

Treatment Preferences and Outcome in a Randomized Controlled Trial for Depression
Comparing Supportive-Expressive Therapy to Medication and Pill Placebo

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Abstract

Previous research regarding the relationship between patient treatment preferences on outcome has been equivocal, with some studies finding a significant relationship between preference match and outcome, and others finding no such evidence. This study examines the effect of patient treatment preference match on outcome using data from a previously published randomized controlled trial comparing supportive-expressive therapy (SET), to antidepressant medication plus clinical management, and to pill-placebo plus clinical management. The original study included 156 participants receiving treatment at the Center for Psychotherapy research at the University of Pennsylvania in Philadelphia, PA. This study is the first to examine the relationship between preferences and outcome in a randomized controlled trial of brief psychodynamic therapy for depression. It was found that treatment preference match or mismatch was not significantly associated with outcome, nor was there a significant interaction with the therapeutic alliance. Treatment preference match or mismatch was also not associated with likelihood of study dropout. Implications are discussed.

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CHAPTER 1: INTRODUCTION

Introduction to Managing Depression

Please note: Portions of this literature review are taken from Winter and Barber (2013).

Depression considerably burdens those who suffer from the disorder, as well as society at large (Moussavi et al., 2007). A number of different treatment options have been developed to manage depression, including psycho- and pharmacotherapies. At present, treatment guidelines for major depressive disorder (American Psychiatric Association, 2010; National Institute for Health and Clinical Excellence [NICE], 2009) recommend the use of antidepressant medication and/or brief focused psychotherapies as the first line treatments.

In many cases, selective serotonin reuptake inhibitors (SSRIs) are the preferred first line pharmacological treatment for depression (NICE, 2009). These include fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. Tricyclic antidepressants (TCAs), serotonin- norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and other medications including bupropion, nefazodone, trazodone, and mirtazapine may also be used (American Psychiatric Association, 2010). Considerations such as side effect burden, previous medication experience, and patient preference factor into physician treatment recommendations.

A number of psychotherapies have been developed for the treatment of depression as well. Several have empirical support, including cognitive therapy, interpersonal therapy, behavior therapy, self-control therapy, social problem-solving therapy, and brief dynamic therapy (Society of Clinical Psychology, American Psychological Association, Division 12, 2013).

Efficacy studies in the treatment of depression

A number of outcome studies have tested different treatment options for depression against control conditions (including placebo) and against other active treatments. While these treatments may vary in the extent of their empirical support, the bulk of studies have supported the notion that both medication and psychotherapy are superior to control conditions, and that in most cases, active treatments are more or less equivalent, with certain exceptions.

Medications. Medications for depression have demonstrated superiority over placebo, and have been found to be efficacious in treating depressive symptoms (American Psychiatric Association, 2010). However, there is some recent and growing evidence from meta-analyses suggesting that mild to moderate depressions may be less responsive to medications than severe depressions (Fournier et al., 2010).

When it comes to comparing antidepressants with each other, generally similarities in effectiveness have been found, though side effect profiles may differ (American Psychiatric Association, 2010). For example, it appears that tricyclic antidepressants and SSRIs realize a comparable magnitude of effect, though they may differ in tolerability. A meta-analysis comparing these antidepressant classes found that while there was no significant difference in efficacy for tricyclic antidepressants and SSRIs, patients receiving a tricyclic were significantly more likely to drop out of treatment due to side effects (MacGillivray et al., 2003).

Psychotherapy. Meta analyses have found moderate- to-large large effect sizes for various psychotherapies compared to control conditions, including behavioral therapies, (Cuijpers, van Straten, & Warmerdam, 2007, Ekers, Richards, & Gilbody, 2008), dynamic psychotherapies (Barber et al., 2013; Driessen et al., 2010), and cognitive therapies (Butler,

Chapman, Forman, & Beck, 2006). However, there is some evidence that publication bias may be inflating estimates of effect size for psychological treatments for depression, and the true effect size may be smaller (Cuijpers, Smit, Bohlmeijer, Hollon, & Andersson, 2010)

When meta-analyses have been conducted comparing different forms of psychotherapy in the treatment of depression, results have generally supported treatment equivalence. Cuijpers, van Straten, Andersson, and van Oppen, (2008) conducted a meta-analysis comparing seven different types of psychotherapy. These treatments included cognitive–behavior therapy, nondirective supportive treatment, behavioral activation treatment, psychodynamic treatment, problem-solving therapy, interpersonal psychotherapy, and social skills training. Interpersonal therapy was found to be somewhat more effective, and nondirective supportive treatment was found to be somewhat less effective than other treatments. All other comparisons yielded non-significant differences. Similar results were found by Barth et al. (2013).

Medication compared to psychotherapy. Several meta-analyses have also been conducted comparing the efficacy of medications and various psychotherapies for depression. The results of these have indicated that antidepressants and psychotherapies are approximately equivalent in terms of efficacy, though psychotherapies may provide some additional prophylactic effect in terms of recurrence of depression (Cuijpers et al., 2013; De Maat, Dekker, Schoevers, & De Jonghe, 2006; Imel, Malterer, McKay, & Wampold, 2008).

Combined treatments. Evidence for combined treatments has been somewhat mixed. In a meta-analysis conducted by Thase et al. (1997), for mild to moderate depression, the addition of antidepressant medication did not improve outcomes. However, for those patients with severe depression, the addition of medication was associated with greater symptom reduction. Cuijpers, van Straten, Hollon, and Andersson (2010) also found a small but significant effect of

medication added to psychotherapy, and Barber, Muran, McCarthy, and Keefe (2013) conducted a meta analysis on three studies showing that medication plus dynamic therapy was more effective than medication alone.

What do patients think is helpful?

