APPENDIX A: SEARCH STRATEGY

Question: 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? Empirically based psychotherapies to be considered are: cognitive behavioral therapy, interpersonal therapy, problem-solving therapy, dialectical behavior therapy, and acceptance and commitment therapy.

Inclusion Criteria- Systematic Reviews

Systematic Review

Does psychotherapy benefit patients who have been previously not responded to adequate pharmacotherapy?

Search Strategy for Systematic Review: Database: **PubMed Medline** – 1950 to February 26, 2009

1	"Depressive Disorder"[Mesh] OR (major AND depression)	71993
2	((problem-solving OR interpersonal OR dialectical behav* OR acceptance OR commitment OR mindfulness) AND (therapy OR psychotherapy)) OR "Psychotherapy"[Mesh] OR "Behavior Therapy"[Mesh]	229473
3	("Combined Modality Therapy"[Mesh] OR Drug resistant[Mesh] OR additive OR augmentation OR augment* OR relaps* OR recurrent OR refractory OR resistant OR persisten* OR treatment failure[Mesh])	1147546
4	#1 AND #2 AND #3	1997
5	Limits: **Humans, English, All Adult: 19+ years**	1078
6	systematic[sb]	116759
7	#5 AND #6	34
8	Cochrane Database Syst Rev [TA] OR search[Title/Abstract] OR meta-analysis[Publication Type] OR MEDLINE[Title/abstract] OR (systematic[Title/Abstract] AND review[Title/Abstract])	140388
9	#5 AND #8	24
10	#7 OR #9	41

For Systematic Reviews, the Medline search yielded 41 articles. Title and abstracts were reviewed by 2 independent persons who identified 12 articles for full text review. Of the 12 reviewed, 0 were identified as meeting the inclusion criteria previously established; therefore no systematic reviews will be included for this question in the final report.

Inclusion Criteria- Randomized Controlled Trials

Randomized controlled trials

Outpatient setting

Patients from general population (not special populations)

Adults who have not remised or responded significantly to anti-depressant medication for > 6 wks and not in therapy (CBT, IPT, Sol. Focused, DBT, ACT, MBT)

If mixed sample, at least 80% must be partial or non-responders or outcomes reported separately

Exclude: patients with MDD where guidelines recommend mental health specialty care (eg. high suicidality, substance abuse, borderline personality d/o)

Relevant comparison

English language articles

Search Strategy for Randomized Controlled Trials: Database: **PubMed Medline** - 1950 to February 26, 2009

1	"Depressive Disorder"[Mesh] OR (major AND depression)	71993
2	((problem-solving OR interpersonal OR dialectical behav* OR acceptance OR commitment OR mindfulness) AND (therapy OR psychotherapy)) OR "Psychotherapy"[Mesh] OR "Behavior Therapy"[Mesh]	229441
3	"Combined Modality Therapy"[Mesh] OR Drug resistant[Mesh] OR additive OR augmentation OR augment* OR relaps* OR recurrent OR refractory OR resistant OR persisten* OR treatment failure[Mesh]	1147546
4	randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])	275228
5	#1 AND #2 AND #3 AND #4	422
6	Limits: Humans, English, All Adult: 19+ years	333

For Randomized Control Trials, the Medline search yielded 333 articles. Title and abstracts were reviewed by 2 independent persons who identified 43 articles for full text review. Of the 43 articles reviewed, 12 were identified as meeting the inclusion criteria previously established.

