

**MetaAnalysis – Systematic Review
Potential PURL Review Form
PURL Jam Version**

**PURLs Surveillance System
Family Physicians Inquiries Network**

**SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]**

- A. Citation: Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. Combining Antidepressants vs Antidepressant Monotherapy for Treatment of Patients With Acute Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2022;79(4):300-312. doi:10.1001/jamapsychiatry.2021.4313
- B. Link to PubMed Abstract: <https://pubmed.ncbi.nlm.nih.gov/35171215/>
- C. First date published study available to readers: 2/16/2022
- D. PubMed ID: 35171215
- E. Nominated By: Jim Stevermer
- F. Institutional Affiliation of Nominator: U of Missouri - Columbia
- G. Date Nominated: 2/28/2022
- H. Identified Through: JAMA Psychiatry
- I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
- J. Nomination Decision Date: 3/8/2022
- K. Potential PURL Review Form (PPRF) Type: Systematic Review
- L. Abstract: Importance: Combining antidepressants is frequently done in the treatment of acute depression, but studies have yielded conflicting results.

Objective: To conduct a systematic review and meta-analysis assessing efficacy and tolerability of combination therapy. Combinations using presynaptic α_2 -autoreceptor antagonists or bupropion were investigated separately.

Data sources: MEDLINE, Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials were systematically searched from each database inception through January 2020.

Study selection: Randomized clinical trials (RCTs) comparing combinations of antidepressants with antidepressant monotherapy in adult patients with acute depression were included.

Data extraction and synthesis: Following guidelines from Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and recommendations from the Cochrane Handbook, 2 reviewers independently performed a literature search, study selection, data extraction, and evaluation of risk of bias. Data were pooled in random-effects analyses.

Main outcomes and measures: Primary outcome was efficacy measured as standardized mean difference (SMD); secondary outcomes were response, remission, change from baseline in rating scale scores, number of dropouts, and number of dropouts due to adverse events.

Results: Thirty-nine RCTs including 6751 patients were eligible. Combination treatment was statistically significantly associated with superior treatment outcomes relative to monotherapy (SMD = 0.31; 95% CI, 0.19-0.44). Combining a reuptake inhibitor with an antagonist of presynaptic α_2 -autoreceptors was superior to other combinations (SMD = 0.37; 95% CI, 0.19-0.55). Bupropion combinations were not superior to monotherapy (SMD = 0.10; 95% CI, -0.07 to 0.27). Numbers of dropouts and dropouts due to adverse events did not differ between treatments. Studies were heterogeneous, and there was indication of publication bias (Egger test result was positive; $P = .007$, $df = 36$), but results remained robust across prespecified secondary outcomes and sensitivity and

subgroup analyses, including analyses restricted to studies with low risk of bias.

Conclusions and relevance: In this meta-analysis of RCTs comparing combinations of antidepressants with antidepressant monotherapy, combining antidepressants was associated with superior treatment outcomes but not with more patients dropping out of treatment. Combinations using an antagonist of presynaptic α_2 -autoreceptors may be preferable and may be applied as a first-line treatment in severe cases of depression and for patients considered nonresponders.

M. Pending PURL Review Date: 5/26/2022

SECTION 2: Critical Appraisal of Validity

[to be completed by the Potential PURL Reviewer]

A. What types of studies are included in this review?

39 total RCTs were included. 23 studies were double blind (59%), 5 trials were single-blind and 11 studies were open label

B. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.

What is the treatment efficacy and tolerability of antidepressant combination therapy compared with monotherapy in the treatment of acute depression and are specific combinations preferable to others?

The SMD was 0.31 (95% CI 0.19-0.44) in favor of combination treatment ($p < .001$). Thirty-one of 38 studies suggested superior efficacy of combination treatments. Combination therapy was associated with superior outcomes when analyses were restricted to studies of low risk bias, among non-responders, and when applied as a first line treatment (SMD 0.52; 95% CI, 0.24-0.79). With respect both to patients dropping out of treatment for any reason and to dropouts due to adverse events, data for combination and monotherapy were similar.

Strengths: Sample size and extent of literature search. Heterogeneity identified and analyzed with subgroup analysis which continued to demonstrate superiority of combination pharmacologic therapy.

Weaknesses: Assumption of tolerability made if patients did not drop out of trials. Publication bias; studies not indicating a difference in treatments less likely to be published.

