Published in final edited form as:
J Affect Disord. 2013 September 25; 150(3): 1179–1183. doi:10.1016/j.jad.2013.05.010.

Sex differences in clinical predictors of depression: a prospective study

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Abstract

Background—Estimating the likelihood of future major depressive episodes (MDEs) would assist clinicians in decision-making regarding the optimal length of treatment for MDE. Unfortunately, little data are available to guide clinical practice.

Methods—We followed 200 females and 152 males who responded to treatment for a MDE for 2 years to determine risk factors for future MDE. Cox Proportional Hazard Regression modeled time to first relapse into MDE and mixed effect logistic regression modeled monthly depression status.

Results—Females were more likely than males to experience a MDE in any month of the study, and marginally more likely to experience a relapse. By 12 months, 60% of females had relapsed compared to 51% of males (median time to relapse 8 vs 13 months, respectively). Several factors predicted worse outcome for both men and women: reported childhood abuse, earlier age of onset of first MDE, Bipolar Disorder, unemployment, and more years of education. For females, but not males, suicidal ideation predicted MDE relapse and both suicidal ideation and prior suicide attempts were associated with more time in a MDE.

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Funding Body Agreement and Policies
The funding source had no role in the design, analysis or outcome of the study.

Contributors: Maria A. Oquendo designed the study, contributed to data analysis and interpretation, and wrote all manuscript drafts. Jason Turret managed the literature searches and assisted in writing and editing manuscript drafts. Michael F. Grunebaum contributed to study design, and editing of manuscript drafts. Ainsley K. Burke participated in data collection, quality control, and training of research raters. Ernest Poh assisted with the statistical analysis. Ellen Stevenson participated in study design and editing of manuscript drafts. J. John Mann contributed to study design, and editing of manuscript drafts. Hanga Galfalvy managed the statistical analysis and contributed to study design, interpretation, and editing of manuscript drafts. All authors contributed to and have approved the final manuscript.

Conflict of Interest Disclosure: Dr. Oquendo receives royalties for the use of the Columbia Suicide Severity Rating Scale and received financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript. She was the recipient of a grant from Eli Lilly to support a year's salary for the Lilly Suicide Scholar, Enrique Baca-Garcia, MD, PhD. She has received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuko, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol Myers Squibb. Dr Mann receives royalties for the use of the Columbia Suicide Severity Rating Scale and received past unrelated grants from Novartis and GSK. The other authors have no conflicts of interest to disclose in connection with this manuscript.

Limitations—The naturalistic treatment of participants, exclusion of individuals with current comorbid alcohol or substance use disorder, and a follow up period of two years are limitations.

Conclusions—Women are more vulnerable to relapse and spend more time depressed compared to men. Identification of general and sex-specific risk factors for future depression may provide clinicians with useful tools to estimate need for ongoing pharmacotherapy in MDE.

Keywords

depression; gender; predictors; relapse; risk; sex

Introduction

When first prescribed antidepressants, patients often ask how long they will need to take medication and whether symptoms will recur. Unfortunately, little data is available to guide counseling, even though anchors for clinical decision-making are sorely needed. Further, although depression prevalence differs in men and women, few studies have examined whether risk for future depression differs across sexes and if so, whether clinical moderators exist.

Predictors of relapse or recurrence of depression include being single (Coryell et al., 1991; Mueller et al., 1999), lower socioeconomic status (Kessler et al., 1994; Rao et al., 1995), childhood abuse (Gopinath et al., 2007; Suija et al., 2011), number of episodes (Bockting et al., 2006; Gonzales et al., 1985; Kessing, 1998; Kessing et al., 2004; Lewinsohn et al., 1989; Maj et al., 1992; Mueller et al., 1999; Winokur et al., 1993), life events (Kendler et al., 1993), comorbidities (Hart et al., 2001; Ilardi et al., 1997; Giles et al., 1989; Grilo et al., 2010), neuroticism (Berlanga et al., 1999; Duggan et al., 1995; Kendler et al., 1993), and suicide attempts (Wilhelm et al., 1999).

While several studies have found females are at higher risk for future major depressive episodes (MDE) than males (Kessing, 1998; Mueller et al., 1999) others have not (Coryell et al., 1991; Kovacs et al., 1984; Kessing et al., 2004; Kovacs, 2001; Rao et al., 1995; Simpson et al., 1997; Wilhelm et al., 2002). In addition, Winokur et al., (1993) found that females with unipolar depression were more likely to have a future MDE; but no sex differences in bipolar participants. None of these studies examined specific clinical risk factors that might contribute to sex differences.