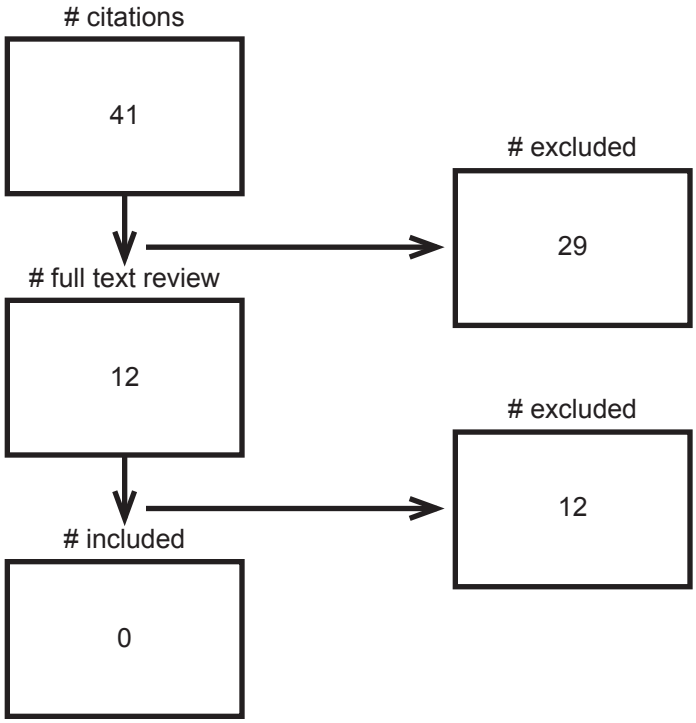

Figure 1. Systematic Reviews Literature Flow

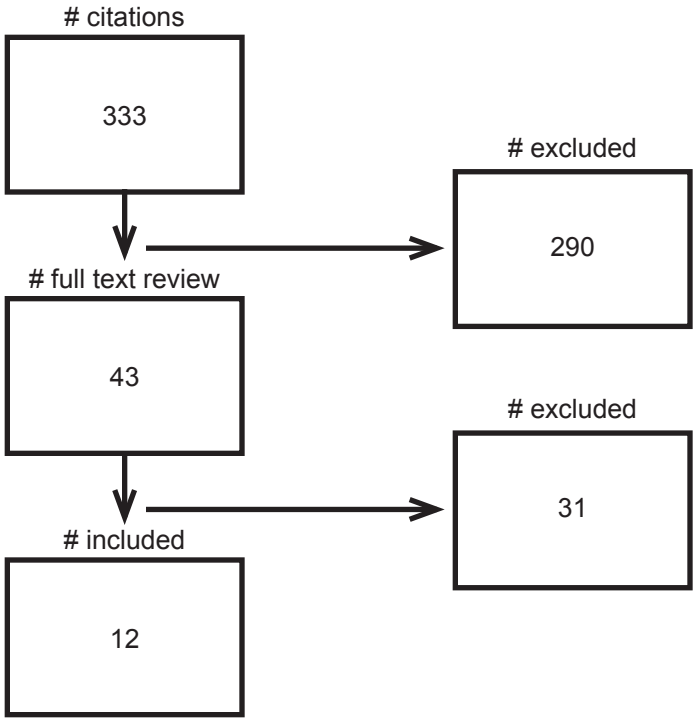

Figure 2. Randomized Controlled Trials Literature Flow

APPENDIX B: PEER REVIEW

Question 1: Are the objectives, scope, and methods for this review clearly described?

Reviewer	Comment	Reply
1	Excellent description of objectives, scope, and methods. This review exposes the scarcity of good studies to answer this question. The conclusions fit the data.	Acknowledged
2	Clearly described, concisely written, comprehensive, well thought out review.	Acknowledged
3	The authors have been particularly thorough in describing clearly the objectives, scope, and methods for this review. I don't believe any reader would be left with any question about these. (As a small matter, on page 15, "solution-focused therapy" was listed as one of the empirically-based psychotherapies that were considered for purposes of the study. However, in Appendix A, this was not listed as one of the search terms; "problem-solving" was listed. I think these are both terms of art, and are different. Do you want to conform the terms? I think the authors likely considered problem solving therapy, but not solution-focused therapy.)	Acknowledged Thank you for pointing out this discrepancy. We have now changed the term "solution-focused therapy" to "problem-solving therapy" to reflect terms included in the literature search (pg 15, 16).

Question 2: Is there any indication of bias in our synthesis of the evidence?

Reviewer	Comment	Reply
1	No indication of bias. This review follows rigorous methods for systematic selection and analysis	Acknowledged
2	No	Acknowledged
3	I see no indication of bias in the synthesis of the evidence. Indeed, it appears that the authors have gone out of their way to eliminate any opportunity for bias.	Acknowledged

Question 3 Are there any studies on responsiveness of depression questionnaires or relapse prevention trials related to this report that we have overlooked?

