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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Received 3 January 2009; received in revised form 2 July 2009; accepted 23 July 2009

KEYWORDS
Atomoxetine; Attention-deficit/hyperactivity disorder; Oppositional defiant disorder

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...
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 (Kuhn et al., 1997).

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., 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., 1992; Bukstein and Kolko, 1998; Pelham et al., 1985). 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...
increased heart rate or increased blood pressure; clinically significant cardiovascular disease (including severe drug allergies; current or past (within 3 months) alcohol or anticonvulsants for seizure control; serious risk of suicide; history of psychosis or pervasive development disorder; history of any seizure

The following conditions were excluded from study participation:

- A K-SADS-PL subscale score of at least 15, and a normal intelligence, i.e. a score ≥70 on an Intelligence Quotient (IQ) test. Patients with any of the following conditions were excluded from study participation: body weight <20 kg; history of bipolar I or II disorder, or history of psychosis or pervasive developmental disorder; history of any seizure disorder (other than febrile seizures) or past/comitant intake of anticonvulsants for seizure control; serious risk of suicide; history of severe drug allergies; current or past (within 3 months) alcohol or drug abuse; clinically significant cardiovascular disease (including hypertension) or other conditions that could be worsened by an increased heart rate or increased blood pressure; clinically significant laboratory or ECG abnormalities; medical conditions likely to increase sympathetic nervous system activity or regular intake of sympathomimetic drugs; narrow-angle glaucoma; uncontrolled thyroid dysfunction; likelihood of start of structured psychotherapy at any time during the study; pregnant or breastfeeding females, or females at risk of pregnancy.

2.2. Study design

The entire study consisted of 4 study periods (Fig. 1):

a) Study period I (screening phase): this was a screening and assessment/evaluation period, ranging from 3 to 28 days, to ensure eligibility for the study, and was started after parent's consent was obtained.

b) Study period II (open-label, parent support phase): during this 6-week phase, the investigators provided a standardized management for the parental support. Parents received weekly series of advice on the management of the behavioural problems of their children from qualified psychologists or child neuro-psychiatrists, based on standardized procedures (Vio et al., 1999). With this program, parents were trained to provide clear, consistent expectations, directions and limits to their children, to use modification principles to reinforce positive behaviours and to eliminate or reduce negative behaviours that create problems for their children. Additionally, the training helped parents to become able to assist their children in making friends and learning to work cooperatively with others. Response criteria were defined as an improvement in CGI-S score of 2 or more from baseline and at least a 30% decrease from baseline in 18 items of the ADHD subscale score of investigator-rated SNAP-IV. Only patients who did not reach both mentioned criteria were randomised to the study period III.

c) Study period III (randomised, double blind, placebo-controlled phase). This was an 8-week period of double blind treatment. At the beginning of this period, patients who did not respond to the 6-week period of parent support were randomly assigned to treatment with atomoxetine or placebo in a ratio of 3:1 (i.e. with approximately 75% of patients receiving atomoxetine and 25% of patients receiving placebo). Patients randomised to atomoxetine were titrated, in 7 days, from 0.5 mg/kg/day (dose ranging from 0.5 to 0.8 mg/kg/day) to the target dose of 1.2 mg/kg/day (range from 1.0 to 1.4 mg/kg/day), to be administered for the first 8 weeks of the study once daily in the morning. In case of onset of fatigue or somnolence during the day, the investigator could decide to administer the dose in the evening.

d) Study period IV (long-term, open-label extension phase). This was an open-label, long-term extension phase for patients who had completed study period III. At the end of the 8-week double blind period, all patients had the choice to receive open label atomoxetine treatment for a long-term period until the drug became commercially available. During this phase information on efficacy, health outcomes and safety were collected.

The study periods I–III included 14 visits: visit 1 was the screening visit, weekly visits were placed during the study period II (parent support phase, visits 2–8) and during the initial 4 weeks of the phase III (randomised double blind phase, visits 8–12); the remaining visits (13 and 14) took place every 2 weeks. As study period IV is already ongoing, this article refers to data measured up at the end of the randomised double blind phase.

