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

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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-hydroxyatomoxetine) for the noradrenaline transporter are similar, but the less common metabolite seen in poor metabolizers (*N*-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.[6,7] 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.[2,6-8] 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.[2,16]

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.[18,19] It was also found beneficial as augmentation therapy in treatment-resistant patients.[20-22] However, in larger studies it was not effective as monotherapy for major depression, despite some promise.[23] 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]

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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 binge-eating episodes and frequency, body weight, body mass index (BMI), obsessive-compulsive features and overall severity of illness.[28] 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.[33] 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,[8] suggesting a low abuse potential. This was also supported by clinical trials among drug users treated with either stimulants, such as methylphenidate and phentermine, or with atomoxetine where the latter was not abused.[34-36] 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,[37-39] and it has been examined for possible efficacy in cocaine addiction and marijuana addiction.[40-41]

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.[42-45] 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 it's 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 word strings: *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 (16-55%), 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.[2,13,14,46-48] In adults these include small increases in heart rates as well as small increases in systolic and diastolic blood pressure,[2,46] possibly particularly in those with autonomic dysfunction.[49] Atomoxetine may also attenuate cocaine-induced hypertension.[38,40] In terms of sudden death, while this has occurred with other drugs used in the treatment of ADHD such as dextroamphetamine and methylphenidate,[47,48] we are not aware of any reports of sudden death occurring after atomoxetine use. However, there has been at least one death when atomoxetine and other drugs were taken together.[49] Recent studies have not found an increased risk of cerebrovascular incidents following the use of atomoxetine.[50-54]

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 the rate. This has been found in children, adolescents, and adults.[2,14,15,55-57] However, not all trials found a statistically significant change in pulse rate.[58,59]

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,[60] Canada,[61] Australia,[62] and Singapore.[63] Thus, 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).*[60] 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*.[64] 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,[47] hyponatremia,[65] hemospermia,[66] and mania.[67] 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.[68] 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.[69] 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.

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.[72] It is possible

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 atomoxetine group	Number of randomized patients	Number taking atomoxetine	Length of treatment	Dose range	Frequency of adverse events (%)	Frequency of adverse events (%) placebo group
1. Dry mouth	536	269	10 weeks	60-120 mg	21.2	6.8
2. Insomnia					20.8	8.7
3. Nausea					12.3	4.9
4. Appetite					11.5	3.4
5. Constipation					10.8	3.8
6. Erectile dysfunction					9.8	1.2
6. ↓ libido					7.1	1.9
7. Dizziness					6.3	1.9
8. Sweating					5.2	0.8
1. ↓appetite	26	12	12 weeks	25-100 mg	50	21.4
2. Dry mouth					40	0
3. Fatigue					25	0
4. ↑HR					17	0
1. Dry mouth	40	20	10 weeks	40-120 mg	55	20
2. Nausea					40	10
3. Nervousness					35	15
4. Insomnia					20	10
5. Constipation					15	0
6. Sweating					10	0
7. Dizziness					10	5
8. Hypertension					10	5
9. Dyspepsia					10	5
10. Hot flash					10	5
11. Depression					10	0
12. Urinary hesitancy					10	0
13. Eructation					10	0
1. Nausea	410	271	6 months (double-blind)	40-100 mg	28.4	5.8
2. Other AE					14.0	2.2
1. Dry mouth	536	unknown	10 weeks	Up to 120 mg	21	7
2. Insomnia					21	9
3. Nausea					12	5
4. ↓Appetite					12	3
5. ↓Libido					7	2
6. Erectile dysfunction					10	1
7. Dizziness					6	1
1. Nausea	551	250	6 months	25-100 mg	32	9
2. Dry mouth					28	8
3. Fatigue					16	8
4. ↓Appetite					14	3
5. Dizziness					10	4
6. Constipation					7	3
7. Urinary hesitancy					6	0.4
8. Erectile dysfunction					11	3
1. Insomnia	442	224	14 weeks	40-100 mg	17	9
2. Nausea					16	7.6
3. Dry mouth					15.6	4.3
4. Dizziness					7.5	2.4
5. Initial insomnia					5.7	2.8
6. Erectile dysfunction					5.2	0.8

↓ appetite, decreased appetite; ↓ libido, decreased libido.

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 serotonergic 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 most at 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.[84]

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 hesitance.[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.