Reviewer	Comment	Reply
1	I don't know of any others	Acknowledged
2	None	Acknowledged
3	I don't know of any studies on the effectiveness of psychotherapy as a second step treatment for MDD in patients who do not achieve remission after initial treatment with antidepressants, per se, that have been overlooked.	Acknowledged

Question 4: Please write additional suggestions or additional comments below for this report. If applicable, please indicate the page and line numbers from the draft report.

Reviewer	Comment	Reply
1	P 6, last line: suggest changing "control" to "comparison group," a term that is more consistent with most patients in this group being on some form of treatment. This review achieves impressive rigor and thoroughness for such a limited number of studies.	We agree with this assertion and have attempted to make this point throughout the review. However, in that specific place, we have opted to retain the wording as initially developed by VA Central Office to avoid confusion regarding the question we were originally attempting to answer with this review.

2	**4.** a. p. 9 typo, 2nd line from bottom: should be "antidepressant medication *with* CT. b. p.10. I think the summary and conclusions understate the equivalence of CT vs medication as a switch choice. The STAR*D data suggested little difference for the between CT and meds for the switch arms, and hence for patients who would prefer CT it may be a reasonable option. c. I'm concerned with the statement: "Based on this sparse evidence, we conclude that current trials do not support a benefit from adding psychotherapy to antidepressant medication for mid-life adults with treatment resistant MDD". While it is technically correct, I think it is at risk of being mis-interpreted too strongly as an indication that there is no role for CT as an adjunct in TRD. It seems the evidence is insufficient to conclude one way or the other, and I think the wording should reflect that the current data do not support a benefit, but that the data is insufficient to make a conclusion and that future studies may likely change this result. d. p.20. Table 1 might benefit from a row that allows a better comparison of the level of depressive severity when beginning psychotherapy treatment, for e.g., clarifying the BDI or QIDS scores as "mild", "moderate" or "severe", and a row that allows comparison of the prior antidepressant treatment (e.g., antidepressant type, dose, duration). Also, can one report the number of prior treatment failures for the current episode? Finally, the definition of persistent depression (listed in the evidence tables in the appendices) is quite information and would be a useful row in Table 1. I realize, however, that some of this information may not be available for many studies. e. Can the authors clarify whether any of the studies directly addressed the research question they pose? If not, how might they suggest designing a future research project to address this question directly? Also, might they suggest a study to address the long term risk benefits of a switch to CT (or an empirically based psychotherapy) vs medications?	a. Thank you for finding this error. The typo has been corrected. b.& c. We agree with the reviewer that our summary and conclusions did not emphasize the equivalence of the two treatment modalities. We have modified the summary statements on pages 9, 10, and 30 to reflect the equivalence that we generally observed in studies comparing CT and meds, and to reflect our belief that CT remains a reasonable treatment option in patients with TRD. As we state repeatedly in the review, the current evidence is not sufficient to determine the superiority of one treatment modality over the other. Future research with rigorous study designs is necessary to definitively answer this question. d. Per the reviewer's suggestion, we report that that depression severity in each study was "moderate." We agree with the reviewer that the number of failures of treatment may be important information in evaluating the extent of TRD; however, this information was not reported in the reviewed studies and hence cannot be included. We agree that describing persistent depression within the text would be helpful. We have incorporated this suggestion by creating a new table (Table 2) that describes the various definitions of persistent depression, and summarizes antidepressant type, dosage, and duration. The Additional information about prior antidepressant treatment was also added to the definitions of persistent depression in the evidence tables in the appendices. e. A sentence was added to the discussion on page 30 clarifying our position that we do not consider the initial key research question adequately answered by our review. Regarding the reviewer's suggestion of designing a study, our current (cont'd.)

