Implications of naturalistic use of pharmacotherapy in CBT treatment for panic disorder

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Abstract

This study examined naturalistic medication use and cognitive behavioral therapy (CBT) treatment outcomes in 105 patients meeting DSM-IV criteria for panic disorder (PD), assessed by structured clinical interview. The association between pre- and post-treatment use of SSRIs, benzodiazepines (BZs), and any anti-anxiety or anti-depressant (A/D) medication were investigated for three indicators of treatment outcome (PD severity, presence of agoraphobia (AG), anxiety sensitivity) at post-treatment and 6-month follow-up. Controlling for pre-treatment severity, pre-treatment SSRI use was associated with worse outcomes for AG (\(p = .04\)) and anxiety sensitivity (\(p = .047\)); post-treatment SSRI use was associated with delayed improvements in PD severity (\(p = .05\)). Pre-treatment use of A/D was associated with poorer PD severity outcomes (\(p = .04\)). Post-treatment use of A/D was associated with higher anxiety sensitivity scores across post-treatment and 6-month follow-up (\(p = .03\)). BZ use was not associated with significantly worse outcomes. However, there was a decrease in the number of patients using BZs from pre-treatment to post-treatment (\(p = .06\)) and follow-up (\(p = .006\)). In conclusion, controlling for pre-treatment severity, pre- and post-treatment use of SSRIs and A/D was associated with poorer outcomes, particularly for PD severity and anxiety sensitivity.

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Keywords: CBT; Panic disorder; Medication; Treatment outcome; SSRI; Benzodiazepine

Introduction

A number of panic disorder (PD) treatment studies have examined randomized clinical trials of pharmacotherapy versus cognitive behavioral therapy (CBT) alone or in combination (e.g. Barlow, Gorman, Shear, & Woods, 2000); fewer have followed naturalistic use of pharmacotherapy in CBT for PD. Among the latter studies, naturalistic medication use typically is associated with poorer treatment outcomes. For example, Brown and Barlow (1995) showed that naturalistic use of anti-anxiety or anti-depressant (A/D) medication during CBT treatment of PD was associated with less favorable outcomes at 24-month follow-up across four measures, including independent clinical severity ratings (CSR) and scores on the Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986). Similarly, Otto, Pollack, and Sabatino (1996) reported that
remaining on medication at initial remission predicted relapse over the course of a 2-year follow-up following CBT for PD. Another study (van Balkom, de Beurs, Koele, Lange, & van Dyck, 1996) demonstrated negative associations between long-term benzodiazepine (BZ) use and CBT outcomes for agoraphobia (AG). For behavioral treatment of PD with AG, Fava et al. (2001) demonstrated that use of anti-depressant drugs at pre-treatment and BZs at post-treatment was associated with worse treatment outcomes. Westra, Stewart, and Conrad (2002) presented evidence that naturalistic, as needed use of BZs was associated with fewer reductions in anxiety sensitivity and anxious arousal from pre- to post-CBT treatment for PD with AG, compared with non- or regular use. Only one study (Oei, Llamas, & Evans, 1997) showed no differences for pre-existing A/D medication use and PD outcomes at long-term CBT follow-up.

The above studies measured different medication classes (BZ use versus any A/D) at different treatment points (pre versus post-treatment) across slightly different therapies (behavioral versus CBT) with various outcome measures at different measurement time points. Nevertheless, they converge upon the finding that naturalistic, concurrent use of pharmacotherapy generally is associated with less favorable outcomes following CBT treatment for PD and AG.

In addition to associations between naturalistic medication use and PD outcomes, Brown and Barlow (1995) reported on changes in medication use during therapy and follow-up. Despite requirements for stabilization of medication use during active CBT treatment, Brown and Barlow (1995) found that the percentage of patients using psychotropic medications dropped by nearly 50% (from 44.4% to 23.8%) from baseline to 3-month follow-up. However, closer examination of medication use over a 2-year follow-up revealed a complex picture in which the number of patients who withdrew from medication between 3- and 24-month follow-up matched the number initiating medication use during the same period (Brown & Barlow, 1995). The extent to which CBT treatment for PD facilitates successful medication withdrawal has important clinical implications, particularly given research documenting difficulties in withdrawal from anti-anxiety medications such as BZs (see Otto, Hong, & Safren, 2002).

