Olanzapine therapy in anorexia nervosa: psychobiological effects

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Dopamine impairments occur in anorexia nervosa. The aim of this study was to see whether treatment with the atypical dopamine antagonist antipsychotic olanzapine improves the disorder. Thirty anorexics, 18 restricted and 12 bingeing–purging, underwent a 3-month course of cognitive behavioral therapy, plus at random and double-blinded oral olanzapine (2.5 mg for 1 month, 5 mg for 2 months) in half and oral placebo in the other half of them. BMI, psychopathological aspects (eating disorder inventory, Hamilton Rating Scale, Buss–Durkee Rating Scale, Yale Brown Cornell for Eating Disorders Rating Scale, temperament–character inventory), and homovanillic acid blood concentrations for dopamine secretion, were monitored at baseline and then monthly during the trial. At the end of the trial BMI, total eating disorder inventory, total Yale Brown Cornell for Eating Disorders Rating Scale, Buss–Durkee Rating Scale, Hamilton Rating Scale scores and in olanzapine-treated patients the subitems of eating disorder inventory ineffectiveness and maturity fear, of Buss–Durkee Rating Scale direct aggressiveness, of temperament–characteristic inventory persistence had improved significantly. When stratified for anorexia nervosa subtype, BMI changes were significant among anorexia nervosa bingeing-purging patient, 'depression' (Hamilton Rating Scale) and 'direct aggressiveness' (Buss–Durkee Rating Scale) among anorexia nervosa bingeing–purging patients, 'persistence' (temprerament–characteristic inventory), among anorexics restricted patients, with a trend toward significance for obsessivity–compulsivity (Yale Brown Cornell for Eating Disorders Rating Scale). homovanilic acid blood levels increased significantly in the cognitive behavioral therapy + olanzapine group. No correlations were observed between homovanilic acid concentrations and psychopathological parameters. The pharmacological treatment can significantly improve specific aspects of anorexia nervosa. *Int Clin Psychopharmacol* 22:197–204

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Introduction

The efficacy of pharmacological treatments for anorexia nervosa (AN) remains controversial, perhaps because psychotropic drugs have not generally been selected to correct a putative biological cause of the disease (Russell *et al.*, 1986; Kaye *et al.*, 1998; Santonastaso *et al.*, 2001; Fassino *et al.*, 2002; Mitchell *et al.*, 2003; De Zwaan and Roerig, 2003; Kim, 2003; Pederson *et al.*, 2003; Gowers and Bryant-Waugh, 2004). In AN, possibly genetically induced alterations in neurotransmitter–neuropeptide functions have been reported to occur, although it is still unclear whether these neurobiochemical impairments precede the disorder or develop during its course as a result of the stressful effects of malnutrition (Halmi and Sherman, 1977; Gerner *et al.*, 1984; Kaye *et al.*, 1984, 1988, 1999; Ebert *et al.*, 1984; Fava *et al.*, 1989; Bowers *et al.*, 1994; Strober *et al.*, 2000; Urwin *et al.*, 2002, 2004; Frank *et al.*, 2005; Kaye *et al.*, 2005). The most amply documented neurotransmitter alteration refers to central serotonin (5-HT) dysfunctions, including reduced 5-HT and 5-HT promoter secretion and altered receptor functions (5-HT-2a/2c, HTRID) (Klump and Gobrogge, 2005). Treatments using 5-HT-stimulating tricyclic antidepressant and specific serotonin reuptake inhibitors have generally been unsuccessful, however (De Zwaan and Roerig, 2003; Gowers and Bryant-Waugh, 2004). During the active phase of AN and after recovery from the disorder, dopamine (DA) secretion has also been reported to occur, with both hypersecretion (Van Binsbergen *et al.*, 1991; Bowers *et al.*, 1994; Halmi, 1996; Brambilla *et al.*, 2001; Castro *et al.*, 2004) and hyposecretion of the amine and its metabolites (Riederer *et al.*,

