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REVIEW

# Sustained treatment effect in attention-deficit/hyperactivity disorder: focus on long-term placebo-controlled randomized maintenance withdrawal and open-label studies



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**Abstract:** Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that often persists throughout life. Approximately two-thirds of patients with a childhood diagnosis of ADHD continue to experience clinically significant symptoms into adulthood. Nevertheless, most of these individuals consider themselves "well," and a vast majority discontinue medication treatment during adolescence. As evidence concerning the adult presentation of ADHD becomes more widely accepted, increasing numbers of physicians and patients will face decisions about the benefits and risks of continuing ADHD treatment. The risks associated with psychostimulant pharmacotherapy, including abuse, dependence, and cardiovascular events, are well understood. Multiple clinical trials demonstrate the efficacy of psychostimulants in controlling ADHD symptoms in the short term. Recent investigations using randomized withdrawal designs now provide evidence of a clinically significant benefit with continued long-term ADHD pharmacotherapy and provide insight into the negative consequences associated with discontinuation. Because many patients lack insight regarding their ADHD symptoms and impairments, they may place a low value on maintaining treatment. Nevertheless, for patients who choose to discontinue treatment, physicians can remain a source of support and schedule follow-up appointments to reassess patient status. Medication discontinuation can be used as an opportunity to help patients recognize their most impairing symptoms, learn and implement behavioral strategies to cope with ADHD symptoms, and understand when additional supportive resources and the resumption of medication management may be necessary.

**Keywords:** psychostimulant, nonstimulant, adult, child

## Introduction

In the United States, an estimated 4.4% of adults meet diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD).[1] The prevalence of syndromic ADHD is estimated to be lower (between 2.8% and 3.3%) in elderly adults aged 60 years and older from countries in the European Union.[2,3] Among adults who received a diagnosis of ADHD in childhood, approximately 65% continued to experience significant ADHD symptoms and functional impairments, although persistence estimates vary widely.[4–6] Also, recent findings suggest that, in addition to those who continue to meet full diagnostic criteria for ADHD, a number of adults display persistence of a subset of ADHD symptoms. They continue to experience substantial functional deficits associated with those symptoms.[7] The factors that determine ADHD persistence are under active investigation. Recent studies suggest that a childhood ADHD symptom profile, along

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with psychiatric comorbidity, may be predictive of ADHD persistence. This profile includes predominant inattentive symptoms; more severe symptoms during childhood; and the presence of psychiatric comorbidities, executive function deficits, and some maternal psychopathologies.[5,8,9]

The behavioral pathology of ADHD is associated with abnormalities in neuroanatomy and neurophysiology in both children and adults.[10–15] ADHD appears to be a highly heritable disorder marked by the presence of familial neuropathologic patterns and specific genetic polymorphisms associated with ADHD pathology.[16–22] Neuroimaging studies of individuals with ADHD have also identified delayed neurodevelopment, volumetric differences in specific brain areas, and differences in neural activation for tasks when compared to those without ADHD.[23,24] Although some of these abnormalities may lessen or resolve as the brain matures, other central neurologic abnormalities persist in adulthood. The functional implications of persistent neurologic abnormalities have not been clearly defined. However, compared with normal controls, cognitive deficits in untreated adults with ADHD appear to persist throughout life.[25]

ADHD, across the lifespan, is marked by varying degrees of hyperactivity, impulsivity, and attentional symptoms across settings.[14] Patients may also exhibit poor emotional control and motivational problems.[15] Recommended first-line pharmacotherapy for ADHD in children and adults includes psychostimulants such as methylphenidate and amphetamines, as well as nonstimulant medications such as atomoxetine.[6,26–28] The nonstimulants guanfacine extended-release and clonidine extended-release are US Food and Drug Administration-approved for the treatment of ADHD in children and adolescents.[29]

