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Pharmacotherapy in Anorexia Nervosa: An Overview.

Walter Milano, Michele De Rosa, Luca Milano, Alessandra Riccio, Anna Capasso*

Center Department for the Study, Diagnosis and Treatment of Eating Disorders Centre ASL Napoli 1 and *Department of Pharmacy, University of Salerno, Italy

Abstract

Anorexia Nervosa (AN) is a serious, debilitating and potentially lethal disease because of the marked dysfunctions it evokes. Therapy for AN is essentially multidisciplinary, with nutritional, medical and psychotherapeutic interventions. Many drugs, particularly psychoactive agents, have been tested during the past decades, trying to improve the clinical and psychopathological conditions on the basis of AN symptomatology. All psychotic drugs, from antidepressants to mood-stabilizers, from antipsychotics to benzodiazepines, have been tried, but results have not been very encouraging. One of the main limitations in the evaluation of pharmacologic therapy is that anorexic patients often refuse drugs, as they consider it invasive for their personality. For this reason, in the literature, there are few controlled and randomized studies over long periods and on wide casuistics of patients. The aim of this review is to evaluate data on drug usage in AN treatment, compared with the more recent evidences on the role of biological factors implicated in AN aetiopathogenesis.

Keywords: Anorexia nervosa, Eating disorder, Pharmacotherapy

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Introduction

Anorexia nervosa (AN) is a serious and potentially lethal disease. The actual psychiatric nosography suggests, that the dramatic loss in weight is due to drastic reduction in food intake, an intense fear of gaining weight or storing fat, despite being underweight, together with or without associated factors such as self-induced vomiting, use of laxatives/ diuretics and so on. The presence of binges, their frequency or their absence, and the presence of amenorrhea in post-menarche women are also considered [1].

The term AN, however, does not necessarily mean that there is any loss of appetite. In fact, although patients refuse food, they actually have appetite and often think too much about food. AN mainly affects young women, with a female-to-male ratio of 10:1. The most sensitive age for this disease is between 15 to19 years [2].

Recent age- and sex-adjusted incidence rates are 4.7 – 8.3 per 100,000 people, while the lifetime prevalence is currently estimate at 0,6 % among women and 0,3 among men. [3].

Amongst all psychiatric diseases, AN has the highest mortality rate, which is between 7 to 18 % [4].

Psychiatric comorbidity is very frequent in AN. The prevalence of depression is very high, with indices between 50 to 60 % of patients [20,5]. Very common are other psychopathological attributes such as, anxiety, observed in more than 60% of patients, obsessive-compulsive symptoms, in about 40% of patients and dyscontrol, in about 10-20% of patients [6-8].

Other systems in the body can also be seriously affected in AN patients e.g., alteration of cardiac rhythm, osteoporosis, acute pancreatitis, pronounced anemia, neutropenia with lymphocytosis, oedema, low renal filtration capacity and nephropathy, hypovolaemia, electrolyte alterations characterized by hypokalemia, hypocalcaemia, hypochlorinemia, hypomagnesemia and metabolic alkalosis. The reproductive system is affected as evident by the presence of amenorrhea and infertility. That the endocrine functions may also be impaired in AN patients are evident by

the presence of hypogonadism characterized by hypoestrogenemia, alterations in LH/FSH ratio, thyroid impairment and high serum cortisol levels [9].

AN course is variable; it can be characterized by a more or less complete remission after a single episode, particularly in young female patients and with a better preexisting social or adaptation capability, while in 50% of cases residual symptoms or psychopathological sequels, such as the presence of depressive symptoms, panic attacks (PAs) or obsessive-compulsive disorders (OCD) have been observed [4].

Despite weight normalization, anomalies in dietary patterns remain and the relationship with food can be altered for long periods, with caloric restrictions and constant anxiety for weight and body.

Although AN was first described in the 19th century, the actual pharmacotherapy for AN remains slightly incisive, both on the psychopathological aspect as well as on the capacity to reduce symptoms and the possible weight recovery.

