Examining Why Patients With Attention-Deficit/Hyperactivity Disorder Lack Adherence to Medication Over the Long Term:
A Review and Analysis

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ABSTRACT

Objective: To investigate the reasons why patients with attention-deficit/hyperactivity disorder (ADHD) adhere poorly to medications over the long term (≥ 1 year).

Data Sources: PubMed was reviewed for studies between 1997 and January 2015 citing the reasons for medication nonadherence using these main keywords: *ADHD*, *amphetamine*, *methylphenidate*, *atomoxetine*, *guanfacine*, *clonidine*, *long term*, and *adverse effects*. Non–English language articles were excluded as were those that had a follow-up of < 1 year.

Study Selection: Of 1,137 entries, 41 published articles citing reasons for subject withdrawal from treatment were included. None were included for clonidine.

Data Extraction: Similar reasons for drug or study withdrawal were grouped together for analysis using a normalized numerical average, while unique reasons were analyzed individually.

Results: Reasons for discontinuing Food and Drug Administration (FDA)–approved medication after 1 year included "own wish/remission/don't need" (19.9%; 95% CI, 9.0–30.80), "withdrew consent" (16.2%; 95% CI, 10.0–22.5), "adverse effects" (15.1%; 95% CI, 10.4–19.8) and "suboptimal effect" (14.6%; 95% CI, 8.5–20.6), with the most common adverse event being "reduction in weight/appetite" (19.2%; 95% CI, 5.1–33.4). Other important factors included age, long- versus short-acting medication, psychosocial stressors, and "stop feeling like him/herself" on medication.

Conclusions: The reasons why patients do not adhere to stimulant medication remain poorly studied and understood, especially over the long term. Standardizing the way studies evaluate patients who stop treatment and including more qualitative measures should lead to better treatment outcome and adherence to medication over the long term.

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Attention-deficit/hyperactivity disorder (ADHD) is a disorder that can be divided into broad presentations based on clinical manifestations. There exist a predominantly inattentive ADHD where a patient is "often easily distracted," a predominantly hyperactive type characterized by being "on the go," and a combined type if enough criteria are met from both presentations. Impulsivity is also a frequent characteristic of the disorder.[1] In addition to the standard symptoms, patients with ADHD may suffer significant mental health comorbidities. Jensen et al[2] went as far as to suggest that 2 new subtypes be devised, one to denote aggression, and the other, anxiety. Other common comorbidities include conduct and oppositional defiant disorders, mental retardation, and even borderline personality disorder[3] and drug use disorders.[4]

Stimulant drugs for treatment of ADHD fall under 2 main classes of molecules called amphetamines and methylphenidates, with many different formulations in each class.[1] According to Anderson and Baldwin,[5] both of these drug classes are roughly equivalent in terms of their efficacy, side effect profile, and potential for abuse. The United States Food and Drug Administration (FDA) guidelines allow for the treatment of children as young as 3 years old with amphetamine formulations,[6] and as young as 6 years old with methylphenidate (see the supplemental information in Wolraich et al[7]). The rate of stimulant use in 6- to 12-year-olds remains constant, while adolescents increasingly use stimulants.[8] Zuvekas and Vitiello[8] have found that as of 2008, stimulant use is growing in the US population overall at 3.4% per year. There are only 3 nonstimulant medications, 2 of which have only recently been approved for the treatment of ADHD. These include atomoxetine, a selective norepinephrine reuptake inhibitor approved in 2002, extended release guanfacine, a selective α_{2A} receptor agonist approved in 2009, and extended release clonidine, an α_2 receptor agonist approved in 2010.[1,9,10]

Along with behavioral therapies, stimulant and nonstimulant medications are among the first-line treatments for ADHD.[11] Unfortunately, there have been insufficient data collected on the long-term side effects to make any real determinations about their safety.[12,13] While current clinical opinion supports the judicious use of stimulants for long-term treatment, more research must be conducted.

ADHD is known primarily as a disease of childhood, with a prevalence of 5% in the childhood population according to the *DSM-5*.[14] The Centers for Disease Control and Prevention[15] estimates this number to be closer to 11% as of 2011. Of children who are diagnosed, 15% continue to meet the full *DSM-IV* criteria for ADHD by age 25, while 65% are considered to be only in partial remission.[16] Kessler et al[17] estimated the prevalence of

Clinical Points

- ADHD treatment is a cornerstone of psychiatric practice, but treatment failure is high and poorly understood. This review article tries to figure out why.
- If a patient is poorly adherent to treatment, think about how he/she feels on medication, the family's bias and understanding, and whether the formulation being used is a long- or short-acting formulation.
- Patients may be more adherent to treatment if given the choice between different pharmacologic and nonpharmacologic options.

ADHD to be 4.4% of the US adult population, while only 10.2% of affected adults were actually being treated. The low prevalence of treatment for both adults and children with ADHD remains poorly explained. Studies regularly cite adverse effects of the medication as primary concerns over the long term,[12] but very few studies attempt to explain why so few patients are pursuing treatment for the disorder. Lack of treatment is especially problematic given ADHD's significant disease burden, estimated at $31.6 billion US dollars in the year 2000.[18]

This review article attempts to show that adverse effects do not explain the majority of reasons why patients with ADHD choose to discontinue their medications over the long term (≥ 1 year). This review also attempts to analyze the existing data in order to elucidate the most common reasons for discontinuing a given ADHD drug treatment.

