Title: Initiating antidepressant therapy? Try these 2 drugs first. *J Fam Pract*. 2009;58:365-369.

Potential PURL Review Form: Systematic reviews and meta-analyses

SECTION 1: IDENTIFYING INFORMATION

1. Citation	Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373:746-758.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/entrez/utils/fref.fcgi?PrId=3048&itool=AbstractPlus-def&uid=19185342&db=pubmed&url=http://linkinghub.elsevier.com/retrieve/pii/S0140-6736(09)60046-5
3. First date published study available to readers	January 28, 2009
4. PubMed ID	19185342
5. Nominated By	Josh Merok
6. Institutional Affiliation of Nominator	University of Chicago
7. Date Nominated	February 1, 2009
8. Identified Through	*Lancet*
9. PURLS Editor Reviewing Nominated Potential PURL	Bernard Ewigman
10. Nomination Decision Date	February 3, 2009
11. Potential PURL Review Form (PPRF) Type	Meta-analysis
12. Other comments, materials, or discussion	
13. Assigned Potential PURL Reviewer	Bernard Ewigman
14. Reviewer Affiliation	University of Chicago
15. Date Review Due	February 26, 2009
16. Abstract	**BACKGROUND:** Conventional meta-analyses have shown inconsistent results for efficacy of second-generation antidepressants. We therefore did a multiple-treatments meta-analysis, which accounts for both direct and indirect comparisons, to assess the effects of 12 new-generation antidepressants on major depression. **METHODS:** We systematically reviewed 117 randomised controlled trials (25,928 participants) from 1991 up to November 30, 2007, which compared any of the following antidepressants at therapeutic dose range for the acute treatment of unipolar major depression in adults: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine. The main outcomes were the proportion of patients who responded to or dropped out of the allocated treatment. Analysis was done on an intention-to-treat basis. **FINDINGS:** Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine (odds ratios [OR] 1.39, 1.33, 1.30, and 1.27, respectively), fluoxetine (1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (1.41, 1.35, 1.30, and 1.27, respectively), paroxetine (1.35, 1.30, 1.27, and 1.22,

respectively), and reboxetine (2.03, 1.95, 1.89, and 1.85, respectively). Reboxetine was significantly less efficacious than all the other antidepressants tested. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine. **INTERPRETATION:** Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost. FUNDING: None.

SECTION 2: CRITICAL APPRAISAL OF VALIDITY

1. What types of studies are included in this review?	RCTs
2. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.	What are the effects of 12 new-generation antidepressants on the acute phase treatment of major depression?
3. Study addresses an appropriate and clearly focused question.	Well covered
4. A description of the methodology used is included.	Well covered
5. The literature search is sufficiently rigorous to identify all the relevant studies.	Well covered
6. Study quality is assessed and taken into account.	Adequately addressed Comments: Quality is assessed only by selecting randomized designs with a minimum of follow-up and outcomes measures, reviewing concealed allocation and the status of blinding.
7. There are enough similarities between selected studies to make combining them reasonable.	Well covered
8. Are patient-oriented outcomes included? If yes, what are they?	Yes, patient response and acceptability.
9. Is funding a potential source of bias? If yes, what measures (if any) were taken to ensure scientific integrity?	Several authors have received funding from pharmaceutical companies. However, this meta-analysis selected studies in an objective manner, analyzed the findings systematically, and came to conclusions that would not necessarily be in the financial interest of pharmaceutical companies (eg, concluding that the generically available antidepressant sertraline is the most effective, best tolerated, and least expensive). We conclude that these authors were not

	influenced by their funding from pharmaceutical companies in this study.
10. To which patients might the findings apply? Include patients in the meta-analysis and other patients to whom the findings may be generalized.	Adults with major depression initiating monotherapy with a second-generation anti-depressant.
11. In what care settings might the findings apply, or not apply?	Primary care, psychiatry
12. To which clinicians or policy makers might the findings be relevant?	Family physicians, general internists, psychiatrists, nurse practitioners

