HSR&D

Evidence Synthesis for Determining the Efficacy of Psychotherapy for Treatment Resistant Depression

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PREFACE

VA's Health Services Research and Development Service (HSR&D) works to improve the cost, quality, and outcomes of health care for our nation's veterans. Collaborating with VA leaders, managers, and policy makers, HSR&D focuses on important health care topics that are likely to have significant impact on quality improvement efforts. One significant collaborative effort is HSR&D's Evidence-based Synthesis Program (ESP). Through this program, HSR&D provides timely and accurate evidence syntheses on targeted health care topics. These products will be disseminated broadly throughout VA and will: inform VA clinical policy, develop clinical practice guidelines, set directions for future research to address gaps in knowledge, identify the evidence to support VA performance measures, and rationalize drug formulary decisions.

HSR&D provided funding for the two Evidence Based Practice Centers (EPCs) supported by the Agency for Healthcare Research and Quality (AHRQ) that also had an active and publicly acknowledged VA affiliation—Southern California EPC and Portland, OR EPC—so they could develop evidence syntheses on requested topics for dissemination to VA policymakers. A planning committee with representation from HSR&D, Patient Care Services, Office of Quality and Performance, and the VISN Clinical Management Officers, has been established to identify priority topics and to ensure the quality of final reports. Comments on this evidence report are welcome and can be sent to Susan Schiffner, ESP Program Manager, at Susan.Schiffner@va.gov.

Financial disclosure: No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability worldwide. 1 The lifetime prevalence of MDD in the general population is estimated at 13%[2], of which approximately 20% will experience chronic depression and 60-85% will experience recurrence and relapse.[3] This number is even higher in the VA medical system, where an estimated one third of veterans experience MDD.[4] MDD is associated with greater health care utilization, greater functional impairment, and increased mortality.[2] In addition, subclinical symptoms of depression can reduce quality of life, worsen disability, and adversely affect co-existing chronic medical conditions.[5-8] Both antidepressant medications and depression-specific psychotherapies are effective as first-line treatments for MDD. In primary care settings, most patients with MDD are treated with antidepressant medications, but a substantial proportion of patients fail to recover with this initial treatment. This evidence synthesis was requested to evaluate the efficacy of psychological treatments as step-2 treatment for patients with MDD who do not achieve remission with an initial course of antidepressant medication.

BACKGROUND

Antidepressant medications are the most commonly prescribed treatment modality in MDD.[9] The most recent American Psychiatric Association (APA) guidelines[10] suggest the use of antidepressants for mild, moderate or severe depressive disorders, a position that has remained consistent in the more recent "guideline watch" by Fochtmann & Gelenberg (2008).[11] The efficacy and effectiveness of antidepressant treatment in primary care have been demonstrated in multiple large scale studies and systematic reviews.[12-16] Several classes and types of antidepressants exist which do not substantially differ in their efficacy or effectiveness for treating MDD.[17] Therefore, primary care physicians have a wide array of antidepressant options that they may prescribe depending on suitability to patient, patient preference, affordability, side effect profile, and the targeted physiological system.[17]

In addition, a sizeable body of literature has examined the efficacy and effectiveness of psychotherapy as acute phase treatment for MDD, either as monotherapy or in combination with antidepressant treatment. Psychotherapy is a heterogeneous class of treatments in which the therapist utilizes interpersonal strategies with the intention of alleviating mental or emotion distress.[18] Cognitive therapy (CT) is the most widely studied form of psychotherapy for depression, although many other psychotherapeutic modalities exist that are depression-specific, empirically validated, and accessible through referral or adoption by the primary care team. Recent reviews and meta-analyses of acute phase treatment for depression have shown that psychotherapy may be as effective as antidepressant treatment and more effective than usual care in treating mild, moderate, and severe MDD.[19-23] When MDD is severe, chronic or recurrent, the combination of medication and psychotherapy as initial treatment appears to be indicated.[17] Combination of psychotherapy with an antidepressant has demonstrated greater treatment gains, lower relapse rates, and increased adherence to treatment when compared to usual care or antidepressant monotherapy.[24-27] Therefore, current evidence suggests that antidepressants and psychotherapy may both form effective first line treatments in patients with MDD, individually or in combination.

However, response to initial treatment for MDD remains poor even when treatment recommendations are rigorously followed.[28, 29] Fewer than 50% of patients fully remit after an adequate trial of antidepressant medication or psychotherapy.[30, 31] Patients who do not fully remit are often considered "treatment resistant" or "treatment refractory." Treatment resistant depression (TRD) is typically defined as an inadequate response to at least one 6-week or longer trial of an antidepressant at an adequate dose.[32] TRD does not include patients who did not adhere to initial treatment recommendations. Clinical factors associated with treatment resistant depression (TRD) include comorbid generalized anxiety and other Axis I disorders (e.g., phobias), early onset of MDD, previous suicide attempts, number of prior depressive episodes, older age, and unemployment.[33-36] In primary care settings, these findings may help physicians *a priori* determine patients who may be most at-risk for TRD.

Primary care physicians have several options when treating patients with TRD: augmenting treatment by adding another medication; switching to a different antidepressant; augmenting treatment through adding psychotherapy; and switching from medication to psychotherapy.[37] However, studies of clinical practice suggest that medications are often the only active treatment provided by primary care providers as a second step treatment for MDD.[17, 38] Several limitations to this approach should be noted. First, the addition of another antidepressant may increase the number and/or severity of side effects that patients experience. Side effects are known to reduce quality of life and increase the chances of non-adherence, interfering with the treatment of MDD.[39] Second, focus on antidepressants may ignore the potential impact of psychosocial factors in TRD. For instance, cognitions and behaviors related to MDD may be interfering with the treatment regimen and may best be modified by skills training. This is especially true when patients are experiencing acute stressors (e.g., bereavement), where psychotherapy may improve patients' long-term outcomes.[23] Third, patients may simply not respond to antidepressant treatment or may not prefer taking medications. In all of these scenarios, the addition or substitution of psychotherapy may be a preferred alternative.

