

Are Serotonin Selective Reuptake Inhibitors Effective in Underweight Anorexia Nervosa?

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Accepted 19 February 1998

Abstract: Objective: Recent data suggest that serotonin selective reuptake inhibitor (SSRI) medication is useful in preventing relapse in weight-restored anorexics. Our clinical impression has been that SSRIs are not effective in patients who are underweight with anorexia nervosa. **Method:** In order to determine whether there was any benefit for SSRI medication in underweight anorexics, we compared two groups of underweight anorexics upon admission to our inpatient hospital using a retrospective chart review. **Results:** Sixty percent of anorexic patients were taking an SSRI upon admission to our inpatient hospital. The 24 subjects taking an SSRI were compared to the 16 subjects not taking an SSRI. These two groups had similar ages and body weights as well as scores for measures of anxiety and depression and most core eating disorder symptoms. **Discussion:** These results suggest that SSRI medication had no effect on clinical symptoms of malnourished underweight anorexics. © 1999 by John Wiley & Sons, Inc. *Int J Eat Disord* 25: 11–17, 1999.

Key words: SSRI medication; weight-restores anorexics; chart review

INTRODUCTION

Anorexia nervosa (AN) (American Psychiatric Association [APA], 1994) is a disorder of unknown etiology that predominantly occurs in women. This illness is characterized by restricted eating, the relentless pursuit of thinness, and obsessive fears of being fat. These symptoms result in profound weight loss and considerable psychological morbidity.

There has been no proven treatment for AN (Herzog, Keller, Strober, Yeh, & Pai, 1992). Consequently, many people with AN have a chronic, relapsing illness (Hsu, 1980; Theander, 1983; Hall & Crisp, 1987). AN has the highest death rate of any psychiatric disorder (Sullivan, 1995).

Extended hospitalizations can be lifesaving because such treatment can restore weight

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to emaciated people, which, in turn, reverses medical complications (Hsu, 1988; Patton, 1988). However, such hospitalizations can be lengthy and expensive. In fact, the hospital utilization rate for people with AN is higher than for any other psychiatric disorder, aside from schizophrenia and organic disorders (McKenzie & Joyce, 1992).

We recently reported (Kaye et al., submitted) that administration of a serotonin selective reuptake inhibitor (SSRI) medication improved outcome and reduced relapse after weight restoration by contributing to maintenance of a healthy normal weight and a reduction of symptoms. We administered a double-blind placebo-controlled trial of fluoxetine to 35 patients with restrictor-type AN. Anorexics were randomly assigned to fluoxetine ($n = 16$) or placebo ($n = 19$) after inpatient weight restoration and then were followed as outpatients for 1 year. Ten of 16 (63%) subjects successfully responded to fluoxetine whereas only 3 of 19 (16%) responded to placebo ($p = .006$). Fluoxetine administration was associated with a significant weight gain and a significant reduction in core eating disorder symptoms, depression, anxiety, and obsessions and compulsions. In summary, this study showed that fluoxetine improves outcomes and reduces core eating disorder symptoms, negative affect, and obsessionality when administered after weight restoration in women with AN. In contrast, a recent longitudinal follow-up study by Strober, Freeman, DeAntonio, Lampert, and Diamond (1997) compared 33 patients with AN who participated in an inpatient treatment program and who also received fluoxetine with matched controls who participated in the same program and did not receive fluoxetine. The results showed that adjunctive fluoxetine did not significantly improve treatment outcome.