Both lay and clinical populations have been surveyed to understand attitudes towards various treatment options for depression. People surveyed about treatments for depression often are concerned about potential for addiction and side effects of antidepressants, and these beliefs may affect their willingness to pursue treatment (Morey, Thacher, & Craighead, 2007; Priest, Vize, Roberts, Roberts, & Tylee, 1996; van Schaik et al., 2003; Wittink, Cary, TenHave, Baron, & Gallo, 2010). Cost and time commitment may prevent patients from pursuing talk therapy (Burg et al., 2011). Studies have found that patients have more positive attitudes towards psychotherapy compared to medication, but may be reluctant to actually seek the help of a professional (Angermeyer, Matschinger, & Riedel-Heller, 1999; van Schaik et al., 2004;).

A significant amount of research exists examining acceptability of various treatment options. When surveyed about treatment preferences, people have generally been found to prefer psychotherapy over medication in the treatment of depression (Churchill et al., 2000; Dwight-Johnson, Sherbourne, Liao, & Wells, 2000; Gum et al., 2006; Löwe, Schulz, Gräfe, & Wilke 2006; van Schaik et al., 2004). Though effect sizes are often not reported, between 23-38% more patients have been found to prefer psychotherapy compared to medication (van Schaik et al., 2004). Combined treatments, that is, medication and psychotherapy, may also be popular with patients (Dwight-Johnson, Lagomasino, Aisenberg, & Hay, 2004; Steidtmann et al., 2012). However, patients often endorse non-empirically supported treatments, such as herbal supplements, self-help books, relaxation, and talking with a friend. Many people may have

negative attitudes towards mental health professionals in general (Angermeyer, et al., 1999; Berner, Kriston, Sitta, & Härter, 2008; Hickie, Luscombe, Davenport, Burns, & Highet, 2007).

In an exception to the commonly found preference for talking therapy over medication, one survey of Veterans Administration primary care patients (a veteran population, 93% male) found that 32% of the sample preferred medication, 19% preferred individual counseling, and 18% preferred a combined treatment (Dobscha, Corson, & Gerrity, 2007). The high proportion of male study participants may be responsible for the greater preference for medication, as previous research has found men to be more accepting of medication than women (Burg et al., 2011; Churchill et al., 2000).

What factors influence treatment preferences?

The relationship between treatment preferences and a number of variables has been studied. The variables most commonly studied have been demographics including age, race, and gender, and depression severity, but other potential contributing factors such as previous treatment experience and etiology beliefs about depression have also been explored, as described below.

Older adults may prefer behavioral interventions over pharmacotherapies (Arean, 2012). The research on the effect of race on treatment preferences has been mixed, with some studies finding no difference in preferences (Chandra et al. 2009, Khalsa, McCarthy, Sharpless, Barrett, & Barber, 2011), and others finding differences in the acceptability of medication and psychotherapy, with minority patients often being found to be less accepting of treatment in general, and particularly less accepting of medication (Cooper et al., 2003; Dwight-Johnson et al., 2000; Givens, Houston, Van Voorhees, Ford, & Cooper, 2007). With regards to gender, men may be more accepting of medication than women (Burg et al., 2011; Churchill et al., 2000), and

women have been found to be more likely to prefer counseling (Dwight-Johnson et al., 2000; Houle et al., 2013). Severity of depression has been found to be associated with less positive attitudes towards antidepressants (Berkowitz, Bell, Kravitz, & Feldman, 2012). Contradictorily, severity has also been found to be associated with a preference for medication (Dobscha et al., 2007). Severity may also be associated with greater preference to receive treatment by a professional in general (Berner et al., 2008).

Researchers have also examined the effect of previous treatment experience on treatment preferences. Previous experience with depression treatment, either personally or through a friend or family member has been associated with more positive attitude towards antidepressants (Berkowitz et al., 2012). Several studies have found that previous experience with counseling or medication is associated with a preference for those interventions (Churchill et al., 2000; Gum et al., 2006). However, other studies have found the opposite result, that previous experience with medication or counseling may be related to a preference for a different treatment (Dwight-Johnson et al., 2000; Khalsa et al., 2011). Finally, beliefs about the causes of depression, and knowledge about the treatment of depression may influence treatment preferences (Dunlop et al., 2012; Dwight-Johnson et al., 2000; Goldstein, & Rosselli, 2003; Khalsa et al. 2011; Lin et al., 2005; Steidtmann et al., 2012).

How do preferences affect treatment course and outcome?

In the last decade, emphasis has been placed on accommodating patient preferences for depression treatment. American Psychiatric Association guidelines for the treatment of depression suggest that, when possible, providers should attempt to follow a patient's preferences when recommending treatments (American Psychiatric Association, 2010; Schulberg, Katon, Simon, & Rush, 1998), and there is emerging evidence that preferences may

impact the course of treatment. In a recent meta-analysis examining the effect of treatment preference match on outcome across psychiatric conditions, a small but significant effect was found such that patients receiving their preferred treatment experienced greater improvement (Swift & Callahan, 2009). In the treatment of depression specifically, there has been an increase in research to determine what kinds of treatment patients tend to prefer, what factors may influence these preferences, and how they may affect treatment course and outcome.

A variety of study designs have been used to examine the relationship between preference and treatment process and outcome. The relationship between preferences and outcome has been explored in a variety of clinical settings, however primary care settings appear to be the most common. The results of these studies have been mixed, with some finding preference match to be significantly associated with outcome, and others finding no such relationship. Studies are organized below by design used.

Randomized trials. Randomized trials are often considered to be the gold-standard of intervention research (Concato, Shah, & Horwitz, 2000). Some of these trials have assessed patient preference, generally as a secondary data analysis in order to determine whether preference match or mismatch is associated with treatment course or outcome. The majority of these studies have compared medication and psychotherapy, though a few have compared different forms of talk therapies or medications.

Two randomized trials of have compared the effect of preferences in studies for CBT compared to medication (Dunlop et al., 2012, Leykin et al., 2007). In these trials, outcome did not appear be influenced by whether the patient received their preferred treatment. Similarly, another randomized controlled trial compared Mindfulness Based Cognitive Therapy to a maintenance dose of antidepressants or pill placebo. Preference for medication or for

Mindfulness Based Cognitive Therapy was assessed, and the effect on preference match or mismatch on outcome was tested. Preference match was not associated with outcome, defined as relapse rate, in this study (Segal et al., 2011).