Antipsychotics, antidepressants, anticonvulsants, anorexics, anticoagulant, benzodiazepines and monoamine oxidase inhibitors were not permitted at any time during the study. Concomitant administration of CYP2D6 inhibitors was not permitted, and in any case they could be used only after consultation and permission of
study staff physicians. Formal individual or family psychotherapy was excluded for the entire duration of the study.

2.3. Outcome measures

Efficacy variables were measured at the start and at the end of period I–III. The primary efficacy measure for this study is the 18 items of the ADHD subscale score of the SNAP-IV. The SNAP-IV is a 26-item scale (0–3 score for each item) that includes 1 item for each of the 18 symptoms contained in the DSM-IV diagnosis of ADHD and 1 item for each of the 8 symptoms contained in the DSM-IV diagnosis of ODD. The SNAP-IV is a widely used measure of the symptoms of ADHD and ODD. It has been validated and normalized in a sample of school-aged children from the US (Swanson, 1992; Gaub and Carlson, 1997). The SNAP-IV yields scores in three domains: inattention (items 1–9), hyperactivity/impulsivity (items 10–18), and oppositional (items 19–26). The inattention, hyperactivity/impulsivity, and combined ADHD scores were considered as the primary efficacy measure while the ODD subscale score was considered a secondary measure in this study.

The CGI-S (Guy, 1976) was used to assess the severity of the patient’s ADHD symptoms, in relation to clinician’s total experience of ADHD patients, on a 7-point scale (from 1=normal, not ill at all, to 7=among the most extremely ill patients).

Other outcome measures of the study included the Conners’ Parent Rating Scale-Revised: Short Form (CPRS-R:S) and the Conners’ Teacher Rating Scale-Revised: Short Form (CTRS-R:S). The CPRS-R:S (Conners, 1997) is a 27-item rating scale completed by the parents to assess problem behaviours related to ADHD. The CTRS-R:S (Conners, 1997) is a 28-item rating scale completed by a teacher to assess problem behaviours related to ADHD in the school setting. Both scales include the oppositional, cognitive problems, hyperactivity ADHD index subscales. In the cases of administration outside of the school sessions, the CTRS-R:S had to be administered at the earliest next time point of school-time or at the last visit prior to the school break in the final assessment.

Patients’ depression and anxiety were scored by means of the Children’s Depression Rating Scale-Revised (CDRS-R) and the Screen for Child Anxiety Related Emotional Disorders (SCARED)-Parent Version, respectively. The CDRS-R (Poznanski and Mokros, 1999) was based on the Hamilton Depression Rating Scale (HAM-D) for adults, but also includes questions about school. This clinician-rated instrument measures presence and severity of depression. A total score below 20 indicates an absence of depression, a score of 20–30 indicates borderline depression and a score of 40–60 indicates moderate depression. The SCARED-Parent Version is a 41-item parent self-report questionnaire (Birmaher et al., 1999), which measures symptoms of DSM-IV linked anxiety disorders in children, aimed at screening for panic disorder, general anxiety disorder, separation anxiety disorder, social phobia, and the presence of a relevant simple phobia, and the school phobia in clinical (Birmaher et al., 1997) and community samples (Muris et al., 1999).

The Health Related Quality of Life (HRQOL) was measured by means of the Child Health and Illness Profile-Child Edition (CHIP-CE). It is a 76-item parent-rated assessment of a child’s health status and level of functioning (Riley et al., 1998) and examines the following domains and sub domains: satisfaction (satisfaction with health, satisfaction with self), comfort (physical comfort, emotional comfort, limitation of activity), risk avoidance (individual risk avoidance, threats to achievement, peer influences), resilience (family involvement, physical activity, social problem solving), and achievement (academic performance, peer relations). Most of the items assess frequency of activities or feelings using a 5-point response format.

Adverse events were recorded at any time during the study. Body weight, height, heart rate and blood pressure were measured at screening and at any visit during the randomised phase.

