Safety Profile of Atomoxetine in the Treatment of Children and Adolescents With ADHD

J. F. Wernicke, M.D., Ph.D., and Christopher J. Kratochvil, M.D.

Atomoxetine is a selective norepinephrine reuptake inhibitor that is being developed for the treatment of attention-deficit/hyperactivity disorder (ADHD). Atomoxetine will be the first nonstimulant medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD. Throughout the testing phases, more than 2000 children and adolescents have been exposed to atomoxetine in clinical trials, with both the number of exposures and the length of exposure time increasing. Serious adverse events have not been clearly associated with the drug, and there have been few discontinuations due to adverse events. The most common drug-related event reported in trials has been decreased appetite and an initial period of weight loss followed by an apparently normal rate of weight gain. These events tend to appear early in the course of treatment with atomoxetine and then decline. Atomoxetine has also been associated with mild increases in blood pressure and pulse that plateau during treatment and resolve upon discontinuation. There have been no effects seen on the QT interval, and the cytochrome P450 2D6 metabolism of patients seems to have little effect on safety or tolerability of the drug. This article will review the data from completed and ongoing clinical trials available at the time the New Drug Application was submitted to the FDA. Described are serious adverse events, discontinuations, and treatment-emergent adverse events. Specifically, cardiac effects and effects on weight, height, and metabolism that are related to treatment of ADHD with atomoxetine in children and adolescents are discussed.
(J Clin Psychiatry 2002;63[suppl 12]:50–55)

While stimulant medications have been proven safe and effective for the treatment of attention-deficit/hyperactivity disorder (ADHD), approximately 30% to 50% of all children and adults with ADHD either do not respond to or do not tolerate treatment with stimulants.[1] For this reason, combined with the abuse potential of stimulants, there is considerable interest in developing effective, nonstimulant medications to treat ADHD.

NONSTIMULANT TREATMENT OF ADHD

Several drugs with noradrenergic and/or dopaminergic effects, such as bupropion[2] and venlafaxine,[3] have shown efficacy for ADHD, but currently there is no nonstimulant approved for use in the treatment of ADHD. Atomoxetine is a potent inhibitor of the presynaptic norepinephrine transporter, with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. It is metabolized through the cytochrome P450 2D6 (CYP2D6) pathway and has a plasma half-life of approximately 5 hours in people who are extensive CYP2D6 metabolizers and 19 hours in poor CYP2D6 metabolizers. The New Drug Application (NDA) for approval of atomoxetine as a treatment for ADHD was submitted to the U.S. Food and Drug Administration (FDA) in October 2001. If approved, it will be the first nonstimulant drug marketed for the treatment of ADHD.

CLINICAL TRIAL EXPERIENCE

There have been more than 2000 exposures to atomoxetine in clinical trials (data on file, Eli Lilly and Company, Indianapolis, Ind.) with preliminary safety data for various subsets having been presented.[4–8] At the time the NDA was submitted, 425 exposures had occurred in acute, placebo-controlled trials, 526 patients had been exposed for 6 months, and 169 patients had been exposed for 1 year (data on file, Eli Lilly and Company, Indianapolis, Ind.). The number of exposures continues to grow as trials continue to enroll patients. The mean modal dose of atomoxetine in completed trials was approximately 1.3 mg/kg/day, which is very close to the target dose of 1.2 mg/kg/day.

From Eli Lilly and Company, Indianapolis, Ind. (Dr. Wernicke); and the University of Nebraska Medical Center, Omaha (Dr. Kratochvil).

Presented at the roundtable "Novel Treatments for Attention-Deficit/Hyperactivity Disorder in Children and Adults," which was held November 15–17, 2001, in Boston, Mass., and supported by an unrestricted educational grant from Eli Lilly and Company.

Corresponding author and reprints: J. F. Wernicke, Ph.D., M.D., Eli Lilly and Company, Lilly Corporate Center DC-6026, Indianapolis, IN 46285.

