

## Supplement 1: Complete search strategy

“Drug Tolerance” [Mesh] OR tachyphyla\* [tiab] OR non-respon\* [tiab] OR nonrespon\* [tiab] OR loss of response\* [tiab] OR toleran\* [tiab] OR resistan\* [tiab] OR "Retreatment"[Mesh] OR retreatment\* [tiab] OR “Recurrence” [Mesh] OR “Secondary prevention” [Mesh] OR recurren\* [tiab] OR relaps\* [tiab] OR re-initiation\* [tiab]

"Anxiety Disorders"[Mesh] OR anxiety disorder\* [tiab] OR generalized anxiety disorder\* [tiab] OR generalised anxiety disorder\* [tiab] OR anxiety state\* [tiab] OR agoraphobi\* [tiab] OR panic\* [tiab] OR phobi\* [tiab] OR obsessive-compulsive [tiab] OR post-traumatic\* [tiab] OR posttraumatic\* [tiab] OR traumatic\* [tiab] OR PTSD [tiab] “Depressive disorder” [Mesh] OR depressive disorder\* [tiab] OR dysthymi\* [tiab] OR major depression\* [tiab]

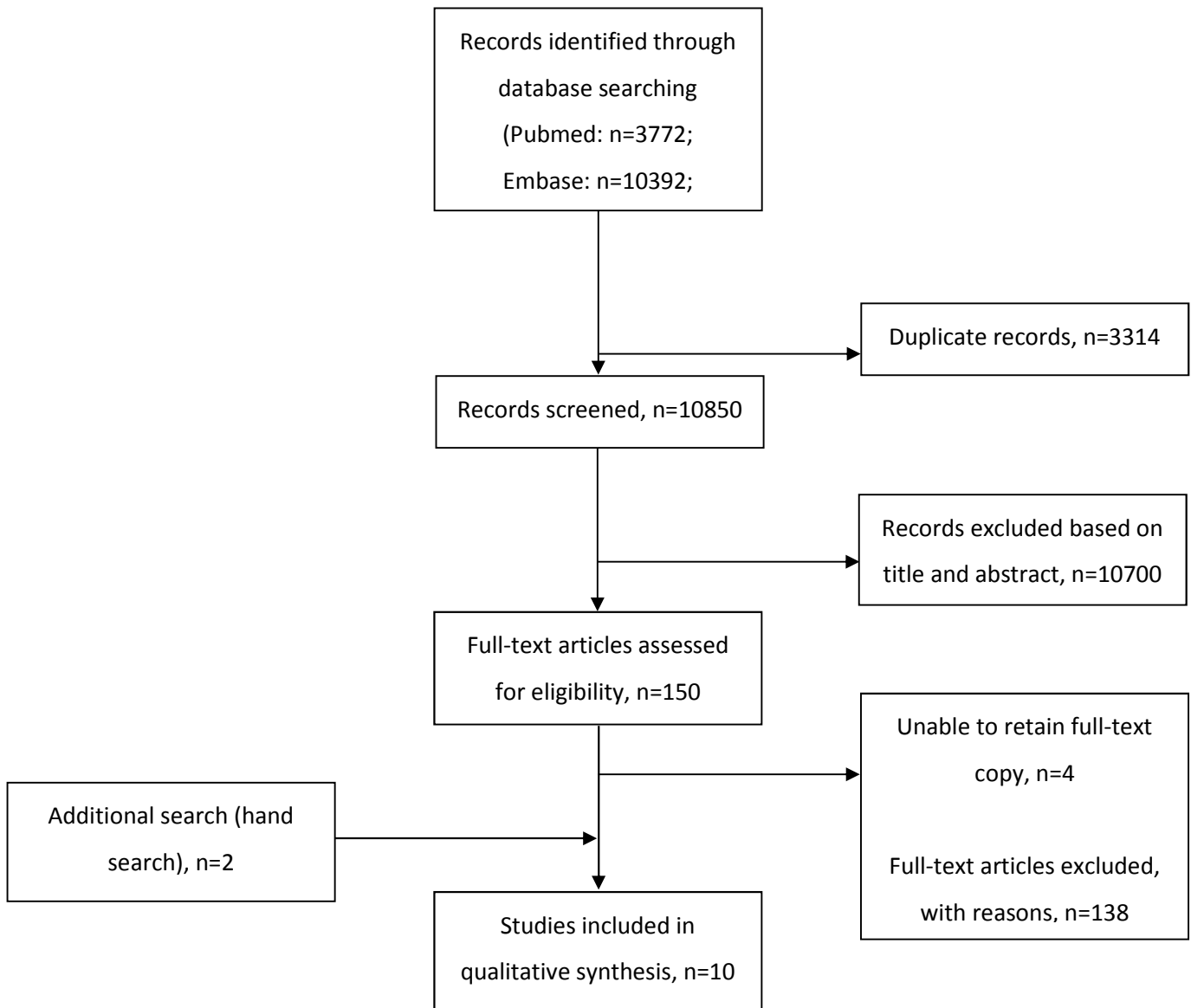
"Antidepressive Agents" [Pharmacological Action] OR "Antidepressive Agents"[Mesh] OR “Serotonin Uptake Inhibitors”[Mesh] OR antidepressiv\* [tiab] OR antidepressant\* [tiab] OR SSRI\* [tiab] OR SNRI\* [tiab] OR TCA\* [tiab] OR serotonin reuptake inhibitor\* [tiab]

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))

This search was unrestricted and has been modified for an additional search in Embase.

