

Atomoxetine Beyond ADHD: A Fact or Arifact

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Abstract: Atomoxetine is FDA-approved in Attention-Deficit/Hyperactivity Disorder (ADHD) with demonstrable efficacy and reasonable tolerability. It is classically a selective norepinephrine reuptake inhibitor but data accrues suggestive of an attractive pharmacologic portfolio speaking to the idea of a pluripotent psychotropic agent beyond ADHD. Heaps of cases in the literature abound portraying a multitude of indications with variable level of evidence oscillating from strong to only flimsy. Here, we shed light on these uses and testing extant evidence.

Keywords: Atomoxetine-Pharmacology-Clinical Uses-Off Label Uses

1. Introduction

Atomoxetine is a selective norepinephrine reuptake inhibitor (NRI), a non-stimulant that is FDA-approved for attention-deficit hyperactivity disorder (ADHD) in children above age of 6, adolescents and adults. It is effective and generally well tolerated. It is significantly more effective than placebo and is not inferior to immediate-release methylphenidate. However, it is significantly less effective than the extended-release methylphenidate formulation, and extended-release mixed amphetamine salts. Atomoxetine can be administered either as a single daily dose or split into two evenly divided doses, has a negligible risk of abuse, and is not a controlled substance due to lack of effect on nucleus accumbens. Atomoxetine is particularly useful for patients at risk of substance abuse, as well as those who have co-morbid anxiety or tics, or when multiple dosing regimens are not practically feasible.¹

As outlined in the next section, the pharmacologic portfolio of atomoxetine is attractive and portends a pluripotent psychotropic agent that goes beyond ADHD.

This translates clinically into a multitude of indications and cases in the literature abound highlighting panoply of uses. This paper sheds light on some of these and available evidence.

2. Pharmacology of Atomoxetine

Atomoxetine inhibits norepinephrine transporter (NET). It

increases NE and dopamine (DA) by 3-folds in prefrontal cortex but not in the nucleus accumbens and hence, low potential for abuse.²

Atomoxetine has been shown to greatly occupy both NET and serotonin transporter (SERT) at clinically relevant doses.³

Also, atomoxetine has been demonstrated to block NMDA-Glut in clinically relevant concentrations.⁴

Moreover, atomoxetine inhibits G-protein-coupled inwardly rectifying potassium channels (GIRK); modulation of which has been proposed as a potential treatment for several neuropsychiatric disorders.⁵

Its major metabolite, 4-hydroxyatomoxetine, has been reported to be mu-opiate antagonist and kappa-opiate partial agonist.⁶

Table. 1 summarizes these proposed mechanisms.

Table 1. ATX proposed mechanism(s) of action. (on page2)

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| <ul style="list-style-type: none">• NRI• DRI• SERT inhibition• NMDA-Glut Antagonist• GIRK inhibition• κ opiate partial agonist |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

This composite mechanism of action would signal a pluripotent agent with wide array of indications in clinical practice as we would see in next sections.

3. Atomoxetine Beyond ADHD

Apart from the only formal indication of atomoxetine in ADHD, it has been tried in a multitude of clinical indications, although evidence for these is highly variable. Its proper use in practice as off-label would be the onus of nimble clinicians and only after exhausting other alternatives at hand with more solid evidence base.

Suffice to say that atomoxetine has been tried, *inter alia*, for depression, binge-eating disorder, freezing-of-gait in Parkinson's disease (PD), cognitive domain in schizophrenia and Huntington's disease (HD) and substance use disorders (SUD), only to name few.

4. Atomoxetine in Depression

Reboxetine, a chemically related agent, is an NRI antidepressant.

And as outlined in the section of ATX pharmacology, it inhibits NET, DAT and SERT and this would portend a robust antidepressant activity, at least theoretically.

Kratochvil ⁷et al. compared atomoxetine monotherapy to combined treatment with fluoxetine in ADHD with comorbid depression and anxiety. In this study, reductions of ADHD, depression and anxiety were marked for both treatment groups.

Berigan⁸ reported 3 cases of MDD responding to SSRI treatment that achieved remissions with adjunctive atomoxetine especially in residual noradrenergic symptoms of fatigue, anergia and aprosexia.

On the other hand, Michelson et al.⁹ conducted a randomized, double-blind, placebo-controlled study for add-on atomoxetine in MDD inadequately responsive to sertraline and it was negative.

Weintraub et al.¹⁰ assessed efficacy of atomoxetine for depression and other neuropsychiatric symptoms in PD. In this study, atomoxetine helped with global cognitive performance and daytime sleepiness but not depression.

Ravindran et al.¹¹ conducted a randomized, double-blind, controlled trial of atomoxetine involving 27 patients with social anxiety disorder-generalized subtype without comorbid ADHD. Atomoxetine did not separate from placebo.

