Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Atomoxetine

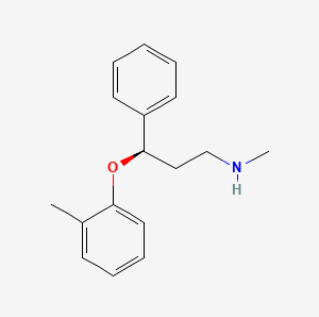
Evidence Summary

Atomoxetine improves attention in ADHD, but results are mixed for MCI, AD, PD, and other neurodiseases. It has many drug interactions and is contraindicated in severe cardiovascular disorders.

Neuroprotective Benefit: Atomoxetine improves attention in people with ADHD. Atomoxetine failed to improve cognitive function in AD and PD, but trends for improvement in fluid and imaging biomarkers were seen in people with MCI.

Aging and related health concerns: No studies have tested atomoxetine for age-related conditions other than those involving the central nervous system.

Safety: Side effects may include increased blood pressure, increased heart rate, nausea, vomiting, constipation, dry mouth, loss of appetite, dizziness, and urination problems. It is contraindicated in people with severe cardiac or vascular disorders.

Availability: Rx for ADHD	**Dose**: For adults with attention deficit disorder, the initial dose is 40 mg/day orally for at least 3 days, followed by 80 mg/day for 2 to 4 weeks. The dose may be increased up to 100 mg/day.	**Chemical formula:** $C_{17}H_{21}NO$ **MW**: 255.35  Source: PubChem
Half-life: 3 to 5.6 hours, depending on CYP2D6 polymorphisms	**BBB**: penetrant	
Clinical trials: A meta-analysis of 13 randomized controlled trials included a total of 1,824 adult patients with ADHD.	**Observational studies**: none available	

What is it? Atomoxetine (marketed as Strattera) is a selective norepinephrine reuptake inhibitor used for the treatment of attention deficit hyperactivity disorder (ADHD) in combination with psychological, social, and other treatment modalities (DrugBank.com). Although the underlying pathology of ADHD remains unclear, it is thought that dysregulation of noradrenergic and dopaminergic pathways plays a role in suboptimal cognitive functions including attention and executive function. Atomoxetine increases norepinephrine and dopamine levels in the prefrontal cortex by inhibiting reuptake, increasing the availability of norepinephrine in the extracellular space, resulting in improved ADHD symptoms.

The locus coeruleus region of the brain innervates and supplies norepinephrine to the forebrain to regulate cognition, behavior, and arousal. The spiking pattern of the locus coeruleus regulates arousal state and alertness, while depletion of norepinephrine in the forebrain leads to attention deficit and cognitive dysfunction. The locus coeruleus degenerates in Alzheimer's disease and contributes to cognitive decline (Marcyniuk et al., 1986; Chalermpalanupap et al., 2013; Levey et al., 2022). Norepinephrine in the brain can suppress the production and release of proinflammatory cytokines. Thus, atomoxetine has also been studied in people with Alzheimer's disease, mild cognitive impairment (MCI), poststroke aphasia, Parkinson's disease, postural orthostatic tachycardia syndrome, and traumatic brain injury.

Neuroprotective Benefit: Atomoxetine improves attention in people with ADHD. Atomoxetine failed to improve cognitive function in AD and PD, but trends for improvement in fluid and imaging biomarkers were seen in people with MCI.

Types of evidence:

- 5 meta-analyses (3 in ADHD, 1 in schizophrenia, and 1 in Parkinson's disease with cognitive deficits)
- 3 clinical trials (1 in mild cognitive impairment, 1 in Alzheimer's disease, and 1 in Parkinson's disease)
- 2 retrospective analyses (1 in people with poststroke aphasia and cognitive impairment and 1 in postural orthostatic tachycardia syndrome)
- 3 reviews
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

People with ADHD: IMPROVES ATTENTION, REDUCES IMPULSIVITY/HYPERACTIVITY
In a meta-analysis of 13 randomized controlled trials including a total of 1,824 adults with ADHD, atomoxetine treatment (25-120 mg/day) for 10-24 weeks showed superior efficacy than placebo on overall adult ADHD scores (standardized mean difference in Conners' Adult ADHD Rating Scale, or CAARS scores; -0.45; 95% CI, -0.54 to -0.34; $p<0.00001$), inattention (-0.42; 95% CI, -0.49 to -0.35; $p<0.00001$) and impulsivity/hyperactivity (-0.36; 95% CI, -0.44 to -0.29; $p<0.00001$)(Ravishankar et al., 2016). Atomoxetine was more efficacious in treating inattention compared to hyperactivity/impulsivity.