2 (cont'd)		version outlines important components of such a study in the Future Research section (pg 35) as well as highlights these in the Summary and Discussion section. Specifically, we highlight the need to study TRD in the context of impact on work, medical comorbidities, relapse, and the need for cost-effectiveness analysis of the different treatments available.
3	This report looked at the *condition* of treatment resistant major depression that failed to respond to an adequate dose of antidepressant treatment. I wonder if it would be worth looking at *individuals* who have treatment resistant major depression that failed to respond to an adequate dose of antidepressant treatment? I know of two recent studies that may be worth reviewing: Watchful waiting for minor depression in primary care: remission rates and predictors of improvement. M.T. Hegel et al. General Hospital Psychiatry 28 (2006) 205–212. This study suggests that for treatment-seeking samples with minor depression in primary care an avoidant coping style seriously interferes with remission, and engaging in regular active pleasant events confers an advantage. It further suggests that feasible interventions for primary care that promote activity and decrease avoidant coping styles may improve outcomes. Cortico-limbic response to personally challenging emotional stimuli after complete recovery from depression. J.M. Hooley et al. Psychiatry Research: Neuroimaging 171 (2009) 106–119. This study suggests that vulnerability to depression may be associated with abnormalities in cortico-limbic activation that are independent of mood state and that remain even after full recovery. Perhaps there are similar processes at work in those with treatment resistant major depression that failed to respond to an adequate dose of antidepressant treatment that would not respond to traditional psychotherapeutic approaches.	The reviewer makes an interesting point. The Hegel study suggests that patients with minor depression may be successfully treated in primary care through pleasant activities and by reducing avoidant coping. The extensive literature on coping and depression supports this conclusion. It is likely that patients with minor depression may be patients who have residual symptoms after an MDD episode, in other words, TRD. However, it seems that a discussion of such interventions is beyond the scope of this review because of our original goal of comparing CT with medications in a treatment resistant population. Future reviews may address this issue by incorporating all treatments provided in primary care settings, and treatments provided to patients who may or may not have TRD. Regarding the Hooley study, it would be certainly worthwhile to determine the neurological mechanisms that may contribute to TRD and/or relapse. Unfortunately, a discussion of such mechanisms is beyond the scope of this review as defined by the VA Central office.

Question 5: Recommendations for future ESP topical areas of interest or programmatic comments may also be included at the end of this section.

Reviewer	Comment	Reply
1	No comment	Acknowledged
2	None	
3	I agree wholeheartedly with the statement on page 34 that there remains a need for trials of depression treatments to inform the specific treatments offered (and to be offered) in primary care mental health integration models. This is a pressing need. I would argue that the population of patients that could benefit from efficacious and effective treatments in such models is far larger than the population of patients who suffer from treatment resistant depression.	Acknowledged

APPENDIX C: EVIDENCE TABLES OF RCTS

Study ID	Persistence Definition & Treatments	Study Information	Participants	Results	Comments/Quality Scoring
Harley et al., 2008	**Persistent Depression:** Despite stable, adequate medication treatment for MDD (as determined by consensus of 2 senior psychiatrists with expertise in MDD), patients still met criteria for MDD on the SCID-I. **Psychotherapy:** Dialectical Behavior Therapy (DBT) Group DBT based depression skills group; 16 weekly sessions lasting 90 minutes each. **Comparator:** Wait List (WL) Pts in this group continued treatment as usual, which included taking prescribed medications and meeting with psychiatrists and other providers as usual.	**Geographical location:** Boston, MA **Setting: MHC; participants were referred by outpatient providers.** **VA sites:** No **Study design:** RCT **Number of participants enrolled:** Total: 24 DBT: 13 WL: 11 **Duration of follow up:** 16 weeks **Inclusion criteria:** - Age 18-65 - Principal diagnosis of MDD on SCID - Have an established treatment relationship with a psychiatrist - Stabilized on adequate dose of antidepressant medication before entering study (no dosage change for at least 6 weeks before study entry) **Exclusion criteria:** - Bipolar disorder - Psychotic spectrum disorders - Active substance abuse or dependence - Mental retardation - Pervasive developmental disorder - Active suicidality - Severe or unstable medical conditions - Patients with previous or current CBT experience - Borderline Personality Disorder	**Age:** [mean] Total: 41.8 **Sex:** [female %] Total: 75% **Race/ethnicity:** [white (%)] Total: 83% **Duration of current episode in days:** [mean (SD)] DBT: 201.00 (131.59) WL: 292.40 (374.94) **Number of lifetime antidepressant trials:** [mean (SD)] DBT: 3.31 (1.70) WL: 4.27 (2.45) **Number of hospitalizations:** [mean (SD)] DBT: 0.85 (0.99) WL: 0.27 (0.65) **Age at first MDE:** [mean (SD)] DBT: 27.08 (14.23) WL: 25.18 (15.20) **Engaged in concurrent non-CBT individual therapy:** Total: 83%	**1) Interviewer rated depression severity:** **HAM-D at baseline:** [mean (SD)] DBT: 16.15 (4.47) WL: 18.64 (4.72) **HAM-D at follow-up:** [mean (SD)] DBT: 11.30 (5.31) WL: 17.11 (6.23) *DBT group had significantly lower HAM-D scores than WL (F=4.63; p<.05; D=1.45).* **2) Self-reported depression severity:** **BDI at baseline:** [mean (SD)] DBT: 27.31 (8.83) WL: 27.44 (11.66) **BDI at follow-up:** [mean (SD)] DBT: 15.10 (12.13) WL: 25.89 (16.30) *DBT group had significantly lower BDI scores than WL (F=9.50; p<.01; D=1.31).*	**Comments:** Small sample sizes, limited information provided on samples' baseline characteristics, and confound of individual therapy. **Quality assessment:** Randomization adequate?: Y Allocation concealment adequate?: Y Baseline comparability?: Y Valid outcome assessment?: Y Subject/providers blind?: N Outcomes assessed blind?: Y Dropout rate < 30%?: Y Differential dropout rate < 10%?: Y Incomplete data addressed adequately?: Unknown Conflict of interest?: N Overall quality rating: Fair

