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Specific expectancies are associated with symptomatic outcomes and side effect burden in a trial of chamomile extract for generalized anxiety disorder

John R. Keefe [a], Jay Amsterdam [b], Qing S. Li [b], Irene Soeller [b], Robert DeRubeis [a], Jun J. Mao [c, *]

[a] Department of Psychology, School of Arts and Sciences at the University of Pennsylvania, PA, USA
[b] Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, PA, USA
[c] Memorial Sloan-Kettering Cancer Center, NY, USA

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ABSTRACT

Objective: Patient expectancies are hypothesized to contribute to the efficacy and side effects of psychiatric treatments, but little research has investigated this hypothesis in the context of psychopharmacological therapies for anxiety. We prospectively investigated whether expectancies predicted efficacy and adverse events in oral therapy for Generalized Anxiety Disorder (GAD), controlling for confounding patient characteristics correlating with outcomes.

Methods: Expectancies regarding treatment efficacy and side effects were assessed at baseline of an eight week open-label phase of a trial of chamomile for Generalized Anxiety Disorder (GAD). The primary outcome was patient-reported GAD-7 scores, with clinical response and treatment-emergent side-effects as secondary outcomes. Expectancies were used to predict symptomatic and side-effect outcomes.

Results: Very few baseline patient characteristics predicted either type of expectancy. Controlling for a patient's predicted recovery based on their baseline characteristics, higher efficacy expectancies at baseline predicted greater change on the GAD-7 (adjusted $\beta = -0.19$, $p = 0.011$). Efficacy expectancies also predicted a higher likelihood of attaining clinical response (adjusted odds ratio = 1.69, $p = 0.002$). Patients with higher side effect expectancies reported more side effects (adjusted log expected count = 0.26, $p = 0.038$). Efficacy expectancies were unrelated to side effect reports (log expected count = −0.05, $p = 0.680$), and side effect expectancies were unrelated to treatment efficacy ($\beta = 0.08$, $p = 0.306$).

Conclusions: Patients entering chamomile treatment for GAD with more favorable self-generated expectancies for the treatment experience greater improvement and fewer adverse events. Aligning patient expectancies with treatment selections may optimize outcomes.

Registration: Trial Number NCT01072344 at ClinicalTrials.gov.

1. Introduction

Patient expectancies for treatment have been identified as a key contributor to therapeutic effects and experience of side effects in both clinical practice and clinical trials (Bingel, 2014; Horing et al., 2014; Mora et al., 2011). For example, the higher the probability of being randomized to an active drug versus placebo arm of a randomized trial, the greater the observed magnitude of placebo effects in adult depression (Rutherford et al., 2009b, 2010, 2014b). Experimentally altering patients' beliefs about whether they are taking an active medication has sometimes been found to enhance the effects of placebos (Vase et al., 2002). Similarly, side effect profiles in the placebo arms of clinical trials often resemble those of the active drug comparator (Mora et al., 2011; Rojas-Mirquez et al., 2014) (i.e., a nocebo effect), and manipulating patients' side effect expectations affects their reports of side effects (Mondaini et al., 2007; Wise et al., 2009).

However, it is less known as to how a patient's own positive and

* Corresponding author. Memorial Sloan-Kettering Cancer Center, The Bendheim Center for Integrative Medicine, 1429 First Avenue, NY 10021 NY, USA.
E-mail address: maoj@mskcc.org (J.J. Mao).

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negative expectancies for a particular treatment shape their experiences while on that specific treatment. Across medical disciplines, prior studies have frequently measured patients' general health optimism or pessimism rather than their expectancy that a *particular* treatment would be helpful for their condition or be likely to cause side effects (Barefoot et al., 2011; Enck et al., 2013; Nestoriuc et al., 2010). While these studies have been cited as providing evidence for expectancy effects in treatments, specific expectancies for treatment are psychometrically distinguishable from health optimism and pessimism (Haanstra et al., 2015).

Expectancy research in psychopharmacology has primarily concerned the treatment of depression (Krell et al., 2004; Leuchter et al., 2014; Mora et al., 2011; Rutherford et al., 2010, 2013, 2014b; Rutherford and Roose, 2013; Sotsky et al., 1991; Weimer et al., 2015), in which naturalistic and manipulated expectancies are typically found to relate to depression treatment outcomes on placebo and often on active medications (though not always; Leuchter et al., 2014). However, negative expectancies are typically not assessed (Colagiuri et al., 2013). Furthermore, no study to our knowledge has assessed positive and negative expectancies in tandem, and often little is done to disentangle expectancies from confounding patient characteristics. For example, the number of prior treatments a patient has had for a condition could relate to both a patient's belief that they can get better on a treatment, and how treatment-resistant their illness is.

