



# THE PRIMARY CARE COMPANION FOR CNS DISORDERS

## **Supplementary Material**

**Article Title:** Impact of Treating Depression on Associated Comorbidities: A Systematic Literature Review

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**Supplementary Table 1. Search strategies (searches conducted November 28, 2019)**

#	MEDLINE	Embase	PsycINFO	Cochrane CCRCT
1	exp Depressive Disorder, Major/	exp major depression/	exp Major Depression/	(major adj2 depress*).ab,ti.
2	(major adj2 depress*).ab,ti.	(major adj2 depress*).ab,ti.	(major adj2 depress*).ab,ti.	(controlled clinical trial or randomized controlled trial).pt.
3	1 or 2	1 or 2	1 or 2	[disease-specific terms, see below]
4	Randomized Controlled Trial/	randomized controlled trial/	Randomized Controlled Trials/	1 and 2 and 3
5	Random Allocation/	controlled clinical trial/	Randomized Clinical Trials/	limit 4 to (case report or comment or editorial or letter or "review")
6	Double-Blind Method/	phase 3 clinical trial/	randomi?ed controlled trial\$.tw.	4 not 5
7	Single-Blind Method/	phase 4 clinical trial/	(random\$ adj2 allocat\$).tw.	limit 6 to english language
8	clinical trial, phase iii.pt.	randomization/	single blind\$.tw.	
9	clinical trial, phase iv.pt.	randomi?ed controlled trial\$.tw.	double blind\$.tw.	
10	controlled clinical trial.pt.	rct.tw.	((treble or triple) adj blind\$).tw.	
11	randomized controlled trial.pt.	(random\$ adj2 allocat\$).tw.	or/4-10	
12	((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.	single blind\$.tw.	[disease-specific terms, see below]	
13	randomly allocated.tw.	double blind\$.tw.	3 and 11 and 12	
14	(allocated adj2 random\$).tw.	((treble or triple) adj blind\$).tw.	limit 13 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)	
15	or/4-14	or/4-14	13 not 14	
16	[disease-specific terms, see below]	[disease-specific terms, see below]	limit 15 to english language	
17	3 and 15 and 16	3 and 15 and 16		
18	(review not systematic review).pt.	limit 17 to (editorial or letter or note or conference abstract or conference paper or "conference review")		
19	17 and 18	17 not 18		
20	17 not 19	limit 19 to english language		
21	limit 20 to (case reports or comment or editorial or letter)			
22	20 not 21			
23	limit 22 to english language			
24	exp Depressive Disorder, Major/			

#	MEDLINE	Embase	PsycINFO	Cochrane CCRCT
25	(major adj2 depress*).ab,ti.			

**Disease-specific search terms**

<b>Autimmune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>
(((AIDS or acquired immune deficiency syndrome or acquired immunodeficiency syndrome or HIV or human immunodeficiency virus or human immun* deficiency virus or ankylosing spondylitis or Bechterew* or ((autoimmun* or auto-immun* or auto immune*) adj (disorder or disease)) or c?eliac or Gee-Herter* or crohn* or enteritis) adj region*) or MS or multiple sclerosis or psoriasis or (psoria* adj (skin or derm*)) or ulcerative colitis or (ulcer* adj (colitis or colon))).ab,ti.	(cancer* or (malignan* adj (neoplas* or tumo?r))).ab,ti.	(dementia or Alzheimer* or epilep* or Parkinson* or paralysis agitans).ab,ti.	(((coronary or isch?emic) adj (artery or heart or cardiac) adj (disease or disorder)) or (cardiovascular adj (disease or disorder or lesion or syndrome)) or IHD or CAD or CVD or hypertens* or (high adj2 blood pressure) or MI or ((myocard* or heart) adj infarct*) or heart attack or stroke or cerebrovascular accident or CVA).ab,ti.	(((gastrointestinal or digestive tract) adj (disease or disorder or syndrome or h?emorrhage or bleeding)) or gastroenteropathy or ?esophagitis or ((Escherichia coli or coliform) adj infection*) or "e.coli infection" or ((cardioesophageal or gastr* or ?esophageal) adj (reflux or regurgitation)) or GERD or (irritable adj (bowel or colon)) or IBS or IBD).ab,ti.
<b>Metabolic/endocrine</b>	<b>Musculoskeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>	
(((metabolic or insulin resistance) adj syndrome) or diabet* or hyperlipid?emi* or lupus or obes* or adipos* or body weight or (polycystic adj ovar*) or PCOS or Stein-Leventhal).ab,ti.	(arthriti* or backache or (chronic adj pain) or fibromyalgia or headache or cephalalgia or cephalgia or migraine or hemicrania or ((back or head) adj2 (ache or pain)) or (joint adj (disease or disorder)) or arthropathy or (joint* adj inflamm*) or osteopor*).ab,ti.	(asthma or (chronic adj2 (pulmonary or lung or bronchopulmonary) adj (disease or disorder)) or COPD or bronchitis or (bronch* adj (infection or inflammation)) or emphysema).ab,ti.	((substance or drug or alcohol) adj2 abus*).ab,ti.	

