**Metaanalysis – Systematic Review**

**Potential PURL Review Form**

**PURL Jam Version**

**Version #12 Sept 21, 2010**

**Consider these medications to help patients stay sober**

***J Fam Pract*. 2015;64:238-240.**

**PURLs Surveillance System**

**Family Physicians Inquiries Network**

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| **SECTION 1: Identifying Information for Nominated Potential PURL** **[to be completed by PURLs Project Manager]** |
| **1.** Citation  | Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA*. 2014 May 14;311(18):1889-900. doi: 10.1001/jama.2014.3628. Review. PubMed PMID: 24825644. |
| **2.** Hypertext link to PDF of full article  | http://www.ncbi.nlm.nih.gov/pubmed/24825644?dopt=Abstract |
| **3.** First date published study available to readers  | 5/14/14 |
| **4.** PubMed ID  | 24825644 |
| **5.** Nominated By  | Other Other: Anne Mounsey |
| **6.** Institutional Affiliation of Nominator  | University of North Carolina Other:  |
| **7.** Date Nominated | 5/30/14 |
| **8.** Identified Through  | Other Other: TOC |
| **9.** PURLS Editor Reviewing Nominated Potential PURL | Kate Rowland |
| **10.** Nomination Decision Date  | 6/12/14 |
| **11.** Potential PURL Review Form (PPRF) Type  | Meta-analysis |
| **12.** Other comments, materials or discussion  |  |
| **13.** Assigned Potential PURL Reviewer  | Anne Mounsey, MD |
| **14.** Reviewer Affiliation  | Other Other: UNC |
| **15.** Date Review Due  |  |
| **16.** Abstract  | IMPORTANCE:Alcohol use disorders cause substantial morbidity and early mortality yet remain greatly undertreated. Medications are considerably underused.OBJECTIVE:To conduct a systematic review and meta-analysis of the benefits and harms of medications (US Food and Drug Administration [FDA]-approved and others) for adults with alcohol use disorders.DATA SOURCES:PubMed, Cochrane Library, PsycINFO, CINAHL, EMBASE, FDA website, and clinical trials registries (January 1, 1970-March 1, 2014).STUDY SELECTION:Two reviewers selected randomized clinical trials (RCTs) with at least 12 weeks' duration that reported eligible outcomes and head-to-head prospective cohort studies reporting health outcomes or harms.DATA EXTRACTION AND SYNTHESIS:We conducted meta-analyses using random-effects models and calculated numbers needed to treat for benefit (NNTs) or harm (NNHs).MAIN OUTCOMES AND MEASURES:Alcohol consumption, motor vehicle crashes, injuries, quality of life, function, mortality, and harms.RESULTS:We included 122 RCTs and 1 cohort study (total 22,803 participants). Most assessed acamprosate (27 studies, n=7519), naltrexone (53 studies, n=9140), or both. The NNT to prevent return to any drinking for acamprosate was 12 (95% CI, 8-26; risk difference [RD], -0.09; 95% CI, -0.14 to -0.04) and was 20 (95% CI, 11-500; RD, -0.05; 95% CI, -0.10 to -0.002) for oral naltrexone (50 mg/d). The NNT to prevent return to heavy drinking was 12 (95% CI, 8-26; RD -0.09; 95% CI, -0.13 to -0.04) for oral naltrexone (50 mg/d). Meta-analyses of trials comparing acamprosate to naltrexone found no statistically significant difference between them for return to any drinking (RD, 0.02; 95% CI, -0.03 to 0.08) or heavy drinking (RD, 0.01; 95% CI, -0.05 to 0.06). For injectable naltrexone, meta-analyses found no association with return to any drinking (RD, -0.04; 95% CI, -0.10 to 0.03) or heavy drinking (RD, -0.01; 95% CI, -0.14 to 0.13) but found an association with reduction in heavy drinking days (weighted mean difference [WMD], -4.6%; 95% CI, -8.5% to -0.56%). Among medications used off-label, moderate evidence supports an association with improvement in some consumption outcomes for nalmefene (heavy drinking days per month: WMD, -2.0; 95% CI, -3.0 to -1.0; drinks per drinking day: WMD, -1.02; 95% CI, -1.77 to -0.28) and topiramate (% heavy drinking days: WMD, -9.0%; 95% CI, -15.3% to -2.7%; drinks per drinking day: WMD, -1.0; 95% CI, -1.6 to -0.48). For naltrexone and nalmefene, NNHs for withdrawal from trials due to adverse events were 48 (95% CI, 30-112) and 12 (95% CI, 7-50), respectively; risk was not significantly increased for acamprosate or topiramate.CONCLUSIONS AND RELEVANCE:Both acamprosate and oral naltrexone were associated with reduction in return to drinking. When directly compared with one another, no significant differences were found between acamprosate and naltrexone for controlling alcohol consumption. Factors such as dosing frequency, potential adverse events, and availability of treatments may guide medication choice. |