METHOD

Figure 1 illustrates the search terms, limits, and number of articles used in this review with a publication date range between January 1997 and January 2014. Articles were retained if they met the following criteria: subjects had ADHD, subjects were followed for more than 12 months, the studies were written in English, the studies had an abstract available on PubMed, and articles provided insight on the reasons why subjects withdrew from treatment or from the study in question. Simply quoting demographic data did not qualify for inclusion. No discrimination was made in considering studies treating adults or children; however, the vast majority of studies treated either children or adolescents, not adults.

The data displayed in Figures 2 and 3 are direct representations of the data obtained from the articles used in this analysis. Data were first modified, if necessary, to account for the number of participants after randomization in each study. The "other" category contains 3 separate groupings of data: (1) data collected and synthesized from some of the less-used categories from some studies, (2) data that were listed in the original study as "other," and (3) placeholder data required to make each study's total percentage reach 100% when such data were not provided by the study.

To compare data between studies in Figures 2 and 3, we first calculated a mean value, called the normalized numerical average, because some studies originally had data in percentage form that added to greater than 100%. It was necessary to normalize these data to equal 100% prior to comparing with other studies. Second, since not all categories were populated with data from each study, summing the numerical averages across all categories yielded a sum greater than 100%. To facilitate comparisons of the data, the numerical average of each individual category was normalized to a sum of 100%. Finally, studies with small numbers of participants (N < 50) were combined to form 1 study for the analysis. This normalized numerical average was performed instead of a weighted average based on the number of participants in a given study, because a weighted average would have biased too strongly against categories not containing data from a given large-population study and would have been inappropriate given the nonuniformity of reporting reasons for drug withdrawal. The normalized numerical average method slightly overestimates categories with fewer data at the expense of those with more data, but deviates less than the weighted average.

The last column of Figures 2 and 3, "% total subjects," is calculated using the standard numerical average, not the normalized numerical average.

Two studies that met the search criteria, Tervo et al[19] and Bereket et al,[20] were excluded from the article for having insufficient contributions toward the goal of this review.

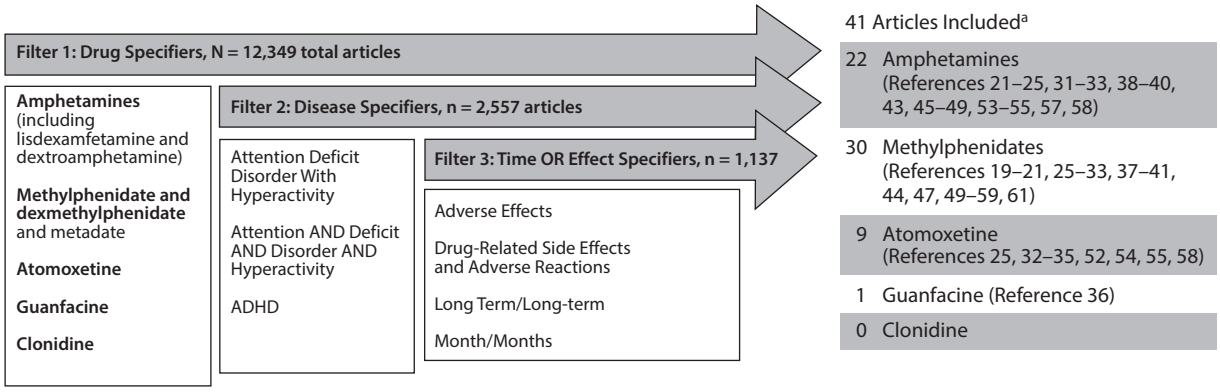
RESULTS

No studies investigating clonidine and only 1 investigating guanfacine[36] in sufficient detail qualified for entry into this review. Forty-one articles documented the varied reasons why subjects either withdrew from the study or withdrew from their respective treatment groups: amphetamines (22 studies), methylphenidate (30 studies), atomoxetine (9 studies), and guanfacine (1 study). The overall proportion of subjects who withdrew from these studies was 44.1% (95% CI, 32.3–55.8). Although dropping out of a study is not equivalent to stopping medication, Figure 2 provides insight into why patients cease treatment.[21–36]

Of note, the retrospective chart review by Ghuman et al[31] (n = 27) and the methylphenidate arm of the randomized controlled trial (RCT) by Didoni et al[32] (n = 34) were combined to achieve n > 50 participants. Some other notable irregularities include a Norwegian questionnaire on amphetamines by Lensing et al[25] that received a response rate of only 34%, the design of the amphetamine RCT followed by an open-label trial by Findling et al[24] that prescreened for adverse effects and willingness to participate, the crossover methylphenidate trial by Hoare et al[29] that allowed participants to remove themselves from the study after 21 days without first recording reasons (15.2% left), and the open-label atomoxetine trial by Spencer et al[33] that had an above-average dropout rate due to its extended 5-year duration.