CNS, central nervous system, CVD, cardiovascular disease, GI, gastrointestinal. Supplementary congress abstract searches conducted for 2018 and 2019 in the Academy of Managed Care Pharmacy (AMCP) Annual Meeting and Nexus, American Psychological Association (APA) annual congress, European Psychological Association (EPA) annual congress, European College of Neuropsychopharmacology (ECNP) annual congress, and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) annual congresses.

**Supplementary Table 2. Study inclusion and exclusion criteria**

	<b>Inclusion criteria</b>	<b>Exclusion criteria</b>
<b>Population</b>	Diagnosis of MDD Adults ≥18 years of age	Mixed population where MDD subgroup is not reported separately Age <18 years
<b>Intervention(s)</b>	Any antidepressant treatment	No restrictions
<b>Comparator(s)</b>	Any comparator, including placebo	No comparator
<b>Outcomes</b>	Improvement in depression outcomes Risk of comorbidity or severity of existing comorbidity	No statistically significant improvement in depression outcomes
<b>Study type</b>	RCTs Meta-analyses of RCTs	Non-human studies Observational studies Commentaries and letters Recommendations/guidelines Methods articles/protocols Hypothetical models Narrative reviews
<b>Other</b>	English language only Located in Europe and North America	Non-English language Local studies in countries outside of Europe and North America

MDD, major depressive disorder; RCT, randomized controlled trial.

**List of congresses searched**

- Academy of Managed Care Pharmacy (AMCP) – Annual Meeting and Nexus
- American Psychological Association (APA)
- European Psychological Association (EPA)
- European College of Neuropsychopharmacology (ECNP)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – all conferences

**Supplementary Table 3. Quality assessment of RCTs—part 1**

Reference(s)	Selection bias			Performance bias					Attrition bias			Risk of bias
	A1	A2	A3	Risk of bias	B1	B2	B3	Risk of bias	C1	C2	C3	
Berkman 2003	Unclear	Yes	Yes	Unclear	Yes	No	No	High	Yes	Yes	Yes	Low
Borson 1992	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Unclear	Low
Cornelius 1997	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Unclear	Unclear
de Jonge 2007	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Low	Yes	Yes	Unclear	Low
Dobkin 2011; Dobkin 2014	Yes	Yes	Yes	Low	Yes	No	No	High	Yes	Yes	Yes	Low
Eli 2010; Eli 2011	Yes	Yes	Unclear	Unclear	No	No	No	High	Yes	Yes	Yes	Low
Fava 2004	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Unclear	Unclear	Unclear
Glassman 2002; Glassman 2007	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	Low	Yes	Unclear	Unclear	High
Huffman 2011	Yes	Unclear	Yes	Low	Yes	No	No	High	Yes	Yes	Yes	Low
Lustman 1997	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Yes	Low
Lustman 1998	Unclear	Yes	Yes	Low	Yes	No	No	High	Yes	Yes	Yes	Low
Lustman 2000	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Unclear	Unclear
Lyketsos 2003; Munro 2004	Yes	Yes	Yes	Low	Yes	Yes	Yes	Low	Yes	Yes	Yes	Low
Marangell 2011	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Unclear	Unclear	Unclear
Mason 1996	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Unclear	Unclear
McIntyre 2014	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Low	Yes	Yes	Yes	Low
Mohr 2007; Kinsinger 2010	Unclear	Unclear	Yes	Unclear	Yes	No	No	High	Yes	Yes	Unclear	Low
Mulick 2018	Yes	Yes	Yes	Low	No	No	No	High	Yes	Yes	Yes	Low
Nunes 1998	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Low	Yes	Yes	Yes	Low

