TITLE: Long-term Use of Acamprosate Calcium for Alcoholism: A Review of the Clinical Effectiveness, Safety, and Guidelines

DATE: 29 May 2015

CONTEXT AND POLICY ISSUES

Alcoholism or alcohol dependence is a chronic and often progressive disease with genetic, psychosocial, and environmental factors influencing its development and manifestation.\(^{1,2}\) It is a major public health problem impacting individuals, their families and society. The worldwide annual estimate of deaths attributed to alcoholism is 2.5 million, which represents approximately 4% of all mortality.\(^{3}\) It was estimated in 2012, that 3.2% of the population in Canada of age 15 years or older, abused or were dependent on alcohol.\(^{4}\) The major challenge in management of alcohol dependence is maintenance of abstinence after detoxification and prevention of relapse.\(^{5}\) Treatment for alcohol dependence includes psychotherapy and pharmacotherapy. Acamprosate is one of the drugs used for treatment of individuals with alcohol dependence.

Acamprosate, or N-acetyl homotaurine appears to modulate the N-methyl-D-aspartate (NMDA) receptor.\(^{6}\) During alcohol withdrawal there is an increased influx of calcium through the NMDA receptors and acamprosate appears to inhibit the calcium influx and thereby restore the balance between inhibitory and excitatory neurotransmitters.\(^{7}\) Its exact mechanism of action is however still unclear.\(^{6,7}\) Systematic reviews have shown that, generally, acamprosate was an effective treatment for supporting abstinence after detoxification in adults with alcohol dependence.\(^{6-9}\) The most common adverse event associated with acamprosate was transient diarrhea but acamprosate was generally considered to be well tolerated and safe.\(^{10,11}\) The long term effectiveness of acamprosate is unclear as the durations of acamprosate use were ≤ 1 year in the studies included in these systematic reviews.

The purpose of this report is to review the available evidence on the clinical effectiveness and safety for long term (> 1 year) use of acamprosate to treat adults with alcoholism and to review evidence-based guidelines on the use of acamprosate for treating alcoholism.
RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of long-term (> 1 year) acamprosate calcium use for adults with alcoholism?

2. What are the evidence-based guidelines regarding the use of acamprosate calcium for the treatment of alcoholism?

KEY FINDINGS

No relevant studies were identified on the clinical effectiveness and safety of long-term (> 1 year) acamprosate use for adults with alcoholism.

Three evidence-based guidelines recommended that acamprosate be initiated in individuals with alcoholism after assisted withdrawal and in combination with psychological or psychosocial therapy but do not provide recommendations regarding use beyond one year.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, MEDLINE, Embase, PsycINFO, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2005 and April 28, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

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<th>Table 1: Selection Criteria</th>
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<tr>
<td><strong>Population</strong></td>
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<td><strong>Intervention</strong></td>
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<td><strong>Comparator</strong></td>
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<td><strong>Outcomes</strong></td>
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<td><strong>Study Designs</strong></td>
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Long-term Use of Acamprosate Calcium
Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 2005. Guidelines were excluded, if the methodology used was unclear.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AGREE II checklist\(^\text{12}\) was used for appraising the guidelines.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 515 citations were identified in the literature search. Following screening of titles and abstracts, 469 citations were excluded and 46 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these 49 potentially relevant articles, 46 publications were excluded for various reasons, while three publications\(^\text{13-15}\) met the inclusion criteria and were included in this report. These three publications\(^\text{13-15}\) were evidence-based guidelines. No relevant HTAs, SRs, RCTs or NRSs were identified. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included guidelines are summarized below and details are provided in Appendix 2.

Guidelines

Three relevant evidence-based guidelines\(^\text{13-15}\) were identified. One guideline\(^\text{15}\) was specifically on alcohol use disorders whereas the other two guidelines\(^\text{13,14}\) were on substance use disorders and included a section on alcohol use disorder. The National Institute for Health and Clinical Excellence (NICE) guideline\(^\text{15}\) on alcohol-use disorders was published in 2011 from the United Kingdom (UK). The Department of Veterans Affairs and Department of Defense (VA/DoD) guideline\(^\text{16}\) on substance use disorders was published in 2009 from United States of America (USA). The American Psychiatric Association (APA) guideline\(^\text{13}\) for substance use disorders was published in 2006 from USA.

Summary of Critical Appraisal

The strength and limitations of the included guidelines are summarized below and details are provided in Appendix 3.