In a pooled analysis of 2 double-blind randomized controlled trials enrolling 1,003 adults with ADHD, atomoxetine treatment (25, 40, 60, 80, or 100 mg/day) for 26 weeks significantly improved the Conners' Adult ADHD Rating Scale (CAARS) compared to placebo, with an effect size of 0.28 at one week, 0.45 at 4 weeks, and 0.52 at 26 weeks (Wietecha et al., 2016). The increase in effect size was most pronounced in the 80 mg group, at 0.82.

In a meta-analysis of 3 randomized controlled trials involving 241 children and adolescents with ADHD, atomoxetine treatment for 6-10 weeks improved parent-rated hyperactivity and parent-rated inattention, though the magnitude of effects is uncertain (Patra et al., 2019).

People with mild cognitive impairment: MIXED FINDINGS

In a double-blind crossover clinical trial of 36 people with mild cognitive impairment (MCI), treatment with atomoxetine for 6 months (starting at 10 mg/day, increased up to 100 mg/day, orally) did not significantly affect cognition or clinical outcomes, but significantly increased plasma and cerebral spinal fluid (CSF) levels of norepinephrine and dopamine, reduced catecholamine metabolites, and reduced CSF tau by 6% and CSF p-tau181 by 4.7% compared to placebo (Levey et al., 2022). Although CSF levels of IL-1α and TECK (measures of neuroinflammation) were prespecified primary outcomes, these were not measurable in most samples (only 15.1% and 49%, respectively). However, there was a trend for atomoxetine treatment to suppress CSF levels of IL-1α levels below detection limit. The odds of having TECK levels below detection limit were not different between atomoxetine and placebo.

There was no significant difference in the proportion of participants who converted from MCI to dementia during the treatment period for atomoxetine (3 out of 39) versus placebo (6 out of 37), which was expected due to the short 6-month duration of each phase (Levey et al., 2022). There were also no treatment effects on general measures of cognition (measured by the MMSE and MoCA). Atomoxetine treatment did not significantly alter neuropsychological measures with the exception of slight worsening on the ADAS-13 and Trails Making B (executive function), but the differences were not significant after statistical adjustment. The authors noted that cognitive benefits from atomoxetine may depend on baseline noradrenergic capacity, with people who have low baseline capacity likely benefiting the most. Longer term studies of atomoxetine could benefit from combining MRI measures of locus coeruleus integrity to enrich the studies. There were no significant treatment effects on the total Neuropsychiatric Inventory (NPI) score or any of the subscales including depression, anxiety, or apathy.

Numerous biofluid biomarkers were investigated in this trial (Levey et al., 2022). There were no significant differences between atomoxetine and placebo for CSF levels of C3, IL-6, IL-7, IL-9, IL-10, IP-10, NfL, TNF, or VEGF. Measures of IL-1β, IL-4, IL-17A, and BDNF were under the limit of detection in all samples. In contrast, plasma brain-derived neurotrophic factor (BDNF) levels were significantly increased by 24.0% (p=0.04; unadjusted) and triglycerides were significantly reduced by −13.4% (p=0.04; unadjusted) with atomoxetine. The locus coeruleus regulates neurotrophin signaling and neurogenesis (Liu et al., 2015). Other plasma biomarkers of lipoprotein-associated oxidative stress and inflammation showed no differences with atomoxetine versus placebo (cholesterol, HDL-c, LDL-c, oxLDL, apoAI, apoB, apoE, hsCRP, nitrotyrosine, and glutamine)(Levey et al., 2022).

In addition, 5 panels of proteins reflecting pathophysiological processes such as synaptic function, glial immunity, metabolism, myelination, and vascular biology were investigated (Levey et al., 2022).

