Published in final edited form as:

Int Clin Psychopharmacol. 2018 September ; 33(5): 249–254. doi:10.1097/YIC.0000000000000225.

Effects of anxiety on suicidal ideation: exploratory analysis of a paroxetine versus bupropion randomized trial

Michelle S. Parris, BS, Julia E. Marver, BA, Sadia R. Chaudhury, PhD, Steven P. Ellis, PhD, Allison V. Metts, BA, John G. Keilp, PhD, Ainsley K. Burke, PhD, Maria A. Oquendo, MD, PhD*, J. John Mann, MD, and Michael F. Grunebaum, MD

Department of Psychiatry, Columbia University, and New York State Psychiatric Institute, New York, NY, USA

*Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Abstract

It is unclear whether anxiety increases or decreases suicidal risk. This may contribute to the lack of guidance on which antidepressant medications are best for suicidal depressed patients who present with high anxiety. This study explored whether anxiety predicts suicidal ideation in depressed individuals treated with paroxetine or bupropion. An 8-week double-blind trial comparing controlled release paroxetine ($N=36$) vs. extended-release bupropion ($N=38$) for effect on suicidal ideation and behavior in depressed patients with suicidal ideation, past attempt or both found an advantage for paroxetine, but anxiety effects were not investigated. This secondary analysis explored the relationship, measured at baseline and weekly, of anxiety with suicidal ideation. Anxiety severity measured weekly correlated with suicidal ideation severity irrespective of treatment ($p=0.012$). Patients with high baseline anxiety showed a trend towards faster reduction of suicidal ideation with paroxetine compared to bupropion treatment (standard $p=0.047$; bootstrap $p=0.077$). The latter finding, if confirmed in larger samples, could enhance choice of antidepressant medication for suicidal, depressed patients presenting with high levels of anxiety.

Keywords

Suicide; suicidal ideation; depression; anxiety; antidepressant

Introduction

There is a lack of evidence to guide pharmacotherapy for suicidal depressed patients. One frequent clinical challenge is how best to manage anxiety in suicidal patients since its effect on suicide risk is controversial (Bolton *et al.*, 2007; Brown *et al.*, 2000; Nakagawa *et al.*,

Correspondence: Michael F. Grunebaum, MD, Molecular Imaging and Neuropathology Division, New York State Psychiatric Institute, 1051 Riverside Drive, Box 42, New York, NY 10032. Tel. 646-774-7573 Fax 646-774-7589
michael.grunebaum@nyspi.columbia.edu.

Conflicts of Interest:

The other authors have no conflicts of interest related to this study.

2008; Nock *et al.*, 2010; Oquendo *et al.*, 1997; Placidi *et al.*, 2000; Sareen *et al.*, 2005; Sokero *et al.*, 2005). There is a lack of consensus as to whether anxiety is a risk factor for suicide attempts (Sokero *et al.*, 2005) or deaths (Brown *et al.*, 2000). Some studies found that anxiety symptoms and disorders predict suicidal ideation, attempts, and death, even adjusting for sociodemographic variables and psychiatric comorbidity (Bolton *et al.*, 2007; Fawcett *et al.*, 1990; Nock *et al.*, 2010; Sareen *et al.*, 2005). Other studies found no association or an inverse one between anxiety and suicidal ideation or behavior (Grunebaum *et al.*, 2005; Placidi *et al.*, 2000).

This knowledge gap is important because depression, the most frequent cause of suicidal ideation and behavior, and anxiety disorders are common and have a lifetime comorbidity estimated at almost 60% (Mineka *et al.*, 1998). Anxious depressed individuals experience greater distress (Papakostas and Larsen, 2011; Roy-Byrne *et al.*, 2000; Seo *et al.*, 2011) and have worse outcomes with antidepressant treatment in terms of symptom relief, side effects and serious adverse events (Fava *et al.*, 2008), particularly in treatment-resistant depression (De Carlo *et al.*, 2016; Wu *et al.*, 2013). Cross-sectional data suggest that lifetime suicidal ideation and behavior are more common in people with anxious depression (Fawcett *et al.*, 1990; Seo *et al.*, 2011). A recent meta-analysis found that anxiety symptoms and the presence of an anxiety diagnosis predicted subsequent suicidal ideation and attempt, though not suicide death, but the effect sizes were small ($OR = 1.39$ to 1.64). The authors suggested that limitations of existing research, such as how comorbidity or time-course are analyzed, may obscure clinically relevant associations between anxiety and suicidal ideation or behavior (Bentley *et al.*, 2016).

