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Psychotropic Medication Use in Anorexia Nervosa between 1997 and 2009

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Abstract

Objective—Despite a lack of data demonstrating benefit, psychotropic medications are frequently prescribed for patients with anorexia nervosa.

Method—We studied 525 women (18–54 years of age) with anorexia nervosa who presented to the Clinical Research Center at the Massachusetts General Hospital between January 1997–December 2009. For this analysis, participants were *a priori* divided into two groups based on date of presentation (group I: participants presenting between 1997–2002; group II: participants presenting between 2003–2009).

Results—Overall, 53% of participants reported current use of any psychotropic medication; 48.4% reported use of an antidepressant and 13% reported use of an antipsychotic. Twice as many participants in group II (18.5%) reported using atypical antipsychotics as compared to group I (8.9%) ($p=0.002$).

Discussion—A majority of participants with anorexia nervosa report using psychotropic medications despite lack of data supporting their efficacy. These data are concerning given the known adverse effects of these medications.

Anorexia nervosa, a psychiatric disorder characterized by extreme, self-induced weight-loss and fear of gaining weight, affects 0.5–1% of college-aged women in the US (1, 2). Anorexia nervosa is a chronic disease with long-term relapse rates approaching 50% (3, 4) and has the highest mortality rate of any psychiatric illness, with the risk of death approaching five to ten times that expected for an age-matched population (5–8). Therefore, effective treatments for this disease are of critical importance.

Potential treatment strategies for adult women with anorexia nervosa have included psychosocial treatments and psychopharmacologic therapies. The American Psychiatric Association guidelines currently recommend psychosocial therapies as first line treatment for adult women with anorexia nervosa, acknowledging that the data supporting specific

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therapeutic techniques are sparse (9). Psychopharmacologic therapies, particularly antidepressants and atypical antipsychotics, have been proposed for the treatment of anorexia nervosa, and randomized controlled trials have been conducted evaluating the efficacy of these medications in the treatment of anorexia nervosa and its co-morbidities.

Anti-depressants, particularly selective serotonin reuptake inhibitors (SSRIs), have not been found to be beneficial in the treatment of anorexia nervosa or in the treatment of women with anorexia nervosa and co-morbid depression (10, 11). As many individuals with anorexia nervosa experience symptoms of depression, anti-depressants have been an attractive potential pharmacologic therapy. Trials with older anti-depressant agents, such as tricyclics and monoamine oxidase inhibitors have demonstrated modest, if any, benefits in decreasing anorexic symptoms and increasing weight and their use is severely limited by adverse side-effects including postural hypotension, tachycardia and psychotic symptoms (12–15). Randomized, placebo-controlled studies with fluoxetine have shown little benefit either to acutely ill or weight-recovered women (16, 17) and SSRIs have also been associated with serious side-effects, including bone loss (18, 19) and an increased risk of fracture (20–22).

Antipsychotics have also been considered in the treatment of individuals with anorexia nervosa, as the distorted body image characteristic of anorexia nervosa can be considered a symptom of psychosis and weight-gain is a known side-effect of this class of medications. The use of first-generation, typical antipsychotics is complicated by potential serious adverse events, such as tardive dyskinesia. The newer, atypical antipsychotics are less likely to cause extrapyramidal side-effects but have other important side-effects including cardiovascular effects, hyperglycemia and hyperprolactinemia, which may be a mediator of bone loss in individuals using these medications (23, 24).

Randomized, placebo-controlled trials investigating the use of atypical antipsychotics for the treatment of anorexia nervosa (25–27) have not demonstrated definitive benefit. The trials have been relatively short in duration and it is unknown whether any appreciated benefits will persist. Although studies of 8–10 weeks duration demonstrated a benefit with respect to weight-gain in olanzapine-treated patients (26, 27), a longer-term randomized trial investigating the use of olanzapine for three months in women with anorexia nervosa did not find a difference in weight-gain between the olanzapine and placebo groups (25). Therefore, current data do not support the use of atypical antipsychotics in the treatment of anorexia nervosa.

We investigated the use of antidepressants, particularly SSRIs, and atypical antipsychotics from 1997–2009 in women with anorexia nervosa. We hypothesized that over the course of this 13-year period there would be a significant increase in both the use of these medications and in polypharmacy, despite the lack of evidence supporting psychopharmacologic treatment with antidepressants and atypical antipsychotics in patients with anorexia nervosa.