In summary, psychotherapy and pharmacotherapy appear to be equally effective as initial approaches to treating MDD in primary care. However, approximately half of patients do not remit after initial treatment even when treatment regimens are rigorously followed. Switching to a different antidepressant or augmenting treatment by adding a second antidepressant medication are both common clinical practices that are recommended in current guidelines as second step treatment strategies. However, the addition or substitution of psychotherapy is not addressed as a step-2 treatment for MDD in published guidelines.

Therefore, the focus of the current review is two-fold:
To review literature examining the use of psychotherapy as a second line treatment for patients with depression who do not remit with initial antidepressant medication; and,
To determine the applicability of these studies to VA patients treated in primary care settings.

The purpose of this review was to generate guidelines that would help determine whether the use of psychotherapy, either as an augmentation or a switch strategy, would lead to better outcomes in patients who had not responded to initial adequate antidepressant treatment.

METHODS

TOPIC DEVELOPMENT

The Veterans Health Administration (VHA) uses quality improvement strategies, including clinical practice guidelines, clinical reminders in the electronic medical record, and performance measurement to improve care processes. For veterans with depression and other mental illnesses managed in primary care settings, the VHA has recently made major investments in integrated primary care-mental health programs. This project was nominated by Ira Katz, Deputy Chief, Patient Care Services for Mental Health, and Carla Cassidy and Joe Francis, Office of Quality and Performance, with input from a technical expert panel. The overall goal was to synthesize data on the efficacy of psychotherapy in patients who do not fully remit with adequate antidepressant treatment.

Therefore, the key question was as follows:
In primary care patients with major depressive disorder who do not achieve remission with acute phase antidepressant treatment, is empirically based psychotherapy used as an augmentation or substitution treatment more effective than control for achieving remission?

For the purposes of this review, cognitive therapy (CT), interpersonal therapy (IPT), problem-solving therapy, dialectical behavior therapy (DBT), acceptance and commitment therapy (ACT), and mindfulness based cognitive therapy (MBCT) were considered as empirically based psychotherapies.

SEARCH STRATEGY

We searched PubMed between 1950 and February 26, 2009 using standard search terms. Appendix A provides details of the search terms. Our strategy was twofold. First, we attempted to identify a good quality, relevant systematic review that would summarize the extant literature. If identified, our strategy would be to search for randomized clinical trials since the original review. No such systematic review was identified. Consequently, we searched PubMed for relevant randomized clinical trials (RCT). Titles, abstracts and full text articles were reviewed in duplicate. Data were extracted in duplicate from articles meeting all inclusion criteria. We then rated the overall quality of each study, assigned a grade, and summarized the data in narrative. Eligible articles were imported into an electronic reference database (EndNote® XI).

STUDY SELECTION

Two trained researchers independently reviewed the titles and/or abstracts of citations identified through the PubMed literature search. If articles did not clearly meet the inclusion criteria, they were excluded at the title and abstract level. The remaining articles were identified for full text review, at which stage those that did not meet inclusion criteria were excluded. In case of disagreement, the two reviewers met to identify and resolve the disagreement. To be eligible, the articles had to be published in English, and include:

- English-speaking adult outpatients from general medical settings.
- Randomized clinical trial involving at least one of the following psychotherapy modalities: cognitive behavior therapy (CBT), interpersonal therapy (IPT), problem-solving therapy, dialectical behavior therapy (DBT), acceptance and commitment therapy (ACT), or mindfulness based cognitive therapy (MBCT).
- Patients with resistant MDD, defined as a sample consisting of at least 80% with either no remission or partial remission after being treated with adequate dose of an antidepressant for at least six weeks.
- Articles were excluded if patients were receiving psychotherapy at the time of recruitment, and/or if patients had comorbid psychiatric conditions that required specialty psychiatric care. These included, but were not limited to, active suicidal or parasuicidal ideation, severe substance abuse, or borderline personality disorder.

DATA ABSTRACTION

The following data were abstracted on the included studies: definition of persistence; type of psychotherapy; type of comparison group; setting (primary care/mental health clinic); VA (Yes/No); sample size; study-specific inclusion/exclusion criteria; age/sex/race of sample; indices of MDD severity (duration of current episode; number of prior episodes; number of hospitalizations; number of suicide attempts); data on interviewer-rated depression severity (if applicable); data on self-reported depression severity (if applicable); duration of follow-up. All data were abstracted by one reviewer with oversight being provided by the other reviewer. All disagreements were resolved using discussion and consensus.

QUALITY ASSESSMENT

Quality of selected articles was assessed using the quality rating tool described in Appendix C. We abstracted data on completeness of follow-up (<30% drop-out rate, <10% differential drop-out rate); method to address incomplete data; adequacy of randomization; adequacy of allocation concealment; outcome assessment blind to intervention allocation; and whether there was a conflict of interest, either stated or implied.

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics and results for all included articles, organized by the unique studies from which they were derived. We critically analyzed studies to compare characteristics, methods, and findings. We compiled a summary of findings and drew conclusions based on qualitative synthesis of the findings.

PEER REVIEW

A draft version of this report was sent to three peer reviewers. Their comments and our responses are presented in Appendix B.

RESULTS

LITERATURE FLOW

Using the search strategy described in Appendix A, 41 systematic reviews were identified, of which 29 were excluded at the title and abstract level and the remaining 12 were excluded after conducting a full-text review (Figure 1). Reviews were excluded primarily because they did not apply to the question we were addressing or were not systematic; therefore, no systematic reviews were included in this report.

Next, we searched for relevant randomized clinical trials. Using the search strategy described in Appendix B, 333 randomized clinical trials were identified for review. Of these, 290 were excluded at the title and abstract level, and 43 were selected for full text review. Thirty-one articles were excluded following full-text review, yielding 12 articles for inclusion (Figure 2). These 12 articles represent five unique studies, of which one of the studies (STAR*D trial) used both augmentation and substitution treatment modalities in separate treatment arms, each with a unique comparison group. These two arms were treated as separate studies in this review. Therefore, the evidence tables and narrative summarize six studies, with the caveat that two of the studies represented separate arms of the same trial. Full consensus was achieved between the two reviewers at each stage.