Atomoxetine treatment significantly decreased the synaptic and metabolic panels compared to placebo, which are typically increased in Alzheimer's disease, thus atomoxetine normalized these biomarkers. The glial immunity panel is similarly elevated in Alzheimer's disease but was numerically decreased following atomoxetine treatment that trended towards statistical significance. In an individual analysis, several synaptic (e.g. LDHA, YWHAB) and metabolic (e.g. PGAM1) proteins were among those most significantly decreased following atomoxetine therapy. The inflammation-associated protein ENO1, and DDAH1 of the myelin panel were also decreased after atomoxetine. The vascular panel is decreased in Alzheimer's disease, but two markers (COL14A1, NID2) were significantly increased following atomoxetine treatment.

Atomoxetine treatment was associated with a significantly increased inter-network connectivity between the insula and the hippocampus, as measured by resting state functional MRI, and an increased glucose uptake in the hippocampus (p=0.036), parahippocampal gyrus (p=0.023), middle temporal pole (p=0.021), inferior temporal gyrus (p=0.022), and fusiform gyrus (p=0.027), measured by FDG-PET (Levey et al., 2022). Significantly decreased standard uptake value ratio due to atomoxetine was found in the inferior frontal orbital gyrus (p=0.046), and the calcarine (p=0.023). Carry-over effects of atomoxetine were significant in these regions.

People with Alzheimer's disease: LACK OF COGNITIVE BENEFIT

In a double-blind randomized controlled trial of 92 patients with mild-to-moderate Alzheimer's disease, atomoxetine treatment (25-80 mg/day; mean final dose of 63.9 mg/day) added to ongoing acetylcholine esterase inhibitor therapy for 6 months did not significantly improve scores of cognitive function, global clinical impression, or neuropsychiatric symptoms (Mohs et al., 2009). The enrollment of 124 patients was originally planned for this clinical trial, but the study was terminated early after a futility analysis. The primary measure of efficacy was the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) total score, but neither the atomoxetine or placebo groups showed a significant change from baseline and the change from baseline were not different between the two groups. When patients were stratified by baseline cognitive function (MMSE at or above 19 vs at or below 18), patients with lower baseline cognitive function receiving atomoxetine showed a significant worsening from baseline in ADAS-Cog score that was not seen in the placebo-treated group. ADAS-Cog scores in higher functioning patients did not change significantly from baseline with atomoxetine or placebo. No significant treatment effects were found for the Clinical Global Impression-Severity (CGI-S), the Clinician's Interview-Based Impression of Change score (CIBIC), or the Neuropsychiatric Inventory (NPI) total score. Though the atomoxetine-treated group showed a worsening on the NPI total and on NPI appetite/eating change item, and the placebo group showed a significant worsening on the agitation/aggression item.

For daily function, the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) score significantly deteriorated from baseline in the placebo group but was not significantly different from the change from baseline observed in the atomoxetine group.

People with Parkinson's disease and cognitive impairment: LACK OF COGNITIVE BENEFIT
In a meta-analysis of 3 clinical trials including patients with Parkinson's disease and cognitive deficits, atomoxetine treatment (dose titrated, up to 80-100 mg/day, orally) for at least 8 weeks did not significantly improve complex attention, executive function, perceptual-motor function, language, social cognition, or learning and memory (Ghosh et al., 2020). An improvement in global cognition (MMSE) was seen in Parkinson's disease patients without mild cognitive impairment, but this was based on a single study. A trend for worsening on executive function was observed after atomoxetine treatment.

In a double-blind crossover trial enrolling 33 patients with Parkinson's disease, a single dose of atomoxetine (40 mg, orally) increased connectivity from the right inferior frontal gyrus to the dorsal anterior cingulate based on a functional MRI study (Borchert et al., 2016). These two brain regions form a critical network for executive function. Also, the atomoxetine-induced change in connectivity from right inferior frontal gyrus to the dorsolateral prefrontal cortex was proportional to the change in verbal fluency. These findings suggest that atomoxetine may restore prefrontal networks related to executive functions.

