Side Effects to Antidepressant Treatment in Patients With Depression and Comorbid Panic Disorder

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ABSTRACT

Objective: Side effects to antidepressant medication can affect the efficacy of treatment, but few predictors foretell who experiences side effects and which side effects they experience. This secondary data analysis examined whether depressed patients with comorbid panic disorder were more likely to experience side effects than those without panic disorder. The study also examined whether greater burden of side effects predicted a poorer treatment course for patients with panic disorder than those without panic disorder. To examine the specificity of these effects, analyses also examined 2 other anxiety disorders—social phobia and generalized anxiety disorder (GAD).

Methods: Between 2002 and 2006, a large sample (N = 808) of chronically depressed individuals (assessed using the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders [SCID-IV]) received antidepressants according to a predetermined algorithm for 12 weeks. Every 2 weeks, depressive symptoms (per the Hamilton Depression Rating Scale) and side effects (specific side effects as well as several indicators of side effect burden) were assessed.

Results: Lifetime diagnosis of panic disorder (assessed using the SCID-IV) at baseline was associated with higher likelihood of gastrointestinal (OR = 1.6 [95% CI, 1.0–2.6]), cardiac (OR = 1.8 [95% CI, 1.1–3.1]), neurologic (OR = 2.6 [95% CI, 1.6–4.2]), and genitourinary side effects (OR = 3.0 [95% CI, 1.7–5.3]) during treatment. Increases in side effect frequency, intensity, and impairment over time were more strongly associated with increases in depressive symptoms for patients with panic disorder compared to those without panic disorder. Neither social phobia nor GAD was associated with these effects.

Conclusions: Potentially due to heightened interoceptive awareness of changes in their body, chronically depressed individuals with panic disorder may be at greater risk than those without panic disorder for antidepressant side effects and to experience a worsening of depressive symptoms as a result of these side effects over time.

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Although antidepressant treatments have advanced considerably over the last several decades, treatment response varies greatly, both between individuals and within individuals across time.[1,2] Contributing to this varied response may be the experience of medication side effects. Although antidepressant side effect profiles vary with the particular pharmacologic agent, across most antidepressants, side effects have been shown to lead to treatment discontinuation and secondary adverse events[3,4] (though see Warden et al[5]). It is therefore important to identify pretreatment variables that may predict side effects in depressed individuals, as clinicians may want to target (or at least be aware of) these pretreatment variables.

One predictor of side effects is the presence of a comorbid anxiety disorder—a class of disorders that frequently co-occur with depression[6,7] and predict a poorer course of depression.[8–10] Indeed, several studies have shown that depressed patients with comorbid anxiety disorder or anxiety symptoms are more likely to experience side effects in response to a broad range of antidepressants.[11–13]

Anxiety disorders, however, are heterogeneous. Hence, an examination of "any comorbid anxiety disorder" (or administration of a nonspecific anxiety symptom scale) may mask critical associations with particular side effect profiles. One particular comorbid anxiety disorder often associated with antidepressant side effects is panic disorder. Numerous studies[14,15] have shown that because individuals with panic disorder exhibit heightened interoceptive awareness (ie, sensing internal bodily changes), they may experience greater attunement to physiologic changes during an antidepressant trial. Thus, heightened interoceptive awareness may render depressed individuals with panic disorder more likely to report antidepressant medication side effects. Supporting this hypothesis, Rollman et al[16] found that a small sample (n = 22) of patients with depression and comorbid panic disorder exhibited more physical symptom side effects during antidepressant treatment than those without comorbid panic disorder. This older study, however, examined the side effects of tricyclic antidepressants and not selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine

Clinical Points

- Patients with major depression often present with comorbid anxiety disorders, but little is known about the relationship between these anxiety disorders and antidepressant treatment.
- It is important to assess for comorbid panic disorder when treating patients' major depression because panic disorder is associated with greater experience of side effects and worse treatment response in depressed patients.

reuptake inhibitor (SNRI) medications, which are the first-line treatments recommended today.[17] Thus, the first aim of the present study is to examine whether a lifetime diagnosis of a comorbid panic disorder predicts more antidepressant side effects among depressed patients.