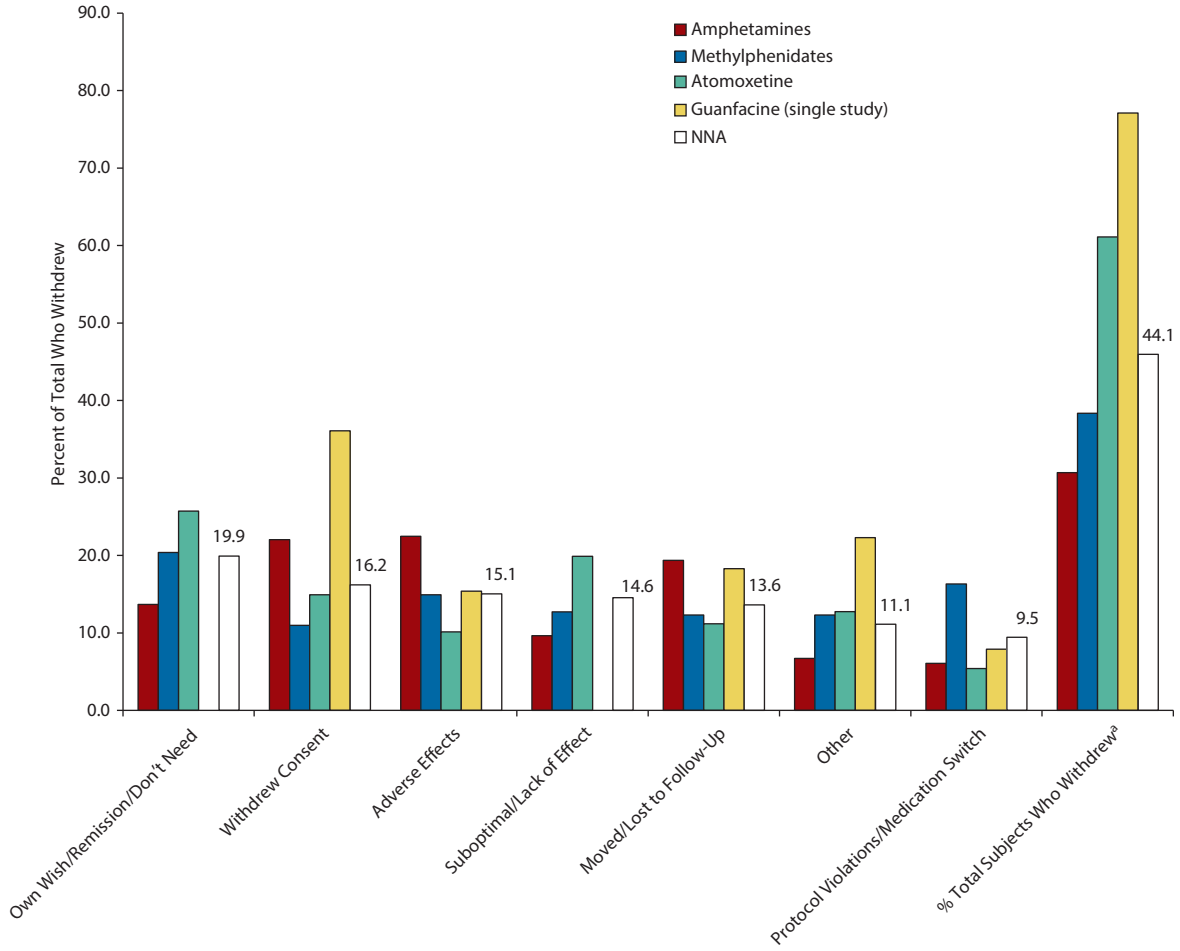
The high interstudy variability for categories was such that only 1 significant difference could be detected within a