| **17.** Pending PURL Review Date |  |
| **sECTION 2: Critical Appraisal of Validity****[to be completed by the Potential PURL Reviewer]** |
| **1.** What types of studies are included in this review? | RCT Other: 1 cohort study |
| **2.** What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses. | Risks and benefits of medications for alcohol disuse disorders |
| **3.** Study addresses an appropriate and clearly focused question - ***select one*** | [x]  Well covered [ ]  Not addressed[ ]  Adequately addressed [ ]  Not reported[ ]  Poorly addressed [ ]  Not applicableComments:  |
| **4.** A description of the methodology used is included. | [x]  Well covered [ ]  Not addressed[ ]  Adequately addressed [ ]  Not reported[ ]  Poorly addressed [ ]  Not applicableComments:  |
| **5.** The literature search is sufficiently rigorous to identify all the relevant studies. | [x]  Well covered [ ]  Not addressed[ ]  Adequately addressed [ ]  Not reported[ ]  Poorly addressed [ ]  Not applicableComments:  |
| **6.** Study quality is assessed and taken into account. | [x]  Well covered [ ]  Not addressed[ ]  Adequately addressed [ ]  Not reported[ ]  Poorly addressed [ ]  Not applicableComments:  |
| **7.** There are enough similarities between selected studies to make combining them reasonable. | [x]  Well covered [ ]  Not addressed[ ]  Adequately addressed [ ]  Not reported[ ]  Poorly addressed [ ]  Not applicableComments: marked heterogeneity in acamproste studies, none in naltrexone 100 mg but moderate in naltrexone 50 mg |
| **8.** Are patient oriented outcomes included? If yes, what are they? | Yes, return to any drinking and heavy drinking (≥4/d for women and 5/d for men) |
| **9.** Are adverse effects addressed? If so, how would they affect recommendations? | No statistical difference in specific adverse events although point estimated favored placebo. Patients treated with naltrexone had a higher rate of withdrawal due to adverse events. NNH 48; 95% CI, 30-112 in 17 trials.Patients treated with acamprosate had a higher risk of anxiety NNH 7, diarrhea NNH 11, and vomiting HHN 42.Naltrexone NNH dizziness 16, nausea 9, and vomiting 24. |
| **10.** Is funding a potential source of bias? If yes, what measures (if any) were taken to insure scientific integrity?  | No |
| **11.** To which patients might the findings apply? Include patients in the meta-analysis and other patients to whom the findings may be generalized. | Patients with moderate to sever alcohol use disorder. Mean age 40 years. Effect unknown in older or younger subgroups, racial or ethnic minorities. Only 2 of the 122 studies were done in primary care settings so applicability cannot be assumed. Authors make the point that these treatments are under utilized and many patients do not have access to specialized treatment centers. |
| **12.** In what care settings might the findings apply, or not apply? | Inpatients and treatment programs. Patients recruited through advertisements. Most patients had abstained for a few days. |
| **13.** To which clinicians or policy makers might the findings be relevant? | Psychiatrists, primary care physicians, hospitalists. |
| **SECTION 3: Review of Secondary Literature****[to be completed by the Potential PURL Reviewer]** |
| **Citation Instructions** | For UpTo Date citations, use style modified from <http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite> & AMA style. Always use Basow DS as 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 dated 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: <http://www.DynamicMedical.com>. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date} |
| **1.** DynaMed excerpts |  |
| **2.** DynaMed citation/access date | Title. Author. In: DynaMed [database online]. Available at: [www.DynamicMedical.com](http://www.DynamicMedical.com) Last updated:. Accessed  |
| **3.**  Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences) |  |
| **4.** UpToDate excerpts |  |
| **5.** UpToDate citation/access date | Always use Basow DS as editor & current year as publication year.Title. Pharmacotherapy for alcohol abuse disorder. Author. Johnson, Bankole In: UpToDate [database online]. Available at: <http://www.uptodate.com>. Last updated: Feb 2014. Accessed 7/30/14 |