C. Study addresses an appropriate and clearly focused question. Well covered

Comments: Explicitly states question

D. A description of the methodology used is included. Well covered

Comments:

E. The literature is sufficiently rigorous to identify all the relevant studies. Well covered

Comments: 5616 records identified with 4244 records reviewed; 146 full text articles read which identified 7 new studies to combine with previous 32 studies included in prior systematic review.

F. Study quality is assessed and taken into account. Well covered

Comments: Table 1 summarizes trials and includes evaluation of potential bias of each study

G. There are enough similarities between selected studies to make combining them reasonable.

Adequately addressed

Comments: Included only studies addressing combination pharmacologic therapy including 21 trials (54%) recruiting non-responders to initial antidepressant treatment. Subgroup analysis conducted to address heterogeneity.

- H. Are patient oriented outcomes included? If yes, what are they?
Yes, primary outcome-Standardized mean difference between monotherapy or combination therapy. Secondary outcome was remission (score below predetermined thresholds; less than 7 on the Hamilton Depression Rating Scale [HDRS]) and response (greater than 50% decrease on the HDRS or the Montgomery-Asberg Depression Rating Scale), change from baseline on a rating scale score, and number of dropouts and dropouts due to adverse events
- I. Are adverse effects addressed? If so, how would they affect recommendations?
Measured as “dropouts” of each study. Combination therapy is noted as not having any more dropouts to their studies than the monotherapy arms; it is surmised that combination therapy is just as safe and effective.
- J. Is funding a potential source of bias? If yes, what measures (if any) were taken to ensure scientific integrity?
None identified
- K. To which patients might the findings apply? Include patients in the meta-analysis and other patients to whom the findings may be generalized.
Adult patients (>18 years of age) with acute depression particularly those refractory to monotherapy
- L. In what care settings might the findings apply, or not apply?
Findings are likely to apply to the ambulatory setting vs initial treatment in psychiatric facilities. Less useful for emergency or acute care settings.
- M. To which clinicians or policy makers might the findings be relevant?
Any clinicians managing depression as a longitudinal condition

SECTION 3: Review of Secondary Literature

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified the AMA style. For example:
Norton JM, Bavendam TG, Elwood W, et al. Research needs to understand self-management of lower urinary tract symptoms: summary of NIDDK workshop. *J Urol*. 2018;199(6):1408-1410. doi:10.1016/j.juro.2017.11.079

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham,Mass: UpToDate; 2009. Available at: <https://www.uptodate.com/login>. {Insert date modified if given.} Accessed February 12, 2009. [whatever date PPRF reviewer did their search.]

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at <https://www.dynamed.com/>. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

- A. DynaMed excerpts

B. DynaMed citation/ Title. Author. In: DynaMed [database online]. Available at: access date <https://www.dynamed.com/>. Last Updated: . Accessed

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

D. UpToDate excerpts

- "For the initial treatment of unipolar major depression, we suggest the combination of pharmacotherapy and psychotherapy, based upon randomized trials that found combination treatment was more effective than either of these treatments alone"
- "For patients with unipolar major depression who do not respond to initial treatment with an optimally dosed antidepressant medication, treatment strategies include augmentation (adding a treatment) and switching treatment (eg, switching antidepressants)"
- "We typically use a drug from a different class when switching antidepressants for treatment-resistant depression, rather than switching to an antidepressant within the same class, especially if there are problematic, class-wide adverse effects (eg, sexual dysfunction, which can occur with most SSRIs) [14]. Evidence supporting a switch to an antidepressant in a different class includes a pooled analysis of four randomized trials involving 1496 patients with unipolar major depression who were resistant to initial treatment with an SSRI, and were switched either to a non-SSRI antidepressant (bupropion, mirtazapine, or venlafaxine) or to a different SSRI [84]. Remission was statistically greater in patients who switched to a different drug class (28 versus 24 percent); in addition, discontinuation due to side effects was comparable for the two groups. However, given the modest difference in remission (4 percent), switching from one SSRI to another is reasonable"
- "For patients who obtain little symptom relief (eg, reduction of baseline symptoms <25 percent) and can tolerate the initial antidepressant, we suggest augmenting antidepressants with a second-generation antipsychotic as first-step treatment and augmentation with lithium for patients who do not respond to second-generation antipsychotics. However, it is reasonable to first augment with lithium. The rationale for using second-generation antipsychotics or lithium is that their efficacy is better established, compared with other drugs that are commonly used for augmentation, such as a second antidepressant or thyroid hormone. However, adverse effects also appear to be greater with second-generation antipsychotics and lithium, and it is thus reasonable to augment with a second antidepressant or thyroid hormone instead."

