

# Effectiveness Outcomes in Attention-Deficit/Hyperactivity Disorder

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Attention-deficit/hyperactivity disorder (ADHD) is common, chronic, and associated with significant functional impairment. It is highly treatable. It is therefore not only a major public health problem but also one that provides a unique opportunity in medicine to make a significant difference. This article will discuss the methodology needed to demonstrate empirically the impact of treatment on actual burden of illness in practice. Where efficacy studies demonstrate whether a treatment *can* work, effectiveness studies tell us whether they actually *do* work. Clinical trials exclude incompetent, non-compliant, and seriously comorbid patients, so that the information obtained from these trials tells us the most about the patients we see the least. Small differences in effect size in pivotal trials of efficacy have become a key variable for rating treatments as first line or second line, without consideration of effectiveness variables such as comorbidity, difficulty with appetite or sleep, patient preference, capacity for compliance, timing of functional impairment, and substance use. These effectiveness variables are less well studied, but critical to clinical decision making. In reality, fewer than 10% of our patients comply with and persist with treatment. To learn more about why patients are discontinuing treatment, we need to explore measures of effectiveness empirically. Effectiveness studies are also important to provide regulatory bodies with the data they need to balance the risk of treatment with the risk of failing to treat. Practical clinical trials and naturalistic follow-up studies will allow us to evaluate the true clinical impact of short-term efficacy trials.

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**A**ttention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric syndrome that is prevalent in 4% to 12% of children<sup>1</sup> and 4.7% of adults.<sup>2</sup> It is not often appreciated that not only does this rate mean that ADHD is among the more common psychiatric disorders, it also means that there are many more cases of adult ADHD than child ADHD, because there are more adults in our population than there are children. Many of these adults are caring for children despite significant impairments. Only a minority of adults have been diagnosed, and even fewer of those diagnosed have received appropriate treatment.<sup>3</sup> Research has demonstrated that ADHD, along with the comorbid symptoms that will accompany it, is associated with a wide range of severe impairments including poor academic outcome,<sup>4</sup> work difficulty,<sup>5</sup> social rejection,<sup>6</sup>

driving accidents,<sup>7–11</sup> a 2-fold increase in smoking,<sup>12</sup> alcohol and drug abuse,<sup>13</sup> and poor self-esteem.<sup>14</sup> The direct cost of medical care for ADHD patients is double that of the rest of the population,<sup>15–18</sup> although no estimates to date include indirect costs of the impairments noted above. The actual cost of the increased risk for smoking, driving accidents, substance abuse, loss of the capacity to work, lost health, and school dropout associated with ADHD makes ADHD one of our most serious public health problems. Decades of research have demonstrated that medication, alone or in combination with psychological treatment, has a robust impact on the symptoms of the disorder in the short term and after 1 to 2 years.<sup>19</sup> The next question research needs to address is whether treatment can in practice prevent or mitigate these functional impairments and their public health impact.

Efficacy studies tell us how a drug impacts symptoms of a disorder in a specific population and in well-controlled conditions. Effectiveness studies tell us how a drug impacts the well-being of the patient in a real practice setting. If efficacy tells us whether a drug has the potential to work, effectiveness tells us whether it actually is working.<sup>20</sup> This distinction implies that if we want to know more about how treatment impacts the well-being of patients, and with what risks, we need to be able to study how drugs are working in clinical settings on nonselected

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patients over periods of time longer than the typical clinical trial time frame.

Effectiveness studies require redefinition of each aspect of research design: the sample, compliance, patient and physician mediators and moderators, access to drug, and the impact of patient education and support. In studies of efficacy, many of these variables are controlled a priori by the protocol. In effectiveness studies, they are the object of study.

### SAMPLE POPULATION AND BIAS

The population studied in efficacy studies is those patients who meet the full criteria for ADHD and do *not* meet criteria for another major disorder requiring treatment in its own right. In the clinic, however, more than three quarters of patients will have one or more clinically significant disorders.<sup>21,22</sup> Therefore the extensive research on medication response done to date is appropriate to less than one quarter of the patients we treat, a fact that is rarely appreciated in using these data to generate practice guidelines. Few studies<sup>23</sup> have empirically looked specifically at the impact of combined or sequential treatment of multiple presenting conditions. While we have studies on ADHD and autism, mental retardation, anxiety, oppositional defiant disorder, and sleep in preschoolers, adolescents, and adults, and each subtype, we rarely see studies that encompass the full range of clinical presentations for any of these populations.