METHOD

Participants

539 women (18–54 years of age) completed a screening visit between January 1, 1997 and December 31, 2009 in the Neuroendocrine Unit at the Massachusetts General Hospital for studies involving bone density determinations in adult women with anorexia nervosa. Participants were recruited through referrals from local eating disorder providers and on-line advertisements. Four participant charts could not be located and these individuals were excluded from the analysis. As only participants who met DSM-IV weight and psychiatric criteria were included in the analysis, 10 women were excluded because they were greater

than 85% of ideal body weight (28, 29). Therefore, 525 participants were included in the final analysis (Figure 1). To investigate changes in medication use over this time period, participants were divided, *a priori*, into two groups based on their date of presentation. Group I consisted of participants who were screened between January 1997–December 2002 (n = 325) and group II consisted of participants screened between January 2003–December 2009 (n = 200).

The study was approved by the Partners Institutional Review Board and complied with the Health Insurance Portability and Accountability Act guidelines. Written informed consent was obtained from all participants.

Evaluation

All participants had a complete medical history and physical exam performed by a physician, physician's assistant or nurse practitioner at our Clinical Research Center. Data obtained at the visit included age of onset of anorexia nervosa, duration of illness and current medication use.

Of the 525 participants, 62 individuals who presented for an initial visit between 1997–2008 presented for a second screening visit at least one year after their initial visit. At the second visit, participants also had a complete medical history and physical exam performed and historical data, including current medication use, was again obtained.

Medication History

Medication history was subdivided into antidepressants, antipsychotics and other psychotropic medications. The antidepressants participants reported using included SSRIs (fluoxetine, sertraline, escitalopram, citalopram, fluvoxamine and paroxetine), serotonin-norepinephrine reuptake inhibitors (venlafaxine and duloxetine), tricyclic antidepressants (amitriptyline, clomipramine and nortriptyline), monoamine oxidase inhibitors (phenelzine and moclobemide) and other antidepressants (trazadone, nefazodone, bupropion and mirtazapine).

Participants reported using the following atypical antipsychotic medications: olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone. The only typical antipsychotic agent participants reported using was perphenazine (n=3). Participants also reported using other psychotropic medications including benzodiazepines (lorazepam, clonazepam, diazepam and alprazolam), buspirone, lithium, gabapentin, valproic acid, lamotrigine, phenytoin, oxcarbazepine, topiramate, methylphenidate, amphetamine and dextroamphetamine, modafinil, zolpidem and clonidine.

Anthropometric Measurements

Height was measured as the average of three readings on a single stadiometer. Elbow breadth was measured using calipers and compared to norms based on NHANES-I data (for estimation of frame size). Participants were weighed on an electronic scale while wearing a hospital gown. BMI was calculated using the formula [weight (kg)/height (meter²)] and percent ideal body weight was calculated based on 1983 Metropolitan Life Height and Weight Tables (29).

Statistical Methods

Two-sided independent sample t-tests, or if the distribution of data was non-normal, Wilcoxon's Rank Sum tests, were used to investigate between-group differences. The Fisher's exact test was used to compare between-group differences in proportions of

medication use. A p -value < 0.05 was considered statistically significant. Data are reported as mean $\pm$ SEM or percentages.

RESULTS

Patient Characteristics

Clinical characteristics of the study participants are presented in Table 1. There were no significant differences in age, years since diagnosis of anorexia nervosa and percent ideal body weight between participants in group I and group II.

Psychotropic medication use

Overall, 53% of participants reported current use of a psychotropic medication. A higher percentage of participants in group II (58.5%) reported psychotropic medication use as compared to group I (49.5%) ($p < 0.05$).

More participants in group II (30%) were taking two or more medications as compared to participants in group I (22.2%) ($p < 0.05$). More individuals in group II (19.5%) were also taking three or more psychotropic medications as compared group I (9.9%) ($p = 0.002$).

Antidepressant use

Overall, 48.4% of participants presenting between 1997–2009 reported current use of an antidepressant and of these, 82.7% reported use of an SSRI. 46.2% of participants in group I and 52% of participants in group II were taking an antidepressant at the time of their visit. There were no significant differences between group I and group II with respect to overall use of antidepressants.

Of the participants using antidepressants, 86.7% in group I and 76.9% in group II were using SSRIs. There were no significant differences in types of anti-depressants prescribed except for serotonin-norepinephrine reuptake inhibitors, which were more commonly used by participants in group II (19.2%) as compared to group I (8%) ($p = 0.01$).

