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Antipsychotics in treatment of eating disorder patients: a study with risperidone

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Introduction. The use of antipsychotic drugs in the treatment of eating disorders (ED) patients is a controversial issue. Although a few studies support the systematic use of antipsychotics, they are frequently used, mainly in severe disorders with other associated psychopathological symptoms.

Methods. 27 EBD patients were included in the study, 7 dropped-out prematurely or did not complete the pharmacological treatment. All the patients were interviewed and diagnosed according to the Structured Clinical Interview for the DSM-IV (SCID-I) and the personality diagnosis was carried out with the Spanish version of the International Personality Disorders Examination (IPDE). Clinical assessment was performed with the Clinical Global Impression (CGI) scale and the Change Severity Assessment (CSA) at baseline and three months after the beginning of the treatment with risperidone.

Results. A significant proportion of patients showed clear clinical and general state improvement in areas like physical state, eating behavior, family and social relationships and work ability.

Conclusions. Risperidone associated to the previous therapeutic treatment in patient with a severe EBD, with comorbid disorders and where other pharmacological treatments have not been effective, could be a useful option.

Key words:
Eating disorders. Anorexia nervosa. Bulimia nervosa. Antipsychotic drugs. Treatment. Risperidone.

Actas Esp Psiquiatr 2005;33(1):33-40

Uso de antipsicóticos en el tratamiento de pacientes con trastorno de la conducta alimentaria: estudio con risperidona

Introducción. El uso de antipsicóticos en el tratamiento de los trastornos de la conducta alimentaria (TCA) es un aspecto controvertido. Pocos estudios avalan su empleo sistemático, pero es frecuente su utilización, sobre todo en pacientes graves con otras alteraciones psicopatológicas asociadas.

Métodos. Veintisiete pacientes diagnosticadas de TCA según criterios DSM-IV fueron incluidas en el estudio, 7 abandonaron prematuramente o no cumplieron la pauta farmacológica. Todas las pacientes fueron entrevistadas según la Entrevista Clínica Estructurada para el DSM-IV (SCID-I) y el diagnóstico de personalidad se realizó con la versión española del *International Personality Disorders Examination* (IPDE). La evaluación clínica se realizó con la escala de Impresión Clínica Global (ICG) y con la valoración del cambio de la gravedad (EC) al inicio y 3 meses después de haber iniciado el tratamiento con risperidona.

Resultados. Una proporción significativa de pacientes presentaron mejoría clínica evidente, así como de su estado general, en áreas como situación física, conducta alimentaria, relaciones sociofamiliares y capacidad laboral.

Conclusiones. El uso de risperidona en pacientes con un TCA grave, con comorbilidad asociada y donde otros tratamientos farmacológicos no han sido eficaces podría ser una opción útil asociada a otros regímenes terapéuticos.

Palabras clave:
Trastornos alimentarios. Anorexia nerviosa. Bulimia. Antipsicóticos. Tratamiento. Risperidona.

INTRODUCTION

Use of antipsychotics in the treatment of eating disorders (ED) is a controversial therapeutical aspect. Although few studies adequately support their use, this is somewhat common in the clinical practice of many professionals. Unfortunately, the presently available drugs achieve very partial relief of the symptoms associated to these pictures, and generally of not very specific symptoms, such as anxiety or depression, which frequently also reverse with nutritional treatment. This lack becomes clear when we consider that these disorders have an important associated morbidity-mortality[1].

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What could justify the use of antipsychotics in ED treatment?

Genetic or biological factors are important in the appearance of ED and this can suggest underlying neurophysiological dysfunctions (their prevalence is 7 to 12 times greater in relatives of patients than in controls). At least 200 different genes have been identified as involved in conditions that include eating, satiety, propensity to physical activity, energetic output, and other related aspects. The estimated heredability indicates that approximately 55 % to 80% of the variance in the appearance of an ED may be attributed to genetic factors[2].

