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ORIGINAL CONTRIBUTION

Comorbid oppositional defiant disorder and the risk of relapse during 9 months of atomoxetine treatment for attention-deficit/hyperactivity disorder

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Abstract *Objective* To examine the influence of comorbid oppositional defiant disorder (ODD) on the relative risk (RR) of relapse during 9 months of treatment with atomoxetine for attention-deficit/hyperactivity disorder (ADHD). *Method* Four hundred and sixteen children and adolescents with ADHD whose symptoms remitted during initial 10-week, open-label atomoxetine treatment were randomly assigned to continue with atomoxetine or placebo. *Results* In all, 43 % met criteria for comorbid ODD. A total of 17 % of patients with comorbid ODD relapsed (CGI-Severity score ≥ 3 and ADHD Rating Scale total score of 90 % or more of baseline at study entry on two consecutive visits) during atomoxetine treatment, compared with 26 % of patients without comorbid ODD (RR 0.67, 95 % CI 0.42–1.06). Mean time to relapse was not significantly different [mean (SE) days to relapse, ADHD/+ODD: 215 (7.38); ADHD/–ODD: 211 (7.61); log rank $p = 0.08$]. This finding is placed within the context of atomoxetine affording an overall protection against relapse compared with placebo (RR 0.59, 95 % CI 0.43–0.80). *Conclusions* Comorbid ODD does not influence the rate of relapse of patients with ADHD during longer-term treatment with atomoxetine. Atomoxetine protects against the relapse of ADHD symptoms regardless of the presence or absence of comorbid ODD.

Key words adolescents – atomoxetine – ADHD – children – ODD

Introduction

The co-occurrence (comorbidity) of child psychiatric disorders is common. Rates of comorbidity are particularly high in clinical settings owing to the influences of referral bias and the Berkson effect [9], but comorbidity is also found in community samples [1]. Angold et al. [1] pooled data from 21 epidemiological studies of childhood psychopathology and derived odds ratio (OR) estimates for the comorbid association of attention-deficit/hyperactivity disorder (ADHD), conduct disor-

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der/oppositional defiant disorder (CD/ODD), depression, and anxiety. The three most common comorbid associations were ADHD with CD/ODD (OR 10.7, 95% CI 7.7–14.8); depression with anxiety (OR 8.2, 95% CI 5.8–12.0); and CD/ODD with depression (OR 6.6, 95% CI 4.4–11.0). Experimental data suggest that some comorbid associations, such as ADHD with CD or ODD, may represent entities that are distinct from the individual disorders [2, 7].

Comorbidity may alter the response to treatment, usually in the direction of rendering the treatment less effective [26]. The lack of demonstrated efficacy of tricyclic antidepressant medications for juvenile depression has been attributed, for example, to the very high rates of comorbidity among young people with depression. Systematic study of the impact of comorbidity on the clinical response to treatment, however, has been limited. A naturalistic study of 788 children treated with psychostimulant medication found that comorbidity with CD/ODD, depression, or anxiety did not exert a significant influence on outcome [9]. Other studies have also found that CD/ODD makes no difference to the response of children with ADHD to psychostimulant medication [12, 20]. There are good clinical grounds for examining the influence of comorbidity on the response to pharmacological treatments, as such data may help to influence the choice of treatment. Such research may examine the influence of comorbidity on the immediate efficacy of medications, the relative rate of side-effects and adverse events, persistence with treatment, or the sustained benefit of treatment over time.

This paper describes a post hoc analysis of the effect of comorbid oppositional defiant disorder (ODD) on the rate of relapse in children with ADHD treated over 9 months with atomoxetine hydrochloride. The primary results of the original relapse-prevention study have been published previously [18]. Atomoxetine afforded an overall protection against relapse (Clinical Global Impressions-Severity score ≥ 3 and ADHD Rating Scale total score of 90% or more of baseline at study entry on two consecutive visits) compared with placebo (RR 0.59, 95% CI 0.43–0.80). Atomoxetine is a selective noradrenergic uptake inhibitor with little or no affinity for other neuronal transporters or neurotransmitter receptor sites (dopaminergic, muscarinic-cholinergic, histaminic, serotonergic, alpha-1, or alpha-2 adrenergic). Atomoxetine is the only member of a group of so-called "nonstimulant" drugs, which includes tricyclic antidepressants, bupropion, alpha-2 agonists, and monoamine oxidase inhibitors [3], that is approved for the treatment of ADHD. These drugs offer an alternative to patients who cannot tolerate the side-effects of psychostimulants or who suffer comorbidities that may be exacerbated by psychostimulant treatment.