Study ID	Persistence Definition & Treatments	Study Information	Participants	Results	Comments/Quality Scoring
Kennedy et al., 2003	**Persistent depression:** Having initially met criteria for MDE with HAM-D-17≥16 and after 8-14 weeks of antidepressant treatment with moclobemide (300-600 mg/day), paroxetine (20-40 mg/day), sertraline (50-200 mg/day), or venlafaxine (75-225 mg/day), patients still had HAM-D=8-15. **Psychotherapy:** Cognitive Therapy (CT) 12 sessions over 8 weeks in combination with AD therapy; pts were also seen every 4 weeks for a medication check up. **Comparator:** Lithium Augmentation (LA) Pts who were considered "partial responders" had their AD therapy augmented with 600 mg/day of lithium carbonate, which clinicians could increase by 300 mg/day after 2-4 weeks. Pts were seen every 2 weeks for routine clinical management.	**Geographical location:** Toronto, Canada **Setting:** MHC **VA sites:** No **Study design:** RCT **Number of participants enrolled:** Total: 44 CT: 23 LA: 21 **Duration of follow up:** 8 weeks **Inclusion criteria:** - Age 18-65 - Partial response after receiving maximum tolerated doses of moclobemide, paroxetine, sertraline, or venlafaxine (choice of antidepressant was at the discretion of the treating psychiatrist) for 8-14 weeks - Initially met criteria for MDE - HAM-D-17≥16 - At least one prior MDE **Exclusion criteria:** - Major medical disorder - Organic brain syndrome - Schizophrenia or schizoaffective disorder - Bipolar disorder - MDD with psychotic features - Substance or alcohol use or dependence within past 6 months	**Age:** [mean (SD)] CT: 40.7 (12.5) LA: 37.7 (11.3) **Sex:** [female, n (%)] CT: 12 (52.2%) LA: 12 (57%) **Race/ethnicity:** Not reported **Duration of current episode in weeks:** [mean (SD)] CT: 126.4 (170.4) LA: 119.8 (160.8) **Number of prior episodes:** [mean (SD)] CT: 2.1 (1.5) LA: 2.3 (1.4) **Age at first MDE:** [mean (SD)] CT: 26.3 (13.5) LA: 24.4 (13.6) **Comorbid psychiatric diagnoses:** [n (%)] CT: 8 (35%) LA: 4 (19%)	**1) Interviewer rated depression severity:** **HAM-D-17 after 8-14 weeks med treatment:** [mean (SD)] CT: 12.1 (2.2) LA: 11.6 (1.9) **HAM-D-17 at follow-up:** [mean (SD)] CT: 14.8 (9.9) LA: 9.2 (6.7) *LA group had significantly lower HAM-D-17 scores than CT group in intent-to-treat analysis (t=2.02; df=42; p=.04; d=.32).* **2) Self-reported depression severity:** **BDI after 8-14 weeks med treatment:** [mean (SD)] CT: 22.7 (8.6) LA: 22.4 (10.3) **BDI at follow-up:** [mean (SD)] CT: 19.9 (10.3) LA: 15.1 (11.4) *No significant differences between groups.*	**Comments:** Only included partial responders; excluded non-responders. **Quality assessment:** Randomization adequate?: Y Allocation concealment adequate?: Y Baseline comparability?: Y Valid outcome assessment?: Y Subject/providers blind?: N Outcomes assessed blind?: Y Dropout rate < 30%?: Y Differential dropout rate < 10%?: Y Incomplete data addressed adequately?: Y Conflict of interest?: N Overall quality rating: Good