Patient preferences were also examined in two studies of Cognitive Behavioral Analysis System of Psychotherapy (CBASP, McCullough, 2000) with chronically depressed patients. In the first study, patients could receive Cognitive Behavioral Analysis System of Psychotherapy, nefazadone, or their combination. It was found that preference match for psychotherapy or medication was associated with greater remission rate (Kocsis et al., 2009). In the other study, all patients received antidepressant medication in the first phase of the study. Study patients who did not reach remission in the first phase were then randomized to receive CBASP plus medication, brief supportive therapy plus medication, or medication alone. The authors report that in the initial phase of the trial, not endorsing any preference was related to better treatment response, but preferences were not associated with improvement in the second phase of the study (Steidtmann et al., 2012).

Two randomized trials with behavioral activation have examined the relationship between preferences and outcome. The first, conducted by Kwan, Dimidjian, & Rizvi. (2010), used data drawn from a randomized controlled trial in which participants could be randomized to receive one of four options, behavioral activation, cognitive therapy, paroxetine, or pill placebo. Patients were asked whether they preferred to receive pharmacotherapy, talking therapy, or if they had no preference. There was no effect of receiving one's preferred treatment on outcome. In another study comparing behavioral activation to sertraline (Moradveisi, Huibers, Renner, & Arntz, 2014) in an Iranian population, a significant three-way interaction in the psychotherapy condition was found for treatment preference by time by condition for outcome as rated on the

Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), though no such association was found when the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) was used as the outcome measure. No significant interactions were found for those assigned to the medication condition.

As part of the Treatment of Depression Collaborative Research Program (Elkin et al., 1989), investigators studied the effect of match between “predilection” (defined as beliefs about the causes of their illness and what would be helpful in treating it) and treatment assignment on BDI scores after four weeks of treatment. In this study, cognitive behavior therapy, interpersonal psychotherapy, imipramine plus clinical management, and placebo plus clinical management were compared. Match between predilection for a particular therapy and therapy assignment was not found to be associated with symptom change at four weeks in this study when controlling for initial scores on the BDI (Elkin et al., 1999). With this study, it must be noted the relation between predilection and symptom change was only examined after four weeks of treatment, not at the time of study termination. It is unclear whether findings would have been different after the full treatment course.

One study took a novel methodological approach. Rather than randomizing patients based on treatments, patients in this study were randomized to be either matched or mismatched with their preferred treatment. Treatments in this study consisted of either escitalopram or interpersonal psychotherapy for depression. In addition to categorical preference, the study authors also assessed strength of preference. Neither preference- assignment congruence nor preference strength was associated with depression remission (Raue, Schulberg, Heo, Klimstra, & Bruce, 2009).

Partially randomized preference trials. Partially randomized preference design trials have been utilized to address the effect that patient preferences may have on outcome. In this design, patients without strong preferences are randomly assigned to treatments, while those who do hold strong preference are offered their choice of treatment. Proponents of this design assert that it allows investigators to parse out the contribution of preferences while controlling for treatment effects, and may encourage participation from patients who might otherwise be reluctant to participate in randomized controlled trials, with the possibility of random assignment to a non-preferred treatment (Bedi et al., 2000). The results of these trials have been mixed with regards to the contribution of patient preference on process and outcome. These studies are described immediately below.

Partially randomized preference trials have been conducted comparing talking therapy and antidepressants (Bedi et al. 2000, Chilvers et al., 2001; Van et al., 2009). In a study utilizing a sequential treatment strategy for depression, comparing medication and short-term psychodynamic supportive psychotherapy, patients choosing psychotherapy and those randomized to it were not found to differ on outcome measures (Van et al., 2009). Bedi et al. (2000) similarly report on data from a primary care trial comparing medication and counseling, ultimately finding that being randomly assigned to a treatment or selecting one's preferred treatment (either medication or counseling) did not appear to improve in outcome assessed at eight weeks. A delayed effect was, however, observed, and at 12 months, patients who chose counseling did better than those who were randomized to receive counseling, though patients randomized to receive antidepressants did not differ in outcome as compared to those who chose it (Chilvers et al. 2001).

A partially randomized preference trial included two different talking therapies (non-directive counseling and cognitive behavior therapy) compared to usual general practitioner care for depressed patients in a general practice setting (King et al., 2000; Ward et al., 2000). Patients who did not have a strong preference were randomized to treatment, while those with a strong preference generally preferred a talking therapy (though did not tend to have clear ideas about which talking therapy they preferred). As patients did not have a clear idea of which talking therapy they preferred, midway through the study, patients refusing general practitioner care were instead randomized between the two psychological interventions. Consistent with other partially randomized preference trials, patients randomized to psychological interventions did not differ in outcome from those choosing them (King et al., 2000; Ward et al., 2000).

Randomized trials with patient preference arms. Another study design that has been utilized to allow examination of patient preferences is that of the randomized trial with patient preference arms. In these studies, the design is similar to that of a traditional randomized trial, with the addition of a patient preference arm. Patients are randomly assigned to the preference arm or to a study treatment. In the preference arm condition, patients are allowed to choose their preferred treatment, while those not assigned to the preference arm are randomly assigned to study treatments. In this way, the effect of choice on treatment outcome may be examined. Two such studies have been conducted comparing treatments for depression (Rokke, Tomhave, & Jovic, 1999; Mergl et al., 2011). In the first, preferences for two kinds of talk therapy were compared. Study treatments included self management therapy focusing on changing cognitions, and self management therapy focusing on changing behavior. These were compared with a control condition. Participants were either randomly assigned or allowed to pick their preferred

treatment. The study authors found no differences in outcome between patients in the choice or no-choice groups. (Rokke et al., 1999).

In another randomized trial with preference arms comparing psychotherapy to sertraline, patients receiving their preferred treatment in both the medication and psychotherapy groups were found to improve significantly more than those who did not receive their preferred treatment (Mergl et al., 2011). However, as found in previous studies examining the effect of patient choice, those in the randomized and choice groups did not significantly differ in outcomes.