| **6.**  Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences) | For patients taking medication, we suggest naltrexone for most patients with alcohol use disorder over other medications (Grade 2B). Depot naltrexone should be used when there is a significant risk of nonadherence with daily administration; patients should be monitored for injection site reactions. Naltrexone is not appropriate for patients with liver disease or who are taking opioids. (See 'First-line medications' above.)* For pharmacotherapy of an alcohol use disorder in patients with acute hepatitis, liver enzymes greater than three to five times normal, or liver failure, we suggest acamprosate over other medications (Grade 2C). Baclofen would be a reasonable alternative. The evidence for the efficacy of acamprosate is mixed. Its use may be considered for individuals with liver disease or those who do not respond to other medications.
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| **7.** PEPID PCP excerpts[www.pepidonline.com](http://www.pepidonline.com)username: fpinauthorpw: pepidpcp | 1. Role is to reduce relapses in patients with alcohol dependency* Naltrexone
* Opioid receptor antagonist
* Reduces craving to drink
* Improves resistance to thoughts about drinking
* Nalmefene
* Newer opioid antagonist
* Same profile as naltrexone
* No dose-dependent liver toxicity
* Disulfiram (Antabuse)
* Used as a deterrent to drinking
* Causes painful symptoms if alcohol consumed
* Mixed results in studies
* Acamprosate
* Structural analog of gamma-aminobutyric acid (GABA)
* Shown to reduce relapse rate in alcohol dependent individuals
* Topiramate
* Mixed outcomes in studies
* Baclofen, lithium & St. John's wort
* Appear to modify drinking behavior
* Still under investigation
 |
| **8.** PEPID citation/access data | Author. Title. Alcohol Abuse:treatment In: PEPID [database online]. Available at: <http://www.pepidonline.com>. Last updated: July 2013. Accessed 7/28/14 |
| **9.** PEPID content updating | 1. Do you recommend that PEPID get updated on this topic?[x]  Yes, there is important evidence or recommendations that are missing[ ]  No, this topic is current, accurate and up to date.If yes, which PEPID Topic, Title(s): 2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon () that should be updated on the basis of the review?[x]  Yes, there is important evidence or recommendations that are missing[ ]  No, this topic is current, accurate and up to date.If yes, which Evidence Based Inquiry (HelpDesk Answer or Clinical Inquiry), Title(s): How effective are pharmacological agents for alcoholism? 2002 |
| **10.** Other excerpts (USPSTF; other guidelines; etc.) |  |
| **11.** Citations for other excerpts |  |
| **12.**  Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences) | Naltrexone and acamprosate recommended but not compared. |
| **SECTION 4: Conclusions** **[to be completed by the Potential PURL Reviewer]** **[to be revised by the Pending PURL Reviewer as needed]** |
| **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)[x] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7  |
| **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)[x] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7  |
| **4.** If 4.3 was coded as 4, 5, 6, or 7,lease 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 [ ] 2 [x] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7  |
| **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. |  |
| 1. **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, 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) [ ] 1 [x] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7  |
| **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) [x] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7  |
| **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) [x] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7  |
| **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? 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
 | Give one number on a scale of 1 to 7(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL) [ ] 1 [ ] 2 [x] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7  |
| **14.** Comments on your response in 4.13 | Unsure how many family physicians are currently using naltrexone to decrease return to drinking. |