Study ID	Persistence Definition & Treatments	Study Information	Participants	Results	Comments/Quality Scoring
Paykel et al., 1999 Paykel et al., 2005 Scott et al., 2003 Scott et al., 2000* Teasdale et al., 2001 *Data were primarily extracted from this reference.	**Persistent depression:** Despite treatment with tricyclic antidepressant, SSRI, atypical AD, or MAOI for at least 8 weeks (with 4 or more weeks of minimum dosage equivalent to at least 125 mg of amitriptyline), patients still had HAM-D≥8 & BDI≥9. **Psychotherapy:** Cognitive Therapy (CT) 16 sessions over 20 weeks. Pts also received CM. **Comparator:** Clinical Management (CM) Antidepressant continuation; pts seen every 4 weeks during tx and every 8 weeks during follow-up for 30 minutes each.	**Geographical location:** Cambridge & Newcastle, England **Setting:** MHC; Psychiatric Outpatient Clinics **VA sites:** No **Study design:** RCT **Number of participants enrolled:** Total: 158 CT: 80 CMT: 78 **Duration of follow up:** 20 weeks **Inclusion criteria:** - Age 21-65 - DSM-III-R MDD within past 18 months but not MDD criteria in past 2 months & HRSD ≥ 8 & BDI ≥ 9. **Exclusion criteria:** - Bipolar disorder - Cyclothymia - Schizoaffective disorder - Drug or alcohol dependence - Antisocial behavior or self-harm - Dysthymia before age 20 - Borderline personality - Learning disability - Organic brain damage - Other primary Axis I disorder - Currently receiving psychotherapy or previously received CT for more than 5 sessions	**Age:** [mean (SD)] CT: 43.5 (9.8) CM: 43.2 (11.2) **Sex:** [female, n (%)] CT: 37 (46%) CM: 41 (53%) **Race/ethnicity:** Not reported **Duration of depressive episode in months:** [median (1st & 3rd quartiles)] CT: 14.5 (9, 18) CTM: 13 (9, 21) **Prior episodes of MDD:** [median (1st & 3rd quartiles)] CT: 2 (1, ≥3) CM: 2 (1, ≥3)	**1) Interviewer rated depression severity:** **HDRS baseline after 8 week drug trial:** [mean (SD)] CT=12.1 (2.7) CM=12.2 (2.9) **HDRS at follow-up:** [mean (SD)] CT=8.7 (5.3) CM=9.4 (5.3) *No significant between group differences or group x time interactions over 20 week treatment phase or 68 week follow-up (F=2.2; df=1324; p=.14)* **2) Self-reported depression severity:** **BDI baseline after 8 week drug trial:** [mean (SD)] CT=21.7 (7.7) CM= 22.3 (8.0) **BDI at follow-up:** [mean (SD)] CT=13.8 (9.6) CM= 16.1 (10.0) *No significant between group differences or group x time interactions over 20 week treatment phase or 68 week follow-up (F=2.3; df=1293; p=.13)*	**Comments:** Not currently depressed; partially remitted but with residual symptoms - because not MDD but still some depressive symptoms on HDRS and BDI In Scott et al. 2000, found that some dep sx showed sig effects on drug refractory residual symptoms Both CT and CM led to improvement in dep sx **Quality assessment:** Randomization adequate?: Y Allocation concealment adequate?: Y Baseline comparability?: Y Valid outcome assessment?: Y Subject/providers blind?: N/Y Outcomes assessed blind?: Y Dropout rate < 30%?: Y Differential dropout rate < 10%?: Y Incomplete data addressed adequately?: Y Conflict of interest?: N Overall quality rating: Good