Collaborative care studies. Several studies have examined the contribution of patient preferences to the process and outcome of depression treatment in primary care settings in the course of investigating collaborative care interventions. In these studies, interventions designed to increase collaborative care are tested. Collaborative care includes coordination between professionals such as social workers, therapists, and psychiatrists in the treatment of a patient, along with symptom monitoring. Unlike other randomized controlled trials, the specific treatment administered is not the focus of the study, as patients receiving collaborative care may have a variety of interventions. Two studies that have examined the effect of preference match in such a setting have been conducted in the Veterans Administration (VA) system. In the first, Lin et al. (2005) found that patients who received their preferred treatment (antidepressant medication or counseling) demonstrated more rapid improvement than those who did not receive their preferred treatment. However, the matched and mismatched patients did not differ significantly in depression improvement at nine months. Dobscha et al. (2007) also did not find receiving one's preferred treatment in a VA primary care setting to be associated with outcome. A third study of collaborative care examining treatment preferences of older adults in a primary

care setting found that receipt of preferred intervention, either medication or counseling, was not associated with improved outcome (Gum et al. 2006).

Treatment preferences and indirect measures of outcome. Although the majority of studies have not found a direct relationship between patient preferences and outcome, there is somewhat more evidence that preferences may have an indirect effect. Factors such as engagement or alliance ratings, adherence, attrition, and satisfaction, may be affected by patient preferences, though the results are mixed for these indirect measures as well.

It appears that the therapeutic relationship and engagement may be affected by patient preferences. In a randomized controlled trial comparing supportive-expressive therapy (Luborsky, 1984) to sertraline or placebo, preference match was found to be related to the therapeutic alliance (Iacoviello et al., 2007). In this study, patients preferring psychotherapy that *received* psychotherapy were found to demonstrate increases in the alliance over the course of treatment, while those preferring psychotherapy that did *not* receive it had decreases in the therapeutic alliance. Treatment congruent or incongruent with a preference for medication was not related to alliance development. Similarly, Kwan et al. (2010) found that patients who did not receive their preferred form of treatment evidenced lower working alliance scores, though preference was not directly related to outcome. Elkin et al. (1999) also did not find a direct relationship between treatment preference and outcome, however, it was found that patients receiving congruent treatment had higher alliance ratings, and more engaged relationships.

Patient adherence to medication may also be impacted by patient preferences. Raue et al. found that neither categorical preference nor preference strength was related to outcome, however, preference strength was related to adherence at 12 weeks (Raue et al., 2009). The authors posit that preference strength may important to assess, rather than simply examining

categorical preference alone. In a study of antidepressant adherence in primary care, Hunot, Horne, Leese, and Churchill (2007) found that patients who preferred to receive a different therapy than what they received were less likely to adhere to their prescribed antidepressant regimen.

Attendance and attrition may be other important factors related to patient preferences, though the results here have been somewhat inconsistent. Bedi et al. (2000) found that patients randomized to receive counseling attended fewer sessions than those who chose to receive counseling. Rokke et al. did not find a difference in outcome between patients who were and were not allowed to pick the treatment of their choice, but patients allowed to choose their treatment were less likely to drop out prematurely (Rokke et al., 1999). Similarly, Kwan et al. (2010) found that patients who did not receive their preferred form of treatment attended fewer sessions and were more likely to drop out of treatment. While there was not a significant direct relationship between preference and outcome, the authors tested an indirect model, which indicated that preference mismatch indirectly affected outcome, largely due to attendance. In the Moradveisi et al. study (2014), a greater preference for psychotherapy and less preference for medication were associated with dropout in the medication condition, though preferences were not related to dropout in the psychotherapy group. Elkin et al. (1999) also found that patients receiving congruent treatment were less likely to drop out at four weeks. However, others (Mergl et al., 2011; Leykin et al., 2007; Kocsis et al., 2009) have not found preference mismatch to be associated with attendance or dropout rates. Dobscha et al. (2008) did not find an association between receipt of preferred intervention and outcome, attendance in therapy was not significantly different, and patients were no more likely to fill antidepressant prescriptions prescribed by their doctor. Several studies have also found that patient preferring medication are

more likely to drop out early regardless of whether or not they received their preferred treatment (Dunlop et al., 2012; Steidtmann et al., 2012). In a study comparing individual and group CBT, while patients initially preferred individual therapy, preferences did not appear to affect attrition in either group (Brown et al., 2011).

Satisfaction with treatment has been inconsistently associated with treatment preferences for depression. For example, Bedi et al. (2000) found that patients who requested to receive antidepressants were more satisfied than those randomized to receive them. Receiving one's preferred treatment was not associated with increased patient satisfaction in the study conducted by Dobscha et al (2007). Similarly, Gum et al. (2006) did not find a relationship between receiving one's preferred treatment and outcome, nor did satisfaction with treatment received vary.

Summary of the literature

Existing guidelines encourage providers to take patient preference into account when deciding on the best course of treatment (APA, 2010). Particularly as various forms of treatment including various pharmac- and psychotherapies have generally demonstrated equivalence in terms of efficacy for the treatment of depression, (De Maat et al., 2006; Imel et al., 2008) accounting for patient preferences may be an important deciding factor when choosing the best course of treatment.

The existing research examining the relationship between treatment preferences and outcome has been equivocal. A number of studies have found no effect of preference match on outcome (e.g. Dobscha et al., 2008; Dunlop et al. 2012; Elkin et al., 1999; Gum et al., 2006; Kocsis et al., 2009; Kwan et al., 2010; Leykin et al., 2007; Raue et al., 2009; Segal et al., 2011). Others have found a significant association between preference match and symptom change (e.g.

Kocsis et al., 2009; Lin et al., 2005; Mergl et al., 2011; Moradveisi et al., 2014; Steidtmann et al., 2012). There is also some evidence that the effect of preferences on outcome may be indirect, with several studies providing support for this model (e.g. Kwan et al, 2010, Iacoviello et al., 2007; Elkin et al., 1999; Hunot et al. 2007). These studies have indicated that preference match or mismatch may influence the development of the therapeutic relationship, and that patients receiving a non-preferred treatment may be more likely to be non-compliant, or drop out before they have completed a recommended treatment course. Given that practice guidelines suggest that patient preferences should be respected when possible in deciding on a course of treatment, greater understanding of when and how treatment preferences may affect outcome is necessary.