Following randomized controlled trial evidence of efficacy in children [4, 5, 17, 19, 25] and adults [16, 24], atomoxetine was released first in the US in late 2002 for the treatment of ADHD. European countries for which approval has been granted by the time of writing include Germany, the Netherlands, Norway, Romania, and the United Kingdom. A recent analysis of data from one of the larger placebo-controlled studies in children and adolescents provided pilot data about the efficacy of atomoxetine in patients with ODD. This analysis showed that, compared with placebo, atomoxetine significantly reduced ODD symptoms and improved social and family functioning in children and adolescents with comorbid ADHD and ODD [22]. The present analysis extends these earlier findings by examining the effects of comorbid ODD on clinical outcomes during long-term treatment in children and adolescents with ADHD. As the emphasis in these post hoc analyses is on relapse rates in two defined subpopulations, and because the main efficacy and safety results of the parent study have already been published [18], no safety data are reported here.

Methods

Participants

Participants were children and adolescents aged 6–15 years who met DSM-IV criteria for ADHD, as assessed by clinical interview and confirmed by a structured diagnostic interview [Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL)] [14]. In addition, all patients had symptom severity at least 1.5 standard deviations above expected age and sex norms on the ADHD Rating Scale-IV (ADHD RS) [6] for the patients' ADHD subtype (predominantly inattentive, predominantly hyperactive/impulsive, combined). Children and adolescents were randomly assigned in the double-blind, placebo-controlled relapse prevention study period if they were deemed responders to 10 weeks of open-label treatment with atomoxetine. Important exclusion criteria included a history of bipolar or psychotic illness, substance abuse, serious medical illness, use of concomitant psychoactive medications, and low IQ. The study was conducted at 33 sites in the United Kingdom, France, Spain, Italy, Belgium, the Netherlands, Germany, Poland, Hungary, Sweden, Norway, Israel, South Africa, and Australia, and enrolment took place over approximately 11 months.

Measures

Baseline ADHD and concurrent psychiatric diagnoses were assessed by the K-SADS-PL interview. Efficacy measures, completed by the investigators following interviews with participant children and their parents,

were the ADHD RS and the Clinical Global Impressions of Severity (CGI-S) [8] scale for ADHD symptoms.

Design and procedures

Following baseline assessment, participants entered a 10-week, open-label period of atomoxetine, titrated from a minimum dose of 0.5 mg/kg/day to a maximum of 1.8 mg/kg/day. Those that completed the open-label trial and met response criteria (defined as a CGI-S score of 2 or less, indicating minimal symptoms and impairment, and a reduction of at least 25 % from baseline in ADHD RS total score) entered an extended, double-blind continuation study period of approximately 42 weeks. During the early weeks of the continuation study phase, patients were randomly assigned to continue atomoxetine or placebo (the precise visit was blinded to investigators and patients). Patient disposition is summarized in Fig. 1. During the continuation study phase, atomoxetine (or placebo) was administered at the same dose and dosing schedule used at the end of the open-label study period. Patients who met relapse criteria were discontinued from the study. The patient was considered to have relapsed if at two consecutive visits the CGI-S score was 3 (mild impairment) or greater, and the ADHD RS total scores returned to 90 % or more of the score obtained at initial study entry.

After description of the procedures and purpose of the study, and prior to the administration of any study procedure or dispensing of study medication, written informed consent was obtained from each patient's parent or guardian, and written assent was obtained from each patient. This study was reviewed by each site's institutional review board and was conducted in accordance with the ethical standards of the Declaration of Helsinki 1975, as revised in 2000 [27].

