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Supplementary Material

Article Title: Dose Increase Versus Unchanged Continuation of Antidepressants After Initial Antidepressant Treatment Failure in Patients With Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized, Double-Blind Trials

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eAppendix 1: Search strategy

Databases searched:

Cochrane/CENTRAL

Embase

MEDLINE and PubMed Central via PubMed

PsycINFO

Search terms and their combination:

CENTRAL:

(depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)

AND

(antidepressant* or agomelatin* or amineptin* or amitriptylin* or amoxapin* or bupropion* or butriptylin* or chlorimipramin* or citalopram* or clomipramin* or desipramin* or desvenlafaxin* or dibenzepin* or dosulepin* or dothiepin* or doxepin* or duloxetin* or escitalopram* or fluoxetin* or fluvoxamin* or imipramin* or isocarboxazid* or lofepramin* or levomilnacipran* or MAOI* or "monoamine oxidase inhibitors" or maprotilin* or mianserin* or milnacipran* or mirtazapin* or moclobemid* or nefazodon* or nortriptylin* or paroxetin* or phenelzin* or protriptylin* or reboxetin* or selegilin* or sertralin* or setiptilin* or SSRI or SSNRI* or SNRI* or "selective serotonin reuptake inhibitors" or "serotonin-norepinephrine reuptake inhibitors" or tetracyclic* or tianeptin* or tranylcypromin* or trazodon* or trimipramin* or tricyclic* or venlafaxin* or viloxazin* or vortioxetin*)

AND

(((dose OR dosage) AND (increase OR escalat* OR elevat* OR raise)) OR ((dose OR dosage) AND ((maxim*) OR (upward AND titrat*)))

OR dose–response relationship, drug OR dose-effect OR high-dose

Embase:

((((depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)

AND

(antidepressant* or agomelatin* or amineptin* or amitriptylin* or amoxapin* or bupropion* or butriptylin* or chlorimipramin* or citalopram* or clomipramin* or desipramin* or desvenlafaxin* or dibenzepin* or dosulepin* or dothiepin* or doxepin* or duloxetin* or escitalopram* or fluoxetin* or fluvoxamin* or imipramin* or isocarboxazid* or lofepramin* or levomilnacipran* or MAOI* or monoamine oxidase inhibitors or maprotilin* or mianserin* or milnacipran* or mirtazapin* or moclobemid* or nefazodon* or nortriptylin* or paroxetin* or phenelzin* or protriptylin* or reboxetin* or selegilin* or sertralin* or setiptilin* or SSRI or SSNRI* or SNRI* or tca or selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors or tetracyclic* or tianeptin* or tranylcypromin* or trazodon* or trimipramin* or tricyclic* or venlafaxin* or viloxazin* or vortioxetin*)

AND

(((dose OR dosage) AND (increase OR escalat* OR elevat* OR raise)) OR ((dose OR dosage) AND ((maxim*) OR (upward AND titrat*))) OR dose–response relationship OR dose-effect OR high-dose)

AND

(random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer* or doubleblind* or singleblind* or double-blind* or single-blind* or double blind* or single blind*)

PubMed:

((((depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)

AND

(antidepressant* or agomelatin* or amineptin* or amitriptylin* or amoxapin* or bupropion* or butriptylin* or chlorimipramin* or citalopram* or clomipramin* or desipramin* or desvenlafaxin* or dibenzepin* or dosulepin* or dothiepin* or doxepin* or duloxetin* or escitalopram* or fluoxetin* or fluvoxamin* or imipramin* or isocarboxazid* or lofepramin* or levomilnacipran* or MAOI* or "monoamine oxidase inhibitors" or maprotilin* or mianserin* or milnacipran* or mirtazapin* or moclobemid* or nefazodon* or nortriptylin* or paroxetin* or phenelzin* or protriptylin* or reboxetin* or selegilin* or sertralin* or setiptilin* or SSRI or SSNRI* or SNRI* or tca or "selective serotonin reuptake inhibitors" or "serotonin-norepinephrine reuptake inhibitors" or tetracyclic* or tianeptin* or tranylcypromin* or trazodon* or trimipramin* or tricyclic* or venlafaxin* or viloxazin* or vortioxetin*)

AND

((((dose[tw] OR dosage[tw]) AND (increase[tw] OR escalat* OR elevat* OR raise)) OR ((dose[tw] OR dosage[tw]) AND ((maxim*[tw]) OR (upward[tw] AND titrat*[tw]))) OR ((dose–response relationship, drug[MeSH] OR dose-effect OR high-dose) OR ("dose-response relationship"))

AND

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]

NOT

(animals[mh] NOT humans [mh])))))

PsycInfo:

(depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)

AND

(antidepressant* or agomelatin* or amineptin* or amitriptylin* or amoxapin* or bupropion* or butriptylin* or chlorimipramin* or citalopram* or clomipramin* or desipramin* or desvenlafaxin* or dibenzepin* or dosulepin* or dothiepin* or doxepin* or duloxetin* or escitalopram* or fluoxetin* or fluvoxamin* or imipramin* or isocarboxazid* or lofepramin* or levomilnacipran* or MAOI* or "monoamine oxidase inhibitors" or maprotilin* or mianserin* or milnacipran* or mirtazapin* or moclobemid* or nefazodon* or nortriptylin* or paroxetin* or phenelzin* or protriptylin* or reboxetin* or selegilin* or sertralin* or setiptilin* or SSRI or SSNRI* or SNRI* or tca or "selective serotonin reuptake inhibitors" or "serotonin-norepinephrine reuptake inhibitors" or tetracyclic* or tianeptin* or tranylcypromin* or trazodon* or trimipramin* or tricyclic* or venlafaxin* or viloxazin* or vortioxetin*)

AND

((((dose[tw] OR dosage[tw]) AND (increase[tw] OR escalat* OR elevat* OR raise)) OR ((dose[tw] OR dosage[tw]) AND ((maxim*[tw]) OR (upward[tw] AND titrat*[tw]))) OR ((dose–response relationship, drug[MeSH] OR dose-effect OR high-dose) OR ("dose-response relationship"))

AND

(SU.EXACT("Treatment Effectiveness Evaluation") OR SU.EXACT.EXPLODE("Treatment Outcomes") OR SU.EXACT("Placebo") OR SU.EXACT("Followup Studies") OR placebo* OR random* OR "comparative stud*" OR clinical NEAR/3 trial* OR research NEAR/3 design OR evaluat* NEAR/3 stud* OR prospectiv* NEAR/3 stud* OR (singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*))

E-table 1: Risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Benkert 1997	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	High risk
Dornseif 1989	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk
Heiligenstein 2006	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk
Kim 2016	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk
Kornstein 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Licht 2002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ruhé 2009	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Schweizer 1990	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
Schweizer 2001	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk