Off-label use of atomoxetine in adults: is it safe?

Rana Dadashova, Peter H. Silverstone
Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada

Abstract

Atomoxetine has been approved for the treatment of attention deficit/hyperactivity disorder in both adults and children. However, it is also being examined for several off-label uses in adults including mood disorders, eating disorders, cognitive dysfunction, and the treatment of addictions. Prior to such use it is important to examine the reported adverse events to see if this represents an appropriate level of risk. This is particularly important in the light of recent warnings from several regulatory bodies about an increase in blood pressure in a significant percentage of patients taking atomoxetine. To understand the risks a literature review was performed, and which identified the following potential problems. The first is that this drug should not be given in patients with known cardiovascular problems, and that all adult patients who receive atomoxetine should be monitored for changes in blood pressure throughout treatment. Secondly, there are several clinical situations in which atomoxetine should be closely monitored, or avoided, including patients who have a history or risk of narrow angle glaucoma, epileptic seizures, Tourette’s syndrome, a history of urinary outflow obstruction, or who are pregnant or lactating. In conclusion, the current literature suggests that atomoxetine can be safely used off-label provided the above precautions are taken.

Introduction

Mechanism of action and current approved use of atomoxetine

Atomoxetine is a highly selective and potent inhibitor of the presynaptic noradrenaline transporter,1,2 acting both centrally and peripherally.3,5 Supporting this, animal studies have shown that atomoxetine increases extracellular noradrenaline concentrations in many brain regions including prefrontal and occipital cortices, lateral hypothalamus, dorsal hippocampus and cerebellum.6,8 The affinity of atomoxetine and its primary metabolite (4-desmethylatomoxetine) has a much lower affinity.5 These differences may also, in part, explain clinical differences seen between these two groups.

Atomoxetine possesses a low affinity for multiple other neurotransmitters including serotonin, dopamine, choline, gamma-aminobutyric acid, adenosine transporters, and ion-channels.1,3,5 Thus, actions of atomoxetine which increase levels of other neurotransmitters are an indirect effect mediated via increased noradrenaline release.5,7 Atomoxetine does not increase dopamine levels in the mesolimbic system; hence, it is thought to have low abuse potential, a finding that has been in clinical trials.2,4 Atomoxetine’s clinical benefits are believed to be due to noradrenergic augmentation in the prefrontal cortex.9,10

Atomoxetine has been widely used in the treatment of attention deficit/hyperactivity disorder (ADHD), and clinical trials have found that atomoxetine treatment was superior to placebo.11-15 Significant improvement was noted in many variables including ADHD symptoms, response rates, and scores for inattention, hyperactivity and impulsivity. Additionally, quality of life and clinical global impression were also significantly improved when compared with treatment and placebo groups. Longer-term clinical trials of atomoxetine compared to placebo also demonstrated that patients on atomoxetine therapy had longer mean time to relapse and exhibited no evidence of drug tolerance.12,16

Potential off-label uses

In addition to its utility in ADHD, atomoxetine has been proposed for clinical use in other therapeutic areas in adults including mood disorders, eating disorders, cognitive dysfunction, and treatment of addictions.

Mood disorders

It has been suggested to be a useful antidepressant because of its noradrenergic actions. A recent review of the role of noradrenaline concluded that even though a pure noradrenergic action might not be sufficient to obtain a full antidepressant effect, noradrenergic action seemed to be related to the motor activity, attention, and arousal.17 In patients with depression atomoxetine has been found to be useful in both case reports and a small study.10,15 It was also found beneficial as augmentation therapy in treatment-resistant patients.20 However, in larger studies it was not effective as monotherapy for major depression, despite some promise.21 It has also been examined in ADHD patients who have depression, and found to potentially be useful.24,26 It has also been examined in Parkinson’s disease patients who were also depressed, although it was not efficacious at a dose of 80 mg/day.27