Efficacy studies have also tended to follow referral patterns rather than reflecting prevalence in the community. We know the most about latency-aged boys with ADHD, combined type. We cannot assume that the data assembled about response to treatment of latency-aged boys with ADHD, combined type, is necessarily identical to what would be found with patients whose primary problem is attention; with preschoolers, adults, adolescents, or girls; or with patients who have serious comorbidities requiring addition of other medications. The findings of empirical studies of both safety and efficacy can be extrapolated only to the population studied.

In clinical trial protocols, patients who do not take their medication are discontinued from the study. However, the likelihood for compliance and persistence with drug treatment in practice will impact profoundly whether the drug works in practice. Recent pharmacoepidemiologic studies<sup>24-31</sup> have demonstrated that compliance with stimulants is poor; less than 10% of patients are still on their medication a year later. It is often assumed that the use of the intent-to-treat model that carries forward the last observation deals with this problem. It should, however, be remembered that the patient's last visit is often within the window of the drug's continued impact and does not tell us anything about how that patient is doing at the time the study concluded. This problem is most evident in present-

ing open-label data because it is often concluded that the drug continued to work well for 1 to 2 years, without noting the percentage of patients who remained in the study. Patients lost to follow-up may or may not have continued to benefit, and how they did at their last visit while still in the study and possibly on treatment with medication does not provide for accurate evaluation of their health status at the study conclusion. This limitation of open-label follow-up would be addressed by studies that carried out a follow-up visit or phone call at the time of study closure.

The sample of efficacy studies is also influenced by the fact that, in order to participate in a research study, a patient has to be competent to read the consent form or to give assent, to understand what is involved in participating in a research study, and to follow through with the demands of the protocol. This requirement excludes patients or parents who are immigrants, have severe learning disabilities, or have ADHD too severe to be reliable and those in the lowest socioeconomic classes, who may be unable to take time off work, afford transportation, or have the education to understand the risks, benefits, and demands of a study. All of these variables impact outcome.<sup>32</sup> This sample bias is important not only in drug trials, but also in practical clinical trials of effectiveness, such as the Multimodal Treatment of ADHD study<sup>33-35</sup> sponsored by the National Institute of Mental Health (NIMH).

In order to participate in a clinical trial, the patient must agree to postpone psychosocial or herbal treatment until after the drug trial is over. In reality, however, patients in the clinic seek out other treatments, such as behavioral management, intervention with a school counselor, melatonin for sleep, omega fatty acids, biofeedback, play therapy, chiropractor or naturopath consultations, and an infinite number of other types of interventions. The exclusion of patients who will want more than medication is another bias of our efficacy studies and not typical of the patients we see.

The impact of these sources of sample bias is that we have many well-designed efficacy studies of treatment that have taught us the most about the patients we are least likely to see in practice.

### PHYSICIAN PRACTICE

Research physicians follow the study protocol, and their patients have consented both to that treatment and to complying with that treatment. Notably, this arrangement represents the antithesis of what many clinicians feel to be the core of medical therapeutics: listening to and accommodating the patient's needs first and foremost. Clinical practice is typically perceived as a physician-patient partnership in which the physician provides information, but the patient decides what treatment he or she will or will not accept. The difference, between clinical practice and clinical execution of a research protocol, along with its

impact on outcome, is not often acknowledged or discussed, and it has not been subject to empirical research.

Several studies<sup>33–35</sup> have noted that careful definition of what physicians do has had a positive impact on outcome. For example, the single most surprising finding of the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA)<sup>33</sup> was not that medication worked so well, but rather that medication worked better when delivered by experts using carefully defined protocols than when used clinically by community physicians. Further study permitted researchers to note the variables associated with improved effectiveness, such as more frequent visits and more careful dosing. This finding provided an impetus to try to develop algorithms of care that could function like a protocol in practice to improve community outcomes. The ingredient of expert care that cannot be measured is the expert's greater familiarity with ADHD and with working with ADHD patients and their capacity to explain and interpret for families what to expect from medication and how to deal with crises. Even a community physician who follows an algorithm to the letter but lacks an understanding of ADHD itself will most likely have a more limited capacity to inspire confidence and compliance.

