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Depression and Eating Disorders: Treatment and Course

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Abstract

Background—We examined the course of major depressive disorder (MDD) and predictors of MDD recovery and relapse in a longitudinal sample of women with eating disorders (ED).

Methods—246 Boston area women with DSM-IV anorexia nervosa-restricting (ANR; n=51), AN-binge/purge (ANBP; n=85), and bulimia nervosa (BN; n=110) were recruited between 1987-1991 and interviewed using the Eating Disorders Longitudinal Interval Follow-up Evaluation (LIFE-EAT-II) every 6-12 months for up to 12 years. 100 participants had MDD at study intake and 45 developed MDD during the study. Psychological functioning and treatment were assessed.

Results—Times to MDD onset (1 week – 4.3 years), recovery (8 weeks – 8.7 years), and relapse (1 week – 5.2 years) varied. 70% recovered from MDD, but 65% subsequently relapsed. ANR patients were significantly less likely to recover from MDD than ANBP patients (p=0.029). Better psychological functioning and history of MDD were associated with higher chance of MDD recovery. Higher baseline depressive severity and full recovery from ED were associated with greater likelihood of MDD relapse; increased weight loss was somewhat protective. Adequate antidepressant treatment was given to 72% of patients with MDD and generally continued after MDD recovery. Time on antidepressants did not predict MDD recovery (p=0.27) or relapse (p=0.26).

Limitations—Small ED diagnostic subgroups; lack of non-ED control group.

Conclusions—The course of MDD in EDs is protracted; MDD recovery may depend on ED type. Antidepressants did not impact likelihood of MDD recovery, nor protect against relapse, which may impact on treatment strategies for comorbid MDD and EDs.

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Keywords

Major Depressive Disorder; Eating Disorders; Anorexia Nervosa; Bulimia Nervosa; Antidepressants

Introduction

Eating disorders (EDs) have high rates of comorbidity with other mental illnesses, especially major depressive disorder (MDD). Multiple studies indicate that MDD is the most common comorbid diagnosis in patients with EDs (Herzog *et al.* 1992; Fichter & Quadflieg, 2004; Kaye *et al.* 2008); the American Psychiatric Association has reported that lifetime rates of MDD in individuals with EDs range between 50% and 75% (American Psychiatric Association Workgroup on Eating Disorders, 2006); and MDD comorbid with EDs has been associated with worse ED outcome (Lowe *et al.* 2001; Berkman *et al.* 2007), including high rates of suicide attempts (Franko *et al.* 2004; Bulik *et al.* 2008; Forcano *et al.* 2009) and suicide-related mortality (Crow *et al.* 2009).

Despite the overlap between EDs and depression, FDA-approved antidepressants have not shown promise in alleviating depression in patients with EDs. Although fluoxetine has been approved to treat bulimia nervosa (BN), the drug has shown mixed efficacy in reducing MDD in this group (Pope *et al.* 1983; Fichter *et al.* 1991; Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldbloom & Olmsted, 1993; Beumont *et al.* 1997; Walsh *et al.* 1997; Romano *et al.* 2002). Moreover, antidepressant treatment does not result in improvement in depressive symptomatology in anorexia nervosa (AN) treatment trials (Attia *et al.* 1998; Walsh *et al.* 2006). In view of the high rates of suicide and treatment resistance in individuals with comorbid MDD and ED, characterizing the course of MDD and identifying predictors of MDD recovery and relapse in individuals with EDs are important avenues for research.

In 1987 we initiated a prospective longitudinal study of treatment-seeking women with AN and BN to map the course and outcome of EDs. We have previously examined psychiatric comorbidity and found high rates of MDD in this sample (Herzog *et al.* 1992). Depression severity was associated with increased risk for attempted suicide in AN participants (Franko *et al.* 2004). By a median of 9 years of follow-up, 11 women had died (Keel *et al.* 2003). In this study we address the following questions about MDD: (a) What is the course of MDD?; (b) What variables are associated with recovery from and relapse to MDD?; and (c) What types of antidepressant medications do women with EDs receive for MDD and are these treatments adequate by current standards? We hypothesized that the course of MDD would be longer if there was no recovery from ED. Likewise, we expected that women who received antidepressants would be more likely to recover from MDD, even if their ED did not significantly improve.