## Need for a long-term approach to adult ADHD management

In the past, ADHD treatment was often routinely discontinued during adolescence; it was unclear whether older patients still exhibited clinically significant symptoms or functional impairments. Moreover, it was uncertain if older patients derived benefits from continued treatment. However, the medical community is now better aware of the changing clinical presentation of ADHD through life transitions and of the need for a longitudinal, developmental approach toward ADHD detection, reassessment, and management.[30] During childhood, ADHD can be readily identified by marked overt physical hyperactivity and impulsivity, especially in boys, whereas inattention was often overlooked; in adulthood, such hyperactivity and impulsivity wane and may be internalized as restlessness or impatience, although inattentiveness and disorganization persist and may become the predominant impairing symptoms.[31,32] Moreover, with time, ADHD symptoms and impairments take on a progressively more distinct adult presentation.[32–35] Impulsivity may be evidenced by sexual promiscuity, financial problems, high job turnover, and/or a short temper; inattention may be evidenced by a high number of traffic citations/accidents, disorganization, chronic tardiness, difficulty finishing projects, forgetfulness, and/or procrastination. Hyperactivity in adults may be experienced as an internal feeling of restlessness or being on edge and expressed outwardly through fidgeting or an inability to sit for long periods of time. Many patients may fail to associate these behaviors with ADHD and may instead consider them to be character traits or part of their personality. Such patients may consider themselves "well" because their childhood symptoms (the reduction of hyperactivity) seem to have resolved; therefore, these patients often discontinue treatment during the transition from adolescence to young adulthood.[36]

Persisting symptoms in adults with ADHD, although less evident than those in childhood, are associated with relatively greater functional impairments.[32] Older adolescents and adults who do not receive treatment for ADHD may suffer lasting consequences related to uncontrolled symptoms and impaired functioning (eg, low occupational/educational attainment, arrest, unintended pregnancy, sexually transmitted diseases, marital problems, and injury).[37] Possibly associated with such functional impairments, the development of certain psychiatric comorbidities (ie, conduct disorders or depression) may also exacerbate poor ADHD symptom control.[38,39]

The socioeconomic and personal burdens of ADHD experienced by patients, their families, and the community may be mitigated through appropriate long-term treatment.[40–42] In addition, in a published systematic review of outcomes, increased substance use disorders or suicidality, compared to untreated ADHD, were not seen with long-term treatment.[42] Some evidence suggests that, aside from reductions in core ADHD symptoms, quality of life may be improved with pharmacotherapy.[43] Although treatment may not "normalize" functioning to the level seen in non-ADHD individuals,[42] large numbers of observational studies worldwide suggest that maintained ADHD treatment over time tends to have a significant beneficial impact on aspects of a patient's life, including driving, obesity, self-esteem, social functioning, and academic performance when compared to individuals with untreated ADHD.[42,44,45] Thus, it is reasonable to examine

how the need to continue therapy can be assessed, weighing relative risks and benefits. These risks and benefits include a balance between the economic impact of long-term pharmacotherapy weighed against the potential for lower occupational attainment and wages, potential increased legal and insurance costs, and overall quality of life for patients and family members.

## Investigating treatment maintenance and long-term efficacy

Because ADHD persists into adulthood in about two-thirds of patients who have a childhood diagnosis and is associated with significant functional impairments, it would seem that long-term treatment maintenance is necessary and – as evidence shows in many cases – beneficial. In about one-third of these patients, persistent ADHD symptoms may not meet current diagnostic thresholds.[5] As with any pharmacotherapy, medications indicated for ADHD are associated with certain risks. In the case of psychostimulants, these include abuse, misuse, addiction, diversion, cardiovascular safety risks such as elevated blood pressure and rare but life-threatening events/cardiac problems (ie, sudden death, myocardial infarction, and stroke); with long-term use, decreases in height and weight have also been a concern with pediatric patients.[46–48] However, there is a lack of high-quality evidence from controlled trials in adults regarding the possible benefits of long-term treatment or the consequences of treatment discontinuation.[49]

Randomized, controlled clinical trials in subjects with ADHD have been conducted in children and have been short-term. Most long-term ADHD treatment trials have been observational and open-label in nature (Table 1).[50–64] Open-label trials are valuable because they often approximate real-world clinical practice, marked by flexible dosing, to address changes in efficacy or treatment tolerability. In all available open-label trials with durations of 1 year or more, a high level of symptom control has been observed throughout the entire study period, in some cases extending up to 24 months (Table 1). Open-label evidence, however, does not rigorously demonstrate maintained treatment efficacy or the consequences of treatment discontinuation.