The first studies carried out using antipsychotic medication in ED were based on the evidence, from the theoretical point of view, that food is at least partially measured by dopaminergic neurons[3]. In fact, the drugs that block the D_2 receptors increase appetite and lead to significant weight gain[4], while those that increase cerebral dopamine concentration are anorexigens[5]. A series of initial studies indicated how chlorpromazine, sometimes associated with insulin, the latter to cause hunger, would produce rapid weight gain and faster hospital discharges[6]. However, the undesired effects that appeared (seizures and binges) and the subsequent follow-up did not show that they were beneficial[7]. Subsequent studies of antipsychotics in anorexia nervosa have been supported by the hypothesis that some characteristics of anorexia nervosa could reflect an increase of dopaminergic activity of the central nervous system[8]. Controlled trials with placebo using high potency antipsychotics, pimozide[9] and sulpiride[10] showed little evidence of clinical efficacy. It is well to take into account that, together with the side effects characteristic of this drug group, patients with ED are especially sensitive to sedation, insomnia and vertigo, even at low doses[11]. Clearly, as in other conditions, the use of antipsychotics may be followed by the appearance of tardive dyskinesia.

In spite of the previous considerations, the use of antipsychotics in ED could be justified by their effects in five aspects.

Antipsychotics as anxiolytics

In the last protocol published by the Spanish Public Health System for the treatment of ED, the use of antipsychotics is based on their sedative and anxyolitic effect and it is warned that the use of benzodiazepines runs the risk of dependence[12]. Treatment with anxyolitics may be indicated in specific clinical conditions, but we understand that the generalized use of antipsychotics as anxiolytics would not be fully justified[13]. However, when the desired effect is to decrease agitation or muscular hyperactivation, a phenomenon frequently associated to severe malnutrition conditions and possibly explained by the dopaminergic activation medication, the use of dopaminergic blockers could be justified.

Antipsychotics for the control of serious behavior disorders, impulsiveness and risk of injury

Different observations verify the usefulness of antipsychotic drugs in the treatment of behavioral disorders derived from organic disorders or those secondary to a personality disorder. In fact, the appreciation that there are neurobiological disorders sensitive to psychopharmacological treatments, subjacent to personality disorders, is increasing. In a controlled trial with placebo, flupentixol was associated to a significant reduction of suicide behavior in patients with a history of such behavior and characteristics of borderline personality[14]. It has been proposed that the alterations in impulse control such as drug addiction, ludopathy, and obesity may reveal a «reward deficit syndrome», that may be partially due to a decrease in dopaminergic D_2 receptors[15]. Other findings correlate low levels of metabolites derived from serotonin and dopamine in cerebrospinal fluid of bulimic patients with frequent binging[16]. In 1986, Condon[17] reported a case of beneficial response in a female patient with anorexia nervosa with depressive episodes and associated suicide attempts with 25 years evolution. Previous treatments with antidepressants were not effective in regards to decrease in the intensity of her symptoms. Once high doses of neuroleptics were established, the patient had the sensation of emotional well-being, good functioning level and maintained a healthy weight.

The new antipsychotics have already been tested in patients with behavior and malnutrition disorders. Specifically, risperidone has been shown to be effective in a patient with anorexia and rapid weight loss secondary to Alzheimer's dementia[18]. However, this response is explained more by the efficacy of risperidone in the behavioral disorders of these patients than by its activity on the baseline psychopathology. In our country, studies have also been performed on the efficacy of the new antipsychotics, in the treatment of borderline personality disorder, with promising results[19].

Antipsychotics as anti-obsessive drug enhancers

Different publications support the effectiveness of the antipsychotic association to the usual regime of Selective Serotonin Reuptake Inhibitors (SSRI) used in the treatment of patients with a refractory Obsessive-Compulsive Disorder (OCD)[20]. Previous trials had pointed at the effectiveness of adding high potency antagonists to the usual treatment of these patients[21,22]. Subsequently, the new antipsychotics were incorporated to these trials[23,24]. The action mechanism could be related with the shared antagonism of 5-HT_{2a}/D_2 receptors. Some authors have theorized that anorexia nervosa itself could be considered as a variation of obsessive-compulsive disorder or as a phobia[25]. There have also been many studies that indicate the comorbidity of the ED with OCDs, both in anorexia nervosa[26,27] and for bulimia[28,29]. Based on this, it could be theorized that antipsychotics could have

some role in patients with serious obsessive symptoms who do not adequately respond to the usual drug regimes.