Methods

Participants

Five hundred and fifty-four women who sought treatment at Massachusetts General Hospital and other treatment centers in the Boston area between 1987 and 1990 were screened to determine whether they met criteria for AN or BN set forth in the 3rd Revised Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; American Psychiatric Association, 1987). Two hundred and twenty-five women originally agreed to participate in the study, and in 1991, 21 additional participants with AN were recruited through Boston-area clinics, increasing the sample size to 246 women. After reclassification into DSM-IV

criteria (American Psychiatric Association, 1994), the sample included 51 women with AN-restricting type (ANR), 85 women with AN-binge/purge type (ANBP), and 110 women with BN.

For study inclusion, participants were required to be female, English-speaking, at least 12 years of age, reside within 200 miles of the study site, and meet full criteria for AN or BN. Exclusion criteria were terminal illness or organic brain syndrome. Characteristics of the full sample at intake have been described elsewhere (Herzog *et al.* 1999). The study was approved by the Institutional Review Board of Massachusetts General Hospital.

Procedure

Following a brief telephone screen, eligible participants were invited for an in-person intake interview during which ED diagnosis was confirmed and psychiatric history obtained. Written informed consent was obtained prior to the interview. Subsequently, participants were interviewed at 6-12 month intervals over a mean and median of 8.6 and 9 years, respectively. All interviews were conducted by a trained research assistant; every attempt was made to conduct follow-up interviews in person; if this was not feasible, follow-up interviews were conducted by phone.

Instruments

Intake—The Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L, modified version EAT-SADS-L; Spitzer & Endicott, 1979): This semi-structured interview was used to assess current and lifetime comorbid diagnoses.

Beck Depression Inventory (BDI): Participants completed this 21-item self-report measure of behavioral, cognitive, and somatic symptoms of depression (Beck *et al.* 1961). Higher scores indicate greater symptom severity.

Global Assessment of Functioning (GAF): Research assistants assigned GAF ratings based on Axis V from the DSM (American Psychiatric Association, 1987; American Psychiatric Association, 1994). Scores range from 1-100; higher scores indicate better psychosocial functioning and lower symptom severity.

Follow-up—Eating Disorders Longitudinal Interval Follow-up Evaluation (LIFE-EAT II): The LIFE-EAT II is a semi-structured interview modified from the LIFE II (Keller *et al.* 1987) that was used to assess eating pathology, comorbid axis I disorders, GAF score, suicidality, and treatment utilization. ED and MDD severity were assessed weekly with a Psychiatric Status Rating (PSR) score (coded 1-6) that corresponded to the Research Diagnostic Criteria (RDC) ratings for the disorders. PSR scores of 1 and 2 indicated no or few symptoms and PSR scores of 5 and 6 equated to full syndrome severity. Body weights were collected via self-report. Therapy (individual, group, and family psychotherapy; psychotropic medication; nutritional counseling; medical management; and hospitalization) was assessed on a week-by-week basis. Further details of the study methodology have been reported elsewhere (Herzog *et al.* 1999).

Interviewer Training

A 5-step training program modeled after the NIMH Collaborative Psychobiology of Depression Study was used in the training of interviewers. The training program has been described previously (Herzog *et al.* 1992).

Analysis Population

Of the 246 participants included in the study population, 156 (63%) had lifetime MDD. Eleven of these women had only a history of MDD, with no new episode at study intake or during follow-up. The current report includes the remaining 145 participants (59% of the total study population) who had either MDD at study intake ($n=100$) or a new onset of MDD during the study ($n=45$).

