

Use of Nutritional Supplements to Increase the Efficacy of Fluoxetine in the Treatment of Anorexia Nervosa

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Abstract: Objective: Selective serotonin reuptake inhibitor (SSRI) medication does not appear to be effective in ill, malnourished anorexia nervosa (AN) patients. However, it may be effective in preventing relapse after weight restoration. The purpose of this study was to determine whether nutritional supplements could potentiate the effects of fluoxetine in underweight AN subjects.

Method: Twenty-six subjects with AN participated in a trial of fluoxetine. In a double-blind, placebo-controlled manner, subjects received either nutritional supplements or a nutritional placebo. The nutritional supplement included tryptophan (the precursor of serotonin), vitamins, minerals, and essential fatty acids believed to influence serotonin pathway function. **Results:** There was no significant difference in weight gain between subjects treated with fluoxetine plus nutritional supplements versus fluoxetine plus a nutritional placebo. Moreover, there were no significant differences between groups on mean changes in anxiety or obsessive and compulsive symptoms. **Discussion:** The results of this study suggest that supplement strategies are not a substitute for adequate nutrition and are ineffective in increasing the efficacy of fluoxetine in underweight AN subjects. © 2003 by Wiley Periodicals, Inc. *Int J Eat Disord* 35: 10–15, 2004.

Key words: nutritional supplements; fluoxetine; anorexia nervosa

INTRODUCTION

Anorexia nervosa (AN) is a disorder of unknown etiology characterized by restricted eating, a relentless pursuit of thinness, and obsessive fears of becoming fat. The onset of AN is typically in early adolescence, with approximately 90% of subjects being female

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(American Psychiatric Association, 1994). AN is often characterized by a chronic and relapsing course (Herzog, Nussbaum, & Marmor, 1996) and it has the highest death rate of any psychiatric disorder (Sullivan, 1995). Moreover, the hospital utilization rate for AN is higher than any other psychiatric disorder, aside from schizophrenia and other organic mental disorders (McKenzie & Joyce, 1992).

Pharmacologic and psychological treatments have been of limited efficacy in the treatment of underweight, malnourished AN individuals (Attia, Haiman, Walsh, & Flater, 1998; Ferguson, La Via, Crossan, & Kaye, 1999; Peterson & Mitchell, 1999; Strober, Pataki, Freeman, & DeAntonio, 1999). In contrast, a recent study (Kaye et al., 2001) showed that when the selective serotonin reuptake inhibitor (SSRI), fluoxetine, was given after weight restoration, it significantly reduced the rate of relapse in AN. Specifically, in a double-blind, placebo-controlled trial of fluoxetine in 35 patients with restrictor-type AN, fluoxetine improved outcome and reduced relapse after weight restoration when patients were followed for 1 year as outpatients. Fluoxetine administration was associated with a significant reduction in core eating disorder symptoms, depression, anxiety, obsessions, and compulsions. Fluoxetine, however, appears to be ineffective in malnourished patients with AN (Attia et al., 1998; Ferguson et al., 1999). The efficacy of fluoxetine in preventing relapse in weight-restored individuals with AN suggests that nutritional factors may play a role in the efficacy of SSRIs.

One potential reason for the effectiveness of fluoxetine during the recovered state may be the drug's actions on serotonin (5-HT), a neurotransmitter system found to be dysregulated in individuals with AN. When assessed after long-term recovery, individuals with AN have increased levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of 5-HT, in the cerebrospinal fluid (CSF; Kaye, Gwirtsman, George, & Ebert, 1991). In addition, recent studies using positron emission tomography have found decreased activity at the 5-HT_{2A} receptor (Frank et al., 2002), indicating a compensatory response of the brain to increased 5-HT output. It has been suggested that fluoxetine may be efficacious during the recovered state in AN by modulating an intrinsic defect of serotonergic activity in these individuals.