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1982; Halmi *et al.*, 1983; Owen *et al.*, 1983; Gillberg, 1983; Kaye *et al.*, 1984, 1999; Lawrence *et al.*, 2003; Frank *et al.*, 2005). To date, no significant correlations have been found between DA or DA receptor gene alterations and the development, course and prognosis of AN (Bruins-Slot *et al.*, 1998). Treatments using typical antipsychotics alone or in combination with psychotherapies, many of them evaluated in open trials and without placebo (PL) control, have usually failed (Dally, 1966; Vandereyken and Pierlot, 1982; Vandereyken, 1984; Ruggero *et al.*, 2001; Cassano *et al.*, 2003). More recently, atypical antipsychotics, olanzapine (OLA), risperidone and amisulpride, in particular, in either single cases or in small patient groups, had been shown to improve eating habits, weight and some psychopathological aspects of AN (depression, anxiety, obsessivity–compulsivity, psychoticism) (Hansen, 1999; Newman Tocker, 2000; Ridley-Siegert, 2000; La Via *et al.*, 2000; Coates, 2000; Gaskill *et al.*, 2001; Mehler *et al.*, 2001; Ruggero *et al.*, 2001; Leucht *et al.*, 2002; Jensen and Mejihede, 2002; Powers *et al.*, 2002; Carver *et al.*, 2002; Ercan *et al.*, 2003; Malina *et al.*, 2003; Boachie *et al.*, 2003; Pederson *et al.*, 2003; Mangano *et al.*, 2004; Barbarich *et al.*, 2004; Mondraty *et al.*, 2005; Attia *et al.*, 2005; Hillebrand *et al.*, 2005; Menaster, 2005; Bosanac *et al.*, 2005). But as these therapies were administered in open trials without PL control, the significance of the positive results is questionable.

In a sample of AN patients, we administered a combined treatment of cognitive behavioral therapy (CBT) which, although effective in a relatively small percent of patients, is most frequently used in AN (Garner *et al.*, 1997; Dare *et al.*, 2001; Wilson, 2003), and double-blinded, OLA in one half of the patients, whereas the other half received CBT + PL. OLA was putatively administered to correct an impaired DA function because, even though OLA has been reported to act on multiple neurotransmitter systems including DA, 5-HT, histamine and α-1-adrenergic receptors (Bymaster *et al.*, 1997; Scheepers *et al.*, 2001), the drug seems to have a more marked effect on DA function than on other neurotransmitters (Bernardo *et al.*, 2001). With this preliminary study, we wanted to investigate the psychobiological effects of an OLA treatment in AN and, in particular, to see whether the OLA-related weight increase reported in experimental animals, normal humans and various psychiatric disorders (Gaudie *et al.*, 2002; Reynold *et al.*, 2002; Goldstein *et al.*, 2002; Backer *et al.*, 2003; Lipkovich *et al.*, 2004; Roerig *et al.*, 2005) is confirmed in our AN patients, whether OLA administration could significantly improve the psychological effects of CBT, which type of AN symptoms was most affected, and whether such improvements were significantly correlated with changes in DA activity.

Methods

Patients

Thirty AN female outpatients, 18 with the restricted (AN-R) and 12 with the bingeing–purging (AN-BP) type entered the study. They were referred to our eating disorder centers by general practitioners who first examined them, and were recruited at random within the patents consecutively attending the centers, without any specific set of selection and in particular no stratification for age, BMI, and type of eating disorder psychopathologies. The eating disorder centers were those of the Mental Health Department of the Sacco Hospital, Milan (seven patients), of the University Psychiatric Departments of Turin (five patients), Pisa (six patients) and Catanzaro (seven patients), and of the University Neuroscience Department of Padua, Italy (five patients). The original study sample consisted of 35 patients; however, three dropped out during the treatment months 1 and 2, and two refused to start pharmacotherapy. Medical history, physical and psychopathological aspects of these five patients did not differ significantly from those of the patients who completed the full course of treatment.

Diagnoses were made according to the *Diagnostic and statistical manual of mental disorder-IV* criteria (DSM-IV) (American Psychiatric Association, 1994) based on the Structured Clinical Interview for DSM-IV (First *et al.*, 1995). Exclusion criteria were general medical impairments, any type of endocrine, metabolic and immune alterations other then those linked to AN, cerebral trauma and epilepsy. Comorbidities manifesting with AN included bipolar disorders type II in two patients, major depressive disorders in two, borderline personality disorders in four, obsessive–compulsive disorder in one, and generalized anxiety in one.

Demographic data are reported in Table 1. Ages of the patients and durations of the disorder were not significantly different between the OLA and the PL treated individuals, and between AN-R and AN-BP patients, and none of the probands was less than 18 years of age.

No significant differences were observed in baseline BMI and psychopathological items between OLA and PL-treated patients.