Table 1. Treatment-Emergent Adverse Events Reported by at Least 5% of Patients Taking Atomoxetine[a]

Event	Atomoxetine (N = 425) N	Atomoxetine (N = 425) %	Placebo (N = 292) N	Placebo (N = 292) %	Fisher Exact p Value
Headache NOS	108	25.4	67	22.9	.480
Upper abdominal pain	82	19.3	42	14.4	.108
Decreased appetite NOS	60	14.1	17	5.8	<.001
Vomiting NOS	52	12.2	20	6.8	.022
Cough	42	9.9	26	8.9	.699
Sore throat NOS	39	9.2	40	13.7	.068
Nausea	34	8.0	18	6.2	.382
Irritability	30	7.1	15	5.1	.348
Nasopharyngitis	30	7.1	30	10.3	.133
Somnolence	30	7.1	15	5.1	.348
Dizziness (except vertigo)	26	6.1	7	2.4	.019
Fatigue	23	5.4	12	4.1	.484
Pyrexia	23	5.4	17	5.8	.869

[a]Data from Allen et al.[9] and Michelson et al.[10,11]
Abbreviation: NOS = not otherwise specified.

Four clinical trials contributed to the 425 atomoxetine exposures in placebo-controlled studies. In 2 identical 9-week studies,[9] atomoxetine was given in divided doses. Patients were started at 0.5 mg/kg/day, and doses were titrated up to 2.0 mg/kg/day. In the third trial,[10] patients were randomly assigned to final target doses of 0.5 mg/kg/day, 1.2 mg/kg/day, or 1.8 mg/kg/day of atomoxetine or placebo, administered as equally divided doses in the morning and late afternoon for approximately 8 weeks. In the fourth study,[11] atomoxetine was given as a single daily dose in the morning.

SERIOUS ADVERSE EVENTS

The FDA defines an adverse event as any undesirable experience associated with the use of a medical product in a patient.[11] The event is deemed serious when the patient outcome is death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, or results in permanent disability. An event may also be designated as serious with a reason of *other* if the investigator chooses to designate it as serious, but none of the above conditions apply. Note that severity of an event in and of itself does not necessarily impact the criteria for *serious*. All serious adverse events are reported to the FDA, regardless of presumed causal relationship to the drug under study.

The focus of this article is the safety of atomoxetine in children and adolescents. However, because this drug is being developed for adults with ADHD also, the entire database of clinical trials with atomoxetine was used to examine serious adverse events (references 4–7, 9–11, 13, and data on file, Eli Lilly and Company, Indianapolis, Ind.). No deaths were reported in ADHD trials. Among 2337 children, adolescents, and adults participating in ADHD studies, 68 were reported to have had an event that met the regulatory definition of serious or was considered serious for other reasons. The most commonly reported events were under the categories of injuries and poisoning (N = 16), psychiatric (N = 13), and gastrointestinal (N = 11). In no case was the serious adverse event clearly attributable to atomoxetine, and psychiatric events were usually related to comorbid behavioral disorders. Several of the serious adverse events thought possibly to be related to treatment with atomoxetine were gastrointestinal in nature, usually nausea and vomiting. One patient developed an allergic reaction manifested by angioneurotic edema and urticaria.

DISCONTINUATIONS

Data that are more revealing about a drug's tolerability are the total number of patients who discontinue due to an adverse event and what the specific adverse events are. Discontinuations due to adverse events in the child and adolescent placebo-controlled trials of atomoxetine were 3.8%, which was not significantly different from placebo, (1.4%; p = .125).[9,10] Pooled data from the ADHD studies in children show that reasons for discontinuation were most often related to decreased appetite, sleep disturbances, and anxiety or nervousness. In a dose-response study,[10] atomoxetine was titrated to a maximum dose of 1.8 mg/kg/day and discontinuations as a result of adverse events were infrequent and occurred at similar rates for all treatment groups.