Several open trials of serotonin (5-HT)-specific agents have been positive. Gwirtsman, Guze, Yager, and Gainsley (1990) reported that 6 chronic, refractory anorexic patients gained weight during an open trial of fluoxetine and had a reduction in depression and a decrease in obsessive thoughts about food and ritualistic preoccupations. In a large-scale open trial (Kaye, Weltzin, Hsu, & Bulik, 1991), fluoxetine prevented relapse after weight restoration and was associated with improvements in eating behavior, mood, and obsessional symptoms. Limited evidence suggests other 5-HT-specific medications are useful in this disorder. Clomipramine (Crisp, Lacey, & Crutchfield, 1987) was associated with increased appetite, hunger, and caloric consumption when administered to anorexics during the early stages of refeeding and weight restoration. Cyproheptadine has been shown to have some limited efficacy in restrictor anorexics, but not bulimic anorexics (Halmi, Eckert, LaDu, & Cohen, 1986).

It has been our clinical impression that fluoxetine is much less effective when people with AN are underweight and malnourished. In fact, it is our recent clinical experience that many underweight anorexics admitted to our treatment program are treated with SSRI medication prior to admission. However, it has been our clinical impression that SSRI medications have little effect on reducing symptoms and preventing hospitalization in these underweight anorexics. In order to assess the efficacy of SSRI medication in severely underweight anorexics, we did a retrospective chart review of the last 40 people with AN admitted to our inpatient treatment unit. We compared the characteristics of those admitted on an SSRI compared to those patients not admitted on an SSRI.

METHODS

Subjects were 40 sequential admissions to the inpatient eating disorders treatment program at the Western Psychiatric Institute and Clinic (WPIC), University of Pittsburgh Medical Center (UPMC). All subjects were female and met criteria for AN described in the

4th ed. of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; APA, 1994). This study included anorexic patients with a history of weight loss due to restrictive eating behavior as well as anorexics who purged. No subjects had binged during their lifetime.

A retrospective chart review was completed to determine whether anorexics were taking an SSRI medication at the time of admission. While this information was routinely documented in the chart, the dose at the time of admission and the length of time taking medication were not always documented. Subjects were included in the group taking SSRIs only if the chart review indicated that they had been taking SSRI medication for longer than 4 weeks prior to admission. To be included in the non-SSRI medication group, subjects had to not have taken SSRI medication in the 4 weeks prior to admission.

Individuals were asked to complete standardized assessment instruments within 1 week of admission in order to characterize symptoms at admission. The assessments consisted of:

The Eating Disorder Inventory (EDI): Subjects completed the EDI (Garner, Olmstead, & Polivy, 1983), a standardized self-report measure consisting of eight subscales relating to specific behavioral and cognitive dimensions of eating disorders, including a measure of perfectionism.

Frost Multidimensional Perfectionism Scale (MPS): Subjects completed the MPS (Frost, Marten, Lahart, & Rosenblate, 1990). This self-rating scale consists of overall assessment of six subscales designed to assess the various dimensions of perfectionism. An "Overall Perfectionism" score combines the individual scores of the six subscales. This scale has been shown to be a reliable and valid measure of perfectionism (Frost, Heimberg, Holt, Mattia, & Neubauer, 1993).

Spielberger State-Trait Anxiety Inventory: This is a widely used self-report instrument (Spielberger, Gorsuch, & Lushene, 1970) that yields separate scores for state and trait anxiety.

Beck Depression Inventory: The BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is a 21-item self-report inventory.

A *t* test was performed using the BMDP statistical software package (BMDP, 1985) to compare the group taking SSRIs to the group not taking SSRIs.

RESULTS

Sixty percent (24 subjects) of the underweight anorexics were taking an SSRI medication at the time of admission. The 24 subjects taking an SSRI were compared to the 40% (16 subjects) not taking an SSRI (Table 1). These two groups had similar ages and past low and high body weights. There was a trend for the group on SSRI medication to have a lower body weight on admission. The different types of medication are shown in Table 2.

These two groups had similar scores ($p < .05$) on all subscales of the EDI aside from differences on the Perfectionism and Bulimia subscales (Table 3). These two groups had similar scores for measures of anxiety and depression. When a Bonferoni correction for multiple *t* tests was applied, there were no significant differences between groups.