SAMPLE CHARACTERISTICS

A total of 567 patients were evaluated across the studies. Patients were recruited from both mental health clinics (MHC) and primary care (PC) clinics. Three studies were conducted in the United States, two in Great Britain, and one in Canada. None of the studies recruited participants from VA clinics. Sample sizes ranged from 24 to 304 participants; two studies contributed 81% of the subjects.[37, 40] Across all studies, participants' average age was approximately 40-years-old, females compromised half to three quarters of the studies' participants, and Caucasians represented at least 75% of the racial makeup in studies that reported ethnicity. The average length of patients' current depressive episodes ranged from 30 to 123 weeks, with the average number of lifetime depressive episodes ranging from 2.2 to 8.5. For all studies, depression severity was moderate as determined by self-report measures. These characteristics are summarized in Table 1 and show significant heterogeneity in depression severity and chronicity. Sample characteristics for the psychotherapy and the comparison groups are provided if reported.

Table 1: Sample Characteristics

Study	Harley et al., 2008	Kennedy et al., 2003	Scott et al., 2000	Thase et al., 2007 (Augmentation Arm)	Thase et al., 2007 (Substitution Arm)	Blackburn & Moore, 1997*†
Sample size, n						
Psychotherapy	13	23	80	65	36	17
Comparator	11	21	78	117	86	20
Age, y (M±SD)						
Psychotherapy		40.7±12.5	43.5 ± 9.8	40.6 ± 11.5	43.4 ± 14.7	37.8 ± 13.1
Comparator	41.8	37.7±11.3	43.2 ±11.2	39.7 ± 13.5	41.5 ± 13.3	40.1 ± 12.7
Female, n						
Psychotherapy		12 (52%)	37 (46%)	41 (63%)	22 (61%)	17 (77%)*
Comparator	18 (75%)	12 (57%)	41 (53%)	78 (67%)	53 (62%)	17 (65%)*
Caucasian, n		–	–			–
Psychotherapy				52 (80%)	28 (78%)	
Comparator	20 (83%)			99 (85%)	63 (73%)	
Duration of current episode, wks (M±SD)						
Psychotherapy	28.7 ± 18.8	126 ± 170	62.9	129 ± 214	76 ± 135	30.4 ± 6.1
Comparator	41.8 ± 53.6	120 ± 161	56.4	87 ± 206	115 ± 234	29.9 ± 5.6
Number of prior MDD episodes (M±SD)						
Psychotherapy	Not	2.1± 1.5	2 (median)	7.3 ± 14.1	8.7 ± 18.8	4.1 ± 3.4
Comparator	Reported	2.3 ± 1.4	2 (median)	4.6 ± 5.4	8.4 ± 16.0	3.2 ± 2.2
Baseline HAM-D[a] scores						
Psychotherapy	16.2 ± 4.5	12.1 ± 2.2	12.1 ± 2.7	17.8 ± 5.7	16.4 ± 6.2	11.8 ± 6.3
Comparator	18.6 ± 4.7	11.6 ± 1.9	12.2 ± 2.9	16.0 ± 6.7	16.0 ± 6.7	10.6 ± 6.8
Baseline self-report scores	BDI[b]	BDI	BDI	QIDS-SR[c]	QIDS-SR	BDI
Psychotherapy	27.3 ± 8.8	22.7 ± 8.6	21.7 ± 7.7	11.9 ± 4.3	11.2 ± 4.3	20.4 ± 11.1
Comparator	27.4 ± 11.7	22.4 ± 10.3	22.3 ± 8.0	12.0 ± 4.6	12.1 ± 4.6	19.7 ± 14.2
Setting	MHC[d]	MHC	MHC	MHC & PC[e]	MHC & PC	MHC
Location	Boston, MA	Canada	England	U.S.A.	U.S.A.	Scotland

*†HAM-D, BDI and QIDS-SR scores based on smaller number that enrolled in phase 2 of the study following initial treatment with ADM

[a] HAM-D=Hamiltion Depresion Scale; [b]BDI=Beck Depression Inventory; [bc]QIDS-SR=Quick Inventory of Depressive Symptoms-Self Report; [d]MHC=Mental Health Clinic; [e]PC=Primary Care Clinic

To determine persistence, studies used different criteria but followed similar methodology. First, authors ensured that patients had a MDD at baseline. Second, patients underwent antidepressant (AD) treatment at adequate dose as first step treatment. Third, authors ensured that patients continued to have residual symptoms of MDD. All studies except Harley et al. (2008) reported criteria used to determine initial depression diagnosis. Two studies provided 1st step AD treatment whereas the others relied on non-study practitioners. HAM-D scores, either singly or in combination with BDI scores, were used predominantly to determine residual depression following AD treatment. The various criteria used to determine persistence are summarized in Table 2.

Table 2: Criteria to Determine Persistent Depression

Study	Harley et al., 2008	Kennedy et al., 2003	Scott et al., 2000	Thase et al., 2007	Blackburn & Moore, 1997
Criteria for initial depression diagnosis	Not Reported	HAM-D=17≥16	MDD episode in previous 18 months according to DSM-III-R; residual symptoms for ≥8 weeks	Hx of MDD; HAM-D≥14	Unipolar MDD using SADS[a]; HAM-D≥16
1St step AD[b] treatment: Type and Dosage	As prescribed by non-study psychiatrists	Moclobemide (300-600 mg/day) OR Paroxetine (20-40 mg/day) OR Sertraline (50-200 mg/day) OR Venlafaxine (75-225 mg/day)	Tricyclic antidepressant, SSRI, atypical AD, or MAOI; Minimum dose equivalent to 125 mg of amitriptyline)	Citalopram 20 mg/day titrated to 40 mg by week 4 if needed; Max. 60 mg/day by week 6	As prescribed by non-study practitioners; Equivalent to 100 mg amitryptiline OR 45 mg phenelzine OR 20 mg of Sertraline
1st Step AD Treatment: Duration	≥6 weeks	8-14 weeks	≥8 weeks (at least 4 weeks of adequate dose)	14 weeks	16 weeks
Was 1st AD step treatment provided in the study?	No	Yes	No	Yes	No
Criteria to Determine Persistence Following 1st Step AD Treatment	MDD on SCID-I[c]	HAM-D=8-15	HAM-D≥8 & BDI≥9	HAM-D≥14	Moderate symptoms on BDI and HAM-D>11

[a]SADS=Schedule for Affective Disorders and Schizophrenia; [b]AD=Antidepressant; [c]SCID-I=Structured Clinical Interview for DSM-III-R, I

STUDY DESIGN & INTERVENTIONS

Four studies used true randomization whereas the two studies from the STAR*D trial used an equipoise stratified randomization design, allowing patients to refuse to be randomized to treatments that would not be acceptable. Follow-up durations ranged from 8 to 104 weeks. Psychotherapy was examined as an augmentation treatment with antidepressant medication in four studies and as a substitution treatment replacing medication in two studies. In terms of the modality of psychotherapy provided, one small study used DBT41 whereas all others used CT.