Antipsychotic use

Overall, 13% of participants reported current use of an antipsychotic agent and of these, 97.1% reported use of an atypical antipsychotic. There were twice as many participants in group II (18.5%) taking atypical antipsychotics as compared to group I (8.9%) ($p = 0.002$) (Figure 2). Two participants in group I (0.6%) and one in group II (0.5%) reported using a typical antipsychotic.

The atypical antipsychotic most commonly reported by participants in group II was quetiapine with 59% of those reporting use of an atypical antipsychotic reporting use of this medication. Two participants in group I and three participants in group II reported taking two atypical antipsychotic medications concurrently. One individual in group II reported taking one atypical and one typical antipsychotic concurrently.

Changes in psychotropic medication use during follow-up

Sixty-two participants who presented for an initial visit between 1997–2008 presented for a second screening visit at least one year after their initial visit. Participants in this cohort were a mean of 27.6 ± 1.0 years old at the initial visit. A mean of 35.3 ± 3.3 months had elapsed between the initial visit and second visit. The mean percent ideal body weight was $76.6 \pm 0.8\%$ at the initial visit and $79.2 \pm 1.1\%$ at the second visit. Ten participants (16.1%) from this group reported atypical antipsychotic use at their initial visit. The mean change in percent ideal body weight between the initial visit and second visit of these 10 participants

($-0.7 \pm 3.4\%$) was similar to participants who were not on an atypical antipsychotic at their initial visit ($3.5 \pm 1.2\%$) ($p=0.28$).

Approximately 30.6% of participants were taking a greater number of psychotropic medications at their follow-up visit as compared to their initial visit. 85% of participants who were on no medications at their baseline visit remained off of all psychotropic medications at their follow-up visit (Table 2). Participants who were on no psychotropic medications at baseline were taking no more than one medication at the time of follow-up. 79% of participants who were on two or more psychotropic medications at baseline were on two or more medications at the follow-up visit and 55% of participants who were taking one psychotropic medication at baseline were taking two or more medications at follow-up (Table 2). As these longitudinal data are presented for a very small subset of the total participants (62 of 525 participants), they should be viewed simply as an illustrative example and concrete conclusions should not be drawn from this subset.

DISCUSSION

We have shown that the use of atypical antipsychotic medications and antidepressants in anorexia nervosa is common. The use of atypical antipsychotics has doubled over a span of 13 years and the number of women with this disorder taking psychotropic medications has increased significantly over this same time period. Despite more recent data reporting that antidepressant medications are not effective in the treatment of anorexia nervosa or in individuals with co-morbid psychopathology (10, 11), we have also shown that the use of antidepressants has remained stable over this 13-year period.

Anorexia nervosa affects 0.5–1% of college-aged women in the US and its incidence has been increasing (1, 2). Anorexia nervosa is a chronic illness with long-term relapse rates approaching 50% (3, 4) and has the highest mortality rate of any psychiatric disorder (5–8). Individuals with this disorder typically display symptoms of depression, obsessive-compulsive behavior and their distorted body image may be considered a symptom of psychosis. Therefore, medications that treat these symptoms in other populations have been prescribed for individuals with anorexia nervosa.

Few randomized, placebo-controlled studies investigating the use of psychopharmacologic agents in anorexia nervosa have been completed. Anorexia nervosa treatment studies are difficult to perform and complete due to high drop-out rates. While early case reports, open-label studies, and non-randomized studies suggested a potential benefit of the use of SSRIs in the treatment of anorexia nervosa (30–37), a randomized, placebo-controlled study of the use of fluoxetine for 7-weeks during inpatient treatment failed to show benefit as compared with placebo (16).

Similarly, randomized, placebo-controlled trials investigating the use of atypical antipsychotics for the treatment of anorexia nervosa (25–27) have not demonstrated definitive benefit. Whereas two shorter-term studies demonstrated a benefit in weight gain with olanzapine after 8–10-weeks (26, 27), a longer-term trial did not demonstrate any difference in weight gain between the olanzapine and placebo groups after three months of treatment (25). Although benefits with respect to psychological symptoms in the group receiving olanzapine were found, these results are in a small group of participants and larger, long-term studies will be needed to determine if there is truly any benefit to these medications and whether these effects persist over time. Therefore, at the present time there is no conclusive evidence that atypical antipsychotics have any benefit in the treatment of anorexia nervosa.

