

Neurochemistry and Pharmacological Treatments: Where is the Field of Anorexia Nervosa Heading?

Nicole C. Barbarich-Marsteller*

Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY, USA; Department of Neuroscience, New York State Psychiatric Institute, New York, NY, USA; Eating Disorders Research Unit, New York State Psychiatric Institute, New York, NY, USA

Abstract: Anorexia nervosa is a debilitating psychiatric disorder characterized by severe dietary restriction and life-threatening weight loss. The onset of the disorder typically occurs during adolescence with 90-95% of all cases occurring in females. Often characterized by a chronic and relapsing course, anorexia nervosa has one of the highest mortality rates of any psychiatric disorder. Although the etiology is unknown, a complex interplay of genetic, neurobiological, and environmental variables appear to factor into the development of the disorder. Accumulating evidence supports altered serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HTT receptor binding in anorexia nervosa, with more recent studies examining dopamine D₂/D₃ receptor binding. Despite this increasing knowledge of neurotransmitter alterations, there are few effective treatment strategies, with pharmacological treatments having minimal efficacy during the acute phase of illness. Thus, the goal of this paper is to provide an overview of neurochemical alterations during the ill state and following long-term recovery. This will be followed by a review of pharmacological treatment studies of anorexia nervosa that will focus on the limited efficacy of SSRIs and more promising findings from atypical antipsychotics. Given the combination of receptors targeted by newer generation atypical antipsychotics, these drugs may provide a more efficient means for modulating the neurobiological disturbances seen in anorexia nervosa.

INTRODUCTION

Anorexia nervosa is a debilitating psychiatric disorder characterized by severe dietary restriction and weight loss [1]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, [1]), the four diagnostic criteria include: a) a refusal to maintain body weight at or above a minimally normal weight for age and height, b) an intense fear of gaining weight or becoming fat, even though underweight, c) a disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight, and d) amenorrhea. The age of onset of anorexia nervosa is typically during adolescence, with 90-95% of all cases occurring in females [1].

There are two diagnostic subtypes of anorexia nervosa. Individuals with the restricting subtype accomplish weight loss through unremitting dietary restriction. Individuals with the binge-eating/purging subtype also exhibit periods of dietary restriction but alternate with periods of binge eating followed by compensatory behaviors, such as self-induced vomiting or misuse of laxatives, diuretics, or enemas. Excessive exercise may be a prominent feature of both anorexia nervosa subtypes [2-5].

While the etiology of anorexia nervosa is unknown, a complex interplay of genetic, neurobiological, and environ-

mental factors interact in the development of the disorder. Although a discussion of nature vs. nurture issues in anorexia nervosa is beyond the scope of this paper, emerging genetic evidence from familial and twin studies suggests a strong heritability for the disorder (for review, see [6, 7]). This argument is further strengthened by the notion that although dieting behavior is extremely prevalent in the general population, the prevalence of anorexia nervosa is only 0.5%-1.0% of women [1, 8]. Thus, although environmental factors play a role, an underlying biological vulnerability may be necessary for an individual to develop anorexia nervosa.

Often characterized by a chronic and relapsing course [9, 10], anorexia nervosa has one of the highest mortality rates of psychiatric disorders [11, 12]. In a review of over 100 outcome studies, approximately 50% of individuals did well over time, 30% did reasonably well but continued to have symptoms, and 20% did poorly [13]. Substantial cross over exists between diagnostic subtypes, particularly in individuals with the restricting subtype who later develop binge eating and/or purging symptoms [14, 15]; however, there is a subgroup of patients that remain in the restricting subtype for the entire duration of illness.

From a temperament perspective, individuals with anorexia nervosa are characterized by increased harm avoidance and persistence and decreased novelty seeking [16, 17]. Individuals with anorexia nervosa are anxious, obsessive, and perfectionistic and display marked rigidity and overcontrol [18-22]. These traits appear to be present premorbidly and remain following long-term recovery from anorexia nervosa, which suggests they may be trait variables that contribute to the underlying disorder [17, 23].

*Address correspondence to this author at the Columbia University, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 98, New York, NY 10032, USA; Tel: (212) 543-5197; Fax: (212) 543-5607; E-mail: nb2299@columbia.edu

Another prominent feature of anorexia nervosa is the high rate of comorbidity with other psychiatric disorders including depression and anxiety disorders [24]. There is often an onset of childhood anxiety disorders prior to the development of anorexia nervosa, particularly with obsessive compulsive disorder (for review, see [25]). Moreover, high rates of comorbidity between anorexia nervosa and obsessive compulsive disorder and the overlap of symptomatology has led some investigators to propose a common neurobiological mechanism between the disorders [25-27]. A shared genetic vulnerability between depression, anxiety, and eating disorders has also been suggested [28], but the evidence is conflicting [29] and needs further clarification. Nonetheless, high rates of comorbidity may result in greater obstacles in developing effective pharmacological treatments.

This paper will review existing data that supports neurochemical alterations in anorexia nervosa, particularly in the serotonin (5-HT) and dopamine (DA) systems. One of the inherent difficulties that arise in conducting studies during the acute phase of illness is determining whether alterations in neurochemistry are a consequence of starvation (state-related) or are inherent features of the disorder (trait-related). Given the difficulty in premorbid identification of individuals that will develop anorexia nervosa, neurobiological studies are often conducted with individuals following long-term recovery. Although the field has not reached a consensus as to what defines "recovery", most studies utilize the criteria of a minimum of one year of a healthy weight and the absence of any eating disorder behavior (i.e., restricting food intake, binge eating, purging).

Following the discussion of neurochemical alterations, the limited number of pharmacological treatment studies that have been conducted in anorexia nervosa will be reviewed. The majority of the studies are open trials, with few double-blind, placebo-controlled trials, thus limiting the interpretation of the results. These two themes will then be integrated in a discussion of where the field of pharmacological treatments for anorexia nervosa is headed.

NEUROCHEMICAL DISTURBANCES

Serotonin (5-HT)

5-HT is a neurotransmitter involved in feeding behavior, impulsivity, depression, and anxiety. There are seven families of 5-HT receptors (5-HT₁₋₇) that are widely distributed throughout the body [30]. Despite only a small amount of 5-HT being located in the brain [31], 5-HT has a prominent role in modulating the behavioral and neurochemical activity associated with psychiatric disorders, and thus has been one of the main targets of pharmacological treatments.

The most widely studied 5-HT receptors in anorexia nervosa are the 5-HT_{1A} and 5-HT_{2A} receptors. The 5-HT_{1A} receptor is both a presynaptic and a postsynaptic receptor and has a high density in limbic areas including the hippocampus, lateral septum, cingulate cortex, entorhinal cortex, and the dorsal and median raphe nuclei [30]. The 5-HT_{2A} receptor is found in high density in cortical forebrain regions such as the neocortex, entorhinal cortex, pyriform cortex, and claustrum, and in the caudate nucleus, nucleus accumbens, olfactory tubercle, and hippocampus [30].

