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Relationship Between Obesity and Depression: Characteristics and Treatment Outcomes with Antidepressant Medication

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Abstract

Objective—Obesity and Major Depressive Disorder (MDD) often co-occur. However, differences between obese and normal-weight depressed patients and the moderating effect of obesity on antidepressant treatment outcome have not been well studied.

Methods—662 subjects in the COmbining Medications to Enhance Depression Outcomes (COMED) were randomized to treatment with escitalopram plus placebo, bupropion plus escitalopram, or venlafaxine plus mirtazapine for a 12 week primary treatment phase and 16 week follow-up. Body Mass Index (BMI) was calculated at baseline. Subjects were divided into BMI classes according to World Health Organization criteria: 1) normal (and low) weight (NW), 2) overweight (OW), 3) obese I (OB1) and 4) obese II+ (OB2). Clinical characteristics were compared using Chi-squared or Kruskal-Wallis testing. Outcomes were assessed using a repeated effects model, unadjusted and adjusted for baseline variables differing across BMI classes.

Results—31.4% of the subjects were normal weight; 46.2% were obese. Higher BMI was associated with greater medical illness ($p < 0.001$), social phobia ($p = 0.003$) and bulimia ($p = 0.026$). Lower BMI was associated with higher rates of Post Traumatic Stress Disorder ($p = 0.002$) and drug abuse. Treatment outcomes, including remission, did not differ across classes. However, lower BMI was associated with more frequent ($p = 0.024$, unadjusted, 0.053 adjusted) and more severe ($p = 0.008$ unadjusted, 0.053 adjusted) side effects.

Conclusions—We found a high rate of obesity compared to the general population and significant differences in presentation and comorbidity, but not medication use and antidepressant outcomes, in subjects across BMI classes. Lower BMI classes had higher rates of comorbidities associated with poor outcome, which may have obscured outcome differences.

Trial Registration—clinicaltrials.gov Identifier: NCT 00270647

Keywords

Depression; Obesity; Treatment Resistance

Background

The life-time prevalence of major depressive disorder (MDD) is 16.2% in the general United States population (1). Perhaps unsurprisingly, as new medications have become available, antidepressant prescriptions doubled in the United States between 1996 and 2005 (2). Despite the increased use of antidepressants, depression continues to be a major public health problem: only 30% of patients remit with initial treatment (3), and 30% of patients completely fail to respond (4). While poor treatment response has been shown to be associated with comorbid psychiatric conditions such as anxiety disorders, substance use disorders, comorbid general medical illnesses or undiagnosed psychosis or bipolar disorder, little is known about the impact of comorbid obesity on illness characteristics and treatment outcome of MDD (5).

Identifying risk factors for Treatment Resistant Depression (TRD) is extremely important since unresolved MDD is associated with tremendous morbidity and increases the cost of both medical and psychiatric care. Obesity has been proposed as a risk factor for depression and may contribute to treatment resistance (6). Like depression, obesity is a common syndrome (7) caused by a complex combination of environment, behavior, and underlying genetic and epigenetic susceptibility (8). It is also associated with tremendous medical morbidity. The relationship between obesity and MDD is often viewed as bi-directional with each condition increasing the risk of developing the other. In many studies there is a positive linear relationship between BMI and depression prevalence (9, 10). In others, there is a U-shaped relationship in which there are increased rates of depression in those who are underweight and those who are obese (11, 12). However, not all studies have found that the increase in risk is bidirectional - some show that obese patients are twice as likely to be depressed, but the converse is not true (13). Interestingly, some authors found that those who have more severe depression, tend to lose weight if they are lean at baseline, but gain weight if initially overweight (11, 14). This suggests that obesity associated MDD may be a specific subtype. On the other hand, these patients also tend to be more physically inactive and have increased caloric intake, which implies this association may not be mechanistically related to obesity (9, 15).

The COmbining Medications to Enhance Depression Outcomes (COMED) study followed a cohort of depressed patients to determine the difference in outcome between antidepressant combination therapy and monotherapy plus placebo in a 12-week primary treatment phase with a subsequent 16 week continuation phase (16). This randomized multi-center trial included adults aged 18–75, and who had chronic and/or recurrent depression. Based on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) finding that remission was achieved in an additional group of subjects in step two using combination therapy, COMED was designed to determine whether early addition of a second antidepressant could produce a higher remission rate in one step. However, COMED found that early combination antidepressant therapy did not have an advantage over SSRI monotherapy (16).

To our knowledge, no published analyses directly address the relationship between BMI and antidepressant treatment outcome. In addition, most studies examining depression and BMI have been cross sectional and often used depression screening assessment scores in lieu of diagnostic assessment because MDD was not a primary focus of the study. In this manuscript we examine whether those with obesity and depression have differences in clinical profile and history from those with depression alone. We also examine whether outcomes differ across BMI classes.

Methods

COMED was designed to naturalistically compare antidepressant combinations to a single SSRI given with placebo. The study was composed of a 12 week primary treatment phase and a 16 week continuation phase for a total duration of 28 weeks. Subjects initially received open label primary medication and followed by single blinded secondary medication versus placebo. A complete description of the design and outcomes of the COMED study is available elsewhere (16). The COMED protocol was approved by the Institutional Review Boards at UTSW (the national coordinating center), the University of Pittsburgh (the data coordinating center) and of each regional center and clinical site participating in the study.

