APPENDIX A: SEARCH STRATEGIES

KEY QUESTION #1

Database: PubMed ® <1950 to February 2, 2009>

1	"Depressive Disorder, Major"[Mesh] OR (major AND depression)	32348
2	PHQ9 OR "Patient Health Questionnaire" OR "Beck Depression Inventory" OR BDI OR BDI-II OR GDS OR "Geriatric Depression Scale" OR SDDS-PC OR "symptom driven diagnostic system primary care" OR PRIMEMD OR "Primary care evaluation of mental disorders" OR DEPS OR "CESD" OR "CES-D" OR ("Center" AND Epidemiologic* AND Stud* AND Depression) OR "CESD-10"	11913
3	(change OR changes OR Improv* OR decreas*) AND (score OR scale* OR scores OR responsiv* OR sensitiv*)	447184
4	#1 AND #2 AND #3	522
5	(questionnaire OR psychometrics) AND ("Depressive Disorder, Major"[Mesh] OR (major AND depression)) AND (((responsiv*[tw] OR sensitiv*[tw]) AND (change[tw] OR changes[tw])) OR (clinical*[tw] AND important[tw] AND (change[tw] OR changes[tw])))	126
6	#4 OR #5	626
7	#6 Limits: Humans, English, All Adult: 19+ years	516

Database: PsychInfo <up to February 2, 2009>

1	major depression/	58084
2	major depression.tw.	16118
3	(PHQ9 or "Patient Health Questionnaire" or "Beck Depression Inventory" or BDI or BDI-II or GDS or "Geriatric Depression Scale" OR SDDS-PC or "symptom driven diagnostic system primary care" or PRIMEMD or "Primary care evaluation of mental disorders" or DEPS).tw.	9324
4	((change or changes or Improv* or decreas*) and (score or scale* or scores or responsiv* or sensitiv*)).tw.	82044
5	#1 or #2	61641
6	#3 and #4 and #5	893
7	limit 6 to (("followup study" or "longitudinal study" or "prospective study" or "systematic review") AND "adulthood age 18 yrs AND older" AND "peer-reviewed journal" AND English AND human)	157

KEY QUESTION #2, SYSTEMATIC REVIEWS

Database: PubMed ® <1950 to March 02, 2009>

1	("Depressive Disorder"[Mesh] OR "major depression")	63463
2	(antidepress* OR "Antidepressive Agents"[Mesh] OR "Antidepressive Agents "[Pharmacological Action])	114617
3	(recurrence[Mesh] OR relaps* OR recurren*)	410446
4	#1 AND #2 AND #3	2073
5	#4 AND systematic[sb]	106

KEY QUESTION #2, RANDOMIZED CONTROLLED TRIALS

Database: PubMed ® <1950 to March 01, 2009>

1	("Depressive Disorder"[Mesh] OR "major depression")	63463
2	(antidepress* OR "Antidepressive Agents"[Mesh] OR "Antidepressive Agents "[Pharmacological Action])	114617
3	(recurrence[Mesh] OR relaps* OR recurren*)	410446
4	(randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])	275051
5	#1 AND #2 AND #3 AND #4	428
6	Limits: Publication Date from 2007/01/01 to 2009/03/1, Humans, English, All Adult: 19+ years	48

APPENDIX B: FULL TEXT EXCLUSIONS

Inclusion Criteria for Key Question #1, Assessment Tools Responsive to Change

1. One of the specified instruments (PHQ-9, Beck Fast Screen, CESD-10, GDS-15, SDDS-PC, DEPS, PRIME MD)
2. Adults with depressive disorder: outpatient setting
3. Comparator: Comparison to an interview-based instrument
4. Study Design: Longitudinal
5. Study Design: Sample > 50
6. English language article

	General Exclusion Criteria*					
Author & Ref #	**NOT 1.**	**NOT 2.**	**NOT 3.**	**NOT 4.**	**NOT 5.**	**NOT 6.**
Ahava, 1998[51]	X					
Adler, 2004[52]			X			
Allard, 2004[53]	X					
Altamura, 1989[54]	X					
Amsterdam, 2008[55]		X				
Babyak, 2000[56]	X					
Baldwin, 2008[57]	X					
Barbosa, 2003[58]	X					
Berkman, 2003[59]	X					
Berlim, 2005[60]						X
Berlim, 2007[61]						X
Boyer, 1998[62]	X					
Brody, 2006[63]			X			
Brown, 2000[64]	X					
Brown, 2005[65]	X					
Cassidy, 2005[66]					X	
Casten, 2000[67]		X				
Chen, 2006[68]						X
Conradi, 2007[69]	X					
Cook,1999[70]					X	
Corney, 2005[71]			X			
Coulehan, 1997[72]	X					
Dalton, 2000[73]					X	
Davies, 2003[74]					X	
DeBattista, 2003[75]					X	
Dori, 1999[76]	X					