People with poststroke aphasia and cognitive impairment: INCONCLUSIVE
Cognitive impairment and aphasia are common after a stroke. In a retrospective analysis of medical charts that included information from 106 patients with poststroke aphasia and cognitive impairment, atomoxetine treatment (initial dose of 10 mg/day, then increased to 18 mg/day, then to 25 mg/day) significantly improved cognitive scores (Korean version of the MMSE; K-MMSE) and the Aphasia Quotient (AQ) scores, but the control group (received treatment other than atomoxetine) also improved ((Park et al., 2022). The improvements in K-MMSE were significantly greater in the atomoxetine-treated group than in the control group. The atomoxetine group also had significantly higher AQ scores than the control group, especially for auditory verbal comprehension and naming. Because this was not a prospective double-blind randomized controlled study, these findings are not conclusive. For example, the atomoxetine group and the control group both received treatments including cerebrolysin, dopamine, methylphenidate, and cholinergic drugs, but there were imbalances. Methylphenidate use was more frequent in the control group compared to atomoxetine group (18 vs 7), and cerebrolysin injections were administered only in the control group (22 vs 0). Also, the duration of speech therapy and cognitive therapy were not accounted for or balanced across the two groups.

People with traumatic brain injury and chronic cognitive impairment: LACK OF BENEFIT
In a Cochrane review of 4 studies including a total of 274 participants with chronic cognitive impairment due to traumatic brain injury, a meta-analysis could not be performed due to the small number and heterogeneity of studies (Dougall et al., 2015). There was only one randomized placebo-controlled crossover trial examining the efficacy of atomoxetine in the treatment of attention impairment following traumatic brain injury (Ripley et al., 2014). Atomoxetine treatment (40 mg, twice daily) for 2 weeks did not significantly improve attention, as measured by the Cognitive Drug Research Power of Attention domain or the Stroop Interference score.

People with postural orthostatic tachycardia syndrome (POTS): LESS EFFECTIVE COMPARED TO METHYLPHENIDATE
POTS is often accompanied by severe fatigue and cognitive dysfunction. In a retrospective analysis of 517 patients with POTS who were chronically treated for fatigue and/or cognitive dysfunction, overall treatment efficacy was 68.8% when all treatments were combined, with medication effectiveness ranging from 53.1% with methylphenidate and 16.5% with atomoxetine (Boris et al., 2018). The majority of patients were treated with methylphenidate, followed by mixed amphetamine salts and atomoxetine. Patients often required a median of two different medications before achieving clinical improvement.

People with schizophrenia: MIXED/INCONCLUSIVE
In a meta-analysis of 22 double-blind randomized controlled trials testing different medications for schizophrenia, 4 studies tested atomoxetine but none of these reported improvement in positive symptoms or negative symptoms (Solmi et al., 2019). Based on 2 studies, atomoxetine failed to improve global measures of intelligence, processing speed, motor speed, verbal fluency, problem solving, verbal learning, visual memory, and attention. In a different study, atomoxetine failed to show treatment effects on cognition compared to placebo, but atomoxetine at a dose of 80 mg/day improved visuospatial working memory and verbal fluency compared to baseline. Also, based on an exploratory meta-analysis including data from 2 studies, atomoxetine treatment improved problem solving (p=0.02).

In a placebo-controlled trial in patients with schizophrenia, atomoxetine treatment (80 mg/day, orally) for 8 weeks did not result in cognitive improvement, but significantly increased working memory-related activation of the dorsolateral prefrontal and left posterior cingulate cortices, measured by functional MRI (Friedman et al., 2008).

Mechanisms of action for neuroprotection identified from laboratory and clinical research: Atomoxetine increases norepinephrine and dopamine levels in the prefrontal cortex by inhibiting reuptake, increasing the availability of norepinephrine in the extracellular space, resulting in improved cognitive functions including attention. Atomoxetine improves the phasic-to-tonic ratio of locus coeruleus firing, which is associated with focused attention (Bari and Aston-Jones, 2013). Atomoxetine may also decrease neuroinflammation through the increase in norepinephrine (Levey et al., 2022).

In a study of rhesus monkeys, atomoxetine treatment (0.03, 0.1, 0.3, or 1.0 mg/kg, i.m.) improved attention and behaviors related to impulsivity, compulsivity, and cognitive flexibility (Callahan et al., 2019). Atomoxetine treatment produced a significant improvement in the delayed match to sample task (DMTS) in aged monkeys and reversed the distractor-induced decline in performance at doses of 0.1, 0.3, and 1.0 mg/kg. However, atomoxetine did not significantly improve accuracy on the DMTS without distractors with short or long delays. But subeffective doses of atomoxetine (0.03 mg/kg, i.m.) combined with donepezil (0.05 mg/kg, i.m.) significantly improved performance on the DMTS with short delays.