All patients in the comparison groups were taking antidepressant medications, from a wide array of antidepressant classes. Three of the comparison groups received medication in a maintenance wait list condition, and three of the comparison groups received an active systematic alteration to their medication regimens (including both arms of the STAR*D trial). Retention rates in the different conditions ranged from 25% to 91%.

All studies used the Hamilton Depression Rating Scale (HAM-D) as their clinician administered diagnostic tool. Four studies used the Beck Depression Inventory (BDI) as their self-report measure whereas the two STAR*D trial studies used the QIDS-SR as their self-report measure. Mean baseline scores ranged from 11.2 to 17.3 on the HAM-D and from 20.0 to 27.3 on the BDI. Three trials were identified as good quality studies, two studies as fair, and one study as poor. Only three studies reported a sample size calculation. Study design and intervention overview is provided in Table 3.

Table 3: Study Design and Interventions

Study	Harley et al., 2008	Kennedy et al., 2003	Scott et al., 2000	Thase et al., 2007 (Augment)	Thase et al., 2007 (Substitute)	Blackburn & Moore, 1997
Duration of follow up, wks	16	8	20	14	14	104
Study design	RCT	RCT	RCT	Equipoise Stratified RCT	Equipoise Stratified RCT	RCT
Augmentation with Medication, or Substitution?	Augment	Augment	Augment	Augment	Substitute	Substitute
Psychotherapy Intervention Used	DBT[a] Group	CT[b]	CT	CT	CT	CT
# of sessions	16	12	16	24	24	27
Comparator	ADM[c] Continue	Lithium Augment	ADM Continue	ADM Augment	ADM Switch	ADM Continue
Power calculation	No	No	Yes	Yes	Yes	No
Quality rating	Fair	Fair	Good	Good	Good	Poor

[a]DBT=Dialectical Behavior Therapy; [b]CT=Cognitive Therapy; [c]ADM=Antidepressant Medication; [d]NS=Not Significant

STUDY RESULTS

Results from the six studies are summarized in Table 4 and are described in detail next. The four studies that describe psychotherapy as augmentation treatment are described first, followed by the two studies that used psychotherapy as a substitute for medications.

Psychotherapy as Augmentation to Antidepressant Medication

Harley et al. (2008) examined psychotherapy as an augmentation treatment to medication by randomizing 24 patients to either a DBT group (n=13) or to a wait list condition (WL; n=11).[41] Patients in the DBT condition received 16 weekly sessions of a 90-minute coping skills group in addition to remaining on antidepressant medication, while patients in the WL condition continued taking antidepressant medication and meeting with their psychiatrists and healthcare providers as usual. Treatment resistance in this study was defined as current depression determined by a structured evaluation after stable, adequate treatment with antidepressant medication for at least six weeks. Post treatment analyses found significant differences between the two groups for mean scores on the HAM-D (DBT=11.3; WL=17.1; $F = 4.63$, $p < .05$) and BDI (DBT=15.1; WL=25.9; $F = 9.50$, $p < .01$), such that patients in the DBT group evidenced more clinical improvement than those in the WL condition. The retention rate was 77% in the DBT group and 82% in the WL condition. Given the small sample size and confound of allowing patients to continue in non-CBT individual therapy, we assigned an overall quality rating of "fair" to this study.

Kennedy et al. (2003) examined psychotherapy as an augmentation treatment to medication by randomizing 44 patients to either cognitive therapy (CT; n=23) or lithium augmentation (LA; n=21).[42] Patients in the CT condition received 12 psychotherapy sessions delivered over eight weeks and were seen every four weeks for a medication checkup, while patients in the LA condition had their antidepressant medication augmented with lithium carbonate (starting dose of 600mg/day) and were seen every two weeks for clinical management. Treatment resistance in this study was defined as having a HAM-D score between 8 and 15 after 8-14 weeks of treatment with antidepressant medication. Post treatment analyses found a significant difference between the two groups for mean scores on the HAM-D (CT=14.8; LA=9.2; $t = 2.02$, $p = .04$), such that patients in the LA condition showed a greater decrease in depressive symptoms than those in the CT condition. No significant post treatment difference was found between the two groups for mean scores on the BDI (CT=19.9; LA=15.1). The retention rate was 74% in the CT condition and 71% in the LA condition. One limitation of this study is that it only included "partial responders" to initial antidepressant medication treatment (i.e., HAM-D score from 8 to 15) and excluded "non-responders" (i.e., HAM-D $\geq$ 16). It also did not report a sample size calculation and probably lacked sufficient statistical power to detect clinically important differences. We assigned an overall quality rating of "fair" to this study.

Multiple articles were identified for a study that examined psychotherapy as an augmentation treatment to medication.[40, 43-46] Data were primarily extracted from Scott et al. (2000).[40] In this good quality study, 158 patients were randomized to either CT (n=80) or clinical management (CM; n=78). An analysis of the pre-set sample size of 160 gave 80% power to detect a reduction in relapse rates from 40% in one group to 20% in the other at $p = .05$. Patients in the CT condition

received 16 psychotherapy sessions over 20 weeks in addition to continuing on antidepressant medication, while patients in the CM condition continued on antidepressant treatment and were seen every four weeks for 30-minite medication management appointments. Treatment resistance in this study was defined as having a HAM-D score ≥ 8 and BDI score ≥ 9 after at least eight weeks of adequate treatment with an antidepressant medication. Participants had an average age of 43 and 49% were female. The average duration of participants' current depressive episode was 60 weeks (CT=63; CM=56), with both groups having a median of two lifetime episodes of depression. While participants in both conditions improved, post treatment analyses found no significant differences between the two groups for mean scores on the HAM-D (CT=8.7; CM=9.4) or BDI (CT=13.8; CM=16.1). Retention was measured as staying in until relapse or until the end of the study at 68 weeks, resulting in a 76% retention rate in the CT condition and an 85% retention rate in the CM condition. A limitation of this study is that it allowed for patients with partially remitted depressive symptoms and no diagnosis of current major depression to participate.