Fluoxetine and other SSRIs depend on neuronal release of 5-HT for their action (Tollefson, 1995). If the release of 5-HT from presynaptic neuronal sites was compromised substantially and net synaptic 5-HT concentration was negligible, a clinically meaningful response to an SSRI might not occur. During the acute phase of illness, individuals with AN have reduced 5-HIAA in the CSF (Kaye, Ebert, Raleigh, & Lake, 1984), suggesting reduced synaptic 5-HT. This may be due to a reduced supply or availability of tryptophan, an essential amino acid precursor of 5-HT that must be obtained through the diet. Depending on dietary intake and the relative proportions of carbohydrates and proteins, meal consumption may enhance brain 5-HT release (Fernstrom & Wurtman, 1971). A restricted diet in animals and healthy humans significantly lowers plasma tryptophan, decreases brain 5-HT synthesis, down-regulates the density of 5-HT transporters, and produces a compensatory supersensitivity of postsynaptic receptors in response to reduced 5-HT turnover (Goodwin, Fairburn, & Cowen, 1987; Huether, Zhou, & Ruther, 1997). Dieting reduces tryptophan availability, thereby limiting potential serotonergic production (Anderson, Parry-Billings, Newsholme, Fairburn, & Cowen, 1990). Low basal (Kumai, Tamai, Fujii, Nakagawa, & Aoki, 1988) and post ingestive (Alderdice, Dinsmore, Buchanan, & Adams, 1985) insulin concentrations in AN may further contribute to the reduced availability of tryptophan for 5-HT synthesis.

Impaired 5-HT functional activity may also be a consequence of an inadequate availability of a number of other nutrients that are essential to normal 5-HT synthesis and function. Zinc is a mineral that influences membrane stability to the extent that zinc

deficiency increases membrane fluidity, causing loss of receptor function (McClain, Stuart, Kasarskis, & Humphries, 1993). Vitamin B6 is a cofactor required in the reaction that converts tryptophan to 5-HT (Sharma & Dakshinamurti, 1994). Vitamin B12 and folate are also required for the formation of tetrahydrobiopterin, a hydroxylase cofactor in 5-HT synthesis (Coppen et al., 1989). Dietary deficiency and lowered biochemical activity of these B vitamins in some individuals with AN (Mira, Stewart, & Abraham, 1989; Nunez, Moreiras, & Carbajal, 1995; Rock & Curran-Celentano, 1994; Rock & Vasantharajan, 1995) may compromise the ability of SSRIs to facilitate serotonergic function.

In theory, the consumption of nutritional supplements containing tryptophan and essential fatty acids might increase levels of available tryptophan and facilitate 5-HT synthesis in the brain. The purpose of this study was to determine if the use of these supplements would increase the efficacy of fluoxetine in underweight AN subjects.

METHODS

Twenty-six individuals with AN were enrolled in a 6-month trial of fluoxetine. Participants were recruited from the eating disorders programs at Western Psychiatric Institute and Clinic (Pittsburgh, PA) and New York Hospital, Cornell Medical Center (New York, NY). All subjects provided written informed consent before the start of the study and the study had the approval of the site's institutional review board. Ten subjects were restricting-type AN, 6 subjects were restricting and purging only-type AN, and 10 subjects were binge eating/purging-type AN.

Subjects enrolled in the study were started on a dose of 20–40 mg of fluoxetine. Individual doses were titrated throughout the study to balance unwanted side effects with beneficial effects on mood. The dose of fluoxetine at the end of the study ranged from 20 mg to 60 mg. Subjects were weighed at weekly intervals for the first 8 weeks, at 2-week intervals for 6 weeks, and at 4-week intervals for 12 weeks.

Psychological assessments were completed at baseline and at 3 and 6 months. The following assessment battery was used: the Frost Multidimensional Perfectionism Scale (Frost, Marten, Lahart, & Rosenblate, 1990), the Spielberger State-Trait Anxiety Inventory (STAI-Y; Spielberger, Gorsuch & Lushene, 1970), and the Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989).

Nutritional Supplements

Using a randomized, double-blind design, subjects were assigned to one of two supplement groups (Table 1). The active group consumed daily dietary supplements consisting of 2.3 g of tryptophan (Ajinomoto, Paramus, NJ), taken in a divided dose in the morning and evening, and one multivitamin/mineral capsule per day in the morning. This regimen provided 100% of the recommended dietary allowance for vitamins and minerals. In addition, subjects in the active group were given four fish oil capsules (Martek Biosciences, Columbia, MD) per day in the morning, which provided 600 mg of docosahexanoic acid and 180 mg of arachadonic acid daily. The placebo group received an equivalent number of inactive capsules containing starch and high oleic sunflower oil taken in the morning and evening.