Acting on the effect that dopamine has on the hedonic effects of intake

The dopaminergic system plays a key role in the regulation of behaviors aimed at self-care and may be fundamental in the role food has as reinforcement[30] through the meso-límbic pathways[31]. Eating is a highly reinforcing behavior that not only provides nutrition for survival but also includes satisfaction and pleasure feelings[32]. Food increases extracellular dopamine concentration in the nucleus accumbens[33]. This is a phenomenon similar to that produced by abuse of drugs and could justify the positive reinforcement capacity of food[34]. Low doses of dopamine agonists stimulate eating and high doses inhibit it[35]. Administration of glucose eliminates activation of the dopaminergic neurons of the «substantia nigra», and there is evidence of an increase in dopaminergic hypothalamic turnover during feeding[36]. Central dopaminergic mechanisms modulate the food reward effects and influence the effects of self-stimulation or self-administration of psychoactive drugs. Some authors[37] associate obesity to decrease of D_2 receptors in the striate nucleus; this decrease was reversely proportional to BMI. Decrease of dopamine in obese subjects could perpetuate pathological intake as a means of compensating hypostimulation of these circuits. The same authors conclude that strategies oriented towards improving dopaminergic function could be beneficial in the treatment of obese patients. Considering the above, it could be postulated that the anorexia nervosa picture may be partially mediated by an increase of extracellular dopamine and this effect could be blocked by dopaminergic receptor antagonists. Dopaminergic blockers, such as pimozide, may decrease self-stimulation or feeding[38]. Self-stimulation behavior is stimulated both by opioid and non-opioid peptides (neurotensin), which activate dopaminergic neurons in the ventral tegmental area (VTA), and these cells project pathways to mesocortical and limbic areas including the nucleus accumbens[39]. The abnormal hedonic response present in both anorexia nervosa and bulimia could be related with dopaminergic function. Halmi et al.[40] demonstrated that patients with anorexia nervosa presented decrease to the growth hormone response with L-dopa stimulation both during emaciation and recovery phases. They also demonstrated that patients with anorexia have a decrease in response to prolactin, also in the emaciation and recovery periods. This suggests that anorexic patients have a deterioration in the post-synaptic dopaminergic receptors. Patients with bulimia without a history of anorexia nervosa seem to have lower levels of homovanilmandilic acid in cerebrospinal fluid and a lower response to clonidine than in normal controls[41,42]. These findings may suggest that the alterations in the dopaminergic pathways may lead to a decrease in satisfaction after intake and, in the long term, may facilitate binging-vomiting behavior. Classical anorexigens such as amphetamines, diethylpropion, phentermine and others act by releasing Dopamine and indirectly stimulating the D_2 receptors[43,44].

Antipsychotics in the treatment of body image alterations

Body image alteration is a fundamental symptom of eating behavior disorders. It not only refers to a perceptive disorder but also to an «overevaluation of the body measurements and the importance of the physical aspect». Psychodelic drugs such as lysergic acid diethylamide (LSD) are structurally similar to 5-HT and act through serotonin receptors to produce profound alterations in one's own and body perception, including changes in body size. It is interesting to mention that these perceptive disorders are not neutral but rather are associated to an emotional component[45,46]. This neurotransmission model can be compared to a certain degree to the sensitive-perceptive and «emotional» disorder of these patients with eating behavior disorder. Dysfunctions in the 5-HT receptor could be related with the self-perception of the body image in both patients with anorexia and bulimia. Ciproheptadine (5-HT antagonist) is mentioned as an agent capable of decreasing «fear of becoming fat» in patients with Anorexia nervosa when compared with placebo[47]. Subsequently, improvement has also been observed regarding body dissatisfaction and perfectionism of bulimic patients treated with fluoxetine in a double blind trial[48].

From the psychopathological point of view, it may also be interesting to consider dysmorphophobia and somatic delusional disorder. Pimozide has shown some efficacy in regards to increasing delusional intensity, but this drug, that blocks the D_2 receptor, also has been partially effective in those in who have no delusional symptoms. Finally, the selective serotonin reuptake inhibitors have shown greater efficacy than antipsychotics in treating these pictures, even when delusional proportions are reached, however in refractory cases, the association of SSRI with atypical antipsychotics would be indicated[49]. The above could partially justify the association of these drugs in the treatment of the body image disorder in ED patients.

What profile can the new antipsychotic contribute?