Data Analysis

Outcome variables—MDD was diagnosed according to the RDC on the basis of the EAT-SADS-L interview at study intake and the LIFE-EAT II interview during follow-up. Outcome variables analyzed were time to first MDD recovery and time to first MDD relapse. Patients were considered to have recovered from MDD if they had an MDD PSR score ≤ 2 for at least 8 consecutive weeks. Patients were considered to have relapsed to MDD if they had an MDD PSR score ≥ 5 at any time.

Predictor variables—A number of fixed and time-varying covariates were examined as predictors of MDD recovery and relapse. Fixed covariates included: intake ED diagnosis (ANR/ANBP/BN); duration (years) of ED illness prior to study intake; percent of ideal body weight (IBW) at study intake; history of suicide gestures or attempts (Yes/No) at study intake; history of MDD before entry into the study (Yes/No); current MDD at study intake (Yes/No); lifetime drug use disorder at study intake (Yes/No); lifetime alcohol use disorder at study intake (Yes/No); BDI score; and age at study intake; and total weeks of individual psychotherapy.

Time-varying covariates were assessed every week (except as noted) on the basis of the follow-up LIFE-EAT II data, and included: ED PSR scores; on-study ED diagnosis (see next paragraph); weight loss (ordinal categories representing *percent below IBW*: 6-9%/10-14%/15-20%/21-29%/30-39%/≥40%); suicide gestures or attempts (Yes/No, assessed monthly and transformed to weekly measurements by assuming constancy over the month); binge eating (Yes/No); purging (Yes/No); compensatory fasting or vigorous exercise (Yes/No); weeks of adequate antidepressant treatment, defined as ≥ 6 consecutive weeks of treatment at the recommended dosage for that particular antidepressant (defined as a dose greater than or equal to a dose usually considered effective, e.g. $\geq 20\text{mg/day}$ of fluoxetine); weeks of therapy (as described above, including both a Yes/No covariate and cumulative number of weeks received); and GAF score (assessed monthly and transformed to weekly measurements by assuming constancy over the month).

Time-varying on-study ED diagnosis was defined using the maximum AN and BN PSR scores achieved over a 13 week period (i.e., 3 months). ANR diagnosis required an AN PSR score ≥ 5 and a BN PSR score ≤ 2 ; ANBP diagnosis required an AN PSR score ≥ 5 and a BN PSR score ≥ 3 ; and BN diagnosis required a BN PSR score ≥ 5 and an AN PSR ≤ 4 . Full recovery required both AN and BN PSR scores ≤ 2 .

Statistical methods

Cox Proportional Hazards (PH) regression was used to identify predictors of MDD recovery and of MDD relapse. To conserve power, univariate analyses were first conducted at the $\alpha=0.05$ level. Significant covariates were then entered into multivariate models, with automated stepwise selection ($\alpha=0.15$ to enter, $\alpha=0.10$ to stay) used to identify a parsimonious model. Finally, interactions between the (marginally) significant predictors were tested individually at the $\alpha=0.10$ level. Descriptive Kaplan-Meier plots of time to MDD recovery and MDD relapse were also generated. No adjustments were made for multiple comparisons to ensure that potential drivers of MDD recovery and relapse are not

obscured in this initial investigation, and because a universal null hypothesis does not exist in this context (Rothman, 1990).

For all time-varying covariates, a lag of 1 week was applied in the Cox PH models to strengthen the case for causality – i.e. at any time point, MDD recovery/relapse was predicted based on patients' covariate values 1 week prior to that time point. Additional lags were investigated, but did not alter the results.

Analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Of the 145 patients with MDD included in the analysis, 102 (70%) recovered from MDD over the course of the study, but 66 (65%) of these 102 patients subsequently relapsed to MDD. The mean and median follow-up time for the analysis population was 8.8 and 10.0 years, respectively (range = 3 months–12 years). Time from MDD onset to recovery (8 weeks–8.7 years) and time from MDD recovery to relapse (1 week–5.2 years) varied greatly, as did time from study entry to new onset of MDD (1 week–4.3 years) for patients without MDD at study intake. Of the 102 patients recovered from MDD, 9 (9%) had previously fully recovered from their ED. By comparison, among the 43 patients who did not recover from MDD, 16 (37%) had previously fully recovered from their ED. Table 1 presents additional descriptive statistics for the analysis population as a whole, and separately for those who recovered from and relapsed to MDD.