All patients gave their written informed consent for treatment after receiving a complete description of the study protocol. The study was conducted with the control and approval of an appropriate named ethics committee.

Design of the study

In a sample of AN patients comprising both the restricted (AN-R) and AN-BP types, we administered a combined treatment of CBT and, double-blinded, OLA in one half of the patients, whereas the other half received CBT + PL. CBT was administered for ethical reasons, as severely ill anorexics could not be kept on PL administration alone for the duration of the treatment.

Table 1 Demographic data of anorexic patients

Demographic data of anorexic patients							
	OLA	PL	*P*				
Cases	15	15					
Restricted anorexics	8	10					
Bingeing–purging anorexics	7	5					
Age (years)	23.7 ± 4.8	26.3 ± 8.5	NS				
Duration of the disease (years)	6.3 ± 5.0	4.4 ± 3.0	NS				
BMI of anorexic patients							
	T0	T1	T2	T3	*P*	F	d.f.
OLA	15.5 ± 1.9	15.9 ± 0.8	16.9 ± 1.8	17.2 ± 2.0	0.0003	13.7	3
PL	15.8 ± 1.1	16.2 ± 1.0	16.5 ± 1.3	16.9 ± 1.2	0.001	17.2	3

d.f., degrees of freedom; OLA, olanzapine; NS, not significant; PL, placebo.

The OLA-induced modification of dopaminergic function was evaluated by measuring plasma concentrations of homovanillic acid (HVA), the main metabolite of DA, which, even deriving from both central and peripheral sources, has been repeatedly reported to mirror significantly brain DA function (Pickar *et al.*, 1990; Glazer *et al.*, 1990; Zhang *et al.*, 2001).

Treatments

All patients received a 3-month course of cognitive-behavioral therapy (CBT) according to the method of Garner *et al.* (1997). Personal CBT sessions were administered to each patient, once a week during the 3 months of the trial, from trained psychotherapists specialized in CBT for eating disorders. Before starting this study, the psychotherapists of each institute met to ensure that they were adhering to the same methodological protocol. Two treatment groups of 15 patients each were formed, one with eight AN-R and seven AN-BP patients and the other with 10 AN-R and five AN-BP patients. In addition to CBT, one group received OLA for 3 months (daily dose of 2.5 mg for 1 month and of 5 mg for the following 2 months) and the other group received a PL for 3 months. The OLA and PL assignments performed at random, were blinded to participants, investigators and the entire medical and nursing staff. OLA and PL were administered orally in a single dose in the morning. This dose schedule was chosen on the basis of the evidence from the literature on OLA administration in AN. Pill count was utilized to check adherence to the medication. No other medications, of any type, were given to the patients. The decision to administer combined treatment for 3 months was made with the view that a shorter course of therapy could hardly reveal very significant results, and that a longer one, if not effective, would be useless and therefore putatively dangerous for the patients.

Nutritional monitoring

BMI was measured to monitor the patient's nutritional status at baseline and then at weekly intervals for 3 months.

Biochemical monitoring

HVA was assayed at baseline and then monthly during therapy. Blood for HVA was collected at the eating disorder centers of the Psychiatric Department of Milan, Turin, Padua, Pisa and Catanzaro, Italy. Patients fasted 12 h before blood withdrawal. In preparation for blood collection, an intravenous cannula kept open by a saline infusion was inserted into an antecubital vein at 0830–0900 h, and blood for HVA was drawn after 30 min of rest, immediately centrifuged and plasma stored at −25°C until assayed. All the samples were assayed together at the eating disorder center of the University Psychiatric Institute and at the University Chair of Phorensic Toxicology, SUN, Naples, Italy, to avoid changes in reagents that could interfere with the results.

HVA was assayed by a gas chromatograph–mass spectroscopy method. The analysis was performed on an HP Series 5890 (Agilens Technologies Italia, Cernusco SN, Milan, Italy) gas chromatograph equipped with an injector operating in the splitless mode and set at 270°C. The carrier gas was helium with a column head pressure of 93 kPa and flow of 1 ml/min. The column was a capillary fused silica MS-5 (30 m × 0.25 mm internal diameter). The oven temperature was monitored during analysis from 150 to 280°C at a step rate of 15°C/min. The detection of the compounds was carried out with an HP 5971 (Agilens Technologies Italia, Cernusco SN, Milan, Italy) mass-selective detector with a capillary interface heated at 280°C, an electron-impact ion source (electron energy 70 eV), a quadruple mass filter and an electron-multiplier detector. The detection was performed in the selected-ion monitoring mode. Ions detected were 326–209–179–267 *m/z*.