Figure 1. PubMed Search Algorithm and Results



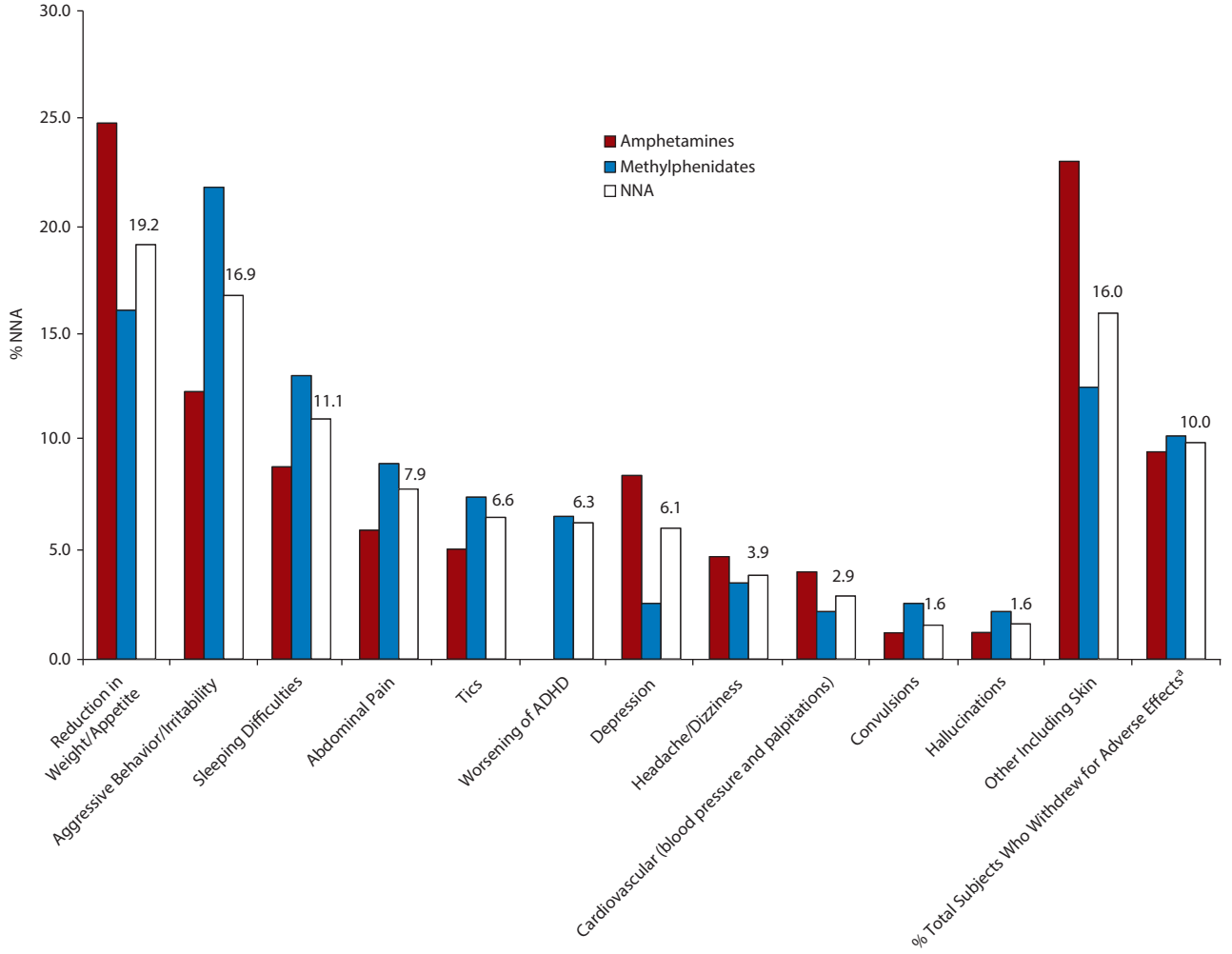
[a]Because some studies report on more than 1 drug type, the total number of articles for drug types sums to more than 41.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 2. Reasons for Stopping Medication, NNA by Drug Type[18–33,61]



[a]The "% total subjects who withdrew" is a straight average, not a normalized numerical average (NNA).

Figure 3. Adverse Effects Leading to Study Withdrawal (Using NNA)[18–20,23,24,26,28,34]



[a]The "% total subjects who withdrew for adverse effects" is a straight average, not NNA.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, NNA = normalized numerical average.

given drug class; more participants exited the amphetamine trials because they "withdrew consent" (22%; 95% CI, 14.0–30.1) than for "other" reasons (6.7%; 95% CI, 0–13.7). No significant differences were observed between drug classes for any of the measured categories. Still, it is notable that the combination category of "own wish/remission/don't need" represented a normalized numerical average of 19.9% (95% CI, 9.0–30.8) of those who withdrew. This category encompasses all participants who felt that the treatment in question was simply not for them, whether due to personal beliefs or no longer feeling sufficiently disadvantaged by their diagnosis. It specifically excludes those who felt that drugs did not sufficiently treat their ADHD (category: suboptimal/lack of effect, 14.6%; 95% CI, 8.5–20.6) and those patients or parents who no longer wanted to participate in the study (category: withdrew consent, 16.2%; 95% CI, 10.0–22.5). "Withdrew consent" was the second most populous category on the list followed by "adverse effects" (15.1%), "suboptimal/lack of effect" (14.6%), "moved/lost to follow-up" (13.6%), "other" (11.1%), and "protocol violations/medication switch" (9.5%). "Moved" and "lost to follow-up" were grouped together because some studies did not follow up with participants who had moved whereas others did. Similarly, "protocol violations" and "medication switch" were grouped together because some studies disqualified participants for switching medications whereas some allowed for the possibility. None of the studies that reported "withdrew consent" as a reason for dropping out from the study went into further detail or explained the methodology behind this category.

Adverse Effects

As a category, "adverse effects" were expanded upon by the majority of studies. Although the majority of studies list the adverse effects experienced by study participants, few explicitly mention whether or not those effects caused study withdrawal. Eight articles[21–23,26,27,29,31,37] in our analysis across 2 drug types, amphetamines and methylphenidate, document sufficient data to be compared in Figure 3. Data that met our initial search criteria for atomoxetine,

clonidine, and guanfacine were insufficient to be included in Figure 3.