Predictors of Recovery from MDD

In univariate analyses, significant predictors of MDD recovery included history of MDD, BDI score, and GAF score (Table 2). Patients with a history of MDD, less severe depression (i.e., lower BDI score), and better psychological functioning (i.e., higher GAF score) were more likely to recover from depression. Intake ED diagnosis was a marginally significant predictor ($p=0.085$), with ANR patients significantly less likely to recover from MDD than ANBP ($p=0.029$) or BN ($p=0.052$) patients.

After multivariate stepwise selection, BDI and GAF remained significant predictors (Figure 1 A,B), but history of MDD was no longer significant. The effect of GAF on MDD recovery varied by MDD history ($p=0.0021$). After controlling for BDI score, a 2-point increase in GAF score led to an 11% greater likelihood of MDD recovery overall (results not shown). But for patients without a history of MDD, a 2-point increase in GAF score led to a 23% greater likelihood of MDD recovery, (Table 2). Total number of weeks of individual therapy (as a fixed covariate) was a non-significant predictor of MDD recovery ($p=0.93$).

Predictors of Relapse to MDD

BDI score was the only significant predictor of MDD relapse univariately. Patients with more severe depression at baseline had the highest likelihood of MDD relapse (Table 3). Weeks of individual psychotherapy, time-varying weight loss and time-varying on-study ED diagnosis were borderline significant, with patients most at risk of relapsing being those who received more psychotherapy, were closer to their ideal body weight, and fully recovered from their ED. After multivariate stepwise selection, BDI score and time-varying weight loss were both significant at the $\alpha=0.10$ level (Figure 1 C,D), but neither weeks of psychotherapy nor time-varying ED diagnosis remained significant. The effect of BDI on MDD relapse varied by on-study ED diagnosis ($p=0.011$). After controlling for weight loss, a 5-point increase in BDI score led to a 22% greater likelihood of MDD relapse overall (results not shown). But for patients who had fully recovered from their ED, a 5-point increase in BDI score led to a 43% greater likelihood of MDD relapse (Table 3).

Treatment of MDD in the Sample

With regard to antidepressant treatment in the participants with MDD, most patients (72%) were found to have received adequate antidepressant treatment at some point during the study, though a few received inadequate treatment, and almost one-fifth went untreated (Table 1). Forty (28%) of the 145 MDD patients received at least 60 mg of fluoxetine at some time point during the study; another 9 patients (6%) received an unknown dosage that could have been as high as 60mg. About 90% of patients received therapy of some type, and 83% received individual psychotherapy (at 79% of weeks during which some form of therapy was administered). Over the course of follow-up, adequate antidepressant treatment was administered to 75% of patients who recovered from MDD and to 85% of patients who subsequently relapsed (Table 1).

Figure 2 graphs the percentage of weeks (per 6-month interval) in which different combinations of psychotherapy and/or antidepressant treatment were administered, separately for participants who did not recover from MDD (A), did recover from MDD (B), and recovered but subsequently relapsed to MDD (C). For example, Figure 2A shows that among patients who did not recover from MDD, antidepressants plus psychotherapy were administered at 13% of weeks, psychotherapy alone was administered at 65% of weeks, anti-depressants alone were administered at 0% of weeks, and no/inadequate therapy was administered in 22% of weeks during the first 6 months of the study. Panel B illustrates that treatment was not stopped once a participant recovered from MDD. On the contrary, among the 77 patients who received adequate treatment with antidepressants and recovered from MDD, 54 (96%) of the 56 who subsequently relapsed continued to receive antidepressant treatment after MDD recovery, as did 16 (76%) of the 21 who did not subsequently relapse.

