Behaviour Research and Therapy 90 (2017) 32–40

Contents lists available at ScienceDirect

Behaviour Research and Therapy

journal homepage: www.elsevier.com/locate/brat

Low pre-treatment end-tidal CO_2 predicts dropout from cognitive-behavioral therapy for anxiety and related disorders

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ARTICLE INFO

Article history:
Received 27 September 2016
Received in revised form
5 December 2016
Accepted 6 December 2016
Available online 8 December 2016

Keywords:
Anxiety disorders
Dropout
Attrition
Obsessive-compulsive disorder
Hyperventilation
Hypocapnia
CO_2

ABSTRACT

Recent clinical trial research suggests that baseline low end-tidal CO_2 ($ETCO_2$, the biological marker of hyperventilation) may predict poorer response to cognitive-behavioral therapy (CBT) for anxiety-related disorders. The present study examined the predictive value of baseline $ETCO_2$ among patients treated for such disorders in a naturalistic clinical setting. Sixty-nine adults with a primary diagnosis of a *DSM-5* anxiety disorder, obsessive-compulsive disorder, or posttraumatic stress disorder completed a 4-min assessment of resting $ETCO_2$, and respiration rate (the first minute was analyzed). Lower $ETCO_2$ was not associated with a diagnosis of panic disorder, and was associated with lower subjective distress ratings on certain measures. Baseline $ETCO_2$ significantly predicted treatment dropout: those meeting cutoff criteria for hypocapnia were more than twice as likely to drop out of treatment, and $ETCO_2$ significantly predicted dropout beyond other pre-treatment variables. Weekly measurement suggested that the lower-$ETCO_2$ patients who dropped out were not responding well to treatment prior to dropout. The present results, along with previous clinical trial data, suggest that lower pre-treatment $ETCO_2$ is a negative prognostic indicator for CBT for anxiety-related disorders. It is suggested that patients with lower $ETCO_2$ might benefit from additional intervention that targets respiratory abnormality.

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Cognitive-behavioral therapy (CBT) is an efficacious treatment for anxiety-related disorders. Meta-analysis of controlled trials indicates a pooled effect size (Hedges's *g*) of 0.73 (moderate effect) for CBT vs. placebo treatment, and a pooled odds ratio for treatment response of 4.06, among treatment completers. However, that same analysis revealed that 23% of CBT patients dropped out of the trials; intent-to-treat analyses that included the dropouts revealed a smaller effect size (*g*) of 0.33 (small effect) and a pooled odds ratio for treatment response of 1.84 (Hofmann & Smits, 2008). Another meta-analysis found that among patients with anxiety disorders, 11% drop out of clinical trials before treatment is initiated, and another 20% drop out during the course of treatment (Fernandez, Salem, Swift, & Ramtahal, 2015). In nonrandomized effectiveness studies, which purport to more closely resemble typical patients and practice patterns, 27% of patients dropped out of treatment (van Ingen, Freiheit & Vye, 2009). Thus, although CBT is both efficacious and effective for anxiety-related disorders, the rate of premature attrition attenuates the public health impact of the treatment.

It is therefore critical to identify those factors present at initial assessment that predict treatment dropout. As predictor variables are identified, research can then aim toward patient-treatment matching, a longtime goal of treatment research (Paul, 1967) that has largely proven elusive (e.g., Menzies, 1996). Although some clinical trials have identified basic demographic factors associated with higher dropout rates among patients with anxiety-related disorders, including male gender (van Minnen, Arntz, & Keijsers, 2002), younger age (Jarrett et al., 2013; Kehle-Forbes, Meis, Spoont, & Polusny, 2016; Rizvi, Vogt, & Resick, 2009), minority status (Jarrett et al., 2013), lower intelligence or educational level (Keijsers, Kampman, & Hoogduin, 2001; Rizvi et al., 2009), and low income or unemployment (Grilo et al., 1998; Jarrett et al., 2013), when trials were combined in a systematic review for one anxiety disorder (social phobia), no demographic variables reliably predicted dropout rates across studies (Eskildsen, Hougaard, & Rosenberg, 2010). Other clinical trials have determined that patients with higher levels of co-occurring affective disturbance such as depression (Garcia, Kelley, Rentz, & Lee, 2011; Issakidis &

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http://dx.doi.org/10.1016/j.brat.2016.12.005
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Andrews, 2004) and anger (Erwin, Heimberg, Schneier, & Liebowitz, 2003; Rizvi et al., 2009), as well as comorbid substance abuse (van Minnen et al., 2002) and total number of diagnoses (Lincoln et al., 2005) predict higher dropout rates, although findings have been mixed in this domain as well (Eskildsen et al., 2010; Hoyer et al., 2016). Overall, there are few known robust predictors of CBT dropout (Salmoiraghi & Sambhi, 2010), and therefore there are few consistent results upon which a clinically sound differential treatment recommendation could be made.

The National Institute of Mental Health's Research Domain Criteria (RDoC; Insel et al., 2010) suggests, among other things, emphasizing research on biological variables that affect and are affected by treatments (Craske, 2012; McKay & Tolin, in press). Although some biological research has examined physiological responses to intervention (e.g., exposure), such research has less practical utility for treatment decision-making, because the responses cannot be measured until treatment has already been initiated. Research investigating pre-treatment physiological predictors of CBT response in anxiety-related disorders has examined genetic factors such as polymorphisms of the serotonin transporter gene (Bryant et al., 2010; Knuts et al., 2014) and the catechol-o-methyl transferase gene (Lonsdorf et al., 2010); neural circuitry abnormalities such as anterior cingulate cortex, insula, and dorsomedial and dorsolateral prefrontal cortex in anxiety disorders (Klumpp, Fitzgerald, & Phan, 2013; Reinecke, Thilo, Filippini, Croft, & Harmer, 2014), amygdala, dorsolateral prefrontal cortex, orbitofrontal cortex, and medial prefrontal cortex in obsessive-compulsive disorder (Brody et al., 1998; Hoexter et al., 2013; Olatunji et al., 2014), and amygdala and anterior cingulate in posttraumatic stress disorder (Bryant et al., 2008); and autonomic variables such as heart rate variability (Davies, Niles, Pittig, Arch, & Craske, 2015).