Subjects

Subjects (N=662) were adults, age 18–75 with chronic or recurrent MDD who had a screening score of at least 16 on the 17-item version of the Hamilton Rating Scale for Depression (HRSD-17) of at least 16. Potential subjects were identified at each site using site specific screening – usually a brief rating scale or via clinician interview – before being referred for further study specific screening with study personnel. At study screen, MDD diagnosis was confirmed using the Mini International Neuropsychiatric Interview (MINI). Subjects were recruited from both primary care and psychiatric specialty sites from March 2008 to September 2009. Those with any history of Mania or Psychosis were excluded but those with secondary comorbid anxiety were included. Comorbid substance use disorders were allowed as long as the acuity at the time of enrollment was low as determined by a study clinician. Complete entry criteria are available at: <http://clinicaltrials.gov/ct2/show/NCT00590863>. All subjects provided written informed consent at the time of study entry.

Study Procedures

Subjects were assessed at baseline and weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, and 28. Subjects were given the primary, open label, medication at baseline and dose adjustments were made based on scores on the Quick Inventory of Depressive Symptomatology – Clinician Version (QIDS-C), as long as side effects were acceptable. Secondary medications were begun at week 2, and were blinded only to subjects. Clinicians, therefore, were free to make appropriate dose adjustments of either medication. Progression to the 16 week follow-up phase was determined by response or remission on the QIDS-C as well as tolerance to medications, with clinician discretion to continue subjects who did not meet formal definitions, but, in the clinician's view, had clinically meaningful response.

Assessments

Baseline assessments included socio-demographic data collection, the HRSD-17, the Psychiatric Diagnostic Screening Questionnaire (PDSQ), and the Self-Administered Comorbidity Questionnaire (SCQ). At baseline we determined anxious features based on the HRSD-17 anxiety subscale (17), and used IDS-C subscales to assess melancholic features (18), atypical features (19) and, sleep disturbance (early, middle, late insomnia or hypersomnia). Substance use diagnosis was determined using the MINI at baseline; clinician interview determined the last period of active use, and if any current use was considered clinically significant. At each study visit, the Quick Inventory of Depressive Symptomatology was administered by the clinician (QIDS-C) and completed by the subject in the self rated (QIDS-SR) form.

The primary outcome instrument was the QIDS-SR, with remission defined using the last two consecutive scores available for each subject. One score had to be less than six and the other less than 8. Response was defined as a drop in QIDS-SR scores of 50%. Additional

assessments included the Altman Self Rated Mania Scale (ASRMS), the Concise Associated Symptoms Tracking Scale (CAST), which measures suicide associated activation symptoms, the Concise Health Risk Tracking Scale (CHRT), which measures suicidal thinking and behavior, the Frequency, Intensity and Burden of Side Effects Scale (FIBSER), and the Systematic Assessment for Treatment Emergent Events (SAFTEE). These measures were included primarily for monitoring subject safety during the study and were also used as secondary outcomes. Additionally the the Quality of Life Inventory (QOLI), and the Work and Social Adjustment Scale (WSAS) were used as secondary outcomes of global function. Height in inches and weight in pounds were measured at baseline using by study personnel. Values were converted to centimeters and kilograms, respectively and BMI was calculated using the formula $BMI = (\text{weight})/(\text{height})^2$.

Statistics

Subjects were divided into normal or underweight (BMI <25), over-weight (BMI 25–29), obese I (BMI 30–34) and obese II+ (BMI ≥ 35) classes (20) for the analysis. Baseline clinical and sociodemographic variables across BMI groups were compared using χ^2 tests, or Kruskal-Wallis tests for continuous variables. For some variables, such as blood pressure, we used ANOVA to determine differences between the distributions of the variable across groups. Similarly, χ^2 tests, ANOVA or Kruskal-Wallis tests for continuous variables were also used to compare BMI classes across baseline or week 12 assessment scores. For analysis of longitudinal outcomes, a repeated effects model was used. We performed an unadjusted analysis, as well as one which adjusted for variables differing between groups: treatment, systolic BP, pulse, PDSQ PTSD and substance use, number of SCQ health problems, clinical setting, and atypical features. These variables were chosen by a step-wise model which selected, from the entire list of subject characteristics, variables which independently associated with BMI class. We used a significance threshold of $\alpha=0.05$.

Results

For the sample of 662 COMED subjects 23.9% were of normal weight, 28.2% were overweight, 20.1% were obese I and 26.1% were obese II or greater. Only 11 (1.6%) of the subjects were underweight, so they were included with the normal weight group in further analyses. The overall rate of obesity was 46.2% and that of at least overweight was 74.5%.

Sociodemographic Characteristics

The normal weight group was significantly younger, with mean age of 38.6 ± 12.8 ($p<0.001$). While each weight group, like the entire sample, contained more women than men, in the obese II+ group, women made up a greater percentage (75.7%) than in the other groups ($p=0.014$). There was no significant difference in distribution across the weight groups by race (e.g. each weight category was about 70% Caucasian), but there was a higher proportion of subjects identifying as Hispanic in the obese I range than in the other weight groups ($p=0.028$). There were no differences across weight category in employment or household income but the lower BMI classes had more years of education on average than the obese classes ($p=0.024$). Additionally, clinical setting varied with BMI, with increasing proportions of subjects presenting to primary care as BMI class increased ($p<0.001$). These results are shown in Table 1.

Illness Characteristics

Lifetime depression characteristics by BMI class are included in Table 2. Age at first episode and illness duration (in years) differed significantly (both, $p=0.043$). No other variable comparing depression history differed across weight class, including young age (<18) at first episode, number of past episodes, lifetime incidence or severity of suicidal

behavior. There were no differences in rates of chronic versus recurrent depression, in percent who reported a current episode length of more than two years, or in the length in months of the current episode. There were no differences in abuse or neglect history. All BMI classes reported similar numbers of past antidepressant trials.