We examined whether risk for future depression differed for men and women and whether clinical predictors differed across sexes. Our sample is one of the largest to date, surpassed only by the NIMH Collaborative Study (n= 955) (Mueller et al., 1999), the STAR-D study (n=943) (Nierenberg et al., 2010), and the Zurich Youth Cohort (n=591) (Angst and Merikangas, 1997).

We hypothesized that females would be at greater risk for future MDE, based on the higher point prevalence of depression for women (Kessler et al., 1994). Since a search engine-assisted literature search uncovered no studies of moderators of risk for future MDE, we explored whether baseline demographic, developmental or clinical moderators would differentially predict relapse into depression or time spent depressed across sexes.

Methods

Participants

Written informed consent, as approved by the Institutional Review Board, was obtained from 200 females and 152 males, ages 18–75, who had responded to treatment for MDE.

Exclusion criteria included current alcohol or substance abuse, neurological illness or active medical conditions that could confound clinical characterization.

Materials and Procedures

Ratings were conducted by trained clinicians with at least a Master's Degree. Axis I diagnoses were made using the SCID (Spitzer et al., 1990). Childhood physical or sexual abuse were rated as present or absent. Depression symptoms were rated using the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). Subjects provided age of onset of their first MDE, number of previous MDEs, and family history of depression. The Scale for Suicide Ideation (SSI) (Beck et al., 1979) measured suicidal ideation. Suicide attempts were recorded using the Columbia Suicide History Form (Oquendo et al., 2003). Life stressors at study entry were evaluated with the St. Paul-Ramsey Questionnaire. Follow up assessments occurred at 3 months, 1 year and 2 years and determined whether patients had suffered any MDEs in the intervening period, and if so, during which month(s).

Statistical Methods

Baseline characteristics of men and women were compared using t-tests and chi square statistics. To analyze time to first relapse into depression, Cox Proportional Hazard Regression was used. A separate survival analysis model was fit for each candidate risk factor, with sex, the risk factor, and their interaction as predictors.

We also tested predictors of time spent depressed during follow-up, using monthly depression status data. 7275 person-months were observed for 352 subjects. A survival analysis model was fit for each candidate risk factor, with sex, the risk factor, and their interaction as predictors and presence/absence of MDE measured in person-months, as the response. The longitudinal logistic regression with correlated errors was performed in SAS 9.2 using proc glimmix with an AR(1) correlation structure between residuals at consecutive time-points for the same subject. Risk factors were considered significant for both sexes if the main effect of the risk factor was significant but not the interaction. A significant interaction between sex and the risk factor was interpreted as denoting a differential risk factor, and the main effect's odds or hazard ratio and significance level determined whether the risk factor was significant for males, females or neither. Since this study is exploratory, we did not adjust for multiple testing.

Results

The sample was mostly female and moderately depressed before response to treatment (Table 1). Time to drop-out or last visit was similar for females and males (25 vs. 24 months respectively, Wilcoxon test W = 15686, p= 0.6067). Women had higher depression scores, earlier onset of mood disorder, and more frequently reported childhood abuse and family history of depression.

Females were marginally more likely than males to experience a MDE during follow-up, (HR=1.30, 95%CI: 1.00–1.70, z=1.9, p= 0.0547). By 12 months, 60% of females had relapsed compared to 51% of males. Estimated median times to first relapse, based on the Kaplan-Meier method, were 8 months for females (95%CI: 6–10) and 13 months (95%CI: 8–19) for males. Females were more likely than males to experience a MDE in any given month (OR=1.47, 95%CI = 1.16–1.86, t=3.21, df=350, p=.0014).

Risk Factors Common to Males and Females

More education, earlier age of onset and childhood abuse predicted relapse for both sexes. Time spent depressed was significantly higher in those unemployed at baseline, with more education, earlier onset of disease, and with bipolar disorder (Table 2).

Risk Factors Specific to Females

For women, suicidal ideation was associated with a higher likelihood of both relapse of depression and of being depressed during follow-up (HR=1.02, z=2.66, p=.0077; and OR=1.02, t=3.24, df=320, p=.0013), while past suicide attempts predicted more time spent depressed (OR=1.39, t=2.09, df=438, p=.0372) and tended to confer risk for relapse (HR=1.39, z=1,91, p=.0557). For men, neither of these factors increased relapse risk. Interaction terms in all these models were significant (Table 2).

Discussion

As hypothesized, females are more likely than males to relapse during a 2-year period. This finding is consistent with some (Kessing, 1998; Mueller et al., 1999; Winokur et al., 1993), but not all (Coryell et al., 1991; Gonzales et al., 1985; Kovacs et al., 1984; Kovacs, 2001; Rao et al., 1995; Simpson et al., 1997) previous work. Negative findings generally have emerged from analyses of smaller sample sizes, possibly due to limited power. Consistent with others (Hart et al., 2001), perhaps the most remarkable finding is the brevity of time between episodes, 8–13 months, supporting the notion that affective disorders are best conceptualized as chronic, relapsing conditions.