Disturbances in 5-HT function in anorexia nervosa have been proposed for several decades. While several early studies assessed 5-HT function in anorexia nervosa, these studies were limited by techniques that measured behavioral effects of 5-HT or 5-HT function outside of the brain. For example, levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, were significantly decreased in the cerebrospinal fluid of individuals during the acute phase of anorexia nervosa [32, 33]. These levels normalized following acute weight restoration, but were significantly increased and correlated with persistent behavioral characteristics following long-term recovery [34]. Moreover, an anxiolytic response to acute tryptophan depletion, the precursor of 5-HT, has been reported in both ill and recovered individuals with anorexia nervosa [35]. Taken together, these studies provided the initial, indirect evidence that serotonergic alterations in anorexia nervosa were present during the acute phase and remained following long-term recovery.

In more recent years, neuroimaging techniques have enabled the more accurate assessment of *in vivo* alterations in neurotransmission. For example, positron emission tomography (PET) is a technique that produces a 3-dimensional image or map of functional processes in the body. Within the brain, it enables the measurement of alterations in neuroactivity through the administration of radiotracers designed to specifically target proteins or enzymes essential to normal metabolic processes. While most of the studies discussed below utilized PET, single photon emission computed tomography (SPECT) also enables the assessment of *in vivo* alterations in neurotransmitter receptor binding. The drawback to SPECT, however, is that it utilizes radiotracers that have a longer half-life and the images are less sensitive and less detailed than in PET. Taken together, both PET and SPECT can be utilized as a mechanism for determining potential pharmacological targets of interest.

A review of PET findings in anorexia nervosa is summarized in Table 1. At the 5-HT_{1A} receptor, binding of the selective antagonist [¹¹C]WAY-100635 was significantly increased (30% to 70%) in prefrontal and lateral orbital frontal regions, mesial and lateral temporal lobes, parietal cortex, and dorsal raphe nuclei during the acute phase of anorexia nervosa compared to control women [36]. Following long-term recovery, individuals with the binge-eating/purging subtype had increased [¹¹C]WAY-100635 binding potential in cingulate, lateral and mesial temporal, lateral and medial orbital frontal, parietal and prefrontal cortical regions, and the dorsal raphe nuclei compared to control women [37]. There were no significant differences in binding potential between individuals recovered from the restricting subtype and control women [37]; however, there was a positive correlation between [¹¹C]WAY-100635 postsynaptic receptor binding in the mesial temporal and subgenual cingulate regions and harm avoidance in individuals recovered from the restricting subtype of anorexia nervosa.

At the 5-HT_{2A} receptor, there were no significant differences in [¹⁸F]altanserin binding potential between individuals with anorexia nervosa during the acute phase and control women [36]; however, there was a positive correlation between [¹⁸F]altanserin binding potential and harm avoidance in supragenual cingulate, frontal, and parietal regions in ano-

Table 1. Overview of PET Imaging Studies of Serotonin (5-HT) and Dopamine (DA) Alterations in Anorexia Nervosa

Study	Compound	CW	ILL AN ^a	REC AN ^a	5-HT _{1A}	5-HT _{2A}	5-HTT	D ₂ /D ₃	Differences in Binding Potential (BP)
[36]	¹¹ CWAY-100635 ¹⁸ Faltanserin	29	15 (8,7)		↑	NS			<ul style="list-style-type: none"> • AN (acute phase) > CW [AN-R=AN-BP] <ul style="list-style-type: none"> - prefrontal and lateral orbital frontal regions, mesial and lateral temporal lobes, parietal cortex, dorsal raphe nuclei • AN (acute phase) = CW [AN-R=AN-BP] • For AN individuals <ul style="list-style-type: none"> - BP positively correlated with harm avoidance in supragenual cingulate, frontal, and parietal regions
[37]	¹¹ CWAY-100635	18		25 (13,12)	↑	NS			<ul style="list-style-type: none"> • AN-BP (recovered) > CW <ul style="list-style-type: none"> - cingulate cortex, lateral and mesial temporal cortex, lateral and medial orbital frontal cortex, parietal cortex, prefrontal cortical regions, dorsal raphe nuclei • AN-R (recovered) = CW • For AN-R (recovered) individuals <ul style="list-style-type: none"> - BP positively correlated with harm avoidance in mesial temporal and subgenual cingulate regions
[38]	¹⁸ Faltanserin	16		10 (0,10)		↓			<ul style="list-style-type: none"> • AN-BP (recovered) < CW <ul style="list-style-type: none"> - left subgenual cingulate, left parietal cortex, right occipital cortex • For AN-BP (recovered) individuals <ul style="list-style-type: none"> - BP positively correlated with harm avoidance and negatively correlated with novelty seeking in cingulate and temporal regions, and negatively correlated with drive for thinness in several cortical regions
[39]	¹⁸ Faltanserin	23		16 (16,0)		↓			<ul style="list-style-type: none"> • AN-R (recovered) < CW <ul style="list-style-type: none"> - mesial temporal cortex (amygdala, hippocampus), pregenual cingulate, subgenual cingulate - SPM analysis also showed reduced BP in occipital and parietal cortex
[40]	¹¹ C-raclopride	12		10 (4 ^b ,6)				↑	<ul style="list-style-type: none"> • AN (recovered) > CW <ul style="list-style-type: none"> - antero-ventral striatum • For AN (recovered) individuals <ul style="list-style-type: none"> - BP positively correlated with harm avoidance in dorsal caudate and dorsal putamen
[41]	¹¹ C-McN5652 ¹¹ C-raclopride	10		18 (11,7)			↑		<ul style="list-style-type: none"> • AN-R (recovered) > AN-BP (recovered) <ul style="list-style-type: none"> - antero-ventral striatum, dorsal raphe nuclei • For all AN (recovered) <ul style="list-style-type: none"> - positive correlation between 5-HTT and D₂/D₃ BP in antero-ventral striatum and dorsal caudate

Abbreviations include: (CW) = control women; (ILL AN) = acute phase of anorexia nervosa; (REC AN) = recovered phase of anorexia nervosa; (AN-R) = restricting subtype of anorexia nervosa; (AN-BP) = binge eating/purging subtype of anorexia nervosa; (NS) = not significant. ^aFor number of subjects in anorexia nervosa groups, parentheses indicate (# of AN-R, # of AN-BP). ^bIncludes 1 AN-R subject with purging behavior.

rexia nervosa. Significant reductions in 5-HT_{2A} receptor binding potential have been reported in anorexia nervosa, however, using SPECT. Audenaert *et al.*, [42] reported significant reductions in 5-HT_{2A} [¹²³I]-5-I-R91150 binding potential in the left frontal cortex, left and right parietal cortex, and left and right occipital cortex in anorexia nervosa. Moreover, a significant left < right asymmetry was found in 5-HT_{2A} binding potential in the frontal cortex of individuals with anorexia nervosa [42].