Baseline clinical characteristic of the current episode are shown in Table 3. At baseline there were no differences by BMI class in the prevalence of lethargic depression, anxious features, sleep disturbance, or in suicidal thoughts/plans on the CHRT. Subjects reported increasing rates of atypical features as BMI class increased ($p=0.037$), but decreasing rates of melancholic features ($p=0.028$). Baseline depression severity was similar regardless of instrument (HRSD, IDS-C, IDS-SR, or QIDS-SR) as were scores on the ASRMS, CPFQ, QOLI and WSAS. Scores on the CHRT and CAST were similar as well, except that lower BMI classes tended to report more anxiety on the CAST ($p=0.002$) and higher overall suicidal ideation on the CHRT ($p=0.028$).

Medical and Psychiatric Comorbidities

Comparisons of psychiatric and medical comorbidity rates across BMI classes are reported in Table 4. On the PDSQ, the number of subjects reporting Bulimia ($p=0.026$) and Social Phobia ($p=0.003$) increased as BMI class increased. On the other hand, more subjects reported Substance Abuse ($p=0.014$), and specifically Drug Abuse ($p<0.001$), and Post Traumatic Stress Disorder (PTSD) ($p=0.002$) in lower BMI classes. Overall, subjects at the highest and lowest BMI classes reported more comorbid psychiatric illnesses on the PDSQ than the middle classes ($p=0.025$).

Systolic and diastolic blood pressure increased with BMI class (both, $p<0.001$). Pulse similarly increased with BMI class ($p<0.001$). Score on the SCQ also increased across BMI classes, as did number of health problems under treatment by a physician (both, $p<0.001$). Although there were no differences in reported back pain or neurological illness (e.g. stroke), higher BMI classes reported greater rates of diabetes ($p<0.001$) and heart disease ($p=0.025$). Number of concomitant medications increased significantly as BMI class increased ($p<0.001$).

Treatment Outcomes

Table 5 shows the results of the model for treatment outcomes. At week 12 there were no significant differences between BMI classes in overall outcome, measured by remission (last two QIDS-SR; one <6 the other <8), percent with last QIDS-SR <6 , or response ($>50\%$ decrease in QIDS-SR score). However, over the 12 week primary treatment phase, significantly more frequent ($p=0.024$), more severe ($p=0.008$), and more burdensome ($p=0.042$) side effects, were reported in the FIBSER as baseline BMI class decreased – i.e. the highest rates were reported by the low/normal BMI class. The week 12 scores for frequency ($p=0.026$), intensity ($p=0.041$), and burden ($p=0.002$) of side effects were also greater in lower BMI classes. However, when the model was adjusted, these differences lost significance. At week 12, there were no differences in adverse events, response, remission, final score on the QIDS-SR, WSAS or QOLI. There was no difference in the level of anxiety reported at week 12 on the IDS-C anxiety subscale.

At week 28, results of the model were similar those at week 12 (Table 6). While there were no differences in depression outcome, functional measures, or adverse events, lower BMI was associated with significantly more frequent ($p=0.004$), and more intense ($p=0.010$) side effects over the 28 week study period. Final (week 28) side effects were also significantly greater in frequency ($p<0.001$), intensity ($p<0.001$), and burden ($p=0.002$) as in subjects with lower BMI class. At 28 weeks, most of these differences remained significant after

adjustment (maximum frequency, $p=0.009$, week 28 frequency $p=0.009$, intensity, $p=0.010$, and burden, $p=0.017$), while maximum intensity lost significance ($p=0.056$). The model examining BMI by treatment group effects showed no significant differences in any outcome for any group at week 12 or week 28 (not shown).

At week 12 treatment course of subjects across BMI class was nearly identical, and did not differ in the proportion of subjects who remained in the study, the total weeks participating, or the number of post baseline visits. Other than a significant difference in the time spent on the final prescribed dose of escitalopram ($p=0.024$) there were no differences in doses of medication prescribed or in how long subjects remained on a stable medication dose across BMI class in any study arm. These results can be found in supplemental Table S1. At week 28 there were no differences in any of these aspects of study participation across BMI class (not shown).

Discussion

This analysis found a much higher rate of obesity in depressed subjects than is found in the general US population: approximately 45% compared to about 35% (7). We also found clinical differences, particularly in psychiatric comorbidity, across BMI classes. Higher BMI was associated with older age, less education and greater prevalence of comorbid medical illness. While all BMI classes had similar longitudinal depression histories, clinical MDD subtypes unsurprisingly varied with BMI, with melancholic features more common in low BMI subjects, and atypical features in high, consistent with the diagnostic criteria for decreased and increased appetite, respectively, for these subtypes. This result is intriguing and suggests that in treatment of patients with melancholic and atypical depression clinicians should consider associated changes in weight, if only to target increased appetite in atypical patients to prevent weight gain. However, outcome of depression treatment, whether measured as remission or response did not depend on BMI in this sample. On the other hand, side effects consistently were reported as less prevalent and severe as BMI class increased.