Pliszka<sup>21–23</sup> and the Children's Medication Algorithm Project (CMAP) have provided empirical data on whether it is possible to improve clinical outcomes by training physicians in the use of an evidence-based algorithm. The CMAP feasibility studies randomized physicians rather than patients to determine whether those physicians who were trained in the algorithm would comply with it in practice and how this would impact patient outcome. It was found that it was possible to modify physician behavior, but training was costly and the impact on patient outcome was modest.

Algorithms may provide physicians with the best summaries of current evidence, but patients are often influenced by what they believe will help, irrespective of evidence. The capacity to hear and understand patients, to modify their environment to be ADHD friendly, and to explain how symptoms impact functioning and development all have a positive effect on treatment outcomes. While efficacy studies inform treatment algorithms, effectiveness studies may inform practice patterns. Physicians and patients benefit from what the algorithms tell us about efficacy of treatments, but the limitation of these algorithms must always be carefully understood. The physician treats a particular person, and all of his or her unique needs. Algorithms bring evidence-based medicine to the clinician, but they do not bring the expert clinical skills acquired by experience with that patient population. When experts develop algorithms and teach primary care physicians their use, they need to add the caution that these are suggestions developed from research studies of research patients and that, in practice, the clinician treats the patient, not the

algorithm. This is not unlike what the senior resident tells the medical student when he or she advises to treat the patient and not the laboratory value.

In summary, we have evidence from both the MTA<sup>33–35</sup> and the CMAP<sup>21–23</sup> that bringing algorithm- or protocol-driven care into clinical practice may improve outcomes. On the other hand, clinicians and patients both hold on deeply to the idea that individualizing care is a crucial ingredient of therapeutic success. In clinical practice, we attempt to balance both approaches. One of the potential contributions of effectiveness studies is to determine what variables distinguish expert care from treatment as usual. The former may include better use of medication, more frequent visits, and the understanding that use of medication is also a psychological treatment in its own right and that experts may have skills that clinicians with little training in ADHD have not yet acquired.

## INFORMANTS

In older studies of children with ADHD, the teacher was the primary informant, whereas in current studies the informant is typically the parent.<sup>24</sup> This change has been driven in part by the emergence of longer treatment periods that permit parents to observe their children in a medicated state and a growing appreciation that we are providing treatment to improve the quality of life of the child, over and above the quality of life of the teacher. Studies of adults have similarly been faced with the question: whom do we ask? Different studies have used self-report, the report of a significant other, or a clinician interview. In general, although the symptom expression of ADHD is well defined, interrater reliability between informants is modest.<sup>25</sup>

In practice, however, the doctor may treat children with problems at school whose parents feel they are doing fine. Conversely, there are going to be children who control their behavior while at school, but unleash their frustration in the more comfortable surroundings of home. There are adults with severe ADHD who still do not see what they do that is troublesome to others, while they may well be aware that others reject them. Conversely, there are adults who have clearly suffered from ADHD whose parents or partner may dismiss and/or deny the symptoms. When the issue is to determine if a patient has symptoms that are driving impairment, we need to know as much as we can. Patients who are impaired and suffering, even if they are impaired relative to their own potential, impaired in only one setting, or impaired now but not in the past, cannot be excluded from care because of a diagnostic set of criteria that fails to recognize their unique and individual needs. We describe these patients as "not otherwise specified" in our diagnostic system, but we do not study them, and we have failed to find out more about how to help them and whether in reality they are as ill as those who match some

of the diagnostic cutoffs we determined through DSM committee consensus. Efficacy studies are based on patients with full syndrome criteria. Effectiveness studies may be able to tell us whether we can help patients who do not meet full diagnostic criteria but who need treatment and suffer impairment. These studies may also tell us more about the clinical validity of our diagnostic criteria.