Study ID	Persistence Definition & Treatments	Study Information	Participants	Results	Comments/Quality Scoring
Rush et al., 2004 Rush et al., 2006 Thase et al., 2007* Wisniewski et al., 2007 STAR*D *Data were primarily extracted from this reference.	**Persistent depression:** Following treatment with citalopram (20 mg/day to start, 40 mg/day by week 4, and maximum potential dosage of 60 mg/day by week 6) for 14 weeks, patients still had HAM-D≥14. **Psychotherapy:** <u>Cognitive Therapy (CT)</u> 16 sessions delivered twice weekly for weeks 1-4, then once weekly for 8 remaining weeks. *Switch to CT*: Pts discontinued citalopram and began CT. *Augment CT*: Pts continued on citalopram and added CT. **Comparator:** <u>Antidepressant Medication (ADM)</u> *Switch ADM*: Pts discontinued citalopram and began bupropion, sertraline, or venlafaxine. *Augment ADM*: Pts continued on citalopram and added bupropion or buspirone.	**Geographical location:** 14 Regional centers across TX, MA, NY, PA, OK, KS, CA: LA and San Diego, NC, IL, MI, VA, TN, AL **Setting:** 18-Primary Care, 23 MHC **VA sites:** No **Study design:** randomized multi-step clinical trial **Number of participants enrolled:** Total: 304 Switch to CT=36 Augment CT=65 Switch ADM=86 Augment ADM=117 **Duration of follow up:** 14 weeks **Inclusion criteria:** - Age 18-75 - Non psychotic MDD - HRSD17≥14 **Exclusion criteria:** - Bipolar, schizophrenia, eating d/o, OCD - Hx of intolerability or resistance to ≥1 Anti-dep with adequate dosage - ≥7 days Citalopram use prior to study enrollment - non-responsive ≥16 session of CT in current MDD episode - Medical contraindication - Pregnant females - Requires psychiatric hospitalization, antipsychotics, or mood stabilizers	**Age:** [mean (SD)] Switch to CT: 43.4 (14.7) Augment CT= 40.6 (11.5) Switch ADM=41.5 (13.3) Augment ADM=39.7 (13.5) **Sex:** [female, n (%)] Switch to CT: 22 (61.1%) Augment CT: 41 (63.1%) Switch ADM: 53 (61.6%) Augment ADM: 78 (66.7%) **Race/ethnicity:** [white, n (%)] Switch to CT: 28 (77.8%) Augment CT: 52 (80.0%) Switch ADM: 63 (73.3%) Augment ADM: 99 (84.6%) **Duration of depressive episode in months:** [mean (SD)] Switch to CT: 17.4 (31.2) Augment CT: 29.6 (49.4) Switch ADM: 26.5 (54.0) Augment ADM: 20.0 (47.5) **Number of prior episodes of MDD:** [mean (SD)] Switch to CT: 8.7 (18.8) Augment CT: 7.3 (14.1) Switch ADM: 8.4 (16.0) Augment ADM: 4.6 (5.4)	**1) Interviewer rated depression severity:** **HRSD at start of Level 2:** [mean (SD)] Switch to CT: 16.4 (6.2) Augment CT: 17.8 (5.7) Switch ADM: 17.7 (6.6) Augment ADM: 16.0 (6.7) **Met remission criteria on (HRSD≤7) at end of Level 2:** Switch to CT: 25.0% Augment CT: 23.1% Switch ADM: 27.9% Augment ADM: 33.3% *No significant differences between groups.* **2) Self-reported depression severity:** **QIDS-C at start of Level 2:** [mean (SD)] Switch to CT: 11.2 (4.3) Augment CT: 11.9 (4.3) Switch ADM: 12.1 (4.6) Augment ADM: 12.0 (4.6) **QIDS-C at end of Level 2:** [mean (SD)] Switch to CT: 9.1 (5.4) Augment CT: 8.2 (5.1) Switch ADM: 9.1 (5.0) Augment ADM: 8.2 (4.8) *No significant differences between groups.*	**Comments:** Due to equipoise-stratified randomization, <1/3 agreed to randomization. Low rates of psychotherapy acceptability are at odds with real world experience of the STAR*D authors. Baseline differences in Augment CT more impaired & lower QOL than Augment ADM and Switch to CT lower income than Switch ADM. Numerous pharmaceutical companies supported the project. **Quality assessment:** Randomization adequate?: Y/N Allocation concealment adequate?: Y Baseline comparability?: Y/N Valid outcome assessment?: Y Subject/providers blind?: N Outcomes assessed blind?: Y Dropout rate < 30%?: Y Differential dropout rate < 10%?: Y Incomplete data addressed adequately?: Y Conflict of interest?: Y Overall quality rating: Good

