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Revealing Anorexia Nervosa Pathophysiology *via* Pharmaco-Elimination Steps

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Abstract

The pathophysiology of Anorexia Nervosa (AN) was revealed using pharmacological stepwise elimination, with each discovery of a new drug class mechanism of action, in the treatment of AN and other mental health states. Both positive and negative elements of the underlying disease required addressing as patient response and drug efficacy were considered. In this perspective, a brief summary of this process is discussed, connecting current knowledge of AN biological etiology with treatment outcomes using the various drug classes, and eventually leading to a more precise, less adverse course of treatment.

Keywords: Anorexia nervosa; Statistical manual; Anxiety disorder

Introduction

Anorexia Nervosa (AN) is an eating disorder characterized by the diagnostic and statistical manual for mental disorders (DSM, 5th edition) 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 indicated the requirement for body weight to be below 85% of that expected accompanied by extreme hyperactivity. The term 'Anorexia' in modern Latin means 'without appetite' and the term 'nervosa', means mental disturbance, 'nervousness'. 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. AN as a clinical term was first defined by the English physician Richard Morton in 1689 [1].

Literature Review

According to the American national association of Anorexia, 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 15-24 year olds. 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 [2].

Treatment by pharmaceutical intervention started long before the exact psychobiological pathology was understood. The pharmacological approach of treating AN includes the use of the following medications antihistamines (cyproheptadine), tri cyclic antidepressants (amitriptyline, clomipramine), serotonin selective reuptake inhibitors (fluoxetine, paroxetine and citalopram) and selective serotonin noradrenaline reuptake inhibitors (venlafaxine), anti-psychotics typical (haloperidol) and atypical (quetiapine, risperidone, aripiprazole, olanzapine). In addition, benzodiazepines (alprazolam) and α_2 agonists (clonidine) had also been used [3-10].

Pharmacotherapy began long before the biological etiology of AN was clear. However, as the pharmacological mechanism of action of each drug group was discovered, this insight aided in unveiling the pathophysiological processes underlying AN. During the 1970's, it was well known that the first generation of antihistamines (and anti-serotonergics) stimulates appetite, resulting in weight gain. Cyproheptadine, a representative of this family, was found to have a minor positive effect on mental health of AN patients, reducing the number of days necessary to achieve normal weight. This medication is still used nowadays as an appetite stimulant for cancer and HIV patients with well-known documented side effect sedation. The next groups to be tested were the Tricyclic Antidepressants (TCA's), developed in the late 1950's, used for anxiety, obsessive-compulsive disorder, and depression. The rationale for 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 1980's. The mechanism of action of TCA's is inhibition of serotonin and noradrenaline reuptake, thus increasing their synaptic concentration. 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, due to a malnutrition induced lack of electrolyte intake, specifically sodium, potassium, and calcium. Furthermore, studies using TCA's among AN patient's showed lower weight gain compared to the placebo group or no change at all. However, as in other cases, the negative result drove

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researchers to use other, 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. The SSRI family was first introduced into clinical use in the treatment of AN during the early 1990's. Among the SSRI's, (fluoxetine, paroxetine, sertraline and citalopram) fluoxetine was found to be the most beneficial medication to induce weight gain, yet no dramatic effect was found on body weight, nor on improving dysphoric mood among AN patient. 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. However, a double-blind, controlled study using fluoxetine with tryptophan supplementation versus placebo did not show any benefit for tryptophan enrichment, suggesting a different underlying mechanism. Furthermore, when compared with Serotonin Noradrenaline Reuptake Inhibitors (SNRI's), no significant difference between groups was found in the clinical effect on AN patient in the improvement of either the mood disturbance or body weight. The surprising failure of treating AN with SNRI's was explained by the central role of the elevated synaptic noradrenaline concentration, associated with satiety and the 'drive' of AN patient to engage in physical activity. Representing another antidepressant family prototype, the Dopamine Noradrenaline Reuptake Inhibitor (DNRI), Bupropion, played a major 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. For this reason, Bupropion is contraindicated in AN patient [11-15].

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, whereas 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 similarly 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. 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 [16].

Discussion

These observations have directly contributed to the understanding that dopamine imbalance (not in the expected level as required) in different brain regions is a major 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 [17].

Among typical antipsychotic medications, the older, first-generation drugs, (chlorpromazine, haloperidol) treat only the "positive symptoms" without influencing negative self-perception. Those belonging to the newer generation called atypical (such as olanzapine, quetiapine, 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 anti psychotics. The most beneficial medication among this family was found to be olanzapine (A dopamine and serotonin antagonist). The new generations of atypical antipsychotic drugs, which act as antagonists in dopamine and serotonin receptors, improve the symptoms and outcome of schizophrenia and AN [18-20].

Conclusion

In this article we 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 simplest pharmacological approach started in the 1960's, using antihistamines (due to their appetite-stimulating effect), and shifted during the 80's towards dealing with the depressive and obsessive-compulsive component of AN by using TCA's. However, due to the dangerous adverse effects and relatively low efficacy profile of TCA's, newer antidepressants (SSRI's, SNRI's and DNRI's) were examined in the late 80's and 90's for the treatment of AN. Among them especially DNRI's, had turned the spotlight precisely on the key 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 common to numerous health disorders, particularly in the field of mental health, 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.

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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.

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