The STAR*D trial[32, 37, 47, 48] was a multistage, multicenter trial that examined both psychotherapy and medication as either augmentation or substitution treatments to initial treatment with citalopram. Treatment resistance in the STAR*D trial was defined as having a HAM-D score ≥ 14 after 14 weeks of treatment with citalopram. The equipoise-stratified randomization design employed in this study allowed patients to refuse randomization to treatment strategies that they found unacceptable, which resulted in asymmetrical sample sizes for different treatment arms. Less than one third of participants agreed to true randomization, which is a significant limitation of the study in terms of internal validity. Analyses conducted prior to data collection indicate that too few patients were randomized to the different treatment conditions to achieve the originally desired power. However, this study represents the best external validity given that they accounted for patient preferences, which is similar to what may be expected in primary care settings. We assigned an overall quality rating of "good" to both the augmentation and substitution arms of this study. Data are presented separately below, first examining psychotherapy and medication as an augmentation to citalopram and then examining psychotherapy and medication as substitution treatments to replace citalopram. Data were primarily extracted from Thase et al. (2007).[37]

In the augmentation arm, 182 patients were assigned to either augmentation cognitive therapy (A-CT; n=65) or augmentation antidepressant medication (A-ADM; n=117). Patients in the A-CT condition received 16 psychotherapy sessions over 12 weeks in addition to continuing on citalopram, while patients in the A-ADM condition had their treatment with citalopram augmented with either bupropion or buspirone. Participants had an average age of 40, 65% were female, and 83% were Caucasian. The average duration of participants' current depressive episode was 102 weeks (A-CT=129; A-ADM=87), with a mean of 5.6 lifetime episodes of depression (A-CT=7.3; A-ADM=4.6). There were no significant between-group differences in mean baseline depression scores on the HAM-D (A-CT=17.8; A-ADM=16.0) or QIDS-C (A-CT=11.9; A-ADM=12.0). While participants in both conditions evidenced significant improvement, post treatment analyses found no significant differences between the two groups for percent remitted on the HAM-D (A-CT=23.1%; A-ADM=33.3%) or for mean scores on the QIDS-C (A-CT=8.2; A-ADM=8.2). However, participants in the A-ADM condition did demonstrate quicker benefit than participants in the A-CT condition. The retention rate was 91% in the A-CT condition (although only 27% of patients completed at least 16 sessions) and 81% in the A-ADM condition.

In summary, the two good quality, moderate sized trials showed equal benefit from augmenting antidepressant medication with 16 to 24 sessions of cognitive therapy and from active management of depression with medication, whereas a small fair quality study showed greater benefit from lithium augmentation than cognitive therapy augmentation. A single fair quality trial showed short-term benefit from 16 sessions of DBT. Because study populations and designs were conceptually heterogeneous, a summary estimate of effect was not calculated.

Psychotherapy as Step-2 Substitution for Antidepressant Medication

In the substitution arm of STAR*D, 122 patients were randomized using an equipoise-stratified randomization design to either substitution cognitive therapy (S-CT; n=36) or substitution antidepressant medication (S-ADM; n=86). Patients in the S-CT condition discontinued treatment with citalopram and received 16 psychotherapy sessions over 12 weeks, while patients in the S-ADM condition discontinued citalopram and switched to treatment with bupropion, sertraline, or venlafaxine. Participants had an average age of 42, 61% were female, and 75% were Caucasian. The average duration of participants' current depressive episode was 103 weeks (S-CT=76; S-ADM=115), with a mean of 8.5 lifetime episodes of depression (S-CT=8.7; S-ADM=8.4). There were no significant between-group differences in mean baseline depression scores on the HAM-D (S-CT=16.4; S-ADM=16.0) or QID-S (S-CT=11.2; S-ADM=12.1). While participants in both conditions evidenced significant improvement, post treatment analyses found no significant differences between the two groups for percent remitted on the HAM-D (S-CT=25.0%; S-ADM=27.9%) or for mean scores on the QID-S (S-CT=9.1; S-ADM=9.1). The retention rate was 83% in the S-CT condition (although only 35% completed at least 16 sessions) and 73% in the S-ADM condition.

The poor quality study by Blackburn and Moore (1997) examined psychotherapy as a substitution treatment to replace antidepressant medication by randomizing 37 patients to either CT (n=17) or antidepressant medication (ADM; n=20).[49] Patients in the CT condition received 27 psychotherapy sessions over 104 weeks, while patients in the ADM condition continued on an antidepressant medication of their prescriber's choice (prescribers were also free to switch medications) and were seen by their providers about every three weeks. Treatment resistance was not specifically defined in this study, but after 16 weeks of treatment with an antidepressant medication, patients continued to have depressive symptoms at a level comparable to that of the other patient populations included in this review (see Table 1). Post treatment analyses found no significant differences between the two groups for mean scores on the HAM-D (CT=8.6; ADM=9.3) or BDI (CT=14.2; ADM=18.1). The retention rate was 35% in the CT condition and was 25% in the ADM condition. The "poor" quality rating was based on the poor retention rate, lack of statistical power, unorthodox length of CT treatment protocol, and lack of operational definition for treatment resistance.

In summary, a moderate-sized, good quality study and a small, poor quality study found equal benefit from substituting cognitive therapy for antidepressant treatment and from continuing management of depression with medication in patients with treatment resistant MDD.