The present study investigated the relationship between hyperventilation and dropout from routine CBT for anxiety-related disorders. Hyperventilation rapidly decreases the partial pressure of carbon dioxide in arterial blood ($PaCO_2$, a state termed *hypocapnia*), which results in a cascade of homeostatic symptoms resulting from vasoconstriction and impaired cerebral blood flow, and contractility changes in smooth muscle (Gilbert, 1999). $PaCO_2$ is commonly measured indirectly via end-tidal CO_2 ($ETCO_2$), an approximation of $PaCO_2$ in exhaled breath. $ETCO_2$ in subjects with normal lung function is usually 3–5 mmHg lower than $PaCO_2$, though the two measures are highly correlated (McSwain et al., 2010). Normal $ETCO_2$ ranges from 35 to 43 mmHg (Siobal, 2013). Hypocapnia is commonly defined as $ETCO_2$ values less than 35 mmHg (Oakes, 1996).

The acute effects of hyperventilation include many physiological sensations that are consistent with those seen in anxiety, including gastrointestinal distress, cold sensations, fatigue, rapid or irregular heartbeat, chest pain, impaired breathing, muscle tension, and paresthesias. Anxious psychological reactions, such as panic, fear of death, restlessness, derealization, and catastrophic misperceptions of bodily sensations, are also noted. Hypocapnia has been examined particularly among patients with panic disorder (Coplan et al., 1998; Hegel & Ferguson, 1997; Liebowitz et al., 1985; Meuret, Wilhelm, Ritz, & Roth, 2008; Munjack, Brown, & McDowell, 1993; Rapee, 1986; Salkovskis, Jones, & Clark, 1986; Wilhelm, Trabert, & Roth, 2001), although some studies have found that hypocapnia can be present in a range of anxiety-related disorders and is not specific to panic disorder (e.g., Davies & Craske, 2014; Studer et al., 2012; van den Hout et al., 1992). In a clinical trial of a 12-week program of CBT vs. Acceptance and Commitment Therapy (ACT; Davies & Craske, 2014), hypocapnia was assessed for 1 min at pre-treatment via $ETCO_2$. At the end of 12 weeks, patients with lower $ETCO_2$ in both treatment groups showed a small but significant tendency toward poorer outcomes on a self-report measure of mood and anxiety symptoms and on a self-report measure of health-related quality of life.

Thus, preliminary evidence suggests that lower $ETCO_2$ may predict poorer outcomes from CBT. One possible explanation for this finding is that hyperventilation plays a key role in the maintenance of anxiety and panic, and therefore counteracts the effects of treatment. Ley's (1985) hyperventilation theory proposes that panic attacks result from acute decreases in $PaCO_2$ secondary to hyperventilation. Klein's (1993) suffocation false alarm theory suggests that individuals with PD are highly sensitive to fluctuations in $PaCO_2$ (as would be seen in irregular breathing), and engage in hyperventilation in order to maintain low $PaCO_2$ and avoid triggering a hypersensitive "suffocation alarm." These theories have been critiqued, however, based on the fact that hyperventilation is neither necessary nor sufficient for the development of panic (Roth, Wilhelm, & Pettit, 2005) and that respiratory symptoms do not strongly differentiate individuals with panic disorder from those with panic attacks but not panic disorder (McNally, Hornig, & Donnell, 1995; Vickers & McNally, 2005). An alternative model proposes that hyperventilation is one of many processes that can lead to the enhanced detection of uncomfortable physiological sensations, triggering a positive feedback loop between physiological sensations, and anxiety, and hyperventilatory response (Margraf, 1993).

In the Davies and Craske (2014) study, pre-treatment $ETCO_2$ did not predict dropout. However, it is possible that dropout is differentially affected in clinical trials vs. routine clinical care. Clinical trial patients often differ from those seen in routine practice (Westen, Novotny, & Thompson-Brenner, 2004); in the sample reported by Davies and Craske (2014), participants were recruited by advertisements, were willing to be randomized to treatments, were either off medications or had a long period of medication stabilization (e.g., 3 months for SSRIs), and were excluded (from the trial or from analysis) for severe depression, PTSD, history of bipolar disorder or psychosis, mental retardation, substance abuse within the past 6 months, or the presence of significant physical illness or pregnancy; 31% of those interviewed were excluded for one or more of these reasons (see Arch et al., 2012). Thus, the trial sample differed from those seen under routine clinical conditions in several non-trivial ways. Participants in that trial also received no-cost treatment, although the dropout rate was still 36% within this brief (12-week), manualized treatment protocol.

It is not clear whether low pre-treatment $ETCO_2$ would predict treatment outcome and dropout in a routine clinical sample in the same manner as observed by Davies and Craske (2014) in their clinical trial. With a less-selected sample, paying for treatment and seen with a (usually) longer and more flexible course of treatment, it is possible that the effects of low pre-treatment $ETCO_2$ would be more clearly observed in dropout rates than on clinical outcome measures. The present study therefore examined the relationship between pre-treatment $ETCO_2$ and dropout in a sample of patients receiving routine (non-trial) CBT for a range of anxiety-related disorders.