As a second aim, this study examined the role of side effects on antidepressant response in patients with comorbid panic disorder. If depressed patients with comorbid panic disorder report more side effects, those side effects might well compromise their treatment response. Thus, greater intercurrent treatment side effects should be associated with worse depressive symptoms for those with comorbid panic disorder compared to those without comorbid panic disorder.

To examine the specificity of comorbid panic disorder, this study examined the impact of 2 other anxiety disorders on side effects: generalized anxiety disorder (GAD) and social phobia. These are good comparison disorders for panic disorder for several reasons. First, individuals with GAD and social phobia often experience panic attacks and, like those with panic disorder, experience a chronic and debilitating course.[18–20] Second, many GAD symptoms overlap with panic disorder (most notably hyperarousal symptoms), but GAD has a weaker association with interoceptive awareness than does panic disorder.[21]

Antidepressant side effects are notably heterogeneous. Thus, rather than examining the impact of comorbid panic disorder, GAD, and social phobia on the presence of any side effect, this study examined side effects in discrete organ systems, eg, gastrointestinal, sexual functioning. The side effect classes selected for the present study were those examined in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[22] and represent the major classes of side effects experienced during antidepressant trials.[23]

Last, the present study focused on patients with chronic depression. Chronic depression is associated with greater anxiety comorbidity, higher rates of suicidality, higher likelihood of relapse, and worse treatment response compared to nonchronic depression.[24–26] Thus, examining side effects as predictors in this particularly difficult to treat subtype has high clinical importance.

In summary, we hypothesized that (1) patients with chronic depression and comorbid panic disorder would be more likely to report antidepressant medication side effects than those without comorbid panic disorder and (2) as antidepressant side effects should interfere with treatment response more for patients with comorbid panic disorder, changes in side effect burden over time in these patients would covary with changes in depressive symptoms over time (ie, as side effects worsen, depression should worsen).

To examine the specificity of these associations with panic disorder, the study also assessed the effects of comorbid social phobia and GAD.

METHODS

Design

The present study's data derived from the Research Evaluating the Value of Augmenting Medication with Psychotherapy (REVAMP) trial (ClinicalTrials.gov identifier: NCT00057551).[27] REVAMP took place at 8 academic centers between 2002 and 2006 and comprised 2 phases. The present study used data only from phase 1. In phase 1, participants meeting criteria for a chronic form of major depression were openly assigned to an antidepressant medication according to a pharmacotherapy algorithm (see later in the Methods section) for 12 weeks. Phase 2 tested whether the addition of psychotherapy improved treatment response beyond changing the phase 1 medication (see Kocsis et al[27] for details regarding phase 2). The present study examined the associations between comorbid anxiety disorders (assessed with the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders [SCID-IV]) and participant report of side effects only in phase 1, as this phase had the largest number of patients and did not confound antidepressant medication with psychotherapy.

For the present study, it was not possible to isolate the effects of specific medications for several reasons. First, there was no washout period prior to a medication switching, making it impossible to determine whether the side effect was related to the old medication, the new medication, or some combination. Second, given the large number of different medication regimens, the study did not have the power to examine the effects of anxiety disorders on specific medications. Given these reasons, the analyses examined the sample as a whole.

Patients

All REVAMP patients met criteria for current major depressive disorder (MDD) assessed with the SCID-IV[28] for at least 4 weeks, with unremitting depressive symptoms for at least 2 years. Participants ranged in age from 18 to 75 years and scored at least 20 on the 24-item Hamilton Depression Rating Scale (HDRS)[29] at study entry.

REVAMP exclusion criteria included pregnancy; current psychosis; history of mania; current primary diagnosis of posttraumatic stress disorder, anorexia nervosa, bulimia nervosa, or obsessive-compulsive disorder; current antisocial, schizotypal, or borderline personality disorder; current dementia; and current, severe alcohol or other substance dependence. Individuals previously treated with Cognitive Behavioral Analysis System of Psychotherapy, having previously failed to respond to >4 medications in

Table 1. Sample Characteristics at Baseline (Total N = 808)

Variable	Value
Age, mean (SD), y	44.16 (12.41)
Female, % (n)	55.9 (452)
Ethnicity, n (%)[a]	
African American	66 (8.2)
American Indian/Native American	20 (2.5)
Asian	29 (3.6)
White	711 (88)
Hawaiian/Pacific Islander	12 (1.5)
Latino	61 (7.5)
Baseline Hamilton Depression Rating Scale score, mean (SD)	28.51 (5.87)
Medication, n (%)	
Sertaline only	361 (44.7)
Sertraline, switching to bupropion	123 (15.2)
Sertraline, switching to escitalopram	83 (10.3)
Bupropion only	37 (4.6)
Other	152 (18.8)