Table 4: Results of the Psychotherapy Intervention

Study	Harley et al., 2008	Kennedy et al., 2003	Scott et al., 2000	Thase et al., 2007 (Augmentation)	Thase et al., 2007 (Substitution)	Blackburn & Moore, 1997
Retention rate, n *Psychotherapy* *Comparator*	 10 (77%) 9 (82%)	 17 (74%) 15 (71%)	 61 (76%) 66 (85%)	 59 (91%) 95 (81%)	 30 (83%) 63 (73%)	 6 (35%) 5 (25%)
Post-treatment HAM-D Scores (M±SD) *Psychotherapy* *Comparator* *Effect Size*	 11.3 ± 5.3 17.1 ± 6.2 d=1.45	 14.8 ± 9.9 9.2 ± 6.7 d=.32	 8.7±5.3 9.4 ± 5.3 NS[a]	 Remission: 23.1% 33.3% NS	 Remission: 25.0% 27.9% NS	 8.6±5.6 9.3±7.2 NS
Post-treatment BDI Scores (M±SD) *Psychotherapy* *Comparator* *Effect Size*	 15.1 ±12.1 25.9±16.3 d=1.31	 19.9 ± 10.3 15.1 ±11.4 NS	 13.8 ±9.6 16.1 ± 10.0 NS	 8.2 ±5.1 8.2 ± 4.8 NS*	 9.1 ± 5.4 9.1 ± 5.0 NS*	 14.2 ± 9.9 18.1 ± 13.1 NS
Quality rating	Fair	Fair	Good	Good	Good	Poor

[a] NS=Not significant at p<.05; *Results are for QIDS-C

SUMMARY AND DISCUSSION

The key observation that emerges from review of the literature is that current evidence examining the effect of psychotherapy as augmentation or substitute therapy in resistant depression is sparse and reveals mixed results. Of the six studies reviewed, four studies examined psychotherapy as augmentation to antidepressant treatment[37, 40-42] and two studies examined psychotherapy as substitution treatment.[37, 49] The STAR*D trial reflects the greatest ecological validity of the studies reviewed, because it accounted for patient preference in randomization and is most reflective of treatment provided in primary care settings. One study suggested that psychotherapy used as augmentation had better impact on clinical symptoms of MDD than medication alone[41] whereas Kennedy et al. found the opposite effect.[42] The remaining studies did not detect any difference between psychotherapy augmentation and continuation on antidepressant treatment.[37, 40] Substitution of antidepressant therapy with psychotherapy appeared to have the same benefit as substituting another antidepressant[37] or continuing previous medication.[49] While each of the studies included in this review addressed at least a portion of the initial key research question, none of the studies provides a complete answer to the initial question nor does an amalgamated consideration of the studies provide an entirely sufficient answer to the initial question. Most studies appeared to be underpowered to detect moderately large treatment effects, and conclusions are tempered by the heterogeneity in study designs and patient populations and limited number of good quality trials. We conclude that although current trials do not support favoring psychotherapy over antidepressant medication for mid-life adults with treatment resistant MDD, psychotherapy appears to be an equally effective treatment compared to antidepressant medication and is therefore a reasonable treatment option for this demographic. Whether these results are directly applicable to Veterans is uncertain. Veterans are on average older and have high rates of psychiatric and medical co-morbidity, clinical characteristics that were not well described in the studies reviewed.

Treatment via psychotherapy continues to face numerous barriers both in primary care and specialty mental health settings. The first consideration is access to psychotherapy. Many Veterans live in underserved areas and may have to travel farther to access facilities that would offer psychotherapeutic interventions. This issue is exacerbated by the greater time commitment required to receive traditional psychotherapy, which often requires weekly or biweekly face-to-face contact for an hour each. A second consideration is the relative cost of delivering psychotherapy versus providing antidepressant medications. The baseline costs of psychotherapy are typically higher, especially when delivered by a mental health professional such as a psychologist.[50, 51] However, there appears to be dispute when mid to long-term outcomes are measured. Some studies have demonstrated that antidepressant medications are more cost-effective within 1 year of follow-up for both direct and indirect costs.[52, 53], whereas other studies have not found differences in direct, aggregate or societal costs.[51, 54, 55] Studies have found psychotherapy to be superior in reducing costs related to missed work [56], treatment of medical comorbidities[57], and relapse.[45] Therefore, the cost-benefit ratio of antidepressant treatment versus psychotherapy remains disputed. A further limitation is that no current study has examined the cost-effectiveness of the two treatments in patients who do not respond to initial antidepressant treatment. Because TRD is both common and costly[58], large, high quality, long-term randomized trials are needed to evaluate the effectiveness and cost-effectiveness of different treatment strategies for patients with TRD.

One strategy to increase access and cost-effectiveness of psychotherapy involves collaborative care. Recent research has shown that training non-mental health professionals (e.g., nurses) to provide brief psychotherapeutic interventions are effective in reducing depressive symptoms.[59-61] Collaborative care models involving depression care managers has been shown to improve the quality of depression care, symptom severity, patient satisfaction, and functional impairment.[50, 62] Some of these trials[59, 63] utilized empirically based psychotherapy as a step-2 treatment option for treatment resistant patients. These studies were conducted in older adults with MDD or dysthymia who are more similar to the Veteran population than most of the studies we reviewed in the current evidence synthesis. Unfortunately, the psychotherapy was delivered as part of a package of collaborative care and its unique contribution to improved outcomes cannot be assessed. Nevertheless, evidence suggests that training non-mental health professionals to deliver brief psychotherapy may improve outcomes in primary care patients without burdening resources within the VA system.

Prior systematic reviews [19-23] have shown that psychotherapy and antidepressant medications have similar benefit in acute phase treatment for MDD. For patients with chronic MDD or dysthymia, current evidence supports the combination of psychotherapy and antidepressant medication for initial treatment. Treatment resistant depression is common and a greater number of effective treatment options are needed. Our evidence synthesis found only limited studies that do not support psychotherapy as a step-2 strategy, either for augmentation or as a substitute for antidepressant medication.

LIMITATIONS

Several limitations of the current literature emerged upon review. First, few RCTs exist that adequately address the question of resistant depression. In the future, this may be addressed in two ways: 1) re-analysis of existing data from trials in which patients with TRD are recruited, or 2) conducting studies designed to examine this question. Second, there was significant heterogeneity in how resistant depression was defined in the different studies. Measures included interviewer rated depression scales (e.g., HAM-D), self-report depression scales (e.g., BDI), DSM diagnostic criteria (DSM-III-R or DSM-IV), and clinical judgment. Future studies should consider a standardized operational definition of TRD to facilitate comparisons across studies. Third, all of the studies involved comparators that received active treatment. True placebo controlled trials may be necessary to compare the relative effects of psychotherapy and antidepressants as second step treatments. Fourth, none of the six studies reviewed involved patients from within the VA. Compared to the general population, Veterans have higher incidences of depression with psychiatric and medical comorbidities.[4] Therefore, results of the current review may have limited generalizability to the VA population. Fifth, only two psychotherapeutic strategies have been considered in the limited literature, with the majority using CT. Traditionally, CT requires a minimum of 12-16 sessions and is often delivered by trained experts. As a result, none of the psychotherapies reviewed were likely to be administered within the primary care setting. This is in contrast with the larger literature, where brief therapies such as problem-solving therapy and interpersonal therapy have been adapted by non-mental health professionals with demonstrated improvements as first step treatments in primary care settings.[50] Studies to compare the effectiveness of differing psychotherapies could inform policy.