There is a need to more thoroughly examine the value of long-term ADHD pharmacotherapy to support the more widespread use of a lifelong care management approach toward ADHD. Because there are well-established, effective treatments available for ADHD, it is considered unethical to randomly assign subjects to long-term placebo treatment. Adequate subject retention in long-term trials is also problematic. The randomized withdrawal study design is one research approach aimed at addressing these challenges. This design has been used to rigorously investigate the value of continued treatment in other lifelong illnesses, such as major depressive disorder[65] and psoriasis.[66] For withdrawal trials, subjects with a clinically significant response to active treatment in a prolonged lead-in phase are randomly assigned to double-blind treatment with a placebo or continued active treatment (Figure 1). For ethical reasons, subjects randomized to a placebo who exhibit significant symptom recurrence and impairments are discontinued from the study and given the opportunity to re-establish active treatment. In this manner, the value of continued treatment may be established; effective treatment is not withheld for an extended period of time. Randomized withdrawal studies can be used to examine maintenance of response, but it should be noted that they do not describe efficacy versus placebos.

## Long-term treatment effectiveness in ADHD

A small number of randomized, placebo-controlled withdrawal trials have examined the maintenance of efficacy in adults with ADHD (Table 2).[67–70] These investigations add to the literature by examining the duration, extent, and nature of symptom control that remain when active treatment is continued compared to when it is discontinued. For these trials, investigators examined ADHD symptom ratings and classroom behaviors[69] or rates and time to ADHD symptom relapse or loss of response, defined as a deterioration of $\geq 2$ points on the Clinical Global Impressions-Improvement (CGI-I) scale and a 50%–90% decline in ADHD symptoms from baseline.[67,68,70]

In the earliest of these trials, Nolan et al examined the impact of randomized medication discontinuation in a small sample of children (aged 6–18 years, n = 19) with ADHD and comorbid chronic tic disorder or Tourette disorder.[69] All subjects were on a stable psychostimulant regimen for at least 1 year prior to enrollment (n = 17 on methylphenidate; n = 2 on dextroamphetamine). Using a two-period crossover design, each subject experienced a randomized, double-blind placebo treatment for 2 weeks and double-blind, continued active treatment for 2 weeks. Analysis of 4-week withdrawal-phase data showed a significant advantage of continued medication treatment compared with a placebo based on all ADHD symptom ratings with mean (SD) Child Symptom Inventory-3R scores of 10.5 (9.7) and 5.5 (6.4) for placebos and active treatment ($P = 0.0004$), respectively. Core ADHD symptoms and aggression by Mother's Method for

