

Review Article

# Psychopharmacology as a Tool for Understanding the Pathophysiology of Anorexia Nervosa

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## Abstract

Anorexia nervosa (AN) is a body image disorder that manifests itself in the feeling that one is obese, even though the objective reality shows otherwise. People with AN resort to preventive behavior (restriction of food intake) or processes that encourage weight loss (use of medications such as diuretics and laxatives or obsessive engagement in vigorous physical activity). Among the mental disorders, AN is characterized by a high percentage of suicidal rate. Drug treatment began with the antihistamine drug Cyproheptadine. As expected, it increased the appetite of AN patients. However, it did not treat the body dysmorphic disorder accompanied by a concomitant depressive disorder and irrational thinking. After that, the treatment was changed to Tri-Cyclic Antidepressants (TCAs). The TCAs exposed the patients to cardiac arrhythmias (due to electrolyte imbalance). Serotonin reuptake inhibitors (SSRIs) slightly improved mood, while Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) increased metabolic rate (which is not desirable). The drug Bupropion, as a representative of Dopamine and Noradrenaline Reuptake Inhibitors (DNRI), pointed to the imbalance in Dopamine levels in different brain regions as one of the main contributors to the pathophysiology of AN disease. This discovery led to the use of the second-generation antipsychotic drugs as very beneficial strategy.

## Keywords

Anorexia Nervosa (AN), Dysmorphic Disorder, Antidepressant, Antipsychotic Drugs, Dopamine Imbalance

## 1. Background

Anorexia Nervosa (AN) is an eating disorder characterized by the Diagnostic and Statistical Manual for Mental Disorders [1] as: "a restriction of energy intake (hypophagia) relative to requirements leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health; an intense fear of gaining weight or becoming fat, even though underweight; a disturbance in the way in which one's body weight or shape is experienced and undue influence of body weight or shape on self-evaluation; or denial of the seriousness of the current low body weight". Previous editions

of the *DSM* [1] indicated the requirement for body weight to be below 85% of what is expected, accompanied by extreme hyperactivity behavior [2, 3]. The term 'Anorexia' in modern Latin means 'without appetite', and the term 'Nervosa' means mental disturbance, 'nervousness' [4]. Historically, this term is derived from ancient Greek mythology: holy anorexic female saints starved and abused their bodies as a symbol of their devotion to the gods. The English physician Richard Morton first defined AN as a clinical term in 1689 [5].

According to the American National Association of Ano-

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rexia [6], 0.9% of American women suffer from AN in their lifetime (lifetime prevalence), affecting all races and ethnic groups. AN usually begins during adolescence and most commonly occurs in females (more than 90% of all cases). It is the third most common chronic illness among adolescent females, with a mortality rate 12 times higher than the expected death rate for 15-to-24-year olds [2]. Twenty percent of all deaths among AN patients are the result of suicide, the highest mortality rate among psychiatric illness patients. About one-third to 50% of all patients have a comorbid mood disorder such as depression or psychosis, many of whom suffer from anxiety disorder, obsessive-compulsive disorder, and social phobia [7].

## 2. Drug Treatment for AN-Historical Aspect

Treatment by pharmaceutical intervention started long before the exact psychobiological pathology was understood. The pharmacological approach to treating AN includes the use of the following medications: antihistamines (Cyproheptadine), Tricyclic Antidepressants (Amitriptyline, Clomipramine), Serotonin Selective Reuptake Inhibitors (Fluoxetine, Paroxetine, Citalopram), Selective Serotonin Noradrenaline Reuptake Inhibitors (Venlafaxine), and antipsychotics: typical (Haloperidol) and atypical (Quetiapine) [2].

Pharmacotherapy began long before the biological etiology of AN was clear. However, as each drug group's pharmacological mechanism of action was discovered, this insight aided in unveiling the pathophysiological processes underlying AN. During the 1970s, it was well known that the first generation of antihistamines (and anti-serotonergic) stimulated appetite, resulting in weight gain [2]. Cyproheptadine, a representative of this family, was found to have a minor positive effect on the mental health of AN patients, reducing the number of days necessary to achieve normal weight [7-9]. This medication is still used nowadays as an appetite stimulant for cancer and HIV patients with a well-known documented side effect: sedation. The next group to be tested were the tricyclic antidepressants (TCA's), developed in the late 1950s and used for anxiety, obsessive-compulsive disorder, and depression. The rationale for the use of this pharmacological family was based upon the hypothesis that AN is a form of depression associated with dysphoric mood and anxiety. This family was first introduced into clinical use during the early 1980s. The mechanism of action of TCA's is inhibition of serotonin and noradrenaline reuptake, thus increasing their synaptic concentration [9, 10]. These medications had a variety of antihistaminic and anticholinergic adverse effects, such as sedation, cardiac arrhythmia, hunger, and weight gain (especially Amitriptyline). Such side effects make this family less safe, especially for AN patients predisposed to electrolyte imbalance [2, 11], due to a malnutrition-induced lack of electrolyte intake, specifically sodium,

potassium, and calcium. Furthermore, studies using TCA's among AN patients showed lower weight gain compared to the placebo group [12], or no change at all [13]. However, as in other cases, the negative result drove researchers to use different, more selective drug families. Members of the selective serotonin reuptake inhibitor (SSRI) family are known to increase serotonin concentration at the synaptic cleft, improving mood, and most of them are associated with weight gain [2]. The SSRI family was first introduced into clinical use in the treatment of AN during the early 1990s. Among the SSRIs (Fluoxetine, Paroxetine, Citalopram), Fluoxetine was found to be the most beneficial medication to induce weight gain [2, 14, 15], yet no dramatic effect was seen on body weight nor on improving dysphoric mood among AN patient [2, 16]. It was speculated that poor nutritional intake leading to a lack of dietary tryptophan intake, the precursor for Serotonin, underlies the failed improvement in the clinical condition of AN patients [2]. However, a double-masked, controlled study using Fluoxetine with Tryptophan supplementation versus placebo showed no benefit for tryptophan enrichment, suggesting a different underlying mechanism [17].