The retrospective chart review by Ghuman et al[31] (n = 27) and the methylphenidate placebo-controlled crossover study by Stein et al[37] (n = 47) were combined to achieve n > 50 participants. Like the analysis for Figure 2, Figure 3 included a subset of data that had very high interstudy variability for each measured category. In addition, certain studies listed "adverse effects" that go ignored or unrepresented in other studies, even within the same drug class. For example, only Janols et al[21] measured motor tics in the amphetamine group compared with Wilens et al,[26] Wigal et al,[27] and Stein et al[37] who all measured motor tics in the methylphenidate group. The single amphetamine entry meant that statistical significance could not be calculated for a difference between groups. One statistically significant trend that did emerge when combining data from both amphetamines and methylphenidates was that reduction in weight/appetite was a significantly more common cause for drug discontinuation (normalized numerical average = 19.2%; 95% CI, 5.1–33.4) than were convulsions (normalized numerical average = 1.6%; 95% CI, 0–4.2).

The prevalence of side effects mentioned in our review does not represent the prevalence of side effects reported by the study populations. Rather, they represent a subset of the total side effects, which were either severe or unpleasant enough to cause patients to exit the study or cease medication. This represents 10% of the total subjects who withdrew from the study, according to Figure 3. Figure 3 reveals that the most common side effect causing drug cessation across drug classes, while not statistically significant, is reduction in weight/appetite, followed by aggressive behavior/irritability (16.9%; 95% CI, 1.7–32), sleeping difficulties (11.1%; 95% CI, 2.0–20.2), abdominal pain (7.9%; 95% CI, 0.6–15.1), motor tics (6.6%), worsening of ADHD (6.3%), depression (6.1%), headache/dizziness (3.9%), cardiovascular (2.9%), convulsions (1.6%), hallucinations (1.6%), and other including skin (16.0%).

In addition to the studies in the quantitative analysis, some others provided more information on adverse effects as they relate to study withdrawal. One retrospective cohort study by Barbaresi et al[38] followed 379 patients from birth to a mean age of 17.2 years old. They found that patients who began stimulant medications at 12–13 years of age were least likely to report side effects, with both younger and older groups reporting more adverse effects. Interestingly, a questionnaire study by Thorell and Dahlström[39] examined the reasons why patients wanted to stop their stimulant medications and found no significant correlation between any somatic side effects with the desire of children to stop taking their medications. A 1-year cohort study done by Didoni et al[32] followed 229 children ranging from 6 to 17 years old who were enrolled at 15 regional centers for treatment with either atomoxetine (n = 96) or methylphenidate (n = 34). Those taking methylphenidate were more persistent than those taking atomoxetine (215 vs 75 days before discontinuation) due mostly to unspecified adverse effects. Finally, 1 study[40] was impeccably executed and provided patients with the flexibility to choose between treatment options. This is perhaps why its attrition rates were so minimal. The Multimodal Treatment Study of Children With ADHD (MTA) Cooperative Group,[40] 289 subjects aged 7–9.9 years were treated for 14 months and assigned to either medication management or combined medication/behavioral therapy, among other modalities. Initial drug titration was done on methylphenidates; 4 (1.2%) left due to adverse effects, 7 (2.4%) left due to inability to follow protocol, and 4 (1.2%) were discontinued from the study due to inadequate data.

Lack of Effect

One reason for abandoning treatment has been identified as a lack of or suboptimal effect of medication. Drug effectiveness is the primary focus of clinical trials whose aim is to study whether or not stimulant medications are successful at treating ADHD. While all clinical trials reviewed in this article demonstrated that stimulants do provide substantial benefit in lowering ADHD symptoms, Figure 2 suggests that the lack of efficacy represents an estimated 14.6% (95% CI, 8.5–20.6) of the reasons why subjects choose either to exit clinical studies or to stop taking medication.

All articles that studied efficacy showed that patients would achieve near-maximum remission of symptoms over the first month of the trial and would maintain this remission for as long as the patient was taking medication.[23,41–44] The simplest way to illustrate how the efficacy of a drug influences adherence to medication is by comparing treatment and control groups for study withdrawal. In an RCT by Gillberg et al,[45] 71% of patients receiving placebo versus 29% receiving amphetamines exited the study due to lack of efficacy, mostly in the first 3 months after randomization ($P < .001$). A similar phenomenon can be observed in 3 other studies.[23,24,46] Findling et al[24] and Mattingly et al[46] demonstrated that, respectively, 75.0% and 79.0% of the placebo group agreed to be enrolled from the short arm into the long arm of the study in contrast with 82.6% and 84.1% from the treatment groups. Two studies by Findling et al[23,24] conducted long-term investigations of amphetamines and measured clinical responsiveness to treatment at 96% and 95%, respectively. Of those who exited the studies, 31.6% of the former study[20] and 80% of the later[24] were clinically unresponsive to treatment.