[a]Participants were permitted to select multiple ethnicities. As such, the sum of the ethnic group members is greater than the participant total.

the pharmacotherapy algorithm, unwilling to stop other psychotropic regimens, and with serious physical illness were excluded as well.[27]

The present study included all 808 phase 1 patient enrollees (see Table 1). The study sample contained more women than men and significantly more white individuals than individuals of other ethnicities.

Materials

Side effects. Every 2 weeks, antidepressant side effects were assessed using 2 measures—the Patient-Rated Inventory of Side Effects (PRISE)[22] and the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER).[22] The PRISE checklist assesses 26 separate side effects in 8 different biological systems: gastrointestinal (diarrhea, constipation, dry mouth, nausea/vomiting), cardiovascular (heart palpitations, dizziness on standing, chest pain), dermatologic (rash, increased perspiration, itching, dry skin), neurologic (headache, tremors, poor concentration, dizziness), eye/ear (blurred vision, ringing in ears), genitourinary (difficulty urinating, painful urination, frequent urination, menstrual irregularity), sleep (difficulty sleeping, sleeping too much), and sexual functioning (loss of sexual desire, trouble achieving orgasm, trouble with erections). Participants were instructed to indicate whether they experienced the side effect during the past 7 days. Within the 8 categories, participants rated whether their worst side effect was distressing or tolerable. In this study, a side effect category was considered present only if a patient deemed it distressing and not if it was tolerable.

Subjective ratings of side effect burden were collected with the FIBSER, developed by Rush et al[22] for the STAR*D study. The questionnaire comprises 3 questions asking patients to rate the frequency, intensity, and impairment caused by their overall side effects on a 7-point Likert scale ranging from 0 to 6. The FIBSER has demonstrated strong reliability and validity.[23]

Depressive symptoms. The 24-question HDRS is a clinician-administered scale assessing the frequency and intensity of and impairment caused by depressive symptoms in the past 7 days. It has adequate internal consistency and interrater reliability.[30] The HDRS was administered every 2 weeks at the same time as the PRISE and FIBSER. Each site has previously demonstrated strong interrater reliability for both the SCID and the HDRS in prior studies.

Pharmacotherapy Algorithm and Study Procedure

The algorithm for antidepressant medication assignment was based on empirically supported and derived algorithms and closely paralleled the STAR*D algorithm.[31] The sequence contained 2 SSRIs, sertraline and escitalopram; bupropion (either sustained or extended release); venlafaxine; mirtazapine; and lithium carbonate. Initial medication assignment reflected patients' prior antidepressant treatment histories. Patients without a history of SSRI nonresponse began with sertraline; those with a history of sertraline nonresponse but no history of escitalopram nonresponse received escitalopram; those with a history of nonresponse to 2 SSRIs received bupropion; those who had not benefited from 2 SSRIs and bupropion were started on venlafaxine; and patients nonresponsive to all of the preceding began with mirtazapine or lithium carbonate.

All study procedures were approved by each study site's institutional review board. Study participants provided informed consent before enrolling in the study. Patients were evaluated for medication efficacy, intolerance, and side effects every 2 weeks during the 12-week trial. If medication-intolerant after 4 weeks, patients were switched to the next step in the algorithm. During the first 6 weeks, patients who only partially responded were switched to the next-level medication in the sequence. During the 12-week trial, 375 participants (46.4%) remained within the first 2 steps in the described medication sequence.

Data Analysis Plan

This study was conducted using data collected for the original REVAMP study. To test whether comorbid anxiety disorders are associated with elevated self-reported medication side effects, a series of 8 logistic regression analyses were conducted. Age (at baseline), gender, and baseline depressive symptom severity (total HDRS scores) were included as covariates. Lifetime comorbid diagnoses of panic disorder, GAD, and social phobia were separate independent variables. The presence of each somatic side effect category was examined as a dependent variable in 8 separate models.