The differences found in comorbidities were in general, not surprising; since that at least certain kinds of drug use (e.g. stimulants) are expected to be associated with lower weight, although findings in the literature between drug abuse/dependence and BMI have varied greatly (21–23) It is also reasonable that bulimia (associated with binge eating) is correlated with higher BMI class. On the other hand, our finding that PTSD is associated with lower BMI classes is somewhat unusual. Some studies in veterans with combat PTSD have shown no relationship between BMI and PTSD (24), and many in those with childhood trauma have shown a positive association (25, 26), especially in women. Shame and concern related to overweight has been shown to be similar to other kinds of social anxiety (27), and may explain the greater rates we found in the higher BMI classes in COMED.

The only outcome related finding that resulted from this analysis is that lower BMI class was associated with increased side effects. Although lower BMI was not associated with increased scores for somatization disorders on the PDSQ, it is possible an increased level of somatic symptoms in lower BMI classes could account for the result. It would also make sense if, because number of medications increased with BMI, that lower weight classes were more likely to notice side effects and attribute them to study medication. Additionally, lower body mass may have lead to higher serum concentration of some of the drugs used, which could in turn result in more side effects, especially given the relatively high doses of drug used in COMED.

There are several factors that may have limited our ability to find an effect of BMI on response and remission. First, higher rates PTSD in the low BMI class may have lowered remission rates in that group, since it is associated with poor outcome of depression treatment (28). In addition we are using BMI as a marker of metabolic dysfunction and inflammation. However, it has been suggested that BMI is not ideally suited to this use (29). More comprehensive data collection of waist circumference, lipids, and possibly inflammatory markers such as C-Reactive Protein would provide a better window into the relationship between treatment resistance and metabolic dysfunction. In addition, although we hypothesize a subtype whose treatment resistance is related to metabolic dysfunction this does not mean that all of those with depression and obesity would fall into this subtype, depending on how these groups overlap we may expect not to find an effect using BMI alone. Finally, our sample was considerably more obese than the general population, and contained a relatively small fraction of those of normal weight. Combined with the use of three treatment arms, each assigned treatments which may have acted differently across BMI groups, we may have lacked power to detect differences across subgroups.

This study highlights the need for further work examining the role of metabolic dysfunction in MDD treatment. While many studies have examined the relationship between weight and mood from an epidemiological perspective in the general population, there is a deficit of information about the role overweight and obesity play in the course of depression. If the high rates of overweight and obesity in our sample are typical of the depressed population, understanding this relationship becomes even more critical. We do not know which clinical or biological markers may be of the most use in identifying this putative subtype of metabolic depression. Secondly, we do not know how this group differs from other depression patients in terms of illness severity, symptom profile, or outcomes. Lastly, it is likely that different treatment options – some perhaps targeting metabolic dysfunction directly – will have superior outcomes in this group. A few small trials of anti-inflammatory agents are beginning to address these questions but much more work remains.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

MDD	Major Depressive Disorder
COMED	Combining Medications to Enhance Depression Outcomes
BMI	Body Mass Index
TRD	Treatment Resistant Depression
SSRI	Selective Serotonin Reuptake Inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
HDRS	Hamilton Rating Scale for Depression
QIDS-C	Quick Inventory of Depression Symptomatology – Clinician Rated
QIDS-SR	Quick Inventory of Depression Symptomatology – Self Rated
PDSQ	Psychiatric Diagnostic Screening Questionnaire

SCQ	Self-Administered Comorbidity Questionnaire
ASRMS	Altman Self Rated Mania Scale
CAST	Concise Associated Symptoms Tracking Scale (CAST)
CHRT	Concise Health Risk Tracking Scale
FIBSER	Frequency, Intensity and Burden of Side Effects Scale
QOLI	Quality of Life Inventory
SAFTEE	Systematic Assessment for Treatment Emergent Events
WSAS	Work and Social Adjustment Scale
PTSD	Post Traumatic Stress Disorder

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Table 1

Sociodemographic Characteristics of the Sample by BMI Class

	NW	OW	OBI	OB2+	Test	p	NWvOW	NWvOBI	NWvOB2	OWvOBI	OWvOB2	OBIvOB2
Age	38.6±12.8	44.6±13.0	44.4±12.8	43.3±12.7	F(3,658)=7.95	<0.001	<.001*	<.0001*	<.0001*	0.87	0.33	0.47
Sex					X ² (3)=10.63	0.014	0.11	0.73	0.11	0.065	0.001	0.26
Male	54(32.0)	75(40.1)	40(30.1)	42(24.3)								
Female	115(68.0)	112(59.9)	93(69.9)	131(75.7)								
Race					X ² (6)=3.85	0.70						
White	114(69.5)	121(66.9)	88(68.8)	105(62.9)								
Black	38(23.2)	49(27.1)	34(26.6)	53(31.7)								
Other	12(7.3)	11(6.1)	6(4.7)	9(5.4)								
Hispanic	19(11.2)	26(13.9)	31(23.3)	25(14.5)	X ² (3)=9.13	0.028	0.45	0.005	0.38	0.030	0.88	0.047
Employed	76(45.0)	102(54.5)	67(50.4)	85(49.1)	X ² (3)=3.31	0.35						
Education	14.1±2.9	14.1±3.1	13.4±2.7	13.3±2.9	F(3,634)=3.17	0.024	0.88	0.046	0.04	0.071	0.022	0.71
Income	2643±4215	2320±3115	2326±2778	3324±8569	X ² (3)=2.52	0.47						
Care Setting					X ² (3)=29.97	<0.001	0.007	<.0001*	<.0001*	0.060	0.015	0.71
Primary	61(36.1)	94(50.3)	81(60.9)	109(63.0)								
Specialty	108(63.9)	93(49.7)	52(39.1)	64(37.0)								

NOTE Chi-square for continuous measures indicates Kruskal-Wallis test.

