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EATING DISORDERS AND PSYCHOFARMACHOLOGY: RETHINK THE TREATMENT OF EATING DISORDERS

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SUMMARY

The pharmacological approach to eating disorders (ED) is effective in a few conditions, and to date, no treatment has shown certain efficacy in treating patients with this disorder. Furthermore, attempts to regulate hunger and satiety through modulation pharmacological effects of neurotransmitters and neuropeptides have shown only short-term benefit. However, in light of the serious impact of DCA on patients and the scarcity of non-pharmacological therapeutic approaches, research in this area should not be abandoned, also because new generation "molecules" become increasingly available.

Many studies looked at efficacy of antipsychotics, Tryciclics, SSRI, mood stabilizers in the treatment of ED. Gabaergic circuit, the opioid one are extremely involved in the neurohormonal mechanisms of regulation of dietary behaviors and that molecules that influence these circuits could be used in the pharmacological treatment of ED as already happens in the case of Naltrexone, gabapentine or gabaergic drugs.

Key words: *anorexia nervosa - bulimia nervosa - eating disorders - opioid system - gabaergic system*

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INTRODUCTION

The pharmacological approach to ED is effective in a few conditions, and to date, no treatment has shown certain efficacy in treating patients with this disorder (Kaye 1999). Furthermore, attempts to regulate hunger and satiety through modulation pharmacological effects of neurotransmitters and neuropeptides have shown only short-term benefit. However, in light of the serious impact of ED on patients and the scarcity of non-pharmacological therapeutic approaches, research in this area should not be abandoned, also because new generation "molecules" become increasingly available.

In contrast to the rather limited efficacy of pharmacotherapy for anorexia nervosa, there have been more fruitful studies on the usefulness of drugs in the management of bulimia nervosa (Mitchell 1993, Freeman 1998).

Despite this, an optimal pharmacotherapeutic treatment strategy for bulimia nervosa has yet to be defined because most patients do not achieve complete remission (Kaye 1999). Furthermore, questions regarding the duration of treatment, continuation and maintenance of pharmacotherapy and the role of drugs when combined with non-drug modalities remain unanswered. Binge eating disorder is a syndrome that has only received attention in the last decade. Due to some phenomenological overlaps between bulimia nervosa and binge-eating disorder, it is not surprising that treatment attempts have derived from those that have been successful for bulimia nervosa. Evidence suggests that drug therapies that have been shown to be effective in treating bulimia nervosa are also useful in treating patients with binge eating disorder (Smith 1998). Furthermore, binge eating disorder is often comorbid with depressive disorders (DeZwaan 1994).

PSYCHOPHARMACOTHERAPY: THE STATE OF THE ART

Antipsychotics

Patients with anorexia nervosa were once treated with first generation antipsychotics because their preoccupation with shape and weight was claimed to resemble a delusion (Vandereycken 1987).

The benefits of chlorpromazine, used to treat patients with anorexia nervosa for 30 years after its introduction into psychopharmacology, (25 mg to 100 mg one hour before meals, and often with insulin) were related to its anxiolytic and sedative effects. However, the initial enthusiasm was short lived due to the notable side effects (Goldbloom 1993).

Furthermore, if weight gain was not accompanied by a change in attitude and an improvement in eating behavior, it was usually not permanent. Thus, the idea of treating anorexia nervosa with chlorpromazine was dropped. A different fate has befallen the second generation antipsychotics which in clinical practice show a great use.

Olanzapine was the most commonly studied psychotropic drug for adolescents with anorexia nervosa (AN). At present, only 1 double-blind placebo-controlled study has been published in this population (Kafantaris 2011) and colleagues 8 examined olanzapine in 20 underweight adolescents treated in inpatient (n 59), day (n 56) and outpatient (n 55) treatment (age range 12.3-21, 8 years). In a 10-week pilot study, they found no difference in the beneficial effect between the olanzapine and placebo groups in the 15 subjects who completed the study; however, the treated group showed a tendency for fasting glucose and insulin levels to rise.