FUTURE RESEARCH

There is a pressing need to conduct RCTs examining psychotherapy as a second step treatment in patients who have not responded to initial antidepressant medication treatment. Studies conducted within the VA would provide the best evidence on how to treat veterans. As more OEF/OIF veterans return with significant medical and psychiatric comorbidities, this question will become critical in the management of MDD.

Future investigations should also address cost-effectiveness of the different treatment options. To our knowledge, no current study has examined the cost-effectiveness of psychotherapy versus antidepressant treatment when used as second step treatment. As a first step, analyses using observational data from the VA depression registry may be informative. Ideally, however, studies designed for this purpose would involve longer follow-up, as well as measures of direct costs, indirect costs, and costs associated with comorbid non-psychiatric conditions. Finally, innovative interventions are needed that adapt validated psychotherapeutic techniques to primary care settings. The VA has already initiated primary care mental health integration techniques; however, there remains a need for trials of depression treatments to inform the specific treatments offered in these integrated models. This will be crucial in improving access for underserved veterans while simultaneously reducing the strain on the VA resources.

REFERENCES

1. Papakostas G, Fava M. Predictors, moderators, and mediators (correlates) of treatment outcome in major depressive disorder. Dialogues in Clinical Neuroscience. 2008;10(4):439-451.

2. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry. 2005;62(10):1097-106.

3. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593-602.

4. Hankin CS, Spiro A, 3rd, Miller DR, Kazis L. Mental disorders and mental health treatment among U.S. Department of Veterans Affairs outpatients: the Veterans Health Study. Am J Psychiatry. 1999;156(12):1924-30.

5. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry. 2003;54(3):216-26.

6. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama. 2003;289(23):3095-105.

7. Kronish IM, Rieckmann N, Halm EA, et al. Persistent depression affects adherence to secondary prevention behaviors after acute coronary syndromes. J Gen Intern Med. 2006;21(11):1178-83.

8. Seelig MD, Katon W. Gaps in depression care: why primary care physicians should hone their depression screening, diagnosis, and management skills. J Occup Environ Med. 2008;50(4):451-8.

9. Olfson M, Marcus SC, Druss B, Elinson L, Tanielian T, Pincus HA. National trends in the outpatient treatment of depression. JAMA. 2002;287(2):203-9.

10. Karasu TB, Gelenberg A, Merriam A, Wang P. *Practice guideline for the treatment of patients with major depressive disorder*. 2nd ed Arlington, VA: American Psychiatric Association; 2000 APA Practice Guidelines).

11. Fochtmann LJ, Gelenberg AJ. *Guideline watch: Practice guideline for the treatment of patients with depressive disorder*. 2nd ed Arlington, VA: American Psychiatric Association; 2005 APA Practice Guidelines).

12. Barbui C, Furukawa TA, Cipriani A. Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials. Cmaj. 2008;178(3):296-305.

13. Cipriani A, Furukawa TA, Geddes JR, et al. Does randomized evidence support sertraline as first-line antidepressant for adults with acute major depression? A systematic review and meta-analysis. J Clin Psychiatry. 2008;69(11):1732-42.

14. Kennedy SH, Andersen HF, Thase ME. Escitalopram in the treatment of major depressive disorder: a meta-analysis. Curr Med Res Opin. 2009;25(1):161-75.

15. Mulrow CD, Williams JW, Jr., Chiquette E, et al. Efficacy of newer medications for treating depression in primary care patients. Am J Med. 2000;108(1):54-64.

16. Watanabe N, Omori IM, Nakagawa A, et al. Mirtazapine versus other antidepressants in the acute-phase treatment of adults with major depression: systematic review and meta-analysis. J Clin Psychiatry. 2008;69(9):1404-15.

17. Simon GE, Ludman E, Unutzer J, Bauer MS. Design and implementation of a randomized trial evaluating systematic care for bipolar disorder. Bipolar Disord. 2002;4(4):226-36.

18. Wampold BE. *The Great Psychotherapy Debate: Models, Methods, and Findings*. Mahwah, NJ: Lawrence Erlbaum Associates; 2001.

19. Bortolotti B, Menchetti M, Bellini F, Montaguti MB, Berardi D. Psychological interventions for major depression in primary care: a meta-analytic review of randomized controlled trials. Gen Hosp Psychiatry. 2008;30(4):293-302.

20. Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin Psychol Rev. 2006;26(1):17-31.

21. Craighead WE, Sheets ES, Brosse AL, Ilardi SS. Psychosocial treatments for major depressive disorder. In: Nathan PE, Gorman JM, eds. *A guide to treatments that work*. 3rd ed. New York: Oxford; 2007:289-293.

22. DeRubeis RJ, Gelfand LA, Tang TZ, Simons AD. Medications versus cognitive behavior therapy for severely depressed outpatients: mega-analysis of four randomized comparisons. Am J Psychiatry. 1999;156(7):1007-13.

23. DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. Archives of General Psychiatry. 2005;62(4):409-16.

24. Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munizza C. Combined pharmacotherapy and psychological treatment for depression: a systematic review. Archives of General Psychiatry. 2004;61(7):714-9.

25. de Maat SM, Dekker J, Schoevers RA, de Jonghe F. Relative efficacy of psychotherapy and combined therapy in the treatment of depression: a meta-analysis. Eur Psychiatry. 2007;22(1):1-8.

26. Fava M, Rush AJ. Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. Psychother Psychosom. 2006;75(3):139-53.

27. Segal Z, Vincent P, Levitt A. Efficacy of combined, sequential and crossover psychotherapy and pharmacotherapy in improving outcomes in depression. J Psychiatry Neurosci. 2002;27(4):281-90.