## Supplement 2: Flow diagram

Based on PRISMA (Moher, 2009)



### Supplement 3: Characteristics of included studies

Supplement 2: Characteristics of included studies.

Reference	Study design	Age Mean (sd)	Gender	Diagnoses	Number of previous episodes Mean (sd)	Duration of treatment before response failure <sup>a</sup>	Duration of treatment with response failure <sup>b</sup>	Discontinuation mode	N participants with response to antidepressant	N participants receiving retreatment	N participants with response failure	Antidepressant (with response failure)	Class	Dose (mg/day)	Plasma levels (ng/ml)	Comedication reported?
<i>Depressive disorders</i>																
Fava et al., 1998 [41]	Prospective	43.7 (2.3);	CBT group: 60% female	MDD	?	3-5 months	≥3 months	Taper	40	24	2	Desipramine	TCA	200	?	-
Fava et al., 2002 [32]	Prospective	40.9 (10.5)	CAU group: 48.5 (3.3) female n=39 (70.9%)	MDD	?	13 weeks	25 weeks	?	501	55	6	Fluoxetine	SSRI	20	NA	-
Fava et al., 2006 [33]	Prospective	44.7 (11.5)	Female: n=48 (82.8%) Male: n=10 (17.2%)	MDD	?	12 weeks	12 weeks	Taper	278	57	15	Duloxetine	SNRI	60	NA	-
Flint & Rifat, 1999 [34]	Prospective	74.4 (6.6)	?	MDD	None	?	?	Taper	21	11	1	Nortriptyline; Phenelzine	TCA/MAOI	?	?/NA	+
Friedman	Prospective	37.3 (13.1)	Female	Dyst or	?	26	?	?	?	12	1	Desipramine	TCA	Range: 75-300	Range:	-

et al., 1995 [35]			: n=7	Dyst with MDD		weeks									150-300		
			Male: n=5														
			Female : n=33												Mean: 201.8 (67.8)	Mean: 324.7 (166.9)	
Kupfer et al., 1989 [40]	Prospective	42.7 (10.4)	Male: n=12	MDD	6.2 (7.5)	≥20 weeks	≥20 weeks	?	45	37	7	Imipramine	TCA			-	
Remillard et al., 1994 [39]	Retrospectiv e chart review	?	?	MDD	≥1	?	?	?	59	35	15	Unspecified TCAs; trazodone; amoxapine; nomifensine <sup>c</sup>		Trial was considered adequate if dose was ≥150mg/d or patient had response at lower dose.	Median : 308 ?/NA	-	
Reynolds et al., 1994 [38]	Prospective	66.8 (5.1)	Female : n=25 Male: n=7	MDD	≥1	?	?	?	?	30	3	Nortriptyline	TCA	80.4 (40.7)	95.1 (25.2)	-	
<i>Obsessive Compulsive Disorder</i>																	
Maina et al., 2001 [36]	Prospective	?	?	OCD	?	6 months	24 weeks	Taper	183	81	13	Clomipramine ; fluoxetine; fluvoxamine; paroxetine	TCA/ SSRI	Clomipramine : 150 Fluoxetine: 40 Fluvoxamine: 300 Paroxetine: 40	?	?	-
<i>Anxiety disorders</i>																	

Versiani et al., 1997 [37]	Prospective	34 (10) <sup>a</sup>	Female : n=43 Male: n=58 <sup>a</sup>	SP	?	Up to 2 years	Up to 2 years	50% taper; 50% abrupt	59	52	2	Moclobemide	MAOI	730	NA	-
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Abbreviations: sd=Standard Deviation; CBT=Cognitive Behavioural Therapy; CAU = Care As Usual; MDD=Major Depressive Disorder; Dyst=Dysthymia; OCD=Obsessive-Compulsive Disorder; SP=Social Phobia; TCA=Tricyclic Antidepressant; SSRI=Selective Serotonin Reuptake Inhibitor; SNRI= Serotonin–norepinephrine reuptake inhibitor; MAOI= Monoamine oxidase inhibitor; mg/d=milligram per day; ng/ml=nanogram per millilitre; NA=Not applicable. <sup>a</sup>This data relates to the baseline data of the study and not to the sample included for reinstatement. <sup>b</sup>Time point as reported in original article. <sup>c</sup>Not described for which antidepressant a failure to respond occurred.

