Introduction[1, 2]

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder characterized by developmentally inappropriate impulsivity, attention deficit and in some cases hyperactivity. Attention-deficit/hyperactivity disorder is a common disorder that is occasionally very difficult to diagnose. In order to diagnose a person with ADHD, these behaviors must be excessive, long term and pervasive. The pathophysiology of ADHD involves alterations in the central dopaminergic and noradrenergic tone. According to the Attention Deficit Disorder Association (ADD) 4-6% of the U.S. population has ADHD[3]. Attention-deficit/hyperactivity disorder is usually diagnosed during childhood but is not limited to children. The prevalence of ADHD in children is about 3-5%. [4,5,6,7] Attention deficit hyperactivity disorder affects 30-50 % of adults who had ADHD in childhood.[8] Children and adults are highly responsive to pharmacotherapy and may benefit from behavioral and psychosocial interventions.[6] Atomoxetine is a medication approved by the Food and Drug Administration (FDA) in November 2002 for the treatment of ADHD in children, adolescents and adults.[9] Atomoxetine is not classified as a controlled substance; it is the first non-stimulant drug labeled for ADHD.

Pharmacology/Pharmacokinetics[1, 2]

Atomoxetine is a selective norepinephrine reuptake inhibitor. The precise mechanism by which the medication produces its therapeutic effects in ADHD is unknown.

PHARMACOKINETIC PARAMETER	
METABOLISM	• Atomoxetine is metabolized by cytochrome P450 (CYP)-2D6 in the liver. • It has an active metabolite, 4-hydroxyatomoxotine, which undergoes significant glucuronidation.
ELIMINATION	• Renally excreted, less than 3% unchanged.
ABSORPTION	• Extent of absorption is unaffected by food. • The rate of absorption is reduced when given with food in adults (by 37%) and time to peak levels prolonged (by 3 hours); however, AUC is unaffected.
HALF-LIFE	• 4-5 hours in extensive metabolizers • 22 hours in poor metabolizers.
BIOAVAILABILITY	• 63% in extensive metabolizers. • 94% in poor metabolizers.
C_{max}	• 1-2 hours
PROTEIN BINDING	• 98% (albumin)

FDA Approved Indication(s) and Off-label Uses[9]

Atomoxetine is indicated in the treatment of ADHD in children, adolescents and adults.

Current VA National Formulary Status

Atomoxetine is not currently on the VA National Formulary. Methylphenidate is currently on the VA National Formulary.

Dosage and Administration[1, 2, 10]

The safety of single doses over 120mg and total daily doses above 150mg has not been systematically evaluated.

Adult*s* - Initiate at a total daily dose of 40mg and increase after a minimum of 3 days to target total daily dose of approximately 80mg administered as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After 2-4 additional weeks, the dose maybe increased to a maximum of 100mg in patients who have not achieved an optimal response. The maximum recommended total daily dose in child and adolescents over 70kg as well as adults is 100mg.

Maintenance/extended treatment – There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with atomoxetine. However, pharmacological treatment of ADHD may be needed for extended periods. Patients should be periodically re-evaluated if on the drug long-term.

Hepatic function impairment – For ADHD patients with hepatic insufficiency, dosage is recommended as follows:

- Moderate hepatic function impairment (Child-Pugh Class B) Initial and target doses should be reduced to 50% of normal dose.
- Severe hepatic function impairment (Child-Pugh Class C) Initial and target doses should be reduced to 25% of normal dose.

Concomitant use with strong CYP2D6 inhibitors – Initiate at 40mg/day and only increase to the usual target dose of 80mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Renal insufficiency – No dosage adjustment required.

Discontinuation – Atomoxetine can be discontinued without being tapered.

Adverse Effects (Safety Data) [1,2]:

Common Treatment-Emergent Adverse Events Associated with the Use of Atomoxetine in Acute (up to 10 weeks) Adult Trials.