While most studies have examined the effect of preference match or mismatch, fewer studies have investigated whether type of preference matters. There is some emerging evidence that what kind of preference patients have may affect treatment process and outcome (e.g. Iacoviello et al., 2007; Moradveisi et al., 2014). Iacoviello et al. found that patients preferring psychotherapy who received psychotherapy experienced increases in the alliance over time, while those preferring psychotherapy and receiving medication or pill placebo experienced decreases in the alliance. Patients who preferred medication showed no effect on alliance based on preference match or mismatch. Moradveisi et al. found that preference for psychotherapy was associated with dropout in the medication condition, while preferring psychotherapy and being assigned to psychotherapy was associated with more rapid improvement. These studies have provided initial evidence that perhaps the effect of preference match on process and outcome may depend on type of preference, rather than match/mismatch alone, but this remains a relative gap in the literature.

The understanding of the effects of treatment preference on process and outcome in the treatment of depression remains somewhat limited. The relationship between preferences and outcome has thus far been examined in only a few RCT's, and as far as we are aware, no study has yet examined the relationship between treatment preferences and outcome in a RCT with short-term dynamic therapy for depression. Although one previous RCT has examined the relationship between preference and symptom change with interpersonal therapy (Elkin et al., 1999), they did not look at symptom change at termination, only week four of treatment. Another study examining preference and outcome using interpersonal therapy did not randomly assign study participants to treatment conditions (Raue et al., 2009). A randomized controlled trial of the effect of preference on psychotherapy process and outcome with a psychodynamic therapy would be a novel contribution to the literature.

Potential moderators of the relationship between preferences and outcome also remain under-studied. The majority of studies which have examined process variables such as alliance and dropout have done so separately from analyses of outcome, and it remains unclear whether these process variables may interact with preference in predicting outcome. As the therapeutic alliance is thought to be an essential component of psychotherapy and remains one of the most highly studied variables in psychotherapy research (Martin, Garske, & Davis, 2000), further research into how the alliance specifically is affected by treatment preferences, and in turn, may affect outcome would be of interest.

CHAPTER 2: METHODS, RATIONALE, AND HYPOTHESES

Methods

Participants

Participants in this study were 156 patients who took part in a previously published RCT conducted at the Center for Psychotherapy Research at the University of Pennsylvania in Philadelphia, PA comparing supportive-expressive therapy (SET), to sertraline plus clinical management (which was titrated to venlafaxine extended release in the case of non response), and to pill-placebo plus clinical management (Barber, Barrett, Gallop, Rynn, & Rickels, 2012). The research presented here represents a secondary examination of this larger study.

All participants in the study received a diagnosis of major depressive disorder at intake, and had a minimum score of 14 on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960). Potential participants were excluded from participating in the study if they had a history of bipolar or psychotic disorders, substance dependence occurring in the past six months, an Axis I disorder appearing to be more severe than depression, high suicide risk, functional illiteracy, or a medical condition that would interfere with study participation.

Participants in this study generally reported lower socioeconomic status, with 76% [$n = 119$] reporting incomes under \$30,000, and reported a mean of 13.5 ($SD = 3.5$) years of education. Many of the study participants were diagnosed with comorbid Axis I [76%, $n = 119$] and Axis II disorders (47%, $n = 73$). With regards to race and gender of the sample, 92 (59%) were female, and eighty-one (52%) patients identified themselves as having a minority racial background. Analyses conducted and presented in the main outcome paper (Barber et al., 2012) indicated that treatment groups did not differ in any demographic or clinical characteristics.

Procedures

Potential study participants were identified through self-referral, referral through a psychiatric department triage line, physician referral, from staff at the Center for Psychotherapy Research, the Mood and Anxiety Disorders Unit or through notices in the media, including newspaper and subway advertisements. Study procedures took place at the University of Pennsylvania Center for Psychotherapy Research. When potential patients initially contacted the study, they underwent a 20-30 minute semi-structured telephone screening evaluation to determine their potential eligibility for the study. If they were depressed, and did not appear to meet any of the exclusion criteria, they were scheduled for an initial evaluation. At the initial evaluation, the purpose of the study and study procedures were reviewed. Written informed consent was obtained at that point.

Following informed consent, potential study participants were evaluated for major depressive disorder by trained MS or PhD level psychologists using the Structured Clinical Interview for DSM-IV for Axis I and II disorders (First et al., 1995; First, Spitzer, Gibbon, Williams, & Benjamin; 1994) and the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Patients returned in one week, at which point they underwent a baseline assessment of their clinical status, and it was ensured that their depression level had not gone below 14 on the HRSD and they still met diagnostic criteria for MDD.

Patients meeting entrance criteria for the study were randomized by urn randomization (Wei & Lachin, 1988) to one of the three treatment groups (SSRI/SNRI plus clinical management, placebo plus clinical management, or SET). Patients were evaluated for symptomatic improvement on the HRSD at weeks 2, 4, 6, 8, 12, 15, and 16. At intake, patients were also administered the Attitudes and Expectations Questionnaire which was adapted from

Elkin, Parloff, Hadley, and Autry (1985) and Sholomskas (1990), and a version of the 12-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989; Tracey & Kokotovic, 1989). which assessed for patient expectations for the therapeutic alliance. Patients completed the WAI again at weeks 2, 4, 8 and 16.