The current study aimed to replicate and extend previous findings by exploring in greater detail the relationship between naturalistic use of specific medication classes and treatment outcomes in CBT treatment for PD (with or without AG). We separately investigated use of three classes of medication: (a) BZ, (b) SSRIs/SNRIs (SSRI), and (c) any A/D medications, which included BZ, SSRI, tricyclic anti-depressants, buspirone, and others. Our analysis examined combined data from two CBT treatment studies for PD (Craske, DeCola, Sachs, & Pontillo, 2003; Craske, Farchionne, Allen, & Barrios, in press). Five major questions were examined: (1) Do pre-treatment demographic and clinical differences exist between medication users and non-users? Relatedly, are there significant pre-treatment differences to be controlled in treatment outcome analyses? (2) How does use of medication change over the course of CBT treatment and follow-up? (3) What clinical or demographic characteristics are associated with significant changes in medication use? (4) Is use of medication at pre-treatment associated with different treatment outcomes than non-use at pre-treatment? (5) Is use of medication at post-treatment associated with different treatment outcomes than non-use?

**Method**

**Patient sample**

Data from two CBT treatment studies for PD (Craske et al., 2003, n = 53; Craske et al., in press, n = 52) were combined to increase statistical power, total n = 105. Inclusion criteria were determined through screening and an independent diagnostic evaluation using the Anxiety Disorder Interview Schedules for DSM-IV (ADIS-IV; Brown, DiNardo, & Barlow, 1994). For the Craske et al. (in press) sample, patients were required to have a principal diagnosis of PD with or without AG and at least one comorbid anxiety or mood disorder. For the Craske et al. (2003) sample, patients were required to meet criteria for PD with AG. Hence, all patients met DSM-IV criteria for PD.

Patients were excluded for presence of psychosis, current substance abuse or dependence, bipolar disorder, organic brain damage, pregnancy, severe medical conditions (e.g. neurological, cardiovascular, thyroid disease), and asthma.
Patients using psychotropic medication were required to maintain a stable dose prior to treatment (1 month for beta-blockers and BZ and 3 months for all other psychotropic medications), or withdraw from medication at least 4 weeks prior to the baseline diagnostic evaluation. Patients who were participating in other psychotherapies targeting general distress or disorders other than anxiety disorders were required to have been stable in them for at least six months prior to CBT treatment for PD. Finally, patients using medication at pre-treatment were requested (but not required) to maintain a stable dose of medication during treatment.

**Treatment**

Treatment for both study samples was based on Panic Control Treatment (Barlow & Craske, 1989; Craske & Barlow, 1993), a cognitive-behavioral treatment for PD with or without AG. Therapists were advanced graduate students and post-doctoral fellows trained and supervised by author M.G. Craske to follow session-specific treatment manuals. Blindly rated treatment adherence was high, with ratings of 5.6 and 6.5 on a 1–7 scale (1 = no adherence, 7 = extensive adherence), respectively, for the Craske et al. (2003) and Craske et al. (in press) samples.

In the Craske et al. (2003) sample, patients received 16 weekly, 90 minute sessions of CBT conducted in small groups (3–5 patients) with two therapists. Patients were randomized to receive CBT for panic control only, or panic control with in vivo exposure for AG. No differences were found between treatment groups across multiple outcomes at post-treatment or 6-month follow-up.

In the Craske et al. (in press) sample, patients received 12 weekly, 90 minute sessions of CBT for PD, similarly conducted in small groups (3–6 patients) with two therapists. In addition, patients were randomized to receive six 1-hour individual CBT sessions (once every 2 weeks), for either panic control or treatment for their most severe comorbid disorder, as assessed at pre-treatment. Results indicated no differences in PD outcomes between the two treatment groups, although there were differences in terms of comorbid outcomes.

**Measures**

Each treatment outcome measure was taken at pre- and post-treatment, 6-month follow-up (FU1) and, in the Craske et al. (in press) sample, at 1-year follow-up (FU2).

Measures included:

1. ADIS-IV CSR for PD, based on a symptom severity, client distress and impairment scale for which adequate reliabilities have been demonstrated (Brown, DiNardo, Lehman, & Campbell, 2001). Ratings ranged from 0 to 8 with 0 = no PD symptoms, distress and impairment, 4 = moderate PD symptoms, distress and impairment, 8 = most severe PD symptoms, distress and impairment. To be rated a 4 or above, clients had to meet DSM-IV criteria for PD. Ratings were made by rigorously trained research assistants and graduate students and reviewed by M.G.C. Inter-rater reliability was established from independent ratings by a primary interviewer and a second rater who listened to a randomly selected subset of audio-taped interviews (~20% total interviews). For the Craske et al. (2003) sample, inter-rater agreement for the diagnosis of PD was perfect, $\kappa = 1.0$. In the Craske et al. (in press) sample, a kappa coefficient of .93 indicated excellent inter-rater agreement regarding the diagnosis of PD ($n = 27$); CSR ratings for PD diagnoses were also reliable between raters (Pearson $r = .86$).