The MTA trial[40] found that, after the initiation of titration from the drug-related treatment groups, some patients were not satisfied with methylphenidate. Eight of those patients left the study, 39 opted to try other medications (≥ 26 due to lack of response), and 48 were nonmedicated (≥ 32 due to robust placebo response). Goetz et al[47] followed 977 ADHD patients in a naturalistic study in which subjects were similarly allowed to change groups, as treatment modalities were unrestricted. At the end of 12 months, 30.6% of treated patients remained in their initially prescribed treatment regimens versus only 10.4% in the "no/other" treatment cohort. However, discontinuation rates in the treatment cohort were higher than in the "no/other" treatment cohort (31.9% and 25.3%, respectively). Cited reasons for

discontinuation across the study were loss to follow-up (18.3%, 179/977) and parent/caregiver decision (7.8%, 76/977). A 52-week open-label trial of lisdexamfetamine by Childress et al,[48] while nonsignificant, showed greater improvement from baseline in study completers than noncompleters. Similarly, a 4-week RCT followed by a 12-month open-label trial of lisdexamfetamine by Ginsberg et al[43] with 349 participants showed that 45% of patients exited the study before the endpoint (7% for lack of efficacy). Of note, the subjects who were rated as clinically worse at baseline improved significantly more on medication therapy than those with less severe disease ($P < .0001$). Baseline Clinical Global Impressions-Severity (CGI-S) scores from least to most severe—CGI-S of 4, 5, and 6 and 7—responded to treatment 78.9%, 83.5%, and 88.4% of the time, respectively. Disease remission was not significantly affected in this study.

Other Reasons

Not feeling like oneself. Studies have convincingly demonstrated that other important reasons not touched upon by prospective or randomized trials account for why patients choose to stop taking medications. The first of these is that stimulant medications cause the patient to "stop feeling like him/herself" ($r = -0.35$, $P < .01$), according to Thorell and Dahlström's study[39] of school-aged children. They also found significant correlations between wanting to continue taking medication and perceiving school as "more fun" ($r = 0.51$, $P < .001$), which explained 27% of the total variance between adhering and not adhering to medications in this study. Overall, 20% of children said they "quite often or very often" wanted to stop taking medication, while 37% reported "sometimes," and 43% reported that they never wanted to stop. The child's willingness to stay on medication therapy is also related to whether or not the child understands the reason why he is on medication, the parent's opinions about medication, and whether the child finds it "easier to play with friends."[39] A cross-sectional analysis of junior/middle school and high school students by Doherty et al[49] showed similar findings. Of the 8 adverse effects in their questionnaire, only "not feeling like yourself" was correlated with wanting to stop medication ($r = -0.25$, $P < .05$). Under the condition "if it were up to you" to stop taking medication, almost half of students expressed a desire to be taken off medication immediately. The majority of respondents were extreme in their desires, either wanting to be off medication immediately or wanting to be kept on, with very few moderate responders.[49]

Demographics: age and sex. A naturalistic study by Atzori et al[50] followed 134 children diagnosed with ADHD and treated with methylphenidate over 36 months. Seventy-two patients withdrew from the study, with age being a statistically significant predictor for withdrawal due to poor compliance ($P < .001$); mean time on therapy was 17 ± 11 months for patients older than 12 years, compared to 26 ± 12 months for those younger than 12 years. Chen et al[51] studied 10,153 newly diagnosed patients younger than 18 years old using an observational design. Of these, 3,081 initiated methylphenidate treatment during the study period. Within a year of starting treatment, 2,879 (93.2%) discontinued, with increased chance of discontinuation if the patients were older than 12 years (hazard ratio [HR] = 1.15; 95% CI, 1.02–1.30) and received their initial methylphenidate prescription from a hospital or larger district clinic (HR = 1.27–1.32; 95% CI, 1.15–1.49). Change in treatment location was inversely related to discontinuation (HR = 0.42; 95% CI, 0.34–0.52). In addition, van den Ban et al[52] questioned 745 Dutch pharmacies from 2001–2006 about trends in methylphenidate and atomoxetine use. A statistically significant 72.0% of females compared to 60.3% of males discontinued ADHD medication (HR = 1.09; 95% CI, 1.04–1.15). Patients from 18 to 45 years old had a 79.7% chance of discontinuation, compared with 72.1% for those aged 12–17 years and 48.8% for those 6–11 years old.

Long-acting versus short-acting medications. Five studies[25,53–56]compared long-acting and short-acting medications and found that long-acting formulations are superior to short-acting formulations in terms of medication adherence. The Texas Medicaid "fee-for-service" program looked at records from 2005 to 2008 to determine utilization patterns of stimulant-type medications in children and adults.[53] Overall, patients taking short-acting formulations were 1.8–2.0 times more likely to stop medication than those taking long-acting amphetamine ($P < .001$). However, adults (> 18 y) were more adherent to amphetamines in general over long-acting methylphenidate ($P < .05$). Setyawan et al[54] investigated 149,189 insurance records for ADHD patients newly treated with amphetamines and methylphenidate for 12 months or until treatment discontinuation. *Discontinuation* was defined as not taking medication for 30 days except between May and September. Previously treated children were significantly more persistent on lisdexamfetamine while treatment-naive children benefited from lisdexamfetamine, atomoxetine, and osmotic-release oral system (OROS)-methylphenidate (all long acting). Highest drug persistence was noted for both long-acting amphetamine and lisdexamfetamine for adult groups. Following this trend, a 1-year retrospective study by Lachaine et al[55] examined drug persistence in 15,838 patients with ADHD taking atomoxetine and short-acting and long-acting stimulants. At 12 months, persistence was 81% for long-acting stimulants, 61.7% for atomoxetine, and 59.6% for short-acting medications.

