Evaluation of the effects of atomoxetine on human organs: A systematic Review

Abstract

Atomoxetine is a norepinephrine reuptake inhibitor. It is used to treat ADHD syndrome through increasing norepinephrine concentration in the synapses and consequently overstimulation of adrenergic receptors. Though, in recent years several reports have been published on the adverse effects and complications of atomoxetine overuse. As a result, this study is conducted to assess the effects of atomoxetine on different human organs. This is a review article in which 54 relevant papers have been evaluated- these studies were found through searching in valid electronic and library databases such as PubMed, Scopus, Google Scholar, Medline, and Embase to assess treatment protocols, effectiveness, and adverse effects of atomoxetine. Clinical and experimental studies have proved the side effects and complications of high-dose atomoxetine on weight loss, urinary system complications, cardiovascular issues, liver disorders, behavioural and nervous system problems**.** Results of the evaluated studies suggest that many patients arbitrarily use high-dose atomoxetine for long-term which may lead to irreversible problems and complications. Consequently, avoiding high-dose atomoxetine is suggested especially in pregnant women and patients with liver disorders.

Key Words: Atomoxetine, Side Effect, ADHD, human organs, review.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a persistent pattern of lack of attention, hyperactivity and impulsive behaviour which is more severe compared to what is usually seen in children with similar growth level. To purpose this diagnosis, some signs should be present before the age of 7. Though, many ADHD cases are diagnosed some years after the onset of the signs. The disorder should be present in at least two fields and the individual's function should be disturbed considering growth level in social, educational, or occupational fields [1].

Medications used in ADHD treatment mainly act by attenuating the function of cerebral neurotransmitters epically serotonin, norepinephrine, dopamine, etc. [1, 2]. Benzodiazepines are medications used as anti-anxiety agents though their usage is limited due to side effects such as addiction, drowsiness and learning disorders [3]. Atomoxetine is a norepinephrine reuptake inhibitor used for in the treatment of children and adults with ADHD, unlike Ritalin, an over-the-counter stimulant. Compared to other ADHD medications, Atomoxetine takes at least two weeks for onset of action. [4]. Atomoxetine (Strattera) is an approved non- CNS stimulant medication. It is a norepinephrine reuptake inhibitor with approved effectiveness in ADHD [5].

Atomoxetine exerts its effects on ADHD treatment through inhibiting the reuptake of norepinephrine. A study which was conducted on the effect of atomoxetine in animal models showed that serotonin is a type of selective reuptake inhibitor which increases serotonin extracellular level through inhibiting serotonin rapid reuptake in presynaptic neuronal receptors and thus provides higher serotonin level for the receptors [6]. In the anterior cerebral cortex, there is an increase in the extracellular levels of norepinephrine and dopamine (but not serotonin) as well as extracellular epinephrine in subcortical regions (but not dopamine). Elevated norepinephrine level may play a role in the effectiveness of atomoxetine in improving ADHD symptoms which support the hypothesis that atomoxetine is involved in the recovery of disorders such as depression and anxiety. Reduced dopamine transfer in subcortical regions may indicate that atomoxetine abuse may be engaged in neural disorders such as ticks and behavioural disorders [6]. The most common atomoxetine side effects include nausea, loss of appetite, drowsiness, fatigue, and high blood pressure; though, it is known lately that atomoxetine, in some cases, may damage nervous, psychological, cardiovascular, and musculoskeletal systems, as well as liver and kidneys [6]. There is a need to evaluate the proposed effects and side effects of atomoxetine on different human organs, hence this review comprises of several different effects of atomoxetine.

This literature database analysis was based on recorder methods in PROSPERO. Study protocol outline includes the evaluation of the effect of atomoxetine on different human organs. In the current study, 83 studies have been used which includes original study, review articles, double-blind studies, and clinical trials. After the initial investigations and exclusion of irrelevant studies and animal studies, 54 relevant studies were chosen for this study. Investigators used electronic database search strategies in valid databases such as PubMed, Scopus, Google Scholar, Medline, and Embase considering Atomoxetine, Cardiovascular, Urinary System, Endocrine System, Liver Function, Nervous System, and Behavioral system key words to obtain relevant studies published until 2019, September, 10 without any language limitation.

In this study, researchers evaluated data of different studies with the analysis of internal consistency and their results.

We extracted the following variables for each study: Setting, eligibility criteria, details of intervention and control regimens, and study duration. Subsequently, the authors reported their findings.

