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Research paper

Interpersonal psychotherapy as add-on for treatment-resistant depression: A pragmatic randomized controlled trial

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ABSTRACT

Background: Treatment-resistant depression (TRD) is an extremely prevalent clinical condition. Although Interpersonal Psychotherapy (IPT) is an established treatment for uncomplicated depression, its effectiveness has never before been studied in patients with TRD in real-world settings. We investigate IPT as an adjunct strategy to treatment as usual (TAU) for TRD patients in a pragmatic, randomized, controlled trial.

Methods: A total of 40 adult patients with TRD (satisfying the criteria for major depressive disorder despite adequate antidepressant treatment) were recruited from a tertiary care facility for this pragmatic trial and blinded to the evaluator. Patients were randomized to one of two treatment conditions: (1) TAU – pharmacotherapy freely chosen by the clinician ($n=23$) and (2) TAU+IPT ($n=17$). Assessments were performed at weeks 8, 12, 19 and 24. Changes in the estimated means of the Hamilton Depression Rating Scale score were the primary outcome measure. Secondary outcomes included patient-rated scales and quality of life scales. We used a linear mixed model to compare changes over time between the two groups.

Results: Both treatments lead to improvements in depressive symptoms from baseline to week 24 with no significant between group differences in either primary: TAU (mean difference: 4.57; CI95%: 0.59–8.55; $d=0.73$) vs. IPT+TAU (mean difference: 5.86, CI95%: 1.50–10.22; $d=0.93$) or secondary outcomes.

Limitations: Our relatively small sample limits our ability to detect differences between treatments.

Conclusions: Both treatments lead to equal improvements in depressive symptoms. We found no evidence to support adding IPT to pharmacotherapy in patients with TRD.

Trial registration: ClinicalTrials.gov-NCT01896349.

1. Introduction

Resistance to therapy is a major concern in major depressive disorder (MDD) treatment. Only one third of patients achieve remission after a pharmacotherapy first attempt and only half exhibit a 50% reduction in depressive symptoms after 12–14 weeks of medication (Trivedi et al., 2006). Treatment-resistant depression (TRD) is associated with a 40–50% increase in direct and indirect costs when compared with nonresistant depression (Gibson et al., 2010). Despite the absence of consensus on the definition of TRD (Berlim and Turecki, 2007) testing efficacious treatments for TRD is currently a major goal for the field.

Treatment options for TRD include switching to a different antidepressant (Rush et al., 2006; Fava et al., 2006) or augmenting with another pharmacological agent (Nierenberg et al., 2006; Bauer et al., 2014). The results, however, are still disappointing: approximately 20% of patients remit after a second antidepressant trial (Rush et al., 2006) and fewer than 20% remit after a third attempt (Fava et al., 2006). Augmentation strategies with psychological treatments have received considerably less attention in

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the literature, and the available evidence is somewhat mixed. One study evaluated cognitive behavioral therapy (CBT) plus medication versus medication alone for TRD and found that the combined treatment was superior (Wiles et al., 2013). On the other hand, another study evaluating cognitive behavioral analysis system of psychotherapy (CBASP) and brief supportive psychotherapy (BSP) associated with pharmacotherapy failed to find any benefit from combined treatments when compared with pharmacotherapy alone (Kocsis et al., 2009). Despite its proven efficacy for treating depression to date, Interpersonal Psychotherapy (IPT) has never before been tested in TRD populations (Gaynes et al., 2011).

There is strong evidence supporting IPT as an option for depression treatment, either as monotherapy or as in combination with pharmacotherapy (Cuijpers et al., 2011). However, the majority of studies evaluating IPT in combination with pharmacotherapy conducted efficacy trials, with strictly controlled medication, which limits the applicability of such results in clinical practice (Reynolds et al., 1999; Lespérance et al., 2007). Almost all of our current treatment recommendations for MDD are mainly based on efficacy trials, with highly homogeneous and well-defined patients. Nevertheless, there is significant concern over the applicability of such results to daily clinical practice (March et al., 2005). Consequently, given the challenges in treating complex cases of TRD, it is imperative for researchers to test the effectiveness of interventions in real-world settings by making use of more pragmatic designs (March et al., 2010; Ware and Hamel, 2011).