2.4. Statistical analysis

The sample size was based on the primary outcome variable, i.e. the 18 items of the ADHD subscale score of the investigator-rated SNAP-IV. Using an estimate of the common standard deviation of 13 points, a sample of 130 patients (in a 3:1 ratio atomoxetine:placebo) gave about 80% power to detect a difference between groups of 8 points on the SNAP-IV, that can be considered as clinically significant. The sample size was determined using a two-sided test with alpha=0.05 and assumed that up to 10% of patients discontinued the study without providing post-baseline efficacy data in the randomised phase.

The analysis of primary and secondary efficacy endpoints, and of vital signs, was carried out using an analysis of covariance (ANCOVA) model on the last observation carried forward (LOCF) change from
baseline to endpoint, in the double blind randomised phase of the study. The baseline score was included in the model as one of the covariates. The results of the ADHD subscale were also expressed as response rate, where response was defined as at least 25%, 30% or 40% improvement (reduction) from the start to the end of the randomised treatment phase of the study.

Raw scores of CHIP-CE were converted in T scores based on established standardized scores (mean of a healthy population, 50; standard deviation from this mean, 10) (Riley et al., 2004).

Adverse events were coded using the MedDRA dictionary. Events were considered treatment emergent adverse events (TEAE) if they started or worsened after the first intake of study medication compared to the pre-baseline period. Rates of patients with TEAE in the double blind phase of the study were compared between groups using the Fisher’s exact test.

3. Results

A total of 156 patients (mean age: 9.9 years, 92.9% males) were screened and entered the parent support phase. The patients’ disposition is shown in Fig. 2. Seventeen patients discontinued the study during the parent support phase, before randomization (mainly due to patient/caregiver’s or Investigator’s decision). All 139 remaining patients were analysed for safety and 137 for efficacy (two did not have post-baseline data). In the atomoxetine group, 5 patients discontinued the study during the double blind randomised phase. Only two patients (1.3% of screened) responded to the parent psychological intervention and were not randomised.

Patients’ demographics are shown in Table 1. No statistically significant differences between groups were found at baseline (visit 8). Previous psychotherapy (of any type) was used in 18 patients (17.1%) in the atomoxetine group and in 6 (18.8%) in the placebo group, while 21 (20.0%) and 4 (12.5%) patients, respectively in the two groups, used previous drug therapy. ADHD diagnosis and anxiety/affective diagnoses at baseline, according with DSM IV, are summarized in Table 2. The mean (±standard deviation) starting atomoxetine dose was 0.61±0.08 mg/kg/day (range 0.44–0.80) and was titrated to 1.10±0.13 mg/kg/day (range 0.85–1.33) at the end of the randomised phase of the study, a dose slightly below the one recommended (SPC Strattera).

3.1. Efficacy

A slight non-significant decrease in all SNAP-IV subscales scores was observed during the parent support phase: the mean scores at the start and at the end of this phase were, respectively, 43.3 ± 6.6 and 42.1 ± 6.9 for the ADHD subscale (i.e. the 18 items of inattention, hyperactivity/impulsivity, and combined domains),

Table 1

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Atomoxetine (n = 105)</th>
<th>Placebo (n = 32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD (range)</td>
<td>9.7 ± 2.2 (6.1–14.6)</td>
<td>10.0 ± 2.4 (6.2–15.4)</td>
<td>0.507</td>
</tr>
<tr>
<td>Gender, M/F, number (%)</td>
<td>M: 98 (93.3); F: 7 (6.7)</td>
<td>M: 29 (90.6); F: 3 (9.4)</td>
<td>0.698</td>
</tr>
<tr>
<td>Weight, kg, mean ± SD (range)</td>
<td>39.3 ± 15.8 (20–90)</td>
<td>41.4 ± 14.1 (22–78)</td>
<td>0.273</td>
</tr>
<tr>
<td>Height, cm, mean ± SD (range)</td>
<td>140.1 ± 15.2 (110–174)</td>
<td>141.6 ± 15.3 (116–177)</td>
<td>0.728</td>
</tr>
<tr>
<td>BMI, kg/m², mean ± SD (range)</td>
<td>19.3 ± 4.2 (13.8–32.8)</td>
<td>20.1 ± 3.5 (14.7–28.5)</td>
<td>0.095</td>
</tr>
</tbody>
</table>
21.9 ± 3.3 and 21.3 ± 3.6 for the inattention subdomain, 21.4 ± 4.2 and 20.8 ± 4.3 for the hyperactivity/impulsivity subdomain, and 18.1 ± 2.5 and 17.2 ± 3.3 for the ODD subdomain.