2. Presence of AG, which was dichotomized as none to mild AG (0) and or moderate to severe AG (1) and has demonstrated good reliability (DiNardo, Moras, Barlow, Rapee, & Brown, 1993). Scoring was assessed via the ADIS-IV, with inter-rater agreement kappas of .75.

3. Anxiety Sensitivity Index (ASI; Reiss et al., 1986): A 16-item measure of discomfort with and fear of panic and anxiety symptoms. Agreement with each item is rated on a 5-point scale, with 0 = very little, and 4 = very much. Research has demonstrated high internal consistency, test–retest reliability, and good validity for the ASI (e.g. McNally, 1989; Peterson & Reiss, 1992).
Medication use was established via questions embedded within the ADIS-IV on current medication type(s), dose, and frequency.

Additional clinical data assessed via the ADIS-IV at each measurement point included Depression CSR, which showed similar inter-rater reliability as PD CSR. In addition, time since the first current panic attack and time since panic attacks first became a problem were assessed via direct questions within the pre-treatment ADIS-IV.

Baseline demographic characteristics including age, gender, ethnicity, and highest grade completed were recorded prior to the pre-treatment ADIS-IV interview.

**Statistical analysis**

Analyses were conducted in SPSS 12.0.

The following clinical variables were used to investigate pre-treatment differences between medication users and non-users: PD CSR, depression CSR, ASI, presence/absence of AG, time since the first current panic attack(s) and time since panic attacks first became a problem. Demographic variables examined include: age, gender, study type, and highest grade completed.

Medication use and treatment outcomes were examined for two periods of medication use (pre- and post-treatment), three classes of medication (BZ, SSRI, and A/D), and for the three indices of treatment outcomes (PD CSR, presence of AG, ASI). 2 × 2 repeated measures ANOVAs (Medication use [No, Yes] × Time [Post-treatment, FU1]) were used to analyze continuous data. These were followed as needed by Univariate ANOVAs to examine differences at each time point. Logistic regression was used for the dichotomous AG outcome; McNemar tests were used to analyze changes in medication use.

To control for pre-treatment differences, pre-treatment CSR for PD was included as a covariate in all CSR analyses. Due to the widespread use of SSRI and A/D to treat depression, pre-treatment depression CSR was additionally covaried for SSRI and A/D-related CSR analyses. For AG and ASI analyses, pre-treatment AG ratings and ASI scores were controlled for, respectively. 1-year follow-up data (FU2) was available only for one study sample (Craske et al., in press), and therefore primary analyses were restricted to FU1 (6 months follow up). 2 × 3 analyses (i.e., including FU2) are reported when they yielded a different set of significant results than the 2 × 2 analyses.

**Results**

**Study groups**

Pre-treatment clinical and demographic characteristics of the two individual study samples were compared. See Table 1a for a summary of pre-treatment continuous demographic and clinical characteristics and Table 1b for dichotomous variables.

### Table 1a
Continuous pre-treatment demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Pre-treatment demographic</th>
<th>N</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>104</td>
<td>35.51</td>
<td>9.06</td>
</tr>
<tr>
<td>Highest grade level completed</td>
<td>102</td>
<td>15.32</td>
<td>2.36</td>
</tr>
<tr>
<td>Severity of panic disorder</td>
<td>105</td>
<td>5.64</td>
<td>9.0</td>
</tr>
<tr>
<td>Severity of depression</td>
<td>105</td>
<td>.96</td>
<td>1.71</td>
</tr>
<tr>
<td>Anxiety Sensitivity Scores (ASI)</td>
<td>89</td>
<td>32.25</td>
<td>11.56</td>
</tr>
<tr>
<td>Time since current panic attack(s) began</td>
<td>75</td>
<td>4.34</td>
<td>7.44</td>
</tr>
<tr>
<td>Time since panic first became a problem</td>
<td>87</td>
<td>6.75</td>
<td>8.02</td>
</tr>
</tbody>
</table>

*aPanic and depression severity ratings were made on a continuous 0–8 scale with 0 = no symptoms, distress and/or impairment, 4+ = clinical significant symptoms, distress and/or impairment, and 8 = the most severe possible symptoms, distress and/or impairment.

