the best treatment decisions. The relevance of future treatment studies can be enhanced by measuring a range of functional outcomes relevant to the impairments displayed by individuals with ADHD in their daily living, social, educational, and vocational function-

ing. Although the studies reviewed to date suggest considerable promise, more clinically relevant treatment studies are needed that address the relative efficacy, safety, and palatability of these new agents. These studies should evaluate effects over longer time periods (vs acute effects), and should use unselected or treatment-naive samples (rather than selecting responders). Treatments should use clinically effective doses (rather than fixed or starter doses), and multiple measures of ADHD symptoms, associated problems, impairment, consumer satisfaction, and cost should be obtained.

The outlook for individuals with ADHD has never been better, in large part because of increased awareness of ADHD and the clinical utility of the long-acting medications. It is hoped that use of these agents will reduce the risk of cumulative social and academic impairments associated with untreated or undertreated ADHD relative to the short-acting treatments. Finally, there may be unique advantages to the longer-acting medications that have not been identified yet, as suggested by increased parent satisfaction with long-acting stimulants when double-dummy procedures are used.

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