A 0.5–1 ml volume of serum was added to a suitable volume of an appropriate internal standard (homovanillic acid) and extracted with Toxi-tubes B (Toxi-Lab Irvine, California, USA). The organic phase was transferred into minivials and evaporated to dryness under a stream of nitrogen. After evaporation of the organic phase, the residue was dissolved in 50 µl of N,O-bis-(trimethylsilyl)-

trifluoro-acetamide and the minivials heated at 60°C for 15 min. Samples of 1 µl were used for gas chromatograph–mass spectroscopy analysis. The limit of detection was 0.010 ng/ml. A linear relationship was observed at the concentration range from 0.010 to 0.500 ng/ml. The limit of quantification in serum was 0.030 ng/ml.

Psychological ratings

At baseline and at monthly intervals during the course of treatments the patients had psychopathological changes assessed by the eating disorder inventory-2 (EDI-2; Garner, 1991), to monitor the typical psychopathology of AN, the Yale Brown Cornell for Eating Disorder Rating Scale(Mazure *et al.*, 1994) to monitor obsessivity–compulsivity, the Buss–Durkee Rating Scale (Buss and Durkee, 1957) to monitor aggressiveness, the temperament and character inventory (TCI; Cloninger *et al.*, 1994), to monitor personality aspects the Hamilton Rating Scale (HRS 1960), to monitor depression.

Statistical analyses

Data were analyzed statistically by one-way analysis of variance (ANOVA) (one-way ANOVA for repeated measures) to control for changes in BMI and HVA levels and in rating scales scores for patients on CBT + OLA treatment and patients on CBT + PL treatment, separately. The difference between the effects of the two treatments was analyzed by a two-way ANOVA for repeated measures. The correlations between HVA levels and rating scales scores were analyzed by Pearson analysis. The BMDP (BMDP, 1985) program was used for the analyses.

Results

Results are reported in Tables 1–4.

The pharmacological treatments, both OLA and PL, were well tolerated. At the low doses used, OLA administration induced only mild sleepiness in the first days of therapy.

BMI (Table 1) increased significantly in both treatment groups; however, no significant differences between the effects of the two treatments emerged on statistical analysis by a two-way ANOVA for repeated measures. When the patients were stratified according to type of AN (AN-R and AN-BP), the increase in BMI was significantly greater in the CBT + OLA-treated AN-BP patients than in all the other participants ($P = 0.01$, $F = 3.77$, d.f. = 3).

The results of the eating disorder inventory-2 (EDI-2) (Table 2) revealed that there was no significant difference between the item values of CBT + OLA and CBT + PL patients at each point of the treatments. Both treatments significantly changed the total values of the whole symptoms and of ineffectiveness and maturity fear in only CBT + OLA-treated patient. No increase in the bulimic symptomatology was observed in the OLA + CBT treated AN-BP patients. When the effects between the two treatments were analyzed together by a two-way ANOVA for repeated measures, no significant differences in total values and various items, however, emerged between the two treatment groups, even when the patients were divided according to AN type (AN-R and AN-BP).

The Yale Brown Cornell for Eating Disorders Rating Scale (Table 3) for obsessivity–compulsivity revealed a significant improvement in total values and in obsessiveness (preoccupations) in both treatment groups, whereas only the CBT + OLA-treated patients showed a significant improvement in compulsivity (rituals). Two-way ANOVA for repeated measures revealed only a trend toward more significant effectiveness for the CBT + OLA versus the CBT + PL treatment, for total values ($P = 0.08$, $F = 2.26$, d.f. = 3) and obsessivity and compulsivity ($P = 0.07$, $F = 2.35$, d.f. = 3). No differences between AN-R and AN-BP patients were seen in either treatment groups.

The Buss–Durkee scale for aggressiveness revealed a significant improvement in total values in both treatment groups (CBT + OLA: $P = 0006$, $F = 7.1$, d.f. = 3; CBT + PL: $P = 0.05$, $F = 3.5$, d.f. = 3), and in the subitem 'direct aggressiveness' in CBT + OLA-treated patients ($P = 0.0009$, $F = 11.1$, d.f. = 3). Two-way ANOVA for repeated measures revealed a more significant improvement in 'direct aggressiveness' in the CBT + OLA-treated versus the CBT + PL-treated patients ($P = 0.006$, $F = 4.47$, d.f. = 3). When stratified according to AN types, CBT + OLA-treated AN-BP patients showed a more significant improvement ($P = 0.05$, $F = 2.67$, d.f. = 3) than the AN-R ones.