In clinical practice and in effectiveness studies, we need to know whether there is improvement in symptoms in the setting where, and at the time when, there is the most impairment. Where efficacy is about the effect of a drug in controlled circumstances, the essence of effectiveness studies is to determine the ecological validity of those findings. To the extent then that effectiveness studies look at ecological validity and functional impact, collateral perspectives offer complementary information. There are 3 areas in ADHD in which we have failed to use informants in an optimal way to determine specific types of impairments: there are few studies<sup>14</sup> that have actually looked at how treatment impacts how an adult performs at work; there are no studies that have looked at how treatment of an adult with ADHD impacts parenting; and there are no studies that have asked patients themselves how medications impact their internal and subjective sense of well-being and carefully evaluated some of the psychiatric side effects that may lead the patient to prefer the disease, with all its disastrous consequences, to how the treatment makes them feel.

### DRUG CHARACTERISTICS

The assumption behind any study of a drug's efficacy is that a given drug behaves the same despite changes in formulation. For example, the pivotal trials of the OROS formulation of methylphenidate (OROS-MPH), an extended-release methylphenidate, demonstrated equivalent efficacy to 3 times a day administration of immediate-release methylphenidate (IR-MPH).<sup>26</sup> It is important to recognize that without a naturalistic study, these trials do not tell us about differences in effectiveness. In evaluating whether a drug should be subsidized by government or an insurance plan, the question is not just how well it works in research settings, but how well it works in the patient population for which it was developed. Steele et al.<sup>27</sup> compared OROS-MPH to IR-MPH in a trial that did not control compliance. In this context, OROS-MPH was found to markedly improve symptom outcomes, rates of remission, compliance, parent well-being, and socialization after school. In this instance, changing the formulation without changing the medication led to a drug with identical efficacy and markedly improved effectiveness. The improved effectiveness of OROS-MPH versus IR-MPH was as impressive as the impact of expert versus community care in the MTA

study<sup>33</sup> or the impact of algorithm-driven care versus treatment as usual. The introduction of a long-duration formulation is a cost-effective and user-friendly way of improving effectiveness. Until recently, the Canadian government declined to place long-duration treatments of ADHD on the formulary on the assumption that the issue of multiple daily dosing was a problem of convenience. A theory and data on effectiveness provide the information regulatory bodies need to understand that the clinical value of a drug, its impact, is as much driven by issues of compliance, persistence, and effectiveness variables as by the pharmacology of the compound itself.

There are other examples. Dexmethylphenidate was assumed to be identical to half of racemic methylphenidate, whereas post hoc studies suggest that the isomer and racemate may have distinct properties and that evaluation of the relationship between efficacy and tolerability might suggest some advantage.<sup>30</sup> We would assume that an individual isomer would have half the efficacy of the racemate; but, if one also looks at effectiveness outcomes such as tolerability, effectiveness may be different.

Even more interesting was the recent decision of Health Canada to withdraw mixed amphetamine salts from the market on the assumption that patients could be just as easily managed with older medications. The assumption was that the efficacy of all medication treatments for ADHD is the same, which is correct. Efficacy data on populations do not always describe individuals, and, in fact, some patients respond only to a particular drug or preparation. Clinicians in Canada noted a significant number of patients who had been stable on mixed amphetamine salts who did not respond as hoped when switched to other medications. This observation led to a deepened awareness of the need to balance the risk of failed treatment, or no treatment, against the risk of any particular adverse event and the need to permit patients to participate in these choices. The evidence base for these decisions needs to be drawn not just from information on a drug's efficacy but also from what happens in practice. Although multiple medications may have identical efficacy, the cost of untreated illness in those individuals with a selective treatment response must be considered in evaluating relative risk, and that information base needs to be drawn from studies of effectiveness that look at functional outcomes of treatment nonresponders.

### OUTCOME VARIABLES

All clinical trials define one primary outcome variable, and typically, in drug studies, this variable is symptom change. Although there is often much discussion of the relative merit of one symptom scale versus another, less discussion has focused on the relative importance of symptoms per se as an outcome measure versus other types of improvement. We have assumed that symptoms

are equivalent to impairment, whereas research has clearly identified that these are overlapping but distinct concepts.<sup>29</sup> Changes in other disorders, changes in associated symptoms or subthreshold symptoms, functioning, risk, quality of life, adverse events, duration of action, and cost are also important targets of outcome.

The absence of data on these outcomes has led to the relative silence of algorithms on the role these outcomes play in clinical decision making.<sup>21,23,30,31,36-38</sup> For example, some algorithms stipulate stimulants as the first-line option for ADHD because of a modest gain in effect size on symptoms over other compounds. Patient acceptance of the stimulant, comorbid sleep problems, tics, anxiety, concomitant substance use, and other outcomes not included in pivotal trials do not receive mention as guiding medication choice, although these variables can be equally important issues for many patients.