*bMissing data accounts for differences in total sample numbers.
Of all demographic and clinical variables tested (10 total), pre-treatment CSR for PD ($M = 5.38$ and $M = 5.90$; $t[103] = -3.12, p = .002$), time since the current period of panic attacks ($M = 6.09$ and $M = .40$; $t[53] = 4.85, p < .001$), and presence of AG (29/53 and 45/52; $\chi^2 < .001$) differed significantly between the two study samples. To control for possible confounding, the variable Study Type (i.e. the Craske et al., 2003 vs. Craske et al., in press, samples) was included as a covariate in all treatment outcome analyses below.

Specific research questions

**Question 1: Do pre-treatment demographic and clinical differences exist between medication users and non-users?**

For pre-treatment BZ users, there were no significant differences on clinical or demographic variables except for age: BZ users were significantly older on average ($M = 39.41 [8.08]$) than non-users ($M = 33.18 [8.89]$), $t(95) = -3.45, p = .001$.

For pre-treatment SSRI users, there were no significant differences between users and non-users on clinical or demographic characteristics.

For use of A/D medications, the only significant difference was age, which was significantly higher for users ($M = 37.80 [8.82]$) than non-users ($M = 33.31 [8.86]$), $t(95) = -2.50, p = .01$. There also was a trend towards less severe baseline PD CSR for A/D users ($M = 5.44 [.92]$) than non-users ($M = 5.76 [.85]$), $t(96) = 1.81, p = .07$.

Due to the small size of the age differences, the lack of theoretical importance of small differences in this age range (e.g. non-elderly, non-adolescent), the modest sample size, the large set of predetermined, theoretically important variables, and statistical power considerations, age was not controlled for in subsequent analyses. Due to the non-significant status of baseline PD CSR differences among baseline A/D users versus non-users, and the fact that this variable is controlled for in all CSR analyses regardless, additional measures were not taken to control for PD CSR borderline differences.

For pre-treatment medication users, please refer Table 2 for a detailed listing of medication type, use and dosage. Of the patients who specified medication dosages (unknown dosages ranged from 17.6% to 34.5%, depending on the medication type and time point), the majority reported dosages in the recommended range: 57.1% of baseline SSRI users, 57.1% of baseline BZ users, 62.5% of post-treatment SSRI users. The exception was post-treatment BZ users: 47.4% reported taking an effective dose. Independent $t$-tests indicated a lack of significant differences in PD CSR at baseline or post-treatment between individuals taking recommended versus below-recommended range doses of medication. Due to the lack of PD CSR differences between dosage groups, the difficulty in determining minimal effective doses for a given individual (see American Psychiatric Association, 1998), the present missing data and the desire to maximize statistical power, medication dose was not controlled for in subsequent analyses.

### Table 1b
**Dichotomous pre-treatment demographic and clinical characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ratio of total sample</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>59/105</td>
<td>56.2</td>
</tr>
<tr>
<td>Caucasian</td>
<td>80/97</td>
<td>83.5</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>9/97</td>
<td>9.3</td>
</tr>
<tr>
<td>African-American/Black</td>
<td>4/97</td>
<td>4.1</td>
</tr>
<tr>
<td>Asian-American/Pacific Islander</td>
<td>1/97</td>
<td>1.0</td>
</tr>
<tr>
<td>Other</td>
<td>3/97</td>
<td>3.1</td>
</tr>
<tr>
<td>Moderate–severe agoraphobia</td>
<td>74/105</td>
<td>70.5</td>
</tr>
</tbody>
</table>

*Agoraphobia severity ratings were conducted such that 0 = none to mild agoraphobia and 1 = moderate to severe agoraphobia.

Missing data accounts for differences in total sample numbers.

1Due to the large amount of missing data for one of the treatment study groups on this measure, group differences on this variable should be interpreted cautiously.
Question 2: How does use of medication change over the course of CBT treatment and follow-up?

At pre-treatment, 36.7% (36/98) of patients were taking BZs, 17.3% (17/98) were taking SSRIs, and 49.0% (48/98) were taking A/D medication. Despite the request that medication use remain stable during treatment, BZ use declined by 9.1% from pre- to post-treatment to 27.6% (27/98), McNemar test, \(p = .06\), and dropped by 14.5% from pre-treatment to FU1 to 22.2% (18/81), McNemar test, \(p = .006\). Whereas only one patient reported initiation of BZ use from pre-treatment to FU1, 19/98 patients (19.4%) reported stable BZs use throughout treatment and follow-up, 9/98 (9.2%) reported varied use (with both increases and decreases over time), 14/98 patients (14.2%) reported discontinuation of use over time and 55/98 patients (56.1%) reported no BZ use.