To test the second aim of whether a worsening of side effects was associated with a worsening of depressive symptoms more so for patients with a comorbid anxiety diagnosis (panic disorder, GAD, or social phobia) than those without, we examined whether changes in side effect burden (frequency, severity, and impairment from side effects) covaried with changes in depressive symptoms over time and, importantly, whether this relation was moderated by comorbid panic disorder, GAD, or social phobia.

Table 2. Logistic Regression ORs (and 95% CIs) for Each Side Effect Category by Comorbid Anxiety Disorder Diagnosis

	Model		
Side Effect Category	Panic Disorder	Social Phobia	GAD
Gastrointestinal			
OR (95% CI)	1.6 (1.0–2.6)*	1.0 (0.6–1.5)	1.5 (0.9–2.5)
With vs without anxiety disorder[a]	47.1% vs 31.8%	34.4% vs 33.3%	42.2% vs 32.4%
Cardiac			
OR (95% CI)	1.8 (1.1–3.1)*	0.7 (0.4–1.2)	1.0 (0.5–1.8)
With vs without anxiety disorder[a]	25.9% vs 14.2%	12.3% vs 16.1%	15.7% vs 15.3%
Dermatologic			
OR (95% CI)	0.9 (0.5–1.7)	0.9 (0.5–1.5)	0.9 (0.5–1.7)
With vs without anxiety disorder[a]	20.0% vs 17.9%	17.2% vs 18.3%	16.9% vs 18.3%
Neurologic			
OR (95% CI)	2.6 (1.6–4.2)*	0.8 (0.5–1.2)	1.5 (0.9–2.4)
With vs without anxiety disorder[a]	58.8% vs 32.7%	33.6% vs 35.8%	43.4% vs 34.4%
Eyes/ears			
OR (95% CI)	0.7 (0.3–1.7)	0.5 (0.2–1.3)	1.2 (0.5–2.7)
With vs without anxiety disorder[a]	7.1% vs 8.1%	4.9% vs 8.5%	9.6% vs 7.8%
Sexual functioning			
OR (95% CI)	1.3 (0.8–2.0)	0.8 (0.6–1.2)	1.4 (0.8–2.2)
With vs without anxiety disorder[a]	48.2% vs 41.1%	39.3% vs 42.3%	51.8% vs 40.7%
Genitourinary			
OR (95% CI)	3.0 (1.7–5.3)*	1.3 (0.7–2.3)	1.7 (0.9–3.5)
With vs without anxiety disorder[a]	23.5% vs 8.4%	12.3% vs 9.6%	14.5% vs 9.5%
Sleep			
OR (95% CI)	1.1 (0.6–1.9)	0.8 (0.5–1.3)	1.0 (0.6–1.7)
With vs without anxiety disorder[a]	76.5% vs 69.8%	70.5% vs 70.5%	72.3% vs 70.4%

[a]Percentages are those with versus those without the anxiety disorder who experienced the side effect during the trial. Covariates in each model were age, gender, and baseline Hamilton Depression Rating Scale score.
*$P < .05$.
Abbreviations: CI = confidence interval, GAD = generalized anxiety disorder, OR = odds ratio.

To conduct these analyses, we used a series of 2-level mixed-growth models examining the slope of HDRS total scores at each assessment within individuals. Mixed-growth modeling suits this aim as it allows continuous modeling of time, accounts for variability in between-observation durations, and handles missing data by weighting slope estimates by number of observations.[32] Time was coded as number of days elapsed since baseline assessment (assessment 1 = time 0). Baseline age and gender were included as covariates. Self-reported side effect frequency, severity, and impairment were separate (level 1) independent variables; panic disorder, GAD, and social phobia were separate (fixed) moderators (level 2); and HDRS score at each assessment was the dependent variable. These models allowed for examination of whether anxiety disorder diagnosis moderated the association between changes in side effects and depression over time. Age, side effect frequency, side effect severity, and side effect impairment were grand-mean centered. Gender, panic disorder, GAD, and social phobia were effects coded (−0.5 and 0.5). Significant interactions were followed up using a standard simple slopes approach.[33,34] Specifically, lifetime diagnosis (yes/no) was recoded as 2 separate conditional moderators representing the group variable for those with and without the disorder. Separate post hoc mixed-growth models were run incorporating the recoded conditional moderators. This approach for following up interactions is superior to selecting patients in a particular group (eg, just those with panic disorder), as the whole sample remains in the analyses, thus increasing power.