The new atypical antipsychotics, on the contrary to conventional neuroleptics, simultaneously antagonize D_2 dopaminergic receptors, and in an especially potent way, 5-HT_2 serotonin receptors[50]. There are cases in the literature of treatments with the new antipsychotics of patients with an ED, most of which refer to olanzapine. However, the mentioned improvement could be due to the effect on weight gain this drug has more than a specific effect *per se*. The effects of olanzapine on weight and appetite could be related with blockage of 5-HT_2 receptors. Treatments that increase intrasynaptic serotonin or activate 5HT receptors tend to

reduce food consumption[51]. Furthermore, interventions that decrease 5-HT neurotransmission increase food consumption and favor weight gain[52]. Theoretically, eating restriction could be related with increase of 5-HT activity, as would be the case of an increase of 5-HT_2 receptors. Alterations of 5HT activity have also been involved in other symptoms that are frequent in anorexia nervosa as obsessive-ness, anxiety and depression[53]. In other studies, the increase of plasma leptin levels has been indicated as action mechanism of some atypical antipsychotics, such as olanzapine and clozapine. This increase was independent of the diet modification and did not occur in patients in patients treated with haloperidol. These drugs may reduce feedback sensitivity of leptin on the SNC, leading to a chain reaction of appetite increase, leptin secretion and weight gain[54].

Objective

The present preliminary study aims to determine the effectiveness of an atypical antipsychotic, risperidone, in a patient sample with ED who have not responded to other drug therapy approaches.

MATERIAL AND METHODS

The initial sample was made up of 27 patients diagnosed of ED, according to DSM-IV criteria[55], who had already undergone treatment in the eating behavior disorder unit of Ciudad Real. Those patients in whom risperidone was associated were included, basically taking into account that they were patients who had had poor evolution with other drug regimes and the seriousness of the clinical picture. None of them had received treatment with any other antipsychotic prior to their enrolment in the study. Seven patients of this initial group (3 because they did not tolerate the prescribed treatment, 3 others who did not continue the follow-up and one who did not comply with the drug regime), were excluded.

Instruments and procedure

This is a prospective observational study. The initial clinical assessment and that after three months were performed by an experienced psychiatrist. The DSM-IV criteria were followed for the diagnosis of ED and comorbidity with other psychiatric disorders. All the patients enrolled in the study were interviewed according to the Structured Clinical Interview for DSM-IV (SCID-I)[56]. To evaluate personality, the Spanish version of the International Personality Disorder Examination (IPDE) was used[57]. Previous treatments, drug regime and treatment duration were recorded both at the onset and in the follow-up. As clinical assessment parameter, the Clinical Global Impression scale (CGI scale) was used[58]. This is a descriptive heteroapplied scale that provides qualitative information on the seriousness of the clinical picture (DS) and on the assessment of the change in the disease seriousness in relationship to previous evaluations (CSA). The examiner performed an assessment of disease seriousness (DS) after an interview with the patient, considering her condition during the last 24 hours, it being possible to extend this up to the previous 72 hours. The instrument consisted of a single item that assesses seriousness using a Likert scale with the following values: 0 (not evaluated), 1 (normal, no disorder), 2 (borderline of the disease), 3 (mildly ill), 4 (moderately ill), 5 (noticeably ill), 6 (seriously ill), 7 (extremely ill). The evaluation of the disease seriousness change (CSA) was performed with the change subscale that goes from: 0 (not evaluated), 1 (much better) to 7 (much worse). Since the patients were already receiving treatment previously and an enrolment criterion in the study was poor course or lack of response to previous drug treatments, this latter subscale was applied at the onset of the study with reference to the condition presented by the patients in regards to three months before. It was also applied three months after the baseline evaluation, taking the onset of treatment with risperidone as reference point.

For the data analysis, the descriptive and non-parametric statistics was used with the SPSS program for Windows V.10[59].

RESULTS

All the patients were women, with a mean age of 20.6 years (SD 5.225). Mean Body Mass Index (BMI) at onset was 20.71, SD 5.07. Thirteen were single (65%), 4 had a partner (20%) and 3 were married (15%). Most, 11 patients (55%), had completed or were studying secondary school; 4 (20%) had primary studies and 5 (25%) junior college or university degree.

In regards to the diagnostic subtypes, 3 patients fulfilled restrictive anorexia criteria (15%), 3 purgative anorexia (15%), 7 purgative bulimia (35%), 1 non-purgative bulimia (5%) and 6 non-specified eating behavior disorder (30%). The patients had the following associated comorbidity in axis 1: 5 patients were diagnosed of non-specified depressive disorder, (25%), one of dysthymia (5%) and 2 OCD (10%). Twelve patients (60%) did not receive another axis I diagnosis. The personality diagnoses in the sample were made after interviews with the IPDE and were the following: personality borderline disorder, 9 patients (45%), obsessive personality disorder, 2 patients (10%), avoidant personality disorder, 1 patient (45%), non-specified personality disorder, 4 patients (20%). Four patients (20%) did not present an associated personality disorder.