* Significant after Bonferroni correction (p<.0083).

Table 2

Depression Characteristics by BMI Class

	NW	OW	OBI	OB2+	Test	p	NWvOW	NWvOBI	NWvOB2	OWvOBI	OWvOB2	OBIvOB2
Age 1 st Episode	21.4±12.4	26.8±15.6	23.4±13.3	24.0±14.1	X ² (3)=8.13	0.043	0.004 [*]	0.29	0.19	0.13	0.14	0.88
1 st Episode <18yrs	83(49.4)	73(39.0)	62(47.0)	77(44.5)	X ² (3)=4.21	0.24						
Years of Illness	17.1±13.0	17.8±13.9	21.1±14.4	19.3±13.1	X ² (3)=8.18	0.043	0.89	0.017	0.087	0.023	0.14	0.36
N Past Episodes	8.1±18.8	9.1±20.6	9.9±20.7	8.6±18.8	X ² (3)=3.76	0.29						
N Past ADs	1.5±1.7	1.5±1.9	1.5±1.5	1.6±1.6	X ² (3)=2.35	0.50						
Lifetime Suicidality					(P)<0.01	0.17						
None	51(31.5)	55(30.9)	38(29.2)	54(31.8)								
Thoughts of Death	40(24.7)	54(30.3)	27(20.8)	55(32.4)								
Thoughts of Suicide	20(12.3)	32(18.0)	21(16.2)	24(14.1)								
Thoughts of Method	20(12.3)	9(5.1)	16(12.3)	13(7.6)								
Made Plan/Gesture	8(4.9)	13(7.3)	11(8.5)	6(3.5)								
Preparation	6(3.7)	1(0.6)	4(3.1)	3(1.8)								
Attempt	17(10.5)	14(7.9)	13(10.0)	15(8.8)								
N Suicide Attempts	0.22±0.80	0.20±1.21	0.17±0.59	0.35±2.06	X ² (3)=0.81	0.85						
Neglect ^{**}	71(42.3)	67(35.8)	45(33.8)	56(32.4)	X ² (3)=4.11	0.25						
Any Abuse ^{**}	87(52.1)	83(44.4)	57(42.9)	82(47.4)	X ² (3)=3.17	0.37						
Emotional Abuse ^{**}	75(44.6)	71(38.0)	51(38.3)	63(36.4)	X ² (3)=2.80	0.42						
Physical Abuse ^{**}	41(24.4)	38(20.3)	22(16.5)	29(16.8)	X ² (3)=4.18	0.24						
Sexual Abuse ^{**}	29(17.4)	39(20.9)	29(21.8)	47(27.2)	X ² (3)=4.95	0.18						

NOTE Chi-square for continuous measures indicates Kruskal-Wallis test.

^{*} Significant after Bonferroni correction (p<.0083).

^{**} Abuse and neglect are reported for childhood, age <18 years at the time of the abuse.

Table 3

Baseline Variables by BMI Class.

	NW	OW	OBI	OB2+	Test	P	NW<OW	NW<OBI	NW<OB2	OW<OBI	OW<OB2	OBI<OB2
Episode Months	62.0±104	53.2±83.6	70.5±124	64.6±110	X ² (3)=0.08	0.99						
Episode >2yrs	91(54.2)	104(55.6)	75(56.8)	96(55.5)	X ² (3)=0.21	0.98						
Course					X ² (6)=5.41	0.49						
Chronic	39(23.2)	49(26.2)	26(19.7)	32(18.5)								
Recurrent	77(45.8)	83(44.4)	57(43.2)	77(44.5)								
Both	52(31.0)	55(29.4)	49(37.1)	64(37.0)								
IDS-C Lethargy	107(63.3)	120(64.2)	96(72.2)	127(73.4)	X ² (3)=6.36	0.10						
Anxious Features	136(80.5)	140(74.9)	91(68.4)	128(74.0)	X ² (3)=5.81	0.12						
Atypical Features	20(11.8)	22(11.8)	28(21.1)	33(19.1)	X ² (3)=8.52	0.037	0.98	0.030	0.064	0.024	0.054	0.67
Melancholic Features	42(26.9)	38(22.8)	16(13.2)	28(17.7)	X ² (3)=9.11	0.028	0.39	0.005*	0.054	0.041	0.26	0.31
IDS-C Disturb. Sleep	148(87.6)	167(89.3)	113(85.0)	156(90.2)	X ² (3)=2.27	0.52						
N Concom Meds	2.2±1.8	2.8±2.3	3.5±3.4	3.7±3.3	X ² (3)=26.79	<0.001	<0.001*	<0.001*	<0.001*	0.21	0.012	0.31
HDRS ₁₇	24.5±5.5	23.6±4.8	23.3±4.3	23.9±4.4	F(3,656)=1.69	0.17						
IDS-C	38.4±9.5	37.5±8.5	37.3±9.1	38.6±9.3	F(3,658)=0.82	0.48						
QIDS-C	15.6±3.7	15.8±3.2	15.7±3.3	16.1±3.6	F(3,658)=0.71	0.55						
QIDS-SR	15.7±4.5	15.5±4.0	15.0±4.4	15.5±4.2	F(3,639)=0.72	0.54						
ASRMS	1.6±2.1	1.5±2.2	1.4±2.1	1.7±2.7	X ² (3)=1.36	0.71						
CAST												
Irritability	12.7±3.8	12.1±4.0	12.0±3.7	12.5±3.6	F(3,657)=1.24	0.29						
Anxiety	6.9±3.0	6.3±2.9	5.7±3.0	6.0±2.9	X ² (3)=14.45	0.002	0.030	<0.001*	0.003*	0.086	0.34	0.39
Mania	3.6±3.0	3.3±2.6	4.0±2.8	3.7±2.8	X ² (3)=4.56	0.21						
Insomnia	5.1±2.5	5.0±2.4	4.9±2.2	5.3±2.2	F(3,657)=1.03	0.38						
Panic	3.0±2.2	2.4±2.2	2.6±2.2	2.6±2.2	X ² (3)=8.35	0.039	0.006*	0.16	0.049	0.23	0.33	0.67
CHRT												
Loneliness	3.3±2.0	3.5±2.1	3.3±2.1	3.4±1.9	F(3,657)=0.54	0.66						
Despair	4.5±2.2	4.3±2.2	4.1±2.3	4.5±2.2	F(3,658)=1.12	0.34						
Ideation	2.5±2.9	2.1±2.7	2.2±2.8	1.6±2.2	X ² (3)=9.12	0.028	0.12	0.19	0.002*	0.91	0.14	0.15