DISCUSSION

These data suggest that SSRI medication had no effect on weight, core eating disorder symptoms, or depression or anxiety in malnourished underweight anorexics. In contrast,

Table 1. Subject characteristics of patients with and without SSRI upon admission in restrictor-type anorexics (RAN) and RAN patients who also purged (RAN-P)

| | Non-SSRI | SSRI | <i>t</i> Value | <i>p</i> Value |
|--------------------------|----------|----------|----------------|----------------|
| Total number of subjects | 16 | 24 | — | — |
| Number of RAN subjects | 7 | 13 | | |
| Number of RAN-P subjects | 9 | 11 | | |
| Age on admission | 21 ± 8 | 23 ± 10 | 0.46 | NS |
| Age onset of ED | 18 ± 8 | 17 ± 6 | 0.48 | NS |
| Admit weight percent IBW | 68 ± 5 | 65 ± 9 | 1.17 | NS |
| High weight percent IBW | 100 ± 18 | 103 ± 17 | 0.43 | NS |
| Low weight percent IBW | 66 ± 6 | 62 ± 10 | 1.40 | NS |

Note: SSRI = serotonin selective reuptake inhibitor; ED = eating disorder; IBW = ideal body weight.

after weight restoration, an open (Kaye, Weltzin, et al., 1991) and double-blind trial (Kaye et al., 1998) showed that fluoxetine administration was associated with a significant weight gain and a significant reduction in core eating disorder symptoms, depression, and anxiety.

In this retrospective chart review study, subjects were taking a variety of SSRIs with a range of doses and duration of treatment. It is possible that not all SSRIs are equally efficacious or that some subjects were noncompliant or on too low of a dose or for too short a time. A limitation of this study is the selection factor of only including patients who failed outpatient treatment and needed to be hospitalized. Thus, it is possible that some underweight anorexics might have responded to SSRIs, gained weight, not have been hospitalized, and thus not included in our sample. However, our clinical experience, from patients treated in our outpatient and partial program, is that few underweight patients respond to an adequate trial of SSRIs. These issues will need to be addressed in a prospective study.

Does this finding make scientific sense? Does malnutrition neutralize the therapeutic actions of SSRIs? Tollefson (1995) noted that the SSRIs are dependent on neuronal release of 5-HT for their action. If the release of 5-HT from presynaptic neuronal storage sites was substantially compromised, and in turn their net synaptic 5-HT concentration was negligible, there is likely to be a poor response to an SSRI. With minimal 5-HT in the synapse, there is little uptake to inhibit. In fact, cerebrospinal fluid (CSF) 5-HIAA concentrations, the major 5-HT metabolite in the brain, are low in underweight anorexics, normalized in short-term weight-restored anorexics, and are elevated in long-term weight-restored anorexics (Kaye, Gwirtsman, George, Jimerson, & Ebert, 1988; Kaye, Gwirtsman, George, & Ebert, 1991). If CSF 5-HIAA levels accurately reflect central nervous system (CNS) 5-HT activity, then this might imply that underweight anorexics have reduced 5-HT activity

Table 2. Medication information

| Medication | Number of Patients | Dosage Range (mg) | Average Length of Trial Prior to Inpatient Admission (weeks) |
|------------|--------------------|-------------------|--------------------------------------------------------------|
| Anafranil | 3 | 25–75 | 52 |
| Luvox | 1 | 100 | 20 |
| Paxil | 4 | 10–40 | 16 |
| Prozac | 10 | 10–40 | 23 |
| Zoloft | 6 | 25–150 | 18 |