Mean evolution time of the disorder was 5.85 years (SD 5.01). Most of the patients, 11 (55%), were under treatment with SSRI, 5 (25%) with venlafaxin and 4 (20%) with benzodiazepines. The mean dose of risperidone was 1.57 mg (SD: 1.13). Table 1 shows data regarding changes experienced

in regards to Disease Seriousness (DS). Of the six patients who were initially «extremely ill», 33.3% continued to be so three months later, however 33.3% became «noticeably ill», 16.6% «moderately ill» and 16.7% «mildly ill». Of the 8 patients who initially were assessed as «seriously ill», 62.5% became only «moderately ill» after three months of treatment with risperidone and of the 6 patients who were «noticeably ill», 50% became «moderately ill». On the other hand, no patient worsened clinically. The changes were statistically significant (Wilcoxon Test for related samples: GE: z = -3.559; p = 0.000).

Table 1 also shows the changes observed in the disease seriousness (DS) in regards to three months prior to the study onset. As has been explained, the patients included in the study had had an unfavorable course, in spite of previous therapeutic approaches. It can be stated that of the 15 patients whose conditions had been assessed as «much worse» three months prior to initiating the antipsychotic treatment, only 20% were still «much worse» three months later and 26.7% had improved. The change was statistically significant (CSA: z = -3.581; p = 0.000) (table 1).

Table 2 shows the evaluation of the patients at three months of treatment with risperidone, comparing it with the previous condition in regards to physical state, eating behavior, family and social relationships, work capacity and other interests. A statistically significant improvement was obtained in all of them (physical condition: z = -3.559; p = 0.003; eating behavior: z = 3.219; p = 0.001; family relationships: z = -2.979; p = 0.003; social relationships: z = –3.228; p = 0.001; work capacity: z = -3.223; p = 0.001; other interests: z = -3.110; p = 0. 009) (table 2).

DISCUSSION

The approach of the present study is based on the idea that the pharmacological approaches could have a greater role in the future of diseases such as ED. The biological mechanisms that participate in eating behavior, hunger and satiety also have an influence on mood, activity level, and cognitive states, which are also altered in anorexia and bulimia nervosa[60]. Thus, it seems reasonable to assume that going deeper into the biological bases of eating behavior

Table 1 Evolution in the Clinical Global Impression (CGI) scale of the disorder

	Initial DS			Total
	Noticeably ill FR (% of the initial DS)	Seriously ill FR (% of the initial DS)	Extremely ill FR (% of the initial DS)	
Final DS				
Very mildly ill	1 (16.7%)	2 (25%)	0 (0%)	3 (15%)
Mildly ill	0 (0%)	0 (0%)	1 (16.7%)	1 (5%)
Moderately ill	3 (50%)	5 (62.5%)	1 (16.7%)	9 (45%)
Noticeably ill	2 (33.3%)	0 (0%)	2 (33.3%)	4 (20%)
Seriously ill	0 (0%)	1 (12.5%)	0 (0%)	1 (5%)
Extremely ill	0 (0%)	0 (0%)	2 (33.3%)	2 (10%)
Total	6 (100%)	8 (100%)	6 (100%)	20 (100%)
	Initial CSA			**Total**
	Much worse Fr (% of the initial CSA)		**Worse Fr (% of the initial CSA)**	
Final				
Much worse	3 (20%)		0 (0%)	3 (15%)
Worse	5 (33.3%)		2 (40%)	7 (35%)
The same	3 (20%)		2 (40%)	5 (25%)
Better	4 (26.7%)		0 (0%)	4 (20%)
Much better	0 (0%)		1 (20%)	1 (5%)
Total	15 (100%)		5 (100%)	20 (100%)

Initial DS: disorder seriousness at onset of treatment; final DS: seriousness of disorder at 3 months of treatment; initial CSA: change subscale assessed at three months prior to onset of treatment with risperidone; final CSA: change subscale assessed at three months of treatment with risperidone.