Here, we evaluate IPT in a pragmatic, randomized trial as an augmentation strategy of pharmacotherapy in patients with TRD that actually look for treatment in a tertiary outpatient service. This study was designed to help the clinician make the decision of whether or not to add IPT with treatment as usual (TAU) for TRD patients. We hypothesized that the IPT add-on group would perform better than the pharmacotherapy-only group.

2. Method

2.1. Study design and implementation

The study is an evaluator-blind, pragmatic, randomized clinical trial comparing (1) TAU versus (2) TAU plus interpersonal psychotherapy (TAU+IPT). Recruitment took place from September 2012 until July 2014 at the Mood Disorder Program (PROTHUM), a tertiary outpatient service of Hospital de Clínicas de Porto Alegre (HCPA) in Brazil. Patients came from primary care units because of treatment failure; most of the patients were already under pharmacological treatment. At the first visit, a diagnostic procedure was performed and inclusion criteria were assessed. All subjects that fulfilled the inclusion criteria and had no exclusion criteria were invited to participate in the study. Once a patient agreed to participate, baseline assessment followed by randomization was performed; the interventions started a week later. The study was approved by the medical ethics committee at HCPA and informed consent was obtained from all participants. The study was registered on ClicalTrials.gov under the following number: NCT01896349. The results of the blood markers will be reported in a future publication.

2.2. Participants

The inclusion criteria were a diagnosis of MDD according to the DSM-IV as assessed with the Mini International Neuropsychiatric Interview (MINI). The exclusion criteria were bipolar disorder, psychotic disorder, inability to complete the questionnaires, intellectual disability, high suicide risk, inability to meet trial demands and currently in or having received psychotherapy in the last 4 weeks.

2.3. Treatment-resistant depression

TRD was defined as a failure to respond to one trial of antidepressant medication in adequate dose and duration. Adequate dose was defined as the equivalent of at least 75 mg of amitriptyline. Adequate treatment duration was defined as at least four weeks. Patients should be under this antidepressant scheme at the moment of randomization.

2.4. Randomization and blinding

Single randomization was carried out by means of sequentially numbered brown sealed envelopes containing the randomization sequence generated by computer prior to the recruitment of subjects. Once a patient agreed to participate and the baseline assessment was performed, the next envelope was opened. Investigators responsible for the outcome assessments were blinded to the treatment assignment.

2.5. Interventions

2.5.1. Interpersonal psychotherapy

IPT was conducted in accordance with treatment guidelines (Weissman, 2000). IPT is a time-limited psychotherapy with proven efficacy in the treatment of MDD (Cuijpers et al., 2011). IPT has two main principles: (1) depression is a medical illness that is treatable and not the patient's fault, and (2) there is a connection between mood and life events. The focus is on the relationship between MDD episodes and current interpersonal problems, trying to find new ways of dealing with these problems, improving relational functioning, and ultimately relieving depressive symptoms. IPT has four problem areas: grief, interpersonal role dispute, role transitions and interpersonal deficits. The patient and therapist chose the problem area most strongly related to the current episode and work on it during sessions. IPT therapists take an active, non-neutral, supportive and hopeful stance.

The trial included 16 individual 40-min weekly sessions. Three instances of appointment rescheduling were allowed so therapy could last from 16–19 weeks. IPT was administered by third-year psychiatry residents and one psychiatrist. All therapists received at least one year of IPT training before the trial. All sessions were audiotaped and supervised weekly by a senior IPT psychiatric therapist.

2.6. Treatment as usual – pharmacotherapy plus clinical management

All participants who enrolled in the study received TAU, i.e., pharmacotherapy plus clinical management. Drug prescription was performed during the clinical management sessions according to MDD treatment guidelines. Clinicians were free to choose antidepressant medication, doses and drug combinations, including augmentations strategies with non-antidepressant drugs, which followed standard clinical guidelines (Bauer et al., 2013; Lam et al., 2009). Clinical management sessions occurred in a monthly basis but clinicians were free to set extra appointments as necessary. The intervention lasted 19 weeks. Clinical management was performed following National Institute of Mental Health (NIMH) guideline recommendations (Fawcett et al., 1987). We focused on psychiatric history, depressive symptoms evaluation and follow-up, drug side effects management, patient education concerning MDD and pharmacological treatment. Clinicians were instructed to build a warm and collaborative patient–doctor relationship, which in turn promoted treatment compliance. Moreover, adherence to clinical management protocol prevented an overlap between clinical management and IPT.