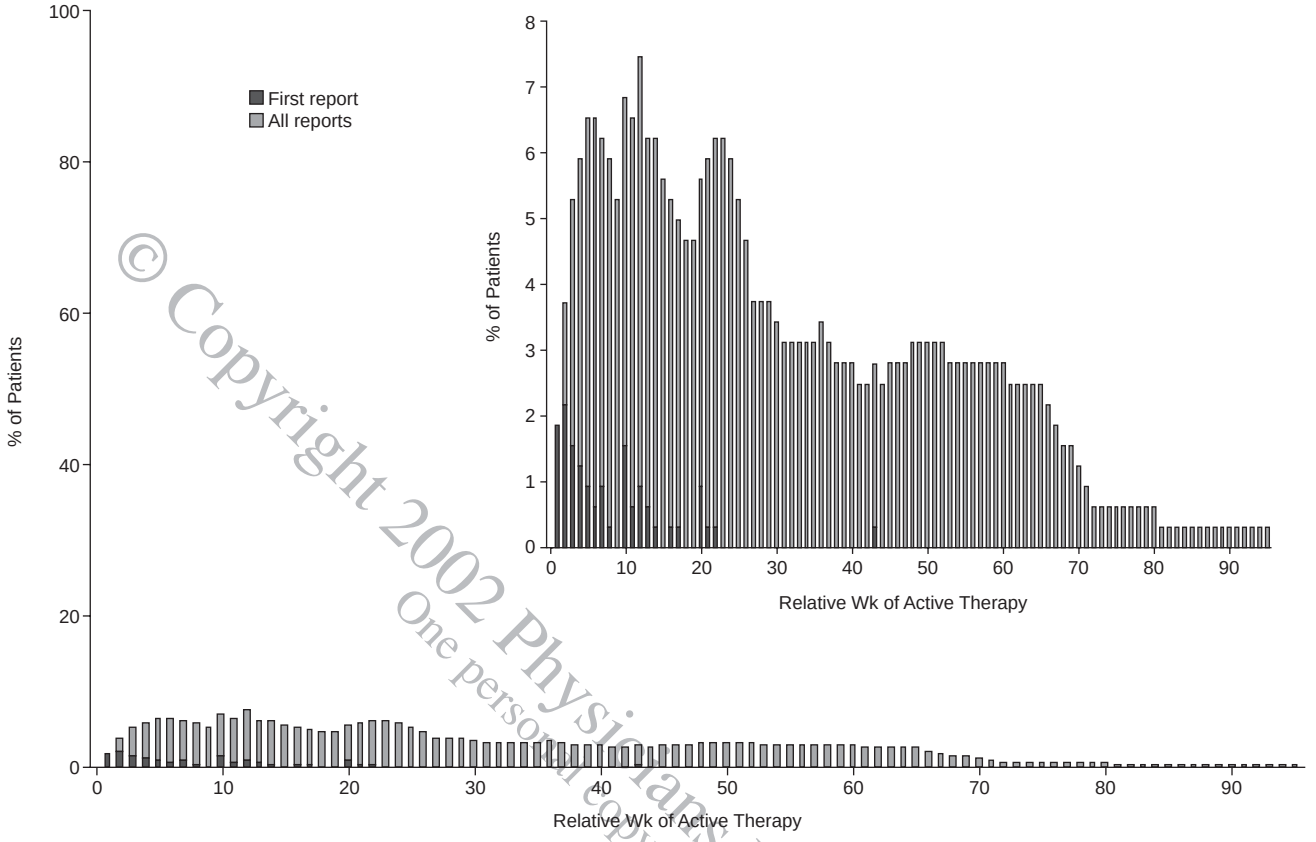
TREATMENT-EMERGENT ADVERSE EVENTS

Treatment-emergent adverse events are those that either first appear during therapy or, if present at baseline, become more severe during therapy. The pooled data from the 4 studies described earlier provided a large database of unsolicited adverse events in placebo-controlled trials.[9–11] Adverse events reported in these trials were gathered by open-ended questions, rather than solicited by a checklist (Table 1). Adverse events that occurred statistically significantly more often than with placebo were decreased appetite, vomiting, and dizziness. In the case of vomiting and dizziness, the observed statistically significant difference is probably an artifact of a placebo rate that was much lower in 1 of the studies than it was in the other 3 studies for these events. The cause for this is not known, but it did magnify the difference between atomoxetine and placebo in the overall group. It appears that decreased appetite is the only adverse event reported at a rate consistently higher by patients taking atomoxetine than by those taking placebo. This phenomenon was investigated in more detail.

