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Brief report

Suggestibility as a predictor of response to antidepressants: A preliminary prospective trial

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ABSTRACT

Background: The growing awareness that so many do not respond adequately to antidepressant (AD) pharmacotherapy has sparked research seeking to characterize those who do. While the pharmacological mechanisms of AD treatment have been extensively evaluated, much remains unknown about the placebo component of the response to medication. This study examined the association between suggestibility levels and response to ADs amongst depressed patients.

Methods: Twenty unipolar depression outpatients, recruited before starting AD monotherapy, received clear, standardized instructions that the therapeutic effects of AD, though not side effects, would require 2–4 weeks. At baseline (T1), 1 week (T2), and 1 month (T3), participants were evaluated for depressive symptoms, using the Hamilton Rating Scale for Depression-17 items (HAM-D); for anxiety by the Hamilton Rating Scale for Anxiety (HAM-A); for side effects by the Antidepressant Side Effect Checklist (ASEC); and for suggestibility, using the Multidimensional Iowa Suggestibility Scale (MISS).

Results: High levels of baseline suggestibility were associated with less improvement in depression level and more side-effects during the first week. In accordance with our hypothesis the more suggestible patients improved more between T2 and T3. No significant correlations were found between baseline suggestibility levels and change in anxiety.

Limitations: Small sample size and a self-report questionnaire assessing suggestibility were limitations.

Conclusion: This study offers a potentially new and clinically useful approach to understanding and predicting who will respond to AD treatment. Suggestibility seems to play a role, presumably by shaping expectation, in response to AD treatment. We hope that this avenue will be further explored.

1. Introduction

The growing awareness that many patients do not respond adequately to antidepressants (ADs) has sparked research seeking to characterize those who do (Khan et al., 2012; Fabbri et al., 2014). While the pharmacological mechanisms of AD treatment have been extensively evaluated, much remains unknown about the placebo effect component of the response to medication. What appears to be common to the various effective uses of the placebo is that a state of expectation is produced in the patient (Price et al., 2008; Kirsch, 1985). When patients expect that the treatment will help, they are indeed more likely to be helped. This effect has been demonstrated using brain fMRI, which has shown that expectancy causes changes in brain areas relevant to sensing and modulating pain (Koyama et al., 2005; Bingel et al., 2011) and depression (Mayberg et al., 2002).

Expectation of a therapeutic response, central to understanding the placebo effect, is relevant to the effect of standard pharmacological therapies as well (Khan et al., 2012; Sinyor et al., 2010). Therefore, a likely factor in therapeutic response is the inclination of the patient receiving treatment to develop the positive expectation. This is measured by suggestibility, by which we mean the inclination of a person to accept and internalize a communication (Kotov et al., 2004). Some evidence indicates that suggestion plays a role in the response to placebo analgesia (De Pascalis et al.,

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2002). Surprisingly, however, despite the widespread use of AD and the prominent psychological component of the response to ADs, the role of suggestibility in the response to treatments of depression has not been evaluated.

In the present study we assess the relation between suggestibility levels and response to AD amongst depressed patients. We hypothesized that higher levels of suggestibility would increase the likelihood of a therapeutic response to AD treatment, as well as the likelihood of experiencing side effects.

2. Methods

2.1. Subjects

A longitudinal prospective study was conducted between March 2013 and December 2013 at a number of primary care and psychiatric outpatient clinics in the Sharon district in Israel. Twenty unipolar depression patients were recruited before the initiation of AD monotherapy with either an SSRI (fluoxetine, sertraline, citalopram, fluvoxamine, escitalopram, paroxetine), or an SNRI (venalflaxine, duloxetine, milnacipran). All subjects were diagnosed with major depressive disorder according to the Diagnostic and Statistical Manual, 4th Edition (DSM-IV-TR) criteria (Association AP., 1994). Exclusion criteria included past or present psychosis, diagnosis of bipolar disorder, active suicidality, agitation, and drug or alcohol abuse. Consent for participation in the study was 70%. Subjects who declined to participate in the study did so due to logistical difficulties. One consenting subject was excluded for lack of cooperation.

2.2. Design and procedure

Subjects were referred to the study by psychiatrists and primary care physicians, and recruitment was executed solely by two research assistants from the study team. The study was approved by the Institutional Review Board (IRB), and all participants provided their signed informed consent.