Recently, the concept of remission has been introduced into the area of ADHD with the hope of emphasizing that clinicians can help many patients to be truly well, rather than simply accepting improvement as the goal of treatment. While this is certainly a worthwhile objective, the definition of remission that is most commonly used is a symptoms score of less than or equal to a mean of 1 on the 18 items of ADHD,<sup>39</sup> and overall this definition works well. Clinicians do, however, need to remember that this score is an arbitrary cutoff and that their objective for remission must be a patient who is comfortable and able to remain on treatment. The true target of remission is not symptoms, it is optimizing patient well-being in such a way as to obtain the best compromise between symptom response, side effects, and functional improvement in different settings.

Recent research is showing a growing appreciation of the importance of including scales that measure attributes other than symptoms. Efficacy studies have one primary outcome variable, and most often this variable is the symptoms that define the disorder. Effectiveness studies typically look at more than one parameter and describe other dimensions of response. Most trials include the Clinical Global Impressions scale (CGI),<sup>40</sup> which provides ratings of a clinician's overall impression of patient improvement and severity. It is of interest, however, that in the age of evidence-based medicine, this scale has never been psychometrically validated. In fact, there are no operational definitions for the anchor points to assure interrater reliability. A recent analysis<sup>41</sup> found that the global view of the physician's impression reported on the CGI correlates with symptom improvement but correlates even more robustly with Global Assessment of Functioning scores<sup>42-46</sup> or overall functional impairment, suggesting that the historical inclusion of the CGI despite absence of psychometric data has been very helpful.

Quality of life represents a multidimensional concept that includes social, health, behavioral, and family compo-

nents of burden of illness. ADHD has been found to be associated with marked decrements in quality of life, which improve when the disorder is treated.<sup>47</sup> A pediatric trial of atomoxetine<sup>48</sup> was one of the first pivotal trials of a new medication to also include quality of life data. Interpretation of these data, however, must take into account that the behavioral items measured by the Child Health Questionnaire (CHQ)<sup>49</sup> used in this study are redundant with symptoms of ADHD itself, so that the improvement in quality of life measured is not independent of the symptom change. In addition, since the CHQ was originally developed for use in medical diseases such as asthma or cancer, it emphasizes both pain and difficulty with mobility, neither of which are inherent issues for children with ADHD.

While there are several general measures of functioning available, none of these are specific to the functional impairments associated with ADHD. ADHD-specific measures of functional impairment for both children and adults are also currently under development.<sup>50,51</sup> These scales have the potential to let us determine how improvement in symptoms is impacting the specific impairments that put the patient at risk. They tell us whether, when symptoms get better, our treatment has worked for the patient as well as the disease. We need better data on different definitions of symptom remission to predict actual functional improvement.

## COST

Medications are useless if patients cannot afford to buy them. Just as compliance is a target of outcome in research on effectiveness, so are the realities of cost. Pharmacoeconomics is the study of costing differentials between treatments, lost productivity from lack of treatment, and the impact of adverse effects. Empirical data are needed to provide an evidence base for the decisions that physicians, insurers, governments, and hospitals must make on how to prioritize funding options.

Better measures of health utility or quality-adjusted life years (QALY) in ADHD are needed. Both direct costs (e.g., teacher time, lost days of work, medical treatment costs) and indirect costs that are known correlates of ADHD can be captured and tabulated. Research in this area is growing quickly<sup>52-66</sup> but requires new standards to measure cost and to translate both cost and suffering into units that can be standardized across different disorders and different studies.

When regulatory agencies determine whether a drug should be approved or the risk associated with low-incidence adverse events, they need to know the cost of taking the drug, the cost of not taking the drug, and the cost of potential harm. Our current research does not adequately measure the risk of failure to treat, and it does not provide a method for balancing these various risks

and benefits against one another. The result is that we ask regulatory agencies to make critical decisions by consensus. We need to practice evidence-based medicine, but we also need to develop an evidence-based methodology for regulatory decisions that draws on effectiveness research.