References

1. Wong DT, Threlkeld PG, Best KL, Bymaster FP. A new inhibitor of norepinephrine uptake devoid of affinity for receptors in rat brain. J Pharmacol Exp Ther 1982;222:61-5.
2. Garnock-Jones KP, Keating GM. Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. Paed Drugs 2009;11:203-26.
3. Gehlert DR, Gackenheimer SL, Robertson DW. Localization of rat brain binding sites for [3H]tomoxetine, an enantiomerically pure ligand for norepinephrine reuptake sites. Neurosci Lett 1993;157:203-6.
4. Zerbe RL, Rowe H, Enas GG, et al. Clinical pharmacology of tomoxetine, a potential antidepressant. J Pharmacol Exp Ther 1985;232:139-43.
5. Sauer JM, Ring BJ, Witcher JW. Clinical pharmacokinetics of atomoxetine. Clin Pharmacokinet 2005;44:571-90.
6. Swanson CJ, Perry KW, Koch-Krueger S, et al. Effect of the attention deficit/hyperactivity disorder drug atomoxetine on extracellular concentrations of norepinephrine and dopamine in several brain regions of the rat. Neuropharmacology 2006;50:755-60.
7. Koda K, Ago Y, Cong Y, et al. Effects of acute and chronic administration of atomoxetine and methylphenidate on extracellular levels of noradrenaline, dopamine and serotonin in the prefrontal cortex and striatum of mice. J Neurochem 2010;114:259-70.
8. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/ hyperactivity disorder. Neuropsychopharmacol 2002;27:699-711.
9. de Jong CG, Van De Voorde S, Roeyers H, et al. Differential effects of atomoxetine on executive functioning and lexical decision in attention-deficit/hyperactivity disorder and reading disorder. J Child Adol Psychopharmacol 2009;19:699-707.
10. Faraone SV, Biederman J, Spencer T, et al. Atomoxetine and stroop task performance in adult attention-deficit/hyperactivity disorder. J Child Adol Psychopharmacol 2005;15:664-70.
11. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: Two randomized placebo-controlled studies. Biol Psychiat 2003;53:112-20.
12. Adler L, Dietrich A, Reimherr FW, et al. Safety and tolerability of once versus twice daily atomoxetine in adults with ADHD. Ann Clin Psychiat 2006;18:107-13.
13. Adler LA, Spencer TJ, Levine LR, et al. Functional outcomes in the treatment of adults with ADHD. J Attention Disord 2008;11:720-7.
14. Adler LA, Spencer T, Brown TE, et al. Once-daily atomoxetine for adult attention-deficit/hyperactivity disorder: a 6-month double-blind trial. J Clin Psychopharmacol 2009;29: 44-50.
15. Santosh PJ Sattar S Canagaratnam M. Efficacy and tolerability of pharmacotherapies for attention-deficit hyperactivity disorder in adults. CNS Drugs 2011;25:737-63.
16. Simpson D Plosker GL. Spotlight on atom-