Adverse Event	% of patients reporting event	
System Organ Class/Adverse Event	STRATTERA (n=269)	PLACEBO (n=263)
CARDIAC DISORDER		
Palpitations	4	1
GASTROINTESTINAL DISORDERS		
Constipation	10	4
Dry mouth	21	6
Dyspepsia	6	4
Flatulence	2	1
Nausea	12	5
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue and/or lethargy	7	4
Pyrexia	3	2
Rigors	3	1
INVESTIGATIONS AND INFESTATIONS		
Sinusitis	6	4
INVESTIGATIONS		
Weight decreased	2	1
METABOLISM AND NUTRITIONAL DISORDERS		
Appetite decreased	10	3
MUSCULOSKELETAL, CONNECTIVE TISSUE, AND BONE DISORDERS		
Myalgia	3	2
NERVOUS SYSTEM DISORDERS		
Dizziness	6	2
Headache	17	17
Insomnia and/or middle insomnia	16	8
Paresthesia	4	2
Sinus headache	3	1
PSYCHIATRIC DISORDER		
Abnormal dreams	4	3
Libido decreased	6	2
Sleep disorder	4	2
RENAL AND URINARY DISORDERS		
Urinary hesitation and/or urinary retention and/or difficulty in micturition	8	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Dysmenorrhoea[2]	7	3
Ejaculation failure and/or ejaculation disorder[1]	5	2
Erectile disturbances[1]	7	1
Impotence[1]	3	0
Menses delayed[2]	2	1
Menstrual disorder[2]	3	2
Menstruation irregular[2]	2	0
Orgasm abnormal	2	1
Prostatitis[1]	3	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Dermatitis	2	1
Sweating increased	4	1
VASCULAR DISORDER		
Hot flushes	3	1

1=Based on total number of males (Strattera, n=174; placebo, n=172)
2=Based on total number of females (Strattera, n=95; placebo, n=91)

Precautions/Contraindications[1, 2]

Atomoxetine is contraindicated in the following:

- Patients with know hypersensitivity to atomoxetine or other constituents of the product.
- Patients with narrow angle glaucoma. In clinical trials, atomoxetine use was associated with mydriasis.
- Patients taking monoamine oxidase inhibitor (MAOI) or within 2 weeks after discontinuation of an MAOI. There have been reports of serious, sometimes fatal reports when taken with other medications that affect the monoamine concentration in the brain. Some of the reactions reported include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma.

Drug Interactions[2]

Precipitant drug	Object drug	Description
Atomoxetine	Albuterol ↑	Administer with caution because the cardiovascular action of albuterol can be potentiated.
CYP2D6 inhibitors	Atomoxetine ↑	Co administration causes an increase in the AUC and C_{max} at steady state. Dosage adjustment may be necessary.
MAOIs	Atomoxetine ↑	Co administration is contraindicated.
Pressor agents	Atomoxetine ↑	Administer with caution because of possible effects on blood pressure.
Atomoxetine	Pressor agents ↑	Administer with caution because of possible effects on blood pressure.

↑=Object drug increased.

Efficacy Measures[11, 12]

The Connors' Adult ADHD Rating Scale (CAARS), Hamilton Depression Rating Scale, Beck Depression Inventory and Hamilton Anxiety Rating scale were utilized to determine the efficacy of atomoxetine in the randomized, placebo-controlled studies

Clinical Trials[11]

Citation	**Michelson D, Lenard A, Spencer T et al. Atomoxetine in adults with ADHD: Two randomized placebo-controlled studies. Biological Psychiatry 2003; 53:112-120.**
Study Goals	To determine the efficacy of atomoxetine in the treatment of attention deficit/hyperactivity disorder (ADHD) in adults.
Methods	• **Study Design** ➢ Two identical studies. ➢ Randomized, prospective, double-blind, placebo-controlled design. ➢ Multi-center ➢ Study I (N=280) and Study II (N=256) ➢ Initial 1-week medication washout and evaluation period ➢ 2-week placebo lead-in phase ➢ Patients were randomized to receive atomoxetine or placebo for 10 weeks. ➢ Patients received a daily dose of atomoxetine 60mg in divided doses. ➢ Patients with residual symptoms after the initial dose received 90mg/day after 2 weeks and 120mg/day after 4 weeks. ➢ Primary outcome measure was a comparison of atomoxetine and placebo using repeated measures mixed model analysis of post baseline values of Conner's Adult ADHD Rating scale. ➢ Intent to treat was utilized. • **Data Analysis** ➢ T-score and Analysis of Variance (ANOVA) were utilized. ➢ Last observation carried forward (LOCF) was utilized for secondary efficacy analysis and safety analysis of continuous measures. ➢ Fisher's Exact Test was utilized to assess the treatment difference in binary measures. ➢ P=0.05
Criteria	• **Inclusion criteria** ➢ Moderate symptom severity. ➢ Diagnosis had to be corroborated by a second reporter for ADHD symptoms (parent or sibling or significant other). • **Exclusion criteria** ➢ Major depression ➢ Anxiety disorder ➢ Current or past diagnosis of bipolar or psychotic disorder ➢ Serious medical illness ➢ Patients who met DSM-IV criteria for alcohol dependence ➢ Patients actively using drugs of abuse at the study time
Results	Please see **Table 1** for efficacy outcomes
Conclusions	The authors concluded that atomoxetine appears to be an efficacious treatment for adult ADHD. Its lack of abuse may be an advantage for many people.
Critique	• **Strengths** ➢ Multi-center ➢ Randomized ➢ Large study size ➢ The objectives were specifically stated and the introduction provided an adequate overview of the study. ➢ The patients and researchers were blinded • **Limitations** ➢ The scales used were not well defined.
Funding	• Eli Lilly and company