### ANALYSES

The gold standard of demonstrating a drug effect has been the randomized controlled trial in which outcome is measured as a statistically significant difference between drug and placebo. Unfortunately, we do not always know how that statistical significance translates into a clinically significant impact. More recently, studies have also reported effect size or the mean difference between 2 treatments divided by the pooled standard deviation of the whole sample. Effect size can provide a sense of the magnitude of the difference between a treatment and placebo. Cohen<sup>67</sup> suggested that an effect size of 0.2 was small, an effect size of 0.5 moderate, and an effect size of 0.8 or greater large. Effect sizes of medication versus placebo treatment of ADHD are generally large, varying from 0.7 to 0.9. The clinical impact of the small effect size (0.2) of the difference between medication treatments has not been empirically demonstrated, although it is the basis for rank ordering first- versus second-line medications.

While the use of effect size calculations has greatly facilitated our understanding of study outcomes, there are limitations to this method. Effect size is highly sensitive to the precision of the instruments used in any given study. Effect size is a reasonable measure of magnitude of impact of a treatment, but it does not translate into clinical significance. Effect size measures the combined impact of a treatment on a group of people and does not provide individual data on whether some patients improved dramatically whereas others did poorly or whether the whole sample showed a modest improvement. Most important, we would suggest that effect size is not the only criterion that should be considered when choosing a medication for a patient. Duration of action, patient preference, baseline side effects, time of impairment, comorbidity, cost, and many other factors may be of equal or greater importance. Patients should be provided with all the information for which we have evidence on the potential impact of all of these various predictors of outcome.

The gold standard of a positive outcome in the randomized clinical trial in the past was a statistically significant separation from placebo. We now use effect size to determine the magnitude of that difference. The gold standard of outcome in effectiveness trials will be a measure of real life differences: the effect size of change in functioning, cost, or quality of life. Furthermore, other ways of measuring impact, such as number needed to treat, number needed to harm, or evaluation of the impact

of various moderators and mediators in a clinical trial, are giving a broader perspective on the clinical meaning of research data.

### STUDY DESIGN

As interest in effectiveness increases, so does the development of novel research designs. Two approaches, the practical clinical trial and naturalistic observational studies, have been used to describe what is actually happening in real clinic settings. The practical clinical trial has been described<sup>68</sup> as a way of modifying the typical randomized clinical trial to include naturalistic conditions, such as minimizing exclusion criteria, permitting flexible treatment regimens, and measuring rather than forcing compliance. The practical clinical trial retains the advantage of randomization to eliminate bias. There are also now naturalistic observational studies of ADHD such as the Attention-Deficit Hyperactivity Disorder Observational Research in Europe (ADORE) study.<sup>69</sup> The limitation of the observational study is the absence of an experimental comparator. The future may bring hybrid designs that marry the best of the practical clinical trial with the naturalistic aspects of observational studies. Whatever the study design, it is becoming increasingly common to see post hoc analyses of the effects of moderators and mediators on targeted outcomes.

### CONCLUSION

The patient wonders if the physician treats what he or she has, and the physician wonders if the patient has what she or he treats. The 2 perspectives differ and that difference is really the essence of what differentiates efficacy from effectiveness. The patient wants to get better, to be able to love, work, and play. The patient hopes to be able to *do* something that he or she is now incapable of doing. The doctor sees a syndrome and a body of knowledge developed to provide palliation for the symptoms of that disorder. Physicians have focused their research on the disorder. The future will see us focus more on the questions patients most want answered: Will they get better? Will this medication work for them?

The disease model of medicine targets functional outcomes indirectly by virtue of the assumption that elimination of the disease is in itself identical to functional remission, although an extensive literature exists to confirm that symptoms and functioning are overlapping but not identical constructs.<sup>70</sup> Effectiveness studies have the potential to tell us how our treatments meet the patient's expectation to be able to achieve a particular functional target. Diseases, and especially those we have defined by DSM-IV,<sup>71</sup> are only a road map to improved well-being; they are not an end in themselves. Effectiveness studies will create an evidence-based medicine in which both physicians and pa-

tients are confident that the efficacy of treatments can truly address patients' concerns in practice.

*Drug names:* atomoxetine (Strattera), dexamethylphenidate (Focalin), dextroamphetamine/amphetamine (Adderall and others), methylphenidate (Ritalin, Metadate, and others).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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