Eating disorders

In other therapeutic areas, atomoxetine was shown to be efficacious and well tolerated in some patients with eating disorders. During a 10 week randomized, double blind, placebo-controlled trial it significantly reduced binging episodes and frequency, body weight, body mass index (BMI), obsessive-compulsive features and overall severity of illness.29 It has also been examined as a possible treatment for obesity in women.29

Cognitive dysfunction

Others have suggested that atomoxetine may improve cognitive functions in schizophrenia patients,30 although this does not appear to be widely replicated. Atomoxetine treatment did not lead to improvement of cognitive impairment associated with Huntington’s disease.31 It has also been suggested for improving executive dysfunction in Parkinson’s disease.32

Addictions

Earlier preclinical studies showed a possible benefit of noradrenergic drugs in the attenuation of drug self-administration in animals, along with the modification of reinforcing...
properties of stimulants. Both findings might suggest a beneficial role for noradrenergic medications in the treatment of stimulant addictions. This notion was further strengthened by data showing that atomoxetine may be preferred in the treatment of addictions because it does not increase dopamine concentrations in striatum and nucleus accumbens, suggesting a low abuse potential. This was also supported by clinical trials among drug users treated with either stimulants, such as methylenidate and phentermine, or with atomoxetine where the latter was not abused. A few clinical trials of atomoxetine have been carried out to date to assess the efficacy of atomoxetine in the treatment of substance disorders co-morbid with ADHD produce, although with mixed results. Still, the attenuation of some subjective effects of psychostimulants by atomoxetine suggest that further exploration of the efficacy of atomoxetine in addictions is warranted and it has been examined for possible efficacy in cocaine addiction and marijuana addiction.

There have also been studies of the potential use of atomoxetine for smoking cessation. Three of these have examined the possible effectiveness of atomoxetine for smoking cessation in volunteers and in patients who have a psychiatric diagnosis in addition to nicotine addiction, one in patients with ADHD and one in patients with schizophrenia. All give tentative support to the possibility that atomoxetine can reduce consumption and/or smoking behaviours. In the context of off-label application of atomoxetine for various disorders other than ADHD, it is important to better understand its safety. It is therefore very important to determine if the safety profile of this drug makes such further use appropriate, and to determine when it is not appropriate to use this drug for safety reasons.

Methodology

The study review included all relevant publications up until the end of October 2011 in which atomoxetine had been used in the treatment of a wide variety of disorders. This review was conducted to determine the extent of all treatment-associated adverse events reported in the medical literature. Articles were retrieved from appropriate databases by utilization of the following two key words: atomoxetine AND side-effects AND adults or atomoxetine AND adverse-events AND adults. There were a total of 127 articles identified by this search, and further studies were identified from references within these publications.

Common adverse events

To be able to clearly identify common side-effects it is important to compare the frequency of specific adverse events with atomoxetine to placebo. Of the identified articles only 35 were included in the preliminary analysis of common treatment-associated adverse events in adults. Many of the other articles didn’t include information about adverse-events or side-effects, or were reviews which reported summary information. Of the 35 studies we examined in more detail, 15 were randomized placebo-controlled trials, 4 were case reports, 3 studies were about overdoses of atomoxetine, and 13 were neither placebo-controlled nor randomized studies. Of the placebo-controlled trials in adults, 12 studies contained data on treatment-associated adverse events, while only 7 studies provided information on the frequency of treatment-associated adverse events in both placebo and atomoxetine arms. It is these 7 studies (one of which is also a review), which are shown in more detail in Table 1, and that form the basis for the determination of the frequency of the more common side effects. It should be noted that the studies examined different time periods of atomoxetine administration, from 1-day up to 6-months of treatment and also examined doses ranging from 25 mg to 160 mg per day.

Results

Common adverse events

The reported adverse events associated with the use of atomoxetine in adults that occurred more often than in the placebo group were dry mouth (16-35%), decreased appetite (12-50%), insomnia (17-35%), nervousness (35%), constipation (7-20%), erectile dysfunction (5-11%), nausea (12-40%), dizziness (6-15%), decreased libido (7%), sweating (5-20%), fatigue (16-25%), increased heart rate (17%), hypertension (10%), hot flashes (10%), depression (10%), and urinary problems (6-10%) (Table 1).