1. Method

1.1. Participants

Participants were recruited from 123 consecutive adult (age 18 and above) patients seeking treatment at an outpatient, hospital-based clinic specializing in CBT for anxiety and related disorders. We included all patients receiving a diagnosis of a *DSM-5* anxiety disorder, obsessive-compulsive disorder (OCD), or posttraumatic stress disorder (PTSD). No patients were excluded from the study

based on comorbidity or other clinical factors. Six patients were referred elsewhere after the intake and were not offered treatment in this clinic. Reasons for referring were representative of usual clinical practices in a setting such as this, and included the presence of serious mental illness such as schizophrenia or uncontrolled bipolar disorder, the presence of severe substance use disorder, serious suicidal ideation, or symptoms that were not severe enough to warrant treatment. Of the 117 remaining patients, 37 declined to participate in the study and 80 agreed to participate. Three participants were excluded from analysis due to technical errors that resulted in unreliable respiratory data, and 8 were excluded from analysis due to a primary diagnosis other than an anxiety disorder or OCD, leaving a final sample size of 69.

1.2. Measures

DSM-5 diagnoses were assessed using the *Diagnostic Interview for Anxiety, Mood, and Obsessive-Compulsive Neuropsychiatric Disorders* (DIAMOND; Tolin et al., in press) a semi-structured clinical interview. DIAMOND anxiety and depressive disorder diagnoses show very good to excellent inter-rater reliability (any anxiety disorder $\kappa = 0.62–0.88$), good to excellent test-retest reliability ($\kappa = 0.59–0.96$), and strong construct validity using self-report measures of anxiety and mood symptoms (Tolin et al., in press).

Affective symptoms were measured using the *Depression Anxiety Stress Scales* (DASS; Lovibond & Lovibond, 1995), a 21-item self-report measure assessing three subscales of negative emotion: depression, anxiety, and stress/tension. Each item is rated on a 4 point scale assessing symptom frequency over the past week. Subscales of the DASS show high internal consistency ($\alpha = 0.89–0.96$) and good discriminant and divergent validity (Brown, Chorpita, Korotitsch, & Barlow, 1997).

Treatment outcome was measured using the *Outcome Questionnaire-45* (OQ-45; Lambert, Hansen, et al., 1996), a 45-item computerized self-report measure of symptom distress, interpersonal relationship impairment, and social role impairment that is designed for repeated measurement over the course of treatment. The OQ-45 shows excellent internal consistency and test-retest reliability (Lambert, Burlingame, et al., 1996), and is adequately sensitive to treatment effects (Vermeersch, Lambert, & Burlingame, 2000). Reliable change is defined as a decrease or increase of 14 or more points from baseline (Lambert, Hansen, et al., 1996). The total score, rather than subscales, was used, as this shows more robust evidence of convergent and criterion-related validity (Umphress, Lambert, Smart, Barlow, & Clouse, 1997).

1.3. Apparatus

Respiratory parameters were assessed using the Freespira Breathing System (Palo Alto Health Sciences, Inc., Danville, CA). The system, which implements a protocol initially developed by Meuret et al. (2008), consists of a custom CO_2 sensor, a Nexus 7 tablet with the Freespira Mobile App, and a nasal cannula. The sensor has a pump that samples the patient's exhaled breath to the sensing chamber where $ETCO_2$ and respiration rate (RR) are measured and uploaded to a secure cloud-based server for analysis. One-hour test-retest reliability in a sample of 11 healthy volunteers was excellent for $ETCO_2$ ($r = 0.93$) and RR ($r = 0.90$) (Tolin, McGrath, Hale, Weiner, & Gueorguieva, 2016). It is noted, however, that in a recent trial of patients with panic disorder (Tolin et al., 2016), baseline $ETCO_2$ values collected with this instrument were higher (less hypocapnic) than in other panic disorder samples collected using other respiratory instruments (Hegel & Ferguson, 1997; Meuret et al., 2008; Wilhelm et al., 2001).

1.4. Procedure

Study procedures were approved by the Hospital Institutional Review Board. Participants completed the baseline measures using RedCap (Harris et al., 2009), a secure online data collection platform approximately 1 week prior to intake. For the diagnostic assessment, they met with a study clinician (a doctoral-level psychologist or advanced graduate trainee under supervision of a doctoral-level psychologist) for a structured diagnostic interview as part of their routine clinic intake. The intake concluded by providing feedback about the patient's diagnosis and making specific recommendations for treatment.

Following the clinical examination, participants were recruited for the present study and provided informed consent. The Freespira system was used immediately thereafter to assess respiratory parameters over the course of 4 min, with the participant sitting quietly and breathing normally with eyes closed.

After the initial assessment, those approved for treatment were assigned to a study clinician (usually a licensed psychologist, but in some cases a postdoctoral fellow or an advanced graduate student under supervision by a licensed psychologist) who was unaware of the patient's baseline respiratory parameters. The number and frequency of CBT sessions was not fixed, but rather (as is the case in most clinical settings) was flexible based on patient need and availability. Treatment did not strictly follow a manual, though in most cases a combination of direct therapeutic exposure and cognitive restructuring was used, based on initial case conceptualization. Patients completed the OQ-45 prior to each treatment session.

Dropout was defined as any failure to complete the agreed-upon course of treatment. Following Fernandez et al. (2015), we examined dropout rates that occurred after the initial assessment but prior to the start of treatment (failure to initiate) and during treatment (failure to complete). We also identified the number of CBT sessions completed prior to treatment cessation.

1.5. Data analytic plan

Although respiratory parameters were assessed over 4 min, for consistency with the Davies and Craske (2014) study, in which these parameters were measured for only 1 min, we examined both the first minute and the entire 4-min period. Results were virtually identical, and only the 1-min data will be described here. For benchmarking purposes, we compared the $ETCO_2$ values in the present sample with those of Davies and Craske (2014) using independent-samples *t*-tests and Cohen's *d* (for which 0.2, 0.5, and 0.8 are considered small, medium, and large effects) with 95% confidence intervals.