**Table 1** Long-term, open-label investigations of ADHD pharmacotherapy

| Author | Design | Subjects (n) | Treatment | Duration | Outcomes |
|---|---|---|---|---|---|
| **MPH** | | | | | |
| Wilens et al[50] | Long-term open-label study | Children aged 6–9 and 10–13 years (n = 407) | OROS MPH 18, 36, 54 mg/day | 24 months | Treatment rated "good" or "excellent" Parents/caregivers: 85% Physicians: 92% |
| Adler et al[51] | Open-label, dose-titration, flexible-dose study | Adults aged 18–65 years (n = 521; responders, n = 383) | OROS MPH 36, 54, 72, 90, 108 mg/day | 6–12 months | Mean decrease in AISRS total score: −18.7 |
| **MAS** | | | | | |
| Biederman et al[52] | Open-label extension study | Adults aged ≥ 18 years (n = 223) | MAS-XR 20, 40, 60 mg/day | 24 months | Mean decrease in ADHD-RS-IV total score: −5.7 for MAS-XR continuous subjects; −11.6 for MAS-XR-naïve subjects ($P < 0.001$ for both) |
| Goodman et al[62] | Open-label, flexible-dose study | Adults aged ≥ 18 years (n = 702) | MAS-XR 10 to 60 mg/day | Core 10-week phase; 20-week extension phase | Mean decreases in ADHD-RS-IV total score ranged from 18.8–21.6 for ITT and prior treatment subgroups ($P < 0.0001$ for all) |
| **LDX** | | | | | |
| Findling et al[53] | Open-label single-arm study | Children aged 6–12 years (n = 272) | LDX 30, 50, 70 mg/day | 12 months | Mean decrease in ADHD-RS-IV total score (ITT): −27.2 ($P < 0.0001$) |
| Weisler et al[54] | Open-label, single-arm study | Adults aged 18–55 years (n = 349) | LDX 30, 50, 70 mg/day Treated, n = 297 Placebo, n = 52 | 12 months | Mean decrease in ADHD-RS-IV total score: −24.8 ($P < 0.0001$) |
| Mattingly et al[55] | Open-label, single-arm study | Adults aged 18–55 years (n = 349) | LDX 30, 50, 70 mg/day Treated, n = 297 Placebo, n = 52 | 12 months | Mean decrease in ADHD-RS-IV total score: 30 mg, −16.2; 50 mg, −17.4; 70 mg, −18.6 ($P < 0.0001$) |
| Findling et al[56] | Open-label extension study | ADHD in children aged 13–17 years (n = 265) | LDX 30, 50, 70 mg/day | 52 weeks | Mean decrease in ADHD-RS-IV total score: −26.2 ($P < 0.001$) |
| **ATX** | | | | | |
| Adler et al[57,63] | Open-label extension study | ADHD in adults Study I: (n = 280) Study II: (n = 256) | ATX 25, 40, 60 mg/twice a day Study I: 141 treated 139 placebo Study II: 129 treated 127 placebo | 97 weeks | Mean decrease in CAARS-Inv; total score: −8.8 ($P < 0.001$) |
| Kratochvil et al[58] | Meta-analysis | Children aged 6 and 7 years (n = 272) | ATX 60, 90, 120 mg/day | ≥ 24 months | Mean decrease in ADHD-RS-IV total score: −19.3 ($P < 0.001$) |
| Wilens et al[59] | Meta-analysis | Children aged 6–16 years (n = 601) | ATX Target: 1.2 mg/kg/day Maximum: 1.8 mg/kg/day | Up to 24 months | Mean decrease in ADHD-RS-IV total score: −20.2 ($P < 0.001$) |
| **GXR** | | | | | |
| Sallee et al[60] | Open-label study | Children aged 6–17 years (n = 272) | GXR 1, 2, 3, 4 mg/day alone/with psychostimulant | 24 months | Mean decrease in ADHD-RS-IV total score: −20.1 ($P < 0.001$) |
| Biederman et al[64] | Open-label extension study | Children aged 6–17 years (n = 240) | GXR 2 mg/day | 24 months | Mean decrease ADHD-RS-IV total score: −18.1 ($P < 0.001$) |
| Rubin et al[61] | Open-label extension study | Children aged 6–17 years (n = 54) | GXR up to 4 mg/day with psychostimulant | 24 months | Mean decrease in ADHD-RS-IV total score: −16.1 ($P < 0.001$) |

**Abbreviations:** ADHD, attention-deficit /hyperactivity disorder; AISRS, ADHD Investigator Symptom Report Scale; ADHD-RS-IV, ADHD Rating Scale IV; ATX, atomoxetine; CAARS-Inv, Conners' Adult ADHD Rating Scale: Investigator-Rated; GXR, guanfacine extended-release; ITT, intention to treat; LDX, lisdexamfetamine dimesylate; MAS, mixed amphetamine salts; MPH, methylphenidate; OROS, osmotic release oral system; XR, extended release.