Despite the fact that individuals in this study by and large received adequate antidepressant treatment, total weeks of antidepressant treatment was neither a significant predictor of MDD recovery ($p=0.27$) nor of MDD relapse ($p=0.26$). To test the robustness of our findings and ensure that lack of significance was not specific to how the covariate was defined in the model, antidepressant treatment was modeled a number of ways, including: total weeks of treatment; any treatment received (Yes/No); and adequate/inadequate/no treatment received. Fluoxetine alone was also isolated, since it was the most commonly prescribed antidepressant (given to 87% of patients who were treated with an antidepressant, and administered at 49% of weeks in which an antidepressant was administered). Finally, we examined the effect of treatment after controlling for time-varying weight loss, and also within time-varying on-study ED categories, to see if the overall effect of antidepressant treatment was obscured by confounding or effect modification. Regardless of how treatment was modeled in our analyses, it did not significantly affect the likelihood of MDD recovery or relapse in this population.

Discussion

To our knowledge, this is the first prospective investigation of the course of MDD in an ED sample, derived from the largest and longest prospective, naturalistic longitudinal follow-up of women with EDs. Consistent with previous reports of MDD in ED samples (Brewerton *et al.* 1995; Godart *et al.* 2004; Fernandez-Aranda *et al.* 2007; Herzog & Eddy, 2007), we found that 59% of the 246 patients recruited had one or more episodes of depression, a prevalence much greater than the 15% or so that would be expected in the general population.

With regard to MDD recovery and relapse, patients who fared the worst had more severe baseline depressive symptoms, and better psychological functioning suggested a higher

chance of recovery. Our findings are consistent with previous studies of depression that have linked more severe depressive symptoms to poorer treatment outcomes (Kirsch *et al.* 2008).

Rates of MDD recovery varied by ED diagnosis at study entry, with patients diagnosed as ANR having a lower chance of recovery from MDD than those diagnosed with ANBP or BN. However, participants with ANR who did recover from MDD were less likely to have had an MDD relapse compared to individuals who had fully recovered from their ED. Likewise, participants were more likely to have a depressive relapse if they were closer to their ideal body weight. This finding is consistent with previous studies that indicate that recovered or weight-restored AN participants continue to experience increased or persistent depressive symptomatology in comparison to healthy controls (Pollice *et al.* 1997; Holtkamp *et al.* 2005; Wagner *et al.* 2006).

These findings were striking, as it is generally thought that recovery from one condition may facilitate recovery from a comorbid condition. There may, however, be other factors in play with regard to patients with EDs. For example, recovering from an ED and/or attaining a healthier weight may mobilize control issues within the patient, which may in turn precipitate feelings of depression. Recovery from an ED may be associated with a loss of identity and routine, and fuel a fear of weight gain. Beresin *et al.* (1989) interviewed women who had recovered from AN who reported that with their recovery, they initially felt a loss of self-respect (for “giving in” to getting well) and that they were losing their ‘specialness’. Such feelings may lead to depressive symptoms, particularly if the ED is chronic.

Lifetime alcohol and drug abuse were relatively uncommon in the sample as a whole (17% and 14%, respectively; Table 1), and rates did not change significantly in the recovered and relapsed samples. We do not have information on whether the history of alcohol or substance abuse represented current or past abuse in these subjects, but the findings suggest that a lifetime history of these did not significantly impact on recovery or relapse from MDD. Consistent with recent reports (Steffen *et al.* 2006), our primary and sensitivity analyses revealed antidepressant treatment did not significantly impact either recovery from or relapse to MDD. This may reflect the increasingly questionable efficacy of antidepressants in general (Moncrieff *et al.* 2004), or a finding specific to an ED population in which greater comorbidity may lead to poorer outcomes. It is also possible that participants may not have been compliant in taking the medication, or that the medications may not have been absorbed due to purging behaviors.