RESULTS

Descriptive Characteristics

Of the 808 patients in the study, 85 (10.5%) had lifetime diagnosis of panic disorder, 123 (15.2%) had lifetime diagnosis of social phobia, and 85 (10.5%) had lifetime diagnosis of GAD. Thirty-nine individuals had more than 1 of these anxiety disorders. Chi-square tests suggested that patients with and without each of the 3 anxiety disorders did not differ in medication(s) taken during the trial. Seven hundred eleven patients (88%) reported at least 1 medication side effect during the 12-week trial. All 808 participants were included in the analyses reported in the following sections, but, as reported in the article by Kocsis et al,[27] 176 (21.8%) dropped out before the end of the 12-week trial. The average frequency, intensity, and impairment of side effects were each associated with likelihood of dropout (P values < .001), but neither comorbid panic disorder, social phobia, nor GAD was associated with dropout.

Association of Comorbid Anxiety Disorder With Medication Side Effects

Patients with a diagnosis of comorbid panic disorder were more likely to report at least 1 of the 8 side effects than those without panic disorder (95.3% vs 86.3%, OR = 1.79 [95% CI, 1.08–3.00]). To follow up this analysis, we examined each of the 8 classes separately. Over and above age, gender, and baseline depression severity, diagnosis of comorbid panic disorder was positively associated with

Table 3. Mixed-Growth Models Examining Main and Interactive Effects of Side Effect Frequency, Severity, Impairment, and Panic Disorder on Course of Depressive Symptoms Over Time

	Frequency		Severity		Impairment	
Variable	*b*	*t*	*b*	*t*	*b*	*t*
Time	−0.09	−11.78*	−0.09	−11.88*	−0.09	−12.47*
Covariate						
Age	0.05	2.25*	0.05	2.26*	0.04	2.27*
Gender	0.15	0.59	0.09	0.34	0.16	0.62
Baseline HDRS score	−4.72	−9.89*	−4.71	−9.78*	−4.69	−9.99*
Main effect						
Panic disorder	1.05	2.22*	1.09	2.28*	1.11	2.37*
Side effect indicator (ie, frequency, severity, or impairment)	0.97	6.65*	0.60	4.74*	1.10	6.21*
Interaction terms						
Side effect indicator × panic disorder	0.30	2.81*	0.29	3.05*	0.24	1.88†
Side effect indicator × time	<0.00	−0.08	<0.00	1.15	<0.00	1.25
Time × panic disorder	<0.00	0.10	8.14	0.01	<0.00	−0.14

*P < .05. †P < .10.
Abbreviation: HDRS = Hamilton Depression Rating Scale.

self-reported gastrointestinal, cardiovascular, neurologic, and genitourinary medication side effects. Panic disorder was not associated with eyes/ears, dermatologic, sleep, or sexual functioning side effects. Unlike panic disorder, GAD and social phobia were not associated with any medication side effect categories. Being female and having greater baseline depression severity each significantly predicted presence of multiple side effects. Table 2 presents all odds ratios from the logistic regressions.

Association Between Course of Side Effect Burden and Course of Depressive Symptoms

Next, analyses examined the association between change in side effect burden and depressive symptoms during the 12 trial weeks. Results indicated that greater side effect frequency, severity, and impairment were associated with less improvement in depressive symptoms over time. There were significant main effects of age, baseline HDRS scores, and time in each model, with greater average side effect burden reported by older patients, patients with more severe baseline depression, and patients earlier in the 12-week trial (Table 3).