Serotonergic antidepressants appear to be efficacious for anxious depression and anxiety disorders in contrast to noradrenergic antidepressants (Baldwin *et al.*, 2005; Fava *et al.*, 2007; Papakostas *et al.*, 2008). In our trial comparing the selective serotonin reuptake inhibitor (SSRI) paroxetine ($N=36$) to the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion ($N=38$), in depressed suicide ideators or attempters, we found that patients with more severe suicidal ideation experienced greater reduction in suicidal ideation with paroxetine. No main effect of treatment on time to first suicide attempt was found (Grunebaum *et al.*, 2012). However, potential moderation of treatment effects by baseline anxiety was not explored (Grunebaum *et al.*, 2012).

We used data from the above trial to explore the effect of baseline anxiety symptoms in suicidal depression in terms of response to treatment of suicidal ideation. Our primary interest was the effect of baseline anxiety, a meaningful characteristic because it may guide clinicians in medication selection when initiating treatment. We hypothesized that higher *baseline* anxiety would predict greater reduction in suicidal ideation with paroxetine compared to bupropion treatment. Secondly, we examined anxiety across the 8-week trial to explore its longitudinal relationship with suicidal ideation. We predicted that decreased anxiety measured *weekly* would be associated with reduction in suicidal ideation over the eight weeks.

Methods

Patients

Methods and initial results have been reported (Grunebaum *et al.*, 2012). This 8-week RCT enrolled patients ($N=74$) with a current episode of DSM-IV major depressive disorder (MDD) who scored ≥ 16 on the Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960). Eligibility also required a history of a suicide attempt or score at screening evaluation ≥ 2 (“wishes to be dead or has any thoughts of possible death to self”) on the HDRS suicide item, or both. Exclusions were: bipolar disorder, psychosis, drug or alcohol dependence within six months, and unstable medical or neurological illness. The study was approved by the Institutional Review Board at the New York State Psychiatric Institute and was conducted in compliance with the standards established in the Declaration of Helsinki. After complete study description, written informed consent was obtained from all participants. After baseline assessments, participants were randomized 1:1 to 8-week treatment with controlled-release oral paroxetine ($N=36$) or extended-release bupropion ($N=38$). Participants met weekly with a research psychiatrist for medication management and a psychologist for research ratings. Dosing began at 25mg paroxetine or 150mg bupropion daily, increasing in standardized increments to 50mg or 450mg, respectively. Participants, psychiatrists, and raters were blind to treatment. Baseline clinical and demographic variables are summarized in Table 1 (for additional variables see Grunebaum *et al.*, 2012). Treatment groups did not differ in demographic characteristics, comorbid Cluster B, lifetime substance use disorders, or history of prior suicide attempts (Grunebaum *et al.*, 2012).

Outcome and Measures

Clinical assessors were masters or doctoral-level psychologists. Inter-rater reliability was high ($ICC_{HDRS-17}=94\%$, $ICC_{SSI}=97\%$) and maintained through weekly consensus conferences and videotapes. The Structured Clinical Interview for DSM-IV (SCID-I and II) was used to diagnose Axis I and Axis II disorders (First *et al.*, 2002; First *et al.*, 1996). Depressive symptoms were measured using the HDRS-24. The Columbia Suicide History Form (Oquendo *et al.*, 2003) was used to classify suicidal events. The clinician-rated Beck Scale for Suicidal Ideation (SSI; Beck *et al.*, 1979) was used to measure frequency and intensity of suicidal ideation at baseline and weekly. Since this exploratory analysis was not pre-planned, the study did not include a specific anxiety scale. To measure anxiety, we used an anxiety symptom cluster extracted through a factor analysis of the HDRS-24, in which we used a polychoric correlation method that corrects for the limited range of rating scale responses (Grunebaum *et al.*, 2005; Keilp *et al.*, 2012). The anxiety cluster comprises HDRS items assessing agitation, psychic anxiety, somatic anxiety and hypochondriasis, and in this sample at baseline had a range of 0 to 9, Mean=3.9 (SD=2.1; Median=4), and a normal distribution.