Table 1.

	STUDY I				STUDY II			
	Placebo (n =134)	Atomoxetine (n = 133)	(95% CI)	P value	Placebo (n = 124)	Atomoxetine (n = 124)	(95% CI)	P value
CAARS-INV								
Total ADHD symptom score	-6.0 (9.3)	-9.5 (10.1)	(-5.61, -0.99)	.005	-6.7 (9.3)	-10.5 (10.9)	(-6.40, -1.49)	.002
Inattentive	-3.1 (5.8)	-5.0 (5.7)	(-3.21, -0.45)	.010	-3.5 (5.3)	-5.8 (6.5)	(-3.84, -0.94)	.001
Hyperactive/Impulsive	-2.9 (4.9)	-4.5 (5.1)	(-2.67, -0.27)	.017	-3.2 (4.7)	-4.7 (5.3)	(-2.78, -0.33)	.013
CAARS-Self (T-Scores)								
Total ADHD symptom score	-9.3 (14.0)	-16.0 (16.2)	(-10.53, -2.47)	.002	-11.6 (16.1)	-17.3 (17.6)	(-10.83, -1.61)	.008
Inattentive	-8.6 (13.8)	-15.9 (16.3)	(-11.00, -2.9)	< .001	-11.3 (16.6)	-17.1 (17.9)	(-10.81, -1.34)	.012
Hyperactive/Impulsive	-7.5 (12.1)	-11.9 (13.5)	(-7.75, -0.94)	.013	-8.8 (13.4)	-12.5 (14.1)	(-8.05, -0.54)	.025
CGI-ADHD-S	-0.4 (1.0)	-0.8 (1.2)	(-0.61, -0.08)	.010	-0.5 (1.0)	-0.9 (1.2)	(-0.67, -0.15)	.002
WRAADDS	-2.9 (4.8)	-5.3 (6.6)	(-3.80, -0.91)	.002	-2.8 (5.7)	-4.5 (5.9)	(-3.27, -0.07)	.041
HAMD-17	-0.6 (4.2)	-0.3 (3.8)	(-0.72, 1.34)	.557	-1.0 (3.5)	0.2 (3.6)	(0.26, 2.21)	.013
HAMA	-1.2 (4.8)	-1.0 (5.3)	(-1.16, 1.38)	.864	-1.0 (5.4)	-0.7 (4.3)	(-1.12, 1.57)	.738
SHEEHAN DISABILITY								
Total	-2.9 (7.7)	-4.5 (8.3)	(-5.14, -0.41)	.022	-4.0 (6.9)	-4.4 (7.9)	(3.21, 1.83)	.589
Work life	-1.0 (3.3)	-1.6 (3.1)	(-2.22, -0.36)	.007	-1.2 (2.9)	-1.8 (3.0)	(-1.76, 0.20)	.118
Family life	-1.0 (2.8)	-1.5 (3.2)	(-1.64, 0.12)	.090	-1.6 (2.7)	-1.4 (2.8)	(-1.08, 0.80)	.773
Social life	-0.9 (3.0)	-1.3 (3.1)	(-1.65, 0.20)	.123	-1.2 (2.8)	-1.2 (2.9)	(-0.77, 1.22)	.654

WRAADDS - Wender Reimher Adult Attention Deficit Disorder Scale
HAMD-17 – 17 Item Hamilton Depression Rating Scale
HAMA – Hamilton Anxiety Rating Scale
CAARS – Conners' Adult Attention Rating Scale; INV – Investigator rated
CGI-ADHD-S – Clinical Global Impressions of Severity of ADHD symptoms
95% CI – 95% confidence interval of the treatment difference (atomoxetine-placebo)

Clinical Trials[12]