	General Exclusion Criteria*					
Author & Ref #	**NOT 1.**	**NOT 2.**	**NOT 3.**	**NOT 4.**	**NOT 5.**	**NOT 6.**
Dubovsky, 2001[77]					X	
Dunner, 1987[78]	X					
Einarson, 2004[79]	X					
Fava, 1999[80]					X	
Fawcett, 1987[81]	X					
George, 1999[82]	X					
George, 2008[83]	X					
Goodnick, 1997[84]					X	
Goodnick, 1998[85]	X					
Judd, 2004[86]	X					
Kates, 2002[87]	X					
Koivumaa-Honkanen, 2008[88]	X					
Koran, 1995[89]	X					
Kroenke, 2006[90]	X					
Lesperance, 2007[91]	X					
Lett, 2007[92]	X					
Levitt, 1999[93]					X	
Liebowitz, 2007[94]	X					
Lustman, 1998[95]			X			
Lustman, 2000[96]	X					
Lydiard, 1997[97]	X					
Mazeh, 2007[98]					X	
McIntyre, 2005[99]	X					
Mohamed, 2006[100]	X					
Mulrow, 1998[101]	X					
Mynors-Wallis, 2000[102]	X					
Patkar, 2006[103]	X					
Perez, 1999[104]	X					
Picardi, 2005[105]		X				
Pollock, 1989[106]		X				
Posternak, 2001[107]	X					
Proudfoot, 2003[108]			X			
Pyne, 2002[109]		X				
Quilty, 2008[110]	X					
Raskin, 2003[111]	X					
Raskin, 2007[112]	X					
Rollman, 2002[113]	X					

	General Exclusion Criteria*					
Author & Ref #	NOT 1.	NOT 2.	NOT 3.	NOT 4.	NOT 5.	NOT 6.
Rush, 2005[114]	X					
Rutherford, 2007[115]						X
Salkovskis, 2006[116]	X					
Shelton, 2001[117]	X					
Singh, 2001[118]						X
Skevington, 2001[119]	X					
Spalletta, 2002[120]						X
Stark, 1985[121]			X			
Szegedi, 2005[122]	X					
Thase, 1997[123]	X					
Trivedi, 2004[124]	X					
Tutty, 2000[125]	X					
van Gurp, 2002[126]	X					
van Marwijk, 2008[127]			X			
Vinkers, 2004[128]		X				
Wade, 2008[129]	X					
Wise, 2007[130]	X					

Items in the table (e.g. Not 1) correspond to the inclusion criteria listed above the table

Inclusion Criteria for Key Question #2, Systematic Reviews

1. Systematic review evaluating anti-depressant vs. placebo. A systematic review contains a methods section with search strategy and approach to synthesizing the data
2. Patients: Adults with major depressive disorder who have remitted or improved substantially with anti-depressant medication, English language article
3. Outcome: Relapse/recurrence

	General Exclusion Criteria*		
Author & Ref #	NOT 1.	NOT 2.	NOT 3.
Bauer 2009[131]			X
Gartlehener 2008[132]			X
Quaseem 2008[133]	X		
Anderson 2008[134]	X		
Papakostas 2007[135]			X
Furukawa 2007[136]	X		
Zimmerman 2007[137]			X
Lam 2004[138]	X		

Items in the table (e.g. Not 1) correspond to the inclusion criteria listed above the table*

Inclusion Criteria for Key Question #2, Randomized Controlled Trials

1. Study Design: Randomized Controlled Trial
2. Patients: Adults
3. Outcome: Relapse/recurrence
4. Compares anti-depressant vs. placebo
5. Patients: Adults with major depressive disorder who have remitted or improved substantially with anti-depressant medication
6. English language article

	General Exclusion Criteria*					
Author & Ref #	**NOT 1.**	**NOT 2.**	**NOT 3.**	**NOT 4.**	**NOT 5.**	**NOT 6.**
Dombrovski 2008[139]					X	
Keller 2007[140]				X		

*Items in the table (e.g. Not 1) correspond to the inclusion criteria listed above the table

APPENDIX C: QUALITY RATINGS

QUALITY RATING FOR KEY QUESTION #1, ASSESSMENT TOOLS RESPONSIVE TO CHANGE

Was the criterion standard applied and interpreted blinded to the results of the depression questionnaire?

Was the depression questionnaire applied and interpreted blinded to the results of the criterion standard?