During the randomized phase, the mean changes from visit 8 to the last visit in the 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). The corresponding 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) (Fig. 3). An analysis in response rate, defined as at least 25%, 30% or 40% improvement (reduction) from visit 8 to the last visit in SNAP-IV ADHD subscale score, showed statistically significant differences between groups, in favour of atomoxetine compared to placebo, in 25% response (39.0% vs. 9.4%, respectively in the two groups, p = 0.001), in 30% response (31.4% vs. 6.3%, p = 0.004) and in 40% response (18.1% vs. 3.1%, p = 0.043). A decrease of mean scores from visit 8 to the last visit was also observed in any subscale for atomoxetine treated patients, compared to no substantial changes with placebo (p < 0.001 between groups for inattention and p = 0.005 for hyperactivity/impulsivity) (Fig. 3).

The results of the CPRS-R:S and the CTRS-R:S in the parent support phase showed small decreases from baseline in all subscales (except for unchanged mean values in the cognitive problems subscale in the CTRS-R:S); the mean changes in the ADHD index were −1.5 in the CPRS-R:S and −1.1 in the CTRS-R:S. The results of the CPRS-R:S and the CTRS-R:S in the randomized phase are summarised in Table 3. An improvement in all CPRS-R:S and CTRS-R:S subscales was observed following treatment with atomoxetine, except in the cognitive problems subscale in the

### Table 2: DSM-IV ADHD diagnosis and anxiety/affective diagnoses at baseline.

<table>
<thead>
<tr>
<th>DSM-IV ADHD subtype</th>
<th>Atomoxetine (n=105)</th>
<th>Placebo (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattentive, number (%)</td>
<td>7 (6.7)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Hyperactive, number (%)</td>
<td>4 (3.8)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Combined, number (%)</td>
<td>94 (89.5)</td>
<td>28 (87.5)</td>
</tr>
<tr>
<td>Age at onset of ADHD symptoms, years, mean±SD (range)</td>
<td>4.2 ± 1.8 (1–12)</td>
<td>3.7 ± 1.4 (2–7)</td>
</tr>
</tbody>
</table>

### Anxiety diagnoses from K-SADS:

<table>
<thead>
<tr>
<th></th>
<th>Atomoxetine (n=105)</th>
<th>Placebo (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised anxiety disorders, number (%)</td>
<td>10 (9.5)</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>Obsessive–compulsive disorder, number (%)</td>
<td>2 (1.9)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Panic disorder, number (%)</td>
<td>2 (1.9)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Separation anxiety disorder, number (%)</td>
<td>5 (4.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Specific phobias, number (%)</td>
<td>8 (7.6)</td>
<td>2 (6.3)</td>
</tr>
</tbody>
</table>

### Affective diagnoses from K-SADS:

<table>
<thead>
<tr>
<th></th>
<th>Atomoxetine (n=105)</th>
<th>Placebo (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjustment disorder, number (%)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dysthymia, number (%)</td>
<td>9 (8.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Major depressive disorders, number (%)</td>
<td>2 (1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Seasonal pattern disorders, number (%)</td>
<td>1 (1.0)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Any other depressive disorders, number (%)</td>
<td>0 (0.0)</td>
<td>1 (3.1)</td>
</tr>
</tbody>
</table>

The median CGI-ADHD-S score did not change from the start to the end (median score: 5.0 at both visits) of the parent support phase. A statistically significant decrease in the atomoxetine group was observed during the randomised double-blind phase (median change at endpoint: −1.0), compared to no changes in the placebo group (p < 0.001 between groups). The cumulative distribution of CGI-ADHD-S scores shows that patients in the placebo group have a similar distribution between baseline and last visit, while almost 50% of patients treated with atomoxetine were moderately ill or mildly ill at last visit (Fig. 4).