Furthermore, when compared with Serotonin Noradrenaline Reuptake Inhibitors (SNRIs), no significant difference between groups was found in the clinical effect on AN patient in the improvement of either mood disturbance or body weight [18]. The surprising failure of treating AN with SNRIs was explained by the central role of the elevated synaptic noradrenaline concentration, associated with satiety and the 'drive' of AN patients to engage in physical activity [14]. Representing another antidepressant family prototype, the dopamine noradrenaline reuptake inhibitor (DNRI), Bupropion, played a significant role in understanding the complexity of the biological pathophysiology of AN: Bupropion was found to decrease food consumption among rats in a dose-dependent manner; an effect which was blocked only by using a direct dopamine antagonist or false precursor of this neurotransmitter, leading to the production of ineffective dopamine [19]. For this reason, Bupropion (as a DNRI representative) is contraindicated in AN patient [2].

## 3. New Insight into AN Pathophysiology

Uncontrolled elevation of central Dopamine levels is involved in the pathophysiology of AN, potentially worsening the state of patients. Dopamine imbalance leading to elevated levels in the limbic system is linked with "positive symptoms" (delusions, hallucinations) in other psychoses, including Schizophrenia. In contrast, lower levels of Dopamine in the frontal lobes (mesocortical system) lead to the "negative symptoms" of Schizophrenia (social closure, inability to maintain a schedule, and inappropriate emotional reactions). Not surprisingly, similar to Schizophrenia, though at lower intensities, AN is characterized by the 'positive symptoms' such as delusions and hallucinations about body weight and shape, and the 'negative symptoms,' related to social isolation,

obsessive-compulsive behavior, and depression [20-23]. The benefits of using antipsychotics are not surprising due to the similarities between Schizophrenia and AN: psychotic attacks, impairments in reality judgment, and social closure [23].

These observations have directly contributed to the understanding that Dopamine imbalance (not at the expected level as required) in different brain regions is a significant player in AN pathophysiology, and the psychotic nature of the disease reinforces this perception, emphasizing the importance of proper Dopamine control in AN. The next logical step involved using antipsychotic medications that attenuate dopamine activity in different brain regions [2, 24, 25].

Among typical antipsychotic medications, the older, first-generation drugs (Chlorpromazine, Haloperidol) treat only the "positive symptoms" (delusions, hallucinations) without influencing "negative" self-perception. Those belonging to the newer generation, called atypical (such as Olanzapine, Quetiapine, and Risedronate), are known to cause less of the extrapyramidal adverse effect associated with the first-generation medications (a disorder characterized by increased involuntary movement) and are more beneficial in weight gain in comparison with the older typical antipsychotics [2, 19, 20]. The most helpful medication in this family was Olanzapine (a partial Dopamine agonist that acts as a Dopamine antagonist in the Limbic system and as a Serotonin antagonist in the pre-frontal cortex). Those medications improve the symptoms and outcomes of schizophrenia and AN [20, 21, 25].

## 4. Conclusion

In this article, I have tried to explain how the use of drugs preceded the understanding of the nature of AN. Understanding the mechanisms of action of the various drugs used in AN treatment revealed the pathophysiological aspects of the AN disorder in a stepwise elimination process. The most straightforward pharmacological approach started in the 1970s, using antihistamines (due to their appetite-stimulating effect), and shifted during the 80s towards dealing with the depressive and obsessive-compulsive component of AN by using TCA. However, due to the dangerous adverse effects and relatively low efficacy profile of TCAs, newer antidepressants (SSRIs, SNRIs, and DNRI) were examined in the late 80s and 90s for the treatment of AN. Among them, especially DNRI, had turned the spotlight precisely on the crucial role of Dopamine in AN manifestation, emphasizing the psychotic nature of the disease.

The course of discovery of the nature of the disease, as described in this article, in which empirical intervention precedes understanding of the underlying pathophysiology, is expected for numerous health disorders, particularly in the mental health field, where evidence arises from behavioral response to treatment. Nonetheless, unlike other mental disorders, the evolution of AN understanding and treatment optimization occurred at a more rapid pace, owing to knowledge stemming from the treatment of

similar psychotic states.

## Abbreviations

AN	Anorexia Nervosa
SSRIs	Selective Serotonin Reuptake Inhibitors
SNRIs	Serotonin Noradrenaline Reuptake Inhibitors
DNRI	Dopamine Noradrenaline Reuptake Inhibitors
TCA	Tricyclic Anti-depressant

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In loving memory of Rona, who succumbed to this terrible disease after a long, hard battle despite being a talented caregiver herself.

## Author Contributions

Uri Eliyahu is the sole author. The author read and approved the final manuscript.

## Conflicts of Interest

The author declares no conflicts of interest.

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