Three relevant evidence-based guidelines\(^\text{13-15}\) were identified. Overall the guidelines were of good quality. For all three guidelines the scope was clearly stated, the guideline development
group comprised of individuals with relevant expertise such as psychiatrists and academics, the
guideline development process included a systematic literature search, external review of the
draft and a process for updating the guideline and the recommendations were clearly stated.
The methodology for selection of studies retrieved from the literature search was unclear in the
guidelines. In all three guidelines,\textsuperscript{13-15} it was unclear if patient input was sought, however one\textsuperscript{15} of
these guidelines included a lay person and a carer representative in the guideline development
group. Implementation issues were not described. Cost implications were considered in one
guideline\textsuperscript{15} but did not appear to be considered in two guidelines.\textsuperscript{13,14} In one guideline\textsuperscript{15} the level
of evidence and the recommendation category for the specific recommendation were not
explicitly stated however it was mentioned that the GRADE method was used. In the second
guideline\textsuperscript{14} the level of evidence was not explicitly stated and the category of recommendation
was sometimes stated however a process for grading was in place. In the third guideline\textsuperscript{13} the
category of recommendation was stated but the level of evidence was not explicitly stated. Of
the three guidelines, in two\textsuperscript{13,15} it was mentioned that the guideline development group members
were required to provide disclosures of conflict of interest and in one guideline\textsuperscript{14} it was unclear.

**Summary of Findings**

The findings are summarized below and the details are provided in Appendix 4.

**What is the clinical effectiveness of and safety of long-term (> 1 year) acamprosate calcium use
for adults with alcoholism?**

No HTAs, SRs, RCTs or NRSs were identified on the clinical effectiveness of and safety of long-
term (> 1 year) acamprosate use for adults with alcoholism.

**What are the evidence-based guidelines regarding the use of acamprosate calcium for the
treatment of alcoholism?**

Three relevant evidence based guidelines\textsuperscript{13-15} were identified. The NICE guidelines\textsuperscript{15} provided
some recommendations for treatment with acamprosate for individuals with alcohol
dependence. It was recommended that after successful withdrawal, acamprosate or oral
naltrexone in combination with individual psychological interventions or behavioural couples
therapy in case of individuals with partners, should be considered. If acamprosate is used, it
was recommended to be started as soon as possible after assisted withdrawal. The
recommended daily dose of acamprosate was 1998 mg for individuals with weight $\geq 60$ kg and a
maximum daily dose of 1,332 mg for individuals with weight < 60 kg. It was to be prescribed for
up to six months, or longer for those benefiting from it and who were willing to continue. It was
recommended that acamprosate be stopped if drinking persists for four to six months after
starting the drug.

The VA/DoD guidelines\textsuperscript{14} stated that treatment with acamprosate should be considered for
patients with alcohol dependence, be initiated after abstinence, and be combined with
psychosocial therapy. The APA guidelines\textsuperscript{13} stated that acamprosate may reduce alcohol
craving in abstinent individuals and may also be used as an effective adjunct together with
psychosocial treatment in motivated individuals.

In summary, the guidelines recommend that acamprosate be initiated in individuals with
alcoholism after assisted withdrawal and in combination with psychological or psychosocial
therapy. There was no recommendation regarding the maximum duration of acamprosate use.
Limitations

No HTAs, SRs, RCTs or NRSs on the long term (> 1 year) clinical effectiveness and safety of acamprosate for the treatment of alcoholism were identified.

No guideline on long term (> 1 year) use of acamprosate for treating adults with alcoholism was identified

No Canadian evidence-based guideline was identified but the recommendations from the guidelines published from UK and USA are likely to apply for individuals with alcoholism in Canada.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No relevant studies were identified on the clinical effectiveness and safety of long-term (> 1 year) acamprosate use for adults with alcoholism. The evidence-based guidelines recommend that acamprosate be initiated in individuals with alcoholism after assisted withdrawal and in combination with psychological or psychosocial therapy, but do not provide recommendations regarding use beyond one year.