5. Atomoxetine in Binge-Eating Disorder

Lisdexamfetamine dimesylate, a stimulant prodrug, is recently FDA-approved for binge-eating disorder (BED).

Anorexigenic effect of ATX could be contributory.

McElroy et al.¹² conducted a 10-week, single-centre, randomized, double-blind, placebo-controlled, flexible-dose trial of atomoxetine for BED. In this study, atomoxetine was efficacious and fairly well-tolerated in the short-term.

To extrapolate, Ball et al.¹³ conducted a 24-week randomized, placebo-controlled trial of atomoxetine for weight reduction in patients with schizophrenia or schizoaffective disorder on olanzapine or clozapine who gained at least 7% from baseline but was negative.

6. Atomoxetine in Schizophrenia

Freidman et al.¹⁴ conducted a pilot study of adjunctive atomoxetine treatment to atypical antipsychotics for cognitive deficits in schizophrenia. In this study, no significant cognitive improvement was associated with atomoxetine treatment. However, atomoxetine treatment was associated with significantly greater increases in working memory-related activation of the left dorsolateral prefrontal and left posterior cingulate cortices.

Kelly et al.¹⁵ conducted a randomized double-blind trial of atomoxetine for cognitive impairments in 32 patients with schizophrenia but was negative.

We¹⁶ reported a case of early-onset schizophrenia where add-on ATM mitigated negative and cognitive domains, disorganized symptom cluster and atypical antipsychotic-induced weight gain. We assume that boosting the noradrenergic tone with subsequent disinhibition of dopamine projections to medial prefrontal cortex could rectify the hypofrontality underlying negative deficits, in tandem with reports of efficacy of nor-adrenergic agents in negative domain schizophrenia.

Poyurovsky et al. enrolled 59 first-episode schizophrenic patients on olanzapine 10 mg/d in a randomized double-blind placebo-controlled study to receive either reboxetine, a congener of ATX, or placebo for 6 weeks. Appetite increase was significantly lower in the olanzapine/reboxetine than olanzapine/placebo group and was correlated with attenuation of weight gain. Reboxetine addition was safe and well-tolerated.¹⁷

7. Atomoxetine in Parkinson Disease

Freezing of gait is one of the most troublesome symptoms associated with Parkinson disease (PD) which usually does not respond to dopaminergic therapy, possibly because it is mediated via noradrenergic, rather than dopaminergic, deficiency.

Jankovic¹⁸ enrolled 5 patients with gait disturbance into a double-blind randomized trial of atomoxetine. Improvement in total Gait and Balance Scale score was noted in those treated with atomoxetine but did not reach statistical significance.

12 patients with PD and disabling executive dysfunction (ED) completed an 8-week pilot open-label, flexible dose trial of ATX. On primary outcome measures, it was associated with improved ED based on the Clinical Global Impression-Change Scale and behavioral measures of ED (Frontal Systems Behavior Scale Executive Dysfunction and Connors Adult ADHD Rating Scale inattention/memory subscales)¹⁹

As shown in the section of depression, ATX helped with global cognitive performance and daytime sleepiness in PD but not depression.

8. Atomoxetine in Huntington Disease

A 10-week randomized, double-blind, cross-over of 20 patients with mild Huntington Disease (HD) of atomoxetine

for cognitive dysfunction was negative.²⁰

Similarly, Mohs *et al.*²¹ conducted a 6-month, randomized, double-blind, placebo-controlled, parallel trial study of ATX augmentation of acetyl-cholinesterase inhibitor therapy in patients with AD. It was generally well-tolerated but did not significantly improve cognitive function.

9. Atomoxetine in Autism

Arnold *et al.*²² conducted a placebo-controlled cross-over pilot study of atomoxetine in hyperkinetic ASD. Atomoxetine was superior to placebo on the hyperactivity subscale of aberrant behaviour checklist.

10. Atomoxetine in Nocturnal Enuresis

Sumner *et al.*²³ conducted an outpatient, multicenter, randomized, double-blind, parallel, placebo-controlled study involving 87 pediatric subjects on the effects of atomoxetine on bladder control in children with nocturnal enuresis (NE)

Atomoxetine treatment was associated with a significant increase in dry nights in children with nocturnal enuresis.

Shatkin²⁴ earlier reported 4 cases of ADHD with comorbid NE treated with ATX and all experienced serendipitous resolution of NE.

Stimulation of the alpha-adrenergic receptors promotes urinary continence via contraction of the bladder trigone and internal sphincter. Stimulation of beta-receptors in the bladder result in smooth muscle relaxation of the bladder wall. Thus, sympathetic stimulation causes bladder wall relaxation and internal urethral-sphincter contraction resulting in urinary continence.²⁵ This could explain role of ATX in treatment of NE.

11. Conclusion

Data from literature robustly supports use of atomoxetine with growing body of evidence in Bing-eating disorder, nocturnal enuresis, hyperkinetic autism, but less so for freezing-of-gait in Parkinson disease. Mixed data exists for ATX use in depression. And its use as a cognitive enhancer in schizophrenia, PD, HD and AD was futile.