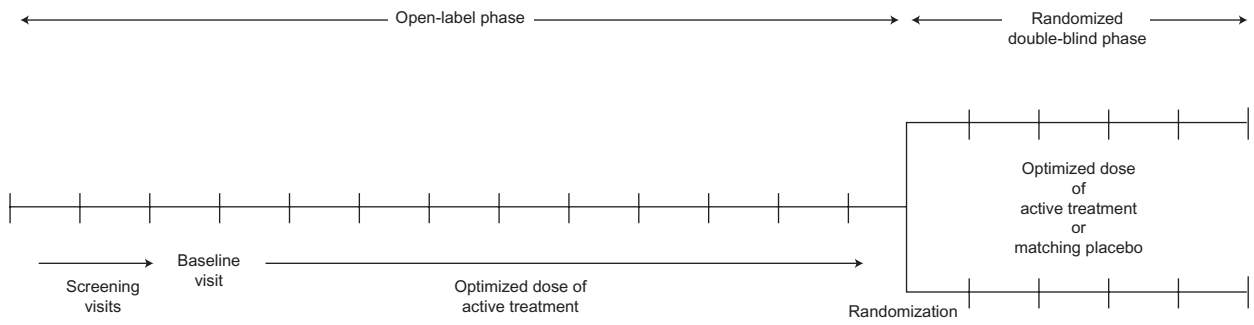


**Figure 1** Hypothetical schematic study design.



Subgrouping (MOMS) and continuous performance tests, as well as observed simulated classroom behaviors such as time on task and worksheet completion, also demonstrated significant advantages for continued treatment.[69]

In another randomized withdrawal trial,[68] children (aged 6–15 years; n = 416) with ADHD who showed adequate clinical response to the nonstimulant atomoxetine were re-randomized to continued active treatment or a placebo after 12 weeks. At the 9-month study endpoint, 22.3% of subjects who continued with atomoxetine exhibited relapse (defined as symptom return ≥ 90% of baseline in ADHD Rating Scale (ADHD-RS) total scores and ≥ 2 points on the CGI-Severity [CGI-S] scale) compared to 37.9% of those given a placebo ($P = 0.002$). A Kaplan–Meier analysis further showed that subjects switched to a placebo relapsed in a significantly shorter time than subjects who continued with atomoxetine (Figure 2).[68] Of note was the significant worsening of psychosocial functioning detected among subjects randomized to a placebo, based on the Child Health Questionnaire.

In a more recent trial, Biederman et al[67] conducted a three-phase investigation of methylphenidate (MPH) delivered via an osmotic-release oral system (OROS®, Alzo Corporation, Mountain View, CA, USA) in adults (aged 19–60 years; n = 223) with ADHD. For the first phase, subjects were randomized to receive either a placebo or clinically optimized doses of OROS MPH for 6 weeks. Subjects who showed an adequate therapeutic response in the first phase (CGI-I of much or very much improved [ie, ratings of 1 or 2] and a reduction in ADHD Investigator Symptom Report Scale [AISRS] score > 30%) were then eligible to continue on to the second phase, in which Phase I treatment (OROS MPH or a placebo) was continued in double-blind fashion for an additional 24 weeks. In Phase III, OROS MPH responders were either re-randomized to a placebo or continued on OROS MPH for 4 weeks; placebo responders were not re-randomized. Figure 3 shows mean AISRS scores for the OROS MPH and placebo groups throughout each phase of the trial.[67] During the randomized withdrawal phase (ie, Phase III), subjects who were re-randomized to a placebo

**Table 2** Maintenance of efficacy: randomized withdrawal investigations of ADHD pharmacotherapy

| Author | Subjects | Treatment | Duration | Outcome |
|---|---|---|---|---|
| Nolan et al[69] | Children aged 6–18 years with ADHD and a tic or Tourette disorder (n = 19) | Immediate-release MPH, dextroamphetamine, or placebo | 2 weeks open-label, 4-week RW | ADHD symptom worsening with placebo ($P < 0.0004$) |
| Michelson et al[68] | Children aged 6–15 years (n = 416) | ATX Target dose: 1.2 mg/kg/day (max: 1.8 mg/kg/day) | 12 weeks open-label, 9-month RW | Relapse ATX: 22.3% Placebo: 37.9% ($P = 0.002$) |
| Biederman et al[67] | Adults aged 19–60 years (n = 223) | OROS MPH Weighted dosing (max 1.3 mg/kg/day) | 6 weeks double-blind efficacy, 24 weeks double-blind continuation, 4-week RW | Relapse OROS MPH: 0% Placebo: 18% (ns) |
| Brams et al[70] | Adults aged 18–55 years (n = 116) | LDX (30, 50, 70 mg/day) or placebo | 3 weeks open treatment, 6-week RW | Relapse LDX: 8.9% Placebo: 75% ($P < 0.0001$) |

**Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; ATX, atomoxetine; LDX, lisdexamfetamine dimesylate; MPH, methylphenidate; ns, not significant; OROS, osmotic release oral system; RW, randomized withdrawal.