Following long-term recovery, individuals recovered from the restricting subtype of anorexia nervosa had reduced [¹⁸F]altanserin binding potential in the mesial temporal cortex (hippocampus and amygdala) and cingulate cortical regions [39]. Individuals recovered from the binge-eating/purging subtype of anorexia nervosa had reduced binding potential in the left subgenual cingulate, left parietal cortex, and right occipital cortex [38]. Moreover, 5-HT_{2A} binding potential was positively related to harm avoidance and negatively related to novelty seeking in cingulate and temporal regions and negatively related to drive for thinness in several cortical regions in individuals recovered from the binge-eating/purging subtype of anorexia nervosa but not control women [38].

While few imaging studies in general have examined the 5-HT transporter (5-HTT), this is the main pharmacological target of selective serotonin reuptake inhibitors (SSRIs), and thus of interest to a number of psychiatric disorders. A recent study reported that individuals recovered from the restricting subtype of anorexia nervosa had significantly increased [¹¹C]-McN5652 binding potential at the 5-HTT in the dorsal raphe nuclei and antero-ventral striatum compared to individuals recovered from the binge-eating/purging subtype [41]. Together, the eating disorder groups showed significant positive relationships between binding at the 5-HTT and D₂/D₃ receptors in the dorsal caudate and antero-ventral striatum, a relationship that was not present in control women. Interestingly, several lines of genetic evidence have suggested that a 5-HTT gene-linked polymorphism may play a role in anorexia nervosa [43, 44], although the results are somewhat inconsistent [45, 46].

Dopamine (DA)

DA is a neurotransmitter involved in reward, motor activity, and novelty seeking [47, 48]. There are several different classes of DA receptors, with D₁ and D₂ playing a known role in food and drug intake [49, 50]. Distribution of D₁ and D₂ mRNA is predominately in the caudate putamen, nucleus accumbens, and olfactory tubercle [51], with 80% of brain dopamine located in the corpus striatum.

There are two major anatomical pathways in the DA system that are of interest to the study of anorexia nervosa. The mesolimbic DA pathway is the primary pathway responsible for reward; it originates from neurons in the ventral tegmental area (and ventral midbrain) and projects to limbic structures, such as the nucleus accumbens, as well as prefrontal cortex and cingulate cortex. In contrast, the nigrostriatal DA pathway originates from neurons in the substantia nigra pars compacta (in ventral midbrain) and projects to the caudate

and putamen (also known as neostriatum). This pathway regulates motor control and is required (along with the basal ganglia) for voluntary movement. Both pathways are of interest to developing treatments for anorexia nervosa given that substantial disturbances in reward function and hyperactivity occur in these individuals.

To date, few studies have focused on dopaminergic alterations in anorexia nervosa, although it is an area of emerging research. In an indirect assessment, Kaye *et al.*, [52] reported that individuals recovered from the restricting subtype of anorexia nervosa had decreased levels of homovanillic acid, a major metabolite of DA, in cerebrospinal fluid [52]. More recently, Bergen *et al.*, [53] reported genetic evidence that specific D₂ receptor polymorphisms may increase the vulnerability to developing anorexia nervosa.

Using PET, increased binding of the dopamine D₂/D₃ receptor antagonist [¹¹C]-raclopride has been reported in individuals recovered from anorexia nervosa compared to control women [40]. Moreover, binding potential was positively related to harm avoidance in the dorsal caudate and dorsal putamen in individuals recovered from anorexia nervosa. This finding is in contrast to imaging studies in drug abusers and obese individuals in which [¹¹C]-raclopride binding potential was significantly decreased [54-56]. Moreover, ratings of "drug-liking" in response to methylphenidate have also been negatively correlated with [¹¹C]-raclopride binding potential at the D₂/D₃ receptor in drug naïve subjects [57], suggesting that there may be an inverse relationship between D₂/D₃ receptor binding and reward.

Of particular interest for developing pharmacological targets for anorexia nervosa is the newest finding of a positive correlation between 5-HTT and D₂/D₃ activity in individuals recovered from anorexia nervosa, but not control women [41]. Although the mechanism of this effect is not understood, a better understanding of this unique relationship in anorexia nervosa may hold important insights into potential alterations in 5-HT/DA modulation.

One final point on the potential benefits of neuroimaging research is that the development of small animal imaging technologies, such as the microPET®, now enables researchers to image animal models of psychiatric disorders as a mechanism for identifying novel treatment targets. Although no animal model exactly mimics the clinical disorder, it provides a mechanism for testing hypotheses and new treatments that may not be feasible in the clinical population. Specifically, our lab has utilized microPET imaging in adolescent female, food-restricted rats to demonstrate alterations in brain metabolism measured with [¹⁸F]FDG [58] and an altered dopaminergic response to a methamphetamine challenge using a paired [¹¹C]-raclopride scan [59]. Studies are currently ongoing examining the neurochemical effects of SSRI treatment on the 5-HT_{1A} receptor in an animal model of activity-based anorexia that may lead to a better understanding as to why SSRIs are ineffective during severe food restriction (N.C. Barbarich-Marsteller, Columbia University). Overall, using a translational approach to study a complex clinical disorder may provide important insights into how to improve pharmacological treatments.

PHARMACOLOGICAL TREATMENTS

Despite the relatively rapid progress in pharmacological treatments in other fields of psychiatry such as depression and schizophrenia, anorexia nervosa has been impressively resistant to treatment. Individuals with anorexia nervosa are often resistant to pharmacological treatments and exhibit denial over the seriousness of their illness. Moreover, the severe state of malnutrition may decrease the efficacy of pharmacological treatments in these patients. It is unclear whether the lack of efficacy reported in drug treatment trials is due to an inability to metabolize the drug efficiently or whether the drugs that have been utilized are targeting the wrong receptors. Thus, the following is a review of the limited number of drug treatment studies that have been conducted in individuals with anorexia nervosa (Table 2; see also [60]). The majority of studies are case reports or open trials, with few double-blind, placebo controlled trials and small sample sizes, thereby limiting the interpretation of the results.

