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Atomoxetine hydrochloride in the treatment of children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: A placebo-controlled Italian study

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Abstract

Objective: The primary aim of this study was to assess the efficacy of atomoxetine in improving ADHD and ODD symptoms in paediatric patients with ADHD and comorbid oppositional defiant disorder (ODD), non-responders to previous psychological intervention with parent support.
Methods: This was a multicentre, randomised, placebo-controlled trial conducted in patients aged 6–15 years, with ADHD and ODD diagnosed according to the DSM-IV criteria by a structured

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clinical interview (K-SADS-PL). Only subjects who are non-responders to a 6-week standardized parent training were randomised to atomoxetine (up to 1.2 mg/kg/day) or placebo (in a 3:1 ratio) for the following 8-week double blind phase. *Results:* Only 2 of the 156 patients enrolled for the parent support phase (92.9% of males; mean age: 9.9 years), improved after the parent training program; 139 patients were randomised for entering in the study and 137 were eligible for efficacy analysis. At the end of the randomised double blind phase, the mean changes in the Swanson, Nolan and Pelham Rating Scale-Revised (SNAP-IV) ADHD subscale were -8.1 ± 9.2 and -2.0 ± 4.7, respectively in the atomoxetine and in the placebo group ($p<0.001$ between groups); changes in the ODD subscale were -2.7 ± 4.1 and -0.3 ± 2.6, respectively in the two groups ($p=0.001$ between groups). The CGI-ADHD-S score decreased in the atomoxetine group (median change at endpoint: -1.0) compared to no changes in the placebo group ($p<0.001$ between groups). Statistically significant differences between groups, in favour of atomoxetine, were found in the CHIP-CE scores for risk avoidance domain, emotional comfort and individual risk avoidance subdomains. An improvement in all the subscales of Conners Parents (CPRS-R:S) and Teacher (CTRS-R:S) subscales was observed with atomoxetine, except in the cognitive problems subscale in the CTRS-R:S. Only 3 patients treated with atomoxetine discontinued the study due to adverse events. No clinically significant changes of body weight, height and vital signs were observed in both groups. *Conclusions:* Treatment with atomoxetine of children and adolescents with ADHD and ODD, who did not initially respond to parental support, was associated with improvements in symptoms of ADHD and ODD, and general health status. Atomoxetine was well tolerated.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterised by a persistent high level of hyperactive, inattentive and impulsive behaviour, which can be prevalent in both child and adolescent populations. Although information on prevalence and incidence of ADHD in Europe is scarce and depending on the used definition, a range from 2 to 5% (for subjects aged 6–16 years) has been reported in most of studies based on the ICD-10 and DSM-IV diagnostic criteria, respectively (Ralston et al., 2004). A few different epidemiological studies conducted in Italy estimated a frequency of ADHD in the paediatric population ranging from 4% to 7% (Gallucci et al., 1993; Camerini et al., 1996; Mugnaini et al., 2006), with a gender ratio of 7:1 between males and females, aligned with data from international literature (Ralston et al., 2004; Polanczyk et al., 2007). Factor analysis of ADHD and oppositional defiant symptoms reports by both Italian parents and teachers indicate a structure similar to that observed in the US and Northern Europe (Zuddas et al., 2006).

ADHD may be associated with additional psychiatric disorders such as mood and anxiety disorders and disruptive behaviour disorders. In particular, oppositional defiant disorder (ODD) is among the most common comorbid psychiatric disorders in patients with ADHD, occurring in up to 67% of clinically referred populations (Steinhausen et al., 2006) and representing a serious clinical problem. ODD is characterized by a pattern of developmentally inappropriate negativistic, hostile and defiant behaviour causing clinically significant impairment in social, familiar or academic functioning. Genetic, family environment and psychometric studies indicate that they have separate aetiologies and pathophysiological mechanisms (Kirley et al., 2004; Satake et al., 2004; Oosterlaan et al., 2005; Zuddas et al., 2006). Children with ADHD combined with ODD tend to have more severe ADHD symptoms, more peer problems, and more family distress compared to children with ADHD alone (Kuhne et al., 1997). Longitudinal data suggest that ADHD predicts academic occupational dysfunction, earlier sexual intercourse, and early parenthood (Fergusson et al., 1997; Barkley et al., 2006), whereas the presence of ODD may modulate persistence of associated disorders (Lavigne et al., 2001) and may predispose affected children to the subsequent development conduct disorders, delinquent behaviour and substance misuse (Fergusson et al., 1993; Barkley et al., 2004; van Lier et al., 2007).

Clinical studies evaluating the effects of stimulants in treating children with ADHD and comorbid ODD reported inconclusive results. Some of these studies that investigate children with mental retardation, were conducted either in laboratory conditions or very specific settings such as partial hospitalization programs or strictly academic situations (Aman et al., 1997; Hinshaw et al., 1992; Bukstein and Kolko, 1998; Pelham et al., 1985), so that the generalization of their findings does not necessarily extend to the home environment or more natural conditions. Others, without specifically assessing oppositional-defiant symptoms, reported the efficacy of methylphenidate for CD symptoms in ADHD patients with comorbid CD, also indicating that the presence of a diagnosis of ODD or CD diminished the effect size of the drug (Connor et al., 2002; Klein et al., 1997; Hinshaw et al., 1989). The Multicenter Treatment Study of Children with ADHD (MTA study) showed that the presence of ODD did not alter the expected pattern of ADHD symptom response and suggested that ODD symptoms may show greater improvement with pharmacological treatment than with behavioural management (MTA Cooperative Group, 1999).

Atomoxetine hydrochloride is a potent inhibitor of the presynaptic norepinephrine transporters, and has minimal affinity for other neurotransmitter transporters or receptors. In comparative placebo-controlled studies conducted in children, adolescents and adults, atomoxetine consistently reduced symptoms of ADHD (Spencer et al., 1998; Michelson