The Hamilton Rating Scale showed that depression improved significantly in both treatment groups (CBT + OLA: $P = 0.01$, $F = 5.7$, d.f. = 3; CBT + PL: $P = 0.01$, $F = 5.5$, d.f. = 3) . Two-way ANOVA for repeated measures revealed that the antidepressant effect was more significant in the CBT + OLA than in CBT + PL-treated patients ($P = 0.05$, $F = 2.69$, d.f. = 3), without showing significant differences between AN-R and AN-BP patients.

The TCI showed that only 'persistence' improved significantly in the CBT + OLA-treated patients ($P = 0.02$, $F = 3.7$, d.f. = 3). Two-way ANOVA for repeated measures revealed a more significant improvement in the CBT + OLA than in the CBT + PL-treated patients ($P = 0.007$, $F = 4.3$, d.f. = 3). When stratified by AN type, the AN-R patients showed a more significant effect of CBT + OLA treatment on 'persistence' than the other patients ($P = 0.04$, $F = 2.77$, d.f. = 3).

Table 2 EDI-2

Item	Therapy	T0	T1	T2	T3	*P*	F	d.f.
EDI-2 total	OLA	112.1 ± 49.0	103.4 ± 46.3	100.1 ± 48.2	89.6 ± 50.2	0.04	3.5	3
	PL	96.7 ± 38.9	83.5 ± 33.9	69.9 ± 36.0	69.2 ± 33.2	0.01	3.5	3
Drive for thinness	OLA	15.1 ± 6.7	15.4 ± 6.9	14.0 ± 6.9	12.4 ± 7.5	NS		
	PL	10.4 ± 7.8	11.3 ± 7.4	9.7 ± 7.9	9.6 ± 7.8	NS		
Interoceptive awareness	OLA	11.5 ± 7.4	10.4 ± 6.7	10.9 ± 5.7	9.7 ± 6.9	NS		
	PL	7.1 ± 6.3	8.2 ± 5.4	7.5 ± 6.4	6.7 ± 6.2	NS		
Bulimia	OLA	7.5 ± 8.3	6.8 ± 6.7	5.7 ± 7.5	4.9 ± 6.8	NS		
	PL	5.5 ± 8.1	4.3 ± 7.1	5.1 ± 7.3	3.7 ± 6.2	NS		
Body dissatisfaction	OLA	15.7 ± 7.2	4.7 ± 7.1	13.1 ± 7.4	13.4 ± 7.9	NS		
	PL	11.9 ± 6.9	12.7 ± 5.9	10.9 ± 5.3	10.6 ± 4.1	NS		
Ineffectiveness	OLA	12.1 ± 5.9	11.5 ± 6.9	11.6 ± 5.8	9.3 ± 6.7	0.05	3.5	3
	PL	7.8 ± 5.9	9.5 ± 5.9	8.1 ± 6.1	7.7 ± 6.5	NS		
Maturity fear	OLA	10.2 ± 6.5	8.3 ± 6.0	7.3 ± 5.7	6.2 ± 5.3	0.04	3.6	3
	PL	5.0 ± 3.6	5.5 ± 4.1	4.0 ± 3.5	4.1 ± 4.0	NS		
Perfectionism	OLA	5.2 ± 3.2	5.2 ± 2.4	4.9 ± 3.4	4.7 ± 3.9	NS		
	PL	3.8 ± 4.6	3.6 ± 3.4	3.0 ± 3.1	3.1 ± 3.1	NS		
Interpersonal distrust	OLA	8.1 ± 7.2	7.4 ± 7.7	7.5 ± 6.6	7.0 ± 5.9	NS		
	PL	7.7 ± 4.8	7.9 ± 6.5	6.1 ± 5.1	7.0 ± 4.6	NS		
Ascetism	OLA	8.1 ± 4.3	7.0 ± 4.5	7.6 ± 4.5	6.5 ± 2.9	NS		
	PL	6.1 ± 4.7	6.4 ± 3.9	4.9 ± 3.6	5.4 ± 2.9	NS		
Impulse regulation	OLA	8.4 ± 6.7	7.4 ± 6.4	7.9 ± 6.6	6.8 ± 6.5	NS		
	PL	5.9 ± 6.3	6.3 ± 5.6	4.5 ± 5.2	4.9 ± 4.6	NS		
Social insecurity	OLA	10.1 ± 7.4	9.3 ± 6.9	9.7 ± 7.5	8.7 ± 8.8	NS		
	PL	7.6 ± 5.3	7.9 ± 5.3	6.3 ± 4.1	6.5 ± 3.9	NS		

d.f., degrees of freedom; EDI-2, eating disorder inventory; NS, nonsignificant; OLA, olanzapine; PL, placebo.