Statistical Methods

The outcome of interest was SSI score during Weeks 1–8 (baseline SSI was excluded from the outcome). Generalized least squares regression for correlated longitudinal data was used to model SSI score across the eight weeks for each subject and compare between treatment groups (Pinheiro and Bates, 2000). Because we expected the rate of change of suicidal

ideation to decrease with time, we used a natural log transformation of time. To test our hypothesis that *baseline* anxiety would moderate the effect of treatment group on SSI score, we first tested a *full* model with main effects of treatment, natural log(time), baseline inpatient status, past suicide attempt (yes/no), baseline SSI, baseline anxiety, the 3-way interaction of treatment X ln(time) X baseline anxiety and the associated 2-way interactions. We then tested a *reduced* model with only the variables essential to the research question, with main effects of baseline SSI, baseline anxiety, treatment, and the interaction of baseline anxiety X treatment.

We fitted regressions comparing nine different correlation structures and the best, ARMA(1,1), was used based on the smallest value of the Bayes Information Criterion (BIC). We checked for data collinearity following the guideline that the variance inflation factor (VIF) should not exceed 10 (Kleinbaum *et al.*, 2008). To compute *p*-values that allow for collinearity, we performed bootstrap calculations (Efron and Tibshirani, 1993) with *B*=10,000 resamples, keeping each subject's time points together. To illustrate the effect of baseline anxiety on differential treatment response, we used the model fitted to the full sample to estimate the mean difference in suicidal ideation between treatment groups for subjects at the median (score=7) of the highest quartile of baseline anxiety. As a check, we bootstrapped this analysis using the full study sample.

To explore the longitudinal relationship of anxiety with suicidal ideation, we fitted the reduced regression model above, substituting anxiety measured weekly instead of the baseline anxiety X treatment interaction term, and also tested for an interaction of weekly anxiety with treatment. All statistical tests were two-sided and used SPSS version 23 or R software version 3.3.2.

Results

Baseline Anxiety

Baseline anxiety did not differ between treatment groups ($t=-3.78$, $df=72$, $p=0.706$). Subjects with higher baseline anxiety (median split) and allocated to bupropion had higher SSI scores at baseline compared to those allocated to paroxetine ($t=-2.31$, $df=40$, $p=0.026$), but as noted above, all models adjusted for baseline SSI. There was evidence of collinearity with the full model (VIF=23.47), but not the reduced model (VIF=5.25), which also had a lower (better) BIC value of 2921. The reduced (best) model showed a significant interaction of *baseline* anxiety with treatment, such that patients with high baseline anxiety experienced a greater reduction in suicidal ideation on paroxetine compared with bupropion ($t=-2.03$, $p=0.047$) (Table 2). The bootstrapped *p*-value was at a trend-level of statistical significance ($p=0.077$). The model of differential treatment effect in the subgroup with baseline anxiety in the highest quartile ($n=17$) predicted 4.36 (SE=1.71) points lower suicidal ideation, on average, with paroxetine compared to bupropion treatment ($p=0.010$). In the full study sample, the bootstrap showed $p=0.055$. Figure 1 illustrates mean SSI score by treatment group for subjects who presented with baseline anxiety in the highest quartile ($n=17$).

Longitudinal Anxiety

Adjusting for baseline anxiety and baseline SSI, anxiety assessed weekly was associated with weekly suicidal ideation severity (Estimate=0.32 (95% CI 0.07 to 0.57), $df=472.31$, $t=2.54$, $p=0.012$) (Table 3). An interaction term for weekly anxiety X treatment group was not significant ($p=0.53$), indicating that the longitudinal correlation of anxiety with SSI score was not different between treatment groups.

Discussion

In this post-hoc analysis of a randomized antidepressant trial in suicide ideators and attempters with MDD, we found that individuals presenting with high anxiety at baseline had less severe suicidal ideation over time with paroxetine compared with bupropion treatment. This moderating effect on treatment was at the trend-level of statistical significance in a rigorous bootstrap analysis. Anxiety assessed longitudinally was significantly associated with suicidal ideation severity irrespective of treatment group.