The results of the CPRS-R:S and the CTRS-R:S in the parent support phase showed small decreases from baseline in all subscales (except for unchanged mean values in the cognitive problems subscale in the CTRS-R:S); the mean changes in the ADHD index were −1.5 in the CPRS-R:S and −1.1 in the CTRS-R:S. The results of the CPRS-R:S and the CTRS-R:S in the randomized phase are summarised in Table 3. An improvement in all CPRS-R:S and CTRS-R:S subscales was observed following treatment with atomoxetine, except in the cognitive problems subscale in the

![Figure 3](image-url)
Statistically significant differences vs. placebo were found in all subscales of the CPRS-R:S and in the oppositional subscale of the CTRS-R:S, while the p value was at the limit of significance level in the hyperactivity subscale and in the ADHD index of the CTRS-R:S.

The mean total scores of CDRS-R and SCARED were below the clinical threshold at baseline and did not change in the parent support phase: the mean changes from baseline to the end of this phase were \(-0.6\pm4.1\) and \(-0.3\pm7.5\), respectively. The mean changes of CDRS-R total score from visit 8 to the last visit were \(-0.5\pm4.4\) in the atomoxetine group and \(-0.1\pm5.0\) in the placebo group (p=0.870 between groups). The corresponding changes of SCARED were \(-2.1\pm7.6\) and \(-1.7\pm6.5\), respectively in the two groups (p=0.836 between groups).

The mean CHIP-CE total, domain and subdomain scores did not change during the parent support phase. Fig. 5 shows the CHIP-CE total and domain T scores during the randomised double blind phase. The mean changes of CHIP-CE total score from visit 8 to the last visit were 3.6 with atomoxetine and 1.2 with placebo (p=0.071 between groups). Improvements in mean scores of all domains were observed in the atomoxetine group. The results of CHIP-CE subdomains in the atomoxetine group showed marked improvements from visit 8 to the last visit in satisfaction with self (mean change: +4.2), emotional comfort (+2.1), individual risk avoidance (+2.7), threats to achievement (+3.3) and peer relations (+2.1). The comparisons between groups showed statistically significant differences, in favour of atomoxetine, for risk avoidance domain (p=0.013), and for emotional comfort (p=0.007) and individual risk avoidance (p=0.007) subdomains.

### 3.2. Safety

Table 4 shows the TEAEs reported in at least 5% of patients in any group during the randomised double blind phase of the study. The most commonly involved system organ classes by MedDRA dictionary were gastrointestinal disorders (mainly nausea, vomiting and abdominal pain), which were reported in 45.8% of patients in the atomoxetine group and 21.9% in the placebo group, and metabolism and nutrition disorders (anorexia/decreased appetite), which were reported in 43.0% and 9.4% of patients, respectively in the two groups.

Almost all adverse events (except in 5 cases) were of mild or moderate severity and only 3 patients treated with atomoxetine discontinued the study due to adverse events. No serious adverse events were reported in both groups. No substantial changes of mean body weight and height were observed during the parent support phase, while the results in the randomised phase showed a small increase (+0.5 kg) of body weight with placebo and a small decrease (−1.2 kg) with atomoxetine (p<0.001), as well as mean height increased slightly more markedly in the placebo group (+1.5 cm) than in the atomoxetine group (+1.0 cm) (p=0.021). The mean changes in vital signs from visit 8 to the end of randomised phase in the atomoxetine group and in the placebo group were, respectively, 1.0 and 5.1 mmHg in systolic blood pressure (p=0.482), −0.2 and 2.3 mmHg in diastolic blood pressure (p=0.557), and 3.7 and 1.5 bpm in heart rate (p=0.312). No difference was observed in body temperature, between study groups at any time and at endpoint.