Table 3 Yale Brown Cornell for Eating Disorders Rating Scale

Item	Therapy	T0	T1	T2	T3	*P*	F	d.f.
Total	OLA	25.5 ± 14.3	22.1 ± 11.3	18.3 ± 9.4	12.6 ± 5.9	0.01	5.3	3
	PL	23.0 ± 11.7	22.1 ± 13.3	19.3 ± 9.0	17.0 ± 9.7	0.003	7.9	3
Preoccupations	OLA	10.9 ± 9.0	9.3 ± 5.3	7.7 ± 4.6	8.2 ± 3.2	0.02	5.9	3
	PL	9.5 ± 6.8	10.6 ± 6.9	8.4 ± 4.6	8.8 ± 4.9	0.01	5.4	3
Rituals	OLA	10.9 ± 6.1	9.3 ± 5.3	7.7 ± 5.4	5.1 ± 3.2	0.01	5.9	3
	PL	9.5 ± 6.9	10.1 ± 6.9	8.4 ± 4.6	7.5 ± 4.9	NS		

NS, nonsignificant; OLA, olanzapine; PL, placebo.

Table 4 HVA plasma concentrations (ng/ml)

	T0	T1	T2	T3	*P*	F	d.f.
OLA	0.43 ± 0.30	0.67 ± 0.62	0.75 ± 1.1	1.1 ± 1.5	0.04	3.6	3
PL	0.36 ± 0.10	0.32 ± 0.13	0.31 ± 0.10	0.32 ± 0.11	NS		

d.f., degrees of freedom; HVA, homovanillic acid; NS, non significant; OLA, olanzapine; PL, placebo.

HVA plasma concentrations (Table 4) did not change in the CBT + PL-treated patients whereas they increased significantly in the CBT + OLA treated group. ANOVA for repeated measures, however, revealed no significant differences between the two treatment groups or between AN-R and AN-BP patients. No significant correlations were observed between single values or changes in HVA concentrations and single values or changes in psychopathological symptoms during the course of the two treatments.

Discussion and conclusions

The results of this preliminary study offers several starting interesting points for considerations. Conducted on an outpatient basis, the study design can be particularly useful in areas where inpatient services are unavailable or insufficient for the needs of the AN population rules. Moreover, our protocol rules out therapeutic effects of hospitalization which, *per se*, could represent a third type of treatment, with all the possible differences in therapeutic protocol between hospitals. Finally, by administering CBT to all patients, our study protocol allowed the use of PL without unethically keeping severely ill patients off therapy for months. The fact that one group of patients received two therapies together, CBT and OLA, does not reduce the significance of the pharmacological treatment *per se*, because, as mentioned, CBT alone does not currently seem to be conclusive for treating AN in all the patients, and the addition of OLA could reveal the drug's effects on specific aspects of the disease.

An interesting point, that emerges from our data is that a 3-month course of CBT alone (the PL cannot be

considered an effective therapy) failed to significantly improve eating habits and the typical AN symptoms, as monitored by the EDI-2 scale. The addition of OLA did not seem to enhance the effects of therapy on these parameters, either. This confirms the reported poor effects of separately administered CBT and psychopharmacological therapies on the most typical pathology of the disease. The results of open trials with OLA that have suggested positive effects on depression, anxiety, obsessivity–compulsivity and aggressiveness (Mehler *et al.*, 2001; Powers *et al.*, 2002; Barbarich *et al.*, 2004; Mondraty *et al.*, 2005), however, were confirmed by our study, indicating that this type of therapy is acting more on disordered emotions than on the commonly considered typical anorexic symptoms. From this, we can postulate that a pharmacological therapy, perhaps by modifying specific brain biochemical alterations, may improve only some but not all aspects of the disease. Thus, suggesting that the complex constellation of AN symptoms cannot be related to a single biological alteration but rather requires multiple therapies acting together to correct different brain biological impairments.

