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ORIGINAL ARTICLE

Olanzapine *versus* placebo for out-patients with anorexia nervosa

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Background. Anorexia nervosa (AN) is a serious psychiatric illness associated with significant morbidity and mortality. There is little empirical support for specific treatments and new approaches are sorely needed. This two-site study aimed to determine whether olanzapine is superior to placebo in increasing body mass index (BMI) and improving psychological symptoms in out-patients with AN.

Method. A total of 23 individuals with AN were randomly assigned in double-blind fashion to receive olanzapine or placebo for 8 weeks together with medication management sessions that emphasized compliance. Weight, other physical assessments and measures of psychopathology were collected.

Results. End-of-treatment BMI, with initial BMI as a covariate, was significantly greater in the group receiving olanzapine [$F(1, 20) = 6.64$, $p = 0.018$]. Psychological symptoms improved in both groups, but there were no statistically significant group differences. Of the 23 participants, 17 (74%) completed the 8-week trial. Participants tolerated the medication well with sedation being the only frequent side effect and no adverse metabolic effects were noted.

Conclusions. This small study suggests that olanzapine is generally well tolerated by, and may provide more benefit than placebo for out-patients with AN. Further study is indicated to determine whether olanzapine may affect psychological symptoms in addition to BMI.

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Key words: Anorexia nervosa, antipsychotic medication, eating disorders, placebo, treatment.

Introduction

Anorexia nervosa (AN) is a serious disorder with substantial morbidity and a lifetime mortality as high as that associated with any psychiatric illness (Sullivan, 1995; Papadopoulos *et al*. 2009). No therapeutic approach for adult patients with AN has been demonstrated by more than a single controlled trial, and none of these has been replicated.

Symptoms of anxiety, obsessionality and near-delusional ideation regarding body weight and shape have led some to hypothesize that antipsychotic medications might be helpful in AN.

Olanzapine, with effects on the dopamine, serotonin and histamine receptor systems, has been described as helpful for AN in several case reports and open trials, and is frequently recommended to patients who are struggling to improve. Recently, a few small controlled trials have been reported (McKnight & Park, 2010).

In the first published double-blind placebo-controlled trial, Brambilla *et al*. (2007) randomly assigned 30 out-patients with AN to receive olanzapine or placebo in addition to cognitive behavioral therapy (CBT) for 3 months. Measures of compulsivity, aggressiveness and persistence improved in the group receiving olanzapine while weight and other psychological measures improved without significant group difference.

More persuasive data were published by Bissada *et al*. (2008) who compared 10 weeks of olanzapine with placebo in 34 patients with AN who also received treatment in a 4 day-per-week day hospital program. Bissada *et al*. (2008) found that, on average, patients in the group assigned to olanzapine had a significantly

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shorter time to reach target body mass index (BMI) than did the group receiving placebo. In addition, the group receiving olanzapine demonstrated significantly more improvement in obsessionality as measured by the Yale–Brown Obsessive Compulsive Scale.

This study's strengths include its larger sample size and its randomized double-blind, placebo-controlled design; however, the study does not provide information about whether olanzapine treatment is of benefit to individuals receiving out-patient treatment in the absence of the considerable benefit of an intensive weight-restoration program.

The current study was conducted to obtain preliminary information regarding the utility of olanzapine for out-patients with AN.

Method

This study was conducted at two sites: New York State Psychiatric Institute/Columbia University Medical Center and Toronto General Hospital/University of Toronto. Ethics review committees at each site approved the recruitment of human subjects for this study. Written informed consent from each participant was obtained prior to randomization.

Participants

Eligible participants were recruited between February 2006 and December 2007. Eligible participants were individuals $\geqslant$16 years of age who met criteria for AN (excluding amenorrhea) by the Structured Clinical Interview for DSM-IV (SCID-I), and had a BMI $\geqslant$14 kg/m^2 and $\leqslant$19 kg/m^2. Exclusion criteria included having a medical or psychiatric problem requiring urgent care, or having a clinical symptom or condition inconsistent with the risk profile of olanzapine, such as diabetes, hyperglycemia, hyperlipidaemia or orthostatic hypotension. Additionally, individuals were excluded from the study with comorbid schizophrenia, schizophreniform, or bipolar disorder.

Participants were free of other psychiatric medication for at least 4 weeks prior to study enrollment, with the exception of selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors which were permitted if doses had not changed for 4 weeks prior to study enrollment. Participants did not receive individual psychotherapy during the conduct of this trial.