Table 2 **Assessment of present condition, comparing it with the condition prior to treatment**

	Much worse	Worse	The same	Better	Much better
Eating behavior					
Before treatment	12 (60%)	8 (40%)	0	0	0
At 3 months	2 (10%)	6 (30%)	4 (20%)	**7 (35%)**	1 (5%)
Physical condition					
Before treatment	8 (40%)	11 (55%)	1 (5%)	0	0
At 3 months	2 (10%)	8 (40%)	3 (15%)	**6 (30%)**	1 (5%)
Family relationships					
Before treatment	8 (40%)	12 (60%)	0	0	0
At 3 months	2 (10%)	9 (45%)	4 (20%)	**4 (20%)**	1 (5%)
Social relationships					
Before treatment	8 (40%)	12 (60%)	0	0	0
At 3 months	3 (15%)	6 (30%)	1 (5%)	**9 (45%)**	1 (5%)
Work capacity					
Before treatment	9 (45%)	10 (50%)	1	0	0
At 3 months	3 (15%)	6 (30%)	2 (10%)	**9 (45%)**	0
Other interests					
Before treatment	8 (40%)	12 (60%)	0	0	0
At 3 months	3 (15%)	6 (30%)	2 (10%)	**9 (45%)**	0

would provide certain knowledge on the aberrant eating patterns that appear in anorexia or in bulimia nervosa and analyzing the response to drug treatments established would supply useful information to that knowledge. In our study, the antipsychotic treatment achieved a decrease of global severity of the disorder and an improvement in the general condition at 3 months of having established it in a significant percentage of patients resistant to other treatments. This improvement was observed both in eating behavior and physical condition as well as in the area of social-family relationships and work capacity.

Several limitations make it necessary to consider our results with caution and to not generalize them: the sample size is small and the heterogeneous sample in regards to diagnostic subtypes and comorbidity with other psychiatric and personality disorders. Thus, the differences according to diagnoses or the changes recorded in the clinical variables, such as BMI, number of bingings or vomitings, could not be considered in the analysis. The strict inclusion criteria, serious patients in whom other treatments have failed, are the main cause of why the participant number was reduced. On the other hand, the evaluating psychiatrist was not blind to the treatments and did not use standardized instruments to evaluate the results. This study is one of the few studies published on the subject and those which we know also use small sample sizes. In spite of the disadvantages mentioned, the interest is found in the fact that the empiric observations that the antipsychotics may play a certain role in severe ED has been somewhat systematized. Future multicenter studies would make it possible to include a larger number of participants. In this way, it would be possible to analyze the patient subgroup with ED and the symptom and behavior profile subsidiary of benefiting with such treatments with standardized instruments. A longer term longitudinal follow-up is also necessary.

The treatment of the eating behavior disorders does not run out when taken from a single perspective, and any therapeutic approach should consider the participation of biological, family, cultural, psychological or biographic factors. Both anorexia nervosa as well as bulimia or the unspecified eating behavior disorders are syndromic pictures in which different etiological factors or etiopathogenic mechanisms will converge for each patient. In a certain way, this can justify the different effectiveness of the pharmacological treatments, not only among the patients with the same clinical picture but also in the same patients in different times of their clinical course. Desiring to establish effective pharmacological regimes for all the patients with anorexia or bulimia would not be an objective appropriate to the phenomenon complexity. In our opinion, we understand that it would be necessary to define the disorders present in an evolutive moment of the patient and administer the drug treatment that would show some efficacy in its remission. Finding response markers for different active principles is seen as a field for near future development. The objective, therefore, would not be treating all the patients having anorexia nervosa or bulimia with a certain drug regime, but rather previously defining the symptoms that may be sensitive to a drug to administer it correctly and comparatively.

We could conclude that the use of atypical antipsychotics in patients with serious ED, with associated comorbidity and in whom other drug treatments have not been effective, could be a useful option associated to previous therapeutic regimes, although new studies would be necessary to confirm the effectiveness of associating antipsychotic drugs in the treatment of these patients.

REFERENCES

1. Trastornos del comportamiento alimentario. Criterios de ordenación de recursos y actividades. Madrid: Publicaciones del Insalud, 2000; p. 1.
2. Kaye WH, Strober M. Serotonin: implications for the etiology & treatment of eating disorders. Eat Dis Rev 1999;10 (3):1-3.
3. Barry VC, Klawans HL. On the role of dopamine in the pathophysiology of anorexia nervosa. J Neural Transm 1976;38:107-22.
4. Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. Acta Psychiatr Scand 1999;100:3-16.
5. Towell A, Muscat R, Willner P. Behavioural microanalysis of the role of dopamine in amphetamine anorexia. Pharmacol Biochem Behav 1988;30:641-8.
6. Crisp JH. A treatment regime for anorexia nervosa. Br J Psychiatry 1996;112:505-12.