Best pharmacotherapeutic practices for depressed, suicidal patients with high anxiety – a relatively frequent clinical scenario – are uncertain. There are few, if any, reliable moderators of antidepressant treatment to guide initial medication choice for patients based upon clinical presentation. Increased anxiety or agitation during the initial days of antidepressant pharmacotherapy has been cited as a possible risk factor for suicidal behavior, and patients with anxious depression may be at greater risk (Sinclair *et al.*, 2009). A recent, patient-level analysis of placebo-controlled SSRI trials ($N=8,262$) found that SSRI-treated patients were more likely to report increased somatic anxiety, but less likely to experience increased psychic anxiety or psychomotor agitation during the first treatment week compared with placebo (Naslund *et al.*, 2017). Our post-hoc analysis results are partially consistent with the latter study in that patients with the highest levels of baseline anxiety experienced a greater decrease in suicidal ideation during the initial weeks of treatment with paroxetine compared with bupropion, suggesting a possible early, anxiolytic SSRI effect.

Anxiety and suicidal ideation are linked theoretically and biologically. Both may partly involve avoidant reactions to aversive emotions and self-appraisals (Barlow *et al.*, 2014; Baumeister, 1990). Reducing anxiety may help relieve a desire to escape by suicide. Serotonin hypofunction is implicated in both anxiety and suicide. Suicide decedents and attempters show lower cerebrospinal fluid levels of 5-hydroxyindoleacetic acid, serotonin's main metabolite, fewer serotonin transporter sites in numerous brain regions, and upregulation of post-synaptic 5-HT_{1A} and 5-HT_{2A} serotonin receptors in ventral prefrontal cortex (Mann, 2003). The efficacy of SSRIs in treating a number of anxiety disorders indicates a role of serotonin dysfunction in anxiety as well (Kent *et al.*, 1998). Other studies have linked serotonin function, including 5-HT_{1A} and 5-HT_{2A} serotonin receptors, to anxiety (Coplan *et al.*, 2014; Ramboz *et al.*, 1998; Sullivan *et al.*, 2013; Sullivan *et al.*, 2005; Weisstaub *et al.*, 2006). Thus, paroxetine's modulation of serotonin functioning may be specifically beneficial for suicidal depressed individuals who present with high anxiety.

Nonetheless, studies of the differential effects of SSRIs versus other antidepressants for anxious versus non-anxious depression have been inconclusive (Fava *et al.*, 2008; Rush *et*

et al., 2001). Serotonin-norepinephrine reuptake inhibitors (Papakostas and Larsen, 2011) and tricyclic antidepressants (Uher *et al.*, 2011) have demonstrated efficacy comparable to SSRIs for depression, but effects on suicidal ideation were not reported. Bupropion is generally avoided in the management of anxiety disorders and anxious depression, because of its potential to exacerbate anxiety and lack of efficacy for panic attacks (Preskorn, 1995), though this concern is debated (Fava *et al.*, 2005; Stahl *et al.*, 2004; Zimmerman *et al.*, 2005). In contrast to SSRIs, bupropion is not approved by the Federal Drug Administration (FDA) for the treatment of anxiety disorders. Nonetheless, trials of SSRIs versus bupropion have yielded equivocal results for differential effects on depression or anxiety symptoms (Fava *et al.*, 2008; Rush *et al.*, 2001). A meta-analysis of data from 10 double-blind RCTs did not find a difference in response to treatment with SSRIs versus bupropion for depression or anxiety symptoms (Papakostas *et al.*, 2008). Randomized trials in suicidal patients are few, and none of the above studies investigated suicidal ideation as an outcome.

The results of this study should be interpreted with the following limitations in mind. The study lacked an anxiety scale, but the HDRS anxiety symptom cluster used was systematically derived (Grunebaum *et al.*, 2012; Keilp *et al.*, 2012) and similar to other post hoc study methods (Naslund *et al.*, 2017). Although baseline anxiety did not differ between groups, randomization was not stratified by anxiety severity. All models adjusted for baseline anxiety and baseline SSI scores. There was evidence of collinearity in the full model, so we focused on the reduced model and used bootstrapping for more rigorous *p*-values. Given that patients with anxious depression were not specifically selected for, the generalizability of these findings to a wider clinical population must be considered. Patients presenting with comorbid Axis I anxiety disorders and suicidal depression may respond differently from patients with anxiety symptoms as studied here. Additional limitations include the chance of false positives or negatives, as with any post hoc analysis, and the relatively small sample size. Finally, subjects with higher average SSI scores across the 8-week trial were more likely to miss visits ($p=0.032$), however the number of missed visits did not differ between treatment groups ($p=0.115$). The main strength of our study is that it is one of relatively few RCTs to purposefully recruit depressed suicide ideators and attempters, and thus was enriched for the outcome of interest. Suicidal patients have often been excluded from clinical trials limiting the evidence base for this population (Zimmerman *et al.*, 2002).