	NW	OW	OB1	OB2+	Test	p	NWvOW	NWvOB1	NWvOB2	OWvOB1	OWvOB2	OB1vOB2
Thoughts/Plans	36(21.3)	29(15.5)	24(18.0)	20(11.6)	$\chi^2(3)=6.27$	0.10						
CPFQ	28.2±5.9	27.7±5.8	27.3±6.1	27.2±5.6	$F(3,658)=0.92$	0.43						
QOLI	-1.4±1.8	-1.1±1.9	-1.0±2.0	-1.2±1.9	$F(3,654)=1.67$	0.17						
WSAS	27.5±8.8	26.8±9.0	25.7±9.3	27.3±8.3	$\chi^2(3)=2.51$	0.47						

NOTE: Chi-square for continuous measures indicates Kruskal-Wallis test.

* Significant after Bonferroni correction ($p < .0083$).

TABLE 4

PSYCHIATRIC AND MEDICAL COMORBIDITIES BY BMI CLASS

	NW	OW	OBI	OB2+	TEST	P	NWVOW	NWVOB1	NWVOB2	OWVOB1	OWVOB2	OBIVOB2
N PDSQ DISORDERS					X ² (12)=23.31	0.025	0.04	0.008*	0.61	0.23	0.09	0.07
0	59(35.1)	96(51.3)	71(53.4)	69(39.9)								
1	46(27.4)	42(22.5)	27(20.3)	43(24.9)								
2	27(16.1)	20(10.7)	20(15.0)	24(13.9)								
3	13(7.7)	9(4.8)	9(6.8)	19(11.0)								
4+	23(13.7)	20(10.7)	6(4.5)	18(10.4)								
PDSQ												
AGORAPHOBIA	21(12.4)	18(9.6)	10(7.5)	20(11.6)	X ² (3)=2.29	0.51						
ALCOHOL ABUSE	23(13.7)	21(11.2)	11(8.3)	11(6.4)	X ² (3)=5.86	0.12						
BULIMIA	10(5.9)	22(11.8)	18(13.5)	28(16.2)	X ² (3)=9.21	0.027	0.054	0.024	0.003*	0.64	0.23	0.52
DRUG ABUSE	18(10.7)	12(6.4)	2(1.5)	3(1.7)	X ² (3)=18.35	<0.001	0.15	0.002*	0.001*	0.034	0.26	1.00
GEN. ANXIETY D/O	43(25.4)	30(16.0)	20(15.0)	38(22.0)	X ² (3)=7.47	0.058						
HYPOCHONDRIASIS	9(5.3)	9(4.8)	6(4.5)	5(2.9)	X ² (3)=1.37	0.71						
OBESS-COMP D/O	22(13.0)	23(12.3)	11(8.3)	23(13.3)	X ² (3)=2.22	0.53						
PANIC DISORDER	21(12.4)	15(8.0)	11(8.3)	18(10.4)	X ² (3)=2.41	0.49						
POST-TRAUM STRESS	31(18.3)	27(14.4)	6(4.5)	17(9.8)	X ² (3)=15.04	0.002	0.32	<0.001*	0.023	0.004	0.18	0.080
SOCIAL PHOBIA	49(29.0)	38(20.3)	28(21.1)	62(35.8)	X ² (3)=13.88	0.003	0.057	0.12	0.18	0.87	0.001*	0.005
SOMATOFORM D/OS	8(4.7)	3(1.6)	5(3.8)	4(2.3)	X ² (3)=3.52	0.32						
SUBSTANCE ABUSE	32(19.0)	27(14.4)	13(9.8)	14(8.1)	X ² (3)=10.67	0.014	0.24	0.025	0.003*	0.21	0.058	0.61
N SCQ PROBLEMS	0.48±0.83	0.93±1.20	1.16±1.43	1.38±1.39	X ² (3)=51.18	<0.001	<0.001*	<0.001*	<0.001*	0.19	<0.001*	0.072
N SCQ TREATED					X ² (9)=52.31	<0.001	<0.001*	<0.001*	<0.001*	0.65	0.01	0.27
0	116(69.0)	94(50.5)	58(43.6)	58(33.5)								
1	31(18.5)	44(23.7)	34(25.6)	48(27.7)								
2	16(9.5)	26(14.0)	23(17.3)	33(19.1)								
3+	5(3.0)	22(11.8)	18(13.5)	34(19.7)								
SCQ SCORE	2.1±2.7	3.3±3.4	3.7±3.7	4.5±3.9	X ² (3)=51.10	<0.001	<0.001*	<0.001*	<0.001*	0.25	<0.001*	0.029
SCQ												