In another survey, Lensing et al[25] authored a Norwegian questionnaire study (34.3% response rate). They found that long-acting stimulant medication positively correlated with both short- and long-term adherence when compared with short-acting formulations (75.7% versus 42.9%, $P < .01$). The only significant predictors for better outcomes were the length of time on treatment (> 24 months) ($P < .05$) and having no psychiatric comorbidities ($P < .001$). Finally, a 1-year prospective observational study by Tzang et al[56] followed 757 children with ADHD aged 6–18 years and found significantly more adherence ($P < .0001$) to

OROS-methylphenidate (67.24%) than to immediate release (IR)-methylphenidate (36.2%). More caregivers were completely satisfied with the OROS-methylphenidate treatment than with IR-methylphenidate treatment (7.51% vs 3.40%, $P = .007$) due to increased functional improvement and remission rates.

Psychosocial stressors. In addition to Lensing and colleagues' correlation between the level of psychiatric comorbidity and drug discontinuation,[25] a prospective study by Thiruchelvam et al[57] followed 71 children 6- to 12-years old and treated with methylphenidate for 3 years. The 8 patients who discontinued treatment scored higher on psychosocial adversity scales than those who remained. In addition, an RCT by Fredriksen et al[58] started 250 adults on methylphenidate, but allowed them to switch to dextroamphetamine or atomoxetine as needed. Sixty-nine patients stopped medication and 18 were lost to follow up. This study notes that those who discontinued were more likely to be "work-disabled" and less educated and had higher mental comorbidities.

DISCUSSION

To validate the statistical method of the normalized numerical average in this application, the number of subjects lost specifically to adverse effects is compared between Figures 2 and 3. Figure 2 shows that 44.1% of total subjects withdrew and that 15.1% did so due to adverse side effects, for a total of 6.7% of study subjects withdrawing due to adverse effects. This value is similar to the estimate of 10.0% in Figure 3 for the same result, suggesting that the normalized numerical average is acceptable to use in this application.

A statistical analysis was performed on all studies reporting numerical data in 3 or more categories from either Figure 2 or 3. There were no statistically significant ($P < .05$) findings within or between drug types worth mentioning, and only 1 notable such finding when analyzing the data as a whole (decrease in weight and/or appetite is a more common reason for study withdrawal than convulsions). Subsequently, this review's discussion on numerical analysis will combine all drug types. The most likely explanations for a lack of statistical significance are that so few studies met criteria for inclusion (low statistical sampling) combined with diverse study designs and the tendency for studies not to ask similar questions regarding treatment failure. One example is a study that encouraged participants to switch treatment groups,[47] which would not produce the same results as a study with more stringent protocols.

Another important confounder is that of long-acting compared with short-acting formulations of the same drug. On one hand, our study did not have the resolution to stratify by duration of action for drugs. Alternately, there exist retrospective observational studies with over 100,000 records that are well equipped to answer the question of which drugs produce better adherence in a given population.[53–55] What our literature review provides is an overview of the motivations behind a lack of adherence to treatment for ADHD experienced by populations.

"Adverse effects" was the most often reported reason for withdrawing from treatment according to prospective studies in this analysis (15 of 17 studies) followed by lack of effect (13 of 17 studies) (Figure 2). This demonstrates the well-studied nature of adverse effects and their relationship with poor adherence to medication. Although adverse effects were one of the main reasons for withdrawing from a study, there is no universally agreed-upon hierarchy explaining lack of adherence to medications, given the lack of uniformity in reporting across all categories. In addition, adverse effects (15.1%) are notable for not being the principal reason for withdrawing. They are the third most common, tertiary to "own wish/remission/don't need" (19.9%) and "withdrew consent" (16.2%). Not surprisingly, both previous reasons are entirely subjective and reliant on a patient and their family's understanding and expectations of treatment as well as their cultural sensitivities, among other mostly unmeasured factors.

The 3 adverse effects that most commonly cause medication to be stopped across all categories are reduction in weight/appetite (19.2% of total adverse reactions), aggressive behavior/irritability (16.9%), and sleeping difficulties (11.1%). Unlike the overall reasons for medication withdrawal, here there is agreement between the most prevalent adverse effects and the number of studies reporting them. Of 8 total studies for Figure 3, the first, second, and third most common categories are supported by 6, 7, and 6 studies, respectively. This suggests that while most studies are aware of the common adverse effects to look for (Figure 3), there is no consensus on the overall reasons why subjects withdraw from treatment (Figure 2).