The panic disorder models showed a main effect for panic disorder due to patients with comorbid panic disorder who reported greater depressive symptoms on average than those without panic disorder across the trial. As hypothesized, panic disorder significantly moderated the association between course of both frequency and severity of side effects and the course of depressive symptoms (see Table 3). Panic disorder also moderated the association between impairments due to side effects and depression, but at the trend level ($P = .06$). Follow-up analyses indicated that, regardless of panic disorder status, changes in both side effect frequency and severity were associated with changes in depressive symptoms. However, these associations were more robust for patients with panic disorder (frequency: $b = 0.88$, $t_{3,369.6} = 4.56$, $P < .01$; severity: $b = 1.27$, $t_{3,334.7} = 5.70$, $P < .01$) than without panic disorder (frequency: $b = 0.31$, $t_{2,525.8} = 2.85$, $P < .01$; severity: $b = 0.67$, $t_{2,702.8} = 5.28$, $P < .01$). Although the impairment × panic disorder interaction was only a trend, we followed up on this interaction and found that, consistent with the other 2 indicators of side effect burden, increases in side effect impairment were more strongly associated with relative increases in depressive symptoms for patients with panic disorder ($b = 1.34$, $t_{3,352.6} = 5.06$, $P < .01$) than for those without ($b = 0.87$, $t_{2,665.7} = 5.52$, $P < .01$).* Unlike the panic disorder models, the models with GAD and social phobia yielded no main effects for GAD or social phobia, and GAD or social phobia did not interact with any of the FIBSER measures to predict depressive symptoms.†

DISCUSSION

There were 2 notable findings in the present study. First, patients with chronic depression and comorbid panic disorder had a higher likelihood of gastrointestinal, cardiac, neurologic, and genitourinary side effects. Second, increases in side effect burden (frequency, intensity, and impairment) over time were more strongly associated with relative increases in depressive symptoms (ie, less symptom reduction) for patients with panic disorder compared to those without panic disorder.

*Panic disorder did not predict average side effect burden (frequency, severity, or impairment) across the trial, whether baseline HDRS or any of the other covariates were in the model or not (all P values > .18). Along with analyses for the second aim of the study, this lack of prediction suggests that chronically depressed patients with panic disorder do not simply report greater burden from their side effects – rather, it is that their depressive symptoms vary over time as a function of their side effects.

†To further examine the specificity of the effects to panic, we also examined the predictive effects of an anxiety symptom dimension (Mood and Anxiety Symptom Questionnaire [MASQ] arousal and general distress anxiety [D. Watson, L. A. Clark, Mood and Anxiety Symptom Questionnaire, unpublished, University of Iowa, Department of Psychology, Iowa City, 1991]) instead of the *DSM* disorder categories. Overall, the MASQ yielded similar, although weaker, effects than panic disorder. Interestingly, when MASQ anxiety was a covariate in the models that tested the second aim, panic disorder continued to moderate the association between side effect burden and depressive symptoms, suggesting the effects were specific to panic disorder and not a broad anxiety dimension.

The observations of higher likelihood of specific side effects in depressed patients with comorbid panic disorder were made after adjusting for baseline depression severity, suggesting that these side effects were not simply due to greater depression severity in patients with comorbid panic disorder. These results corroborate several prior studies[11,13,35] that have shown greater side effects in patients with comorbid anxiety and depression relative to patients without comorbid anxiety (although see Boulenger et al[36]). However, this study is one of few (eg, Rollman et al[16]) to examine panic disorder, and the only one to compare the effects of panic disorder to those of other anxiety disorders. The present study expands this literature by reporting which classes of side effects had greater association with comorbid panic disorder. These results have clinical importance, as side effects vary in their tolerability, need for clinical management, and effects on attrition and outcome.[3,37–39] Thus, ability to predict which side effects will more likely occur matters for adequate pharmacologic management.

Importantly, side effects were associated only with comorbid panic disorder and not with comorbid GAD or social phobia. As discussed, anxiety disorders are heterogeneous,[40] and previous studies[36] that examined only the moderating effect of an anxiety symptom scale (eg, the Hamilton Anxiety Rating Scale[41]) may have lacked sensitivity to detect important differences among different comorbid anxiety disorders. These findings are also consistent with the possibility that a different diathesis contributes to the development of comorbid MDD with panic disorder compared with the development of comorbid MDD with GAD and MDD with social phobia. For example, 1 study[42] found that GAD and social phobia are more likely to precede MDD, whereas panic disorder is more likely to emerge after MDD has already developed.