Data analysis

An initial sample size of 250 patients (200 atomoxetine, 50 placebo) was chosen to provide approximately 85 % power to detect a treatment difference in the distributions of time to relapse following the first randomization, assuming that time to relapse was exponentially distributed with hazard rates of 0.75 on atomoxetine and 1.5 on placebo [15]. These rates correspond to per-

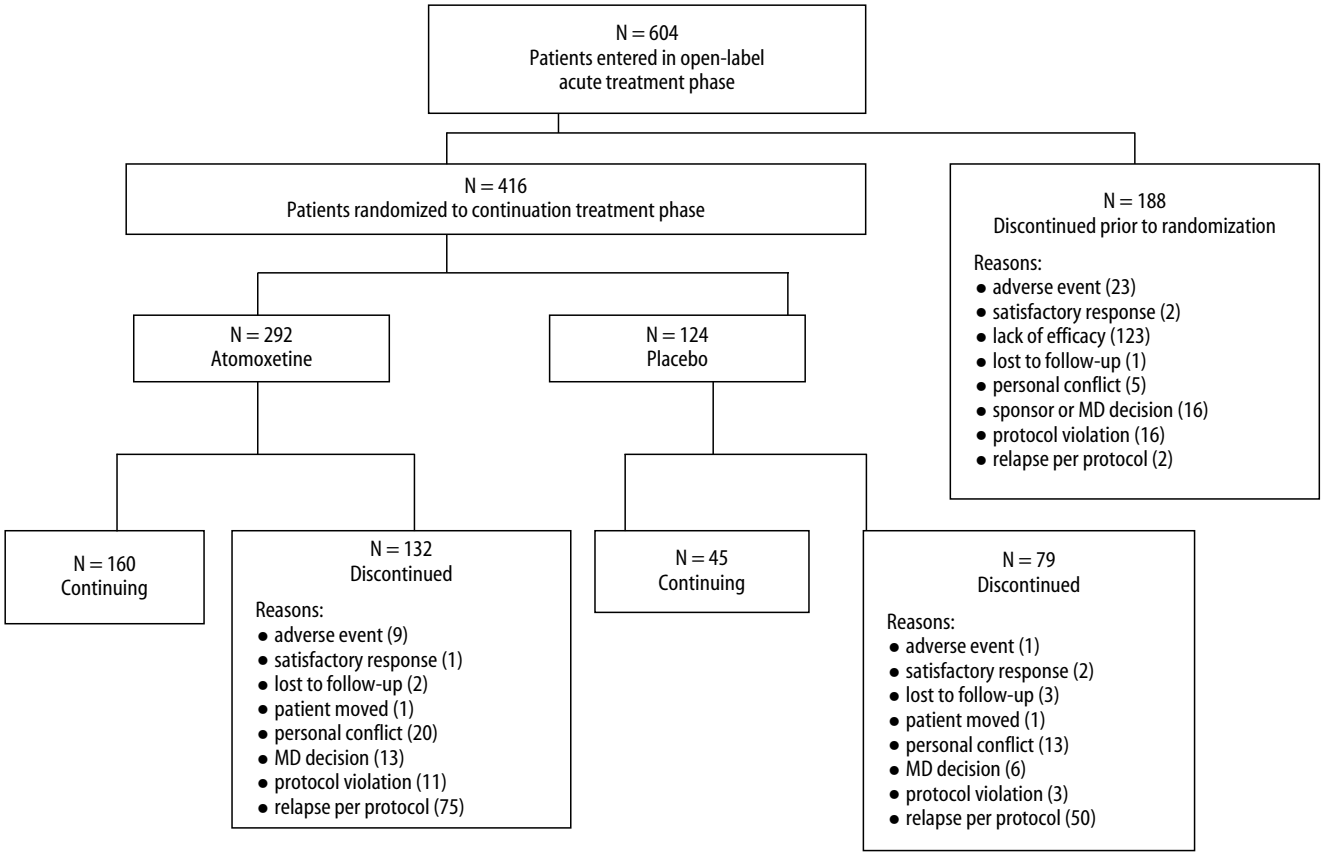

Fig. 1 Disposition of participants in the open-label and double-blind, placebo-controlled phases of the relapse prevention trial

centages of relapse of 31 % on atomoxetine and 53 % on placebo after 6 months. This calculation assumed a two-sided, 0.05 level test, and that drop-out due to reasons other than relapse followed an exponential distribution with a hazard rate of 0.4 (approximately 20 % over 6 months).

The primary analysis for this paper was the relative risk (RR) of relapse during the continuation phase of treatment. Relative risk calculations were oriented such that estimates less than a value of 1 favoured the comorbid condition over the noncomorbid condition. The distribution of number of days to relapse was estimated for each of the treatment and placebo control groups by comorbidity condition using the Kaplan-Meier product limit estimator [13]. Treatment differences in the distributions were assessed using a two-sided log-rank test at the 0.05 level.