The mean dose of olanzapine was 8.5 mg per day. Note that only 21% of eligible patients were recruited into the study, and there was a high dropout rate. Additionally, patients were enrolled in each of the inpatient, day hospital, and outpatient treatment settings as part of the study design. Although other research groups have also attempted randomized controlled trials using olanzapine in this population, the studies have been hampered by a myriad of confounding and recruiting issues (Norris 2011).

The other antipsychotic widely used in clinical practice is aripiprazole. Some authors (Frank 2017) have completed a case series and a retrospective review of medical records on the use of aripiprazole in adolescents with AN. The case series reported 4 adolescents who benefited in terms of weight and improved ED cognitions. Review of the medical record described 22 adolescents with AN taking aripiprazole at a mean dose of 3.59 mg per day compared to an untreated comparison group of 84 adolescents with AN. These researchers found a greater increase in BMI in the treated group.

Tricyclics

In the 1970s, several researchers focused on the presence of depressive symptoms in patients with anorexia nervosa; for several years there was a debate on the hypothesis of anorexia as a "variant of affective disorder" (Hatsukami 1984). I The use of tricyclic antidepressants seemed appropriate for patients with anorexia nervosa because, in depressed patients, tricyclics not only relieved mood symptoms but also led to considerable weight gain and increased appetite. However, most studies have reported only minimal significant evidence of the efficacy of tricyclic antidepressants in promoting weight gain, improving attitudes towards nutrition, and ultimately treating anorexia nervosa (Lacey 1980).

In light of the overlap in symptoms between anorexia nervosa and depression and the higher prevalence of mood disorders in relatives of those suffering from anorexia nervosa, it is surprising that tricyclic antidepressants do not appear to be of much benefit. It appears that depression is a secondary feature to core anorexic symptoms and that improvement in depression does not positively affect eating behavior and behavior. Weight gain in patients with anorexia nervosa treated with tricyclic antidepressants is more of a side effect of the drug and may not be permanent.

Regarding BN, there are two studies on the use of imipramine, which show a slight benefit on binge eating within 6 weeks and an improvement in the "anti-bulimic" effect after 16 weeks of treatment. No association was found between the severity of depressive symptoms and imipramine response. However, in 2 other studies (Mitchell & Pyle 1990) imipramine was not well tolerated and was associated with a high relapse rate. In summary, although some tricyclic antidepressants may be of some benefit in the treatment of bulimia nervosa, their use cannot be recommended due to the side effect profile and lack of long-term efficacy.

SSRI

There is considerable evidence that when they are underweight, patients with anorexia nervosa have significantly lower baseline concentrations of serotonin (5-HT) and of the 5-hydroxyindolacetic metabolite (5-HIAA) in cerebrospinal fluid (CSF) than in healthy controls. These results suggest reduced serotonergic activity which could be a state-related phenomenon because low-calorie diets are known to reduce the availability of tryptophan, the precursor of serotonin.

Despite biological evidence of serotonin dysfunction in the etiology of anorexia nervosa, the therapeutic use of SSRIs remains controversial. There have been open studies on fluoxetine published (Kaye 1991, Gwirtsman 1990). In one, 29 of 31 patients with anorexia nervosa had gained weight with fluoxetine therapy maintained their weight at 85% or more of mean body weight. Fluoxetine also reduced depression, obsessive-compulsive symptoms, and anxiety. In the other study, 4 all 6 patients with chronic refractory anorexia treated with fluoxetine gained weight. There is also a case report supporting these findings. Conversely, however, Ferguson and underweight patients.

It has been argued that SSRI treatment should be started after nutritional improvement for 2 reasons. Tryptophan depletion caused by food restriction may inhibit the therapeutic effects of fluoxetine because tryptophan depletion limits serotonin production. Furthermore, food restriction is also known to reduce 5-HT synthesis and down-regulate the density of 5-HT receptors in the brain (Haleem 1996, Huether 1997).

In light of the many unresolved issues surrounding the use of SSRIs to treat patients with anorexia nervosa and diet-related factors that may impair SSRI function, more thorough studies are needed to investigate the efficacy of fluoxetine and other SSRIs. (for example, fluvoxamine, sertraline, paroxetine, citalopram) in the treatment of anorexia nervosa. Such studies should also focus on subgroups of patients with anorexia nervosa, including those of the "binge-eating / purging" subtype, those with prominent depressive symptoms, obsessive thoughts or severe ritual behaviors around food, and those for whom psychotherapy is not of any particular benefit.