oxetine in adults with attention-deficit hyperactivity disorder. CNS Drugs 2004; 18:397-401.
17. Dell'osso B, Palazzo MC, Oldani L, Altamura AC. The noradrenergic action in antidepressant treatments: pharmacological and clinical aspects. CNS Neurosci Ther 2011;17:723-32.
18. Blier P. Psychopharmacology for the clinician. Treating depression with selective norepinephrine reuptake inhibitors. J Psychiatry Neurosci 2006;31:288.
19. Chouinard G, Annable L, Bradwejn J. An early phase II clinical trial of tomoxetine (LY139603) in the treatment of newly admitted depressed patients. Psychopharmacology 1984;83:126-8.
20. Carpenter LL, Milosavljevic N, Schecter JM, et al. Augmentation with open-label atomoxetine for partial or nonresponse to antidepressants. J Clin Psychiatry 2005;66: 1234-8.
21. Kratochvil CJ, Newcorn JH, Arnold LE, et al. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. J Am Acad Child Adolesc Psychiatry 2005;44: 915-24.
22. Michelson D, Adler LA, Amsterdam JD, et al. Addition of atomoxetine for depression incompletely responsive to sertraline: a randomized double-blind placebo-controlled study. J Clin Psychiat 2007;68:582-7.
23. Preti A. Tomoxetine (Eli Lilly & Co). Curr Opin Investig Drugs 2002;3:272-7.
24. Spencer TJ, Faraone SV, Michelson D, et al. Atomoxetine and adult attention-deficit/hyperactivity disorder: the effects of comorbidity. J Clin Psychiat 2006;67: 415-20.
25. Bangs ME, Emslie GJ, Spencer TJ, et al. Efficacy and safety of atomoxetine in adolescents with attention-deficit/hyperactivity disorder and major depression. J Child Adolesc Psychopharmacol 2007;17:407-20.
26. Michelson D, Adler LA, Amsterdam JD, et al. Addition of atomoxetine for depression incompletely responsive to sertraline: a randomized double-blind placebo-controlled study. J Clin Psychiat 2007;68:582-7.
27. Weintraub D, Mavandadi S, Mamikonyan E, et al. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. Neurology 2010;75: 448-55.
28. McElroy SL, Guerdjikova A, Kotwal R, et al. Atomoxetine in the treatment of binge-eating disorder: A randomized placebo-controlled trial. J Clin Psychiat 2007;68: 390-8.
29. Gadde KM, Yonish GM, Wagner HR, et al. Atomoxetine for weight reduction in obese women: a preliminary randomised controlled trial. Int J Obesity 2006;30:1138-42.
30. Morein-Zamir S, Robbins T, Turner D, Sahakian B. UK government's foresight project mental capital and wellbeing: making the most of ourselves in the 21st century. State-of-Science Review: SR-E9 Pharmacological Cognitive Enhancement, 2005.
31. Beglinger LJ, Adams WH, Paulson H, et al. Randomized controlled trial of atomoxetine for cognitive dysfunction in early huntington disease. J Clin Psychopharmacol 2009;29:484-7.
32. Marsh L, Biglan K, Gerstenhaber M, Williams JR. Atomoxetine for the treatment of executive dysfunction in Parkinson's disease: a pilot open-label study. Mov Disord 2009;24:277-82.
33. Weinshenker D, Schroeder JP. There and back again: a tale of norepinephrine and drug addiction. Neuropsychopharmacol 2007;32:1433-51.
34. Jasinski DR, Faries DE, Moore RJ, et al. Abuse liability assessment of atomoxetine in a drug-abusing population. Drug Alcohol Depend 2008;95:140-6.
35. Heil SH, Holmes HW, Bickel WK, et al. Comparison of the subjective physiological and psychomotor effects of atomoxetine and methylphenidate in light drug users. Drug Alcohol Depend 2002;67:149-56.