Prior to the initiation of AD treatment a uniform explanation of the expected efficacy and side-effects of the AD drug was phrased as follows: "*You were diagnosed with depression, and you are about to start a new treatment with a drug that was proved to be efficient in reducing depressive symptoms. The medicine affects the activity of neurons in the brain and you are expected to feel better. Some people who take the medication experience an improvement in their depressive symptoms shortly after the initiation of the medication, but in most cases it takes two to four weeks until the effect of the medication is felt. Like all medication, the medication you take could have side-effects. In a minority of the cases it can cause nausea, diarrhea, headache or a rash. If you take it in the evening it can affect the quality of your sleep. The medication can also affect sexual functioning and desire. If any of the above side-effects appear, it is crucial to speak about them with your physician.*"

At baseline [T1], 1 week [T2], and 1 month [T3], participants were evaluated for depressive symptoms using the Hamilton Rating Scale for Depression-17 items (HAM-D) (Hamilton, 1960). Anxiety was measured with the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959). Side effects were evaluated with the Antidepressant Side Effect Checklist (Uher et al., 2009). A standard socio-demographic questionnaire was administered (including data on past AD treatments and their effectiveness).

Participants were also evaluated at T1 and at T3 for suggestibility levels, using the Multidimensional Iowa Suggestibility Scale (MISS), a 95-item self-report measure of suggestibility (Kotov et al., 2004). The MISS includes five suggestibility subscales (Consumer Suggestibility [CS], Persuadability [PER], Physiological Suggestibility [PS], Physiological Reactivity [PHR], Peer Conformity [PC]) and two companion scales (Psychosomatic Control, Stubborn Opinionatedness). The five suggestibility subscales can be summed to obtain the Suggestibility Total score (TOT).

The primary outcome measure was the change in HAM-D total score and secondary measures were the change in HAM-A total score, and ASEC total score. After completing the study every subject was given the equivalent of 75 US$ in exchange for participation in the study.

2.3. Data analysis

Correlations of Suggestibility Total score [TOT] with demographic variables (e.g., age and education level) and clinical measures (e.g., HAM-D total score, HAM-A total score, side-effects) were performed using Pearson product-moment correlations and Spearman's Rank-Order Correlations. A repeated-measures analysis of variance (ANOVA) was conducted in order to assess changes in depression during the study. The within-subjects variable was *time of assessment* (baseline [T1], one week [T2], and one month [T3]). Post-hoc paired-samples *t*-tests (T1 compared to T2, and T2 compared to T3) were performed in order to ascertain the source of significant findings (a Bonferroni correction was employed in light of the multiple comparisons; α set at .025). Next, Pearson product-moment correlations between baseline TOT and depression (HAM-D) at the three assessments (T1, T2 and T3) were calculated. Correlations were also calculated between baseline suggestibility levels and *change* in depressive symptoms (change in symptoms was calculated after a week [T1–T2], after one month [T1–T3] and between T2 and T3). Similar correlations were calculated between the MISS subscales and change in depressive symptoms. The analyzes were repeated for anxiety using the HAM-A total score. Finally, response to AD (change in HAM-D total score) was compared between patients that did or did not receive AD prior to study entry using independent-samples *t*-tests (at T2 and T3).

Statistical significance was set at $p<.05$ for all comparisons, unless otherwise stated (only significant correlations are reported). Analyzes were conducted using the IBM Statistical Package for Social Sciences (SPSS), Version 21.

3. Results

Depression severity of patients was moderate (HAM-D=15.55, SD=4.48) and mild (HAM-D=9.60, SD=5.06) at T1 and T3, respectively.

There was a significant decrease in depression (HAM-D total score) during the study [$F(2,38)=21.61$, $p<.001$, $\eta_p^2=.53$]; follow-up analyzes indicated that the decrease was significant between T1 and T2 [$t(19)=4.404$, $p<.001$] and approached significance between T2 and T3 [$t(19)=1.759$, $p=.095$]. Suggestibility levels stayed stable over time [i.e., the change between T1 and T3 was not significant; $t(18)=.288$, $p=.777$], as also evident in the significant correlation between T1 and T3 TOT ($r=.543$, $p=.016$). See Table 1 for demographic and clinical data.

Baseline TOT was inversely correlated with response to AD after one week (*change* in HAM-D total from T1 to T2; $r=-.595$, $p=.007$). In other words, high levels of baseline suggestibility were associated with less improvement in depression level during the first week. The correlation between baseline TOT and the change in HAM-D from T2 to T3 approached significance ($r=.406$, $p=.085$). Note that these correlations were in the opposite direction to those found for the change between T1 and T2 (see Fig. 1). Comparison of these dependent *r*s ($r=-.595$ and $r=.406$) revealed a significant difference ($t_{\text{Difference}}=-2.909$, $p<.01$). The