Literature database analysis

Antidepressants and hypnotics are widely used in the treatment of neural and psychological disorders. Atomoxetine is the first non-stimulant approved medication in the treatment of ADHD. Atomoxetine is classified as a norepinephrine reuptake inhibitor (for children, adolescents, and adults), though the effectiveness of this medication is not yet approved in children below 6 years old. The superiority of this medication is lower abuse potential, compared with stimulant medications. Atomoxetine is introduced as an appropriate medication in ADHD treatment, agitation reduction and hypnotic. Yet, high-dose atomoxetine may lead to a variety of disorders. Consequently, we tried to assess the effects of atomoxetine on different human body organs.

Atomoxetine effects of the cardiovascular system

Hennissen et al. (2017) showed in a systematic review that atomoxetine and amphetamine may increase heart rate, systolic and diastolic blood pressure in both children and adults with ADHD [7]. In 2013, Fuentes et al. conducted a study to assess the effect of 0.5-1.8 mg/kg atomoxetine on heart rate, systolic and diastolic blood pressure during 6 months in children and adults with ADHD. Results of this study suggested that atomoxetine increases heart rate by 2.9 beats per minute, systolic blood pressure by 0.8 mmHg, and diastolic blood pressure by 0.2 mmHg [8]. Go et al. (2017), in a case report of a 14-year-old boy with ADHD who was treated with 1mg/kg/day atomoxetine since being 5 years old, showed that long-term atomoxetine increased the heart rate from 97 bpm to 150-160 bmp. Authors of this study concluded that atomoxetine may induce hyperadrenergic postural tachycardia syndrome(POTS) [9].

Green et al. (2013) studied 27 adults with ADHD who received 40 mg atomoxetine and demonstrated that long-term atomoxetine may worsen hyperadrenergic postural tachycardia syndrome (POTS) [10]. In a meta-analysis, researchers concluded that atomoxetine may increase systolic and diastolic blood pressures and heart rate in children [21] which was consistent with the results of this study [12-21]. Moreover, different studies suggest that long-term atomoxetine and methylphenidate may be involved in cardiac events in children and adults with ADHD [12-26].

Takotsubo cardiomyopathy is a cardiac disorder caused by coronary artery vasospasm induced by catecholamines [27, 28]. Naguy et al. (2016) stated in a case report that 40 mg/kg atomoxetine in adults with ADHD may be involved in the pathogenesis of Takotsubo cardiomyopathy [29]. In Michelson et al. study in 2007, authors concluded that atomoxetine with doses above 1.8 mg/kg/day in poor CYP2D6 metabolizers may be involved in the pathogenesis of cardiovascular diseases [30]. Kelly et al. (2005) concluded that acute atomoxetine dose (60 mg) in patients with ADHD increases blood pressure and heart rate [31].

Atomoxetine effects on the behavioural system

Geller et al. (2007) conducted a double-blind clinical trial on 176 children and adolescents with ADHD and anxiety disorder and social phobia ageing 8-17 years who were under atomoxetine treatment. Results of their study indicated that 1.3 mg/kg/day atomoxetine for 10 weeks significantly improves the symptoms of ADHD and anxiety disorders [33]. Kratochvil et al. (2005) performed a study on 173 patients with ADHD and depression ageing 7-17 years. A group of patients received 20 mg/day fluoxetine in whom depression symptoms were reduced in 3 weeks. Another group of patients were treated with 1.2 mg/g/day atomoxetine in whom no symptom reduction was reported. The other group received both fluoxetine and atomoxetine in whom symptoms of depression and ADHD were significantly relieved [33]. Harfterkamp et al. (2012) conducted a double-blind clinical trial on 97 patients with ADHD and autism ageing 6-17 years under treatment with 1.2 mg/kg/day atomoxetine for 8 weeks. Results of their study purposed that atomoxetine is effective in reducing ADHD symptoms and relatively effective in the reduction of autism symptoms [34]. A randomized clinical trial was conducted on 147 alcohol-dependent adults with ADHD who received 25-100 mg/day atomoxetine. Results of this study proved relative improvement of ADHD symptoms and 26% reduction in alcohol consumption days [35].

Atomoxetine effects on the urinary system

Sumner et al. (2006), in a randomized clinical trial on 87 ADHD patients with enuresis under treatment with 1.42 mg/kg/day atomoxetine, concluded that atomoxetine not only improves ADHD symptoms but also reduces enuresis compared with the placebo group [36]. Glazener and Evans (2002) demonstrated that 0.4 mg DDAVP or 50 mg Imipramine in patients with enuresis completely relieves their symptoms. Moreover, in this study, several patients with enuresis were treated with 1.2 mg/kg/day atomoxetine which showed relatively similar results compared with DDAVP or Imipramine [37]. Atomoxetine is the selective inhibitor of norepinephrine reuptake which significantly empowers norepinephrine effects. Efficacy of atomoxetine and imipramine in relieving enuresis symptoms support this theory that noradrenergic agonist drugs may be helpful in the treatment of these patients [38-43].