Decreased Appetite and Weight Loss

One way of assessing the natural history of an adverse event is to examine the time course of first occurrence and

Figure 1. Treatment-Emergent Decreased Appetite Over Time in Children and Adolescents Treated With Atomoxetine for More Than 1 Year[a]



[a]Data from Allen et al.,[9] Michelson et al.,[10,11] and data on file, Eli Lilly and Company, Indianapolis, Ind.

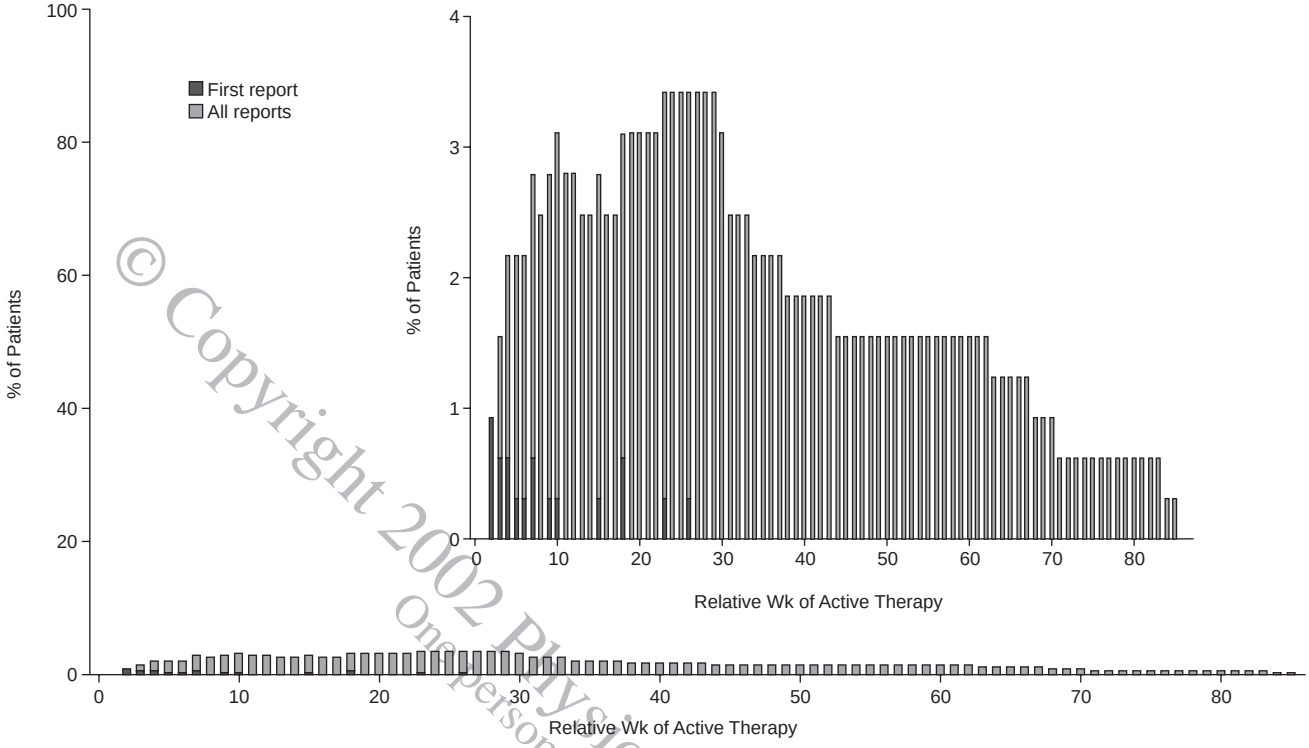
all occurrences. If reported at all (peak, less than 10% at any time), patients tended to report decreased appetite at the beginning of treatment, as indicated by the early peak of *first report* (Figure 1) (references 9–11, and data on file, Eli Lilly and Company, Indianapolis, Ind.). Overall, reports tended to peak as the dose escalated and then declined over time, as indicated by *all reports*, which shows the percentage of patients reporting that event at the given timepoint. The decrease cannot be attributed to dropout rates because few patients dropped out of the studies. It is also unlikely that patients simply stopped reporting the event because clinicians followed up with every patient for every adverse event until it completely subsided. Therefore, it appears that patients either became tolerant to the decrease in appetite or the decreased appetite resolved over time.