7. Dally P, Sargant W. Treatment and outcome of anorexia nervosa. Br Med J 1966;2:793-5.
8. Walsh T, Devlin M. The phamacologic treatment of eating disorders. Psychiatric Clin North Am 1992;15:1.
9. Vandereycken W, Pierloot R. Pimozide combined with behavior therapy in the short-term treatment of anorexia nervosa. Acta Psychiatr Scand 1982;66:445-50.
10. Vandereycken W. Neuroleptics in the short-term treatment of anorexia nervosa: a double-blind placebo-controlled study with sulpiride. Br J Psychiatry 1984;144:288-92.
11. Hoffman L, Halmi D. Psychopharmacology in the treatment of anorexia nervosa and bulimia nervosa. Psychiatr Clin North Am 1993;16(4):767-78.
12. Trastornos del Comportamiento Alimentario. Criterios de ordenación de recursos y actividades. Madrid: Publicaciones del Insalud, 2000; p. 44.
13. Antipsychotic drugs. En: Manual of clinical psychopharmacology, 3.ª ed., 1999.
14. Montgomery SA, Montgomery D. Pharmacological prevention of suicidal behavior. J Affective Dis 1982;28:325-38.
15. Blum K, Cull JG, Braverman ER. Reward deficiency syndrome. American Scientist 1996;84:132-45.
16. Jimerson D, Lesem M, Kaye W, Brewerton T. Low serotonin and dopamine metabolite concentrations in cerebrospinal fluid from bulimic patients with frequent binge episodes. Arch Gen Psychiatry 1992;49:132-8.
17. Condon JT. Long-term neuroleptic therapy in chronic anorexia nervosa complicated by tardive dyskinesia. A case report. Acta Psychiatr Scand 1986;73(2):203-6.
18. Rohrbaugh RM, Siegal AP. Reversible anorexia and rapid weight loss associated with neuroleptic administration in Alzheimer's disease. J Geriatr Psychiatry Neurol 1989;2(1):45-7.
19. Rubio Larrosa V, Pérez Urdániz A, Granada López JM. Risperidona y trastorno límite de personalidad. Póster presentado en el I Congreso Nacional de Trastornos de Personalidad. Zaragoza, 1998.
20. McDougle CJ, Epperson CN, Pelton GH. A Double-blind, placebo-controlled study of risperidone addition in serotnin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 2000;57:794-801.
21. McDougle CJ, Goodman WK, Price LH. Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder. Am J Psychiatry 1990;147:652-4.
22. McDougle CJ, Goodman WK, Leckman JF. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry 1994;51:302-8.
23. Ravizza L, Barzega G, Bellin S. Therapeutic effect and safety of adjunctive risperidone in refractory obsessive-compulsive disorder (OCD). Psychopharmacol Bull 1996;32:677-82.
24. Stein DJ, Bouwer MB, Hawkridge S. Risperidone augmentation of serotonin reuptake inhibitors in obsessive-compulsive and related disorders. J Clin Psychiatry 1997;58:119-22.
25. Crisp AH. The possible significance of some behavioral correlates of weight and carbohydrate intake. J Psychosom Res 1967;11:117.
26. Rastan Nm, Gillberg C. Anorexia nervosa 6 years after onset: II. Comorbid psychiatric problems. Compr Psychiatry 1995;36:70.
27. Halmi KA, Eckert E, Marchi P. Comorbidity of psychiatric diagnoses in anorexia nervosa. Arch Gen Psychiatry 1991;48:712.
28. Mitchell JE, Specker SM. Comorbidity and medical complications of bulimia nervosa. J Clin Psychiatry 1991;52:13.
29. Braun DL, Sunday SR, Halmi KA. Psychiatric comorbidity with eating disorders. Psychol Med 1994;24:859.
30. Balcioglu A, Wurtman RJ. Effects of phentermine on striatal dopamine and serotonin release in conscious rats: in vivo microdialysis study. Int J Obes Relat Metab Disor 1998;22:325-8.
31. Martel P, Fantino M. Mesolimbic dopaminergic system getivity as a function for food reward: a microdialysis study. Pharmacol Biochem Behav 1996;53:221-6.
32. Hoebel BG. Brain neurotransmitters in food and drug award. Am J Clin Nutr 1985;42(Suppl. 5):S1133-50.
33. Bassareo V, Di Chiara G. Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. Neuroscience 1999;89:637-41.
34. Pontieri FE, Tanda G, Orzi G, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 1996;382:255-77.
35. Leibowitz SF. Opioids and food selection. En: Morgan PG, Panksepp PP, editores. Handbook of the Hypothalamus. New York: Marcel Dekker, 1982;3:299-437.
36. Heffner TG, Hartman JA, Seiden LS. Dopamine turnover in feeding. Science 1986;208:1168-70.
37. Wang GJ, Volkow N, Logan J, Pappas NR. Brain dopamine and obesity. Lancet 2001;357:354-7.
38. Wise RA, Spindler J, DWit H, Gerber GJ. Sub-stimulation behaviors. Science 1978;201:262-4.
39. Glimcher P, Margolin D. Dopamine pathways. Brain Res 1986; 266:348-52.
40. Halmi KA, Owen WP, Lasley E, Stokes P. Dopaminergic regulation in anorexia nervosa. Int J Eating Disord 1983;21:192-233.
41. Jimerson DC, Lessem Md, Kaye WH. Low serotonin and dopamine metabolite concentrations in cerebral spinal fluid from bulimic patients with frequent binge episodes. Arch Gen Psychiatry 1992; 49:132-8.
42. Kaplan AS, Garfinkel PE, Walsh FC. Clonidine challenge test in bulimia nervosa. Int J Eating Disord 1989;8:425-35.
43. Stahl SM. Neuropharmacology of obesity: my receptors made me do it. J Clin Psychiatry 1998;59:447-8.
44. Curzon G, Gibson EL. Appetite suppression by commonly used drugs depends on 5-HT receptors but not on 5-HT availability. Trends Pharmacol Sci 1998;18:21-5.
45. Grof S. Critical variables in LSD therapy. En: LSD Psychotherapy. Pomona: Hunter House, 1980; p. 47.
46. Masters REL, Houston J. Experiencing the body and body image. En: Masters REL, Houston J, editores. The Varieties of Psychedelic Experience. New York: Dell Publishing, 1966; p. 67.
47. Goldberg SC, Eckert ED, Halmi DA, Casper RC. Effects of cyproheptadine on symptoms and attitudes in anorexia nervosa. Arch Gen Psychiatry 1980;37:1083.
48. Goldbloom DS, Olmsted MP. Pharmacotherapy of bulimia nervosa with fluoxetine: assessment of clinically significant attitudinal change. Am J Psychiatry 1993;50:770-4.
49. Allen A, Hollander E. Body dysmorphic disorder. Psychiatr Clin North Am 2000;23(3):617-28.
50. Schotte A, Janssen PMF, Megens AAHP, Leysen JE. Occupancy of Central neurotransmitter receptors by risperidone, clozapine