Tricyclic Antidepressants (TCAs)

TCAs exert their mechanism of action by inhibiting norepinephrine and 5-HT uptake into central nerve terminals, thereby increasing concentrations of neurotransmitters at the receptor sites. Two studies of amitriptyline in anorexia nervosa reported no significant effect on outcome [66, 67]. Studies of clomipramine have also demonstrated little efficacy; one study reported increased hunger, appetite, and energy intake [68] in individuals with anorexia nervosa, whereas a second study reported no effect [69].

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs have been used successfully in the treatment of a number of psychiatric disorders, including depression and anxiety. The pharmacological mechanism of SSRIs is potentiation of 5-HT by inhibition of its neuronal reuptake pump and desensitization of the 5-HT_{1A} receptor [70]. Given the high rate of comorbidity with depression and anxiety disorders and the more benign side effect profile compared to other classes of drugs, the use of SSRI treatment in anorexia nervosa was a logical progression from classic antipsychotics, which were the first class of treatments utilized. Despite this argument, the results of trials for fluoxetine [69, 71-81], citalopram [82-84], fluvoxamine [80], sertraline [80], and venlafaxine [75] have been disappointing. Open trials and small controlled studies have suggested no direct effect on weight gain during the acute phase of illness and minimal effects in reducing eating disorder and depressive symptoms.

In 2001, Kaye *et al.*, [77] reported the first double-blind, placebo controlled trial of fluoxetine in weight restored patients as a mechanism for relapse prevention. Results suggested that fluoxetine was effective in preventing relapse when drug administration was initiated after weight restoration, although drop out rate from the placebo group was high. In a more recent study, Walsh *et al.*, [81] reported that fluoxetine had no effect on time-to-relapse or eating disorder outcome measures in ninety-three inpatients with anorexia nervosa that were followed for one year. Although there were substantial methodological differences across SSRI

studies, overall results suggest that SSRIs are ineffective during both the acute phase of illness and in preventing relapse.

Classic Antipsychotics

Antipsychotic drugs were the first class of drug treatments utilized in the treatment of anorexia nervosa. While pimozide [61, 62] and sulpiride [63] had no effect on outcome, chlorpromazine [64] increased initial weight gain, but also increased seizures and purging. More recently, in a 6-month open trial, haloperidol had some improvement on body weight and outcome measures [65]. Despite this finding, the overall use of older antipsychotics in the treatment of anorexia nervosa has proven difficult, in that patients will often refuse treatment given that significant weight gain is a known side effect of this class of drugs.

Atypical Antipsychotics

More recently, the field of eating disorders has turned to atypical antipsychotics as a mechanism for increasing weight gain and improving symptoms in anorexia nervosa. To date, the most common atypical antipsychotic studied in anorexia nervosa is olanzapine. A selective monoaminergic antagonist, olanzapine is thought to exert its mechanism of action through a combination of DA and 5-HT₂ receptor antagonism. Several case studies and open trials of olanzapine have reported preliminary efficacy in decreasing anxiety and promoting weight gain [85-89] and decreasing anorexic rumination [90, 91]. The exact mechanism of weight gain-induced effects is unclear, but ongoing animal studies may shed light on the neurobiological mechanisms underlying this effect.

WHERE IS THE FUTURE HEADED?

Overall, the use of drugs that specifically target the 5-HT system (e.g., SSRIs) have demonstrated limited efficacy in treating and preventing relapse in anorexia nervosa. There are several hypotheses for this lack of efficacy. First, although SSRIs may effectively block the 5-HT transporter, starvation may decrease whole brain 5-HT content to the extent that the effect of increasing synaptic 5-HT is minimal, and therefore fails to provide any significant relief from symptoms. Second, SSRI treatment in the context of starvation may fail to desensitize the 5-HT_{1A} receptor; 5HT_{1A} desensitization reduces activation of inhibitory presynaptic 5-HT_{1A} receptors. In the absence of desensitization, this inhibitory activation will continue, thereby reducing postsynaptic levels of 5-HT, and reducing SSRI effectiveness. Finally, the potentiation of 5-HT alone may not effectively compensate for the complex alterations seen in 5-HT_{1A}, 5-HT_{2A}, 5-HTT, and D₂/D₃ receptor activity in anorexia nervosa.

In contrast, the use of drugs that target combined 5-HT and DA activity (e.g., atypical antipsychotics) have shown preliminary effects on weight gain and mood [85-89]. Along this line, the newer generation of atypical antipsychotics may be effective in the treatment of anorexia nervosa. Quetiapine, for example, exhibits moderate to high affinity for a number of receptors; however, its efficacy is believed to be modulated through a combination of antagonist activity at D₂ and 5-HT₂ receptors. Aripiprazole also exhibits affinity for a

Table 2. Pharmacological Treatment Studies of Serotonergic and Dopaminergic Drugs in Anorexia Nervosa

Study	Class	Drug Group	Control Group	Study Design	N	Outcome
Attia <i>et al.</i> , [74]	SSRI	fluoxetine	placebo	R, DB, PC	31	no significant effect on outcome
Gwirtsman <i>et al.</i> , [71]	SSRI	fluoxetine	none	OT	6	associated with improvement in depressive symptoms which was associated with weight gain
Kaye <i>et al.</i> , [72]	SSRI	fluoxetine	none	OT	31	associated with some efficacy in maintaining weight after inpatient discharge
Kaye <i>et al.</i> , [77]	SSRI	fluoxetine	placebo	DB, PC	35	associated with reduced relapse as determined by increased weight and reduction in symptoms
Strober <i>et al.</i> , [73]	SSRI	fluoxetine	matched historical case-controls	PLF	33	no significant effect on outcome
Strober <i>et al.</i> , [76]	SSRI	fluoxetine	matched historical case-controls	OT	66	no significant effect on outcome
Walsh <i>et al.</i> , [81]	SSRI	fluoxetine	placebo	R, DB, PC	93	no significant effect on outcome
Barbarich <i>et al.</i> , [79]	SSRI	fluoxetine + nutritional supplementation	fluoxetine alone	DB, PC	26	no significant effect on outcome
Ruggiero <i>et al.</i> , [78]	SSRI	nutritional management + fluoxetine	nutritional management	SB	95	associated with increased body weight and decreased physical exercise levels
Holtkamp <i>et al.</i> , [80]	SSRI	fluoxetine, fluvoxamine, or sertraline	no SSRI	RCA	32	no significant effect on outcome
Ricca <i>et al.</i> , [75]	SSRI	fluoxetine or venlafaxine (combined with cognitive behavior therapy)	none	CT	24	associated with some improvement in weight and symptoms
Calandra <i>et al.</i> , [83]	SSRI	citalopram (combined with systemic psychotherapy)	none	OT	6	associated with some improvement in body image dissatisfaction
Pallanti <i>et al.</i> , [82]	SSRI	citalopram	none	OT	32	associated with some improvement in weight and symptoms
Fassino <i>et al.</i> , [84]	SSRI	citalopram	wait-listed controls	R	52	associated with some improvement in depression and anxiety measures; no difference in weight gain between groups
Ferguson <i>et al.</i> , [92]	SSRI or TCA	fluoxetine, fluvoxamine, sertraline, paroxetine, or clomipramine	no SSRI	RCR	40	no significant effect on outcome
Ruggiero <i>et al.</i> , [69]	SSRI, AAP, or TCA	fluoxetine, amisulpride, or clomipramine	none	SB	35	amisulpride associated with a greater effect on weight gain
Biederman <i>et al.</i> , [66]	TCA	amitriptyline	placebo or other treatment	DB, PC	43	no significant effect on outcome
Halmi <i>et al.</i> , [67]	TCA	amitriptyline	cyproheptadine or placebo	R, DB	72	cyproheptadine associated with some effect on depressive symptoms

(Table 2) contd....