Was the interview-based criterion standard a validated measure of depression severity?

Did follow-up of the enrolled sample exceed 80%?

Was the analysis appropriate to the study question?

Was the study funded by the pharmaceutical industry?

Was a conflict of interest disclosure given? If given, was there a potential conflict of interest?

QUALITY RATING FOR KEY QUESTION #2, SYSTEMATIC REVIEWS

Was a focused clinical question clearly stated?

Was the search for relevant studies detailed and exhaustive?

Were inclusion/exclusion criteria clearly defined and appropriate?

Were primary studies evaluated for quality and appropriateness?

Were assessments of studies reproducible?

Were analyses conducted to measure variability in effect?

Were differences in how outcomes were reported and analyzed across studies were taken into consideration?

Was publication bias assessed?

Were clinically important outcomes (harms and benefits) reported?

Were the conclusions supported by the data presented?

QUALITY RATING FOR KEY QUESTION #2, RANDOMIZED CONTROLLED TRIALS

Were the groups similar at baseline in terms of baseline characteristics and prognostic factors?

Were depression outcomes assessed using a valid methodology and criteria?

Were subjects and providers blind to the intervention/exposure status of participants?

Were outcome assessors blind to exposure/intervention status?

Were incomplete outcome data adequately addressed?

Was there an important differential loss to follow-up between the compared groups (defined as ≥ 10%)?

Was there an overall high loss to follow-up (≥ 20% for studies <12 months and ≥ 30% for studies of 12 month or longer duration)

Was there a conflict of interest?

Were the methods used for randomization adequate?

Was allocation concealment adequate?

APPENDIX D: PEER REVIEW

Question: Are the objectives, scope, and methods for this review clearly described?		
Reviewer	**Comment**	**Reply**
1	YES. The objectives, scope were very clear and appropriate. The methods were transparent and appropriately rigorous for a best evidence review, even though the types of studies sought to answer KQ1 and KQ2 were very different. It was helpful to have all of the information on search strategies, inclusion/exclusion criteria and data extraction in the appendices.	Acknowledged
2	The inclusion and exclusion criteria for Key Question 1 greatly diminish the synthesis's scope. Given this limitation, I know of no additional studies that should have been included in the review for Key Question 1 or 2. In general, the Synthesis needs a strong editing (e.g. ensuring consistency in abbreviations, defining abbreviations before applying them, correcting punctuation and formatting) In addition, there were several places within the synthesis where this reviewer could not understand the meaning of a sentence. Specifically: • Page 8, line 11-12 – "For the finding that the MCID is 5" would be best to define this as the Mean Change in Depression Score for MDD • Page 16, line 11 – "the similarity of groups similar at baseline" • Page 25, line 2 – "the number needed"…(number of what?) • The Evidence Tables 1-5 are very difficult to read because of inconsistent formatting and text layout.	The inclusion/exclusion criteria were developed with the stakeholders to focus on the questions of interest. Editing has been completed to ensure consistency These sentences have been edited to clarify the meaning. We did not find the Page 25, line 2 reference; on page 26 we state the "number needed to treat to prevent one relapse…"
3	Yes, all of these aspects are clearly described.	Acknowledged
4	a) Objectives are clearly defined. b) Scope is also clearly defined, with the exception that the assessment tools that are surveyed are those immediately referable to depressive disorders and their symptoms (i.e., disease-specific). One could also perceive quality of life, functional capacities, health services utilization and costs as relevant outcomes. I agree with focusing on disease-specific assessment, and this is clear as the manuscript goes on, but I would make it absolutely clear up front so as to frame the boundaries of this review explicitly. c) Methods are clearly defined.	Acknowledged Edits made to clarify that focus is limited to depression symptom questionnaires Acknowledged