APOE4 interactions: Unknown.

Aging and related health concerns: No studies have tested atomoxetine for age-related conditions other than those involving the central nervous system.

Types of evidence:

- Few laboratory studies

No studies have examined the efficacy of atomoxetine for age-related conditions other than those related to neurological or neurodegenerative diseases described above. One study in Drosophila flies have reported that atomoxetine prolongs lifespan, but the effects were sex-specific (Shen et al., 2022).

Safety: Side effects may include increased blood pressure, increased heart rate, nausea, vomiting, constipation, dry mouth, loss of appetite, dizziness, and urination problems. It is contraindicated in people with severe cardiac or vascular disorders.

Types of evidence:

- 8 meta-analyses (7 in ADHD, 1 in schizophrenia)
- 2 clinical trials (1 in MCI and 1 in Alzheimer's disease,
- 1 retrospective analysis
- Several reviews

Atomoxetine is contraindicated in patients with severe cardiac or vascular disorders based on the US label, and in patients with severe cardiovascular or cerebrovascular disorders based on the European Summary of Product Characteristics (Reed et al., 2016). Both the US and European labels report the possibility of sudden deaths in people with structural cardiac abnormalities.

Common side effects of atomoxetine include nausea, vomiting, upset stomach, constipation, dry mouth, loss of appetite, mood changes, feeling tired, dizziness, urination problems, and impotence (Drugs.com). Atomoxetine may cause serious side effects, including heart problems, chest pain, psychosis, liver problems, jaundice, painful urination, or painful erection.

Carriers of CYP2D6 genetic variants, which occur in about 10% of the population, slowly metabolize atomoxetine and may accumulate plasma concentrations over 700 ng/ml, while non-carriers show median plasma concentrations of 224.4 (placebo→atomoxetine arm) and 313.8 ng/ml (atomoxetine→placebo arm)(Levey et al., 2022). In a pooled analysis of children and adolescents with ADHD who were treated with atomoxetine for 6-8 weeks, CYP2D6 genotype information was available for 3,254 patients (Michelson et al., 2007). Poor metabolizers had markedly greater reductions in mean symptom severity scores compared with extensive metabolizers, but they also had greater increases in heart rate and diastolic blood pressure, and smaller increases in weight. Several adverse events, including decreased appetite and tremor, were more frequent in poor metabolizers. Differences in tolerability of atomoxetine can occur as a result of CYP2D6 genetic variation or as a result of concurrent intake of other drugs that inhibit CYP2D6.

ADHD patients: In a meta-analysis of 3 randomized controlled trials involving 241 children and adolescents with ADHD, atomoxetine treatment for 6-10 weeks was associated with increased risk of

non-serious adverse effects such as nausea, vomiting, decreased sleep, and decreased appetite (Patra et al., 2019). Fatigue, irritability, tiredness, mood swings, headache, and restlessness were also reported. Although the overall risk of serious adverse events was increased in the atomoxetine group (RR=3; 95% CI, 0.32 to 27.76), the quality of evidence was low, and the increase was not statistically significant.

In a meta-analysis of 22 studies including a total of 46,107 young people and adults with ADHD, who were treated with methylphenidate, atomoxetine, or placebo for 8 to 240 weeks, there were no differences in the number of adverse cardiac events across methylphenidate, atomoxetine, and placebo (Liang et al., 2018). However, children and adolescents treated with atomoxetine had a greater increase in heart rate and systolic blood pressure than those receiving methylphenidate or placebo.