Conclusion

FDA-approved medications for mood disorders take weeks to work while suicidal patients need rapid relief. The American Psychiatric Association's guideline states, "evidence for a lowering of suicide rates with antidepressant treatment is inconclusive" (Jacobs *et al.*, 2003), and the 26.5% increase in US suicide rates from 1999 to 2015 (CDC, 2017) underscores this gap in treatment. Depression predicts suicide attempts partly via its effect on suicidal ideation (Nock *et al.*, 2010). Our exploratory results find that higher ongoing anxiety correlates with higher suicidal ideation, irrespective of treatment. Future studies should examine possible stratification factors (e.g., trait anxiety versus Axis I anxiety disorders) that may affect this relationship, given the mixed results reported in the literature. The trend-level results, suggesting a moderating effect of *baseline* anxiety on treatment, generate a

hypothesis that suicidal, depressed patients presenting with high anxiety may get faster relief of suicidal ideation with an SSRI compared with a noradrenergic medication. This possibility merits testing in a larger sample or existing dataset.

Acknowledgments

Source of Funding: Dr. Mann receives royalties from the Research Foundation for Mental Hygiene for use of the Columbia Suicide Severity Rating Scale (C-SSRS), which was not used in this study. Dr. Oquendo receives royalties for use of the C-SSRS. Her family owns stock in Bristol Myers Squibb. Dr. Burke receives royalties for use of the C-SSRS. No pharmaceutical company was involved in the design or conduct of the study, had access to data or any role in data analysis or presentation.

This work was supported by NARSAD Young Investigator (Grunebaum), NIMH K23 MH076049 (Grunebaum) and MH62185 (Mann) grants. Paroxetine CR and bupropion XL pills were donated by GSK in the study's first 3 years and then purchased with grant funds. Dr. Grunebaum received no other support from GSK for this study. NARSAD, NIMH and GSK had no role in the design and conduct of the study, the collection, analysis, and interpretation of the data, or preparation, review, or approval of the manuscript.

None.

References

- Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson JRT, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2005; 19:567–596. [PubMed: 16272179]
- Barlow DH, Sauer-Zavala S, Carl JR, Bullis JR, Ellard KK. The nature, diagnosis, and treatment of neuroticism: back to the future. *Clin Psychol Sci*. 2014; 2:344–365.
- Baumeister RF. Suicide as escape from self. *Psychol Rev*. 1990; 97:90–113. [PubMed: 2408091]
- Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol*. 1979; 47:343–352. [PubMed: 469082]
- Bentley KH, Franklin JC, Ribeiro JD, Kleiman EM, Fox KR, Nock MK. Anxiety and its disorders as risk factors for suicidal thoughts and behaviors: a meta-analytic review. *Clin Psychol Rev*. 2016; 43:30–46. [PubMed: 26688478]
- Bolton JM, Cox BJ, Afifi TO, Enns MW, Bienvenu OJ, Sareen J. Anxiety disorders and risk for suicide attempts: findings from the Baltimore epidemiologic catchment area follow-up study. *Depress Anxiety*. 2007; 25:477–481.
- Brown GK, Beck AT, Steer RA, Grisham JR. Risk factors for suicide in psychiatric outpatients: a 20-year prospective study. *J Consult Clin Psychol*. 2000; 68:371–377. [PubMed: 10883553]
- Centers for Disease Control and Prevention. [Accessed 24 May 2017] Fatal injury reports, national, regional and state, 1981–2015. Available from: <https://webappa.cdc.gov/sasweb/ncipc/mortrate.html>
- Coplan JD, Fulton SL, Reiner W, Jackowski A, Panthangi V, Perera TD, et al. Elevated cerebrospinal fluid 5-hydroxyindoleacetic acid in macaques following early life stress and inverse association with hippocampal volume: preliminary implications for serotonin-related function in mood and anxiety disorders. *Front Behav Neurosci*. 2014; 8(440):1–14. DOI: 10.3389/fnbeh.2014.00440 [PubMed: 24478648]
- De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: a systematic review. *Psychiatry Res*. 2016; 240:421–430. [PubMed: 27155594]
- Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. New York: Chapman & Hall; 1993
- Fava M, Martinez JM, Greist J, Marangell LB, Brown E, Chen L, et al. The efficacy and tolerability of duloxetine in the treatment of anxious versus non-anxious depression: a post-hoc analysis of an open-label outpatient study. *Ann Clin Psychiatry*. 2007; 19:187–195. [PubMed: 17729021]

- Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry*. 2008; 165:342–351. [PubMed: 18172020]
- Fava M, Rush AJ, Thase ME, Clayton A, Stahl SM, Pradko JF, et al. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry*. 2005; 7:106–113. [PubMed: 16027765]
- Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, et al. Time-related predictors of suicide in major affective disorder. *Am J Psychiatry*. 1990; 147:1189–1194. [PubMed: 2104515]
- FirstMB, , SpitzerRL, , GibbonM, , WilliamsJB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P) New York: New York State Psychiatric Institute, Biometrics Research; 2002
- FirstMB, , SpitzerRL, , GibbonM, , WilliamsJB, , BenjaminL. Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II), version 2.0 New York: Biometrics Research Department, New York State Psychiatric Institute; 1996
- Grunebaum MF, Ellis SP, Duan N, Burke AK, Oquendo MA, Mann JJ. Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. *Neuropsychopharmacology*. 2012; 37:697–706. [PubMed: 21993207]
- Grunebaum MF, Keilp J, Li S, Ellis SP, Burke AK, Oquendo MA, et al. Symptom components of standard depression scales and past suicidal behavior. *J Affect Disord*. 2005; 87:73–82. [PubMed: 15923041]
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; 23:56–62. [PubMed: 14399272]
- JacobsDG, , BaldessariniRJ, , ConwellY, , FawcettJA, , HortonL, , MeltzerH. Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors Washington DC: American Psychiatric Publishing, Inc; 2003
- Keilp JG, Grunebaum MF, Gorlyn M, LeBlanc S, Burke AK, Galfalvy H, et al. Suicidal ideation and the subjective aspects of depression. *J Affect Disord*. 2012; 140:75–81. [PubMed: 22406338]
- Kent JM, Coplan JD, Gorman JM. Clinical utility of the selective serotonin reuptake inhibitors in the spectrum of anxiety. *Biol Psychiatry*. 1998; 44:812–824. [PubMed: 9807637]
- KleinbaumDG, , KupperLL, , NizamA, , MullerK. Applied Regression Analysis and Other Multivariable Methods fourth. Belmont, CA: Duxbury Applied; 2008
- Mann JJ. Neurobiology of suicidal behaviour. *Nature Rev Neurosci*. 2003; 4:819–828. [PubMed: 14523381]
- Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. *Annu Rev Psychol*. 1998; 49:377–412. [PubMed: 9496627]
- Nakagawa A, Grunebaum MF, Sullivan GM, Currier D, Ellis SP, Burke AK, et al. Comorbid anxiety in bipolar disorder: does it have an independent effect on suicidality? *Bipolar Disord*. 2008; 10:530–538. [PubMed: 18452449]
- Naslund J, Hieronymus F, Emilsson JF, Lisinski A, Nilsson S, Eriksson E. Incidence of early anxiety aggravation in trials of selective serotonin reuptake inhibitors in depression. *Acta Psychiatr Scand*. 2017; 136:343–351. [PubMed: 28859218]
- Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010; 15:868–876. [PubMed: 19337207]
- OquendoMA, , HalberstamB, , MannJJ. Risk factors for suicidal behavior: the utility and limitations of research instruments. In: FirstMB, editor Standardized evaluation in clinical practice Washington, DC: APPI Press; 2003 103130
- Oquendo MA, Malone KM, Mann JJ. Suicide: risk factors and prevention in refractory major depression. *Depress Anxiety*. 1997; 5:202–211. [PubMed: 9338112]
- Papakostas GI, Larsen K. Testing anxious depression as a predictor and moderator of symptom improvement in major depressive disorder during treatment with escitalopram. *Eur Arch Psychiatry Clin Neurosci*. 2011; 261:147–156. [PubMed: 20859636]
- Papakostas GI, Trivedi MH, Alpert JE, Seifert CA, Krishen A, Goodale EP, et al. Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of anxiety symptoms in