Question: Is there any indication of bias in our synthesis of the evidence?		
Reviewer	**Comment**	**Reply**
1	NO. Appropriate precautions were used to minimize bias including 1) having 2 researchers review the titles and/or abstracts of articles for potential inclusion, 2) having 1-2 reviewers over-read the data abstraction forms to assure accurate abstraction, 3) using well known criteria to assess the quality of the studies that included items about funding source and conflict of interest (Appendix C) and strength of evidence (GRADE), 4) providing readers with enough detail to assure transparency, and 5) including comments from outsider reviewers in an Appendix.	Acknowledged
2	It was not clear how this group of authors was selected to conduct the evidence synthesis. Was this a competitive application or were the authors selected based on their willingness to conduct the synthesis, their expertise in the area of study, or other factors?	This has been addressed in the topic refinement section
3	No, there is no indication of bias	Acknowledged
4	No	Acknowledged
Question: 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	NO. These are difficult studies to do well and get funded appropriately since they require a diagnostic interview as a reference standard (KQ1) and have a long follow-up period (KQ2). I was not surprised that few studies were found.	Acknowledged
2	None	
3	No, there are no responsiveness studies missed to include in the analysis. However, in the discussion of results, the authors refer to a UK qualitative study suggesting clinicians are skeptical of depression questionnaires. If this study is cited, the authors should also cite two recent studies showing US primary care physicians (Nease et al, 2008) and psychiatrists (Duffy et al) found the PHQ-9 clinically useful and continued to use. Also, the authors did not include the 10-item CES-D short-form (Andresen et al, 1994). There are probably no studies testing its responsiveness, but I mention it simply because it does fall within the authors' 10-item inclusion criteria for brief measures. • Nease DE, Nutting PA, Dickinson WP, Bonham AJ, Graham DG, Gallagher KM, Main DS. Inducing sustainable improvement in depression care in primary care practices. Joint Commission Journal on Quality and Patient Safety 2008;34:247-255. • Duffy FF, Chung H, Trivedi M, Rae DS, Regier DA, Katzelnick DJ. Systematic use of patient-rated depression severity monitoring: is it helpful and feasible in clinical psychiatry? Psychiatric Services 2008;59:1148–1154. • Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med. 1994; 10: 77–84.	The discussion has been revised and the additional studies referenced The CESD-10 was not excluded but our search did not include terms specific to this instrument. We have updated the search and results. 49 additional citations were identified but none met eligibility criteria
4	None that meet the defined criteria, to my knowledge	Acknowledged

Question: 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	The target audience for this report includes administrators and policy makers. They would benefit from a conclusion section at the end of the Executive Summary that simply stated the conclusions followed by quality of the evidence supporting the conclusion. This could even be 2 bullet points. Administrators and policy makers are likely to start with this bottom line and read backwards if they need more detail. For example, you could use lines 14-16 on page 24, lines 11-15 on page 23, and lines 44-46 and 1-4 on pages 24 and 25 after editing them. For KQ2, it helps to have both the RR and NNT.	We have followed this suggestion
	The results section in the Executive Summary was difficult to follow for KQ1, lines 31-43, page 7. The methods paragraph describes the standardized response mean (SRM) then the results start with the mean change score. I would list the mean change score and SRM for 3 months, then for 6 months. Although you save words in the current version, it is harder to read. Also in line 41 define the abbreviation MCID since you use it later.	We have followed this suggestion
	Figure 1 on page 13 is difficult to read in its current size. It would be good if it could be enlarged.	The figure has been enlarged
	In Table 7 on page 26, it would be helpful to include some data in the comments section after the summary comment, e.g., mean change score expected of responders. Also, I would include the NNT with the RR.	We have followed this suggestion
	Appendix B is important to document why studies were excluded/include. Using "not 1," "not 2," etc is a bit confusing, but I could not think of a better way to concisely describe these criteria for the table headers.	Modified to improve clarity
	In Appendix C, page 37, line 30 has a typo. I think it should read "... evaluated for quality and appropriateness?"	Thank you. Typo corrected
	The evidence tables are dense, but the details are important for transparency.	Acknowledged

2	**Key Question 1** In general, this reviewer felt that Key Question 1 was not an "assessment of tools that were responsive to change", but rather a review of the PHQ-9's (and at times the PHQ-2's) responsiveness to change. This apparent bias first appears in the background section in which the synthesis first author's work (reference 15) concluded that the PHQ-9 had better performance characteristics and gave more information for depression diagnosis than other instruments. Thus, from the very beginning, this reviewer was confused on why Key Question 1 was requested for a synthesis review. Given these issues, the background on Depression Questionnaires either 1) needs to be expanded to describe the 7 other questionnaires that have < 10 items, or 2) for the sake of transparency, the background section should clearly state in the text that the work that identified the PHQ-9 as the optimal self reported primary care depression measure was conducted by the first author of this synthesis. The fact that the primary manuscripts reviewed for Key Question 1 (references 29-32) were all conducted by the same first author (Lowe) should be noted in the limitations. Since the authors note that there has been no work to date measuring responsiveness to change in instruments was for the PHQ-9 and was applied in a population greater than age 60, the Future Research section should also call for additional studies to identify whether or not the PHQ-9 (and other measures) respond to change in younger populations. **Key Question 2** Given that the number of prior episodes is a major risk for relapse, did any of the RCT's reviewed for Key Question 2 address this issue? Though this is alluded to on page 22, lines 17-20, it should be more clearly stated.	We have attempted to strengthen the message that we searched for ALL feasible instruments, but only found data for the PHQ. The background has been modified to briefly describe the eligible questionnaires. Discussion has been updated to note this issue. No change; the PHQ9 has been evaluated in mid-life and older adults The number of prior depressive episodes was not systematically reported in the trials
3	Page 6, lines 17-36: In paragraph, authors state "Clinical guidelines recommend continuation treatment for 4-6 months … However, clinical guidelines for longer-term maintenance phase treatment are more variable and performance indicators (e.g., HEDIS) do not address maintenance phase treatment." But Key Question #2 is: "What is the minimum duration of continuation phase treatment to decrease risk of relapse?" Continuation (1st 4-9 months after remission) and maintenance (long-term treatment after continuation) phases of treatment have distinct meanings in some guidelines, and the authors' going back and forth between these 2 terms (and in other places the vaguer phrase "long-term treatment" leaves the reader confused whether their review is focused on evidence for continuation phase treatment, maintenance phase, or both. Please clarify for reader. Page 8, Lines 31-46: This section clarifies the answer to the question above (i.e., this review looks at both continuation and maintenance treatment) – this should be clarified on p. 6	This comment and the following comment have been addressed in the revision. The background on page 6 clarifies that the review addressed continuation and maintenance phase treatment As above