Patients in all three conditions received 16 weeks of treatment. With regards to the psychotherapy condition, therapy was conducted by therapists experienced in SET. SET is a form of dynamic psychotherapy that is conceptualized as focusing on both the supportive and expressive aspects of intervention. Supportive interventions are those that foster the development of the therapeutic alliance, while expressive interventions in this case are designed to help the patient gain understanding of Core Conflictual Relational Themes (CCRT). The CCRT is made up of a patient's wish, a response of the other, and response of the self (Leichsenring & Leibing, 2007; Luborsky, 1984). Therapy consisted of twice-weekly 45-minute sessions for the first four weeks of treatment, reduced to once weekly sessions for the remainder of treatment. Fifty-one patients were assigned to the SET group, and five of these did not start treatment. Of the forty-six patients who began treatment, 12 dropped out.

For those assigned to the pharmacotherapy condition, they met with their prescriber weekly for the first six weeks of treatment, with meetings reduced to every two weeks for the remainder of time. Patients were prescribed 50 mg per day of Sertraline. This dose was raised in 50-mg increments up to a maximum dose of 200 mg by week 4. If by week 8 patients had not responded, medication was then titrated from sertraline to venlafaxine extended release (ER) over the course of two weeks. Patients were initially given a dose of 37.5 mg per day, which was increased to 75mg by week nine, up to 375 mg per day by week 12. Fifty-five patients were assigned to the active medication group, and 4 of those did not attend the first appointment. A

further 22 patients in this condition dropped out. Patients in the placebo condition were put on the same titration schedule as those in the active treatment condition, with non-responding patients switched to a second placebo. After week 16, patients in the placebo group were offered a free course of medication. Fifty patients were assigned to the placebo condition, with two patients failing to attend the first appointment. A further 20 patients dropped out in this condition. Pairwise comparisons revealed no significant difference in attrition between groups (Barber et al., 2012).

Measures

Attitudes and Expectations Questionnaire. (adapted from Elkin et al., 1985; Sholomskas, 1990). The Attitudes and Expectations Questionnaire is a measure of patient attitudes and expectations with regards to treatment for depression. For the purposes of this study, only one item from this measure was of interest. This item assessed for patient treatment preferences at intake. This forced-choice dichotomous item asked patients to respond to the following question: “In coming in for treatment of depression, I would *prefer* to receive (circle *one* answer): (a) drug treatment or (b) talking treatment.”

Working Alliance Inventory. (WAI; Horvath & Greenberg, 1989). In this study, a 12-item, shortened, client version of the WAI was used, based on the scale developed by Tracey and Kokotovic (1989). The WAI is a widely used measure of the therapeutic alliance. Patients rate items related to the therapeutic relationship on a 7-point Likert scale ranging from 1 (*Never*) to 7 (*Always*). Although therapist and observer rated alliance measures also exist, for the purposes of the present study, the patient-rated version will be used in this study, as patient ratings of the alliance have been shown to be more strongly related to treatment outcome than therapist or observer ratings (Horvath & Symonds, 1991). The WAI is made up of three specific factors,

task, goal, and bond, with a total score representing general alliance. In this study, we will focus on total alliance score. The scale has good internal consistency, and Cronbach's alpha for the scale was found to be .9 for the 12-item version (Tracey & Kokotovic, 1989).

Hamilton Rating Scale for Depression. (HRSD; Hamilton, 1960). The HRSD one of the most widely-used clinician-administered measure of depression. The scale is composed of 17 items, which assess for presence and severity of depressive symptoms. Items are rated in terms of categories of increasing severity. The reliability and validity of the scale have been widely studied, and have generally indicated good psychometric properties (Hamilton, 1969; Trajković et al., 2011). A meta analysis of studies utilizing the scale indicated a mean alpha of 0.789, indicating good reliability, and in terms of inter-rater reliability, a mean intraclass correlation coefficient (ICC) of 0.93, indicating good inter-rater reliability. It has been suggested that a score of 17-23 may indicate moderate depression, while scores greater than 24 indicate severe depression (Zimmerman, Martinez, Young, Chelminski, & Dalrymple, 2013).

Rationale for Study

This study represents the first examination of the relationship between treatment preferences and outcome in a RCT with a brief dynamic therapy. It is unclear at this point whether the effect of preference may differ based on type of preference or treatment condition, and this study seeks to provide clarification. Further, the role of the therapeutic alliance in the relationship between preferences and symptom change remains under-studied. The examination of the alliance as a moderating variable may help explain potential mechanisms of an association between preference and outcome.

Hypotheses

Hypothesis 1: It is hypothesized that congruence of patients' treatment preference and treatment assignment will be associated with outcome, such that patients receiving the therapy they prefer will realize outcomes superior to those patients not receiving their preferred therapy.

Supplemental Hypotheses

Hypothesis 2: The relation between preference match and symptom change will depend on the alliance, or, in other words, patient-rated alliance during treatment will moderate the relation between preference match and symptom change over the course of treatment. Namely, those patients receiving their preferred treatment and who have higher alliance scores will experience greater symptom change than patients not receiving their preferred treatment and those with lower alliance scores.

Hypothesis 3: We predict that preference match groups will be associated with dropout, such that those who are assigned to a non-preferred treatment will be more likely to drop out.

CHAPTER 3: RESULTS

Hypothesis 1: We predicted that if preference is associated with outcome, patients receiving a therapy congruent with preference would realize more improvement at termination than those participants receiving a non-preferred treatment. As some previous research has indicated that the effect of preference match may differ based on type of preference (e.g. Iacoviello et al. 2007; Moradveisi et al. 2014), each preference match condition was examined (wanted medication, received psychotherapy; wanted medication received medication; wanted psychotherapy, received medication; wanted psychotherapy, received psychotherapy; wanted medication, received placebo, wanted psychotherapy, received placebo), rather than examining simply match/mismatch. A total of 88 study participants reported their preferred treatment at intake and completed the HRSD at termination, and thus were included in analysis. Of those included, 12 preferred medication and received medication, 9 preferred medication and received psychotherapy, 14 preferred medication and received placebo, 18 preferred psychotherapy and received medication, 22 preferred psychotherapy and received psychotherapy, and 13 preferred psychotherapy and received placebo. The GLM procedure in SPSS was used with a Bonferroni correction in order to run an ANOVA to test whether the six preference match condition groups differed in outcome with pretreatment HRSD scores covaried out. No significant effect of preference match group was found on outcome with initial HRSD score covaried out ($F(5, 81) = 1.37, p = .25$). Please see Table 1 for termination HRSD group means with intake HRSD scores covaried out (all tables may be located in the appendix).