Study	Class	Drug Group	Control Group	Study Design	N	Outcome
Lacey & Crisp [68]	TCA	clomipramine	placebo	DB, PC	16	associated with increased hunger, appetite, energy intake, but reduced rate of weight gain; improved body weight maintenance
Cassano <i>et al.</i> , [65]	AP	haloperidol	none	OT	13	associated with some improvement in body weight and symptoms
Dally & Sargent [64]	AP	chlorpromazine	no medication	OT	57	associated with increased initial weight gain, but also increased seizures and purging
Vandereycken & Pierloot [61]	AP	pimozide	placebo	DB, PC, CO	18	associated with an improved attitude towards treatment
Weizman <i>et al.</i> , [62]	AP	pimozide	behavior therapy	OT	10	no significant effect on outcome
Vandereycken <i>et al.</i> , [63]	AP	sulpiride	placebo	DB, PC, CO	18	associated with an early effect on weight gain
Barbarich <i>et al.</i> , [88]	AAP	olanzapine	compared to historical case controls	OT	17	associated with a reduction in depression, anxiety, and core eating disorder symptoms and an increase in weight
La Via <i>et al.</i> , [85]	AAP	olanzapine	none	OT	2	associated with weight gain and maintenance and reduced agitation and resistance to treatment
Powers <i>et al.</i> , [86]	AAP	olanzapine	none	OT	18	associated with weight gain
Malina <i>et al.</i> , [87]	AAP	olanzapine	none	RCA	18	associated with reductions in anxiety, difficulty eating, and core eating disorder symptoms
Hillebrand <i>et al.</i> , [89]	AAP	olanzapine	no medication	OT	18	no effect on body weight, but associated with decreased activity levels
Mondraty <i>et al.</i> , [90]	AAP	olanzapine or chlorpromazine	none	R	15	olanzapine reduced anorexic rumination
Dennis <i>et al.</i> , [91]	AAP	olanzapine	none	CS	5	associated with increased body weight, decreased anxiety and rumination, and improved sleep

*Abbreviations: (AAP) = atypical antipsychotic; (AP) = antipsychotic; (CO) = cross-over analysis; (CS) = case report/study; (CT) = controlled trial; (DB) = double-blind; (OT) = open trial; (PC) = placebo controlled; (PLF) = prospective longitudinal follow-up; (R) = randomized; (RCA) = retrospective case analysis; (RCR) = retrospective chart review; (SB) = single-blind; (SSRI) = selective serotonin reuptake inhibitor; (TCA) = tricyclic antidepressant

**Case reports that included only 1 subject were not included in chart

number of receptors; however, its efficacy is believed to be modulated through a combination of partial agonist activity at D₂ and 5-HT_{1A} and antagonist activity at 5-HT_{2A}. Given that 5-HT_{1A} receptor binding is significantly increased in individuals with anorexia nervosa [36], and antagonism of D₂ and 5-HT_{2A} has demonstrated preliminary efficacy with olanzapine, these newer generation drugs may provide a more comprehensive modulation of the 5-HT/DA systems.

In conclusion, anorexia nervosa is a life-threatening disorder, with a complex clinical presentation including high rates of comorbidity and mortality. The chronic effects of starvation on drug metabolism complicate the use of pharmacological treatments during the ill state. Alternatively, inpatient hospitalization is costly and insurance companies often deny coverage after initial weight restoration, leading to early discharge and high rates of relapse. Thus, there is an increasing need for effective pharmacological treatments that

encompass not only the pure clinical characteristics of anorexia nervosa, but also the comorbid symptoms of anxiety and depression that may play a role in maintenance and relapse. Future research should move beyond current therapeutic agents, such as SSRIs, to the development of new compounds that more efficiently target the interaction between 5-HT and DA systems.

ACKNOWLEDGEMENTS

The author would like to thank the Eating Disorders Research Unit (NYSPI, Columbia University) and Dr. Douglas A. Marsteller (Lundbeck Research USA, Inc.) for their thoughtful reviews of this manuscript.

REFERENCES

- [1] APA, In Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-R), American Psychiatric Association: Washington, D.C., 2000.