As expected, decreased appetite was associated with weight loss (Figures 2 and 3). For many patients, a slight transient weight loss was recorded, but few reported it as an adverse event. When compared with United States normative data,[13] it was found that mean standardized weight declined over the first 9 months of treatment, then stabilized. Most of the decline occurred early in therapy, and most of the weight was lost by the heaviest patients. Standardized weight scores indicated that the patients who lost weight began treatment weighing slightly more than the average child.

CARDIAC EFFECTS

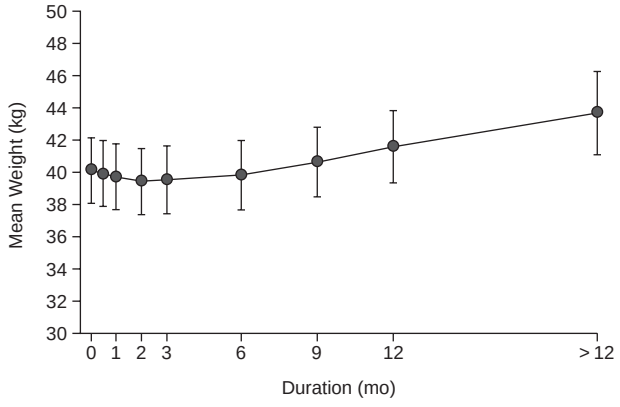
Treatment with atomoxetine has been associated with a mild increase in blood pressure.[9,10] The mean change from baseline to endpoint over about 8 weeks of treatment with atomoxetine compared with placebo is an increase of approximately 2 mm Hg in the diastolic blood pressure and almost 3 mm Hg in the systolic blood pressure. Blood pressure does not appear to continue to increase over time; rather, it plateaus and persists for the duration of treatment (Figure 4). This is clearly the case with diastolic blood pressure, but mean systolic blood pressure may not have reached the plateau point. Once the drug is discontinued, however, blood pressure quickly normalizes (references 9–11 and data on file, Eli Lilly and Company, Indianapolis, Ind.). There is also an increase in pulse of about 8 beats per minute over time,[9,10] which tends to plateau (Figure 5). This increase seems to be dose-dependent and also sub-

Figure 2. Treatment-Emergent Weight Loss Over Time in Children and Adolescents Treated With Atomoxetine for More Than 1 Year[a]



[a]Data from Allen et al.,[9] Michelson et al.,[10,11] and data on file, Eli Lilly and Company, Indianapolis, Ind.

Figure 3. Actual Weight Over Time in Children and Adolescents Treated With Atomoxetine for More Than 1 Year[a]



[a]Data from Allen et al.,[9] Michelson et al.,[10,11] and data on file, Eli Lilly and Company, Indianapolis, Ind.

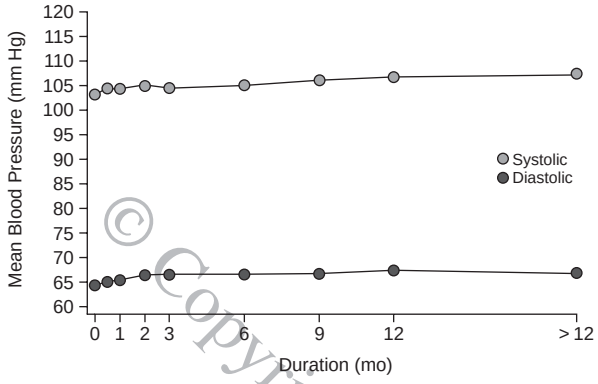
sides when the drug is discontinued. There are no data on whether atomoxetine increases the risk of a cardiovascular event for the child who is already borderline hypertensive.