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts

2. DynaMed citation/access date	Depression: treatment. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated June 4, 2009. Accessed June 5, 2009.
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Selection of initial therapy should be made on the basis of past response, consideration of side effect profiles, or cost. There is no systematic difference in efficacy.
4. UpToDate excerpts	
5. UpToDate citation/access date	Depression treatment In: Basow DS, ed. *UpToDate* [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. Accessed February 24, 2009.
6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)	There is no clear difference in efficacy of various antidepressants.
7. PEPID PCP excerpts	Is any single pharmacologic option for major depressive disorder superior to others? **Summary** 1. Different classes of antidepressant medication are likely to be equally effective for the treatment of major depression o Based on systematic reviews 2. Recent review found that: o Serotonin and noradrenaline reuptake inhibitor venlafaxine (Effexor) may be superior to selective serotonin reuptake inhibitors (SSRIs), but further study is needed to verify this finding

3. SOR: A, based on systematic reviews

Evidence

1. Systematic review of randomized controlled trials (RCTs) published in 2000 examined the efficacy and safety of newer versus older antidepressants (1)
   - Newer antidepressants included
     - SSRIs
     - Serotonin and noradrenaline reuptake inhibitors (eg, venlafaxine)
     - Norepinephrine reuptake inhibitors (eg, reboxetine)
     - Dopamine reuptake inhibitors (eg, bupropion)
   - Older antidepressants included
     - First- and second-generation tricyclics
     - Tetracyclic antidepressants
     - Trazodone
     - Monoamine oxidase inhibitors
   - Analysis included 150 RCTs involving 16,000 patients
2. Reviewers found no difference between newer and older antidepressants in achieving the primary efficacy outcome (50% reduction of depressive symptoms), with 54% of patients in both groups responding to treatment
   - Participants in the trials of newer antidepressants most commonly used SSRIs
     - Results showed that SSRIs were as effective as the other newer antidepressants
     - In 1 comparison, dropout rates were higher among patients using tricyclic antidepressants than among patients using SSRIs (16% vs 11%; absolute difference 5%; 95% CI, 2%-6%; number needed to treat [NNT]=5-50)
3. Recent systematic review compared the efficacy and safety of venlafaxine with that of SSRIs and other antidepressants (2)
   - Funded by the manufacturer of venlafaxine, study incorporated the findings of 32 RCTs comparing the use of venlafaxine with other antidepressants (tricyclics, SSRIs, trazodone, mirtazapine) for a mean of 10 weeks
   - Venlafaxine was more effective than SSRIs with respect to the outcome of clinical response
     - Defined as 50% reduction in depression scale rating at the end of each study
     - Pooled OR 1.26; 95% CI, 1.02-1.58; NNT=11-63
   - No difference in efficacy was noted between venlafaxine and the non-SSRI antidepressants in the review
   - Dropout rates for patients taking venlafaxine
     - Were not significantly different from those for patients taking other antidepressants
   - One reviewer of this report cautioned against generalizing these results

- Because of drug-manufacturer funding
- Possibility that patients enrolled in the RCTs may have previously had no response to SSRIs, and
- Failure to include quality-of-life measures (3)

4. Reviews have failed to demonstrate a consistent superiority of 1 class of antidepressant for treating major depressive illness
   - Possible improved efficacy of venlafaxine found in 1 review (3) will require further study to clarify the magnitude and clinical importance of this finding
   - Decision of which antidepressant to choose as initial therapy
     - Should be based on a discussion of potential side effects and cost
   - Despite the 50% response rate found in most reviews of antidepressant therapy
     - Failure to respond to 1 class does not necessarily predict failure to respond to a different drug class (4)

References

1. Williams JW Jr, Mulrow CD, Chiquette E, et al. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. *Ann Intern Med*. 2000;132:743-756.

2. Smith D, Dempster C, Glanville J, et al. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. *Br J Psychiatry*. 2002;180:396-404.

3. Simon GE. Review: venlafaxine is more effective than selective serotoninreuptake inhibitors for depression. *ACP J Club*. 2002;137:101.

4. Thase ME, Rush AJ, Howland RH, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Arch Gen Psychiatry*. 2002;59:233-239.

Originally published in the *Evidence-Based Practice* newsletter, August 2005.

8. PEPID citation/access data

PEPID Primary Care Plus. Psychiatry: Mood disorders, depression. Evidence-based inquiry: is any single pharmacologic option for major depressive disorder superior to others? http://www.pepidonline.com. Accessed February 24, 2009.