The observation that, unlike what occurs in experimental animals, normal humans and in other psychopathologies (Allison and Casey, 2001; Gaudie *et al.*, 2002; Newcomer, 2005; Roerig *et al.*, 2005), OLA did not lead to dramatic weight increase in our patients, the changes being not substantially different from those in the CBT + PL-treated group seems to suggest that the abnormal OLA-related weight increases reported in the literature may not result from peripheral metabolic alterations or central dopaminergic manipulation but rather from abnormally increased food consumption. This did not occur in our patients who, despite decreased obsessiveness, continued to carefully control their amount and selection of food intake in the attempt to avoid as best as possible excessive calories consumption and too rapid weight increase. In other words, the BMI increase in our OLA-treated patients was still conceptually planned and pursued and not indiscriminately or unwillingly obtained.

An additional consideration is that the effects of OLA treatment on the psychopathological parameters of our patients were not really unspecific. In fact, obsessivity–compulsivity, 'persistence', depression and aggressiveness which make up part of the psychopathological aspects of AN, are highly negative factors working against adherence to the treatments. Therefore, the OLA-related significant improvements in these symptoms, whether confirmed in larger groups of patients and in longer-lasting treatments, can provide evidence for the drug's usefulness in anorexic patients.

The observed differences in the responses of specific groups of alterations (BMI, persistence, aggressiveness) to CBT + OLA therapy in AN-R and AN-BP is intriguing. Currently, no available data significantly differentiate the biological background of anorexic symptoms *in toto* or in part of them in AN-R and AN-BP subjects. But the hypothesis that such a difference may exist should be entertained and studies investigating this aspect are required.

Our data seem to rule out the possibility that the observed psychological improvements were related to OLA–induced modifications of brain DA function. In fact, whereas CBT + OLA treatment did show a significant increase in HVA blood concentrations, a possible expression of postsynaptic D-2 receptor inhibition and consequent increased presynaptic DA secretion, which seemed not to be present in the CBT + PL-treated patients, no significant differences between the two type of therapies were seen. Moreover, the changes in HVA concentrations did not correlate with any modification of the symptoms monitored in our patients. Several explanations can be given for this. First, the size of our patient groups was too small to ensure that the observed effects and their statistical significance were not actually casual. Second, OLA may have acted by modifying other than DA brain biological parameters, since it is well known that the drug also intervenes on 5-HT, histamine and α-1-adrenergic receptor function (Bymaster *et al.*, 1997; Scheepers *et al.*, 2001). This observation suggests that other biological parameters need to be controlled, and that the investigation should be extended to other non-DA-related psychopathological parameters, to better define the effects of OLA therapy in AN.

One important bias of our study is that we report only the results of 3 months of treatment, which is obviously preliminary and must be confirmed by data from long-lasting therapies. A second bias is that we tried to study brain DA function by measuring HVA blood concentrations and not the central secretion metabolism of DA and its metabolites. Whereas peripheral HVA concentrations seem to rather precisely mimic the central DA secretion, our protocol would have requested performing four cerebrospinal fluid analysis of HVA during the 3 months of the trial, which would have been ethically unacceptable. A second bias is that DA secretion fluctuates over 24 h (Odink *et al.*, 1986), whereas we assayed HVA only once in the morning. Another bias could be that CBT was performed by different psychotherapists in the various eating disorder centers. They, however, confronted each other and agreed on the method to use.

Taken together, our data show that pharmacological treatments can be significantly effective in improving specific aspects of AN but not all symptoms, suggesting that, in the future, pharmacotherapies must be targeted to well-known and carefully controlled brain biochemical impairments responsible for specific psychopathological aspects. Presently, given the complexity and diversity of

the pathology of the biological background of AN, it seems difficult to suggest that treatments with a single drug acting on a specific neurotransmitter function could induce a therapeutic response to the disease. A therapy with OLA, however, may be of use to reduce the cachectic body weight-oriented obsessivity–compulsivity and persistence, typical aspects of the disease, and to reduce the hostility toward therapists and therapies, which interfere with the possibility to treat the patients. Our data suggest that the improvement of these pathologies might improve in the long run the course of the treatments and of the disease, this drug being possibly part of the multifactorial pharmacotherapies and psychotherapies needed to obtain consistent, lasting positive results.

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