We first examined the relationship between pre-treatment respiratory and clinical variables using Pearson correlation coefficients (for continuous variables) and independent-samples *t*-tests (for categorical variables). Due to the small N, analyses that examined DSM-5 diagnoses included all participants for which that diagnosis was present; we did not require the diagnosis to be primary. We also calculated effect sizes (Cohen's *d* for continuous variables, and odds ratios for categorical variables) with 95% confidence intervals.

To predict treatment dropout, we first conducted independent-samples *t*-tests (for continuous predictors) and χ^2 (for categorical variables) to determine which variables (both respiratory and clinical) were significantly associated with dropout at the univariate level. Effect sizes (Cohen's *d* and odds ratio) were also calculated. In addition to examining $ETCO_2$ as a continuous variable, we also examined the presence or absence of categorical hypocapnia (defined as $ETCO_2 < 35$ mmHg). To further clarify the incremental

predictive capacity of $ETCO_2$, we then conducted a logistic regression analysis with dropout as the dependent variable. All significant univariate predictors were entered in the first block, and $ETCO_2$ was entered in the second block. Model fit was tested using χ^2 and odds ratios.

We next sought to investigate whether dropout occurred prior to receiving efficacious treatment. First, we examined this issue from the perspective the number of sessions received. We selected three different cutoffs for number of sessions: 0 sessions (i.e., the person dropped immediately after the intake assessment but before the first treatment session), in which it is certain that no active CBT was provided; 5 sessions, considered an "ultra-brief" course of CBT (Otto et al., 2012), and 12 sessions, the treatment duration used by Davies and Craske (2014) in their clinical trial. We then examined pre-treatment $ETCO_2$ levels among these groups using a oneway ANOVA. Next, we examined the relationship between $ETCO_2$ and clinical outcomes. Using standard criteria for reliable change on the OQ-45 (Lambert, Hansen, et al., 1996), we divided patients into three groups, based on their last observation: reliably better, no reliable change, and reliably worse. A oneway ANOVA and Cohen's *d* with 95% confidence intervals were used to compare $ETCO_2$ values among the groups.

Finally, we explored patient's stated reasons for dropout, categorized into no stated reason, no stated positive outcome, and stated positive outcome. We compared pre-treatment $ETCO_2$ levels among these groups using a oneway ANOVA and Cohen's *d* with 95% confidence intervals, and calculated the rate of reliable change on the OQ-45 for the groups.

2. Results

2.1. Sample description

Table 1 shows a description of the sample at pre-treatment. The sample was fairly evenly comprised of men and women, with an average age of 37 years, and approximately 1 in 5 were nonwhite. Most (80%) were diagnosed with a *DSM-5* anxiety disorder (with 39% diagnosed with panic disorder); nearly a third were diagnosed with OCD, and a small number were diagnosed with PTSD. The majority (62%) were taking psychiatric medications, most commonly SSRI/SNRI antidepressants or benzodiazepines. The age, gender, and race/ethnicity distributions in the present sample were very similar to those in the Davies and Craske (2014) sample, as were the proportions with various anxiety disorders.

The sample's mean $ETCO_2$ of 39.02 (range = 31.49–45.35) was significantly higher (less hypocapnic) than that of Davies and Craske's (2014) CBT group (Cohen's $d = 0.87$) and ACT group ($d = 1.04$). Of the 69 participants, only 10 (14.5%) had a baseline $ETCO_2$ value below 35 mmHg; this is substantially less than the 28% of Davies and Craske's (2014) sample who met this criterion (C. Davies, personal communication, September 23, 2016).

2.2. Relationship between respiratory and other pretreatment variables

Table 2 shows the relationships between the respiratory variables ($ETCO_2$ and RR) and other variables collected at baseline. Lower $ETCO_2$ was significantly associated with lower scores on DASS-Stress, presence of social phobia, and absence of PTSD. The effect size for GAD ($d = 0.44$) approached the moderate range, suggesting higher $ETCO_2$ values among patients with this diagnosis. The remaining effects were small and considered unlikely to be replicated. High RR was significantly associated with the presence of OCD. A large (though not significant) effect was found for specific phobia, suggesting lower RR among patients with this diagnosis. A moderate effect was found for the presence of a DSM-5 anxiety disorder, with lower RR among this group (this is likely the inverse of the increased RR among patients with OCD). Effect sizes for nonwhite status ($d = 0.49$) and PTSD ($d = -0.47$) approached the moderate range, suggesting higher RR among nonwhite patients and lower RR among those with PTSD. $ETCO_2$ and RR were not associated with anxiety severity or depression (as a diagnosis or on the DASS).

2.3. Prediction of dropout

Of the 69 participants, 5 (7.2%) dropped out immediately after the intake assessment but before any treatment was administered. Twenty-four (34.8%) dropped out after treatment had been initiated. Forty (58.0%) completed treatment. The small number of

Table 1
Sample description at pre-treatment (N = 69).

		Primary Diagnosis	Any Diagnosis
Anxiety disorder [N (%)]		46 (66.7%)	55 (79.7%)
Panic disorder [N (%)]		20 (29.0%)	27 (39.1%)
Agoraphobia [N (%)]		3 (4.3%)	19 (27.5%)
Social phobia [N (%)]		11 (15.9%)	18 (26.1%)
Generalized anxiety disorder [N (%)]		8 (11.6%)	20 (29.0%)
Specific phobia [N (%)]		2 (2.9%)	6 (8.7%)
Obsessive-compulsive disorder [N (%)]		18 (26.1%)	22 (31.9%)
Posttraumatic stress disorder [N (%)]		0 (0.0%)	3 (4.3%)
Depressive disorder [N (%)]		0 (0.0%)	28 (40.6%)
Substance use disorder [N (%)]		0 (0.0%)	6 (8.7%)
Age [M (SD)]	36.59 (14.13)		
Female [N (%)]	38 (55.1%)		
Nonwhite [N (%)]	14 (20.3%)		
DASS-Anxiety [M (SD)]	7.28 (4.49)		
DASS-Depression [M (SD)]	7.37 (5.64)		
DASS-Stress [M (SD)]	8.59 (4.88)		
Number of diagnoses [M (SD)]	2.38 (1.35)		
Medicated [N (%)]	43 (62.3%)		
SSRI/SNRI [N (%)]	29 (42.0%)		
Benzodiazepine [N (%)]	26 (37.7%)		
$ETCO_2$ [M (SD)]	39.02 (3.32)		
RR [M (SD)]	13.82 (4.80)		

DASS = Depression Anxiety Stress Scales. CGI = Clinical Global Impression Scale. $ETCO_2$ = end-tidal CO_2. RR = respiration rate.