### 4. Discussion

ADHD treatment guidelines suggest that pharmaco-therapy should be used as part of a multi-modal treatment package including parent training, family or school interventions.

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Table 3 Results of the CPRS-R:S and the CTRS-R:S in the randomised double blind phase.

<table>
<thead>
<tr>
<th>Subscales</th>
<th>Atomoxetine</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 8</td>
<td>Last visit</td>
<td>Visit 8</td>
</tr>
<tr>
<td>CPRS-R:S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oppositional</td>
<td>11.7±3.8</td>
<td>10.5±4.4</td>
<td>12.2±3.0</td>
</tr>
<tr>
<td>Cognitive problems</td>
<td>14.3±3.1</td>
<td>12.0±4.2</td>
<td>14.2±3.2</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>12.0±3.8</td>
<td>9.8±4.4</td>
<td>12.0±4.0</td>
</tr>
<tr>
<td>ADHD index</td>
<td>28.2±4.9</td>
<td>23.1±7.1</td>
<td>28.4±5.2</td>
</tr>
<tr>
<td>CTRS-R:S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oppositional</td>
<td>7.6±4.3</td>
<td>6.5±4.1</td>
<td>10.8±3.8</td>
</tr>
<tr>
<td>Cognitive problems</td>
<td>8.2±4.3</td>
<td>12.0±4.2</td>
<td>8.5±3.7</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>12.8±5.5</td>
<td>10.7±5.6</td>
<td>16.3±3.4</td>
</tr>
<tr>
<td>ADHD index</td>
<td>25.3±8.4</td>
<td>21.8±8.9</td>
<td>29.9±6.0</td>
</tr>
<tr>
<td>CGI-ADHD-S</td>
<td>5.1±0.8</td>
<td>4.5±1.0</td>
<td>5.1±0.9</td>
</tr>
</tbody>
</table>

Values are means±standard deviation. p values refer to comparisons between groups in changes from visit 8 to the last visit.
and psychotherapy. In Europe, pharmaco-therapy is largely through psycho-stimulant medications such as methylphenidate and dexamphetamine (Taylor et al., 2004; NICE, 2000). Although the Italian guidelines of diagnosis and treatment of ADHD recommend the use of pharmaco-therapy for children and adolescents with severe and disabling ADHD (SINPIA, 2004), psychotherapy and psychosocial intervention is still the main (often the only) type of treatment, for both ADHD and ODD. In this trial only subjects who failed to respond to a 6-week validated and standardized behavioural management training for the parents of all the eligible patients were randomised to atomoxetine or placebo.

This study included only paediatric patients meeting criteria for ADHD and comorbid ODD, and used a wide spectrum of validated outcome measures, including ADHD symptoms, ODD symptoms, comorbid anxiety and depression, problem behaviours related to ADHD (including the school setting), and emotional and social well-being of the patient and the family.

The manualized psychological intervention with parental support resulted in a very low rate of response and the mean values of all efficacy outcome measures of the study did not vary in this phase accordingly. In non-responder patients, treatment with atomoxetine was associated with improvements of symptoms of both ADHD and ODD, which resulted significant compared to placebo not only in the primary variable 18 items of the ADHD subscale score of the SNAP-IV, but also in each of the three examined domains (inattention, hyperactivity/impulsivity and oppositional). A significantly higher number of patients on atomoxetine compared to placebo showed various degrees of response to therapy, consistently with the improvement observed in the ADHD subscale.