<table>
<tr><td>Citation</td><td>Thomas T, Biederman J, Wilen T et al. Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. American Journal of Psychiatry 1998; 155(5): 693-695.</td></tr>
<tr><td>Study Goals</td><td>To determine the effectiveness and tolerability of atomoxetine in the treatment of attention deficit/hyperactivity disorder (ADHD) in adults.</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Randomized, double-blind, placebo-controlled, crossover study.
➢ Study design included two 3-week treatment periods separated by 1 week of washout.
➢ 21 patients (11 women and 10 men) participated in the study.
➢ Study medication was titrated up to 40mg/day by week 1 and 80mg/day by week 2 and maintained at 80mg/day by week 3 unless adverse effects emerged.
➢ ADHD Rating Scale was administered weekly.
➢ A reduction in ADHD Rating Score of 30% or more was considered an improvement.
• Data Analysis
➢ McNemar test was used to compare paired data between two time points.
➢ Wilcoxon signed rank test was used for nonparametric testing.
➢ T test was utilized for parametric testing of continuous data.</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Between 19-60 years of age.
➢
• Exclusion criteria
➢ Clinically significant chronic medical conditions
➢ Abnormal baseline laboratory values
➢ Mental retardation (IQ less than 75)
➢ Organic brain disorders
➢ Clinical unstable active psychiatric conditions
➢ Drug or alcohol abuse within the last 6 months
➢ Current use of psychotropics
➢ Pregnant and breast-feeding females.</td></tr>
<tr><td>Results</td><td>• 11 of 21 patients showed improvement in ADHD symptoms while on tomoxetine compared to 2 who improved while on placebo. Chi squared 7.4 df=1 p< 0.01

<table>
<tr><td colspan="3">Superiority of tomoxetine over placebo in improving ADHD symptoms</td></tr>
<tr><td>z</td><td>n</td><td>p</td></tr>
<tr><td>3.2</td><td>21</td><td><0.01</td></tr>
</table>

<table>
<tr><td colspan="3">ADHD Rating Scale mean Scores</td></tr>
<tr><td>Tomoxetine</td><td></td><td></td></tr>
<tr><td></td><td>Baseline</td><td>SD</td></tr>
<tr><td></td><td>30</td><td>6.7</td></tr>
<tr><td></td><td>After 3 weeks</td><td>SD</td></tr>
<tr><td></td><td>21.5</td><td>10.1</td></tr>
<tr><td>Placebo</td><td></td><td></td></tr>
<tr><td></td><td>Baseline</td><td>SD</td></tr>
<tr><td></td><td>29.4</td><td>6.7</td></tr>
<tr><td></td><td>After 3 weeks</td><td>SD</td></tr>
<tr><td></td><td>29.7</td><td>8.8</td></tr>
</table>
</td></tr>
<tr><td>Conclusions</td><td>The authors concluded that this preliminary study showed that tomoxetine was effective in treating adult ADHD and was well tolerated.</td></tr>
</table>

Critique	• **Strengths** ➢ Multi-center ➢ Randomized, double blind ➢ Intent-to-treat was utilized • **Limitations** ➢ Small number of patients.
Funding	• Eli Lilly and Company & NIMH grant

Acquisition Costs

Drug	Cost/capsule	Average dose	Cost/month
Atomoxetine	$1.84	80 mg/day	$110.40
Methylphenidate ER(generic) 20 mg	$1.00	20-30 mg/day	$30.00-45.00
Methylphenidate LA(Ritalin LA) 20 mg	$1.29	20-30 mg/day	$38.70-58.05
Mixed salts of dextro-amphetamine (Adderall XR)	$1.40	20-30 mg/day	$42.00-63.00

Conclusions

Atomoxetine has been proven efficacious in the treatment of adult ADHD. Currently, it is the only FDA approved agent for this indication. It offers a unique mechanism of action as well as not having an addiction potential. Concerning side effects in the adult population include, sexual dysfunction, dysmenorrhea, urinary retention and transient increases in heart rate and blood pressure. Additionally, there is the potential for multiple drug interactions with the agent since it is a strong CYP2D6 inhibitor.

Recommendations

The incidence of ADHD in adults is 3-5%. Of this population approximately 13% will require treatment. Although atomoxetine provides a unique mechanism of action and is not considered addictive, its side effect profile and possible drug interaction profile may limit use in an adult population. It is recommended to keep the agent non-formulary at both a national and VISN level.

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12. Spence T, Biederman J, Wilens T at al. Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. The American Journal of Psychiatry 1998; 155 (5): 693-695.

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