Reference(s)	Selection bias			Performance bias				Attrition bias			Risk of bias	
	A1	A2	A3	Risk of bias	B1	B2	B3	Risk of bias	C1	C2		C3
Petrak 2015	Yes	Unclear	Yes	Unclear	Yes	No	No	High	Yes	Yes	Unclear	Unclear
Poleshuck 2014	Yes	Yes	Yes	Low	Yes	No	No	High	Yes	Yes	Yes	Low
Raskin 2008	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	Low	Yes	Yes	Unclear	Low
Sherwood 2016	Yes	Yes	Yes	Low	Yes	Unclear	Unclear	Low	Yes	Yes	Yes	Low
Stewart 2014	Yes	Unclear	Yes	Unclear	Yes	No	No	High	Yes	Yes	Unclear	Low
Walker 2014;	Yes	Yes	Yes	Low	No	No	No	High	Yes	Yes	Yes	Low
Mulick 2018	Yes	Yes	Yes	Low	No	No	No	High	Yes	Yes	Yes	Low
Wuart 2000	Unclear	Unclear	Yes	High	Yes	Yes	Unclear	Low	Yes	Yes	Yes	Low

A1, appropriate method of randomization was used; A2, adequate concealment of allocation; A3, groups were comparable at baseline; B1, groups received the same care and support apart from the intervention(s) studied; B2, participants were kept 'blind' to intervention allocation; B3, individuals administering care and support were kept 'blind' to intervention allocation; C1, all groups were followed up for an equal length of time; C2, groups were comparable for intervention completion; C3, groups were comparable with respect to the availability of outcome data.

**Supplementary Table 4. Quality assessment of RCTs—part 2**

Reference(s)	Detection bias					Risk of bias	Overall	
	D1	D2	D3	D4	D5		Internal validity	External validity
Berkman 2003	Yes	Yes	Yes	No	Unclear	Unclear	+	++
Borson 1992	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Cornelius 1997	Yes	Yes	Yes	Unclear	Unclear	Unclear	+	++
de Jonge 2007	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Dobkin 2011; Dobkin 2014	Yes	Yes	Yes	No	Unclear	Unclear	++	++
Ell 2010; Ell 2011	Yes	Yes	Yes	Yes	Unclear	Unclear	+	+
Fava 2004	Yes	Yes	Yes	Unclear	Unclear	Unclear	+	++
Glassman 2002; Glassman 2007	Yes	Yes	Yes	Yes	Unclear	Low	+	++
Huffman 2011	Yes	Yes	Yes	Yes	Unclear	Unclear	++	++
Lustman 1997	No	Yes	Yes	Yes	Unclear	Unclear	+	++
Lustman 1998	Yes	Yes	Yes	Yes	Unclear	Unclear	++	++
Lustman 2000	No	Yes	Yes	Yes	Unclear	Unclear	+	++
Lyketsos 2003; Munro 2004	Yes	Yes	Unclear	Yes	Unclear	Unclear	++	++
Marangell 2011	Yes	Yes	Yes	Unclear	Unclear	Unclear	+	++
Mason 1996	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
McIntyre 2014	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Mohr 2007; Kinsinger 2010	Yes	Unclear	Yes	Yes	Unclear	Unclear	+	++
Mulick 2018	Yes	Yes	Yes	No	Unclear	Unclear	++	++
Nunes 1998	No	Yes	Yes	Yes	Unclear	Unclear	+	++
Petrak 2015	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Poleshuck 2014	Yes	Yes	Yes	Yes	Unclear	Unclear	++	+
Raskin 2008	Yes	Yes	Yes	Yes	Unclear	Unclear	+	++
Sherwood 2016	Yes	Yes	Yes	Yes	Unclear	Unclear	++	++
Stewart 2014	Yes	Yes	Yes	No	Unclear	Unclear	+	++
Walker 2014; Mulick 2018	Yes	Yes	Yes	No	Unclear	Unclear	++	++
Wiert 2000	Unclear	Yes	Yes	Unclear	Unclear	Unclear	+	++

D1, appropriate length of follow-up; D2, used a precise definition of outcome; D3, a valid and reliable method was used to determine the outcome; D4, investigators were kept 'blind' to participants' exposure to the intervention; D5, investigators were kept 'blind' to other important confounding factors.

**Supplementary Table 5. Quality assessment of meta-analyses**

Reference(s)	Screening questions					Overall assessment	
	1	2	3	4	5	Internal validity	External validity
Baumeister 2014	Yes	Yes	Yes	Yes	Yes	++	++
Nunes 2004	Yes	Yes	Yes	Yes	Yes	++	++
Thompson 2007	Yes	Yes	Yes	Yes	Yes	++	++
Torrens 2005	Yes	Yes	Yes	Yes	Yes	++	+

1, the review addresses an appropriate and clearly focused question that is relevant to the review question; 2, the review collects the type of studies you consider relevant to the guidance review question; 3, the literature search is sufficiently rigorous to identify all the relevant studies; 4, study quality is assessed and reported; 5, an adequate description of the methodology used is included, and the methods used are appropriate to the question.