PREPARED BY:
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REFERENCES


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations: Assessment, Development and Evaluation</td>
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<td>HTA</td>
<td>Health Technology Assessment</td>
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<td>MA</td>
<td>Meta-analysis</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>NRS</td>
<td>non-randomized study</td>
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<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<td>SR</td>
<td>Systematic review</td>
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<td>UK</td>
<td>United Kingdom</td>
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<td>USA</td>
<td>United States of America</td>
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<td>VA/DoD</td>
<td>Veterans Affairs/ Department of Defense</td>
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APPENDIX 1: Selection of Included Studies

515 citations identified from electronic literature search and screened

469 citations excluded

46 potentially relevant articles retrieved for scrutiny (full text, if available)

3 potentially relevant reports retrieved from other sources (grey literature, hand search)

49 potentially relevant reports

46 reports excluded:
- irrelevant treatment duration (33)
- guidelines with no specific recommendation regarding acamprosate (4)
- non-english article (1)
- other (review article, commentary) (8)

3 reports included in review
### APPENDIX 2: Grading of Recommendations and Levels of Evidence

<table>
<thead>
<tr>
<th>Guideline Society, Country, Year</th>
<th>Recommendation grade</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE, UK, 2011</td>
<td>Guidelines were drafted based on the clinical summaries and GRADE profiles</td>
<td></td>
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<tr>
<td>VA/DoD, USA, 2009</td>
<td><strong>A</strong>: “A strong recommendation that the clinicians provide the intervention to eligible patients. Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.” P.96</td>
<td>I: “At least one properly done RCT” P.95</td>
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<td><strong>B</strong>: “A recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.” P.96</td>
<td>II-1: “Well-designed controlled trial without randomization” P. 95</td>
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<td></td>
<td><strong>C</strong>: “No recommendation for or against the routine provision of the intervention is made. At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.” P.96</td>
<td>II-2: “Well-designed cohort or case-control analytic study, preferably from more than one source” P. 95</td>
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<td><strong>D</strong>: “Recommendation is made against routinely providing the intervention to asymptomatic patients. At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.” P.96</td>
<td>II-3: “Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment” P.95</td>
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<td></td>
<td><strong>I</strong>: “The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.” P.96</td>
<td>III: “Opinion of respected authorities, descriptive studies, case reports, and expert committees” P.95</td>
</tr>
<tr>
<td>APA, USA, 2006</td>
<td>Level 1: “Recommended with substantial clinical confidence.” P. 9 Level II: “Recommended with”</td>
<td>“[A] Randomized, double-blind clinical trial. A study of an intervention in which subjects are prospectively followed over time; there</td>
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<tr>
<td>Guideline Society, Country, Year</td>
<td>Recommendation grade</td>
<td>Level of Evidence</td>
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<td></td>
<td>moderate clinical confidence.&quot; P. 9</td>
<td>are treatment and control groups; subjects are randomly assigned to the two groups; and both the subjects and the investigators are “blind” to the assignments.</td>
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<td></td>
<td>Level III: “May be recommended on the basis of individual circumstances.&quot; P. 9</td>
<td>[A–] Randomized clinical trial. Same as above but not double blind.</td>
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<td></td>
<td></td>
<td>[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial.</td>
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<tr>
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<td></td>
<td>[C] Cohort or longitudinal study. A study in which subjects are prospectively followed over time without any specific intervention.</td>
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<td>[D] Control study. A study in which a group of patients and a group of control subjects are identified in the present and information about them is pursued retrospectively or backward in time.</td>
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<td>[E] Review with secondary data analysis. A structured analytic review of existing data, e.g., a meta-analysis or a decision analysis.</td>
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<td>[F] Review. A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.</td>
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<td>[G] Other. Opinion-like essays, case reports, and other reports not categorized above.&quot; P. 3 of Practice Guideline development Process</td>
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## APPENDIX 3: Summary of Strengths and Limitations

<table>
<thead>
<tr>
<th>Guideline Society, Country, Year</th>
<th>Strengths</th>
<th>Limitations</th>
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| **NICE,¹³ UK, 2011**             | • The scope was clearly stated.  
• The guideline development group comprised of individuals from relevant areas such as clinical psychologist, psychiatrist, nurse specialist, academics, health economist, lay person, and carer representative  
• Guideline development method was systematic. Literature search methods, criteria for selecting evidence, strength and limitations were described. The guideline draft was externally reviewed. A process for updating the guideline was in place  
• Cost implications and implementation issues were considered  
• Recommendations were clear  
• Disclosure statements from all committee members had been received | • Unclear if patient input was sought but the guideline development group included a lay person and a carer representative  
• The recommendation category and level of evidence for the specific recommendation was not explicitly stated however it was mentioned that the GRADE system was used |
| **VA/DoD,¹⁴ USA, 2009**           | • The scope was clearly stated.  
• The guideline development group comprised of individuals from relevant areas such as psychiatrists, clinical pharmacist, and academics  
• Guideline development method was systematic. Literature search methods, criteria for selecting evidence, strength and limitations were described. The guideline draft was externally reviewed. The guidelines were to be updated whenever possible.  
• Recommendations were clear | • Unclear if patient input was sought  
• Cost implications were not discussed.  
• The recommendation category was stated sometimes and the level of evidence for the specific recommendation was not explicitly stated however a process for grading recommendations was in place.  
• Unclear if disclosure statements from all committee members had been received |
| **APA,¹³ USA, 2006**             | • The scope was clearly stated.  
• The guideline development group comprised of individuals from relevant areas such as psychiatrists, and academics  
• Guideline development method was systematic. Literature search | • Unclear if patient input was sought  
• Cost implications were not discussed.  
• The level of evidence for the specific recommendation was not explicitly stated however the |
<table>
<thead>
<tr>
<th>Guideline Society, Country, Year</th>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td></td>
<td>methods, criteria for selecting evidence, strength and limitations were described but not in detail. The guideline draft was externally reviewed. A process for updating the guideline was in place. Recommendations were clear. Guideline development group members were required to disclose conflict of interest.</td>
<td>category of the recommendation was stated</td>
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APA = American Psychiatric Association, NICE = National Institute for Health and Clinical Excellence, UK = United Kingdom, USA = United States of America, VA/DoD = Veterans Affairs/ Department of Defense,
APPENDIX 4: Guidelines and Recommendations