Risk Factors Common to Males and Females

Those with reported childhood abuse had earlier reappearance of MDE than those without such history, evidence for the lasting impact of childhood adversity. Childhood abuse is a predictor of MDE in clinical samples of men and women (Gopinath et al., 2007; Suija et. al, 2011). However, neither study assessed time to future MDE or length of the new episode, nor did they examine effects of childhood abuse by sex. Whether childhood abuse has different effects in men and women has not been studied extensively. A handful of population studies report no differences in outcomes for males and females reporting abuse (Eisenberg et al., 2007; Fergusson et al., 2008; for review see Gershon et al., 2008), although not all agree (Robinson et al., 2001; Banyard et al., 2004).

Life events did not predict risk, although events were measured at baseline only, since we were seeking moderators. This finding is in contrast to some evidence (Keller et al., 2007) that links life events to depression onset, even suggesting that different life events predict subsequent depressive symptom patterns. Nonetheless, more recent work (Kendler et al., 2011) suggests life events are not causal, and thus their importance in predicting or precipitating depression remains unclear.

Earlier onset of depression predicted earlier relapse and more time depressed for both sexes. Earlier onset and family history of depression may be markers of depression heritability (Bland et al., 1986; Moldin et al., 1991; Zubenko et al., 2001) and familial compared to sporadic depression may constitute a more severe, chronic form, leading to more time spent in a MDE. However, not all studies have found that age of onset predicts future depression. Of interest, a review examining risk for relapse (Burcusa and Iacono, 2007) noted that studies that do not find age of onset of depression to be predictive have small sample sizes and young participants. Our study had a wide age range, which perhaps allowed detection of this effect.

Our sample has an average of 15 years of education in both men and women. That more years of education increased risk for relapse or time spent depressed is counterintuitive since mood disordered individuals have poorer educational attainment (Chazelle et al., 2011), possibly due to illness effects. As well, less education has been associated with greater depression severity (Klabbers et al., 2010). Given the high unemployment (>64 and 68% in women and men, respectively) in this sample, we explored whether highly educated individuals who were unemployed were at greater risk for depression during follow-up and found this to be so (HR=1.19, z=5.7, p<.0001). We also found that unemployment predicted more time depressed, but unemployed participants also tended to have more past MDEs (6.3 v 5.0, respectively; t = 1.73, df = 331, p-value = 0.084). This finding comports well with the literature, which suggests that the role of unemployment in depression is complex because it can be both a consequence of (Jefferis et al., 2011; Patten et al., 2009) and a risk factor (Barkow et al., 2003) for mood disorder.

Risk Factors Specific to Females

Women are at greater risk for relapse and although past suicide attempts have been reported to increase risk for recurrent depression (Wilhelm et al., 1999), that suicidal ideation is a significant predictor of relapse for females, but not males, has not been previously reported. Insofar as suicidal ideation and behavior may represent limitations in coping strategies and problem solving abilities, it may be that there are shared risk factors for suicidal ideation or behavior and depressive episodes. Of note, we previously reported that for women, suicidal ideation and prior suicide attempts increased risk for future suicidal acts (Oquendo et al., 2007). Perhaps risk for suicidal acts relates to increased risk for depressive episodes. We are currently examining this possibility.

Limitations

Limitations of this study include the naturalistic treatment and that follow up was for only two years. Longer follow-up periods have produced different results in analyses of the Collaborative Depression Study. As well, variations in duration or intensity of treatment may affect time spent depressed. Our sample also excluded current comorbid alcohol or substance abuse or dependence, limiting generalizability. Furthermore, inclusion of both unipolar and bipolar patients may add heterogeneity.

Summary

Identification of risk factors for relapse may improve prognostic accuracy in major depression. In this study, women were more at risk for relapse. However being more educated, earlier age of onset of depression and being abused as a child increased risk for future depression in men and women. Only suicidal ideation was specific to women. Variables that predicted more time spent depressed included unemployment, more years of education, earlier age of onset and having bipolar disorder. Suicidal ideation and past suicide attempt were also important markers for more time in depressive episodes, but for women only. Both the sample size and the breadth of clinical characteristics examined lend weight to our findings.

Acknowledgments

This work was supported by PHS grants MH48514 and MH62185.