Study ID	Persistence Definition & Treatments	Study Information	Participants*	Results	Comments/Quality Scoring
Blackburn & Moore, 1997	**Persistent depression:** Despite showing significant reduction in depressive symptoms over 16 weeks of treatment with antidepressant medication of the general practitioner's choice (prescribed at or above therapeutic doses), patients on average continued to have depressive symptoms in the moderate range on the BDI and above the traditional cut point of 11 on the HAM-D. **Psychotherapy:** Cognitive Therapy (CT) 27 sessions delivered over 2 years, with pts being seen 3 times in 1st month, twice in 2nd month, and monthly thereafter. **Comparator:** Antidepressant Medication (ADM) Maintenance ADM was of general practitioner's choice (tricyclics, MAOIs, SSRIs), as long as prescribed at or above recognized maintenance dose.	**Geographical location:** Scotland **Setting:** MHC; participants were recruited from outpatient referrals to consultants in a large teaching psychiatric hospital and from 2 general practices. **VA sites:** No **Study design:** RCT **Number of participants enrolled:** Total: 37 (48 initially) CT: 17 (22 initially) ADM: 20 (26 initially) **Duration of follow up:** 24 months **Inclusion criteria:** - Age 18-65 - Diagnosis of primary major unipolar depression, non-psychotic - Score of at least 16 on HRSD - Current episode had to be at least second MDE **Exclusion criteria:** - Having another primary Axis I disorder - Organic brain damage - History of bipolar illness - Alcohol or drug misuse - Could not be prescribed antidepressant medication for medical reasons - Unwilling to be randomly allocated to treatment	**Age:** [mean (SD)] CT: 37.8 (13.1) ADM: 40.1 (12.7) **Sex:** [female, n (%)] CT: 17/22 (77%) ADM: 17/26 (65%) **Race/ethnicity:** Not given **Duration of current episode in months:** [mean (SD)] CT: 7.0 (1.4) ADM: 6.9 (1.3) **Number of prior episodes:** [mean (SD)] CT: 4.1 (3.4) ADM: 3.2 (2.2) **Number of hospitalizations:** [mean (SD)] CT: 0.7 (0.9) ADM: 0.8 (2.3) **Number of suicide attempts:** [mean (SD)] CT: 0.4 (0.7) ADM: 0.9 (1.9) *Data based on initially enrolled participants.	**1) Interviewer rated depression severity:** **HRSD baseline after 16 weeks acute med treatment:** [mean (SD)] CT: 11.8 (6.3) ADM: 10.6 (6.8) **HRSD interpolated over 24 months follow-up:** [mean (SD)] CT: 8.6 (5.6) ADM: 9.3 (7.2) *ANCOVA showed no significant difference between treatments (F=0.31; d.f.=2, 55; NS).* **2) Self-reported depression severity:** **BDI baseline after 16 weeks acute med treatment:** [mean (SD)] CT: 20.4 (11.1) ADM: 19.7 (14.2) **BDI interpolated over 24 months follow-up:** [mean (SD)] CT: 14.2 (9.9) ADM: 18.1 (13.1) *ANCOVA showed no significant difference between treatments (F=0.72; d.f.=2, 53; NS).*	**Comments:** Reviewers decided based on data after 16 weeks of treatment that samples met criteria for persistent depression. ANCOVAs compared 3 groups, not just the 2 groups of interest. 35% retention for CT and 25% retention for ADM. **Quality assessment:** Randomization adequate?: Y Allocation concealment adequate?: Y Baseline comparability?: Y Valid outcome assessment?: Y Subject/providers blind?: N Outcomes assessed blind?: Y Dropout rate < 30%?: N Differential dropout rate < 10%?: N Incomplete data addressed adequately?: Y Conflict of interest?: N Overall quality rating: Poor