Results

Of 416 patients who met efficacy criteria at the end of the 10-week, open-label study period, 292 were randomly assigned to continue with atomoxetine, and 124 were randomly assigned to receive placebo in a double-blind fashion. A summary of demographics and other patient characteristics is presented in Table 1. ODD was a common comorbidity, affecting 179 patients (43 % of the sample). There was no statistically significant difference in rates of ODD comorbidity between the atomoxetine treatment group and the placebo control group.

Twenty-one of 123 patients (17 %) with ADHD and comorbid ODD (ADHD/+ODD) assigned to atomoxetine relapsed, compared with 43/168 (26 %) patients without comorbid ODD (ADHD/–ODD) assigned to atomoxetine (RR 0.67, 95 % CI 0.42–1.06). There was no statistically significant difference in mean time to relapse between the atomoxetine-treated groups with or without comorbid ODD [mean (SE) days to relapse, ADHD/+ODD: 215 (7.38); ADHD/–ODD: 211 (7.61); log rank $p = 0.08$]. Twenty-four of 56 patients (43 %) with ADHD/+ODD assigned to placebo relapsed, compared with 23/68 patients (34 %) with ADHD/–ODD assigned to placebo (RR 1.27, 95 % CI 0.81–1.99). There was no statistically significant difference in mean time to relapse for the placebo groups, regardless of the presence or absence of ODD [mean (SE) days to relapse, ADHD/+ODD: 136 (11.35); ADHD/–ODD: 151 (9.13); log rank $p = 0.22$]. Relapse rates according to ODD comorbidity are illustrated in Fig. 2 and referenced against overall relapse rates by treatment condition, as reported by Michelson et al. [18].

Discussion

In the context of 9 months of treatment with atomoxetine for ADHD, the presence of comorbid ODD did not significantly alter the rate of relapse in symptoms attributable to the ADHD. The finding is placed within the context of atomoxetine affording an overall protective effect against relapse in the sample compared with placebo. Those who did relapse while taking atomoxetine derived benefit for longer than those who relapsed while taking placebo. Examination of Fig. 2 reveals a statistically nonsignificant trend toward a protective effect against relapse from the presence of comorbid

Table 1 Summary of demographics and patient characteristics

Variable	ADHD only		ADHD + ODD	
	Atomoxetine (N = 168) n (%)	Placebo (N = 68) n (%)	Atomoxetine (N = 123) n (%)	Placebo (N = 56) n (%)
Sex				
Male	145 (86.3)	63 (92.6)	115 (93.5)	49 (87.5)
Female	23 (13.7)	5 (7.4)	8 (6.5)	7 (12.5)
Origin				
Caucasian	160 (95.2)	66 (97.1)	122 (99.2)	56 (100.0)
Other	8 (4.8)	2 (2.9)	1 (0.8)	0
Age group				
< 12	121 (72.0)	55 (80.9)	86 (69.9)	45 (80.4)
≥12	47 (28.0)	13 (19.1)	37 (30.1)	11 (19.6)
Previous stimulant treatment	88 (52.4)	29 (42.6)	68 (55.3)	33 (58.9)
ADHD subtype				
Hyperactive/impulsive	9 (5.4)	5 (7.4)	4 (3.3)	1 (1.8)
Inattentive	57 (33.9)	17 (25.0)	10 (8.1)	9 (16.1)
Combined	102 (60.7)	46 (67.6)	109 (88.6)	46 (82.1)