	Page 14, Lines 36-37: There is a short-form of the CES-D (10 items). The reference is provided under #3 above. The authors might note why this was not included in their search.	Previously addressed
	Page 15, Lines 7-8: The authors might add to their parenthetical examples of measures longer than 10 items the Inventory for Depressive Symptoms (since it was used in the landmark STAR*D trial where 40% of patients were from primary care) and the CES-D.	This recommendation was followed
	Page 18, Lines 7-9: The authors state: "In addition the study team included a biostatistician from Pfizer, and Pfizer funded the current study and the PHQ-9 development, suggesting a potential conflict of interest." However, unlike drugs sold for profit, the PHQ-9 always has been made available free of charge. Thus, the potential conflict of interest is much weaker than if drug trials were being analyzed.	This is a valid point about the availability free of charge. However, potential COI still exists as increased identification of depression may increase sales or related for-profit products. No change
	Page 24, Lines 35-42: The authors state: "Qualitative studies show that patients favor questionnaires to measure depression severity but general practitioners in the UK were cautious about the validity and utility of these measures and skeptical about the motives behind their introduction. General practitioners specifically valued clinical judgment more than objective assessment. Practitioners were aware of the potential for manipulation of indicators for economic reasons. If these findings hold true for VA clinicians, these barriers would need to be addressed for successful implementation of the PHQ-9 (or any other measure) for routine monitoring." However, two recent studies in the US showed good uptake of the PHQ-9 by primary care physicians (Nease et al 2008) and psychiatry (Duffy et al 2008).	Previously addressed

Question: 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	Topics: 1. Treatment of chronic obstructive pulmonary disease 2. Palliative chemotherapy for lung, colon, and possibly other cancers Programmatic Comments: 1. Translating evidence syntheses into policy and organizational decisions will be a difficult step. I assume the ESPs are linked to OQP, but there should be outreach to VISNs and medical centers.	Acknowledged Acknowledged
2	None	
3	None at this time	
4	If feasible, a review of evidence-based methods and data on suicide risk evaluation in primary care settings would be helpful	Acknowledged

APPENDIX E: EVIDENCE TABLES

Evidence Table 1. Key Question #2 Systematic Review, Hansen, 2008[35]