Cardiovascular changes

Blood pressure changes

In several clinical trials atomoxetine has been shown to produce cardiovascular effects in both short-term and long-term studies. In adults these include small increases in heart rates as well as small increases in systolic and diastolic blood pressure, possibly particularly in those with autonomic dysfunction. Atomoxetine may also attenuate cocaine-induced hypertension. In terms of sudden death, while this has occurred with other drugs used in the treatment of ADHD such as dextroamphetamine and methylphenidate, we are not aware of any reports of sudden death occurring after atomoxetine use. However, there has been at one death when atomoxetine and other drugs were taken together. Recent studies have not found an increased risk of cerebrovascular incidents following the use of atomoxetine.

Change in heart rate

In addition to effects on blood pressure, there is also evidence that atomoxetine therapy, in a variety of age groups, can alter the heart rate. This has been found in children, adolescents, and adults.

Regulatory warnings

More recently additional clinical information has become available about the effects of atomoxetine on heart rate and blood pressure. This has led to a lot of regulatory activity during the period October - December 2011, when there were warnings from several regulatory bodies including those in Europe, Canada, Australia, and Singapore. For example the regulatory authority for the European Union stated that a new analysis by the pharmacovigilance working party showed that approximately 6-12% of children and adults with ADHD treated with atomoxetine experienced clinically relevant changes in heart rate (20 bpm or greater) and/or blood pressure (15-20 mmHg or greater). For this reason they recommended pre-treatment screening and periodic cardiovascular monitoring during treatment. The United States Food and Drug Administration (FDA) also released guidance, but stated that FDA recommendations for the use of medications to treat ADHD have not changed although patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure. Thus, all regulatory bodies are recommending on-going measurement of pulse and blood pressure during treatment with atomoxetine.

Less frequent adverse events

Rare adverse reactions have also been published as single case reports including cardiac arrhythmia, hyponatremia, hemopermea, and mania. Atomoxetine has also been reported to affect hepatic function. In of 7961 pediatric and adult patients treated with atomoxetine in clinical trials, 41 were identified as having hepatobiliary events requiring additional analysis. Most of these events were mild increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Post drug launch and additional 351 reports of possible liver involvement were
reported, but it was felt that in only 3 cases was liver failure probably due to atomoxetine, and none were in adults.68

**Adverse events occurring after overdose**

Following overdose of atomoxetine several symptoms are commonly seen including tachycardia (58%), emesis (34%), agitation (17%), as well as dizziness and tremor.68 Seizures and QTc prolongation have also been reported following overdose.70,71

**Possible issues in specific conditions**

There are also reports that suggest caution needs to be taken when using atomoxetine in one of the following conditions.

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**Table 1. Most commonly observed adverse events of atomoxetine (incidence of 5% or greater and at least twice the incidence in placebo patients) in 7 randomized, double blind, placebo-controlled studies in adult subjects.**

| Treatment-associated adverse events | Number of randomized patients | Number taking atomoxetine | Length of treatment | Dose range | Frequency of adverse events (%) | Frequency of adverse events (%) in placebo group |
|-------------------------------------|-------------------------------|---------------------------|---------------------|------------|-------------------------------|-----------------------------------------------|
| 1. Dry mouth                        | 536                           | 269                       | 10 weeks            | 60-120 mg  | 21.2                          | 6.8                                           |
| 2. Insomnia                         |                               |                           |                     |            |                               |                                               |
| 3. Nausea                           |                               |                           |                     |            |                               |                                               |
| 4. Appetite                         |                               |                           |                     |            |                               |                                               |
| 5. Constipation                     |                               |                           |                     |            |                               |                                               |
| 6. Erectile dysfunction             |                               |                           |                     |            |                               |                                               |
| 7. Dizziness                        |                               |                           |                     |            |                               |                                               |
| 8. Sweating                         |                               |                           |                     |            |                               |                                               |
| 9. Mydriasis and narrow angle closure glaucoma |