Limitations of this study warrant acknowledgement. The ED diagnostic subgroups in our study were small, and ideally this study should be replicated in a larger sample with all diagnostic subgroups. Our study also lacked a control group of participants without EDs, and thus we cannot attribute effects observed specifically to the presence of an eating disorder, nor rule out the confounding effect of time in this longitudinal study.

This study was initiated in 1987 and we used RDC criteria for MDD because of the consideration regarding its stability over time. The DSM is now used for research and clinical work on MDD, and diagnostic instruments have been modified for the updated criteria. During the study period, selective serotonin reuptake inhibitors (SSRIs), particularly fluoxetine, were the most commonly prescribed medications for depression, and thus it may be difficult to generalize these findings to the larger range of antidepressants currently available. It was difficult to determine whether any improvements seen among ED subjects were due to either anti-depressants or to psychotherapy, since most patients received both, and only 9 patients (6%) received antidepressants alone at some point in the course of the study. Also, data were available only for treatment received, and not the specific reason for treatment. Finally, because there was no accepted therapy for AN or BN at the time, we did

not gather details about psychotherapy administered. It is possible that cognitive behavioral therapy (often the initial treatment of choice for BN now) may have had an impact on MDD symptoms.

In conclusion, our findings support an overlap between EDs and MDD, and suggest that the presence and type of ED may affect recovery from MDD and relapse to MDD. While these findings may suggest a relationship between EDs and MDD, they do not demonstrate any specific causal link. Antidepressants do not seem to significantly impact MDD recovery or relapse in this population, which may have implications for the development of treatment strategies in individuals with comorbid MDD and EDs.

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Figure 1.
Time to MDD Recovery / Relapse by Significant Predictors in Multivariate Models

Figure 2. Utilization Of Anti-Depressants And Psychotherapy Over Time

In the figure above, the percentage of weeks during which different types of treatment were received is summarized in 6-month intervals (e.g. time 0 in panel A represents the percentage of weeks in the first 6 months of the study that various treatments were given). Participants in 2C (who relapsed) are a subset of those represented in 2B (who recovered). The vertical lines at time 0 in B and C represent the time at which first MDD recovery and relapse occurred, respectively. In general, treatment patterns were fairly stable over time, though the percentage of weeks in which an anti-depressant was received (with or without psychotherapy) increased after MDD recovery (B) and also after MDD relapse (C).

Table 1

Descriptive Characteristics of Analysis Population

Characteristic	Overall (N = 145)		Recovered from MDD (N = 102)		Relapsed to MDD (N = 66)		
	Mean	SD	Mean	SD	Mean	SD	
Years of Follow-Up	9	2.4	9	1.8	9	1.8	
Age (years)	25	6.8	24	6.3	24	5.4	
Years of ED Prior to Study Entry	9	6.4	8	6.1	8	5.3	
Percent of Ideal Weight (%)	90	19.6	91	18.4	92	16.3	
Beck Depression Inventory Score	25	10.8	23	11.0	25	10.8	
Weeks of Adequate Antidepressant Treatment	159	156.7	162	166.9	171	165.5	
Weeks of Any Therapy ^a	92	56.0	91	57.7	98	62.3	
Weeks to MDD Onset ^a / Recovery ^b / Relapse ^c	71	64.8	57	77.6	73	74.4	
	N	%	N	%	N	%	
History of MDD	89	61%	67	66%	45	68%	
MDD at Intake	100	69%	68	67%	44	67%	
MDD Onset during Study	45	31%	34	33%	22	33%	
Intake ED Diagnosis	28	19%	14	14%	7	11%	
	ANR						
	ANBP	56	39%	42	41%	29	44%
	BN	61	42%	46	45%	30	45%
Suicidal Gestures/Attempts	50	34%	35	34%	25	38%	
Lifetime Drug Abuse	20	14%	14	14%	10	15%	
Lifetime Alcohol Abuse	24	17%	15	15%	11	17%	
Antidepressant Treatment	105	72%	77	75%	56	85%	
	Adequate						
	Inadequate	13	9%	7	7%	5	8%
	None	27	19%	18	18%	5	8%
Individual Psychotherapy	120	83%	84	82%	57	86%	
Any Therapy ^a	130	90%	92	90%	63	95%	