Studies	Study Characteristics Study Designs	Patient Characteristics	Outcomes Assessed	Relative risks/other summary effect measures	Comments Quality Rating
Doogan & Caillard, 1992[141] Feiger, 1999[142] Gelenberg, 2003[143] Gilaberte, 2001[144] Hochstrasser, 2001[145] Keller, 1998[146] Klysner, 2002[147] Kornstein, 2006[42] Lepine, 2004[43] Lustman, 2006[148] Montgomery, 1993[149] Montgomery, 2004[150] Montgomery & Dunbar, 1993[151] Rapaport, 2004 [not found] Reimherr, 1998[44] Reynolds, 2006[152] Robert & Montgomery, 1995[153] Schmidt, 2000[154] Simon, 2004[155] Terra & Montgomery, 1998[156] Thase, 2001[157] Weihs, 2002[158] Wilson, 2003[159]	**No. of studies:** 23 placebo controlled RCT **Study countries:** Most included US Many in UK, France, & Europe Several multinational **Study intervention:** Second-generation antidepressant: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazadone, paroxetine, sertraline, trazodone, venlafaxine **Clinical settings (22/23 articles):** Mixed settings: 4 "Outpatient": 12 Not Given: 6 VA: 0 Civilian: 22	**Total no. of patients:** 8241 **Age:** Mean age range generally 40-50. Two trials w/ range 65-87 **Gender:** Most >60% female Many >65% female **Depressive Disorder:** 26 required MDD diagnosis, 1 required only QIDS-C-16 > 5. **Severity of initial symptoms:** Many used HDRS. Some had requirement for # episodes. **Race/ethnicity:** NG **Exclusion:** Use of other psychotropics, presence of comorbid psychiatric or medical disease most common	**Relapse definition:** most used increase in HAM-D or MADRS above predefined cutoff pt. Some added clinical criteria. **Treatment duration (after acute phase):** Continuation: 14-72 weeks Maintenance: 36-100 weeks. 12 trials: f/up <1yr (redefined as continuation) 11 trials: f/up 1+ yr (redefined as maintenance) **Outcomes:** 1) Continuation phase relapse rate compared to placebo 2) Maintenance phase recurrence rate compared to placebo **Other Outcomes:** 4) Rates of adverse events 5) Rates of loss to f/up attributed to adverse events	Relapse re-defined as relapse w/in 1 yr continuation Recurrence re-defined as relapse w/in 1 yr maintenance **Outcomes:** 1) Unadjusted frequency of relapse was 22% active treatment, 42% placebo 2) Unadjusted frequency of recurrence was 26% for active treatment, 48% placebo **Other Outcomes:** 3) Adverse events rates given for individual studies when reported (compared w/ acute-phase studies, relative incidence of most common adverse events was lower) 5) Loss to f/up attributed to adverse events was 7% for active treatment and 4% for placebo (did not report significance)	**Comments:** -In meta-regression, duration of follow-up did not impact effect size -Authors reported fair quality of studies included -Moderate grade evidence **Quality Rating**: high Focused clinical question? Yes Detailed & exhaustive search? Yes Inclusion/exclusion criteria clearly defined & appropriate? Yes Studies evaluated for quality & appropriately? Yes Assessments of studies reproducible? Yes Measured variability in effect? Yes Differences in how outcomes were reported and analyzed across studies considered? Yes Publication bias assessed? Yes, Clinically important outcomes (harms & benefits) reported? Yes Conclusions supported by data presented? Yes

Evidence Table 2. Key Question #2 Randomized Controlled Trials

Study Characteristics	Research Objective Duration Study Design	Patient Baseline Characteristics	Inclusion/Exclusion Criteria	Outcome Results	Adverse Events (%)	Analysis Quality Rating
Author: Kocsis et al., 2007[37] **Country and Setting:** United States Outpatient **Funding:** Wyeth (manufacturer of venlafaxine)	**Research Objective:** To compare time to recurrence of depression with venlafaxine ER versus placebo **Duration of Study:** 12-month maintenance phase for venlafaxine ER responders **Study Design:** Randomized Placebo controlled **Overall Total N:** 258 (randomized) **Intervention:** Group 1: Venlafaxine ER 75-300 mg daily Group 2: Placebo	**Mean Age:** Venlafaxine ER 42.0 Placebo 42.6 **Sex (% female):** Venlafaxine ER 69% Placebo 67% **Race (% white):** Venlafaxine ER 81% Placebo 88% **Baseline (HDRS)** Venlafaxine ER 4.3 Placebo 4.9	**Inclusion Criteria:** • ≥ 18 years old • MDD by DSM-IV • Depression symptoms for ≥ 1 month • ≥3 prior depressive episodes, 2 in the past 5 years • Two months between episodes • HDRS-17 score ≥ 20 at screening and ≥18 at randomization • Response or remission of intake episode at end of continuation phase **Exclusion Criteria:** • Failed trial of study medications • Treatment resistant, defined as failure of three med trials, ECT, or psychotherapy • Hypersensitivity to study medications • Alcohol or illicit drug use within 6 months • Seizure disorder • Other serious medical diseases • Other mental illnesses • Pregnant or lactating • ECT within 3 months • Fluoxetine or MAO-I within 30 days • Other antidepressant within 14 days • Any other psychotropic drug 7 days	**Venlafaxine ER was associated with significantly lower risk of recurrence in comparison to placebo.** **Probability of recurrence:** **Month 6:** Venlafaxine ER: 18.8% Placebo: 28.4% **Month 12:** Venlafaxine ER: 23.1% Placebo: 42%	**Headache:** Venlafaxine ER 25 Placebo 24 **Upper Respiratory Infection:** Venlafaxine ER 17 Placebo 12 **Dry Mouth:** Venlafaxine ER 15 Placebo 11 **Insomnia:** Venlafaxine ER 14 Placebo 13 **Sweating:** Venlafaxine ER 14 Placebo 12 **Weight Gain:** Venlafaxine ER 12 Placebo 7 **Dizziness:** Venlafaxine ER 11 Placebo 21 **Nausea:** Venlafaxine ER 11 Placebo 10 **Sexual Problems:** Venlafaxine ER 11 Placebo 7	**Overall Attrition Rate:** Venlafaxine = 50% Placebo = 73% (p<.001) **ITT Analysis:** Yes **Quality Rating: fair?** Grps similar at baseline? Yes Outcomes used valid methodology & criteria? Yes, HDRS-17 Subjects & providers blind to intervention status of participants? Yes Outcome assessors blind? Yes Incomplete outcome data adequately addressed? Yes, ITT >10% differential loss to f/up between grps? Yes Overall >30% loss to f/up? Yes, 40% Conflict of interest? Funded by venlafaxine manufacturer Adequate randomization methods? NG Allocation concealment adequate? NG