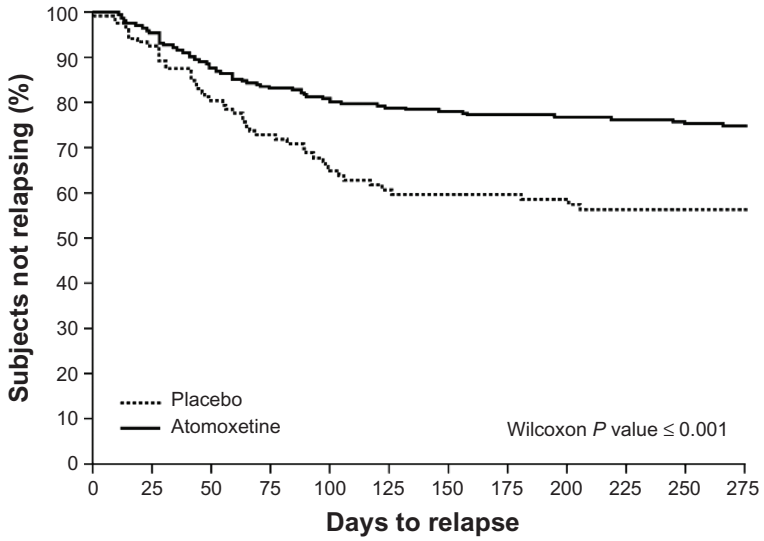


**Figure 2** Time to ADHD relapse with atomoxetine versus a placebo.
**Notes:** Proportion of subjects meeting relapse criteria (≥ 90% of baseline ADHD-RS-IV total score and CGI-S increase ≥ 2) for atomoxetine group compared with placebo group based on Kaplan–Meier analysis. Reprinted from *J Am Acad Child Adolesc Psychiatry*, 43(7), Michelson D, Buitelaar JK, Danckaerts M, et al, Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomized, double-blind, placebo-controlled study, pages 896–904, Copyright 2004, with permission from the American Academy of Child and Adolescent Psychiatry.[68]
**Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale IV; CGI-S, Clinical Global Impressions-Severity.

showed a gradual small worsening of ADHD symptoms, but these symptoms did not return to baseline severity, whereas subjects who continued with OROS MPH showed a small improvement. No significant changes in AISRS scores were seen during double-blind withdrawal. The investigators noted that a robust therapeutic response among subjects treated with a placebo was indistinguishable from the responses among subjects given OROS MPH.

No significant difference in relapse rate (defined as a deterioration in CGI-I rating of ≤ 2 points or an AISRS improvement < 15% from baseline) was detected between the subjects who continued active treatment (0%) versus those who were discontinued (18%). Biederman et al propose that, with up to 30 weeks' treatment with OROS MPH, ADHD symptom control may have allowed subjects to develop more effective, adaptive coping skills.[67]

In the most recently published randomized withdrawal study, Brams et al enrolled adults (aged 18–55 years; n = 116) with ADHD who had been receiving a stable dose of lisdexamfetamine dimesylate (LDX) (30, 50, or 70 mg/day) in a community setting for at least 6 months with an acceptable safety profile.[70] During the first study phase, all subjects received their usual prestudy doses of LDX for 3 weeks. All subjects were then randomized for 6 weeks to receive either a placebo

