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]

C. First date published study available to readers: 9/13/2017
D. PubMed ID: 28903922
E. Nominated By: Jim Stevermer
F. Institutional Affiliation of Nominator: University of Missouri
G. Date Nominated: 12/17/2017
H. Identified Through: POEMs
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 2/17/2018
K. Potential PURL Review Form (PPRF) Type: Systematic Review
L. Assigned Potential PURL Reviewer: Greg Castelli
M. Reviewer Affiliation: UPMC St. Margaret’s
N. Abstract: Objectives To examine the risk of relapse and time to relapse after discontinuation of antidepressants in patients with anxiety disorder who responded to antidepressants, and to explore whether relapse risk is related to type of anxiety disorder, type of antidepressant, mode of discontinuation, duration of treatment and follow-up, comorbidity, and allowance of psychotherapy. Design Systematic review and meta-analyses of relapse prevention trials. Data sources PubMed, Cochrane, Embase, and clinical trial registers (from inception to July 2016). Study selection Eligible studies included patients with anxiety disorder who responded to antidepressants, randomised patients double blind to either continuing antidepressants or switching to placebo, and compared relapse rates or time to relapse. Data extraction Two independent raters selected studies and extracted data. Random effect models were used to estimate odds ratios for relapse, hazard ratios for time to relapse, and relapse prevalence per group. The effect of various categorical and continuous variables was explored with subgroup analyses and meta-regression analyses respectively. Bias was assessed using the Cochrane tool. Results The meta-analysis included 28 studies (n=5233) examining relapse with a maximum follow-up of one year. Across studies, risk of bias was considered low. Discontinuation increased the odds of relapse compared with continuing antidepressants (summary odds ratio 3.11, 95% confidence interval 2.48 to 3.89). Subgroup analyses and meta-regression analyses showed no statistical significance. Time to relapse (n=3002) was shorter when antidepressants were discontinued (summary hazard ratio 3.63, 2.58 to 5.10; n=11 studies). Summary relapse prevalences were 36.4% (30.8% to 42.1%; n=28 studies) for the placebo group and 16.4% (12.6% to 20.1%; n=28 studies) for the antidepressant group, but

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prevalence varied considerably across studies, most likely owing to differences in the length of follow-up. Dropout was higher in the placebo group (summary odds ratio 1.31, 1.06 to 1.63; n=27 studies). Conclusions Up to one year of follow-up, discontinuation of antidepressant treatment results in higher relapse rates among responders compared with treatment continuation. The lack of evidence after a one year period should not be interpreted as explicit advice to discontinue antidepressants after one year. Given the chronicity of anxiety disorders, treatment should be directed by long term considerations, including relapse prevalence, side effects, and patients' preferences.

O. Pending PURL Review Date: 7/10/2018

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. What types of studies are included in this review?
Eligible studies included patients with anxiety disorder who responded to antidepressants, randomised patients double blind to either continuing antidepressants or switching to placebo, and compared relapse rates or time to relapse.

B. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.
We meta-analysed relapse prevention trials that included patients with anxiety disorder, obsessive-compulsive disorder, or post-traumatic stress disorder (PTSD) who responded to antidepressants, randomised these patients in a double blind fashion to either continuing the antidepressant or switching to placebo, assessed the prevalence of relapse per treatment group, and compared the risk of relapse or time to relapse between these groups.

C. Study addresses an appropriate and clearly focused question. Adequately addressed
Comments: Not clearly expressed other than in the title.

D. A description of the methodology used is included. Well covered
Comments: Yes. In-depth description about where articles were searched for and utilized a librarian for help with the search. Two independent reviewers assessed the trials for inclusion and bias.

E. The literature is sufficiently rigorous to identify all the relevant studies. Well covered
Comments: Reviewed from several databases.

F. Study quality is assessed and taken into account. Well covered
Comments: Study selection criteria consisted of the following. (1) Studies focused on patients with panic disorder, agoraphobia, social phobia, generalised anxiety disorder, obsessive-compulsive disorder, PTSD, or specific phobia; comorbidity was allowed. (2) Patients were classified as responders after treatment with antidepressants; studies focusing on drug treatment while allowing concomitant psychotherapy were included. (3) A double blind, placebo controlled design was used, randomising patients to long term use of antidepressants (antidepressant group) or switching to placebo (placebo group). (4) Relapse and/or time to relapse were assessed after a follow-up period. (5) Articles not presenting original data or consisting of only abstracts were excluded. We used the definitions of response and relapse as used in the original studies.
G. There are enough similarities between selected studies to make combining them reasonable. Well covered
Comments: Yes many of the I2 test for heterogeneity were mostly less than 50%.

H. Are patient oriented outcomes included? If yes, what are they?
Yes, OR for relapse of depression is a POEM.

I. Are adverse effects addressed? If so, how would they affect recommendations?
Yes, but Data on tolerability and withdrawal symptoms were limited and non-systematic in the studies included, not allowing a meta-analysis.

J. Is funding a potential source of bias? If yes, what measures (if any) were taken to ensure scientific integrity?
No funding source.

K. To which patients might the findings apply? Include patients in the metaanalysis and other patients to whom the findings may be generalized.
We meta-analysed relapse prevention trials that included patients with anxiety disorder, obsessive-compulsive disorder, or post-traumatic stress disorder (PTSD) who responded to antidepressants, randomised these patients in a double blind fashion to either continuing the antidepressant or switching to placebo, assessed the prevalence of relapse per treatment group, and compared the risk of relapse or time to relapse between these groups. Additionally, we explored whether this relapse risk is related to the type of anxiety disorder, type of antidepressant, mode of discontinuation, duration of previous treatment, duration of follow-up, whether studies allowed concurrent psychotherapy, whether studies excluded comorbidity, and involvement of drug companies. Finally, we briefly report on tolerability, given the importance for daily clinical practice.