Pharmacotherapy for Anorexia Nervosa

The necessity for a suitable pharmacotherapy comes from the evidence that pure nutritional therapy and different psychotherapies over long periods induced a substantial recovery only in a small percentage of cases, which is unacceptable for such serious and potentially lethal diseases (10). Besides, pharmacotherapy is becoming more and more popular, after the assessment of biochemical alterations typical of AN.

During the last years several studies about the utilization of different psychiatric drugs were reported, many of which were included in psychiatric practice since the ‘60s. However, the various pharmacological trials on AN did not show any distinctive results when compared to the placebo trials, in improving the symptoms.

The ideal pharmacologic treatment should be effective in inducing weight recovery, in reducing alterations about bodily aspects, obsessive ideas, anxiety and depression-related symptoms and in preventing relapses. Besides, it should have a good tolerance profile, and few interactions with other drugs [10,11]. Unfortunately no drug having all these properties exists at this moment.

Treatment with antidepressant

The rationale for treatment AN with antidepressant (AD) is the hypothetical dysfunction in the serotoninergic and noradrenergic system in the pathophysiology of AN and the frequent psychopathological comorbidity [21].

As patients suffering from AN often have a comorbidity-with obsessive-compulsive symptoms, anxiety and depression, several antidepressant drugs were administred, particularly SSRIs (sertraline, citalopram, fluoxetine, escitalopram and paroxetine), both in acute phases and in relapse prevention [10].

Results were quite disappointing, also considering that they were used for short periods, in heterogeneous groups of patients, searching for a recovery of their lost weight. A reasonable effect was found in terms of improvement of depression symptoms and anxiety, alleviating by and large the severity of the disease [12-15].

Some clinical studies suggest that SSRIs are ineffective, both in depression symptoms and in anxiety and obsessiveness, in patients in acute phase, with a very low body weight. This is because their malnutrition provokes a hyposerotoninergic state secondary to a poor tryptophan intake due to dietary restrictions. A pronounced serotonine reduction seems to prevent SSRIs action [16].

One study conducted with a high dosage of Fluoxetine (60 mg/day) showed a reduction of relapses, better long-term weight maintenance and fewer depression symptoms. This study, however, was conducted in the patients after the acute phase was over and there was an improvement in the BMI [17].

Tricyclic antidepressant drugs (TCAs), mainly desipramine, clomipramine, nortriptyline and amitriptyline, studied in the past in AN treatment, should not be administered in this kind of disease, because of their established poor efficacy and possible side effects. TCA can often induce relevant side effects, such as hypotension and arrhythmia, particularly QT interval prolongation, to which AN patients are already exposed. [18,19]. At this moment, there are no data supporting the SSRIs and SNRIs administration in AN therapy [21].

As far as other antidepressants are concerned, bupropion is contraindicated because it inhibits appetite and reduces food intake. Although mirtazapine can increase appetite, it is not recommended in AN, as it can induce neutropenia and increase the risks of haematic disorders, which is very frequent in AN patients [18].

The danger of side effects of drugs is a relevant aspect to consider in AN psychotherapeutic treatment.

Underweight and undernourished patients are more sensitive to side effects. So it is important to begin with very low doses, in order to minimize any probable adverse events and to strictly observe their appearance, at the same time not jeopardising the pharmacological compliance in patients who are so reluctant to a therapy often considered invasive and against their will (18). Besides,

especially for SSRIs, it is opportune to start therapy with the lowest dosage, as these drugs can provoke nausea, or diarrhoea, worsening an already precarious electrolyte balance, through stimulation of serotonin 3 receptors in the hypothalamus or brainsterm [22].

Treatment with antipsychotic.
Antipsychotic drugs are used in AN treatment too, as they can induce an increase in appetite and body weight in patients with major psychiatric disorders as Schizophrenia or bipolar disorder [23,41].