In contrast, SSRI use increased by 3.7% from pre- to post-treatment, to 21.0% (20/98). From pre-treatment to FU1, overall SSRI use increased by 7.4 to 24.7% (18/81) of patients, \(p = .006\). Over treatment and follow-up, 11/98 (11.2%) initiated SSRI use, 13/98 (13.3%) remained stable, 4/98 (4.1%) stopped use, 2/98 (2.0%) reported variable use, and 68/98 (69.4%) did not use SSRIs at any time point. Only 2/14 patients who eliminated BZs at any point during the study increased their use of SSRIs. Therefore, the reduction in BZs appears to have been largely accomplished without an increase in SSRI medications.

Driven by the strong trend in BZ reduction, there was a 8.2% drop in A/D use from pre- to post-treatment to 40/98 (40.8%), McNemar test \(p = .08\). The trend became non-significant at FU1, likely due to increases in SSRI use.

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Table 2
Psychotropic medication use at pre-treatment

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Medication brand/range in dose</th>
<th>(N)</th>
<th>% of patients in medication class</th>
<th>% of patients taking effective dose(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>2 mg/day; .25–.5 mg/prn</td>
<td>13</td>
<td>38.9</td>
<td>40.0 (2/5)</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>.375–4.5 mg/day; .5 mg/prn</td>
<td>10</td>
<td>25.0</td>
<td>60.0 (4/10)</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>.25–10 mg/day; 1–5 mg/prn</td>
<td>9</td>
<td>22.2</td>
<td>62.5 (5/8)</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>2.5–5 mg/day; 2.5–5 mg/prn</td>
<td>4</td>
<td>11.1</td>
<td>100.0 (3/3)</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>unknown</td>
<td>1</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td><strong>BZ use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular daily use</td>
<td></td>
<td>16</td>
<td>44.44</td>
<td></td>
</tr>
<tr>
<td>Per-as-needed use</td>
<td></td>
<td>15</td>
<td>41.67</td>
<td></td>
</tr>
<tr>
<td>Unknown frequency use</td>
<td></td>
<td>5</td>
<td>13.89</td>
<td></td>
</tr>
<tr>
<td><strong>SSRIs/SNRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>(10–40 mg/day)</td>
<td>5</td>
<td>29.4</td>
<td>75.0 (3/4)</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>(10–150 mg/day)</td>
<td>4</td>
<td>23.5</td>
<td>66.7 (2/3)</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>(5–25 mg/day)</td>
<td>4</td>
<td>23.5</td>
<td>0.0 (0/3)</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>(30 mg/day)</td>
<td>1</td>
<td>5.88</td>
<td>100.0 (1/1)</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>(50 mg/day)</td>
<td>1</td>
<td>5.88</td>
<td>0.0 (0/1)</td>
</tr>
<tr>
<td>Escitalopram (Lexepro)</td>
<td>(15 mg/day)</td>
<td>1</td>
<td>5.88</td>
<td>100.0 (1/1)</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>(112.5 mg/day)</td>
<td>1</td>
<td>5.88</td>
<td>100.0 (1/1)</td>
</tr>
</tbody>
</table>

\(^a\)Note that each medication a given patient was taking is included; hence patients may be represented more than once. Additional medications in the A/D category included one patient each on imipramine (Tofranil), mirtazapine (Remeron), Olanzapine (Zyprexa), Gabapentin (Neurontin), and Nortriptyline (Aventyl, Pamelor) and three patients taking buspiron (BuSpar).

\(^b\)Effective dosages were defined by recommendations from the American Psychiatric Association's (1998) Practice Guidelines for the Treatment of Patients with Panic Disorder. Please note that panic disorder patients have highly variable responses to psychotropic medication. Hence, these percentages are mere approximations and patients taking below-recommended dosages may still benefit from medication use. Percentages do not include unknown dosages, which ranged from 0% (Clonazepam) to 100% (Triazolam).

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\(^2\)A chi-square analysis of patient drop-outs between post-treatment and FU1 indicates drop-outs were no more likely to be pre- or post-treatment BZ users than non-drop outs (Pearson’s \(\chi^2\) \(p = .46\) and \(.66\), respectively). A chi-square analysis of overall drop-out rates from pretreatment to FU1 by pre- and post-treatment BZ users were also non-significant. Therefore, the McNemar analyses appear to represent true declines in BZ use over time.

\(^3\)The raw number of users did not increase (most likely) due to drop-outs.
Question 3: What clinical or demographic characteristics are associated with significant changes in medication use?