- [2] Davis, C.; Katzman, D.K.; Kaptein, S.; Kirsh, C.; Brewer, H.; Kalmbach, K.; Olmsted, M.P.; Woodside, D.B.; Kaplan, A.S. *Compr. Psychiatry*, **1997**, *38*, 321-6.
- [3] Penas-Lledo, E.; Vaz Leal, F.J.; Waller, G. *Int. J. Eat. Disord.*, **2002**, *31*, 370-5.
- [4] Klein, D.A.; Bennett, A.S.; Schebendach, J.; Foltin, R.W.; Devlin, M.J.; Walsh, B.T. *CNS Spectr.*, **2004**, *9*, 531-7.
- [5] Shroff, H.; Reba, L.; Thornton, L.M.; Tozzi, F.; Klump, K.L.; Berrettini, W.H.; Brandt, H.; Crawford, S.; Crow, S.; Fichter, M.M.; Goldman, D.; Halmi, K.A.; Johnson, C.; Kaplan, A.S.; Keel, P.; LaVia, M.; Mitchell, J.; Rotondo, A.; Strober, M.; Treasure, J.; Woodside, D.B.; Kaye, W.H.; Bulik, C.M. *Int. J. Eat. Disord.*, **2006**, *39*, 454-61.
- [6] Bulik, C.M.; Reba, L.; Siega-Riz, A.M.; Reichborn-Kjennerud, T. *Int. J. Eat. Disord.*, **2005**, *37 Suppl*, S2-9; discussion S20-1.
- [7] Slof-Op 't Landt, M.C.; van Furth, E.F.; Meulenbelt, I.; Slagboom, P.E.; Bartels, M.; Boomsma, D.I.; Bulik, C.M. *Twin. Res. Hum. Genet.*, **2005**, *8*, 467-82.
- [8] Kaye, W.; Barbarich, N., Biological basis of eating disorders. In *Handbook of Medical Psychiatry*, Soares, Gershon, Eds. Marcel Dekker, Inc.: New York, **2003**; pp 633-641.
- [9] Herzog, D.B.; Dorer, D.J.; Keel, P.K.; Selwyn, S.E.; Ekeblad, E.R.; Flores, A.T.; Greenwood, D.N.; Burwell, R.A.; Keller, M.B. *J. Am. Acad. Child Adolesc. Psychiatry*, **1999**, *38*, 829-37.
- [10] Lowe, B.; Zipfel, S.; Buchholz, C.; Dupont, Y.; Reas, D.L.; Herzog, W. *Psychol. Med.*, **2001**, *31*, 881-90.
- [11] Sullivan, P.F. *Am. J. Psychiatry*, **1995**, *152*, 1073-4.
- [12] Birmingham, C.L.; Su, J.; Hlynsky, J.A.; Goldner, E.M.; Gao, M. *Int. J. Eat. Disord.*, **2005**, *38*, 143-6.
- [13] Fisher, M. *Adolesc. Med.*, **2003**, *14*, 149-58.
- [14] Bulik, C.M.; Sullivan, P.F.; Fear, J.; Pickering, A. *J. Nerv. Ment. Dis.*, **1997**, *185*, 704-7.
- [15] Eddy, K.T.; Keel, P.K.; Dorer, D.J.; Delinsky, S.S.; Franko, D.L.; Herzog, D.B. *Int. J. Eat. Disord.*, **2002**, *31*, 191-201.
- [16] Klump, K.L.; Bulik, C.M.; Pollice, C.; Halmi, K.A.; Fichter, M.M.; Berrettini, W.H.; Devlin, B.; Strober, M.; Kaplan, A.; Woodside, D.B.; Treasure, J.; Shabbout, M.; Lilenfeld, L.R.; Plotnicov, K.H.; Kaye, W.H. *J. Nerv. Ment. Dis.*, **2000**, *188*, 559-67.
- [17] Klump, K.L.; Strober, M.; Bulik, C.M.; Thornton, L.; Johnson, C.; Devlin, B.; Fichter, M.M.; Halmi, K.A.; Kaplan, A.S.; Woodside, D.B.; Crow, S.; Mitchell, J.; Rotondo, A.; Keel, P.K.; Berrettini, W.H.; Plotnicov, K.; Pollice, C.; Lilenfeld, L.R.; Kaye, W.H. *Psychol. Med.*, **2004**, *34*, 1407-18.
- [18] Bastiani, A.M.; Rao, R.; Weltzin, T.; Kaye, W.H. *Int. J. Eat. Disord.*, **1995**, *17*, 147-52.
- [19] Srinivasagam, N.M.; Kaye, W.H.; Plotnicov, K.H.; Greeno, C.; Weltzin, T.E.; Rao, R. *Am. J. Psychiatry*, **1995**, *152*, 1630-4.
- [20] Halmi, K.A.; Sunday, S.R.; Strober, M.; Kaplan, A.; Woodside, D.B.; Fichter, M.; Treasure, J.; Berrettini, W.H.; Kaye, W.H. *Am. J. Psychiatry*, **2000**, *157*, 1799-805.
- [21] Bulik, C.M.; Tozzi, F.; Anderson, C.; Mazzeo, S.E.; Aggen, S.; Sullivan, P.F. *Am. J. Psychiatry*, **2003**, *160*, 366-8.
- [22] Halmi, K.A.; Tozzi, F.; Thornton, L.M.; Crow, S.; Fichter, M.M.; Kaplan, A.S.; Keel, P.; Klump, K.L.; Lilenfeld, L.R.; Mitchell, J.E.; Plotnicov, K.H.; Pollice, C.; Rotondo, A.; Strober, M.; Woodside, D.B.; Berrettini, W.H.; Kaye, W.H.; Bulik, C.M. *Int. J. Eat. Disord.*, **2005**, *38*, 371-4.
- [23] Wagner, A.; Barbarich-Marsteller, N.C.; Frank, G.K.; Bailer, U.F.; Wonderlich, S.A.; Crosby, R.D.; Henry, S.E.; Vogel, V.; Plotnicov, K.; McConaha, C.; Kaye, W.H. *Int. J. Eat. Disord.*, **2006**, *39*, 276-84.
- [24] Kaye, W.; Bulik, C.; Thornton, L.; Barbarich, N.; Masters, K.; Fichter, M.; Halmi, K.; Kaplan, A.; Strober, M.; Woodside, D.; Bergen, A.; Crow, S.; Mitchell, J.; Rotondo, A.; Keel, P.; Plotnicov, K.; Pollice, C.; Klump, K.; Lilenfeld, L.; Devlin, B.; Quadflieg, N.; Berrettini, W. *Am. J. Psychiatry*, **2004**, *161*, 2215-21.
- [25] Barbarich, N. *Eat. Weight. Disord.*, **2002**, *7*, 221-31.
- [26] Halmi, K.A.; Sunday, S.R.; Klump, K.L.; Strober, M.; Leckman, J.F.; Fichter, M.; Kaplan, A.; Woodside, B.; Treasure, J.; Berrettini, W.H.; Al Shabbout, M.; Bulik, C.M.; Kaye, W.H. *Int. J. Eat. Disord.*, **2003**, *33*, 308-19.
- [27] Steinglass, J.; Walsh, B.T. *Int. J. Eat. Disord.*, **2006**, *39*, 267-75.