Table 2
Relationship between end-tidal CO_2 and clinical variables.

Correlations (95% CI)				
Age				0.22 (−0.02–0.43)
DASS-Anxiety				0.14 (−0.10–0.36)
DASS-Depression				0.20 (−0.04–0.42)
DASS-Stress				0.26* (0.02–0.47)
t-tests	Variable Present	Variable Absent	*t*	*d* (95% CI)
Female	38.56 (3.46)	39.57 (3.11)	1.26	−0.31 (−0.78–0.17)
Nonwhite	38.95 (4.06)	39.03 (3.15)	0.08	−0.02 (−0.49–0.45)
Anxiety disorder	39.16 (3.50)	38.45 (2.50)	0.71	0.23 (−0.24–0.71)
Panic disorder	39.57 (3.38)	38.66 (3.27)	1.11	0.27 (−0.20–0.75)
Agoraphobia	39.05 (3.63)	39.00 (3.23)	0.05	0.02 (−0.46–0.49)
Social phobia	37.42 (3.59)	39.58 (3.06)	2.47*	−0.65 (−1.13–−0.16)
GAD	39.99 (2.76)	38.62 (3.47)	1.57	0.44 (−0.04–0.91)
Specific phobia	38.09 (4.30)	39.10 (3.24)	0.71	−0.26 (−0.74–0.21)
OCD	39.06 (3.14)	39.00 (3.44)	0.08	0.02 (−0.45–0.49)
PTSD	43.35 (1.63)	38.82 (3.25)	2.39*	1.76 (1.21–2.32)
Depressive disorder	38.96 (3.62)	39.05 (3.14)	0.12	−0.03 (−0.50–0.44)
Substance use disorder	39.58 (2.42)	38.96 (3.40)	0.44	0.21 (−0.26–0.68)
Medicated	39.39 (3.19)	38.39 (3.49)	1.22	0.30 (−0.78–0.77)
SSRI/SNRI	38.48 (2.93)	39.40 (3.56)	1.14	−0.28 (−0.76–0.19)
Benzodiazepine	39.78 (3.23)	38.55 (3.33)	1.50	0.38 (−0.10–0.85)

*$p < 0.05$. **$p < 0.001$. DASS = Depression Anxiety Stress Scales. CI = confidence interval.

patients who dropped out before treatment was initiated precludes significance testing for this group, although effect size estimates suggest that their $ETCO_2$ levels were comparable to those of patients who dropped out after attending at least 1 session ($d = 0.08$) and were lower than those of patients who completed treatment ($d = -0.63$).

Table 3 shows the relationship between pre-treatment variables and dropout. Only three variables were significantly associated with increased dropout rate: nonwhite status, absence of medications (driven primarily by benzodiazepines), and lower $ETCO_2$. Pre-treatment DASS scores were not significantly related to dropout, and effect sizes were minimal to small (with slightly lower baseline anxiety and depression ratings among patients who dropped out). No diagnosis was significantly related to dropout, though odds ratios suggested a trend for dropouts to be somewhat more likely to be diagnosed with OCD, and somewhat less likely to be diagnosed with panic disorder or agoraphobia, than treatment completers. Baseline RR was not significantly associated with dropout, though a small effect size suggested a somewhat higher RR among patients who dropped out.

We examined whether hypocapnia, categorically defined as $ETCO_2 < 35$ mmHg, predicted dropout. As noted previously, the number of patients meeting this criterion was small ($n = 10$). Four (10.0%) of treatment completers, vs. 6 (20.7%) of dropouts, were hypocapnic at pre-treatment; this difference was not significant ($\chi^2 = 1.55$, $p = 0.30$), though an odds ratio of 2.35 (95% CI = 0.60–9.23) suggested a more than double dropout risk increase among hypocapnic patients.

As this was a naturalistic treatment study, there was no standardized treatment and therefore it is difficult to determine whether dropout occurred prior to receiving efficacious treatment. We examined this issue from the perspective of clinical outcomes (see next section) as well as number of sessions received. Of the patients who dropped out, 5 (17.2%) dropped out with 0 sessions ($ETCO_2$ $M = 37.70$, $SD = 2.83$), 10 (34.5%) dropped out after 1–4 sessions ($ETCO_2$ $M = 38.13$, $SD = 3.97$), 8 (11.6%) dropped out after 5–11 sessions ($ETCO_2$ $M = 37.56$, $SD = 5.01$), and 6 (20.7%) dropped out after receiving 12 or more sessions ($ETCO_2$ $M = 36.10$, $SD = 3.25$). A oneway ANOVA of $ETCO_2$ values among these groups was not significant ($F_{3,25} = 0.33$, $p = 0.80$, $\eta^2_p = 0.04$), and baseline $ETCO_2$ did not correlate significantly with the number of sessions received prior to dropout, $r = -0.18$, $p = 0.36$.