Successful discontinuation of BZ. 14 of 36 pre-treatment BZ users eliminated BZ use at some point during treatment or FU1, with the vast majority (13/14) eliminating by post-treatment. These were compared to pre-treatment continued users (22/36). In a univariate ANOVA controlling for pre-treatment CSR and Study Type, BZ discontinuation was significantly associated with less severe CSR for PD at post-treatment (M = 2.46[.40]) relative to non-eliminators (M = 3.83[.25]), F(1,32) = 7.89, p = .008, partial eta² = .20. BZ discontinuation was not associated with CSR for PD at FU1, though patterns were in the same direction. Notably, pre-treatment CSR did not predict BZ discontinuation, p ≥ 1.

Due to the fact that reductions in A/D use and increases in SSRI use did not reach full statistical significance, similar analyses were not performed for these medication classes.

Question 4: Is use of medication at pre-treatment associated with different treatment outcomes than non-use at pre-treatment?

Pre-treatment medication use and PD CSR outcomes. Pre-treatment use of BZ and SSRI did not relate significantly to CSR for PD ratings. Most likely due to greater statistical power, there was a main effect of A/D medication such that pre-treatment use was associated with higher PD CSR across post-treatment and FU1, F(1,78) = 4.18, p = .04, partial eta² = .05. Follow-up univariate ANOVAs indicate trends in associations between pre-treatment A/D medication use and higher PD CSR at post-treatment, F(1,93) = 2.91, p = .09 and follow-up, F(1,78) = 3.58, p = .06. See Fig. 1 for an illustration of these findings.

Pre-treatment medication use and AG outcomes. There were no significant associations between use of BZs or A/D medications at pre-treatment and AG outcomes at post-treatment or FU1.

SSRI use at pre-treatment was associated with a greater likelihood of moderate-severe AG at post-treatment, Exp(B) = 3.60 (95% OR: 1.06–12.20), p = .04. The trend was in the same direction but was not significant at FU1, likely due to the low statistical power from the reduced number of moderate–severe AG cases (n = 14).

Pre-treatment medication use and ASI outcomes. Pretreatment BZ use did not relate significantly to ASI outcomes at post or FU1. Pretreatment SSRI use showed a main effect F(1,37) = 4.21, p = .047, partial
eta^2 = .10, with users displaying ~7 points higher ASI scores across post-treatment and FU1 (with covariates in the model). Follow-up univariate ANOVAs, controlling for pre-treatment ASI and study type, revealed a trend association between pre-treatment SSRI use and ASI at FU1, F(1,39) = 3.20, p = .08, partial eta^2 = .08, with similar, non-significant results at post-treatment. See Table 3 for raw ASI data at each time point. As Table 3 illustrates, pre-treatment SSRI users and non-users show similar ASI scores at pre- and post-treatment, but by follow-up, users scored ~4.5 points higher than non-users. This pattern remained relatively stable at FU2.

For pre-treatment A/D medication use, there was a non-significant pattern in the same direction as the SSRI analysis.

Question 5: Is use of medication at post-treatment associated with different treatment outcomes than non-use? Post-treatment medication use and PD CSR outcomes. For post-treatment BZ use, 2 × 2 analyses were non-significant for PD CSR outcomes. Similarly, there was no relationship with post-treatment SSRI use, although in the smaller 2 × 3 analyses involving FU2\textsuperscript{4} there was a borderline significant interaction such that post-treatment SSRI users had higher PD severity at post-treatment and FU1 than non-users, but reduced to the level of non-users by FU2: F(2,34) = 3.20, p = .05, partial eta^2 = .16, with a significant within-subject linear contrast, F(1,34) = 5.93, p = .02 (see Fig. 2). Post-treatment A/D medication use did not relate to CSR for PD outcomes, though results were in the same direction as the SSRI results.

Post-treatment medication use and AG outcomes. There were no significant associations between post-treatment BZ, SSRI, or A/D medication use and AG outcomes at post-treatment, FU1, or FU2.

Post-treatment medication use and ASI outcomes. There were no significant associations between post-treatment BZ or SSRI use and ASI outcomes. The analysis of post-treatment A/D medication users, however, included higher numbers of users in the analysis (17 versus 9 for each BZ and SSRI) and therefore, greater

\textsuperscript{4}To maximize statistical power in this smaller 2 × 3, FU2 sample, baseline depression was not covaried in the reported analysis. When it was included as a covariate, the results were similar.
A significant main effect of post-treatment A/D medication use was revealed, $F(1,35) = 5.42, p = .03$, partial $\eta^2 = .13$, with users maintaining a steady $\sim 6$ points higher ASI scores than non-users across both post-treatment ($F[1,57] = 6.40, p = .01$, partial $\eta^2 = .10$) and FU1 ($F[1,37] = 4.37, p = .04$, partial $\eta^2 = .09$), compared with non-users. Table 3 gives raw ASI scores at each time point, revealing that post-treatment A/D users display lower ASI scores at pre-treatment, followed by higher ASI scores at post-treatment through FU2.