Evidence Table 3. Key Question #2 Randomized Controlled Trials

Study Characteristics	Research Objective Duration Study Design	Patient Baseline Characteristics	Inclusion/Exclusion Criteria	Outcome Results	Adverse Effects	Analysis Quality Rating
Author: Kornstein et al., 2008[39] **Country and Setting:** United States Outpatient **Funding:** Wyeth (manufacturer of venlafaxine)	**Research Objective:** Evaluate the long-term efficacy of venlafaxine ER =< 225mg/day in patients with recurrent MDD **Duration of Study:** Two years for venlafaxine ER responders **Study Design:** Randomized Placebo controlled **Overall Total N:** 114 **Intervention:** Group 1: Continue venlafaxine ER 75-225mg/day Group 2: Placebo	**Mean Age:** Venlafaxine ER 41 Placebo 43.1 **Sex (% female):** Venlafaxine ER 73 Placebo 63 **Race (% white):** NG **Baseline (HDRS)** Venlafaxine 3.2 Placebo 4.5	**Inclusion Criteria:** • ≥18 years old • MDD by DSM-IV • Depression symptoms for ≥ 1 month • ≥ 3 prior depressive episodes, 2 in the past 5 years • Two months between episodes • HDRS-17 score ≥20 at screening and ≥18 at randomization • Response or remission of intake episode at end of continuation phase **Exclusion Criteria:** • Failed trial of study medications • Treatment resistant, defined as failure of three med trials, ECT, or psychotherapy • Hypersensitivity to study medications • Alcohol or illicit drug use within 6 months • Seizure Disorder • Others serious medical diseases • Other mental illnesses • Pregnant or Lactating • ECT within 3 months • Fluoxetine or MAO-I within 30 days • Other antidepressant within 14 days • Any other psychotropic drug 7 days	**Kaplan-Meier probability estimate for not experiencing recurrence OR increasing dose to 300mg/day:** **67% for venlafaxine ER =< 225 mg** **41% for placebo** NNT of 4.5 Estimated probability of not having recurrence greater in venlafaxine ER group vs. placebo (76% versus 58%) but did not reach level of statistical significance	Not reported	**Overall Attrition Rate:** NG **ITT Analysis:** Not done **Quality Rating: fair or poor?** Grps similar at baseline? Yes Outcomes used valid methodology & criteria? Partial, HDRS-17 & dose increase of antidepressant Subjects & providers blind to intervention status of participants? Yes Outcome assessors blind? Yes Incomplete outcome data adequately addressed? No, reasons not reported >10% differential loss to f/up between grps? No Overall >30% loss to f/up? No Conflict of interest? Funded by venlafaxine manufacturer Adequate randomization methods? NG Allocation concealment adequate? NG