Our data demonstrate that despite published data, these medications continue to be commonly used in anorexia nervosa and the use of atypical antipsychotics has doubled. These data are concerning because of the potential adverse effects of these medications. Side-effects of atypical antipsychotics include hyperglycemia, hyperlipidemia, cardiovascular effects, hyperprolactinemia and neuroleptic malignant syndrome. Side-effects of SSRIs include headache, nausea and importantly both SSRIs and atypical antipsychotics may negatively impact bone health and increase fracture risk. Use of SSRIs has been shown to be associated with bone loss (18, 19) and a two-fold increased risk of fracture in older adults (20–22). The mechanism of bone loss is thought to be due to the antagonistic effects of SSRIs on the serotonin (5– hydroxytryptamine) transporter, as mouse models demonstrate decreased bone mineral accrual in mice lacking this transporter and in mice treated with SSRIs (22, 38). Similarly, atypical antipsychotic agents may also affect bone mineral density. Hyperprolactinemia, a side-effect commonly associated with typical antipsychotic agents and the atypical antipsychotic, risperidone, causes suppression of the hypothalamic-pituitary-ovarian axis which results in hypoestrogenemia and subsequent bone loss. While risperidone is the atypical antipsychotic most commonly associated with hyperprolactinemia, a number of other atypical antipsychotics, including quetiapine (39) and ziprasidone (40) have also been associated with increased prolactin levels and atypical antipsychotic agents have been associated with decreased bone mineral density in both postmenopausal women (24) and in premenopausal women with schizophrenia (23).

Women with anorexia nervosa are at risk for severe bone loss. Nearly ninety percent of women with anorexia nervosa have some degree of bone loss (41) with 30% meeting WHO criteria for osteoporosis (41). Thirty percent of women with anorexia nervosa also have a history of fracture (41) and the fracture rate in women with anorexia nervosa is seven-times greater than that of age-matched controls (42). Therefore, medications which may have a negative impact on bone health should be avoided in this population.

Rapid weight-gain is also a known side-effect of atypical antipsychotics (43) and is thought to be a potentially beneficial effect in anorexia nervosa. Studies suggest that the weight-gain associated with atypical antipsychotic medication use is due to increases in both visceral and subcutaneous fat (44, 45). Visceral fat has recently been associated with decreased bone mineral density (46, 47) and therefore may be a potential mediator of the decreased bone density seen in individuals on atypical antipsychotics. Furthermore, whether this rapid weight-gain would in fact be beneficial to women with anorexia nervosa, or whether it may be detrimental to the psychological state of these women and potentially lead to relapse, is currently unknown.

The limitations of our study include the fact that our participants were women presenting to a clinical research center for a research study and therefore may not be representative of all women with anorexia nervosa. However, our group of patients is drawn from a large number of community-based practitioners and is representative of participants receiving treatment for anorexia nervosa. Another limitation of our study is the fact that medication use was self-reported by participants. We believe that this likely underestimates the number of medications prescribed for this group of women, as participants may not report medications they have been prescribed. Therefore, it is likely that more psychotropic medications are being prescribed for the treatment of anorexia nervosa than our data reflect.

We have demonstrated that 48.4% of women with anorexia nervosa report the use of antidepressants and 13% report the use of antipsychotics between 1997 and 2009. While the use of antidepressants has remained stable over the 13 year period, the rate of atypical antipsychotic use has doubled over this time period despite the fact that these medications have not been shown to be efficacious in anorexia nervosa and may have significant

negative consequences on the bone health of this population. Longer-term studies investigating the use of these medications are needed to evaluate the efficacy and benefit of these medications prior to their continued wide-spread use.

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Figure 1.
Flow diagram of participants included in the analysis.

Figure 2.

Twice as many participants in Group II (18.5%) reported use of atypical antipsychotics as compared to Group I (8.9%) (* $p=0.002$).

Table 1

Baseline characteristics of study participants (n=525)

	All participants (n=525)	Group I (n=325)	Group II (n=200)
Year of presentation for screening visit	1997–2009	1997–2002	2003–2009
Age (years)	25.5 ± 0.3	25.5 ± 0.4	25.4 ± 0.5
Years since diagnosis	5.4 ± 0.3	5.6 ± 0.4	5.2 ± 0.5
% ideal body weight	76.9 ± 0.3	76.5 ± 0.4	77.6 ± 0.4

Table 2

Percentage of participants on 0, 1, or 2 medications at follow-up visit as compared to baseline visit

Psychotropic medication use		Follow-up visit		
		0 medications	1 medication	2medications
Baseline	0 medications	85%	15%	0%
	1 medication	18%	27%	55%
	2 medications	8%	13%	79%