It has been demonstrated that medications remain effective in patients who take them, over the short and long term. Mattingly et al[46] and Findling et al[24] estimate that over the course of 1 year, 65.7% and 40.6% of those on lisdexamfetamine and amphetamines, respectively, had achieved and maintained clinical remission. Although this review's analysis has estimated "suboptimal/lack of effect" to be the cause of 14.6% of study withdrawal, a more nuanced exploration is possible. Both Childress et al[48] and Ginsberg et al[43] found that those with worse ADHD at baseline were most improved at endpoint. Goetz et al[47] showed that a higher proportion of patients receiving no treatment either switched to a treatment group or dropped out of the study as compared to those patients receiving some form of treatment. However, discontinuation rates in the treatment cohort were higher than in the cohort not receiving medications. One possible interpretation is that patients with low efficacy (no treatment) gladly remain in the study with the hope of improvement. Conversely, if treatment is for some reason undesirable, more people are likely to simply give up than to remain in the study. Three studies[24,45,46] in support of this interpretation show that patients in placebo groups but without a chance to change to treatment groups are more likely to exit the study than their treated counterparts.

Age was found to be an influential factor in this review. One study by Barbaresi et al[38] found the key age to begin treatment in order to minimize medication side effects is 12–13 years old. While this has not been reproduced by other articles in this review, Atzori et al,[30] Chen et al,[59] and van den Ban et al[60] all agree that patients younger than 12 years old tend to be significantly more adherent to treatment than those older than 12 years of age. This may be in line with the assertion by Thorell and Dahlström[39] that there is no significant correlation between any somatic side effects and the desire of children to stop taking their medications. For this age group, it is perhaps parents, teachers, and physicians who decide medication regimens and not the children themselves. Alternately, 2 studies[39,49] report that "not feeling like oneself" when taking stimulant medications may be a significant contributor to dropout trends in children. These studies show that patients who have more fun at school are more likely to want to stay on medication treatment, bolstering the idea that qualitative measures of drug efficacy (how does the patient feel?) are similar to quantitative measures (by how much are the ADHD symptoms reduced?) or somatic symptoms (which side effects do you experience?) in their predictive capacities for estimating drug withdrawal. Other qualitative aspects that were found to impact retention in children, like a parent's opinion about medications, may have a significant influence on overall adherence. These reasons are likely the types of responses that fill up the "own wish/remission/don't need" and "withdrew consent" categories as seen in Figure 3.

The 5 articles[25,53–56] in this review that compared both long- and short-acting formulations of common ADHD medications are almost all in agreement that long-acting medications are superior to their short-acting counterparts. In addition, Lawson et al[53] and Setyawan et al[54] both support the use of amphetamine formulations over methylphenidate in the adult population, while Lachaine et al[55] show that atomoxetine is worse than long-acting, but better than short-acting stimulant formulations in terms of patient adherence. These conclusions are a particularly plausible reason why the statistical analysis in this review, which grouped drugs by class, yielded so few significant findings. It also invites a paradigm shift in the way clinicians prescribe: by duration of action rather than by class.

Two studies, one by the MTA cooperative[40] and the other by Goetz et al,[47] suggest that being allowed to switch from one treatment modality to another within the confines of a single study improves patient adherence, and it may not be a stretch to broaden this conclusion beyond treatment modality trials. It is possible that by offering alternatives to medication therapy, fewer patients will cease treatment of their ADHD.

It is not surprising that psychosocial stressors have been found to affect adherence to ADHD medication, given their far-reaching consequences in almost all aspects of health and well-being. Three studies analyzed in this review have noted such trends.[25,57,58] While some simply note that the trend exists, Fredriksen et al[58] name 3 significant factors influencing adherence in the adult population: work disability, level of education, and psychiatric comorbidities.

A final note is on the relative absence of guanfacine in this analysis (1 article) and the total absence of clonidine (0 articles). Given that these agents were FDA-approved in 2009 and 2010 for treatment of ADHD, their recent addition to the physician's toolkit among other, possibly more effective but certainly better known alternatives may explain their absence here.

CONCLUSION

While the science has consistently shown that medications are very effective at treating ADHD symptoms, this review questions whether these drugs are effective at treating patients. Study attrition rate is estimated at 44.1%, and reasons for this high number include the classics of "adverse effects" and "lack of efficacy" but, more commonly, subjective measures. Examples of these include "not feeling like oneself" and psychiatric comorbidities. Other impactful factors include age at treatment, long- versus short-acting formulations, and whether or not practitioners are willing to support consideration of other treatment modalities. It is apparent that researchers in many studies are missing an opportunity to investigate why patients are not adhering to their medications by being unaware of the reasons patients leave in the first place.

The major limitation of this review is that, of the very few studies investigating why patients with ADHD stop taking their medication over the long term, most are in disagreement as to which significant contributing factors to consider. The majority of prospective studies and RCTs do not take into account the qualitative aspects of patient adherence and therefore miss valuable opportunities to collect solid data. This oversight slows the development of an effective model for patient therapy and for predictors of stimulant treatment success. Both adverse effects of medications and medication effectiveness do play an important role in explaining why patients choose to stop taking their medications, but subjective reasons must take priority in building a model for treatment adherence.

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Drug names: atomoxetine (Strattera), clonidine (Catapres, Duraclon, and others), guanfacine (Intuniv, Tenex, and others), lisdexamfetamine (Vyvanse), methylphenidate (Focalin, Daytrana, and others).

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