Atomoxetine effects on weight loss

Some studies showed that atomoxetine stimulates GABA Receptors-A through increasing insulin plasma level and reducing glucagon plasma level, reduce blood sugar level and lead to weight loss [44-46]. The effect of atomoxetine in controlling ADHD in children was comprehensively evaluated in a study. The most common reported the adverse effect of atomoxetine was loss of appetite. Nausea and drowsiness are often reported in the initial steps of atomoxetine therapy and patients may refuse to eat in a situation. Weight loss can be explained by its hypnotic nature [47]. Thus, atomoxetine leads to weight loss by sleep induction and prevention to awaking probably via reducing leptin level. Moreover, studies have shown that high-dose atomoxetine may lead to gastrointestinal disorders such as diarrhoea and malabsorption which may lead to weight loss [48].

On the other hand, atomoxetine may directly affect neuronal and endocrine systems engaged in growth hormone inhibition [48]. Deshmukh et al. (2016) concluded in their study 'Appetite and weight loss in children on atomoxetine therapy: an exploratory clinical study' that atomoxetine is widely used in the treatment of patients with ADHD. Frequency and severity of side effects of loss of appetite and weight loss were assessed in ADHD patients under treatment with 0.5-1

mg/kg/day atomoxetine which revealed significant weight loss in 61% of patients after receiving atomoxetine [49].

Atomoxetine effects on the nervous system (Facial nerve paralysis)

Unilateral facial nerve paralysis leads to the paralysis of facial muscles of the same side which leads to a facial deformity due to muscular asymmetry [50]. Bell's palsy is the most common facial nerve functional disorder. Facial never originate from the brainstem and innervates facial muscles. Several evidences support immune-inflammatory-viral mechanism of bell's palsy. Herpes zoster, infections, immunologic disorder, brain tumours, trauma, and hypertension may cause this reaction. Since atomoxetine increases blood pressure, it may increase the risk of bell's palsy. Kobayashi et al. (2008) studied facial paralysis of a 9-year-old Japanese son and concluded that 1.1 mg/kg/day atomoxetine resulted in hypertension and facial paralysis. Drug discontinuation significantly reduced blood pressure and relieved symptoms of facial paralysis [50].

Atomoxetine effects on Liver

Liver damage is a common side effect of many drugs. Almost all drugs can lead to liver damage to some extent. The risk of liver damage varies for different drugs, thus, some drugs may cause liver injury in some individuals if used for a long time. The hepatotoxicity of some drugs is well approved including antibiotics, anti-tuberculosis, NSAIDs, antidepressants, Statins, and herbal medicines [51]. Different kinds of liver damages are among the side effects of antidepressants which may be lethal in some cases of long-term use [52]. On the other hand, long-term atomoxetine (for ADHD treatment), increases the level of hepatic enzymes. In 2004, the FDA issued a serious warning on the hepatic injury caused by high-dose atomoxetine. Atomoxetine is metabolized by P450 (CYP) 2D6. As the dose of atomoxetine increases, the level of hepatic enzymes goes up. Oxidative stress increases the level of hepatic enzymes through increased expression of growth factor in the endothelial and mesenchymal cells in hepatic tissue [53]. Although atomoxetine is associated with less adverse effects compared with stimulant medications, its long-term use disturbs the balance of hepatic enzymes and increases their levels [54]. Potnis et al. concluded in their study 'Drug-Induced Liver Injury in Children: Atomoxetine and Nonstimulants for ADHD' in 2015 that atomoxetine with doses higher than 40 mg/day not only causes side effects (insomnia, nausea, loss of appetite) but also exerts significant destructive effects of hepatic enzymes [51].

Conclusion

Evaluation of several studies on the side effects and complications of atomoxetine suggests that short-term use of atomoxetine with therapeutic dose does not result in any specific side effect both in animal models and human beings. However, high-dose atomoxetine may lead to weight loss, cardiovascular problems, liver dysfunction, urinary system issues, behavioural problems, and nervous system complications. Consequently, considering the available safety experiments on atomoxetine, atomoxetine should be avoided during pregnancy. Furthermore, several clinical trials are required for healthy individuals as well as patients with cardiovascular, renal, hepatic, neural, and psychological diseases.

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