Moreover, for anxiety disorders—and generalized anxiety disorder (GAD) in particular—there has been very limited research into the role of patient-held expectancies in psychopharmacological treatment. This is unfortunate, as anxiety disorders as a class may evidence a less strong response to placebo or "common factors" interventions compared to unipolar depression (Cuijpers et al., 2012; Hofmann and Smits, 2008). Thus, it is possible that expectancy-driven responses differ in the treatment of anxiety as compared to depressive disorders, and that expectancies may have less or no relationship to outcomes for this disorder class.

On the other hand, a recent meta-analysis of psychopharmacological treatment of anxiety found that improvement on active medication was significantly greater in active-comparator studies (e.g., Drug A vs. Drug B) relative to placebo-controlled studies, replicating findings in depression (Rutherford et al., 2015). Patients have a higher expectancy for improvement in active-comparator designs relative to placebo-controlled designs (Gaudiano et al., 2013; Rutherford et al., 2009a), and these heightened expectancies are hypothesized to contribute to effects observed in active-comparator trials. Supportively, a recent randomized controlled trial treating depression reported a superiority of randomization to open-label citalopram versus placebo-controlled citalopram, and found that increases in expectancy in the open-label group mediated this superiority (Rutherford et al., 2016). Thus, it is possible that expectancy effects enhance treatment response in anxiety as they do in depression (Rutherford et al., 2009b, 2016). Ultimately, however, the relevance of the full body of depression-focused expectancy research in psychopharmacology to anxiety treatment is unclear. Observation of a relationship between patient-held expectancies and anxiety outcomes on a drug would further support an expectancy-based account of this meta-analytic finding (Rutherford et al., 2015).

Direct evidence does exist concerning the predictive value of patient expectancies in the psychotherapeutic treatment of anxiety. Early treatment expectancies have been found to correlate positively with outcomes in evidence-based psychotherapies for GAD (Borkovec and Costello, 1993; Newman and Fisher, 2010), social anxiety (Chambless et al., 1997; Safren et al., 1997), simple phobia (Price et al., 2008), and mixed anxiety disorders (Brown et al., 2014; Westra et al., 2007). Nevertheless, given that expectancies may act differently in a psychotherapy as compared to pill treatment—for example, as a motivation to engage in psychotherapeutic procedures such as exposures to feared stimuli or completing homework (Westra et al., 2007)—the transferability of this research to the psychopharmacology context is uncertain.

To help elucidate the role that particular expectancies may play in predicting symptomatic and side effect outcomes in psychopharmacological treatments for anxiety, we prospectively evaluated treatment-specific patient expectancies during a clinical trial of chamomile treatment for GAD. Expectancies for treatment efficacy and side effect emergence were assessed separately. We hypothesized that higher expectancy for treatment response would predict greater improvements in core anxiety symptoms and well-being. We also hypothesized that higher expectancy of side effect emergence would predict more reports of treatment-related side effects during treatment. Furthermore, we hypothesized that these relationships would be specific to their respective outcomes, and would not reflect general optimism or pessimism. Finally, we aimed to clarify whether any observed effects of expectancies were potentially attributable to their correlation with baseline patient characteristics that predict outcome (e.g., number of prior treatments), and hypothesized that expectancies would uniquely predict variance in outcomes even when adjusting for these baseline characteristics.

2. Methods

2.1. Patients

Patients were adults (≥18 years) with a DSM-IV diagnosis of GAD as a primary disorder recruited from a psychiatric clinic at a major research hospital and from primary care practices. All diagnoses were determined using the MINI-SCID/P (First et al., 2001) structured interview to assess for the presence of specific DSM-IV Axis I disorders. Discrepancies in diagnostic assessment for inclusion into the study were resolved by conferencing and consensus between the investigators of the trial. Patients diagnosed with Axis I psychosis, bipolar disorder, or substance abuse or dependence were excluded from participation.

The details of the trial design have been published previously (Mao et al., 2014). The overall study is a randomized-placebo controlled trial (RCT) to evaluate whether long-term use of chamomile will result in decreased relapse of GAD symptoms as compared to placebo. A prior RCT found a significant advantage for chamomile over placebo in acute-phase treatment of GAD (Amsterdam et al., 2009, 2012), with a response rate comparable to that of tested anxiolytic and antidepressant therapies for GAD (Mitte et al., 2005). For this manuscript, we analyzed the data from phase I, when all participants were given an open-label administration of pharmaceutical-grade, standardized chamomile extract capsules totaling 1500 mg/daily for 8 weeks (Mao et al., 2014).

2.2. Measurement of expectancies

2.2.1. Mao Expectancy of Treatment Effects (METE)

The METE was modified from the Acupuncture Expectancy Scale developed and validated by the senior author (see online supplement for instrument) (Mao et al., 2010). The modified instrument is a 4-question patient-report questionnaire rated on a scale of 1–5 (wherein 1 is total disagreement with a statement and 5 is total agreement), which assesses a patient's expectation that chamomile will relieve his/her primary anxiety symptoms and increase his/her coping abilities and vitality. Sample items include a patient's relative agreement with the statements that with chamomile treatment "I will be able to cope with my anxiety better" and that "The