- major depressive disorder: a meta-analysis of individual patient data from 10 double-blind, randomized clinical trials. *J Psychiatr Res.* 2008; 42:134–140. [PubMed: 17631898]
- PinheiroJC, , BatesDM. *Mixed-Effects Models in S and S-PLUS*New York: Springer Science & Business Media; 2000
- Placidi GP, Oquendo MA, Malone KM, Brodsky B, Ellis SP, Mann JJ. Anxiety in major depression: relationship to suicide attempts. *Am J Psychiatry.* 2000; 157:1614–1618. [PubMed: 11007715]
- Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry.* 1995; 56(suppl 6):12–21. [PubMed: 7649968]
- Ramboz S, Oosting R, Amara DA, Kung HF, Blier P, Mendelsohn M, et al. Serotonin receptor 1A knockout: an animal model of anxiety-related disorder. *Proc Natl Acad Sci USA.* 1998; 95:14476–14481. [PubMed: 9826725]
- Roy-Byrne PP, Stang P, Wittchen HU, Ustun B, Walters E, Kessler RC. Lifetime panic-depression comorbidity in the National Comorbidity Survey: association with symptoms, impairment, course and help-seeking. *Br J Psychiatry.* 2000; 176:229–235. [PubMed: 10755069]
- Rush AJ, Trivedi MH, Carmody TJ, Donahue RMJ, Houser TL, Bolden-Watson C, et al. Response in relation to baseline anxiety levels in major depressive disorder treated with bupropion sustained release or sertraline. *Neuropsychopharmacology.* 2001; 25:131–138. [PubMed: 11377926]
- Sareen J, Cox BJ, Afifi TO, de Graaf R, Asmundson GJG, ten Have M, et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. *Arch Gen Psychiatry.* 2005; 62:1249–1257. [PubMed: 16275812]
- Sareen J, Houlihan T, Cox BJ, Asmundson GJ. Anxiety disorders associated with suicidal ideation and suicide attempts in the National Comorbidity Survey. *J Nerv Ment Dis.* 2005; 193:450–454. [PubMed: 15985839]
- Seo HJ, Jung YE, Kim TS, Kim JB, Lee MS, Kim JM, et al. Distinctive clinical characteristics and suicidal tendencies of patients with anxious depression. *J Nerv Ment Dis.* 2011; 199:42–48. [PubMed: 21206246]
- Sinclair LI, Christmas DM, Hood SD, Potokar JP, Robertson A, Isaac A, et al. Antidepressant-induced jitteriness/anxiety syndrome: systematic review. *Br J Psychiatry.* 2009; 194:483–490. [PubMed: 19478285]
- Sokero TP, Melartin TK, Rytsala HJ, Leskela US, Lestela-Mielonen PS, Isometsa ET. Prospective study of risk factors for attempted suicide among patients with DSM-IV major depressive disorder. *Br J Psychiatry.* 2005; 186:314–318. [PubMed: 15802688]
- Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion J Clin Psychiatry.* 2004; 6:159–166. [PubMed: 15361919]
- Sullivan GM, Ogden RT, Huang YY, Oquendo MA, Mann JJ, Parsey RV. Higher in vivo serotonin-1A binding in posttraumatic stress disorder: a PET study with [¹¹C]WAY-100635. *Depress Anxiety.* 2013; 30:197–206. [PubMed: 23408467]
- Sullivan GM, Oquendo MA, Simpson N, Van Heertum RL, Mann JJ, Parsey RV. Brain serotonin-1A receptor binding in major depression is related to psychic and somatic anxiety. *Biol Psychiatry.* 2005; 58:947–954. [PubMed: 16039621]
- Uher R, Dernovsek MZ, Mors O, Hauser J, Souery D, Zobel A, et al. Melancholic, atypical and anxious depression subtypes and outcome of treatment with escitalopram and nortriptyline. *J Affect Disord.* 2011; 132:112–120. [PubMed: 21411156]
- Weisstaub NV, Zhou M, Lira A, Lambe E, González-Maeso J, Hornung J-P, et al. Cortical 5-HT_{2A} receptor signaling modulates anxiety-like behaviors in mice. *Science.* 2006; 313:536–540. [PubMed: 16873667]
- Wu Z, Chen J, Yuan C, Hong W, Peng D, Zhang C, et al. Difference in remission in a Chinese population with anxious versus nonanxious treatment-resistant depression: a report of OPERATION study. *J Affect Disord.* 2013; 150:834–839. [PubMed: 23570952]
- Zimmerman M, Mattia JJ, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry.* 2002; 159:469–473. [PubMed: 11870014]