Typical antipsychotics have a predominant antagonistic activity at dopamine receptors, especially at D2 receptors. They even affect acetylcholine, histamine and alpha-adrenergic receptors. Atypical antipsychotics exert blocking effects on dopaminergic, histaminergic, alpha-adrenergic receptors and serotonergic receptors, especially 5HT2a receptors [22].

Until some years ago, the first generation antipsychotics (typical antipsychotics), particularly chlorpromazine, sulpiride and pimozide were used, with encouraging short-term results on weight recovery, but very insignificant effect on the psychopathologic status of anorexia [24]. They are no longer used in AN because of various side effects like extrapyramidal symptoms, tardive dyskinesia, alterations in myocardial activity and hyperprolactinemia.

The second-generation antipsychotic (atypical antipsychotic) have proved more useful in the treatment of AN, in particular olanzapina, an antagonist D2/5HT2 [25]. Mondraty [26], in a small sample of patients with AN, compared the olanzapina (10 mg/die) with chlorpromazine (50mg/die) showing a net effectiveness of olanzapina in reducing the “anorexic ruminations”.

Olanzapine was proved to be useful during the acute phase of the disease to reduce the other associated symptoms of AN such as, serious obsession and compulsion states, low insight of disease, delirium about body image, hostility and loss in reality perception. Several studies were reported in the literature, most of them case-reports, which were non-controlled studies or done on a low number of patients, with olanzapine dosages between 5 -10 mg/day, that highlighted a slight improvement of weight, a reduction of fear of getting fat, of anxiety and opposition to the treatment [27-30].

A recent study [31] compared a group of anorexic women treated with olanzapine combined with a cycle of cognitive behavioral therapy (CBT) with a second group having CBT and placebo. The combination of therapies induced an increase in BMI only in anorexic women of the compensatory behavior subgroup and an improvement of anxiety, depression, hostility, obsessivity and compulsivity in all of the subgroups.

Till now, there are no studies using other second-generation antipsychotics, such as quietapine, aripiprazole risperidone and ziprasidone, as extensively as those done using olanzapina [18].

At moment the main international guidelines fit the use of SGA among the secondary possibility [21,32,33].

Treatment with other medications
Other drugs, such as those acting on gastric motility (cisapride and metoclopradine) were used in AN treatment, but controlled studies did not show any weight recovery [34,35]. Even ciproheptadine was used but with modest and uncontrolled results [36].

Based on the observation that some mood-stabilizing agents, particularly lithium, could induce appetite in bipolar patients, several researches were conducted on anorexic patients, but they did not show any efficacy compared to controls [18].

In anorexic patients with extensive amenorrhea, osteopenia and osteoporosis are very common. This is probably related to hypoestrogenism and hypercortisolism due to undernourishment. Estroprogestinic substitutive therapy is commonly used in patients showing a bone density reduction. Different controlled studies on anorexic women, using such therapy did not show any advantage on bone mineralization, compared to controls [37,38]. Besides, estrogens could induce in growing young girls, an early welding of bone epiphyses [39]. At present, the only recommendation in young anorexic women, to prevent bone demineralization, is to gain weight with the help of vitamin D supplementation [39].

Conclusion

According to data available in the literature, pharmacological treatments can be useful in some aspects, but not for all of the AN symptoms. Actually, considering the few documented data on biochemical implications and the symptomatologic complexity of anorexia, it is quite difficult to identify a single drug, which is able to modulate the actions of specific neurotransmitters, and neuropeptides, that could improve all of the disease-related symptoms.

At present, a combination of nutritional therapy, pharmacologic therapy with the best efficacy profile along with the appropriate psychotherapeutic treatment, while adjusting from time to time the intervention strategy suitable for the individual patient (clinical indicators) [40], remains the only advisable solution.

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Correspondence to:

W. Milano
Center Department for the Study
Diagnosis and Treatment of Eating Disorders Centre ASL
Napoli 1, Italy