28. Cornwall PL, Scott J. Partial remission in depressive disorders. Acta Psychiatr Scand. 1997;95(4):265-71.

29. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry. 2003;53(8):649-59.

30. Stimpson N, Agrawal N, Lewis G. Randomised controlled trials investigating pharmacological and psychological interventions for treatment-refractory depression. Systematic review. Br J Psychiatry. 2002;181:284-94.

31. Trivedi MH. Major depressive disorder: remission of associated symptoms. J Clin Psychiatry. 2006;67 Suppl 6:27-32.

32. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Controlled Clinical Trials. 2004;25(1):119-42.

33. Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. Archives of General Psychiatry. 2008;65(8):870-80.

34. Corey-Lisle PK, Nash R, Stang P, Swindle R. Response, Partial Response, and Nonresponse in Primary Care Treatment of Depression. Archives of Internal Medicine. 2004;164(11):1197-1204.

35. Sherbourne C, Schoenbaum M, Wells KB, Croghan TW. Characteristics, treatment patterns, and outcomes of persistent depression despite treatment in primary care. General Hospital Psychiatry. 2004;26(2):106-14.

36. Souery D, Oswald P, Massat I, et al. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. Journal of Clinical Psychiatry. 2007;68(7):1062-70.

37. Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. American Journal of Psychiatry. 2007;164(5):739-52.

38. Markowitz JC. When should psychotherapy be the treatment of choice for major depressive disorder? Current Psychiatry Reports. 2008;10(6):452-7.

39. Mitchell AJ. Depressed patients and treatment adherence. Lancet. 2006;367(9528):2041-3.

40. Scott J, Teasdale JD, Paykel ES, et al. Effects of cognitive therapy on psychological symptoms and social functioning in residual depression. British Journal of Psychiatry. 2000;177:440-6.

41. Harley R, Sprich S, Safren S, Jacobo M, Fava M. Adaptation of dialectical behavior therapy skills training group for treatment-resistant depression. Journal of Nervous and Mental Disease. 2008;196(2):136-43.

42. Kennedy SH, Segal ZV, Cohen NL, Levitan RD, Gemar M, Bagby RM. Lithium carbonate versus cognitive therapy as sequential combination treatment strategies in partial responders to antidepressant medication: an exploratory trial. Journal of Clinical Psychiatry. 2003;64(4):439-44.

43. Paykel ES, Scott J, Cornwall PL, et al. Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. Psychological Medicine. 2005;35(1):59-68.

44. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy: a controlled trial. Archives of General Psychiatry. 1999;56(9):829-35.

45. Scott J, Palmer S, Paykel E, Teasdale J, Hayhurst H. Use of cognitive therapy for relapse prevention in chronic depression. Cost-effectiveness study. British Journal of Psychiatry. 2003;182:221-7.

46. Teasdale JD, Scott J, Moore RG, Hayhurst H, Pope M, Paykel ES. How does cognitive therapy prevent relapse in residual depression? Evidence from a controlled trial. Journal of Consulting and Clinical Psychology. 2001;69(3):347-57.

47. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. American Journal of Psychiatry. 2006;163(11):1905-17.

48. Wisniewski SR, Fava M, Trivedi MH, et al. Acceptability of second-step treatments to depressed outpatients: a STAR*D report. American Journal of Psychiatry. 2007;164(5):753-60.

49. Blackburn IM, Moore RG. Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in out-patients with recurrent depression. British Journal of Psychiatry. 1997;171:328-34.

50. Wolf NJ, Hopko DR. Psychosocial and pharmacological interventions for depressed adults in primary care: a critical review. Clinical Psychology Review. 2008;28(1):131-61.

51. Bower P, Gilbody S, Richards D, Fletcher J, Sutton A. Collaborative care for depression in primary care. Making sense of a complex intervention: systematic review and meta-regression. Br J Psychiatry. 2006;189:484-93.

52. Lave JR, Frank RG, Schulberg HC, Kamlet MS. Cost-effectiveness of treatments for major depression in primary care practice. Archives of General Psychiatry. 1998;55(7):645-51.

53. Barrett B, Byford S, Knapp M. Evidence of cost-effective treatments for depression: a systematic review. J Affect Disord. 2005;84(1):1-13.

54. Leff J, Vearnals S, Brewin CR, et al. The London Depression Intervention Trial. Randomised controlled trial of antidepressants v. couple therapy in the treatment and maintenance of people with depression living with a partner: clinical outcome and costs. British Journal of Psychiatry. 2000;177:95-100.

55. Simpson S, Corney R, Fitzgerald P, Beecham J. A randomized controlled trial to evaluate the effectiveness and cost-effectiveness of psychodynamic counselling for general practice patients with chronic depression. Psychological Medicine. 2003;33(2):229-39.

56. Mynors-Wallis L, Davies I, Gray A, Barbour F, Gath D. A randomised controlled trial and cost analysis of problem-solving treatment for emotional disorders given by community nurses in primary care. Br J Psychiatry. 1997;170:113-9.

57. Guthrie E, Moorey J, Margison F, et al. Cost-effectiveness of brief psychodynamic-interpersonal therapy in high utilizers of psychiatric services. Arch Gen Psychiatry. 1999;56(6):519-26.

58. Russell JM, Hawkins K, Ozminkowski RJ, et al. The cost consequences of treatment-resistant depression. J Clin Psychiatry. 2004;65(3):341-7.

59. Unutzer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. JAMA. 2002;288(22):2836-45.

60. Williams JW, Jr., Gerrity M, Holsinger T, Dobscha S, Gaynes B, Dietrich A. Systematic review of multifaceted interventions to improve depression care. Gen Hosp Psychiatry. 2007;29(2):91-116.

61. Katon W, Von Korff M, Lin E, et al. Stepped collaborative care for primary care patients with persistent symptoms of depression: a randomized trial. Arch Gen Psychiatry. 1999;56(12):1109-15.

62. Williams JM, Teasdale JD, Segal ZV, Soulsby J. Mindfulness-based cognitive therapy reduces overgeneral autobiographical memory in formerly depressed patients. Journal of Abnormal Psychology. 2000;109(1):150-5.

63. Bruce ML, Ten Have TR, Reynolds CF, 3rd, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. JAMA. 2004;291(9):1081-91.