For the logistic regression predicting dropout, in the first block, we entered those variables that were significantly related to dropout status other than $ETCO_2$: nonwhite status and benzodiazepine use (categorical variables). This step was significant ($\chi^2 = 12.63$, $p = 0.002$), and correctly classified 69.6% of participants (sensitivity = 0.38, specificity = 0.92). In the second block, we entered $ETCO_2$ (continuous variable). This step was significant ($\chi^2 = 6.99$, $p = 0.008$), as was the model at this step ($\chi^2 = 19.62$, $p < 0.001$), correctly classifying 73.9% of participants (sensitivity = 0.59, specificity = 0.85). Table 4 shows coefficients for the predictor variables at each step of the model. As the values for the full model show, each increase of 1 mmHg in baseline $ETCO_2$ is associated with a decrease in the odds of dropout by a factor of 0.79 (conversely, each decrease of 1 mmHg in baseline $ETCO_2$ is associated with a 21% increase in the odds of dropout).

Reasons for dropout, in order of frequency, were that the patient never returned and gave no stated reason ($n = 15$), terminated by therapist due to patient noncompliance ($n = 4$), patient no longer perceived a need for treatment ($n = 4$), patient was too busy to continue with treatment ($n = 3$) emergence of other psychiatric symptoms ($n = 2$), and patient found treatment too distressing ($n = 1$). These were combined into three groups: no stated reason [$n = 15$, $ETCO_2$ 36.89 (2.66)], no stated positive outcome [$n = 10$, $ETCO_2$ 38.60 (5.03)], and stated positive outcome [$n = 4$, $ETCO_2$ 36.92 (4.89)]. A oneway ANOVA of $ETCO_2$ among these groups was not significant ($F_{2,26} = 0.62$, $p = 0.55$). Patients who dropped with a stated positive outcome had baseline $ETCO_2$ values that were virtually identical to those who dropped with no stated reason ($d = 0.01$, 95% CI = −0.87–0.89), although they were somewhat lower than were those of patients who dropped with no stated positive outcome ($d = -0.34$, 95% CI = −1.22–0.55).

2.4. Prediction of treatment outcome

Repeated OQ-45 data were available for 49 patients who attended at least one treatment session. Of these, 23 (46.9%) were characterized as reliably better ($ETCO_2$ $M = 39.00$, $SD = 3.36$), 19 (38.8%) as having no reliable change ($ETCO_2$ $M = 39.34$, $SD = 3.19$), and 7 (14.3%) as reliably worse ($ETCO_2$ $M = 36.27$, $SD = 3.53$). A oneway ANOVA of baseline $ETCO_2$ values among these three groups

Table 3
Relationship between pre-treatment variables and dropout.

	Completers	Dropouts	*t*	*d* (95% CI)	χ^2	OR (95% CI)
Age [M (SD)]	37.92 (13.46)	34.76 (15.04)	0.92	−0.22 (−0.70–0.25)		
Female [N (%)]	22 (55.0%)	16 (55.2%)			0.00	1.01 (0.39–2.63)
Nonwhite [N (%)]	3 (7.5%)	11 (37.9%)			9.63*	7.54 (1.87–30.42)
DASS-Anxiety [M (SD)]	7.71 (4.86)	6.61 (3.87)	0.92	−0.25 (−0.72–0.22)		
DASS-Depression [M (SD)]	7.89 (5.76)	6.52 (5.48)	0.91	−0.24 (−0.72–0.23)		
DASS-Stress [M (SD)]	8.58 (4.96)	8.61 (4.86)	0.02	0.01 (−0.47–0.48)		
Anxiety disorder [N (%)]	33 (82.5%)	22 (75.9%)			0.46	0.67 (0.21–2.17)
Panic disorder [N (%)]	19 (47.5%)	8 (27.6%)			2.80	0.42 (0.15–1.17)
Agoraphobia [N (%)]	14 (35.0%)	5 (17.2%)			2.66	0.39 (0.12–1.24)
Social phobia [N (%)]	11 (27.5%)	7 (24.1%)			0.10	0.84 (0.28–2.51)
Generalized anxiety disorder [N (%)]	12 (30.0%)	8 (27.6%)			0.05	0.89 (0.31–2.56)
Specific phobia [N (%)]	4 (10.0%)	2 (6.9%)			0.20	0.67 (0.11–3.91)
Obsessive-compulsive disorder [N (%)]	11 (27.5%)	11 (37.9%)			0.84	1.61 (0.58–4.35)
Posttraumatic stress disorder [N (%)]	3 (7.5%)	0 (0.0%)			2.27	–
Depressive disorder [N (%)]	15 (37.5%)	13 (44.8%)			0.37	1.35 (0.51–3.58)
Substance use disorder [N (%)]	3 (7.5%)	3 (10.3%)			0.17	1.42 (0.27–7.61)
Number of diagnoses [M (SD)]	2.58 (1.52)	2.10 (1.05)	1.44	0.37 (−0.11–0.84)		
Medicated [N (%)]	29 (72.5%)	14 (48.3%)			4.20*	0.35 (0.13–0.97)
SSRI/SNRI [N (%)]	18 (45.0%)	11 (37.9%)			0.34	0.75 (0.28–1.98)
Benzodiazepine [N (%)]	20 (50.0%)	6 (20.7%)			6.15*	0.26 (0.09–0.78)
$ETCO_2$ [M (SD)]	39.91 (3.09)	37.79 (3.29)	2.74*	−0.66 (−1.14–−0.18)		
RR [M (SD)]	13.28 (4.69)	14.58 (4.93)	1.12	0.27 (−0.20–0.74)		

*$p < 0.05$. DASS = Depression Anxiety Stress Scales. $ETCO_2$ = end-tidal CO_2. RR = respiration rate. OR = odds ratio. CI = confidence interval.

Table 4
Logistic regression predicting dropout.