36. Lile JA, Stoops WW, Durell TM, et al. Discriminative-stimulus self-reported performance and cardiovascular effects of atomoxetine in methylphenidate-trained humans. Exp Clin Psychopharmacol 2006; 14:136-47.
37. Sofuoglu M Sewell RA. Noradrenaline and stimulant addiction. Addict Biol 2009; 14:119-29.
38. Levin FR, Mariani JJ, Secora A, et al. Atomoxetine treatment for cocaine abuse and adult attention-deficit hyperactivity disorder (ADHD): a preliminary open trial. J Dual Diagnosis 2009;5:41-56.
39. Thurstone C, Riggs PD, Salomonsen-Sautel S, Mikulich-Gilbertson SK. Randomized controlled trial of atomoxetine for attention-deficit/hyperactivity disorder in adolescents with substance use disorder. J Am Acad Child Adolesc Psychiatry 2010;49:573-82.
40. Stoops WW, Blackburn JW, Hudson DA, et al. Safety tolerability and subject-rated effects of acute intranasal cocaine administration during atomoxetine maintenance. Drug Alcohol Depend 2008;92:282-5.
41. Tirado CF, Goldman M, Lynch K, et al. Atomoxetine for treatment of marijuana dependence: a report on the efficacy and high incidence of gastrointestinal adverse events in a pilot study. Drug Alcohol Depend 2008;94:254-7.
42. Ray R, Rukstalis M, Jepson C, et al. Effects of atomoxetine on subjective and neurocognitive symptoms of nicotine abstinence. J Psychopharmacol 2009;23:68-176.
43. Gehricke JG, Hong N, Wigal TL, e al. ADHD medication reduces cotinine levels and withdrawal in smokers with ADHD. Pharmacol Biochem Behav 2011;98:485-91.
44. Sacco KA, Creeden C, Reutenauer EL, et al. Effects of atomoxetine on cognitive function and cigarette smoking in schizophrenia. Schizophren Res 2009;107:332-3.
45. Silverstone PH Dadashova R. Atomoxetine treatment for nicotine withdrawal: a pilot double-blind, placebo-controlled, fixed-dose study in adult smokers. Annals General Psychiatry 2012;11:6.
46. Product monograph. Strattera. Eli Lilly Canada.Available from: http://www.lilly.ca/en?t=/contentManager/selectCatalog&i=130694318569 6&l=0&e=UTF-8&ParentID=1246635267998. Accessed on: September 26th, 2011.
47. Rajesh AS, Bates G, Wright JGC. Atomoxetine induced electrocardiogram changes. Arch Dis Child 2006;91:1023-4.
48. Dworkin N. Increased blood pressure and atomoxetine. J Am Acad Child Adolesc Psychiatry 2005;44:510.
49. Shibao C, Raj SR, Gamboa A, et al. Norepinephrine transporter blockade with atomoxetine induces hypertension in patients with impaired autonomic function. Hypertension 2007;50:47-53.
50. McCarthy S, Cranswick N, Potts L, et al. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: a retrospective cohort study of children adolescents and young adults using the general practice research database. Drug Saf 2009;32:1089-96.
51. Schelleman H, Bilker WB, Strom BL, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. Pediatrics 2011;127:1102-10.
52. Garside D, Ropero-Miller JD, Riemer EC. Postmortem tissue distribution of atomoxetine following fatal and nonfatal doses three case reports. J Forensic Sci 2006; 51:179-82.
53. Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. JAMA 2011;306:2673-83.
54. Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 2011;365:1896-904.
55. Kratochvil CJ, Milton DR, Vaughan BS, Greenhill LL. Acute atomoxetine treatment of younger and older children with ADHD: a meta-analysis of tolerability and efficacy. Child Adolesc Psychiatry Ment Health 2008;2:25.
56. Wernicke JF, Faries D, Girod D, et al. Cardiovascular effects of atomoxetine in children adolescents and adults. Drug Saf 2003;26:729-40.
57. Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism

spectrum disorders: placebo-controlled crossover pilot trial. J Am Acad Child Adolesc Psychiatry 2006;45:1196-205.
58. Johnson M, Cederlund M, Rastam M, et al. Open-label trial of atomoxetine hydrochloride in adults with ADHD. J Attention Dis 2010;13;539-45.
59. Quintana H, Cherlin EA, Duesenberg DA, et al. Transition from methylphenidate or amphetamine to atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder - a preliminary tolerability and efficacy study. Clin Ther 2007:29:1168-77.
60. European Medicines Agency, Pharmacovigilance working party, 24th November 2011 plenary meeting. Available from: http://www.ema.europa.eu/ docs/en_GB/document_library/Report/2011/11/WC500117988.pdf
61. Grossman L. Association of STRATTERA (atomoxetine) with increased blood pressure and increased heart rate. Health Canada letter to Health Care Professionals 21st October 2011. Available from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2011/strattera_2_hpc-cps-eng.pdf
62. Australian Government, Department of Health and Aging, Safety Advisory, 2nd November 2011. Available from: http://www.tga.gov.au/safety/alerts-medicine-atomoxetine-111102.htm
63. Health Sciences Authority, Singapore Government, 8th November 2011. Available from: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/DHCPL/2011.html
64. United States Food and Drug Administration (FDA). FDA Drug Safety Communication: Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children and young adults, 1st November 2011. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm277770.htm
65. Singh T. Atomoxetine-induced hyponatremia. Aust N Z J Psychiatry 2007;41:458.
66. Raj YP. Atomoxetine-associated hemospermia: a case report. J Clin Psychiat 2008;69:1189.
67. Steinberg S, Chouinard G. A case of mania associated with tomoxetine. Am J Psychiatry1985;142:1517-8.
68. Bangs ME, Jin L, Zhang S, et al. Hepatic events associated with atomoxetine treatment for attention-deficit hyperactivity disorder. Drug Safety 2008;31:345-54.
69. Lovecchio F Kashani J. Isolated atomoxetine (Strattera) ingestions commonly result in toxicity. J Emerg Med 2006;31:267-8.
70. Sawant S Daviss SR. Seizures and prolonged QTc with atomoxetine overdose. Am J Psychiatry 2004;161:757.
71. Kashani J, Ruha AM. Isolated atomoxetine overdose resulting in seizure. J Emerg Med 2007;32:175-8.
72. Alhatem FJ, Decker DH. Atomoxetine-induced mydriasis. J Am Acad Child Adolesc Psychiatry 2008;18:539-41.
73. Yu Y, Koss MC. Functional characterization of alpha-adrenoceptors mediating pupillary dilation in rats. Eur J Pharmacol 2003;471:135-40.
74. Robertson MM. Attention deficit hyperactivity disorder tics and Tourette's syndrome: the relationship and treatment implications. A commentary. Eur Child Adolesc Psychiatry 2006;15:1-11.
75. Block SL, Kelsey D, Coury D, et al. Once-daily atomoxetine for treating pediatric attention-deficit/hyperactivity disorder: comparison of morning and evening dosing. Clin Pediatr 2009;48:723-33.
76. Spencer TJ, Sallee FR, Gilbert DL, et al. Atomoxetine treatment of ADHD in children with comorbid Tourette syndrome. J Atten Disord 2008;11:470-81.
77. Wolraich ML, McGuinn L, Doffing M. Treatment of attention deficit hyperactivity disorder in children and adolescents: safety considerations. Drug Safety 2007; 30:17-26.
78. Lee TS, Lee TD, Lombroso PJ, King RA. Atomoxetine and tics in ADHD. J Am Acad Child Adolesc Psychiat 2004;43:1068-9.
79. Sears J, Patel NC. Development of tics in a thirteen-year-old male following atomoxetine use. CNS Spectrums 2008;13:301-3.
80. Ledbetter M. Atomoxetine use associated with onset of a motor tic. J Child Adolesc Psychopharm 2005;15:331-3.
81. Parraga HC, Parraga MI, Harris DK. Tic exacerbation and precipitation during atomoxetine treatment in two children with attention-deficit hyperactivity disorder. Int J Psychiat Med 2007;37:415-24.
82. Jaworowski S, Benarroch F, Gross-Tsur. Concomitant use of atomoxetine and OROS-methylphenidate in a 10-year-old child suffering from attention-deficit/hyperactivity disorder with comorbid bipolar disorder and Tourette syndrome. J Child Adolesc Psychopharm 2006;16:365-70.
83. Parraga HC, Parraga KL, Harris DK, Campbell TS. Abdominal tics during atomoxetine treatment in a child with ADHD: evaluation and differential diagnosis. CNS Spectrums 2008;13:E1.
84. Torres AR, Whitney J, Gonzalez-Heydrich J. Attention-deficit/hyperactivity disorder in pediatric patients with epilepsy: review of pharmacological treatment. Epilep Behav 2008;12:217-33.
85. Sawant S, Daviss SR. Seizures and prolonged QTc with atomoxetine overdose. Am J Psychiatry 2004;161:757.
86. Spiller HA, Lintner CP, Winter ML. Atomoxetine ingestions in children: a report from poison centers. Ann Pharmacother 2005;39:1045-8.
87. Kashani J, Ruha AM. Isolated atomoxetine overdose resulting in seizure. J Emerg Med 2007;32:175-8.
88. Graham J, Coghill D. Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology prevention and management. CNS Drugs 2008;22:213-37.
89. Wernicke JF, Holdridge KC, Jin L, et al. Seizure risk in patients with attention-deficit-hyperactivity disorder treated with atomoxetine. Dev Med Child Neurol 2007;49:498-502.
90. McAfee AT, Holdridge KC, Johannes CB, et al. The effect of pharmacotherapy for attention deficit hyperactivity disorder on risk of seizures in pediatric patients as assessed in an insurance claims database. Curr Drug Saf 2008;3:123-31.
91. McElroy SL, Guerdjikova A, Kotwal R, et al. Atomoxetine in the treatment of binge-eating disorder: a randomized placebo-controlled trial. J Clin Psychiat 2007;68: 390-8.
92. Surman C, Hammerness P, Petty C, et al. Atomoxetine in the treatment of adults with subthreshold and/or late onset attention-deficit hyperactivity disorder-not otherwise specified (ADHD-NOS): a prospective open-label 6-week study. CNS Neurosci Ther 2010;16:6-12.
93. Sumner CR, Schuh KJ, Sutton VK, et al. Placebo-controlled study of the effects of atomoxetine on bladder control in children with nocturnal enuresis. J Child Adolesc Psychopharm 2006;16:699-711.
94. Desarkar P, Sinha VK. Acute urinary retention associated with atomoxetine use. Aust N Z J Psychiatry 2006;40:936.
95. Humphreys C, Garcia-Bournissen F, Ito S, Koren G. Exposure to attention deficit hyperactivity disorder medications during pregnancy. Can Fam Physician 2007;53:1153-55.
96. Alessi NE, Spalding S. Atomoxetine and pregnancy. J Am Acad Child Adolesc Psychiat 2003;42:883-4.
97. Heiligenstein J, Michelson D, Wernicke J, et al. Atomoxetine and pregnancy. J Am Acad Child Adolesc Psychiat 2003;42:884-5.