- [28] Wade, T.D.; Bulik, C.M.; Neale, M.; Kendler, K.S. *Am. J. Psychiatry*, **2000**, *157*, 469-71.
- [29] Lilenfeld, L.R.; Kaye, W.H.; Greeno, C.G.; Merikangas, K.R.; Plotnicov, K.; Pollice, C.; Rao, R.; Strober, M.; Bulik, C.M.; Nagy, L. *Arch. Gen. Psychiatry*, **1998**, *55*, 603-10.
- [30] Barnes, N.M.; Sharp, T. *Neuropharmacology*, **1999**, *38*, 1083-152.
- [31] Cooper, J.R.; Bloom, F.E.; Roth, R.H., In *The Biochemical Basis of Neuropharmacology, Seventh Edition*, Oxford University Press: New York, **1996**.
- [32] Kaye, W.H.; Ebert, M.H.; Raleigh, M.; Lake, R. *Arch. Gen. Psychiatry*, **1984**, *41*, 350-5.
- [33] Kaye, W.H.; Gwirtsman, H.E.; George, D.T.; Jimerson, D.C.; Ebert, M.H. *Biol. Psychiatry*, **1988**, *23*, 102-5.
- [34] Kaye, W.H.; Gwirtsman, H.E.; George, D.T.; Ebert, M.H. *Arch. Gen. Psychiatry*, **1991**, *48*, 556-62.
- [35] Kaye, W.H.; Barbarich, N.C.; Putnam, K.; Gendall, K.A.; Fernstrom, J.; Fernstrom, M.; McConaha, C.W.; Kishore, A. *Int. J. Eat. Disord.*, **2003**, *33*, 257-67; discussion 268-70.
- [36] Bailer, U.F.; Frank, G.K.; Henry, S.E.; Price, J.C.; Meltzer, C.C.; Mathis, C.A.; Wagner, A.; Thornton, L.; Hoge, J.; Ziolk, S.K.; Becker, C.R.; McConaha, C.W.; Kaye, W.H. *Biol. Psychiatry*, in press.
- [37] Bailer, U.F.; Frank, G.K.; Henry, S.E.; Price, J.C.; Meltzer, C.C.; Weissfeld, L.; Mathis, C.A.; Drevets, W.C.; Wagner, A.; Hoge, J.; Ziolk, S.K.; McConaha, C.W.; Kaye, W.H. *Arch. Gen. Psychiatry*, **2005**, *62*, 1032-41.
- [38] Bailer, U.F.; Price, J.C.; Meltzer, C.C.; Mathis, C.A.; Frank, G.K.; Weissfeld, L.; McConaha, C.W.; Henry, S.E.; Brooks-Achenbach, S.; Barbarich, N.C.; Kaye, W.H. *Neuropsychopharmacology*, **2004**, *29*, 1143-55.
- [39] Frank, G.K.; Kaye, W.H.; Meltzer, C.C.; Price, J.C.; Greer, P.; McConaha, C.; Skovira, K. *Biol. Psychiatry*, **2002**, *52*, 896-906.
- [40] Frank, G.K.; Bailer, U.F.; Henry, S.E.; Drevets, W.; Meltzer, C.C.; Price, J.C.; Mathis, C.A.; Wagner, A.; Hoge, J.; Ziolk, S.; Barbarich-Marsteller, N.; Weissfeld, L.; Kaye, W.H. *Biol. Psychiatry*, **2005**, *58*, 908-12.
- [41] Bailer, U.F.; Frank, G.K.; Henry, S.E.; Price, J.C.; Meltzer, C.C.; Becker, C.; Ziolk, S.K.; Mathis, C.A.; Wagner, A.; Barbarich-Marsteller, N.C.; Putnam, K.; Fudge, J.; Kaye, W.H. *Submitted*.
- [42] Audenaert, K.; Van Laere, K.; Dumont, F.; Vervaeke, M.; Goethals, I.; Slegers, G.; Mertens, J.; van Heeringen, C.; Dierckx, R.A. *J. Nucl. Med.*, **2003**, *44*, 163-9.
- [43] Matsushita, S.; Suzuki, K.; Murayama, M.; Nishiguchi, N.; Hishimoto, A.; Takeda, A.; Shirakawa, O.; Higuchi, S. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.*, **2004**, *128*, 114-7.
- [44] Rybakowski, F.; Slopian, A.; Dmitrak-Weglarz, M.; Czerski, P.; Rajewski, A.; Hauser, J. *Neuropsychobiology*, **2006**, *53*, 33-9.
- [45] Hinney, A.; Barth, N.; Ziegler, A.; von Prittwitz, S.; Hamann, A.; Hennighausen, K.; Pirke, K.M.; Heils, A.; Rosenkranz, K.; Roth, H.; Coners, H.; Mayer, H.; Herzog, W.; Siegfried, A.; Lehmkuhl, G.; Poustka, F.; Schmidt, M.H.; Schafer, H.; Grzeschik, K.H.; Lesch, K.P.; Lentes, K.U.; Remschmidt, H.; Hebebrand, J. *Life Sci.*, **1997**, *61*, PL 295-303.
- [46] Sundaramurthy, D.; Pieri, L.F.; Gape, H.; Markham, A.F.; Campbell, D.A. *Am. J. Med. Genet.*, **2000**, *96*, 53-5.
- [47] Alexander, G.E.; Crutcher, M.D.; DeLong, M.R. *Prog. Brain Res.*, **1990**, *85*, 119-46.
- [48] Volkow, N.D.; Fowler, J.S.; Wang, G.J. *Behav. Pharmacol.*, **2002**, *13*, 355-66.
- [49] Beninger, R.J.; Hoffman, D.C.; Mazurski, E.J. *Neurosci. Biobehav. Rev.*, **1989**, *13*, 113-22.
- [50] Self, D.W. *Ann. Med.*, **1998**, *30*, 379-89.
- [51] Kuhar, M.J.; Couceyro, P.R.; Lambert, P.D., In *Catecholamines*, Lippincott Williams & Wilkins: New York, **1999**.
- [52] Kaye, W.H.; Frank, G.K.; McConaha, C. *Neuropsychopharmacology*, **1999**, *21*, 503-6.
- [53] Bergen, A.W.; Yeager, M.; Welch, R.A.; Haque, K.; Ganjei, J.K.; van den Bree, M.B.; Mazzanti, C.; Nardi, I.; Fichter, M.M.; Halmi, K.A.; Kaplan, A.S.; Strober, M.; Treasure, J.; Bacanu, S.-A.; Devlin, B.; Berrettini, W.H.; Goldman, D.; Kaye, W.H. *Neuropsychopharmacology*, **2005**, *30*, 1703-1710.
- [54] Volkow, N.D.; Fowler, J.S.; Wang, G.J.; Hitzemann, R.; Logan, J.; Schlyer, D.J.; Dewey, S.L.; Wolf, A.P. *Synapse*, **1993**, *14*, 169-77.
- [55] Wang, G.J.; Volkow, N.D.; Fowler, J.S. *Expert. Opin. Ther. Targets*, **2002**, *6*, 601-9.
- [56] Wang, G.J.; Volkow, N.D.; Thanos, P.K.; Fowler, J. *J. Addict. Dis.*, **2004**, *23*, 39-53.