Discussion

Initial research questions

Do pre-treatment demographic and clinical differences exist between medication users and non-users?

Other than BZ and A/D users being significantly older, no differences were found between pre-treatment medication users and non-users on demographic and clinical variables. The age-related findings are consistent with a study by Hazlett-Stevens et al. (2002) in which older age was associated with greater willingness to consider medication treatment for PD. In the current study, despite the slight age differences between medication users and non-users, there were no statistically significant differences in the time since the first panic attack or time since panic first became a problem. For a discussion of the dosage data findings and implications, please see below.

How does use of medication change over the course of CBT treatment and follow-up?

BZ use significantly declined over time and generally was not replaced by SSRI use, despite a pattern of overall increase in SSRI use from pre-treatment to 6-month follow-up. The results are noteworthy given observed difficulties for BZ discontinuation in PD (e.g., Otto et al., 2002) and the request to patients that medication use be stabilized during treatment. On the other hand, discontinuation may have been indirectly supported by treatment protocol encouraging elimination of safety signal-related behaviors, of which carrying BZs is one. Driven by reductions in BZ use, there was also a trend towards reduction in A/D medication use from baseline to post-treatment.

What clinical or demographic characteristics are associated with significant changes in medication use?

For pre-treatment BZ users, BZ discontinuation (most of which occurred by post-treatment) was associated with better post-treatment PD outcomes. Importantly, BZ discontinuation not predicted by baseline PD severity ratings. These results are consistent with findings by Fava et al. (1994) which reported that BZ discontinuation following behavioral treatment for PD was associated with significant decreases in state

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5 A greater percentage of ASI scores were missing compared with PD CSR or agoraphobia scores, which reduced power for ASI analyses.
anxiety and anxiety sensitivity. Future studies should include symptom and distress measures at multiple mid-treatment time points to determine whether better mid-treatment response to CBT predicts elimination of medication use by post-treatment or vice versa. Furthermore, future research would benefit from systematically inquiring about the basis for changes in medication use.

*Is use of pharmacotherapy at pre-treatment associated with different treatment outcomes than non-use at pre-treatment?*

Taking SSRIs at pre-treatment was associated with significantly poorer treatment outcomes for AG and anxiety sensitivity but not PD severity (though the patterns were in the same direction). The raw data indicates that anxiety sensitivity differences between pre-treatment SSRI users and non-users actually did not emerge until 6-month follow-up, indicating a potential reduced long-term effectiveness of treatment. For AG, worse outcomes were demonstrated at post-treatment but not follow-up, likely due to lower power in the latter analysis.

With covariates in the model, pre-treatment A/D use resulted in significantly higher PD severity ratings across post-treatment and follow-up with univariate analyses showing trends in the same directions. A possible explanation is that medication use inhibited the success of CBT via the creation of a state-dependent (i.e. medication-dependent) learning context (see Craske & Mystkowski, 2006), or via service as a safety signal, which has likely inhibitory effects on the success of exposure to feared stimuli (Hermans, Craske, Mineka, & Lovibond, 2006).

*Is use of pharmacotherapy at post-treatment associated with different treatment outcomes than non-use?*

For post-treatment SSRI use, 1-year follow-up data revealed an interaction such that worse panic severity outcomes were seen at post-treatment and 6-month follow-up, but not at 1-year follow-up. Thus, post-treatment use of SSRIs was linked with delayed improvements in PD severity. Post-treatment users of A/D displayed significantly higher anxiety sensitivity scores at both post-treatment and 6-month follow-up, compared with non-users. Separate analyses of post-treatment BZ or SSRI use and anxiety sensitivity yielded similar but non-significant results likely due to lower statistical power. These combined findings are consistent with the 24-month follow-up findings of Brown and Barlow (1995) associating higher anxiety sensitivity with psychotropic medication use during CBT treatment of PD. Taking A/D medication during treatment and/or post-treatment may reinforce catastrophic cognitions about anxiety and detract from exposure-based learning opportunities (see Westra & Stewart, 1998). As mentioned above, medication may serve as a safety signal, create a state-dependency learning context, or allow for medication-based attributions of improvement, each of which has been associated with reduced success of CBT for anxiety disorders (Başoglu, Marks, Kılıç, Brewin, & Swinson, 1994; Westra & Stewart, 1998; Craske, 1999; Craske & Mystkowski, 2006; Hermans et al., 2006). More research is needed to directly test these hypotheses.