^aFrom study entry (n=45 patients)

^b From MDD onset (i.e. at intake / during follow-up)

^c From MDD recovery

* Inclusive of medications and psychotherapy/psychosocial treatment, as well as medical management

Table 2
(Marginally) Significant Predictors of MDD Recovery based on Cox PH Regression

Outcome	Covariate Type	Predictor	Estimate	Standard Error	Hazard Ratio [95% CI]	p-value
MDD Recovery	Fixed	MDD History (Yes vs. No)	0.44	0.21	1.55 [1.03 – 2.34]	0.036
	Fixed	BDI Score *	-0.031	0.0098	1.17 [1.06 – 1.28] ^a	0.0016
	Time-varying	GAF Score *	0.050	0.0081	1.11 [1.07 – 1.14] ^b	<0.0001
		GAF Score if have MDD History ^I	-	-	1.07 [1.03 – 1.11] ^b	-
		GAF Score if no MDD History ^I	-	-	1.23 [1.14 – 1.33] ^b	-
Fixed		ED Diagnosis at Intake *	-	-	-	0.085
		ANBP vs. ANR	0.67	0.31	1.95 [1.07 – 3.55]	0.029
		BN vs. ANR	0.60	0.31	1.82 [0.99 – 3.34]	0.052

Note: Unless otherwise noted, the results reported are based on Univariate Cox PH regression models

* Significant predictor of MDD Recovery in a multivariate model

^a Hazard Ratio is calculated for a 5-point decrease in BDI score

^b Hazard Ratio is calculated for a 2-point increase in GAF score (e.g. from Fair to Very Good, or Very Poor to Fair)

^I The effect of GAF is based on an interaction with the covariate listed, after controlling for BDI Score and main effects in the final multivariate model

Table 3

(Marginally) Significant Predictors of MDD Relapse based on Cox PH Regression

Outcome	Covariate Type	Predictor	Estimate	Standard Error	Hazard Ratio [95% CI]	p-value
MDD Relapse	Fixed	BDI Score *	0.035	0.012	1.19 [1.06 – 1.34] ^a	0.0032
		BDI Score if ANR ^I	-	-	1.00 [0.80 – 1.26] ^a	-
		BDI Score if ANBP ^I	-	-	30.88 [0.30 – 3180] ^a	-
		BDI Score if BN ^I	-	-	1.27 [1.05 – 1.54] ^a	-
		BDI Score if Fully Recovered ^I	-	-	1.43 [1.07 – 1.90] ^a	-
		Weeks of individual psychotherapy	0.0033	0.0019	1.09 [0.99 – 1.20] ^b	0.084
Time-varying	Time-varying	Weight Loss *	-0.18	0.094	0.83 [0.70 – 1.01]	0.058
		ED Diagnosis On-Study	-	-	-	0.062
Time-varying	Time-varying	Fully Recovered vs. ANR	0.85	0.38	2.33 [1.10 – 4.90]	0.026
		Fully Recovered vs. ANBP	1.62	0.77	5.05 [1.12 – 22.73]	0.035
		Fully Recovered vs. BN	0.58	0.34	1.79 [0.92 – 3.46]	0.086

Note: Unless otherwise noted, the results reported are based on Univariate Cox PH regression models

* Significant predictor of MDD Relapse in a multivariate model

^a Hazard Ratio is calculated for a 5-point increase in BDI score

^b Hazard Ratio is calculated for a 26-week (i.e. 6-month) increase in weeks of psychotherapy

^I The effect of BDI is based on an interaction with the covariate listed, after controlling for Weight Loss and main effects in the final multivariate model