Zimmerman M, Posternak MA, Attiullah N, Friedman M, Boland RJ, Baymiller S, et al. Why isn't bupropion the most frequently prescribed antidepressant? J Clin Psychiatry. 2005; 66:603–610. [PubMed: 15889947]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

FIGURE 1.

Beck Scale of Suicidal Ideation mean score by study week in suicidal, depressed subjects at highest quartile of baseline HDRS anxiety factor randomized to controlled-release paroxetine or extended-release bupropion¹.

¹Predicted difference in SSI score between groups = 4.36 (SE=1.71) points lower, on average, with paroxetine compared to bupropion (assumes baseline HDRS Anxiety factor at highest quartile median=7; p=0.010; bootstrapped p=0.055; based on fitted reduced model using all subjects' data). Error bars are SEM.

Table 1Baseline demographic and clinical characteristics by treatment group ($N=74$).

Variable	Bupropion ($N=38$), mean (SD) ¹	Paroxetine ($N=36$), mean (SD) ¹
Age	38.0 (12.0)	35.2 (12.7)
Female, no. (%)	21 (55.3)	21 (58.3)
Scale for Suicidal Ideation	10.0 (7.4)	8.0 (6.7)
Suicide item of Hamilton Depression Rating Scale	1.95 (1.09)	1.75 (1.23)
Hamilton Depression Rating Scale (17-item)	19.5 (5.5)	18.7 (6.4)
Anxiety severity ²	4.1 (1.9)	3.9 (2.4)
Number of past major depressive episodes, median (IQR) ³	4.0 (1.8–12.0)	3.0 (2.0–19.5)
History of past suicide attempt at randomization, no. (%)	22 (57.9)	21 (58.3)

¹Except where otherwise noted.²Anxiety symptom cluster of Hamilton Depression Rating Scale: sum of items assessing agitation, psychic anxiety, somatic anxiety, and hypochondriasis.³Truncated at 50.

Table 2

Reduced (best) model¹ of baseline anxiety effect on suicidal ideation during 8-week treatment of depressed suicide ideators and attempters randomized to controlled-release paroxetine (N=36) or extended-release bupropion (N=38).²

Variable	Estimate (95% CI)	df	t	p-value
Baseline suicidal ideation	0.47 (0.34 to 0.61)	64.98	6.90	<0.001
Treatment	2.25 (−1.86 to 6.36)	65.69	1.09	0.278
Log Time	−1.01 (−1.72 to −0.29)	154.25	−2.80	0.006
Baseline anxiety	0.90 (0.18 to 1.62)	69.61	2.49	0.015
Baseline anxiety X treatment	−0.93 (−1.85 to −0.01)	66.56	−2.03	0.047

¹ ARMA(1,1) covariance structure.

² BIC = 2884.39

Table 3

Generalized least squares model of relationship of anxiety measured weekly to suicidal ideation during 8-week treatment of depressed suicide ideators and attempters randomized to controlled-release paroxetine (N=36) or extended-release bupropion (N=38).

Variable	Estimate (95% CI)	df	t	p-value
Baseline suicidal ideation	0.49 (0.36 to 0.62)	67.11	7.71	<0.001
Treatment	-1.31 (-3.11 to 0.49)	68.97	-1.45	0.152
Log Time	-0.94 (-1.64 to -0.24)	153.81	-2.67	0.008
Baseline anxiety	0.15 (-0.28 to 0.58)	74.60	0.71	0.482
Anxiety measured weekly	0.32 (0.07 to 0.57)	472.31	2.54	0.012