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## Supplement 4: Definitions of response and remission

Supplement 3: Definitions of response and remission after reinstatement of antidepressant medication		
Reference	Definition response	Definition remission
<i>Depressive disorders</i>		
Fava et al., 1998 [41]	Patients rated as 'better' or 'much better' according to Kellner's global rating scale of improvement (Kellner 1972)	Full remission according to criteria provided by Frank et al. 1991
Fava et al., 2002 [32]	Response: $\geq 50\%$ reduction of modified HAMD <sub>17</sub> and CGI-severity score of $\leq 2$	Not provided
Fava et al., 2006 [33]	Reduction $\geq 50\%$ in the HAMD <sub>17</sub> score from the time of relapse to the end of study participation	Total HAMD <sub>17</sub> score of $\leq 7$
Flint & Rifat, 1999 [34]	HAMD <sub>17</sub> of $\leq 10$	
Friedman et al., 1995 [35]	Not provided	<i>Partial remission:</i> a 50% reduction in 24-item HAMD score and a total score of 12 or less; and a GAS score of $\geq 60$ and completion of 10 weeks of acute treatment <i>Full remission:</i> total score on 24-item HAMD of $\leq 7$ ; and a GAS score of $\geq 70$ and absence of symptoms sufficient to meet the DSM-III-R criteria for dysthymia
Kupfer et al., 1989 [40]	HAMD <sub>17</sub> score $\leq 7$ at week 8 and $\leq 7$ at week 16, and a HAMD change score of $\geq 50\%$ at week 16, and Raskin score $\leq 5$ for 3 consecutive weeks	Not provided
Remillard et al., 1994 [39]	If the chart included phrases such as 'improved' or 'recovered' regarding depressive symptoms, and if the patient was discharged without further change in antidepressant prescription.	Not provided
Reynolds et al., 1994 [38]	Not provided	Three consecutive weekly HAMD scores of $\leq 10$ and subsequently maintained for 16 weeks
<i>Obsessive Compulsive Disorder</i>		
Maina et al., 2001 [36]	Decrease of $\geq 35\%$ in Y-BOCS total score and being rates as 'much improved' or 'very much improved' on CGI with respect to baseline condition	Not provided
<i>Anxiety disorders</i>		
Versiani et al., 1997 [37]	Final CGI-change scores of 1-2	Not provided

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Abbreviations: HAMD: Hamilton Depression Rating Scale; CGI: Clinical Global Impression; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3<sup>rd</sup> revised edition; GAS: Global Assessment Scale; Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

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## Supplement 5: Quality assessment

Supplement 4: Quality assessment of included studies. Items are derived from Cochrane Collaboration Tool for bias assessment.

Ref	Population at reinstatement				Antidepressant treatment				Antidepressant reinstatement				Confounders		Statistical analysis including attrition bias and reporting bias)			Selection bias		Performance bias		Detection bias	
	Age	Gender	Diagnosis	Diagnostic tool	Antidepressant(s)	Dose and frequency	Place and level <sup>a</sup>	Duration of treatment	Discontinuation method	Antidepressant(s) with response failure	Dose and frequency	Place and level <sup>a</sup>	Duration of reinstatement	Co-medication	Psychotherapy	Comorbidity	Who included into analysis	Selective outcome reporting <sup>b</sup>	Randomisation	Allocation concealment <sup>c</sup>	Blinding of assessors	Double blind or not	Outcome assessment
<i>Depressive Disorders</i>																							
Fava et al., 1998 [34]	Yes	Yes	Yes	Yes	Yes	Yes	No	Partly	Yes	Yes	Yes	No	Partly	?	Partly	Partly	No	Yes	No	NA	No	No	?
Fava et al., 2002 [25]	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	No	Yes	Yes	NA	Yes	No	No	Yes	Yes	Yes	No	NA	Yes	No	?
Fava et al., 2006 [26]	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	No	No	Yes	No	Yes	No	NA	Yes	No	?
Flint & Rifat, 1999 [27]	Yes	No	Yes	Yes	Yes	No	No	No	Partly	Partly	No	No	No	Partly	No	Yes	Yes	Yes	No	NA	No	No	No
Friedman et al., 1995 [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	?	Partly	?	No	?	Yes	Yes	No	NA	No	No	?
Kupfer et al., 1989	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partly	No	Yes	Yes	Yes	Partly	No	Yes	Yes	Yes	Yes	No	NA	No	No	No



[33]	Remillard et al., 1994	No	No	Yes	Yes	Partly	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	NA	NA	NA	NA	NA
[32]	Reynolds et al., 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	NA	No	No	No
[31]	<i>Obsessive Compulsive Disorder</i>																							
[29]	Maina et al., 2001	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	Partly	Yes	Partly	No	NA	No	No	No
[30]	<i>Anxiety disorders</i>																							
[30]	Versiani et al., 1997	Partly	Partly	Yes	Yes	Yes	Yes	NA	Partly	Yes	Yes	Yes	NA	Partly	No	No	Partly	No	No	No	NA	No	No	No

Abbreviations: NA: not applicable.

<sup>a</sup> Only applicable to studies using tricyclic antidepressants. If a study included multiple classes of antidepressants, this item was only assessed for tricyclic antidepressants. <sup>b</sup> When a study reported only subgroup analysis, this was considered to be selective reporting. <sup>c</sup> Only applicable when patients are randomised.