It was found that the largest difference between groups was for those who preferred medication and received medication. That group had slightly lower termination HRSD scores than those in the other preference groups, particularly those who preferred medication and

received therapy, though this difference was not significant (nor were any other group comparisons). We also examined the effect size for this comparison, and found a partial eta squared of .08, which is considered a small effect (Cohen, 1992). Due to our large p value, any such group comparisons should be interpreted with extreme caution. Our observed power for this analysis was .46. A sample size calculation based on the small effect size observed and a standard recommended power of .8 (Cohen, 1992), indicated that we would need a sample size of 211 in order to observe significant results.

Hypothesis 2: The procedure for Hypothesis 2 was the same as for Hypothesis 1, with the addition of the alliance variable. We predicted that there would be a significant interaction between preference match condition and alliance. The alliance variable was made up of average alliance scores for each patient over the course of treatment for the purposes of this analysis. An alpha of .05 indicated statistically significant results. There was no significant interaction between the preference match groups and the alliance in predicting outcome ($F(5, 73) = .40, p = .85$). Please see Table 2 for termination HRSD group means with intake HRSD scores and average alliance scores covaried out.

It was found that those who preferred medication and received medication had slightly lower termination HRSD scores than those in the other preference groups, particularly those who preferred medication and received therapy, though this difference was again not significant (nor were any other group comparisons). When we calculated the effect size for this analysis, we found a small effect size (Cohen, 1992), with a partial eta squared of .03. Our observed power for this analysis was .15. A sample size calculation based on the small effect size observed and a power of .8 indicated we would need a sample size of 1289 for significance.

Hypothesis 3: We conducted a 2(dropout or completer status) x 6 (treatment preference group) chi-square analysis in order to test whether those assigned to a non-preferred treatment were more likely to drop out. An alpha of .05 was used to determine if there was statistically significant difference between groups in dropout rate. No significant difference in dropout rate was found between preference match groups $\chi^2(5, N = 151) = 5.23, p = .39$.

We found that those who preferred therapy and received therapy were slightly less likely to drop out than would be expected, but this was not a significant difference. When we conducted a calculation to determine the effect size for differences in group dropout rates, it was found that the phi value was .19, which is considered a small effect size (Cohen, 1992). We also conducted a power analysis, and observed a power of .74. This indicates that our lack of significant findings are likely not due to being underpowered, that there are likely no differences between groups in dropout rates. A sample size calculation indicated that we would need a sample size of 218 for a power of .8 in order to potentially reach significance. Please see Table 3 for a comparison of observed versus expected dropout and completion counts by treatment preference group.

CHAPTER 4: DISCUSSION

There is a wealth of evidence supporting the efficacy of both medication and psychotherapy in the treatment of depression (American Psychiatric Association, 2010; Cuijpers, van Straten, Andersson, and van Oppen, 2008). Given that treatments have been broadly established as efficacious, it is important for researchers to examine whether certain patients respond better to certain interventions, and the mechanisms through which change occurs. One possible variable of interest has been the extent to which patient preferences may interact with treatment to produce outcome. More specifically, researchers have begun to analyze the extent to which receiving a non-preferred treatment may impact how much improvement patients realize, and whether preference match or mismatch may interact with treatment process variables such as the therapeutic alliance and dropout. These process variables may serve as mechanisms through which receiving a non-preferred treatment may compromise improvement. Researchers have attempted to address these questions using a variety of study designs, including randomized trials, partially randomized preference trials, randomized trials with patient preference arms, and collaborative care studies. The results of these studies have been mixed, with some finding a relationship between preference match and outcome, and other studies finding a lack of relationship.

The purpose of this study was to examine whether there was a relationship between treatment preferences and outcome in a randomized controlled trial for depression comparing supportive-expressive therapy to medication and pill placebo. None of our hypotheses were supported by the data. We found that the preference groups (wanted medication, received psychotherapy; wanted medication received medication; wanted psychotherapy, received medication; wanted psychotherapy, received psychotherapy; wanted medication, received

placebo, wanted psychotherapy, received placebo) did not differ in outcomes on the HRSD when controlling for pretreatment HRSD score. In testing our supplemental hypotheses, we did not find a significant interaction between preference match groups and the alliance in predicting outcome on the HRSD. Dropout rates were also not found to differ between preference match groups. Effect sizes for all analyses were found to be small.

These findings are perhaps not entirely unexpected, as several other studies have previously found no relationship between treatment preferences and outcome (e.g. Dobscha et al., 2008; Dunlop et al. 2012; Elkin et al., 1999; Gum et al., 2006; Kocsis et al., 2009; Kwan et al., 2010; Leykin et al., 2007; Raue et al., 2009; Segal et al., 2011). However, previous studies have found treatment preferences to be indirectly linked to outcome through the alliance (Iacoviello et al., 2007, Kwan et al. 2010; Elkin et al. 1999). Our finding that preference match group was not associated with dropout replicates what some others have previously found (e.g. Mergl et al., 2011; Leykin et al., 2007; Kocsis et al., 2009).

It is possible that the fact that our study utilized data from a randomized controlled trial may have contributed to the observed lack of relationship between preference and outcome. Some researchers have argued that the possibility of assignment to a non-preferred treatment may impact the type of patient that is willing to participate in RCTs, as some patients are not willing to risk being assigned to a non-preferred treatment (Ten-Have et al., 2003). It is possible that the patients in this study may have had less strong treatment preferences than what is found in real-world clinical settings, as they were willing to undergo random assignment with the possibility of receiving a non-preferred treatment.

The demographic makeup of participants in this study may have also contributed to our null results. This study had a large proportion of African-American participants. Previous

research has indicated that African-Americans may be less accepting of both psychotherapy and medication than Caucasians (e.g. Cooper et al., 2003). Perhaps such ambivalence towards treatment could have contributed to the lack of observed relationship between preferences and outcome. Although we did not examine the strength of preferences, and were unable to assess whether there were racial differences in preference strength in this study, it is possible that due to our study's large proportion of African-American participants, our sample had weaker preferences than might be found in other populations.

