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Review article

A review of atomoxetine effects in young people with developmental disabilities

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ABSTRACT

This review summarizes the pharmacokinetic characteristics, pharmacodynamic properties, common side effects, and clinical advantages and disadvantages associated with atomoxetine (ATX) treatment in typically developing children and adults with ADHD. Then the clinical research to date in developmental disabilities (DD), including autism spectrum disorders (ASD), is summarized and reviewed. Of the 11 relevant reports available, only two were placebo-controlled randomized clinical trials, and both focused on a single DD population (ASD). All trials but one indicated clinical improvement in ADHD symptoms with ATX, although it was difficult to judge the magnitude and validity of reported improvement in the absence of placebo controls. Effects of ATX on co-occurring behavioral and cognitive symptoms were much less consistent. Appetite decrease, nausea, and irritability were the most common adverse events reported among children with DD; clinicians should be aware that, as with stimulants, irritability appears to occur much more commonly in persons with DD than in typically developing individuals. Splitting the dose initially, starting below the recommended starting dose, and titrating slowly may prevent or ameliorate side effects. Patience is needed for the slow build-up of benefit.
Conclusions: ATX holds promise for managing ADHD symptoms in DD, but properly controlled, randomized clinical trials of atomoxetine in intellectual disability and ASD are sorely needed. Clinicians and researchers should be vigilant for the emergence of irritability with ATX treatment. Effects of ATX on cognition in DD are virtually unstudied.

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1. Introduction

Overactivity and inattention are among the most common behavioral concerns for individuals with developmental disabilities (DD; Emerson, 2003). The prevalence of attention-deficit hyperactivity disorder (ADHD) in this population has been estimated at 9–16% (Emerson, 2003; Strømme & Diseth, 2000), substantially exceeding the rate of ADHD in typically developing (TD) individuals. Stimulants such as methylphenidate are the most extensively studied treatment for ADHD in individuals with DD (Handen & Gilchrist, 2006). Findings indicate that individuals with DD are less likely to show therapeutic benefit and more likely to experience negative side effects from stimulants than are TD individuals (Aman, Farmer, Hollway, & Arnold, 2008; Handen & Gilchrist, 2006; Research Units on Pediatric Psychopharmacology Autism Treatment Network [RUPP], 2005). Thus, there remains a need to identify additional treatment options for this common and impairing set of symptoms in individuals with DD.

Atomoxetine (ATX; Strattera) is a nonstimulant medication of considerable interest. Although ATX only received Food and Drug Administration approval in 2002 for treatment of ADHD, there is a large literature base on effectiveness in TD children, adolescents, and adults (Cheng, Chen, Ko, & Ng, 2007; King et al., 2006; Kratochvil, Milton, Vaughan, & Greenhill, 2008). Not surprisingly, because of the difficulties in recruiting and testing individuals with DD, the research on any therapeutic agent tends to lag behind that of the TD population. Comparatively speaking, the literature on ATX in people with DD is very small. Moreover, as illustrated by the research on methylphenidate (Research Units on Pediatric Psychopharmacology Autism Treatment Network [RUPP], 2005), medication effects for individuals with DD may differ from effects seen in TD individuals. It is essential that, to the extent possible, clinical decision making is based on findings on the population with DD. We conducted this review in an effort to summarize the available findings in patients with DD and to compare some of these findings relative to TD patients (e.g., data on adverse events [AEs]). Our aims in this paper were to: (a) provide a general context for assessing ATX in individuals with DD by first providing pharmacological data (pharmacodynamics, pharmacokinetics, side effects) from the general/TD population, (b) comment on general advantages and disadvantages of ATX relative to other ADHD medicines, (c) critically review the existing literature on ATX therapeutic effects in DD, (d) characterize the side effects observed in DD samples to determine if they differ from those seen in the TD population, and (e) provide an overall summary and conclusion about the status quo of ATX research in the field of DD. To the best of our knowledge, there is no similar published review to date.

1.1. Atomoxetine pharmacodynamics

ATX enhances norepinephrine (NE) activity by selectively and potently blocking its reuptake through transporter inhibition and increasing presynaptic concentrations in noradrenergic pathways (Hammerness, McCarthy, Mancuso, Gendron, & Geller, 2009). In the rat, ATX increases NE in regions such as the occipital cortex, lateral hypothalamus, dorsal hippocampus, and cerebellum (Swanson et al., 2006). Increased NE neurotransmission in the prefrontal cortex (PFC) is associated with enhanced attention and higher cognitive processes (Bymaster et al., 2002). ATX increases DA in the PFC because, in contrast to other areas of the brain, DA is taken up by NE transporters in that location. Dopamine is increased in the PFC in animals and is attributed to a common regional uptake inhibition of monoamines (Hammerness et al., 2009; ATX has relatively low affinity for other dopamine and serotonin uptake sites. ATX does not increase the dopamine levels in the nucleus accumbens and associated reward pathways or in the striatum. As a result, it has limited abuse potential and is not associated with tics (Garnock-Jones & Keating, 2009).