L. In what care settings might the findings apply, or not apply?
Not discussed separately, but likely can apply to inpatient and outpatient use of antidepressants.

M. To which clinicians or policy makers might the findings be relevant?
Many including family medicine clinicians.

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 from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

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: http://www.uptodate.com. {Insert
 date modified if given.) Accesses February 12, 2009. [whatever date PPRF reviewer did their search.]

For DynaMed, use the following style:

A. DynaMed excerpts


No information on GAD.

OCD

continuing therapy with selective serotonin reuptake inhibitor antidepressants associated with relapse reduction in patients with anxiety disorders including obsessive compulsive disorder (level 2 [mid-level] evidence)

- based on systematic review with assessment of trial quality not reported
- systematic review of 22 randomized trials evaluating continuing antidepressant treatment for relapse prevention in 4,121 patients with anxiety disorders included 6 trials evaluating patients with obsessive compulsive disorder
- for OCD, relapse defined as ≥ 5-point increase in Yale-Brown Obsessive-Compulsive Scale (or increase to ≥ 20 or return to baseline), and/or ≥ 1-point increase in Clinical Global Impressions scale (or increase to ≥ 5–6)
- continuing therapy associated with reduced relapse in patients with OCD in analysis of 6 trials with 951 patients
  - odds ratio 0.38 (95% CI 0.29-0.51)
  - NNT 4-7 with 41.6% relapse rate in controls
- Reference - J Affect Disord 2010 Jun;123(1-3):9

PTSD

continued antidepressant treatment in patients who responded to treatment associated with lower risk of PTSD relapse(level 2 [mid-level] evidence)

- based on systematic review with assessment of trial quality not reported
- systematic review of 22 randomized trials of adults with anxiety disorders assessing rate of relapse after continued antidepressant treatment vs. placebo
- 3 trials with 272 patients assessed relapse in adults with PTSD who responded (according to individual study) to 12-36-week treatment with selective serotonin reuptake inhibitors (SSRIs)
- continued antidepressant treatment compared with placebo associated with lower risk of PTSD relapse in pooled analysis
  - risk ratio 0.35 (95% CI 0.19-0.62)
  - NNT 5-10 with 27% relapse with placebo
- Reference - J Affect Disord 2010 Jun;123(1-3):9

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

Information from OCD and PTSD but not GAD.

C. UpToDate excerpts

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**OCD**  
**Duration of treatment** — Although clinical trials of current medications for OCD are mostly short-term, extended trials of SSRIs and clomipramine, which randomly assigned drug responders to continued medication treatment or to placebo, have generally found that patients who continue medication have a lower rate of relapse than patients on placebo [21, 29-32]. Relapse rates have varied widely, in part due to methodological differences among studies. As a result, American Psychiatric Association practice guidelines suggest that OCD patients who respond to an adequate trial of a serotonergic antidepressant should stay on that medication for at least one to two years [19]. However, this needs further study. If the medication is discontinued, American Psychiatric Association practice guidelines recommend that it should be slowly tapered (eg, 10 to 25 percent every one to two months).

**PTSD**  
**DURATION OF TREATMENT** — If effective, oral medication should be continued for at least six months to a year to prevent relapse or recurrence. A clinical trial randomly assigned 96 patients with PTSD who had completed 12 weeks of acute treatment with sertraline to either 28 weeks of maintenance treatment with sertraline or to placebo. Patients who continued sertraline were less likely to relapse than patients receiving placebo (5 versus 26 percent) [34].

**GAD**  
**Robust response** — If the patient experiences a robust response to an SRI or other medications, the treatment should be continued for at least 12 months [33]. If the patient experiences a relapse following termination of an effective medication, the medication can be resumed and the length of treatment extended. After two relapses when tapering off the medication, ongoing maintenance treatment should be considered. (See "Pharmacotherapy for generalized anxiety disorder in adults", section on 'Duration of pharmacotherapy'.)

**D. UpToDate citation**

**GAD**  

**PTSD**  

**OCD**  

**E. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)**  
Generally, relapse is reduced when medication is continued.

**F. Other excerpts (USPSTF; other guidelines; etc.)**
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? 1 (extremely well)

B. If A was coded 2 or 3, 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?

Authors did a great job minimizing bias. The only consideration is that of any meta-analysis. You are evaluating the trial and not the individual patients in each trial. 10 of the 28 trials did not show a different. Are there certain patient populations who would not benefit from continued therapy?

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? 1 (extremely well)

D. If C was coded 2 or 3, 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? 2 (uncertain)

F. If E was coded as 1, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

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? 1 (definitely could be done in a medical care setting)
H. If G was coded as a 2 or 3, please explain.

I. **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?  1 (definitely could be immediately applied)

J. If I was coded 2 or 3, please explain why.

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?  1 (definitely clinically meaningful or patient oriented)

L. If K was coded 2 or 3, please explain why.

M. In your opinion, is this a pending PURL?  2 (uncertain)
   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.

Overall I think this is a good study. Covered POEM data and is a very relevant topic. Sometimes when the trial is too statistical in nature, it can detract from the results. However, this is likely a pending PURL.