	NW	OW	OBI	OB2+	TEST	P	NWVOW	NWVOBI	NWVOB2	OWVOBI	OWVOB2	OB1VOB2
BACK PAIN	21(12.4)	33(17.7)	22(16.5)	36(20.8)	$X^2(3)=4.39$	0.22						
DIABETES	3(1.8)	17(9.1)	16(12.0)	38(22.0)	$X^2(3)=36.24$	<0.001	0.003	<0.001*	<0.001*	0.39	<0.001*	0.024
HEART DISEASE	3(1.8)	14(7.5)	7(5.3)	16(9.2)	$X^2(3)=9.38$	0.025	0.012	0.11	0.003*	0.43	0.55	0.19
NEUROLOGICAL	2(1.2)	8(4.3)	5(3.8)	3(1.7)	(P)<0.01	0.22						
HEART RATE	70.7±9.7	73.6±11.9	72.9±12.3	76.4±11.5	$F(3,652)=7.30$	<0.001	0.011	0.094	<0.001*	0.59	0.027	0.011
SYSTOLIC BP	117±17	125±17	128±15	131±18	$F(3,652)=22.64$	<0.001	<0.001*	<0.001*	<0.001*	0.13	<0.001*	0.075
DIASTOLIC BP	73.9±11.7	79.1±11.4	81.1±10.6	82.5±10.8	$F(3,652)=18.82$	<0.001	<0.001*	<0.001*	<0.001*	0.12	0.004	0.25

NOTE CHI-SQUARE FOR CONTINUOUS MEASURES INDICATES KRUSKAL-WALLIS TEST.

* SIGNIFICANT AFTER BONFERRONI CORRECTION (P<.0083).

Table 5

Week 12 outcome by BMI Class (given as N (%) or mean $\pm$ std)

	NW	OW	OB1	OB2+	Unadjusted OR ^{***}	p	Adjusted [*] OR ^{***}	p
Remission	61 (36.2)	74 (39.6)	57 (42.9)	64 (37.0)	1.06	0.97	1.11	0.69
Last QIDS-SR <6	64 (38.1)	64 (34.4)	54 (42.2)	60 (34.7)	0.85	0.85	0.85	0.75
Response	83 (50.6)	95 (52.5)	68 (52.7)	88 (53.0)	1.03	1.03	1.07	1.00
Last QIDS-SR	8.6 $\pm$ 6.0	8.1 $\pm$ 5.0	7.8 $\pm$ 5.6	7.9 $\pm$ 5.0	-0.49	-0.77	-0.68	0.68
% drop QIDS-SR score	43 $\pm$ 38.1	46 $\pm$ 32.1	47 $\pm$ 35.9	48 $\pm$ 31.1	-2.74	-3.20	-4.22	0.86
Exited Primary Phase	54 (32.0)	48 (25.7)	38 (28.6)	41 (23.7)	0.86	0.91	0.83	0.70
Max FIBSER Frequency					0.94	0.71	0.88	0.024
No SE's	15 (9.4)	24 (13.4)	20 (15.9)	31 (18.8)				
10-25% (time)	47 (29.4)	52 (29.1)	46 (36.5)	60 (36.4)				
50-75%	60 (37.5)	56 (31.3)	32 (25.4)	53 (32.1)				
90-100%	38 (23.8)	47 (26.3)	28 (22.2)	21 (12.7)				
Max FIBSER Intensity					0.94	0.75	0.97	0.008
None	16 (10.0)	22 (12.3)	16 (12.7)	30 (18.2)		0.51	0.76	0.55
Minimal/Mild	41 (25.6)	51 (28.5)	47 (37.3)	62 (37.6)				
Moderate/Marked	72 (45.0)	71 (39.7)	46 (36.5)	52 (31.5)				
Severe/Intolerable	31 (19.4)	35 (19.6)	17 (13.5)	21 (12.7)				
Max FIBSER Burden					0.95	0.73	0.91	0.042
None	20 (12.5)	37 (20.7)	29 (23.0)	41 (24.8)		0.57	0.72	0.55
Minimal/Mild	75 (46.9)	67 (37.4)	57 (45.2)	77 (46.7)				
Moderate/Marked	45 (28.1)	52 (29.1)	31 (24.6)	37 (22.4)				
Severe/Intolerable	20 (12.5)	23 (12.8)	9 (7.1)	10 (6.1)				
Last FIBSER Frequency					0.96	0.61	1.03	0.026
No SE's	55 (34.6)	69 (39.2)	59 (46.8)	79 (47.9)		0.58	0.68	0.74
10-25% (time)	69 (43.4)	68 (38.6)	45 (35.7)	63 (38.2)				
50-75%	24 (15.1)	31 (17.6)	16 (12.7)	19 (11.5)				
90-100%	11 (6.9)	8 (4.5)	6 (4.8)	4 (2.4)				
Last FIBSER Intensity					0.10	0.60	1.07	0.041
None	54(34.0)	69(39.2)	61(48.4)	79(47.9)		0.64	0.66	0.79

	NW	OW	OB1	OB2+	Unadjusted OR**	p	Adjusted* OR**	p
Minimal/Mild	71(44.7)	68(38.6)	44(34.9)	57(34.5)				
Moderate/Marked	25(15.7)	33(18.8)	16(12.7)	25(15.2)				
Severe/Intolerable	9(5.7)	6(3.4)	5(4.0)	4(2.4)				
Last FIBSER Burden								
None	72(45.3)	89(50.6)	74(58.7)	108 (65.5)	0.86	0.52	0.44	0.002
Minimal/Mild	61(38.4)	67(38.1)	40(31.7)	45(27.3)			0.65	0.54
Moderate/Marked	20(12.6)	15(8.5)	9(7.1)	9(5.5)				
Severe/Intolerable	6(3.6)	5 (2.8)	3(2.4)	3(1.8)				0.065

NOTE Models assume either OR=1 or $\beta=1$ for reference category of the analysis variable.