Table 3. Baseline assessment scores for patients with and without SSRI on admission

| Measurement | Non-SSRI | SSRI | <i>t</i> Value | <i>p</i> Value |
|-------------------------------------------|---------------|---------------|----------------|-----------------|
| Eating Disorder Inventory | <i>N</i> = 14 | <i>N</i> = 23 | | |
| Drive for Thinness | 12 ± 7 | 11 ± 8 | 0.638 | NS |
| Bulimia | .4 ± 1 | 1 ± 2 | 0.147 | <i>p</i> < .043 |
| Body Dissatisfaction | 14 ± 7 | 14 ± 8 | 0.767 | NS |
| Ineffectiveness | 6 ± 6 | 12 ± 9 | 0.030 | NS |
| Perfectionism | 5 ± 4 | 7 ± 5 | 0.213 | <i>p</i> < .038 |
| Interpersonal Distrust | 3 ± 3 | 6 ± 4 | 0.022 | NS |
| Interoceptive Awareness | 9 ± 8 | 9 ± 7 | 0.995 | NS |
| Maturity Fears | 4 ± 5 | 6 ± 7 | 0.362 | NS |
| Frost Multidimensional Perfectionism | | | | |
| Scale—Overall Perfectionism | 67 ± 23 | 88 ± 21 | .010 | NS |
| Beck Depression Inventory—Total | 14 ± 10 | 20 ± 13 | 0.138 | NS |
| Spielberger Trait Anxiety Inventory—State | 46 ± 14 | 53 ± 14 | 0.145 | NS |
| Spielberger Trait Anxiety Inventory—Trait | 45 ± 13 | 52 ± 14 | 0.141 | NS |

Note: SSRI = serotonin selective reuptake inhibitor.

and long-term weight-restored anorexics have increased 5-HT activity. In fact, studies in animals show that food restriction decreases 5-HT and its synthesis rate in the brain (Jaleem & Haider, 1996).

There are several possible explanations for reduced 5-HT activity in underweight anorexics. First, 5-HT is derived from tryptophan, an essential amino acid that can only be obtained in the diet. In healthy women, dieting significantly lowers plasma tryptophan, the precursor of 5-HT (Anderson, Parry-Billings, Newsholme, Fairburn, & Cowen, 1990). This results in a decreased plasma ratio of tryptophan to neutral amino acids, which, in turn, reduces the availability of tryptophan to the brain and reduces brain 5-HT synthesis (Gibbons, Barr, Bridger, & Leibowitz, 1979; Messing, Fisher, Phebus, & Lytle, 1976). Women with AN, when malnourished and underweight, have reduced plasma tryptophan availability (Schweiger, Warnhoff, Pahl, & Pirke, 1986). These data raise the provocative possibility that SSRI medication is not effective in underweight anorexics because they may have reduced synaptic 5-HT. In support of this possibility is a study showing that depletion of tryptophan will reverse the effects of antidepressants in depressed patients (Delgado et al., 1990).

Second, reduced gonadal steroids in the starved state may directly alter 5-HT activity in the brain. Gonadal steroids modulate the synthesis of 5-HT uptake by effects on the 5-HT transporter (Pecins-Thompson, Schutzer, & Bethea, 1996), on the 5-HT receptor transcription (Sumner & Fink, 1995) and density (Fischette, Biegion, & McEwen, 1983), and the response to serotonergic stimulation (Matsuda, Nakno, Kanda, Iwata, & Baba, 1991).

In summary, adequate treatment for AN has become more difficult to provide in this era of managed care (Baran, Weltzin, & Kaye, 1995; Huon, Brown, & Morris, 1988), although the need for hospital care is well documented. In the absence of data on the relative efficacy of treatment, it has been difficult to counter industry pressure to cut costs for treatment (Litt, 1995). Together these studies suggest that SSRI medications may be useful in improving outcome and preventing relapse of anorexic patients, but may only be effective after weight restoration. These data (Kaye et al., 1998) suggest that SSRI medication may prevent relapse in many women with AN after weight restoration. However, if patients with AN are not able to obtain the resources for weight restoration, they may not be able to take advantage of this treatment. These data argue that it is more cost

effective and humanistic to support adequate length of treatment early in this disorder, rather than pay for brief, but frequent, psychiatric and medical hospitalizations over the course of the illness.

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