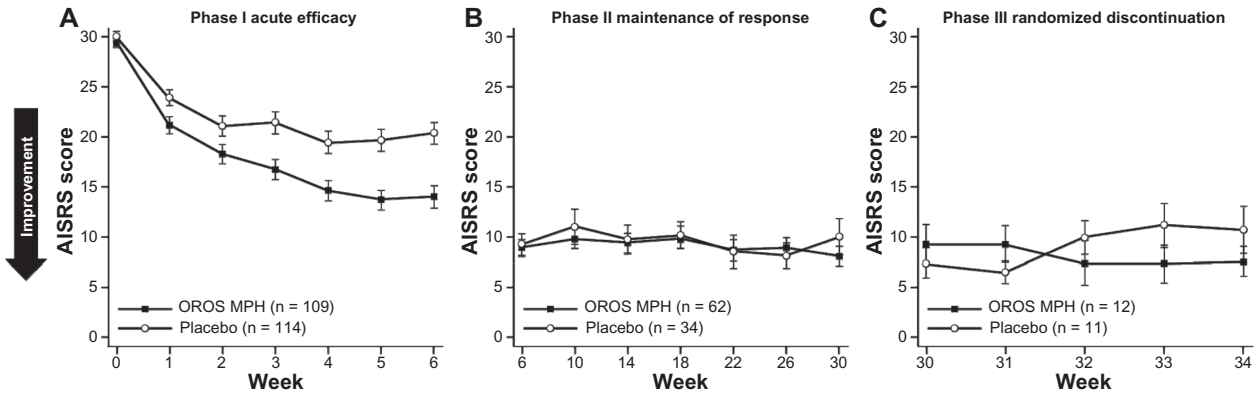


**Figure 3** ADHD symptom scores during acute treatment, maintenance, and randomized withdrawal phases.
**Note:** Mean AISRS scores by week for each phase of the study. Bars represent the standard error of the mean at each time point. Adapted with permission from Biederman J, Mick E, Surman C, et al, A randomized, 3-phase, 34-week, double-blind, long-term efficacy study of osmotic-release oral system–methylphenidate in adults with attention-deficit/hyperactivity disorder, *J Clin Psychopharmacol*, 30(5), 549–553.[67]
**Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; AISRS, ADHD Investigator Symptom Report Scale; MPH, methylphenidate; OROS, osmotic release oral system.

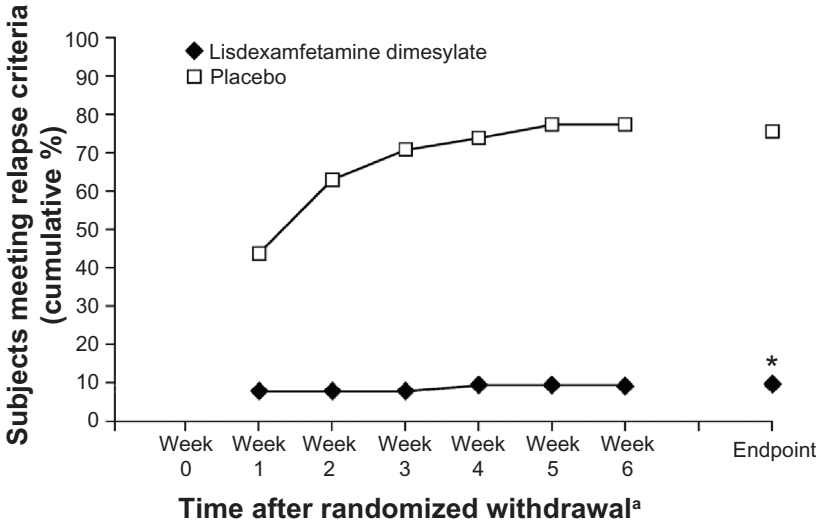


**Figure 4** Percentage of subjects exhibiting relapse with lisdexamfetamine dimesylate or placebo.
**Notes:** Percentage of adult subjects with ADHD meeting relapse criteria (≥ 50% increase in ADHD-RS-IV total score and ≥ 2 point increase in CGI-S rating) during a 6-week randomized withdrawal phase. [a]Weeks after randomized withdrawal, weeks 1 to 6, are analogous to weeks 4 to 9 of the overall study scheme. *$P < 0.0001$ lisdexamfetamine dimesylate versus placebo. Brams M, Weisler R, Findling RL, et al. Maintenance of efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: randomized withdrawal design. *The Journal of Clinical Psychiatry*. 7:977–983, 2012.[70] Copyright 2012. Physicians Postgraduate Press. Reprinted by permission.
**Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale IV; CGI-S, Clinical Global Impressions-Severity.



or the same dose of LDX as that given in the open-label phase. At the endpoint of the open-label treatment period, nearly all subjects were rated as not at all or mildly ill based on the CGI-S scale. During the randomized withdrawal phase, symptom relapse (defined as ≥ 50% increase in ADHD-RS-IV score and an increase in CGI-S rating ≥ 2, indicating deterioration of symptom control) was seen in 8.9% of subjects who continued on LDX, compared with 75% of subjects assigned a placebo ($P < 0.0001$) (Figure 4).[70] For subjects maintained on LDX, least squares (LS) mean changes in ADHD-RS-IV scores from baseline of the randomized withdrawal phase to the endpoint showed only a small change (+1.6 points), compared to larger changes in the placebo group (+16.8 points).[70]