Treatment

A total of 23 subjects were randomly assigned to receive either olanzapine or matched placebo for 8 weeks in order to collect preliminary experiences regarding risks, benefits and effect size. This small pilot study was not intended to establish efficacy. Randomization lists, stratified by site and with a block size of four, were generated by a computer program. Identical, sequentially numbered bottles containing medication or placebo were prepared by pharmacy staff who did not interact with the patients. Randomization assignments were kept in sealed envelopes and all clinical staff involved in the care of patients, as well as study coordinators, remained blind to medication assignment during the study. Medication dose was initiated at one pill (2.5 mg) per day, and was increased every 2 weeks, first to two pills (5 mg), and then four pills (10 mg) if the patient was tolerating medication. Subjects remained on four pills daily of study medication for the final 4 weeks of the trial unless lower doses were necessary secondary to side effects.

Subjects were evaluated weekly for change in weight and eating disorder symptoms, medication side effects, medication compliance and general medical status. Additionally, physicians used several compliance-enhancement strategies, including weekly reminder phone calls. Serum medication levels were obtained at the end of the trial in order to confirm compliance.

Participants were withdrawn from the study if they lost weight at four consecutive sessions, reached a BMI $<$14 kg/m^2, if their clinical status required a different treatment, or if they wished to terminate participation.

Assessments

At the baseline visit, height and weight were measured and diagnostic status was assessed via SCID-I (First *et al*. 1996) and the Eating Disorders Examination (Fairburn & Cooper, 1993). Patients were weighed at every study visit. Psychological assessments included the Beck Anxiety Inventory (BAI; Beck *et al*. 1988), Beck Depression Inventory (BDI; Beck *et al*. 1961), Body Shape Questionnaire (BSQ; Cooper *et al*. 1987), Eating Disorders Inventory (EDI; Garner & Olmsted, 1984), Yale–Brown–Cornell Eating Disorders Scale (YBC-EDS; Mazure *et al*. 1994) and the Positive and Negative Syndrome Scale (PANSS; Kay *et al*. 1987).

Statistical analysis

Groups were compared on continuous measures using Student's *t* tests or analysis of covariance (ANCOVA) using data from all subjects randomized (i.e. intent to treat); the effect size of olanzapine *versus* placebo was assessed using η^2 (full, not partial). To assess the effect of medication *versus* placebo on BMI using all

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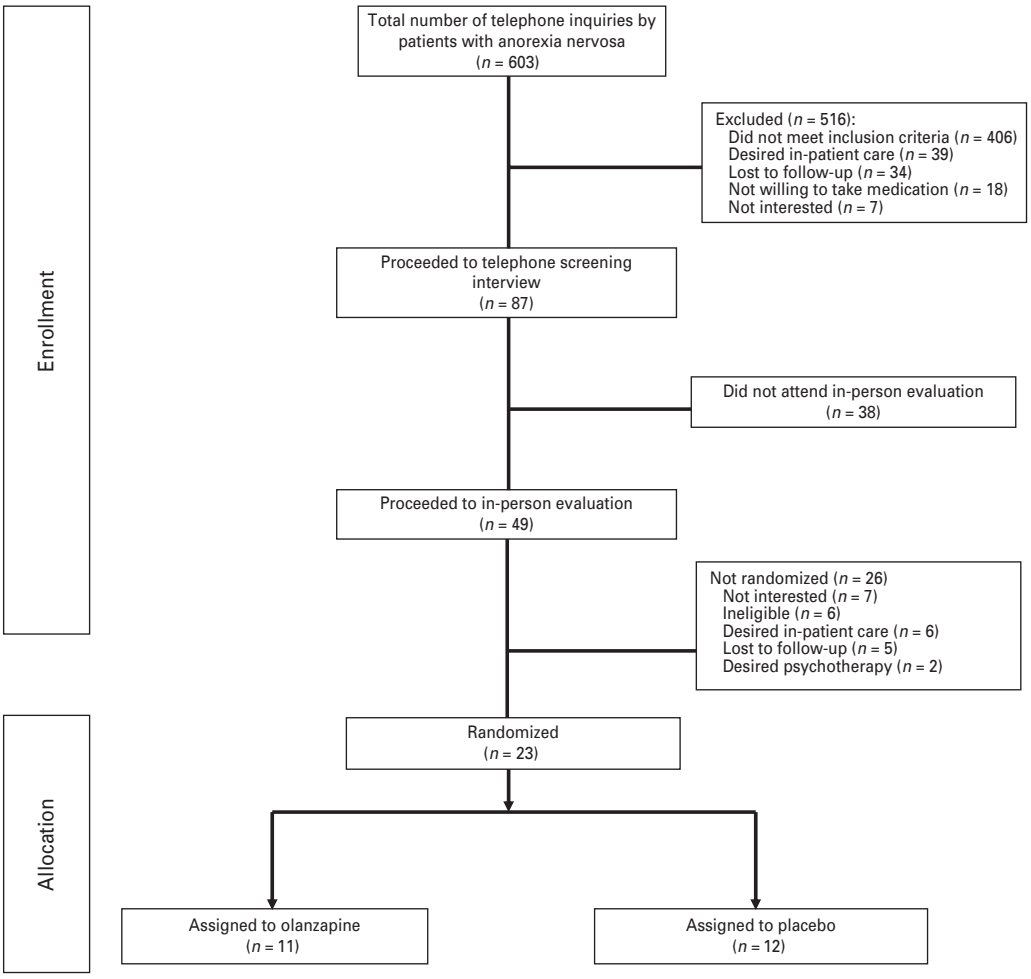

