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Psychotropic Drugs in Anorexia Nervosa: Waiting for Clear Evidence from Randomized Controlled Trials

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Anorexia Nervosa (AN) is a potentially severe Eating Disorder (ED) characterized by modifications of eating behavior leading to an abnormally low body weight, an intense fear of gaining it, and body image distortion [1].

AN has the highest mortality rate among all psychiatric illnesses, with a standardized mortality ratio of 5.86 [2]; one in five deaths in AN patients is by suicide [2]. In fact, regarding psychiatric comorbidity, AN patients often present mood disorders, anxiety disorders and obsessive-compulsive symptoms [3]. Furthermore, obsessive thoughts regarding body shape and weight can become delusional and AN patients can be completely unaware of the altered way they perceive their own body [1]. Some authors demonstrated higher rates of psychiatric comorbidity and self-injurious or suicidal behavior in the binge-purging subtype, when compared with the restrictive subtype [4].

Furthermore, medical complications caused by prolonged starvation and malnutrition are very common in AN [5], and cardiovascular complications have been considered the main cause of the poor prognosis of this disorder [6]. Patients with AN have shown to have higher prevalence of sinus bradycardia, hypotension and longer corrected QT intervals [6]. These medical comorbidities have represented the main limitation in the pharmacological treatment of AN, as several psychotropic drugs such as antidepressants and antipsychotics display common side effects that can worsen these medical conditions [7-9]. This not withstanding, psychotropic drugs have been widely used in AN with two different aims: to treat the above-mentioned psychiatric comorbidities and to treat the core eating psychopathological features of the disorder.

The aim of the present paper is to narratively review the current literature in order to summarize evidence coming from published randomized-controlled trials (RCT) investigating the potential efficacy of psychotropic drugs on anorectic patients.

Antidepressants

The rationale of prescribing antidepressants in AN may be explained by their effects on the serotonergic neuronal system, which has shown to be altered in these patients [10]. Among the tricyclic antidepressants, amitriptyline is the most studied in AN. The few available clinical trials agree that there is no difference between this drug and placebo in treating depressive and specific ED symptomatology [11,12]. On the other hand, data on weight recovery are conflicting, as Biederman et al. [11] report no difference in weight recovery, whereas Halmi et al. [13] observed a more rapid weight gain when compared with placebo.

Fluoxetine has been compared with placebo for the treatment of AN in a randomized double-blind clinical trial, where patients received treatment or placebo alongside supportive and cognitive-behavioral therapy (CBT) for 7 weeks [14]: this study failed to demonstrate additional benefits of fluoxetine, since both groups showed similar improvements in specific and general psychopathology. Ruggiero et al. compared fluoxetine to clomipramine and amisulpride in AN patients treated with a nutritional and psychoeducational program, and while there was an increased body weight after the 3-months studied period in all groups, no significant differences were observed among them; no improvement was found in weight phobia or body image disturbance [15]. Fassino et al. compared the use of Citalopram with placebo in AN and found no differences in weight gain or specific ED symptomatology, while there was a greater effect on depression, obsessive-compulsive symptoms, impulsiveness and trait-anger [16].

Antipsychotics

Given their known effect on weight gain [17,18], first- and second-generation antipsychotics (FGA and SGA respectively) have drawn much attention of the scientific community for treating AN patients. Additionally the anti-dopaminergic effect of antipsychotic drugs may be helpful in reducing, body image distortion, obsessions, irrationals and delusional beliefs related to weight and body shape [19].

Mixed results were observed for olanzapine, as some randomized controlled trials (RCT) reported a greater weight gain [20,21] and an improvement in general psychopathology when compared with placebo [21,22], while others observed no differences neither in weight [22-24] nor in psychopathology [20,24]. Additionally, olanzapine showed similar effects on weight gain and a better improvement of cognitive rumination when compared to chlorpromazine [25].

Similar RCTs failed to demonstrate a significant superiority of quetiapine and risperidone compared to placebo for weight gain, general and ED specific psychopathology [26-28], while a significant effect was found for amisulpride on weight gain when compared to fluoxetine and clomipramine [15].

The only two available RCTs studying FGAs (pimozide, sulpiride) versus placebo in AN found no significant effect on weight gain or psychopathology [29,30].

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Mood Stabilizers

A single study by Gross et al. investigated the effect of lithium on AN in a placebo-controlled, randomized trial [31]. Lithium seemed to be effective on weight gain, but no significant differences have been found regarding psychopathological variables.

Conclusions

No specific pharmacological treatment has emerged as a completely valid tool in AN. Some psychotropic drugs have shown to be effective in treating psychiatric comorbidities, especially antidepressants [32,3], but all RCTs that investigated the efficacy on the core psychopathological features of AN lead to negative results [11,14,15,16,22,26-28,].

As an overall, the most convincing results were obtained when considering weight gain. In fact, some studies showed positive results for second generation antipsychotics and amitriptyline [13,15,20,21]. The observation that these drugs did not display any effect on specific ED psychopathology could suggest that weight gain could be solely mediated by the known side effects regarding appetite and metabolism, rather than a reduction in body image disturbance, drive for thinness or fear of gaining weight [17,18,33].

There are several possible explanations for the lack of efficacy of psychotropic drugs in AN. It has been postulated that malnourishment could lead to an impaired serotonin function [34]. A reduction of the concentrations of 5-hydroxyindoleacetic acid, a known metabolite of serotonin, in cerebrospinal fluid of AN patients has been observed [35], and weight loss is linked to an impaired pharmacokinetics [36]. These data suggest that drugs' efficacy, especially that of SSRIs, could be substantially impaired in anorectic patients [14,37]. Available data on AN patients after weight restoration showed an efficacy of fluoxetine even on specific ED psychopathology [38], suggesting the role of underweight status as a moderator of AN pharmacological treatment efficacy.

Since the paucity of available evidence does not support the use of pharmacological treatment for AN except for psychiatric comorbidities [39], tolerability and side effects of psychotropic drugs should be careful taken into consideration before administering a pharmacological treatment. Well-tolerated drugs, with a low profile in terms of side effects, should be privileged (e.g. vortioxetine among antidepressants). Drugs with antiobsessive and antidepressant properties could play a therapeutic role, especially if associated to aside effect profile of weight gain (e.g. olanzapine among antipsychotics). Further RCTs are needed in this field, investigating efficacy and tolerability of molecules that have shown promising results in previous RCTs performed in this field of research.

Competing Interests

The authors declare that they have no competing interests.

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