A different meta-analysis of 18 clinical trials examining methylphenidate, amphetamines, and atomoxetine for the treatment of ADHD in children and adolescents also noted that all 3 medications were associated with a small but statistically significant increase in systolic blood pressure (Hennissen et al., 2017). Atomoxetine was also associated with a significant increase in diastolic blood pressure and heart rate. The majority of studies reported data on cardiovascular effects, such as hypertension, heart rate above the 90th percentile, tachycardia, bradycardia, arrhythmia, palpitations, and ECG abnormalities. 12.7%, 12.6%, and 13.1% of subjects experienced cardiovascular effects with methylphenidate, amphetamines, and atomoxetine, respectively, but there were no significant differences across the 3 treatments. Cardiovascular events resolved spontaneously or after doses were changed and the vast majority of patients continued with their medication. The European guidelines on managing adverse effects of ADHD medications recommended that before initiating an ADHD medication, the prescriber should conduct a clinical interview to detect any cardiovascular risk factor, measure baseline heart rate and blood pressure, repeat these measures every 3 to 6 months, perform an auscultation to identify any murmurs, and when specifically indicated, perform a systematic electrocardiogram (Graham et al., 2011).

In a meta-analysis of 11 randomized controlled trials comparing atomoxetine with methylphenidate in children and adolescents with ADHD, methylphenidate showed a higher response rate (RR=1.14), decreased inattention, and a lower risk of adverse events including drowsiness (RR=0.17), nausea (RR=0.49), and vomiting (RR=0.41) compared to atomoxetine (Liu et al., 2017). However, methylphenidate had a significantly higher risk of insomnia (RR=2.27) compared to atomoxetine.

In a review written by authors affiliated with Eli Lilly on the safety of atomoxetine for the treatment of children and adolescents with ADHD, the hazard ratio for suicide-related events during treatment were

calculated as 0.96, based on a large register-based study including 6,818 people receiving atomoxetine (Reed et al., 2016). The frequency of aggression or hostility was not significantly higher with atomoxetine (1.6%) compared to placebo (1.1%). During a 2-year period when 2.233 million adult and pediatric patients took atomoxetine, the reporting rate for seizures was 8 per 100,000 patients. With regards to cardiovascular effects, in a comprehensive review of a clinical trials database (n=8417), most pediatric patients experienced modest increases in heart rate and blood pressure, and 8-12% of patients experienced more pronounced changes (≥20 bpm, ≥15 to 20 mmHg). Approximately 15-26% of the children and adolescents who experienced more pronounced changes in blood pressure and heart rate during treatment with atomoxetine had sustained or progressive increases, which based on the European Summary of Product Characteristics, warns "long-term sustained changes in blood pressure may potentially contribute to clinical consequences such as myocardial hypertrophy''. Also, the European Summary of Product Characteristics and the US label indicate that there is a small but potential risk of QT interval prolongation. Based on placebo-controlled trials, tachycardia was identified in 0.3% (5 out of 1,597) of atomoxetine-treated pediatric patients, relative to 0% (0 out of 934) of placebo-treated patients. In an open-label study, QT interval prolongation was observed in 1.4 % of 711 children and adolescents (≥450 ms in males, ≥470 ms in females), which were not clinically significant at ≥3 years of treatment with atomoxetine. With regards to hepatic adverse events, 133 hepatic adverse events had possible confounding factors and were possibly related to atomoxetine during a 4-year period when atomoxetine was used by about 4.3 million patients. There have been rare cases of severe liver injury, with one case requiring a liver transplantation (described in the US label). In children and adolescents, decreases in weight and height gain occurred with atomoxetine treatment and were greatest in patients of above average weight and height, but appeared to recover over 2-5 years of atomoxetine treatment.

Alzheimer's disease patients: In a double-blind randomized controlled trial of 92 patients with mild-to-moderate Alzheimer's disease, atomoxetine treatment (25-80 mg/day; mean final dose of 63.9 mg/day) added to ongoing acetylcholine esterase inhibitor therapy for 6 months did not result in a significantly different incidence rate of adverse events compared to placebo (Mohs et al., 2009). The only significant differences between groups with laboratory chemistry values were in end point changes of mean cell volume (atomoxetine, +0.5 fL; placebo, −1.3 fL) and urinary specific gravity (atomoxetine, +0.0013; placebo, −0.0024). Five patients (10.6%) discontinued treatment due to an adverse event with atomoxetine, compared to 4 patients (8.9%) in the placebo group. The atomoxetine group showed a significantly greater increase in heart rate (+9.1 bpm compared to +0.9 bpm in placebo; $p<0.001$). Changes in QT intervals were not significantly different between atomoxetine and placebo groups. The mean increase in diastolic blood pressure (+3.7 mmHg) and decrease in weight (-2.1 kg) differed

significantly from the decrease in pressure (-1.2 mmHg) and weight increase (0.7 kg) in the placebo group.