Evidence Table 4. Key Question #2 Randomized Controlled Trials

Study Characteristics	Research Objective Duration Study Design	Patient Baseline Characteristics	Inclusion/Exclusion Criteria	Outcome Results	Adverse Events (%)	Analysis Quality Rating
Author: Gorwood et al., 2007[38] **Country and Setting:** 7 European countries Outpatient **Funding:** H. Lundbeck A/S (manufacturer of escitalopram)	**Research Objective:** To test the hypothesis that fewer older patients will relapse on escitalopram compared with placebo **Duration of Study:** 24 week maintenance phase for escitalopram responders after 12 weeks of open label treatment **Study Design:** Randomized Placebo controlled **Overall Total N:** 305 (randomized) **Intervention:** Group 1: escitalopram 10-20 mg/day Group 2: placebo	**Mean Age:** Escitalopram 73 Placebo 72 **Sex (% female):** Escitalopram 78% Placebo 79% **Race (% white):** Escitalopram 99.7% Placebo 100% **Baseline (MADRS):** Escitalopram 5.1 Placebo 5.1	**Inclusion Criteria:** • >= 65 years old • MDD by MINI • Response to a 12 week trial of escitalopram • MADRS score >= 22 • Duration of t index episode of at least 4 weeks • MMSE score >= 24 • **Exclusion Criteria:** • Current or past history of manic or hypomanic episode, psychotic disorder (including MDD with psychotic features), MR, or mental disorders resulting from a general medical condition • Any substance abuse disorder, presence or history of a clinically significant neurologic disorder, neurodegenerative disorder, and any personality disorder. • Significant suicide risk • Recent receipt prior to screening of the following treatments: □ antipsychotic drugs, ECT, lithium, carbamazepine, valproate, or valpromide □ antidepressants, benzodiazepines, non-benzodiazepine anxiolytics or hypnotics (other than zolpidem, zopiclone, or zaleplon); serotonin agonists (for example, triptans), psychotherapy □ hypersensitivity to citalopram and/or escitalopram □ resistance to two trials of antidepressants or resistance to citalopram or escitalopram	**Escitalopram was four times as effective as placebo in preventing relapse over 24 weeks in older patients with MDD who had achieved full remission** **Percentage who relapsed:** Escitalopram: 9% (13 patients) Placebo: 33% (50 patients)	**Any adverse event:** Escitalopram 35.3 Placebo 34.9 **Diarrhea:** Escitalopram 3.3 Placebo 2.6 **Dizziness:** Escitalopram 4.6 Placebo 3.3 **Nausea:** Escitalopram 0 Placebo 0 **Headache:** Escitalopram 2.6 Placebo 3.3	**Overall Attrition Rate:** Escitalopram = 15% Placebo = 8.5% (excluding relapsers) **ITT Analysis:** Yes **Quality Rating:** Grps similar at baseline? Yes Outcomes used valid methodology & criteria? Yes, MADRS Subjects & providers blind to intervention status of participants? Yes Outcome assessors blind? Yes Incomplete outcome data adequately addressed? Yes, ITT >10% differential loss to f/up between grps? No Overall >30% loss to f/up? No Conflict of interest? Funded by escitalopram manufacturer Adequate randomization methods? Yes Allocation concealment adequate? Yes

Evidence Table 5. Key Question #2 Randomized Controlled Trials

Study Characteristics	Research Objective Duration Study Design	Patient Baseline Characteristics	Inclusion/Exclusion Criteria	Outcome Results	Adverse Events (%)	Analysis Quality Rating
Author: Dobson et al., 2008[36] **Country and Setting:** United States Outpatient **Funding:** NIMH	**Research Objective:** To compare relapse rates among prior behavioral activation, prior cognitive therapy, and antidepressant medication (ADM) to placebo **Duration of Study:** 2 years of follow up after 16 week acute phase treatment. Pts were all withdrawn from ADM after 1 year. **Study Design:** Randomized Placebo controlled **Overall Total N:** 106 (randomized) **Intervention:** Group 1: paroxetine (28) Group 2: placebo (21)	Baseline characteristics of those randomized to ADM and placebo in the maintenance phase were not separately reported. **For all subjects randomized to AMD or placebo:** Female 78.2% Caucasian 80.0% Minority 20.0% Married 36.3% Have children 43.6% College education 63.8%	**Inclusion Criteria:** • response to acute phase treatment for depression with 16 weeks of paroxetine • diagnosis of MDD for index episode on the basis of diagnostic interviews • 20 or above on the Beck Depression Inventory II and scores of 14 or above on the 17-item version of the HDRS **Exclusion Criteria:** Not explicitly stated in this report	**Rates of relapse** after 1 year follow up from Cox regression analysis: paroxetine: 53% placebo: 59% (not statistically significantly different)	Not reported	**Overall Attrition Rate:** ADM = 7% Placebo = 19% **ITT Analysis:** Unclear **Quality Rating: Poor - Fair?** Grps similar at baseline? NG Outcomes used valid methodology & criteria? Yes, HRSD Subjects & providers blind to intervention status of participants? Yes Outcome assessors blind? Yes Incomplete outcome data adequately addressed? No, reasons not reported >10% differential loss to f/up between grps? Yes Overall >30% loss to f/up? No Conflict of interest? No, funded by NIMH Adequate randomization methods? Yes Allocation concealment adequate? Yes

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