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing patient recruitment into the study of olanzapine *versus* placebo.

available weights, an analysis using multi-level modeling was also conducted (Singer & Willett, 2003). Stata (version 10.1; StataCorp LP, USA) was used to perform statistical analysis.

Results

Fig. 1 presents the CONSORT (Consolidated Standards of Reporting Trials) diagram describing how patients were recruited to participate. Included in the study were 23 participants (22 females, one male; 16 in New York and seven in Toronto), with a mean age of 27.7 (S.D. = 9.1) years. They were randomly assigned to olanzapine ($n = 11$) or placebo ($n = 12$). Of the participants, nine were taking antidepressant medication upon study enrollment. Of the 17 (74%) patients who completed the full 8-week trial, eight (73%) were assigned to olanzapine and nine (75%) to placebo. During the course of the study, there were statistically significant improvements in the average BMI, and in the average scores on the BAI, BDI, EDI and YBC-EDS (see Table 1).

There were no statistically significant differences between olanzapine and placebo groups at baseline in mean BMI or in the mean scores on any of the measures of psychopathology (see Table 1). ANCOVA, with baseline BMI as a covariate, found that the end-of-treatment BMI differed significantly between the olanzapine and placebo groups. Assessment of the change in BMI over time, using all available weight data in a multi-level linear growth model, also found that the difference between olanzapine and placebo groups was statistically significant [0.105 (S.E. = 0.05) kg/m² per week, $p = 0.04$]. There were no statistically significant effects by ANCOVA of olanzapine *versus* placebo on any of the measures of psychopathology (see Table 1).

Because a substantial minority of patients was taking concomitant antidepressant medication, we examined whether this might have affected response

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Table 1. *Characteristics of patients assigned to olanzapine and placebo at baseline and at the end of the study*

	Olanzapine				Placebo				Combined						
	Baseline		End of study		Baseline		End of study		Baseline		End of study		ANCOVA[a]		
	Mean (S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.D.)	*n*	Mean (S.D.)	*n*	df	F	*p*	η^2
BMI, kg/m²	16.7 (1.5)	11	17.8 (2.3)	11	17.4 (1.0)	12	17.6 (1.3)	12	17.1 (1.3)	23	17.7 (1.8)*	23	1, 20	6.64	0.02	0.067
Beck Anxiety Inventory	16.3 (10.5)	11	9.7 (6.1)	8	17.8 (11.1)	12	5.9 (6.3)	9	17.1 (10.7)	23	7.7 (6.3)*	17	1, 14	1.49	0.24	0.062
Beck Depression Inventory	23.7 (8.4)	10	18.5 (11.0)	8	28.4 (9.8)	12	23.9 (9.4)	9	26.3 (9.3)	22	21.3 (10.2)*	17	1, 13	0.46	0.51	0.018
Body Shape Questionnaire	136 (44)	11	128 (52)	8	125 (41)	12	116 (48)	9	130 (42)	23	122 (48)*	17	1, 14	0.19	0.67	0.003
Eating Disorder Inventory	80.6 (39.8)	11	78.3 (44.1)	8	82.2 (34.7)	12	66.6 (26.1)	9	81.5 (36.4)	23	72.1 (35.1)*	17	1, 14	0.43	0.52	0.010
YBC-EDS	20.3 (7.6)	11	19.4 (8.1)	8	22.1 (8.4)	12	18.4 (6.5)	9	21.3 (7.9)	23	18.9 (7.1)*	17	1, 14	2.21	0.16	0.035
PANSS	35.0 (7.6)	11	30.3 (7.5)	8	29.4 (6.4)	12	28.0 (9.1)	9	32.1 (7.4)	23	29.1 (8.2)	17	1, 14	0.26	0.62	0.012

ANCOVA, Analysis of covariance; S.D., standard deviation; df, degrees of freedom; BMI, body mass index; YBC-EDS, Yale–Brown–Cornell Eating Disorders Scale; PANSS, Positive and Negative Syndrome Scale.

Values are given as mean (S.D.) and the number of patients for whom data were available.

* Statistically significant change from baseline in the combined group (paired *t* test, $p < 0.05$).