9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic?
Yes, there is important evidence or recommendations that are missing.

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review?
Yes, there is important evidence or recommendations that are missing.

If yes, which Evidence-Based Inquiry (HelpDesk Answer or Clinical Inquiry), Title(s):
Is any single pharmacologic option for major depressive disorder superior to others? Originally published as a HelpDesk Answer in *Evidence-Based Practice*, August 2005.

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

11. Citations for other excerpts	New Zealand Guidelines Group. Identification of common mental disorders and management of depression in primary care. Wellington, NZ: New Zealand Guidelines Group; July 2008. http://www.guideline.gov/summary/summary.aspx?doc_id=12994&nbr=006690&string=depression. Accessed February 24, 2009.
12. Bottom line recommendation or summary of evidence from other sources (1-2 sentences)	Where antidepressant therapy is planned, SSRIs are recommended as first-line treatment, but no particular SSRIs.

SECTION 4: CONCLUSIONS

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	2
2. If 4.1 was coded as 4, 5, 6, or 7, 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?	
3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	1
4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.	
5. Practice-changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)	1
6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.	Because sertraline more often results in a positive clinical response, is among the most acceptable in terms of discontinuation, and is available generically (and is therefore one of the least expensive agents), one practice change would be to consider sertraline as the drug of choice when starting monotherapy for moderate to severe major depression in adults. Exceptions would be prior positive response to another drug, adverse experience with sertraline, or other considerations based on individual preferences. Having this new evidence on effectiveness and acceptability is valuable and, if incorporated into decision making, could improve depression care significantly.
7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something	1

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, educating or counseling a patient; or creating a system for implementing an intervention? Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)	
8. If you coded 4.7 as a 4, 5, 6, or 7, please explain.	
9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market? Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)	1
10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.	
11. Clinical meaningful outcomes or patient-oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented? Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)	1
12. If you coded 4.11 as a 4, 5, 6, or 7, please explain why.	
13. In your opinion, is this a Pending PURL? Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL) Criteria for a Pending PURL: • Valid: Strong internal scientific validity; the findings appears to be true. • Relevant: Relevant to the practice of family medicine • 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. • Applicability in medical setting • Immediacy of implementation	2
14. Comments on your response in 4.13	This is by far the largest and most comprehensive meta-analysis (117 RCTs including ~26,000 patients) comparing the

effectiveness of 12 second-generation antidepressants, which are currently the most commonly used drugs for the initial monotherapy treatment of major depression in adults. The findings show sertraline (Zoloft) more often results in a positive clinical response, is among the most acceptable in terms of discontinuation, and because it is available generically, it is one of the least expensive. One practice change would be to consider sertraline as the drug of choice when starting monotherapy for major depression in adults. Exceptions would be prior positive response to another drug, adverse experience with sertraline, or other considerations based on individual preferences.

SECTION 5: EDITORIAL DECISIONS

1. FPIN PURLs editorial decision	Pending PURL
2. Follow-up issues for pending PURL Reviewer	
3. FPIN PURLS Editor making decision	Bernard Ewigman
4. Date of decision	February 26, 2009

5. Brief summary of decision

This is a well-done and large meta-analysis (117 RCTs and ~26,000 patients) comparing 12 second-generation antidepressants that was published electronically by *Lancet* in January 2009. We believe this is a practice changer.

Contrary to past evidence and current recommendations that all antidepressants have the same efficacy for treating major depression, this study demonstrates differences among these antidepressants in terms of patient response and acceptability when used as monotherapy during the initial phase of treating major depression (the first 8 weeks). Prior to this meta-analysis, no single study had a sufficient sample or number of comparison groups to answer the complex question of which antidepressant works best and has the greatest acceptance.

In favor of this being a practice changer (a PURL):
1. The task of choosing initial monotherapy is a common one in family medicine and primary care.
2. This meta-analysis has the statistical power and sufficient comparisons to draw some useful conclusions.
3. We believe it could alter the pattern of choices of antidepressants.

Against this being a practice changer:
1. The practice change itself is nuanced. Side effect profiles, coexisting illnesses, drug interactions, and cost would still be important factors. However, having this new evidence on effectiveness and acceptability is valuable and, if incorporated into decision making, could improve

depression care significantly.