E. Rush JA. Unipolar major depression in adults: Choosing initial treatment. *UpToDate*. 2020. Available at: https://www.uptodate.com/contents/unipolar-major-depression-in-adults-choosing-initial-treatment?search=combinati%20therapy%20for%20depression&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3#H21696590. Last Accessed: 11 May 2022.

Thase M, Connolly KR. Unipolar depression in adults: Choosing treatment for resistant depression. *UpToDate*. 2021. Available at: https://www.uptodate.com/contents/unipolar-depression-in-adults-choosing-treatment-for-resistant-depression?search=combinati%20therapy%20for%20depression&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H925759895. Last Accessed: 11 May 2022.

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

First line for unipolar depression treatment is psychotherapy in combination with a first-line anti-depressant medications (ie SSRI, SNRI, etc). If depression is found to be resistant or has a minimal effect with first medication and desire is to augment with second medication, consideration is made for second generation antipsychotics,

lithium, a second anti-depressant, or thyroid hormone; generally, side effect profile higher for second generation antipsychotic and lithium.

G. Other excerpts (USPSTF; other guidelines; etc.)

Gelenberg, A. J. (n.d.). *Practice guideline for the treatment of patients with ... - psychiatry*. Practice Guidelines for the treatment of patients with MDD. Retrieved May 11, 2022, from https://www.psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/eatingdisorders.pdf

H. Citations for other excerpts

- "Combining a depression-focused psychotherapy and pharmacotherapy may be a useful initial treatment choice for patients with moderate to severe major depressive disorder. Other indications for combined treatment include chronic forms of depression, psychosocial issues, intra psychic conflict, interpersonal problems, or a co-occurring Axis II disorder. In addition, patients who have had a history of only partial response to adequate trials of single treatment modalities may benefit from combined treatment."
- "For patients who exhibit a partial response to treatment, doses of antidepressant medications should be maximized, side effects permitting, before changing to a different antidepressant medication."
- "One option is to add a second non-MAOI antidepressant medication from a different pharmacological class, taking care to avoid drug-drug interactions. Another option is to add an adjunctive, nonantidepressant medication—such as lithium, thyroid hormone, an anti-convulsant, a psychostimulant, or a second-generation(atypical) antipsychotic"

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

First line for unipolar depression is a combination of pharmacotherapy and psychotherapy. If patients do not achieve remission with single agent, methods for treatment include increasing dose of medication, switching medications, or addition of a second anti-depressant.

SECTION 4: Conclusions

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

- A. **Validity:** Are the findings scientifically valid? Yes
- B. If A was coded "Other, explain or No", please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?
- C. **Relevance:** Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?
Yes
- D. If C was coded "Other, explain or No", please provide an explanation.
- E. **Practice changing potential:** If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?
Yes

- F. If E was coded as “Yes”, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.
Combinations of reuptake inhibitors with an antagonist of presynaptic alpha-2 was superior to other combinations which may be preferable as a second-step treatment in severe cases of depression and nonresponders as opposed to switching antidepressants or increasing doses of medications (if already at an effective dose).
- G. **Applicability to a Family Medical Care Setting:**
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? Yes
- H. Please explain your answer to G.
Those with severe depression would likely benefit from combination therapy rather than monotherapy; could easily be accomplished in the primary care setting
- I. **Immediacy of Implementation:**
Is the service, device, drug, therapy, or other essentials readily available on the market? Additionally, does immediate implementation lack major barriers such as cost, challenges for reimbursement, or regulatory barriers?
Yes
- J. If I was coded “Other, explain or No”, please explain why.
Comparable cost to addition of alternative adjunctive medications
- K. **Clinically meaningful outcomes or patient oriented outcomes:**
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?
Yes
- L. If K was coded “Other, explain or No”, please explain why.
- M. In your opinion, is this a pending PURL? Yes
1. Valid: Strong internal scientific validity; the findings appear to be true.
 2. Relevant: Relevant to the practice of family medicine.
 3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
 4. Applicability in medical setting.
 5. Immediacy of implementation
- N. Comments on your response for question M.