Block 1	B	S.E.	95% CI	Wald	Sig.	Exp(B)
Nonwhite	1.71	0.74	0.26–3.16	5.38	0.02	5.51
Benzodiazepine	0.97	0.59	−0.19–2.13	2.71	0.10	2.63
Constant	−1.29	0.48	−2.23–−0.35	7.39	0.01	0.28
Block 2	**B**	**S.E.**		**Wald**	**Sig.**	**Exp(B)**
Nonwhite	2.09	0.83	0.46–3.72	6.37	0.01	8.12
Benzodiazepine	0.73	0.62	−0.49–1.95	1.38	0.24	2.07
$ETCO_2$	−0.23	0.09	−0.41–−0.05	6.21	0.01	0.79
Constant	7.81	3.64	0.68–14.94	4.60	0.03	2473.95

$ETCO_2$ = end-tidal CO_2. CI = confidence interval.

was not significant ($F_{2,46} = 2.15$, $p = 0.13$). However, medium effects were found suggesting that the "reliably worse" group had lower baseline $ETCO_2$ than did the "reliably better" group ($d = -0.83$, 95% CI = −2.01–0.34) and the "no reliable change" group ($d = -0.98$, 95% CI = −2.18–0.24). The "reliably better" and "no reliable change" groups did not differ from each other ($d = -0.11$, 95% CI = −1.08–0.86).

Among patients who completed treatment, repeated OQ-45 data were available for 29. Sixteen were classified as reliably better, 11 as no reliable change, and 2 as reliably worse. We condensed these three groups into two: reliably better ($n = 16$) and not reliably better ($n = 13$). An independent-samples *t*-test of baseline $ETCO_2$ values was not significant ($t_{27} = 0.26$, $p = 0.80$), with a negligible effect size ($d = -0.09$, 95% CI = −0.97–0.78).

We examined, for patients who dropped out, whether the stated reason for treatment discontinuation was associated with reliable change on the OQ-45. Of the 15 who dropped with no stated reason, 4 (26.7%) were reliably better, 10 (66.7%) had no reliable change, and 1 (6.7%) was reliably worse. Of the 7 who dropped with no stated positive outcome and had repeated OQ scores, 3 (42.9%) were reliably better, 3 (42.9%) had no reliable change, and 1 (14.3%) was reliably worse. Of the three who dropped with a stated positive outcome and had repeated OQ scores, all 3 (100%) were reliably worse.

3. Discussion

In a clinical trial of fixed duration, Davies and Craske (2014) found that lower $ETCO_2$ predicted poorer clinical outcomes but not dropout. The present study builds on this previous research by demonstrating that in a naturalistic clinical sample of approximately the same size and with the same range of primary diagnoses, lower $ETCO_2$ predicts treatment dropout. Hypocapnia ($ETCO_2 < 35$ mmHg) was associated with a more than twofold risk of dropout; however, respiratory abnormality falls on a continuum from mild to severe, and it is noteworthy that even outside of the categorical definition of hypocapnia, each reduction of 1 mmHg was associated with a 21% increase in dropout risk.

The present sample's overall dropout rate (42%) was somewhat higher than that seen in the shorter Davies and Craske (2014) trial (36%), though the dropout rates after treatment initiation but before session 12 were nearly identical between the present sample and the Davies and Craske (2014) sample (28% and 27%, respectively). In both studies, lower $ETCO_2$ was a poor prognostic marker, although poor outcomes were detected in different ways. In the Davies and Craske (2014) trial, poor outcome was demonstrated via decreased reduction on measures of anxiety and impairment. In the present study, we did obtain some evidence of poorer clinical outcomes on the OQ-45, with lower $ETCO_2$ associated with an increased risk of being considered reliably worse. However, the effect of lower $ETCO_2$ was most clearly evident in the prediction of dropout rates. We suspect that the different pattern between the present study and the Davies and Craske (2014) trial might be due to inherent differences between controlled clinical trials and naturalistic treatment. In particular, paying for sessions creates a natural disincentive to continue with unsuccessful treatment, and it is quite possible that fee-for-service patients will simply drop out when the treatment is not helpful. We note as well that patients' stated reasons for dropout may not have reflected clinical reality: in contrast to patients' statements that they dropped because they were feeling better, these patients were disproportionately likely to be classified as reliably *worse* on the OQ-45.

It is also possible that sample differences played some role: the present sample had a higher rate of OCD than did the Davies and Craske (2014) sample (and in the present sample, OCD patients

showed a trend toward higher dropout rate compared to anxiety-disordered patients), although it is noted that the two samples were quite similar in terms of gender ratio, mean age, proportion of minority patients, and the rate of panic disorder. The present sample's mean baseline $ETCO_2$ level was significantly higher (closer to normocapnias) than that in the clinical trial, though method variance cannot be ruled out. As noted in the introduction, prior research with this device (Tolin et al., 2016) has yielded higher $ETCO_2$ levels than those of studies using similar samples but different methodology (Hegel & Ferguson, 1997; Meuret et al., 2008; Wilhelm et al., 2001). In addition to using different data capture devices (Freespira vs. Datex Normocap), the present study used a nasal cannula, whereas Davies and Craske (2014) used a face mask, which may have elicited more acute anxiety in some participants during the procedure (e.g., Chasens, Pack, Maislin, Dinges, & Weaver, 2005). Additional clarification of optimal ways to measure pre-treatment hypocapnia is warranted.

Importantly, baseline $ETCO_2$ predicted treatment dropout beyond the capacity of demographic variables and standardized clinical measures. Like others (e.g., Jarrett et al., 2013), we found that dropout was more likely among ethnic and racial minority patients, though ethnicity and race were unrelated to $ETCO_2$. The patients who dropped out were not more symptomatic at baseline than were those who completed treatment; the presence of depressive disorder, or the severity of depression on the DASS, did not predict dropout as has been found elsewhere (Garcia et al., 2011; Issakidis & Andrews, 2004).