## Conclusion and summary

Despite clear evidence that approximately two-thirds of adults with a childhood ADHD diagnosis continue to experience persistent symptoms and functional impairments, many older adolescent and adult patients believe they are "well" and do not adhere to treatment over the long term. Patients, family members, and some physicians who believe the patient is "well enough" may consider the use of medication to treat ADHD as "unnecessary" due to safety concerns. "Well enough" needs to be operationally defined by the patient and physician. Patients who lack insight into the presence of symptoms may agree that they are still underachieving at school, at their job, and at home even while denying ongoing ADHD symptoms. A growing body of evidence from high-quality clinical trials demonstrates that many patients with ADHD continue to benefit from long-term therapy, whereas discontinuation is often accompanied by a return of symptoms. Continued clinical investigation is needed regarding factors that affect the risk of symptom relapse on discontinuation of pharmacotherapy. Findings will assist clinicians and patients in considering the balance of potential risks and benefits.

Long-term consistent use of medication may increase a patient's awareness of ADHD impairments independent of the symptoms experienced. When symptom insight is lacking, daily underachievement may encourage the development of effective compensatory skills that persist after medication is stopped.[67] On a clinical note, patients may be aware of their symptoms and the resulting daily impairments. These patients may readily adopt behavioral skills to compensate. Patients who have little insight into their ADHD symptoms may acknowledge daily underachievement and be receptive to behavioral techniques. When patients have little insight into their ADHD symptoms and deny daily underachievement, pharmacologic and behavioral treatments are often rejected. Identifying which of these three categories a patient falls into will help a physician determine the best approach when discussing treatment options. Ultimately the discontinuation of medication is likely to lead to a fairly rapid recurrence of the symptoms and worsening of the functional impairments of the disorder. Brams et al demonstrated that, when physicians

and patients discontinue medication, follow-up visits within the first few weeks may allow the physician and patient to assess the return of symptoms.[70] Such an assessment will allow the physician to understand the degree of insight the patient has gained about changing ADHD symptoms and daily productivity, and may also enhance long-term management of the disorder.

Given that ADHD symptoms – particularly hyperactivity/impulsivity symptoms – tend to decrease with age in adolescents and young adults,[71] and also based on clinical experience, some patients may be able to successfully discontinue ADHD pharmacotherapy. Brief drug holidays under clinician supervision may help patients become more aware of their symptoms and functioning when they are on medication compared to when they are off. The odds of these holidays being successful may also be increased by timing the discontinuation of medication. A period when environmental demands are reduced or when patients may have increased support from a spouse or family member may limit the impact of ADHD-impaired functioning. Conversely, a patient's request to discontinue medication during environmentally demanding times is very likely to result in a severe escalation of ADHD impairments and should be delayed for "quieter" times.

It is important for clinicians to discuss the risks/benefits of discontinuing medication with their patients who have ADHD and highlight important symptoms and impairments that should be monitored following discontinuation. However, if the patient wishes to stop medication for reassessment or as an act of asserting control over treatment, the physician needs to remain supportive so as to maintain the therapeutic relationship and not discourage patients' active participation in managing their health care plan. Performing adequate follow-up allows clinicians to act as a resource upon which patients can rely should they experience a setback or have questions. Encouraging those patients already engaged in psychotherapy or behavioral therapy to continue that form of treatment may help them develop insight into their symptoms and learn behavioral strategies to manage impairments. In addition, participation in therapy may allow patients to see the strengths and limitations of behavioral techniques. If follow-up assessment indicates the return of symptoms or impairments, physicians should facilitate the discussion of resuming treatment. If the patient has not relapsed, it is important to discuss sentinel "red flag" symptoms the patient can easily recognize that may return at a later date. For patients who have successfully discontinued medication, it is crucial to maintain regular periodic follow-up, even if no treatment is prescribed. Patients may be relieved to know their physician remains available when life transitions or stressful events require additional support consisting of a number of options (eg, organizational or goal coaching, cognitive behavioral therapy, psychological counseling, and/or a resumption of pharmacotherapy).

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