and haloperidol measured *ex vivo* by quantitative autoradiography. Brain Res 1993;631:191-202.
51. Blundell JE, Hill AJ. Dexfenfluramine and appetite in humans. Int J Obesity 1992;16:S51-9.
52. Liebowitz SF. The role of serotonin in eating disorders. Drugs 1990; 39:895-903.
53. La Via M, Gray N, Kaye W. Case reports of olanzapine treatment of anorexia nervosa. Int J Eat Disord 2000;27:363-6.
54. Kraus T, Haack M, Schuld A. Body weight and leptin plasma levels during treatment with antipsychotic drugs. Am J Psychiatry 1999; 156:312-4.
55. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington: American Psychiatric Association, 1994.
56. First M, Spitzer R, Gibbon M, Williams JB. Structured clinical interview for DSM-IV (SCID-I). American Psychiatric Press, Inc. Versión española publicada por Editorial Masson, 1999.
57. Loranger A, Sartorius N, Andreoli A, Berger P, et al. The International Personality Disorder Examination. The World Health Organization/Alcohol, Drug Abuse and Mental Health Administration International pilot study of personality disorders. Arch Gen Psychiatry 1994;51(3):215-24.
58. Guy W. Early Clinical Drug Evaluation (ECDEU) assessment manual. Rockville: National Institute Mental Health, 1976.
59. Norusis M.J. SPSS for windows: release 10.0. Chicago: SPSS Inc, 1999.
60. Grossman SP. Eating behavior, the biology of motivation. Ann Rev Psychol 1979;30:209-42.