The capacity of $ETCO_2$ to function as a transdiagnostic predictor variable is evidenced by its lack of specificity to panic disorder, and its association with other conditions such as social phobia, replicating other research showing the presence of lower $ETCO_2$ in a range of anxiety disorders (e.g., Studer et al., 2012; van den Hout et al., 1992). Indeed, $ETCO_2$ was not strongly associated with any clinical variables captured by traditional (interview or questionnaire) means. Patients with lower $ETCO_2$ actually showed *lower* scores on DASS-Stress. This finding was unexpected and awaits replication. It could be argued that patients with lower $ETCO_2$ are truly less distressed, though this seems intuitively unlikely. It is also possible that these patients exhibit a positive self-report response bias, perhaps related to poor insight or to social desirability. The correlations with all DASS subscales, showing lower self-reported distress among patients with lower $ETCO_2$, would be consistent with this hypothesis, as would stating that one is dropping out because of feeling better and not requiring further treatment, despite reliable worsening. To the extent that there is a positive response bias among patients with lower $ETCO_2$, this would further highlight the clinical importance of collecting objective data such as respiratory biomarkers at pre-treatment.

It is somewhat encouraging that when patients with lower $ETCO_2$ remained in treatment, they appeared to improve approximately as much as did patients with higher $ETCO_2$. Here we did not replicate Davies and Craske (2014)'s finding that lower $ETCO_2$ predicted worse outcomes on standardized clinical measures for treatment completers. It might be argued, therefore, that if patients with lower $ETCO_2$ can be persuaded to remain in treatment, they will perform reasonably well. If that is the case, then treatment retention strategies such as motivational interviewing (Miller & Rollnick, 2013), increased pre-treatment psychoeducation (Reis & Brown, 2006), providing more treatment choices (Vandereycken & Vansteenkiste, 2009), more intensive treatment (Hoffman et al., 1994), or treatment contracting (Otto, Reilly-Harrington, Kogan, & Winett, 2003) could be explored for these patients.

We suggest, however, that solely targeting retention is unlikely to resolve the issue. The preponderance of evidence here suggests that individuals with lower $ETCO_2$ were not responding well to treatment prior to dropout, and it is likely that in a naturalistic treatment setting, dropout may often reflect nonresponse to intervention. The mechanism by which lower $ETCO_2$ influences poorer treatment retention and response is not clear. It is generally believed that hyperventilation maintains anxiety symptoms by creating a positive feedback loop between physiological sensations and fear (Ley, 1985; Margraf, 1993). This phenomenon has been most clearly explicated in panic disorder, though it is likely that similar processes can operate across the anxiety disorders, resulting not in unexpected panic attacks but rather in chronic physiological arousal and subjective anxiety. The effects of traditional CBT on $ETCO_2$ are not clear, although in studies of patients with panic disorder, $ETCO_2$ did not improve over the course of exposure-based therapy (Meuret, Seidel, Rosenfield, Hofmann, & Rosenfield, 2012) or cognitive therapy (Meuret, Rosenfield, Seidel, Bhaskara, & Hofmann, 2010). Traditional CBT, therefore, may not effectively target a critical mechanism in patients with lower $ETCO_2$.

Therefore, it might be helpful to target $ETCO_2$ directly for patients with that risk factor. As one example, capnometry-assisted respiratory training (CART) which has been demonstrated to be efficacious in the treatment of panic disorder (Meuret et al., 2008), leads to increases in $ETCO_2$, suggesting a different mechanism of action for this treatment (Meuret et al., 2010). The effects of CART for anxiety disorders other than panic disorder are not known, although preliminary data suggest some incremental efficacy in conditions such as PTSD (Polak, Witteveen, Denys, & Olff, 2015). It could be argued that patients with lower $ETCO_2$ at pre-treatment, regardless of diagnosis, might benefit from CART or a similar respiratory intervention instead of, or prior to, other CBT interventions. Future research should determine whether such intervention improves treatment retention and outcome among low- $ETCO_2$ patients with anxiety-related disorders.

Several limitations of the present study are noted. First, the sample size ($N = 69$) was rather small, and with only 40 treatment completers and 29 dropouts, it is not clear how well the present results will translate to a larger treatment-seeking population. Furthermore, the small N precludes more fine-grained analyses of certain variables such as diagnosis, timing of dropout, and stated reasons for dropout. Few patients had categorical hypocapnia, and at this time it is not clear whether that is due to sample issues, measurement issues, or both. Finally, our assessment of dropout was based on chart review, and in the absence of a prespecified number of treatment sessions, there is likely substantial error in this variable.

Although lower $ETCO_2$ was demonstrated to predict dropout in the present study, and to predict clinical outcomes in the Davies and Craske (2014) study, additional research is needed to determine whether lower $ETCO_2$ is a *moderator* of treatment outcome. Treatment moderation is demonstrated via an interactive effect with treatment on clinical outcomes, rather than a simple prediction (e.g., Baron & Kenny, 1986). Lower $ETCO_2$ might simply predict dropout or nonresponse, regardless of what treatment is administered. To determine a moderating effect, research would need to show an interactive effect of $ETCO_2$ X treatment, in which lower $ETCO_2$ predicts poorer outcome for one treatment, but not (or to a lesser extent) for an alternative treatment (McKay & Tolin, in press). The present study included no alternative treatment, and therefore does not permit a test of moderation. The Davies and Craske (2014) study did include two treatments (CBT and ACT); although lower $ETCO_2$ predicted poorer outcome in the total sample, interactive effects were not reported. Going forward, the identification of treatment moderators will benefit clinicians and patients by identifying which patients are likely to respond to a given treatment, and may identify subpopulations with possibly different mechanistic treatment targets (Kraemer, Wilson, Fairburn, & Agras, 2002).

Author notes

Material support for this study was provided by Palo Alto Health Sciences, Inc.

The authors thank Allison Canfield for her assistance with data entry.

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