Having said so, it remains incumbent on the clinician's part to decide when using ATX in these off-label indications only after exhausting other options with more solid evidence-base.

References

- [1] Garnock-Jones KP, Keating GM. Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. *Paediatr Drugs*. 2009;11(3):203-26
- [2] 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. *Neuropsychopharmacology*. 2002;27(5):699-711
- [3] Ding YS, Naganawa M, Gallezot JD *et al.* Clinical doses of atomoxetine significantly occupy both norepinephrine and serotonin transports: Implications on treatment of depression and ADHD. *Neuroimage*. 2014;86:164-71
- [4] Ludolph AG, Udvardi PT, Schaz U, *et al.* Atomoxetine acts as an NMDA receptor blocker in clinically relevant concentrations. *Br J Pharmacol*. 2010;160(2):283-91
- [5] Kobayashi T, Washiyama K, Ikeda K. Inhibition of G-protein-activated inwardly rectifying K⁺ channels by the selective norepinephrine reuptake inhibitors atomoxetine and reboxetine. *Neuropsychopharmacology*. 2010;35(7):1560-9
- [6] Creighton CJ, Ramabadran K, Ciccone PE, *et al.* Synthesis and biological evaluation of the major metabolite of atomoxetine : elucidation of a partial kappa-opioid agonist effect. *Bioorg Med Chem Lett*. 2004;14(15):4083-5
- [7] 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(9):915-24
- [8] Berigan TR. Atomoxetine used adjunctively with selective serotonin reuptake inhibitors to treat depression. *Prim Care Companion J Clin Psychiatry*. 2004;6(2):93-94
- [9] 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 Psychiatry*. 2007;68(4):582-7
- [10] Weintraub D, Mavandadi S, Mamikonyan E, *et al.* Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. *Neurology*. 2010;75(5):448-55
- [11] Ravindran LN, Kim DS, Letamendi AM, *et al.* A randomized controlled trial of atomoxetine in generalized social anxiety disorder. *J Clin Psychopharmacol*. 2009;29(6):561-4
- [12] McElroy SL, Guerdjikova A, Kotwal R, *et al.* Atomoxetine in the treatment of binge-eating disorder : a randomized placebo-controlled trial. *J Clin Psychiatry*. 2007;68(3):390-8
- [13] Ball MP, Warren KR, Feldman S, *et al.* Placebo-controlled trial of atomoxetine for weight reduction in people with schizophrenia treated with clozapine or olanzapine. *Clin Schizophr Relat Psychoses*. 2011;5(1):17-25
- [14] Friedman JI, Carpenter D, Lu J, *et al.* A pilot study of adjunctive atomoxetine treatment to second-generation antipsychotics for cognitive impairment in schizophrenia. *J Clin Psychopharmacol*. 2008;28(1):59-63
- [15] Kelly DL, Buchanan RW, Boggs DL, *et al.* A randomized double-blind trial of atomoxetine for cognitive impairments in 32 people with schizophrenia. *J Clin Psychiatry*. 2009;70(4):518-25
- [16] Naguy A, Al-Mutairi H. Add-on atomoxetine mitigated different symptom domains in a case of Early-onset schizophrenia. *J Psychiatry*. 2015;18:279
- [17] Poyurovsky M, Fuchs C, Pashinian A, *et al.* Attenuating effect of reboxetine on appetite and weight gain in olanzapine-treated schizophrenia patients: a double-blind placebo-controlled study. *Psychopharmacology (Berl)*. 2007;192(3):441-8

- [18] Jancovic J. Atomoxetine for freezing of gait in Parkinson disease. *J Neurol Sci.* 2009;284(1-2):177-8
- [19] Marsh L, Biglan K, Gerstenhaber M, et al. Atomoxetine for the treatment of executive dysfunction in Parkinson's Disease : a pilot open-label study. *Mov Disord.* 2009;24(2):277-82
- [20] 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(5):484-7
- [21] Mohs RC, Shiovitz TM, Tariot PN, et al. Atomoxetine augmentation of cholinesterase inhibitor therapy in patients with Alzheimer disease : 6-month, randomized, double-blind, placebo-controlled, parallel trial study. *Am J Geriatr Psychiatry.* 2009;17(9):752-9
- [22] Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders : placebo-controlled cross-over pilot study. *J Am Acad Child Adolesc Psychiatry.* 2006;45(10):1196-205
- [23] 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 Psychopharmacol.* 2006;16(6):699-711
- [24] Shatkin JP. Atomoxetine for the treatment of pediatric nocturnal enuresis. *J Child Adolesc Psychopharmacol.* 2004;14(3):443-7
- [25] Clark N. Conventional Antipsychotic and clozapine-induced urinary incontinence. *JCPNP.* 2003;2(2).