Journal of Affective Disorders 152-154 (2014) 146–154

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Predicting response to cognitive therapy and interpersonal therapy, with or without antidepressant medication, for major depression: A pragmatic trial in routine practice

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ARTICLE INFO

Article history:
Received 20 March 2013
Received in revised form
22 August 2013
Accepted 27 August 2013
Available online 3 September 2013

Keywords:
Depression
Evidence-based treatments
Psychotherapy
Antidepressant medication
Prediction of response

ABSTRACT

Background: Identifying patient characteristics that predict response within treatments (prognostic) or between treatments (prescriptive) can inform clinical decision-making. In this study, we sought to identify predictors of response to evidence-based treatments in a sample of depressed patients seeking help in routine practice.

Methods: Data come from a pragmatic trial of 174 patients with major depression who received an evidence-based treatment of their own choice: cognitive therapy (CT), interpersonal therapy (IPT), antidepressant medication (ADM) alone or in combination with either of the two psychotherapies. Patient characteristics measured at baseline were examined to see if they predicted subsequent response as measured with the Beck Depression Inventory (BDI) over the course of 26 weeks of treatment, using mixed regression modeling.

Results: Higher agoraphobia scores at baseline predicted more change in depression scores across treatments, irrespective of the treatment received. Physical functioning moderated the response to treatment: patients with high physical functioning fared better in combined treatment than patients with low physical functioning, whereas physical functioning did not predict a differential response in the psychotherapy group. Moreover, the lowest levels of physical functioning predicted an increase of depressive symptoms in combined treatment.

Limitations: A relatively small sample size, and selection of several predictors that were less theory-driven, which hampers the translation to clinical practice.

Conclusions: If replicated, the prognostic and prescriptive indices identified in this study could guide decision-making in routine practice. Development of more uniform requirements for the analysis and reporting of prediction studies is recommended.

1. Introduction

Numerous trials have demonstrated that cognitive therapy (CT) and interpersonal therapy (IPT) are effective, well-established treatments for unipolar depression (Anderson, 2001; Cuijpers et al., 2008; Gibbons et al., 2012), and the same can be said for antidepressant medications (ADM) (Anderson, 2001; Gibbons et al., 2012). Psychotherapy and antidepressants are frequently delivered concurrently, and when combined have somewhat greater effectiveness than either modality alone (Cuijpers et al., 2009a, 2009b).

Predictors of treatment outcome are valuable, as they can guide decision-making in routine practice. Predictors come in two types, are generated by different types of designs, and can have different uses (Fournier et al., 2009). *Prognostic* variables derive from designs that hold treatment constant (or ignore differences in modality) and seek

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http://dx.doi.org/10.1016/j.jad.2013.08.027

to determine whether individual differences measured at baseline predict subsequent variation in response (Kraemer et al., 2002). Prognostic indices tell us which patients benefit most from a given treatment, but not which treatment is best for a given patient. They identify which patients require special attention, such as different types or doses (i.e., more medication or sessions) of treatment.

Prescriptive variables, also known as moderators, derive from comparative treatment designs and seek to determine whether individual baseline differences predict subsequent variation in response as a function of treatment type (Kraemer et al., 2002). Prescriptive indices can determine the optimal treatment for a given patient. As Kazdin (2007) has noted, moderation always implies differential mediation, as differential effects imply differential causal pathways to change. Understanding how treatments work can inform improving existing treatments and developing new ones. Thus, identifying predictive indices (both prognostic and prescriptive) has both clinical and scientific importance.

In the past decades, many prediction models have been reported, often from randomized treatment studies. Reviewing the vast literature on predictors of treatment outcome reveals mixed and sometimes even conflicting results (Papakostas and Fava, 2008; Nilsen et al., 2012). Mood disorders and most other psychopathology domains lack a consistent evidence base for predictors of treatment outcome. To draw conclusions from the extant literature is virtually impossible given the heterogeneity in reported study designs, patient samples, treatments, outcome measures, and statistical approaches. Prediction models are particularly prone to arbitrary findings, statistical errors, and misinterpretation, as they typically allow a large variety of modeling options in combination with large numbers of variables to study within each other's context. Moreover, as Fournier et al. (2009) point out, most prediction studies have derived from a single treatment modality (prognostic only), whereas prediction analyses encompassing more than one treatment condition might yield more information (prescriptive), especially in identifying moderators.

Rather than providing another exhaustive overview of the existing literature, we focus on three eminent randomized treatment prediction studies of greatest relevance to the present study because of the treatments they compare: Sotsky et al. (1991), Fournier et al. (2009), and Carter et al. (2011).