* Adjusted for treatment, systolic BP, pulse, PDSQ PTSD and SUD, N treated SCQ health problems, clinical setting, and atypical features.

** Or for continuous measures, β

† Models are unestimable.

‡ An extremely non-normal distribution required binning

Table 6

Week 28 Outcome Measures by BMI Class (given as N(%) or mean $\pm$ std)

	NW	OW	OB1	OB2+	Unadjusted OR	***	p	Adjusted OR	***	p
Remission	76 (45.0)	84 (44.9)	57 (42.9)	81 (46.8)	0.93	0.97	1.08	0.93	0.95	1.08
Last QIDS-SR <6	82 (49.1)	81 (43.5)	55 (42.0)	74 (43.3)	0.79	0.72	0.81	0.60	0.79	0.83
Response	99 (60.7)	105 (58.0)	68 (52.7)	101 (61.6)	0.88	0.66	0.96	0.37	0.85	0.96
Last QIDS-SR	7.9 $\pm$ 6.2	7.5 $\pm$ 5.2	7.7 $\pm$ 5.5	7.2 $\pm$ 5.3	1.06	1.06	0.98	0.84	1.06	0.98
% drop in QIDS-SR	49 $\pm$ 37.5	50 $\pm$ 34.3	47 $\pm$ 36.5	53 $\pm$ 32.5	-1.14	3.10	-3.08	0.56	-1.33	3.33
Exited Continuation Phase	68 (40.2)	76 (40.6)	48 (36.1)	51 (29.5)	1.11	0.84	0.63	0.11	1.21	0.95
Max FIBSER Frequency					0.87	0.63	0.49	0.004	0.82	0.57
No SE's	12 (7.5)	24 (13.4)	19 (15.1)	27 (16.4)						
10-25% (time)	44 (27.5)	52 (25.1)	44 (34.9)	59 (35.8)						
50-75%	60 (37.5)	57 (31.8)	34 (27.0)	58 (35.2)						
90-100%	44 (27.5)	53 (29.6)	29 (23.0)	21 (12.7)						
Max FIBSER Intensity					0.98	0.77	0.52	0.010	1.00	0.79
None	12 (7.5)	22 (12.3)	14 (11.1)	26 (15.8)						
Minimal/Mild	41 (25.6)	44 (24.6)	41 (32.5)	57 (34.5)						
Moderate/Marked	76 (47.5)	76 (42.5)	53 (42.1)	60 (36.4)						
Severe/Intolerable	31 (19.4)	37 (20.7)	18 (14.3)	22 (13.3)						
Max FIBSER Burden					0.95	0.80	0.59	0.069	0.90	0.77
None	17 (10.6)	36 (20.1)	22 (17.5)	39 (23.6)						
Minimal/Mild	75 (46.9)	64 (35.8)	60 (47.6)	70 (42.4)						
Moderate/Marked	48 (30.0)	55 (30.7)	34 (27.0)	45 (27.3)						
Severe/Intolerable	20 (12.5)	24 (13.4)	10 (7.9)	11 (6.7)						
Last FIBSER Frequency					1.21	0.63	0.50	<0.001	1.34	0.72
No SE's	69 (43.1)	80 (44.9)	67 (53.2)	96 (58.5)						
10-25% (time)	62 (38.8)	59 (33.1)	45 (35.7)	52 (31.7)						
50-75%	16 (10.0)	27 (15.2)	12 (9.5)	14 (8.5)						
90-100%	13 (8.1)	12 (6.7)	2 (1.6)	2 (1.2)						
Last FIBSER Intensity					1.21	0.62	0.51	<0.001	1.32	0.69
None	68(45.2)	80(44.9)	69(54.8)	94(57.3)						

	NW	OW	OB1	OB2+	Unadjusted OR ^{**}	p	Adjusted OR ^{**}	p
Minimal/Mild	61(38.1)	56(31.5)	41(32.5)	53(32.3)				
Moderate/Marked	22(13.8)	35(19.7)	12(9.5)	14(8.5)				
Severe/Intolerable	9(5.6)	7(3.9)	2(1.6)	3(1.8)				
Last FIBSER Burden								
None	84(52.5)	98(55.1)	78(61.9)	113(68.9)	0.97	0.64	0.42	0.002
Minimal/Mild	51(31.9)	57(32.0)	34(27.0)	41(25)				
Moderate/Marked	20(12.5)	17(9.6)	12(9.5)	9(5.5)				
Severe/Intolerable	5(3.1)	6(3.4)	2(1.6)	1(0.6)				

NOTE: Models assume either OR=1 or $\beta=1$ for reference category of the analysis variable.

* Adjusted for treatment, systolic BP, pulse, PDSQ PTSD and SUD, N treated SCQ health problems, clinical setting, and atypical features.

** Or for continuous measures, β

[†] Models are unestimable.

[‡] An extremely non-normal distribution required binning.