Drug-induced prolongation of cardiac repolarization has been associated with potentially life-threatening cardiac arrhythmias with a variety of medications. The QT interval corrected for heart rate (QTc) is a measure of cardiac repolarization, and prolongation of this interval suggests an inhibition of vital potassium ion channels in cardiac myocytes.[15,16] The possibility that atomoxetine may have an effect on repolarization as measured by the QTc interval was evaluated in great detail (data on file, Eli Lilly and Company, Indianapolis, Ind.). There has been no evidence of prolongation of the QTc interval or arrhythmia with atomoxetine.

RELEVANCE OF CYP2D6 GENOTYPE

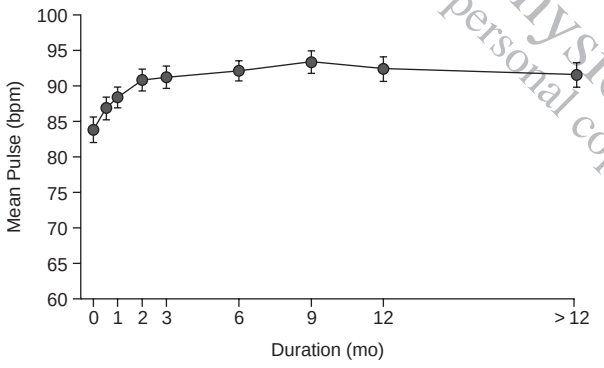
The average maximum plasma concentration (C_{max}) of atomoxetine in extensive metabolizers is about 1200 ng/mL to 1500 ng/mL, but patients who are poor metabolizers achieve a C_{max} between 2 and 3 times higher. In earlier clinical trials, patients were dosed in accordance with their genotype.[9,10] That is, poor metabolizers received lower doses than did extensive metabolizers. In order to establish a standard dose range for atomoxetine that does not require dose adjustments based on genotype, it was important to determine whether poor metabolizers could tolerate the higher plasma concentrations achieved with atomoxetine. After demonstrating safety in initial clinical pharmacology studies, later clinical trials dosed atomoxetine without regard for genotype.[13] A comparison of 1290

Figure 4. Mean (observed case) Blood Pressure Over Time in Children and Adolescents Treated With Atomoxetine for More Than 1 Year[a]



[a]Data from Allen et al.,[9] Michelson et al.,[10,11] and data on file, Eli Lilly and Company, Indianapolis, Ind.
[b]Average treatment duration for patients treated longer than 12 months was 20 months.

Figure 5. Actual Pulse Over Time in Children and Adolescents Treated With Atomoxetine for More Than 1 Year[a]



[a]Data from Allen et al.,[9] Michelson et al.,[10,11] and data on file, Eli Lilly and Company, Indianapolis, Ind.

extensive metabolizers with 67 poor metabolizers taking at least 1.2 mg/kg/day of atomoxetine, which is the initial target dose, showed little difference in discontinuations or reporting rates of adverse events. Poor metabolizers, however, did develop a slightly higher increase in pulse rate and lost slightly more weight than extensive metabolizers (Table 2).

CONCLUSION

In comparison with other drugs that have been studied for the treatment of ADHD, atomoxetine has been subjected to an unusually rigorous investigation of its safety, tolerability, and efficacy in children and adolescents with ADHD. Enrollment in trials is ongoing, and the cumulative duration of trial therapy continues to grow. There are increasing numbers of long-term trial patients being followed for up to 2 years and longer. The data up to this point have shown few serious adverse events associated with atomoxetine, and there are few discontinuations overall due to adverse events. Decreased appetite has been the most commonly reported drug-related event, with an overall rate of about 14%, compared with 6% of patients taking placebo (data on file, Eli Lilly and Company, Indianapolis, Ind.). There is an initial weight loss associated with atomoxetine treatment, followed by weight gain. Adverse events that do appear tend to appear early in treatment, then decline. There has been no pattern of adverse event onset later in treatment. Mild increases in both blood pressure and pulse do not appear to be of long-term clinical significance, and studies have shown no effect on the QT interval. The adverse event profile of poor metabolizers is similar to that of extensive metabolizers in all regards except for a slight difference in pulse and weight loss. All indications are that atomoxetine is a safe and well-tolerated drug for the treatment of ADHD in children and adolescents.