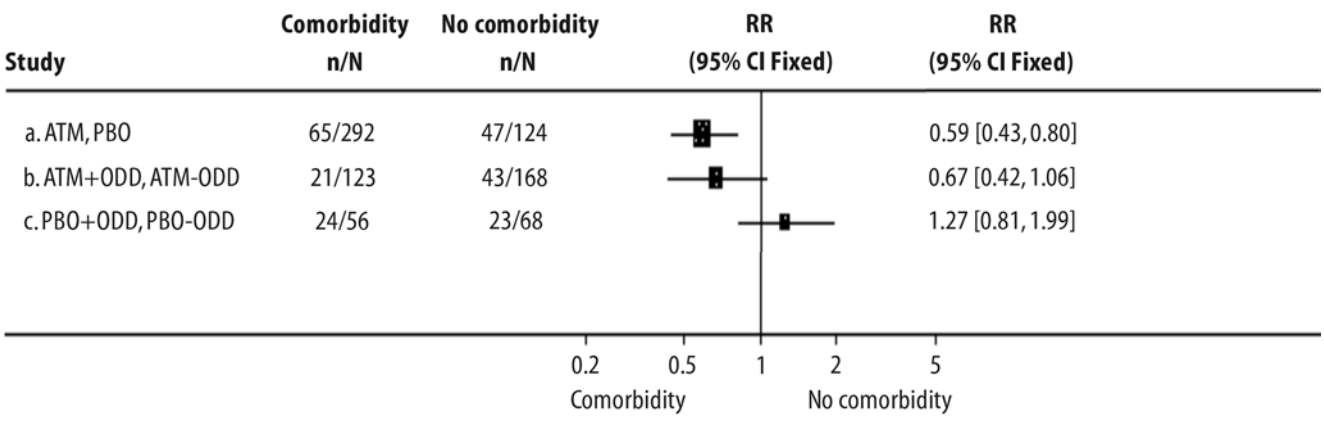

Fig. 2 Relative risk of relapse (and 95 % confidence interval) by treatment condition (atomoxetine vs. placebo) and the presence or absence of comorbid oppositional defiant disorder (*ATM* atomoxetine; *PBO* placebo; *ODD* oppositional defiant disorder)

ODD during treatment with atomoxetine, with an absolute risk reduction of about 9 %, while the trend for the placebo group was in the opposite direction. The observation adds further weight to the conclusion that atomoxetine is at least as effective for children with ADHD and comorbid ODD as it is for children with ADHD alone. The finding is consistent with short- and longer-term treatment studies of methylphenidate for ADHD [11, 12, 20, 21, 23], in which the presence of comorbid ODD does not reduce the likelihood of a treatment response. We speculate, however, that, although the primary outcome measures focused on ADHD symptoms, the rating of these symptoms was probably influenced by fluctuation in the severity of ODD symptoms. If atomoxetine exerts a direct effect on ODD symptoms, as suggested in one short-term, placebo-controlled trial [22], then improvement in ODD symptoms may have been misattributed in the present study to an improvement in ADHD symptoms. Conversely, the relapse in ODD symptoms occurring in patients randomly assigned to the placebo condition may have been identified early and attributed to a relapse in ADHD. It is quite plausible that atomoxetine exerts a direct benefit on aggression and defiance, as such benefits have been observed with other noradrenergic "nonstimulant" medications, such as clonidine [10]. Unfortunately, the present results are equivocal in this regard, and additional studies will be needed to clarify the issue.

A number of limitations of the study warrant mention. As this study was post hoc in nature, it was not designed specifically to assess ODD symptoms. This is relevant because, if atomoxetine exerts a direct effect on ODD symptoms, as suggested in one short-term placebo-controlled trial [22], then improvement in ODD symptoms may have been misattributed in the present study to an improvement in ADHD symptoms, as discussed in the preceding paragraph. The study was not powered to detect drug effects in other comorbid subgroups, such as depression and anxiety, thus preventing us from examining the effect of multiple comorbidities on treatment response. Owing to the requirement that patients met efficacy criteria following 10 weeks of treatment with atomoxetine before they could be randomly assigned, it is possible that more severely affected and treatment-resistant patients with ADHD/+ODD were excluded from the study, thus biasing the result. There was a slight difference in response in the open-label phase of the study, with 24.7 % of patients with ADHD/+ODD dropping out due to inefficacy, compared with 16.8 % of patients with ADHD/–ODD ($p = 0.02$). However, this made little difference ultimately, with 45.5 % of the open-label sample having comorbid ODD compared with 43 % of the sample who proceeded to randomization. The rate of relapse among patients randomly assigned to receive placebo was low in the present study (< 40 %), which limited the capacity to discriminate between the active treatment and placebo conditions. The relatively high placebo response rate may have been a function of setting the threshold for relapse too high, or it may have been due to the patients deriving nonspecific benefit through the regular monitoring they received during the course of the study.

Comorbidity is common in clinical settings. It is, therefore, important to determine whether psychiatric treatments are effective for various combinations of disorders. The data from the present study indicate that atomoxetine is effective in patients with ADHD and comorbid ODD. As nearly half of the patients presenting for the treatment of ADHD have comorbid ODD, this is an important observation.

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