The association between SSRI and A/D use and higher Anxiety Sensitivity scores at post-treatment and 6-month follow-up, respectively, may be cause for concern. Anxiety sensitivity has been shown to predict the development of spontaneous panic attacks during stressful periods (Schmidt, Lerew, & Jackson, 1997, 1999), and is associated with greater risk of relapse in PD following discontinuation of antidepressants (Mavissakalian & Guo, 2004). Thus, higher anxiety sensitivity may indicate a greater risk of relapse for naturalistic SSRI and A/D users. However, due to the relatively small sample sizes and lack of consistently significant findings at both medication use time points (e.g. baseline and post-treatment), these findings should be interpreted cautiously.

To our knowledge, the association between naturalistic use of SSRIs and outcomes in CBT treatment for PD has not been explicitly examined in previous research, which has focused primarily on findings for BZs or mixed groups of anti-depressants (e.g. Brown & Barlow, 1995; Westra & Stewart, 1998; Fava et al., 2001; Westra et al., 2002). It is surprising that the typical negative predictive value of BZs observed in prior research was not replicated here. Perhaps separating BZ users into long and short-term users or by type of use (e.g. Westra et al., 2002) would yield different findings.

The goal of the current study was to examine the correlates of naturalistic medication use regardless of medication effectiveness. Our approach is based on past research suggesting that using medication concurrently with CBT may result in poorer outcomes due to factors discussed above (e.g. safety signals,
treatment attributions) that are largely independent of medication dosage. Of the patients who specified dosages, the majority reported taking doses in the recommended range according to American Psychiatric Association guidelines (1998). However, a significant group took dosages below those of the APA recommendations. According to the APA guidelines, there is substantial individual variability in what constitutes an effective dosage, particularly among PD patients. As a result, it is extremely difficult to determine whether a lower than recommended dose of medication is effective for a given PD patient. Furthermore, work by Heldt et al. (2003, 2006), Otto, Pollack, Penava, and Zucker (1999), and Pollack, Otto, Kaspi, Hammerness, and Rosenbaum (1994) demonstrates that PD patients who are non-responsive to pharmacologic treatment are generally responsive to CBT. Hence, even if our sample includes a sub-group of non-medication responsive patients, past research would suggest that they should respond to CBT. Consistent with these findings, in the current study, comparisons between individuals taking recommended versus below recommended medication doses revealed no differences in PD severity ratings at baseline or post-treatment.

Limitations

The naturalistic study design limits the strength of conclusions that can be drawn from the results and requires replication in randomized controlled trials. The possibility that an unmeasured variable may explain the outcome differences between medication users and non-users cannot be ruled out. For example, in comparing medicated and non-medicated patients it is possible that a variable such as initial (e.g. pre-medication use) PD severity was significantly worse for the patients seeking medication, even though there was a trend at baseline in the opposite direction in the current study. Despite the complexity inherent in an uncontrolled study, naturalistic designs are more generalizable to real-world, non-research clinic settings in which use of psychopharmacology is not randomly assigned.

Due to the exploratory nature of this study, a relatively large number of tests were performed and results are in need of replication. Nevertheless, results converged on similar findings across multiple categories of medication use and significant results were consistently in the direction of poorer (rather than superior) outcomes for medication use. Analysis of clinical severity outcomes for PD and AG were limited by the restricted range in outcome due to the efficacy of the CBT treatment. In a sample with more variable outcome, the statistical test of CSR may be more robust.

It may be argued that the combination of two study samples for the sake of increased power does not result in a cohesive sample. However, both studies involved CBT treatment of PD by the same research group at the same university clinic, pre-treatment characteristics revealed relatively few clinical or demographic differences between study groups, and study type was controlled in all analyses.

Conclusion

Naturalistic SSRI use was associated with a variety of negative outcomes including greater anxiety sensitivity and AG (for pre-treatment use) and delayed reductions in PD severity (for post-treatment use), controlling for pre-treatment differences. A/D use also was associated with poorer outcomes for PD severity (for pre-treatment use) and anxiety sensitivity (for post-treatment use). BZ use significantly declined over the course of treatment and patients who eliminated use displayed lower post-treatment PD severity. Unlike previous findings, BZ use did not reveal an association with worse outcomes. Given the growing popularity of SSRIs in the treatment of anxiety disorders, further investigation of SSRI use in the context of CBT for PD is warranted.

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