Given our lack of significant findings, there are some implications for the effects of patient preferences on outcome, particularly in randomized trials. The concern has been raised that random assignment, and the likelihood that patients will receive a non-preferred treatment, may interfere and produce an inaccurate picture as to the true efficacy of treatments (Corrigan & Salzer, 2003). We found small, non-significant effects for treatment preference match on outcome and dropout. Although the effects were generally in the direction that would support the idea that preferences may affect treatment process and outcome, the effect sizes were so small and non-significant any interpretations should be made with extreme caution. This study lends evidence to the idea that if treatment preferences do impact patient engagement and outcome in randomized controlled trials, at the most, they are so small as to not be reliably detectable.

Limitations of the present study

There are several limitations to the present study. First, we did not examine strength of preferences. As some previous research has shown that strength of preference may be more important than type of preference alone (Raue et al., 2009), we may not be truly capturing the impact of patients' treatment preferences on the treatment process and outcome. Perhaps only for patients with a very strong preference is there an association between preference match and

outcome.

Our findings may have also been limited by the statistical procedures utilized. In the main analysis, only study completers were included. This had the consequence of reducing our sample size, and also potentially excluding a group that may have been dissatisfied with the treatment they received for reasons including receiving a non-preferred treatment. Another limitation related to the analytical procedure adopted is that it did not allow us to examine in detail the process of change over time. It is possible that by simply examining pre-post scores, we may have missed potential effects on the treatment process, which could be present in phases of treatment other than termination (i.e. early alliance development or symptom reduction could be affected by receiving a non-preferred treatment, but as a patient adjusts to their treatment, such effects may disappear).

Directions for future research

As this study represents the first RCT that has examined the role of treatment preferences with a short-term dynamic therapy, future studies could focus on replication, to provide further confirmation or refutation of the lack of relationship between treatment preferences and outcome. Particularly as patients participating in RCTs may have less strong preferences than patients receiving treatment in a naturalistic setting, it is possible that RCTs may not be the ideal study design to use to study the effects of treatment preferences. Utilization of alternative study designs, including partially randomized preference design trials, randomized trials with patient preference arms, or naturalistic study designs could provide further clarification as to what, if any, effect patients' preferences have on the course and outcome of their treatment.

More examination of the process effects of preference mismatch could also be potentially enlightening. Future studies could utilize a different statistical approach, such as hierarchical

linear modeling to test whether the effect of receiving a non-preferred treatment may have differences in alliance and symptom change over the course of treatment, rather than simply looking at pre-post change. It is possible that differences may emerge using this more fine-grained approach. For example, it could be the case that receiving a non-preferred treatment may initially interfere with the development of the alliance, or be related to slower symptom reduction, but that over time, this effect disappears. Perhaps this more detailed examination of the potential treatment process effects would reveal the effects of treatment preference that were not found in this examination.

Conclusion

This study represents the first examination of the effects of patient treatment preference on outcome in randomized controlled trial of brief psychodynamic therapy for depression. We found that preference match group was not significantly associated with treatment outcome. There was also no significant interaction between preference match groups and the alliance in predicting outcome. Finally, preference match group was not associated with dropout in this study. Further research should attempt to clarify the nature of the relationship between treatment preferences and outcome, particularly as current American Psychiatric Association guidelines (American Psychiatric Association, 2010) suggest that treatment preferences should be taken into account as much as possible when deciding on a treatment course. Although preference match or mismatch has been widely proposed as an important factor in symptom improvement in psychotherapy and pharmacologic treatment for depression, existing research has failed to support a strong effect.

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Appendix

Table 1. Corrected Group Mean HRSD Scores with Intake HRSD Scores Covaried Out

Preference Match Group	Mean	N	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
1.00	9.98	12	1.97	6.05	13.91
2.00	17.37	9	2.30	12.79	21.95
3.00	11.49	14	1.83	7.84	15.13
4.00	12.56	18	1.60	9.38	15.74
5.00	11.45	22	1.46	8.55	14.36
6.00	12.47	13	1.89	8.72	16.22

Note: 1= preferred medication, received medication, 2= preferred medication, received psychotherapy, 3= preferred medication, received placebo, 4= preferred psychotherapy, received medication, 5= preferred psychotherapy, received psychotherapy, 6= preferred psychotherapy, received placebo

Table 2. Corrected Group Mean HRSD Scores with Intake HRSD Scores and Average Alliance Scores Covaried Out

Preference Match Group	Mean	N	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
1	9.54	12	3.06	3.44	15.64
2	18.23	9	2.43	13.40	23.07
3	10.72	14	2.18	6.38	15.08
4	12.16	18	1.78	8.61	15.71
5	11.46	22	1.65	8.16	14.75
6	11.63	13	2.28	7.09	16.17

Note: 1= preferred medication, received medication, 2= preferred medication, received psychotherapy, 3= preferred medication, received placebo, 4= preferred psychotherapy, received medication, 5= preferred psychotherapy, received psychotherapy, 6= preferred psychotherapy, received placebo

Table 3. Observed Versus Expected Dropout and Completion Counts by Treatment Preference Group

Preference Match Group		Completed	Dropped Out
1	Observed Count	12	11
	Expected Count	13.4	9.6
2	Observed Count	9	8
	Expected Count	9.9	7.1
3	Observed Count	14	8
	Expected Count	12.8	9.2
4	Observed Count	18	13
	Expected Count	18.1	12.9
5	Observed Count	22	8
	Expected Count	17.5	12.5
6	Observed Count	13	15
	Expected Count	16.3	11.7

Note: 1= preferred medication, received medication, 2= preferred medication, received psychotherapy, 3= preferred medication, received placebo, 4= preferred psychotherapy, received medication, 5= preferred psychotherapy, received psychotherapy, 6= preferred psychotherapy, received placebo

Vita

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