It has been reported that the use of atomoxetine can be associated with an increased risk of mydriasis. Mydriasis is a risk factor for narrow angle glaucoma. Atomoxetine-induced mydriasis has been found in healthy rats and there has been a case report of mydriasis following atomoxetine therapy.70,71 It is possible...
that atomoxetine may induce mydriasis via indirect α-1 adrenoceptor activation, mediated in turn via noradrenaline reuptake inhibitor effects.73

**Tourette’s syndrome and tics**

There is significant comorbidity between tics, Tourette’s syndrome, and ADHD. It has been suggested that atomoxetine is a possible therapeutic alternative for the treatment of ADHD with co-morbid tic and Tourette disorders,74-75 and studies have found significant symptom improvement in these patients.76-77 Nonetheless, case reports have reported that atomoxetine can cause and/or exacerbate tics in children with ADHD when administered alone,78-81 as well as precipitate and/or exacerbate dyskinesia when combined with other dopaminergic, noradrenergic or serotoninergic drugs.80-83 For these reasons, and because of ongoing uncertainty in the literature, it is not wise to prescribe atomoxetine to adults who have a history of either tics or Tourette’s syndrome.

**Epileptic seizures**

Preclinical data regarding the effect of atomoxetine on convulsive behaviour suggests an increased risk of seizure in animals treated with high doses of atomoxetine.84 Similarly, the majority of published case reports suggest that atomoxetine overdose causes seizures in children and adolescents.85-87 Individuals with pre-existing disorders may be at most risk, with one study reporting that 12 out of 17 individuals had an existing seizure disorder.88 Additionally, an increase in epileptic seizures within 2 weeks of treatment initiation in one out of seventeen children with epilepsy was reported.89

In a retrospective analysis of 31 clinical trials and post-market spontaneous adverse event reports from two independent Eli Lilly databases it was concluded that the risk of seizure is not increased in ADHD adults who were treated with atomoxetine, provided that they did not have a past seizure history.89 Another large database analysis also found no increased risk of seizures with atomoxetine.90 Although the data is not fully consistent, given the potential risks of seizures, atomoxetine should not be prescribed for adults with a pre-existing history of seizure disorder.

**Urinary outflow obstruction**

Symptoms of urinary retention and hesitancy in ADHD adults treated with atomoxetine have been reported regularly. In two randomized placebo-controlled studies in adults urinary hesitancy, as an atomoxetine-associated adverse event, was reported in more than 5% in one large study and at a rate of 10% of study participants who had binge-eating in a small study.91 One open-labeled atomoxetine trial in adults with sub-threshold and/or late onset ADHD found that 13% had the side-effect of urinary hesitancy.92 Indeed, this side-effect is so well recognized in children that it has been utilized in the treatment of children with nocturnal enuresis.93 Additionally, acute urinary retention has also been reported.94 For these reasons adults with a positive history of urinary retention or hesitancy should not take atomoxetine.

**Pregnancy and lactation**

There are very limited data about the effects of atomoxetine on fertility and reproduction. Decreased fetal survival in rats has been reported.95 Others have noted that exclusion of pubertal girls from many studies because of the possibilities of pregnancy may make the data less helpful. There is currently very limited human data on the safety of prenatal exposure to atomoxetine, and in the course of the clinical studies (including almost 400 female patients of childbearing potential) three pregnancies occurred of which 2 resulted in healthy newborns and one was lost to follow-up.96,97 There are no studies to our knowledge that examine possible excretion of atomoxetine in human breast milk. Taking this together, it appears prudent that atomoxetine is not given to pregnant or lactating women.

**Conclusions**

The two key findings for clinicians from this review are firstly that all patients who receive atomoxetine should have their blood pressure and pulse monitored while they are on treatment. This is not currently standard clinical practice, but it is advice now recommended by several regulatory agencies internationally based on a larger set of data. The second key point is that the published literature to date shows that, other than the cardiovascular concerns, other serious adverse events appear rare and atomoxetine is generally well tolerated in adults.

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