It should be highlighted that, despite that the results did not show initial response to the psychoeducational phase, the duration of the parental support phase was relatively short and, therefore, potential carry-on positive effects of this training program effect might have been produced during the randomized phase of the study: an informal non-structured psychoeducational support to the parents was provided during the pharmacological double blind phase of the study. In the present study, treatment with atomoxetine or placebo could be considered as an ‘add-on’ therapy given in combination with the psychoeducational support. This particular design might explain the, minimal or no placebo effects observed in the present study. With this respect, the results of a recently published study conducted in Europe and Australia (Bangs et al., 2008), in which treatment with atomoxetine or placebo of children with ADHD and comorbid ODD was not preceded by psychotherapy, showed that ADHD

![Graphs showing CHIP-CE total and domains scores during the randomised double blind phase](image)

*Figure 5* CHIP-CE total and domains scores during the randomised double blind phase (atomoxetine: full diamonds; placebo: empty circles). Values are mean scores.
symptoms in the atomoxetine arm improved in a similar extent to that of the present trial, whereas no significant differences between atomoxetine and placebo were found on ODD symptoms due to a placebo effect. Similarly, in a Northern American study (Kaplan et al., 2004), atomoxetine was effective for the treatment of ADHD symptoms but appeared to not significantly reduce oppositional symptoms compared to placebo; in another study (Newcorn et al., 2005), significant improvements vs. placebo in ADHD, ODD, and quality-of-life measures in patients with concomitant ODD symptoms were obtained at a dose level (1.8 mg/kg/day) higher than that of the present trial. It should also be considered that although severity of ADHD and ODD symptoms was similar in all the studies published (Newcorn et al., 2005; Kaplan et al., 2004; Bangs et al., 2008; Biederman et al., 2007) and in the present study, patients of the Newcorn study were older (mean age 11 compared 9 of the other studies), with a higher proportion of inattentive subtype (about 30% compared to the 10% of other studies) and with medication administered twice a day, in comparison to the single daily dose of the other studies.

In the present study, pre-selected children and adolescents meeting the DSM-IV diagnostic criteria for ADHD (any subtype) and ODD were shown to benefit from an 8-week treatment with atomoxetine (and significantly compared to a placebo control group) not only in ADHD, but also in oppositional symptoms. Additionally, the effects on ODD symptoms were obtained at a mean atomoxetine dose (final dose: 1.10 ±0.13 mg/kg/day) that approximates the mean dose used with success in ADHD symptoms in children (Kelsey et al., 2004; Michelson et al., 2001) and that is recommended for the maintenance of symptoms’ control (Newcorn et al., 2006).

Patients with ADHD and comorbid oppositional symptoms exhibit significantly greater ADHD symptom severity and social dysfunction than ADHD patients without such comorbidity (Kuhne et al., 1997). A recent metanalysis (Biederman et al., 2007) suggests that much of the improvement in oppositional symptoms by atomoxetine, pemoline, psychostimulants, or the tricyclics may be mediated by the improvement in symptoms of ADHD. On the other hand, Spencer et al. (2006) showed that improvements by amphetamine salts on ODD subscale of the SNAP-IV can be measured, even in subjects with pure ODD, suggesting that the improvement in symptoms of oppositionality may be independent of any change in ADHD symptoms. Moreover, it has also been suggested that environment can also play a crucial role on the effects of ADHD medication on ODD symptoms. Kolko et al. (1999) showed that methylphenidate appears to improve symptoms of hyperactivity and impulsivity in a traditional classroom setting without significant effects on symptoms of oppositionality. Contrarily, in a structured program of therapeutic, educational, and recreational activities, subjects appeared to improve with methylphenidate treatment in both their hyperactive/impulsive and oppositional symptoms. Taken together, these findings further suggest the independence of oppositional and hyperactive/impulsive symptoms to treatment, and the crucial effect that psychoeducation intervention can play on clinical efficacy of ADHD medication on ODD symptoms.

In the Bangs et al. study (2007), patients with dysthymia, generalized or separation anxiety, showed a smaller reduction in ODD symptoms during atomoxetine treatment, although excluding these patients from the overall LOCF analysis had no effect because their small number. In the present study, only few patients (approximately 20% of patients in total) presented evidence of comorbid anxiety or affective disorders, and the mean baseline scores of CDRS-R and SCARED were indicative of no or borderline symptoms in most of the participants. Consequently, the mean total scores of both scales did change neither in the parent support phase, nor in the randomised treatment phase in both groups.