Panic disorder predicted occurrence of gastrointestinal, cardiac, neurologic, and genitourinary side effects but not dermatologic, eyes/ears, or sexual functioning side effects. This pattern of results may reflect panic disorder's robust association with greater interoceptive awareness.[15] That is, those with panic disorder may have been more attuned to these particular changes in their body that occurred during their antidepressant treatment. For example, cardiac symptoms (eg, palpitation, chest pain) may have been particularly salient for depressed patients with comorbid panic disorder, as several studies[15,21,43] have shown that individuals with panic disorder have greater cardiac awareness (eg, detecting one's own heartbeat) than controls and individuals with other anxiety disorders. The side effect class with the largest (by odds ratio) association with panic disorder was genitourinary side effects, noteworthy in light of the growing literature associating panic disorder and urological difficulties.[44,45] Another possible explanation for the present findings may be that individuals with panic disorder in the sample had higher anxiety sensitivity, which may have contributed to their greater endorsement of side effects. Whereas interoceptive awareness is a heightened awareness of internal body cues, anxiety sensitivity is the tendency to fear anxiety-related sensations.[46] Importantly, not only is anxiety sensitivity elevated in people with panic disorder,[47] but it has also been associated with treatment dropout in an MDD treatment study.[48] Thus, it is possible that greater anxiety sensitivity may be contributing, either independently or in conjunction with elevated interoceptive awareness, to the experience of side effects in patients with comorbid panic disorder.

We must acknowledge that presence of side effects depended upon patient self-report. The results could therefore reflect a bias in reporting side effects (particularly cardiac symptoms) rather than a true experience of side effects. A related, crucial point is that specific side effects may not have been necessarily due to the medication. That is, the presence of side effects, occurring as they did during an antidepressant medication trial, does not necessarily mean that the antidepressants caused them in these anxious, inwardly focused, chronically depressed patients. It is also possible that the depressed patients with panic disorder were more likely to experience nocebo effects. Nocebo effects are nonspecific, distressing physical symptoms that may not be due to the pharmacologic action of the drug, but due to patients' anticipation of negative effects from medication (an anticipation that may have arisen from the lengthy list of possible side effects that was provided in the consent forms).[49–51] Nocebo effects to medications might be particularly likely in patients with panic disorder given their tendency to catastrophize, greater interoceptive awareness, and/or anxiety sensitivity. However, regardless of their validity, the patients' side effect reports bore clinical importance, as greater side effect frequency, severity, and impairment predicted worse symptoms during the trial, a finding consistent with other studies.[4,5]

That side effects and depressive symptoms were more strongly correlated for patients with panic disorder than for those without has important clinical implications. Clinicians treating chronically depressed individuals should pay particular attention to gastrointestinal, cardiac, neurologic, and genitourinary side effects reported by patients with comorbid panic disorder and perhaps adjust the treatment accordingly. Additionally, clinicians may want to consider treating these patients' panic disorder (or at least heightened interoceptive awareness[52]) concurrent with the antidepressant treatment.

The study has several noteworthy limitations. First, patients received different medications, and these regimens changed during the trial period (although a large percentage either took sertraline throughout or switched from sertraline to bupropion or escitalopram—see Table 1). As medication side effect profiles differ,[3,17] different medications may have interacted with comorbid panic disorder to produce the reported side effects. Thus, the results may generalize only to medications patients took in this study. Relatedly, there is evidence showing that antidepressant medication, particularly bupropion, may lead to an increase in panic symptoms,[53] which could explain why outcomes were worse for those with panic disorder. Panic attacks were, unfortunately, not measured during the trial, and the lack of a washout period between medications during treatment makes it impossible to know what side effects were associated

with which medications. A second limitation is that, to reduce the number of comparisons, this study examined only those side effects within the 8 broad PRISE checklist domains. Side effects within these domains vary (eg, frequent urination and menstrual irregularity were collapsed within the "genitourinary" domain), possibly influencing the results. Third, the longitudinal analyses examined the contemporaneous association between side effect burden and depressive symptoms—thus, we are unable to determine the causal relation between the two.

In summary, the study results suggest that chronically depressed patients with comorbid panic disorder, but not comorbid GAD or social phobia, have greater likelihood of reporting gastrointestinal, cardiac, neurologic, and genitourinary difficulties during antidepressant treatment. The burden of these side effects (in frequency, severity, and [at a trend level] impairment) were associated with worse depressive symptoms during treatment in patients with comorbid panic disorder than in those without comorbid panic disorder, and these effects were not observed for GAD or social phobia. Clinicians working with these difficult-to-treat patients should perform a detailed assessment of side effect profiles to maximize the efficacy of their antidepressant treatment.

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Drug names: bupropion (Wellbutrin and others), escitalopram (Lexapro and others), mirtazapine (Remeron and others), sertraline (Zoloft and others).

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