<table>
<thead>
<tr>
<th>Guideline Society, Country, Year</th>
<th>Recommendations</th>
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<tr>
<td>NICE, UK, 2011</td>
<td>“For harmful drinkers and people with mild alcohol dependence who have not responded to psychological interventions alone, or who have specifically requested a pharmacological intervention, consider offering acamprosate[63] or oral naltrexone[64] in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) or behavioural couples therapy” P.451</td>
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“After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone[71] in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) focused specifically on alcohol misuse” P. 454

“After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with behavioural couples therapy to service users who have a regular partner and whose partner is willing to participate in treatment” P.454

“Before starting treatment with acamprosate, oral naltrexone[73] or disulfiram, conduct a comprehensive medical assessment (baseline urea and electrolytes and liver function tests including gamma glutamyl transferase [GGT]). In particular, consider any contraindications or cautions (see the SPC), and discuss these with the service user.” P. 455

“If using acamprosate, start treatment as soon as possible after assisted withdrawal. Usually prescribe at a dose of 1,998 mg (666 mg three times a day) unless the service user weighs less than 60 kg, and then a maximum of 1,332 mg should be prescribed per day. Acamprosate should:
● usually be prescribed for up to 6 months, or longer for those benefiting from the drug who want to continue with it[74]
● be stopped if drinking persists 4–6 weeks after starting the drug.” P.455

“Service users taking acamprosate should stay under supervision, at least monthly, for 6 months, and at reduced but regular intervals if the drug is continued after 6 months. Do not use blood tests routinely, but consider them to monitor for recovery of liver function and as a motivational aid for service users to show improvement.” P.455

("[63] Note that the evidence for acamprosate in the treatment of harmful drinkers and people who are mildly alcohol dependent is less robust than that for naltrexone. At the time of publication of the NICE guideline (February 2011), acamprosate did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

[64] At the time of publication of the NICE guideline (February 2011), oral naltrexone did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

[71] At the time of publication of the NICE guideline (February 2011), oral naltrexone did..."
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<th>Guideline Society, Country, Year</th>
<th>Recommendations</th>
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<td></td>
<td>not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.</td>
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<tr>
<td>[73]</td>
<td>At the time of publication of the NICE guideline (February 2011), oral naltrexone did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.</td>
</tr>
<tr>
<td>[74]</td>
<td>At the time of publication of the NICE guideline (February 2011), acamprosate did not have UK marketing authorisation for use longer than 12 months. Informed consent should be obtained and documented P. 451, 454 and 455.)</td>
</tr>
<tr>
<td>VA/DoD, USA, 2009</td>
<td>&quot;Routinely consider oral naltrexone, an opioid antagonist, and/or acamprosate for patients with alcohol dependence. [A]&quot; P.67 Treatment with acamprosate should be initiated after abstinence and should be combined with psychosocial therapy.</td>
</tr>
<tr>
<td>APA, USA, 2006</td>
<td>&quot;Acamprosate, a γ-aminobutyric acid (GABA) analog that may decrease alcohol craving in abstinent individuals, may also be an effective adjunctive medication in motivated patients who are concomitantly receiving psychosocial treatment&quot; (Level 1), P. 13</td>
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APA = American Psychiatric Association, NICE = National Institute for Health and Clinical Excellence, UK = United Kingdom, USA = United States of America, VA/DoD = Veterans Affairs/ Department of Defense