Parkinson's disease patients: In a double-blind randomized controlled trial of 30 patients with Parkinson's disease and mild cognitive impairment, atomoxetine treatment (target dose of 80 mg/day) for 10 weeks did not result in any clinically significant changes in vital signs, serum chemistry, or liver function (Hinson et al., 2016). There was also no evidence of the development of suicidal thoughts, based on the Columbia-Suicide Severity Rating Scale. Adverse events in the atomoxetine group included jitteriness (n=3), reduced urine stream (n=2), a brief episode of chest pain (n=1), kidney stone (n=1), nausea (n=1), syncope (n=1), and possible atrial fibrillation (n=1; the study physician read an electrocardiogram as atrial fibrillation, and the Emergency Department physician read it as an artifact). Adverse events in the placebo group were jitteriness (n=3), worsening memory (n=3), hypertension (n=1), atrial fibrillation (n=1), freezing of gait (n=1), erectile dysfunction (n=1), insomnia (n=1), and fatigue (n=1).

People with mild cognitive impairment: In a double-blind crossover clinical trial of 36 people with mild cognitive impairment (MCI), treatment with atomoxetine for 6 months (starting at 10 mg/day, increased up to 100 mg/day, orally) did not result in significant differences in dropout rates or serious adverse events compared to placebo (Levey et al., 2022). The dropout rate was 5.1% (2 out of 39) in the subjects treated with atomoxetine and 2.7% (1 of 37) in those treated with placebo. Three serious adverse events (7.7%) occurred with atomoxetine (2 of which may have been related to study drug; dizziness and dysautonomia) and 3 (8.1%) with placebo. There were 145 adverse events reported with atomoxetine treatment and 88 with placebo, including some considered definitely related and possibly related to the study drug. The most common adverse events associated with atomoxetine treatment were gastrointestinal symptoms (12 atomoxetine; 4 placebo), dry mouth (10 atomoxetine; 2 placebo), and dizziness (10 atomoxetine; 8 placebo). Heart rate increased 8-9 bpm on atomoxetine. Blood pressure did not change significantly while subjects received atomoxetine compared to placebo, although there was a trend for an increase in diastolic blood pressure. Body weight decreased about 4 pounds on atomoxetine, which after adjustment for baseline corresponds to 2.4% loss of weight (p=0.0001).

Drug interactions: Atomoxetine has 78 major, 221 moderate, and 12 minor drug interactions (Drugs.com). These include antidepressants, asthma medications, blood pressure medications, cold/allergy medications (e.g., pseutoephedrine or phenylephrine), and others. Taking monoamine oxidase inhibitors (e.g., isocarboxazid, linezolid, metaxalone, methylene blue, moclobemide, phenelzine,

procabazine, rasagiline, safinamide, selegiline, and tranylcypromine) with atomoxetine may cause a serious, possibly fatal, drug interaction (WebMD.com).

Sources and dosing: Atomoxetine is marketed as Strattera (Eli Lilly) for the treatment of ADHD. For adults with ADD, the initial dose is 40 mg/day orally for at least 3 days, followed by 80 mg/day for 2 to 4 weeks (Drugs.com). The dose may be increased up to 100 mg/day.

Research underway: There are currently 23 ongoing clinical trials testing atomoxetine, based on ClinicalTrials.gov. While most studies are in ADHD patients, studies are also investigating atomoxetine for obesity, alcohol use disorder, vasovagal syncope, obstructive sleep apnea, Tourette syndrome, Parkinson's disease, and neurogenic orthostatic hypotension.

Search terms:
Pubmed, Google: atomoxetine

- + Alzheimer, + clinical trial, + cognitive, + meta-analysis, + Cochrane, + APOE4, + apolipoprotein, + lifespan

Websites visited for atomoxetine:

- Clinicaltrials.gov
- NIH RePORTER
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma (0)
- Pharmapro.com (0)

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