In BN Among the SSRIs, fluoxetine has been shown to interrupt the bingeing / vomiting cycle, and is the most rigorously studied for the treatment of bulimia nervosa.

Goldbloom and Olmsted reported that short-term fluoxetine treatment has been associated with attitudinal and behavioral changes in patients with bulimia nervosa, which were independent of depressive symptoms. Fluoxetine was shown to be superior to placebo and tolerated with minimal side effects in a large placebo-controlled study involving 387 patients at 60 mg/day (Goldbloom 1993).

As with tricyclic antidepressants, fluoxetine was effective in reducing binge eating and compensatory behaviors, even in the absence of depressive symptoms. Some authors (Fichter 1996) conducted a double-blind, placebo-controlled study to evaluate the role of fluvoxamine in preventing relapse in 72 patients with bulimia nervosa and found that, despite a high dropout rate, fluvoxamine was effective. in reducing the relapse of binges and compensatory behaviors.

Another 8-week open-label study of fluvoxamine (50-150 mg/day) in 20 patients with bulimia nervosa 90 suggested that the drug was a safe and effective treatment for bulimia nervosa and that it not only reduced binges and purges, but attitude towards patients also improved.

Antiepileptics and Lithium

In all the studies conducted in patients with AN treated with lithium, it led to weight gain in all patients; however, this is not surprising, because weight gain is one of the most common side effects of lithium (Gross 1981, Baptista 1995).

There is very little evidence for valproate and carbamazepine. Lamotrigine in the last decade is frequently used in the case of AN but even in this case there is no evidence.

However, as there is not enough evidence demonstrating the benefits of mood stabilizing drugs for patients with anorexia nervosa, their use in the treatment of anorexia nervosa is not recommended. The use of anticonvulsants dates back to observations of EEG abnormalities in patients with bulimia nervosa and subsequent treatment with phenytoin.

Frequent mood swings and impulse dysregulation in patients with bulimia nervosa have led to trials with the mood stabilizer lithium and the anticonvulsant carbamazepine. Lithium showed no "anti-bulimic" efficacy when administered to 91 patients with bulimia a study. A double-blind, placebo-controlled study of carbamazepine was conducted in 16 patients with bulimia nervosa with no significant benefit for the majority of patients (Hsu 1991, Kaplan 1983). There are no controlled studies of other mood stabilizing agents (e.g., valproate, lamotrigine, gabapentin), but judging by the results of the lithium and carbamazepine studies, their use should be limited.

NEUROBIOLOGY OF ED

Food is a salient or "natural reward" stimulus, and the neuronal reward circuits they are activated when we crave food, approach or eat food (Kelley 2002).

Important regions in this circuit include the ventral striatum (receives dopaminergic input from the motivational and reward-approaching midbrain), orbitofrontal cortex (reward evaluation), and anterior cingulate (error monitoring, reward expectation) . Several, but not all, studies in the past in adolescents or young adults have found an altered response of the reward system in AN to visual stimuli related to food or the body (Fladung 2010, Cowdrey 2011, Schultz 2002).

One paradigm that has been closely associated with the brain's dopamine response is the prediction error model, a learning paradigm in which individuals learn to associate unconditional taste with conditioned visual stimuli (O'Doherty 2003).

These studies have suggested a heightened dopamine-related brain response that does not normalize easily with weight regain (Frank 2017). In summary, altered reward circuits in AN may be associated with impaired learning and dopamine function in the brain (Frank 2018).

In BN, negative affect correlated positively with striatal and pale brain response when receiving a shake (Bohon 2012). A low mood can, therefore, increase the reward value of food cues in BN and trigger the binge. Others showed less frontal cortical, ventral striatal and hippocampal activation in BN which correlated with binge frequency (Cyr 2016, Frank 2013).

Compared to the mechanisms involved in body perception, on the other hand, the self-perception of being fat while underweight could be due to an abnormal central enteroceptive neurocircuit mainly driven by cognitive-emotional processes. Some studies in AN implicated parietal and occipital cortices in the visualization of self or others (Phillipou 2015, Fonville 2014).