The assessment of the problem behaviours related to ADHD, as measured by parents with the CPRS-R:S, showed that treatment with atomoxetine was associated with improvements in all subscales (oppositional, cognitive problems, hyperactivity and ADHD index) and significantly compared to placebo. Similarly, patients treated with atomoxetine

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Treatment-emergent adverse events reported in at least 5% of patients in any group during the randomised double blind phase of the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
<td><strong>Atomoxetine (n=107)</strong></td>
</tr>
<tr>
<td>Anorexia</td>
<td>36</td>
</tr>
<tr>
<td>Somnolence</td>
<td>32</td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>11</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
</tr>
<tr>
<td>Influenza</td>
<td>9</td>
</tr>
<tr>
<td>Nervousness</td>
<td>7</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4</td>
</tr>
</tbody>
</table>

n=number of patients; p values refer to comparisons between groups.
experienced improvements of the problem behaviours related to
ADHD in the school environment (by teacher-rated CTRS-R: S), except in the cognitive problems subscale. Consistently
with previous published data (Brown et al., 2006), these
findings suggest that both parents and teachers are able to
detect improvements in a wide spectrum of functional
behaviours, including the school setting.

The mean CHIP-CE total score at the start of the ran-
domised phase was indicative of a moderate impairment of
HRQOL, which was lower than that reported in another trial
conducted in the UK that used the same scale (Prasad et al.,
2007). Although this previous study (Prasad et al., 2007)
showed greater improvements than those observed in our
study, caution should be used in the interpretation of the results
due to the open-label design of this study and to
possible cross-cultural differences in the perception of
quality of life. Moreover, another analysis of effects of
atomoxetine on HRQOL that used a different scale pointed
to evidence that the likelihood of obtaining improvements
in physical functioning correlates with a worse baseline
perception of HRQOL (Perwien et al., 2004). The results of
our study showed that an HRQOL improvement was observed
in some subdomains; other scores improved but did not reach
statistical significance maybe because of the small sample
size due to the study design based on SNAP-IV improvement.
Importantly, patients treated with atomoxetine greatly
benefited in domains, such as risk avoidance or achievement,
and showed greater improvements than those observed in our
study. The results in the open-label extension phase will
provide further insight on the long-term safety of atomoxetine
on growth and cardiovascular effects.

In conclusion, the results of this study indicate that, in
children and adolescents with ADHD and ODD, who initially
did not respond to short term psychological intervention with
parental support, the treatment with atomoxetine was
associated with improvements on symptoms of both ADHD
and ODD measured by both parents and teachers, as well as
in specific aspects of quality of life and general health.
Atomoxetine exhibited a satisfactory safety profile, with
low incidence of dropouts and no serious adverse events
observed. The results in the open-label extension phase will
assess whether the benefits observed after 8 weeks of
treatment are maintained in a long-term exposure to
atomoxetine.

Role of the funding source

The study is fully sponsored by Eli Lilly Italy.

Contributors

G. Dell’Agnello has written the study protocol, coordinated research
activities and substantially contributed to data analysis and
interpretation. D. Maschietto, A. Pascotto, F. Calamoneri, G. Masi,
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and data collection. F. Mancini has coordinated study activities and
A. Rossi has contributed to data analysis and interpretation of the
results and coordinated publication’s activities; L. Poole has
defined the study design and interpretation of the results. R.
Escobar has contributed to study design, data interpretation and
general study coordination. A. Zuddas has substantially contributed
to study design, data collection, analysis and interpretation and
general study coordination. All authors have critically revised the
article and approved the manuscript before submission.

Conflict of interest

G. Dell’Agnello, F. Mancini, A. Rossi are full time employees at Eli
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& Co. D. Maschietto is a consultant for Eli Lilly and Shire, has
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received research grants from Eli Lilly and Janssen Cilag and has been
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Eli Lilly and Sanofi-Aventis.

Acknowledgments

The authors thank Luca Cantini and Andrea Rossi for their support in
medical writing of this article, Pierluigi Crisà and Roberto Pino for
their contribution in the study organization.
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References