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Table 1

Baseline Demographic Characteristics of Men and Women Followed for 2 Years after a Major Depressive Episode (MDE)

Variable	Women's Mean	SD	Men's Mean	SD	t-value	df	p
Age (years)	37.29	11.18	38.80	12.65	−1.19	350	0.235
Education (years)	15.30	2.90	15.32	2.76	−0.07	344	0.941
Annual Income($)	21049	23035	28093	33347	−2.14[a]	314	0.037
17-item Hamilton Depression Rating Scale	20.54	6.40	18.92	5.99	2.58	350	0.010
Age of Onset of Depression	22.83	12.99	25.99	13.17	−2.2	334	0.028
Number of Prior MDEs	5.73	6.04	5.97	6.51	−0.35	331	0.727
Scale for Suicidal Ideation Score	13.33	10.70	12.34	10.76	0.84	322	0.402
St. Paul-Ramsey Questionnaire Score	3.90	1.22	4.03	1.07	−1.01	313	0.312
	N with Characteristic	**%**	**N with Characteristic**	**%**	**X^2**	**df**	**p**
Married	54	27%	35	23%	0.72	1	0.396
Currently employed	72	36%	48	32%	0.75	1	0.386
Childhood Abuse	99	53%	46	34%	10.62	1	0.001
Family History of Depression	114	57%	59	39%	11.06	1	0.001
History of Suicide Attempt	107	54%	80	53%	0.03	1	0.872
Bipolar Diagnosis	58	29%	47	31%	0.16	1	0.696

J Affect Disord. Author manuscript; available in PMC 2014 September 25.

J Affect Disord. Author manuscript; available in PMC 2014 September 25.

TABLE 2

Risk Factors for Men (N=152) and Women (N=200)

	Females Hazard Ratio	Males Hazard Ratio	Interaction Hazard Ratio	Interaction Standard Error	Interaction Test statistic	Interaction DF	Interaction P Value
Risk Factors for Time to a Future Major Depressive Episode							
Marital Status	0.98	0.94	0.99	0.31	−0.04	1	0.9714
Personal Income (per $10000)	1.00	1.00	1.00	0.06	−0.02	1	0.9850
Employment status	0.80	0.86	1.07	0.29	0.06	1	0.8160
Education years	**1.09**[1]	**1.13**	1.04	0.05	0.74	1	0.4578
Childhood Abuse	**1.49**	**1.46**	0.87	0.28	−0.51	1	0.6138
Scores on 17-item HAM-D	1.02	1.02	1.0	0.02	0.04	1	0.9720
Age of Onset of Depression	**0.98**	**0.99**	1.01	0.01	1.27	1	0.2050
Number of Prior MDE	1.02	1.03	1.0	0.02	0.13	1	0.8987
Family History of Depression	1.33	1.00	0.72	0.28	−1.21	1	0.2260
Suicidal Ideation	**1.02**	0.99	0.97	0.01	−2.50	1	**0.0124**
Any Past Suicide Attempt	1.39	0.74	0.53	0.27	−2.31	1	**0.0207**
Stressful Life Events	1.08	1.06	0.97	0.13	−0.22	1	0.829
Bipolar Disorder	1.35	1.40	1.06	0.29	0.19	1	0.8461
Risk Factors for Presence of Major Depressive Episode in Monthly Data During Follow-up							
Marital Status	0.97	1.14	1.18	0.26	0.62	348	0.5333
Personal Income (per $10000)	1.00	1.00	1.00	0.06	−0.02	348	0.4156
Employment status	**0.72**[1]	**0.65**	0.90	0.25	−0.40	348	0.6930
Education years	**1.06**	**1.09**	1.03	0.04	0.79	342	0.4295
Childhood Abuse	1.21	**1.75**	1.44	0.24	1.53	318	0.1265
Scores on 17-item HAM-D	1.01	1.03	1.01	0.02	0.66	348	0.5110
Age of Onset of Depression	**0.98**	**0.99**	1.01	0.01	0.68	332	0.4963
Number of Prior MDEs	1.02	1.05	1.03	0.02	1.45	329	0.1492
Family History of Depression	1.31	0.81	**0.62**	0.24	−2.03	347	**0.0436**
Suicidal Ideation	**1.02**	0.99	**0.97**	0.01	−2.75	320	**0.0063**
Any Past Suicide Attempt	**1.35**	0.70	**0.52**	0.24	−2.78	348	**0.0058**
Stressful Life Events	1.10	1.0	0.92	0.11	−0.77	311	0.4402

Risk Factors for Time to a Future Major Depressive Episode	Females Hazard Ratio	Males Hazard Ratio	Interaction Hazard Ratio	Interaction Standard Error	Interaction Test statistic	Interaction DF	Interaction P Value
Bipolar Disorder	**1.52**	**1.28**	0.84	0.25	−0.68	348	0.4979

[1] Bold effect sizes are significant.