- [57] Volkow, N.D.; Wang, G.J.; Fowler, J.S.; Thanos, P.P.; Logan, J.; Gatley, S.J.; Gifford, A.; Ding, Y.S.; Wong, C.; Pappas, N. *Synapse*, **2002**, *46*, 79-82.
- [58] Barbarich-Marsteller, N.C.; Marsteller, D.A.; Alexoff, D.L.; Fowler, J.S.; Dewey, S.L. *Synapse*, **2005**, *57*, 85-90.
- [59] Barbarich-Marsteller, N.C.; Marsteller, D.A.; Fowler, J.S.; Alexoff, D.L.; Dewey, S.L. *Submitted*.
- [60] Attia, E.; Schroeder, L. *Int. J. Eat. Disord.*, **2005**, *37*, Suppl, S60-3; discussion S87-9.
- [61] Vandereycken, W.; Pierloot, R. *Acta Psychiatr. Scand.*, **1982**, *66*, 445-50.
- [62] Weizman, A.; Tyano, S.; Wijsenbeek, H.; Ben David, M. *Psychother. Psychosom.*, **1985**, *43*, 136-40.
- [63] Vandereycken, W. *Br. J. Psychiatry*, **1984**, *144*, 288-92.
- [64] Dally, P.J.; Sargant, W. *Br. Med. J.*, **1960**, *5188*, 1770-3.
- [65] Cassano, G.B.; Miniati, M.; Pini, S.; Rotondo, A.; Banti, S.; Borri, C.; Camilleri, V.; Mauri, M. *Int. J. Eat. Disord.*, **2003**, *33*, 172-7.
- [66] Biederman, J.; Herzog, D.B.; Rivinus, T.M.; Harper, G.P.; Ferber, R.A.; Rosenbaum, J.F.; Harmatz, J.S.; Tondorf, R.; Orsulak, P.J.; Schildkraut, J.J. *J. Clin. Psychopharmacol.*, **1985**, *5*, 10-6.
- [67] Halmi, K.A.; Eckert, E.; LaDu, T.J.; Cohen, J. *Arch. Gen. Psychiatry*, **1986**, *43*, 177-81.
- [68] Lacey, J.H.; Crisp, A.H. *Postgrad. Med. J.*, **1980**, *56*, Suppl. 1, 79-85.
- [69] Ruggiero, G.M.; Laini, V.; Mauri, M.C.; Ferrari, V.M.; Clemente, A.; Lugo, F.; Mantero, M.; Redaelli, G.; Zappulli, D.; Cavagnini, F. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2001**, *25*, 1049-59.
- [70] Vaswani, M.; Linda, F.K.; Ramesh, S. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2003**, *27*, 85-102.
- [71] Gwirtsman, H.E.; Guze, B.H.; Yager, J.; Gainsley, B. *J. Clin. Psychiatry*, **1990**, *51*, 378-382.
- [72] Kaye, W.H.; Weltzin, T.E.; Hsu, L.K.; Bulik, C.M. *J. Clin. Psychiatry*, **1991**, *52*, 464-71.
- [73] Strober, M.; Freeman, R.; DeAntonio, M.; Lampert, C.; Diamond, J. *Psychopharmacol. Bull.*, **1997**, *33*, 425-31.
- [74] Attia, E.; Haiman, C.; Walsh, B.T.; Flater, S.R. *Am. J. Psychiatry*, **1998**, *155*, 548-51.
- [75] Ricca, V.; Mannucci, E.; Paionni, A.; Di Bernardo, M.; Cellini, M.; Cabras, P.L.; Rotella, C.M. *Eat Weight Disord.*, **1999**, *4*, 10-4.
- [76] Strober, M.; Pataki, C.; Freeman, R.; DeAntonio, M. *J. Child Adolesc. Psychopharmacol.*, **1999**, *9*, 195-201.
- [77] Kaye, W.H.; Nagata, T.; Weltzin, T.E.; Hsu, L.K.; Sokol, M.S.; McConaha, C.; Plotnicov, K.H.; Weise, J.; Deep, D. *Biol. Psychiatry*, **2001**, *49*, 644-52.
- [78] Ruggiero, G.M.; Mauri, M.C.; Omboni, A.C.; Volonteri, L.S.; Dipasquale, S.; Malvini, L.; Redaelli, G.; Pasqualinotto, L.; Cavagnini, F. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2003**, *27*, 425-30.
- [79] Barbarich, N.C.; McConaha, C.W.; Halmi, K.A.; Gendall, K.; Sunday, S.R.; Gaskill, J.; La Via, M.; Frank, G.K.; Brooks, S.; Plotnicov, K.H.; Kaye, W.H. *Int. J. Eat. Disord.*, **2004**, *35*, 10-5.
- [80] Holtkamp, K.; Konrad, K.; Kaiser, N.; Ploenes, Y.; Heussen, N.; Grzella, I.; Herpertz-Dahlmann, B. *J. Psychiatr. Res.*, **2005**, *39*, 303-10.
- [81] Walsh, B.T.; Kaplan, A.S.; Attia, E.; Olmsted, M.; Parides, M.; Carter, J.C.; Pike, K.M.; Devlin, M.J.; Woodside, B.; Roberto, C.A.; Rockert, W. *JAMA*, **2006**, *295*, 2605-12.
- [82] Pallanti, S.; Quercioli, L.; Ramacciotti, A. *Eat Weight Disord.*, **1997**, *2*, 216-21.
- [83] Calandra, C.; Gulino, V.; Inserra, L.; Giuffrida, A. *Eat. Weight Disord.*, **1999**, *4*, 207-10.
- [84] Fassino, S.; Leombruni, P.; Daga, G.; Brustolin, A.; Migliaretti, G.; Cavallo, F.; Rovera, G. *Eur. Neuropsychopharmacol.*, **2002**, *12*, 453-9.
- [85] La Via, M.C.; Gray, N.; Kaye, W.H. *Int. J. Eat Disord.*, **2000**, *27*, 363-6.
- [86] Powers, P.S.; Santana, C.A.; Bannon, Y.S. *Int. J. Eat Disord.*, **2002**, *32*, 146-54.
- [87] Malina, A.; Gaskill, J.; McConaha, C.; Frank, G.K.; LaVia, M.; Scholar, L.; Kaye, W.H. *Int. J. Eat Disord.*, **2003**, *33*, 234-7.
- [88] Barbarich, N.C.; McConaha, C.W.; Gaskill, J.; La Via, M.; Frank, G.K.; Achenbach, S.; Plotnicov, K.H.; Kaye, W.H. *J. Clin. Psychiatry*, **2004**, *65*, 1480-2.
- [89] Hillebrand, J.J.; van Elburg, A.A.; Kas, M.J.; van Engeland, H.; Adan, R.A. *Biol. Psychiatry*, **2005**, *58*, 651-7.
- [90] Mondraty, N.; Birmingham, C.L.; Touyz, S.; Sundakov, V.; Chapman, L.; Beumont, P. *Australas. Psychiatry*, **2005**, *13*, 72-5.
- [91] Dennis, K.; Le Grange, D.; Bremer, J. *Eat Weight Disord.*, **2006**, *11*, e53-6.
- [92] Ferguson, C.P.; La Via, M.C.; Crossan, P.J.; Kaye, W.H. *Int. J. Eat Disord.*, **1999**, *25*, 11-7.