The National Institute of Mental Health Treatment of Depression Collaborative Research Project (TDCRP) compared the effects of 16 weeks of randomly assigned CT, IPT, ADM (imipramine) with clinical management, and placebo with clinical management. Investigators found no overall outcome differences among the groups (Elkin et al., 1989), although a reanalysis found CT to be less efficacious than ADM in more severely depressed patients, an instance of moderation (Elkin et al., 1995). Sotsky et al. used the TDCRP data to investigate other potential prognostic and prescriptive predictors of outcome (1991). Controlling for baseline depressive severity and marital status, they found six prognostic indices of depressive severity at the end of the 16-week trial: social dysfunction; cognitive dysfunction; (low) expectation of improvement; "endogenous" depression; double depression; and duration of current episode. They also identified three prescriptive indices (moderators) of treatment outcome relative to pill-placebo; patients with low social dysfunction showed a better (specific) response to IPT; patients with low cognitive dysfunction showed a better (specific) response to CT or ADM; and patients with high work dysfunction showed a better (specific) response to ADM. None of these indices predicted differential response among the active treatments.

As questions have been raised about the adequacy of the implementation of CT in the TDCRP (Jacobson and Hollon, 1996b, 1996a), a more recent treatment study was designed to investigate whether ADM truly outperforms CT in treating more severely depressed patients when both are adequately implemented (DeRubeis et al., 2005; Hollon et al., 2005). In that trial, both CT and ADM (paroxetine) were superior to pill-placebo at 8 weeks in terms of categorical response and virtually identical to one another at week 16. Using an elegant, multivariate data analytic strategy, Fournier et al. (2009) found three prognostic indices that predicted less favorable outcome at 16 weeks regardless of treatment condition: chronic depression, older age, and lower intelligence. They also found three prescriptive indices (moderators) of outcome, indicating subsets of patients who did better in CT than in ADM: patients who were married, unemployed, or had a greater number of recent life events. They concluded that these prognostic indices might usefully identify subgroups of patients who required more or different treatments, whereas the prescriptive indices identified might define subgroups of patients who might particularly benefit from CT relative to ADM. Two previous analyses of the same sample that focused on single moderators found: (1) depressed patients with comorbid personality disorders responded better to ADM than to CT, whereas patients without comorbid personality disorders responded better to CT than to ADM (Fournier et al., 2008); and (2) patients who had previously taken ADMs responded better to CT than to ADM, whereas patients without a medication history responded similarly to either (Leykin et al., 2007a).

Finally, the Christchurch Psychotherapy for Depression Study, comparing the effectiveness of randomly assigned IPT or CT for major depression, found no differences in outcome between the two psychotherapies in the full sample (Luty et al., 2007). However, separate analyses found that patients with severe depression (Luty et al., 2007) or with a comorbid personality disorder (Joyce et al., 2007) fared better in CT than in IPT, suggesting that each was a prescriptive index that moderated response to differential treatment. A subsequent multiple prediction analysis identified three prognostic and one prescriptive indices: a single episode of depression (versus recurrent depression), a higher perceived logicalness of therapy, and a moderate belief that childhood factors caused the depression were all associated with better overall outcomes post-treatment (all prognostic), whereas patients with more comorbid personality disorder symptoms did better in CT than in IPT (prescriptive) (Carter et al., 2011).

Despite the evident relevance of these findings, the results from RCTs do not necessarily translate to the routine practice they ultimately intend to inform. It can be argued that patient samples in RCTs do not represent populations in general practice (Zimmerman et al., 2005), as randomization by definition excludes patients unwilling to be randomized and general practice often delivers less optimal treatment than in controlled trials (Westen et al., 2004). Moreover, patient preference is an essential variable in general practice that most RCTs ignore or even contravene. The transportability of evidence-based treatments to regular treatment settings and the perceived gap between science and practice in the (mental) health field has received much discussion (e.g. Chalkidou et al., 2012; Leykin et al., 2007b; Shafran et al., 2009). Nevertheless, it remains an empirical question whether the predictors and moderators identified in RCTs translate to routine practice, where choice of treatment more often reflects limited treatment availability and access than a true choice of options.

We present data from a sample of depressed patients who received an evidence-based treatment of their own choice in a naturalistic setting, using a controlled but non-randomized study design. Patients could choose between cognitive therapy (CT) or interpersonal psychotherapy (IPT), with or without antidepressant medication (ADM), or ADM alone. We previously reported on the relative effectiveness of the interventions and lack of outcome differences between them, aside from a time × treatment interaction wherein patients who received CT improved faster across the first 16 weeks in monotherapy than combined treatment, although outcomes