Table 1. Distribution of eating disorder diagnoses

	Active Group		Placebo Group	
	RAN	BAN	RAN	BAN
Early drop-out	0	3	3	1
Mid-drop-out	3	1	5	1
Completion	3	4	2	0

Note: RAN = restricting and purging only-type anorexia nervosa;
BAN = binge eating/purging-type anorexia nervosa.

Data Analysis

Independent sample *t* tests were used to assess differences in overall changes in weight and mood between the active and placebo groups.

RESULTS

Subjects with AN were 23.0 ± 6.3 years old and had a mean age of onset of 16.1 ± 4.6 years. Of the initial 26 subjects, 15 subjects were assigned randomly to the active group and 11 subjects were assigned to the placebo group. Nine subjects completed the full 26 weeks of the study (completion group), 13 subjects completed 5–18 weeks of the study (mid-drop-out group), and 4 subjects dropped out within 4 weeks of entering the study (early drop-out group; see Table 1 for a distribution of diagnoses within groups). Of the 17 subjects who dropped out of the study at or before 18 weeks, 58.8% of subjects were in the placebo group. Of the 9 subjects who completed 26 weeks of the study, 77.8% of subjects were in the active group. Given the substantial rate of drop-out, an analysis of group differences (completion vs. drop-out groups) was performed on demographic variables (Table 2). Start age of laxative abuse was the only variable that showed a significant group difference. Therefore, all 9 subjects who completed the full 26 weeks (the completion group) were included in the analyses of weight gain and changes in mood.

Mean weight gain per week was not significantly different between the active group and the placebo group (0.27 ± 0.3 kg per week vs. 0.10 ± 0.1 kg per week), $t(7) = 1.58$, $p = ns$.

Table 2. Comparison of group variables ($M \pm SD$)

	Drop-out ($n = 17$) ^a	Completion ($n = 9$)
Current age	21.0 ± 4.6	25.7 ± 7.4
Dieting start age	14.7 ± 2.4	16.9 ± 5.2
Age of onset	15.1 ± 2.3	17.3 ± 6.3
Duration of eating disorder (years)	6.2 ± 4.8	8.4 ± 8.1
Binge eating start age	15.1 ± 1.6	17.8 ± 6.9
Laxative abuse start age	16.3 ± 1.6	$21.3 \pm 1.2^*$
Vomiting start age	17.0 ± 2.6	20.2 ± 6.9
Low BMI	14.6 ± 1.3	14.4 ± 1.4
High BMI	21.4 ± 2.8	20.8 ± 2.3
Baseline perfectionism scores	92.0 ± 30.3	87.8 ± 28.4

Note: BMI = body mass index.

^aDrop-out group includes both early drop-outs and mid-drop-outs.

* $p < .01$.

Overall, there were no significant differences between the active group and the placebo group on baseline scores on the STAI-Y (43.5 ± 17.6 vs. 54.5 ± 3.5), $t(4) = -0.83$, $p = \text{ns}$, or the Yale-Brown Obsessive Compulsive Scale (11.8 ± 14.2 vs. 12.0 ± 11.3), $t(6) = -0.02$, $p = \text{ns}$. When assessed at end point, there were no significant differences between the active group and the placebo group on mean changes in anxiety (-7.8 ± 23.8 vs. -10.5 ± 0.7), $t(4) = 0.15$, $p = \text{ns}$, or obsessive and compulsive symptoms (-9.2 ± 12.9 vs. -6.5 ± 3.5), $t(6) = -0.27$, $p = \text{ns}$.

DISCUSSION

The use of nutritional supplements containing tryptophan and essential fatty acids did not increase the efficacy of fluoxetine in individuals with AN who were underweight. The potential reason why nutritional supplementation was ineffective in these individuals remains uncertain. It may be that a combination of long-term malnutrition and decreased serotonergic activity altered the potential effectiveness of nutritional supplementation. Caloric content and insulin secretion interact through a dynamic process with continuous changes throughout the day. Therefore, modest nutritional supplementation may not be sufficient to offset the physiologic changes in these systems caused by malnutrition.

The limitations of this study included a small sample size, two different sites, and a significant drop-out rate before the full 26 weeks. In summary, this study suggests that supplement strategies are not a substitute for adequate nutrition and are ineffective in increasing the efficacy of fluoxetine in underweight AN individuals.

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