Table 2. Discontinuations, Adverse Events, and Vital Signs in Extensive Metabolizers Versus Poor Metabolizers Taking Atomoxetine ≥ 1.2 mg/kg/day[a]

Events During Treatment	Extensive Metabolizers (N = 1290)	Poor Metabolizers (N = 67)
Discontinuations due to adverse events (%)	2.9	3.0
Adverse events reported (%)		
Headache	34.7	35.8
Decreased appetite	16.9	11.9
Weight loss	3.8	3.0
Tachycardia	3.4	3.0
Change in vital signs		
Diastolic blood pressure (mm Hg)	+3.3	+4.6
Systolic blood pressure (mm Hg)	+3.0	+3.5
Pulse (bpm)	+6.9	+10.6
Weight (kg)	+0.8	–1.2

[a]Reprinted from Allen et al.[13] with permission.

Drug names: bupropion (Wellbutrin and others), venlafaxine (Effexor).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, bupropion, venlafaxine, and atomoxetine are not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder (ADHD).

REFERENCES

1. Wilens TE, Biederman J, Spencer TJ, et al. Pharmacotherapy of adult attention deficit/hyperactivity disorder: a review. J Clin Psychopharmacol 1995; 15:270–278
2. Wilens TE, Spencer TJ, Biederman J, et al. A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. Am J Psychiatry 2001;158:282–288
3. Findling RL, Schwartz MA, Flannery DJ, et al. Venlafaxine in adults with attention-deficit/hyperactivity disorder: an open clinical trial. J Clin Psychiatry 1996;57:184–189
4. Heiligenstein J, Biederman J, Faries D, et al. Atomoxetine efficacy versus placebo in school-age girls with ADHD [poster]. Presented at the 48th

annual meeting of the American Academy of Child and Adolescent Psychiatry; Oct. 23–28, 2001; Honolulu, Hawaii
5. Spencer T, Biederman J, Heiligenstein J, et al. An open-label, dose-ranging study of atomoxetine in children with attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 2001;11:251–265
6. Kratochvil CJ, Bohac D, Harrington M, et al. An open-label trial of tomoxetine in pediatric attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 2001;11:167–170
7. Spencer T, Biederman J, Wilens T, et al. Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. Am J Psychiatry 1998;155:693–695
8. Wernicke JF, Allen AJ, Faries D, et al. Safety of tomoxetine in clinical trials. Biol Psychiatry 2001;49(suppl 8):159S
9. Spencer TJ, Heiligenstein JH, Biederman J, et al. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. J Clin Psychiatry. In press
10. Michelson D, Faries D, Wernicke J, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Pediatrics 2001; 108:E83
11. Michelson D, Allen AJ, Busner J, et al. Once-daily atomoxetine treatment for children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study. Am J Psychiatry 2002;159: 1896–1901
12. U.S. Food and Drug Administration Web site. MedWatch, The FDA Medical Products Reporting Program: what is a serious adverse event? Available at: http://www.fda.gov/medwatch/report/desk/advevnt.htm. Accessed March 13, 2002
13. Allen AJ, Wernicke JF, Dunn D, et al. Safety and efficacy of atomoxetine in pediatric CYP2D6 extensive vs poor metabolizers. Biol Psychiatry 2001; 51(suppl 8):37S
14. U.S. CDC National Center for Health Statistics Clinical Growth Charts. Available at: http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm. Accessed June 17, 2002
15. Ackerman MJ. The long QT syndrome: ion channel diseases of the heart. Mayo Clin Proc 1998;73:250–269
16. Vincent GM. The molecular genetics of the long QT syndrome: genes causing fainting and sudden death. Ann Rev Med 1998;49:263–274