Neuropsychological studies have implicated an alteration of non-visual perception, such as tactile perception, proprioception (sense of one's position in space) or enteroception (sense of internal organs) in the AN, showing an altered insula response in the AN (Kerr 2016).

This suggested that the insula may have an essential function at the intersection of enteroception and cognitive-emotional processing in the AN. Some studies have implicated taste perception in AN.

NEW FRONTIERS

Innovative techniques such as optogenic neuronal stimulation have been particularly effective in identifying neural circuits that are sufficient to drive or inhibit feeding (Gropp et al. 2005). For example, the

optogenetic activation of fibers in the lateral hypothalamus (LH) by GABAergic neurons in the base nucleus of the terminal stria (BNST) is sufficient to stimulate nutrition in the presence of calorically palatable food (Jennings et al. 2013). The authors suggested a specificity of the GABA-BNST -> LH circuit in the diet. However, GABA-BNST neurons constitute a very heterogeneous population and are known to project to additional sites such as periaqueductal gray (PAG), parabrachial nucleus (PBN) and Central Amygdala (CeA). Furthermore, the precise population of neurons in the LH receiving GABA-BNST input is still unclear.

Conversely, there are now more circuits that are sufficient to drive anorexic responses after activation. Carter and colleagues identified a population of PBN neurons linked to the calcitonin gene that activate under conditions that normally suppress appetite, inhibit feeding when activated, are able to drive hunger after chronic activation, and orchestrate anorexic behavior through glutamatergic axon terminals projecting to CeA (Carter et al. 2013). Complicating matters are a number of modulators such as melanocortins and their precursors which are known to decrease food intake through various mechanisms. Beta-endorphin, one of the precursors, influences mood and food intake; alpha-MSH also reduces food intake. Both substances are encoded by Pro-opiomelanocortin (POMC). Interestingly, k-opiodid receptors are expressed in postsynaptic POMC neurons. The activation of GABA neurons presynaptically inhibits POMC neurons through these receptors. These pre- and post-synaptic effects of opioids, both synthetic and endogenous agonists synthesized and secreted by POMC neurons, exemplify this important interaction between the two systems.

Treatment with naloxone helps reduce the stimulation of food intake, which is usually enhanced by agouti-related peptide (AgRP), an endogenous melanocortin receptor antagonist. Melanocortin receptor agonists have been observed to have an inhibitory action on the orexigenic action of the MOR ligand, providing further evidence of this interaction. Selective mu receptor antagonists also blunt the orexigenic action of melanocortin receptor antagonists (MC3R / MC4R) (Hruby 2011). It is important to note that most individuals suffering from anorexia nervosa (AN) and bulimia nervosa expose antibodies against the melanocortin peptide alpha-MSH, which is responsible for the decrease in food intake and is affected by pre and post action. -synaptic of endogenous opioids (Fetissov 2005). In line with this, data obtained from experimental models support the hypothesis that opioids are involved in the processes of learned and associative appetite that influence food selection and acceptance (Cottone 2008).

It is evident that the gabaergic circuit, the opioid one are extremely involved in the neurohormonal mechanisms of regulation of dietary behaviors and that molecules that influence these circuits could be used in the pharmacological treatment of ED as already happens in the case of Naltrexone, gabapentine or gabaergic drugs.

Naltrexone associated or not with buproprion is used in the case of obesity and BED and there have been several trials where it was administered for BN (Marrazzi 1995). Its receptor antagonism on the opioid system could modulate the melanocortin circuit and the reward system. Drugs such as gabapentine could act on the hypothalamic and striatal system by modulating food-related emotional responses. Among the interesting drugs of the gabergic system, Tiagabine should not be forgotten, which acts very well on resistant anxiety and bipolar disorders without having a metabolic impact (Ansara 2020). These molecules associated with dopaminergic modulators that can regulate the cortico-limbic networks represent an alternative to classical pharmacological treatments that have shown little efficacy and poor tolerability.

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Contribution of individual authors:

Leonardo Mendolicchio : conceptualization, contributed to literature search, writing - original draft preparation, writing - review and editing.

Emanuela Apicella: conceptualization, writing - review and editing.

Enrica Ventura: review and editing.

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