[a] ANCOVA statistics assess differences between olanzapine and placebo groups at end of the study with the baseline measure as a covariate.

during the study. Very similar fractions of patients assigned to olanzapine and to placebo were on antidepressants (olanzapine: 5/12 = 42%; placebo: 4/11 = 36%), and their average BMIs at baseline were similar [on antidepressants: 16.9 (S.D. = 1.2) kg/m²; not on antidepressants: 17.2 (S.D. = 1.4) kg/m²; $t = 0.51$, $p = 0.6$]. Finally, by ANCOVA, being on an antidepressant had no effect on BMI at termination [$F(1, 20) = 0.09$, $p = 0.77$].

The characteristics of the participants at the New York and Toronto sites did not differ significantly except for the mean score on the PANSS [34.6 (S.D. = 1.6) *v.* 26.3 (S.D. = 2.3), respectively, $t = 2.9$, $p = 0.009$]. As analysed by ANCOVA with the baseline assessment as the covariate, there were no statistically significant differences between the sites in the average BMI at the end of treatment or in the average score on any measure of psychopathology except the BSQ. On that measure, mean baseline and end-of-treatment scores of patients in New York were 143 (S.D. = 44) and 128 (S.D. = 47), respectively, and, for the Toronto group, they were 97.5 (S.D. = 34) and 109 (S.D. = 53) [$F(1, 14) = 5.28$, $p = 0.04$]. The response of the single male patient, who was assigned to receive olanzapine, did not appear to differ from those of the female patients.

The average medication dose during the final week of study treatment was 7.95 (S.D. = 2.70) mg (olanzapine) and 8.75 (S.D. = 2.50) mg equivalent (placebo). Of the eight participants receiving olanzapine who completed the trial, one had an undetectable medication level upon study termination and the remaining seven had a mean level of 22 (S.D. = 12.7) ng/ml. Medication side effects were uncommon except for sedation. The average subjective ratings of sedation during the trial on a four-point scale (where 0 = not at all, 1 = slight, 2 = moderate and 3 = severe) were significantly greater for patients receiving olanzapine compared with placebo [1.39 (S.D. = 0.76) *v.* 0.67 (S.D. = 0.62), $t = 2.41$, $p = 0.03$]. All patients receiving olanzapine rated sedation as moderate or severe during at least 1 week, compared with seven patients receiving placebo. However, there was no clear relationship between the level of sedation and dropping out of the trial. No participant developed hyperglycemia, or laboratory changes suggestive of liver function or lipid profile abnormalities.

Discussion

AN is a serious mental illness without clear empirical support for any specific treatments, especially for adult patients. Symptoms typical of AN, including persistent, intrusive thoughts about body shape and weight, provide a theoretical basis for considering

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antipsychotic medication. These observations, together with a small amount of anecdotal clinical data, suggest that olanzapine may be helpful in AN.

This 8-week study demonstrated that, in a small group of out-patients with AN, olanzapine was associated with a greater increase in BMI than was placebo. Our finding is consistent with that of Bissada *et al*. (2008). However, unlike Bissada *et al*. (2008) and Brambilla *et al*. (2007), we were unable to detect psychological improvement associated with olanzapine compared with placebo. Consistent with other reports, including that of Bissada *et al*. (2008) we did not note any adverse metabolic effects among participants receiving olanzapine. This may have resulted from the fact that our sample was small. It is also possible that the metabolic risks of olanzapine well documented in other clinical populations may not be as severe in AN. Before this can be concluded, however, a substantial number of additional patients with AN receiving olanzapine must be examined.

This study, while small in size, adds to the placebo-controlled data of Brambilla *et al*. (2007) and Bissada *et al*. (2008) in suggesting a possible role for olanzapine in the treatment of AN. Unlike these studies, in which olanzapine was added to CBT or to an intensive day program, patients in the current study gained weight while receiving no additional specific treatment for their eating disorder or participating in a structured program. Thus, our data suggest that olanzapine may be of help even in the context of a very limited treatment program. These findings, while encouraging, must be viewed as preliminary until larger trials of longer duration are conducted.

Even if additional studies of a greater number of patients lend support to the use of olanzapine in AN, there will challenges in implementing this treatment. Individuals with AN are typically reluctant to take medication (Halmi *et al*. 2005), and the metabolic side effects of olanzapine described in other populations will probably increase patients' reluctance, even if the side effect profile in AN is found to be more benign.

This study had a number of significant limitations. Primary among them is the very small sample size. This reduced our ability to detect both potentially beneficial effects of olanzapine, such as on psychological symptoms, and adverse effects, such as impaired glucose control. Another limitation is the absence of a manipulation check to determine the frequency with which clinicians were able to detect whether a patient was taking placebo or olanzapine. However, the assessment of the primary outcome measure, weight, was not dependent on clinician judgment.

Despite these limitations, the data from the current study add to existing literature indicating that olanzapine may be helpful in AN and suggest that larger, more definitive trials are warranted.

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Declaration of Interest

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