

Article Title: Complementary and Alternative Medicine Mention and Recommendations in Guidelines for Anxiety: A Systematic Review and Quality Assessment

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This is an author-produced postprint of an article accepted for publication on 08 January 2022 and published on 10 January 2022 in Psychiatry Research following peer review. The sharing of this postprint is compliant with the publisher policy as listed on Sherpa Romeo and can be found here: <https://v2.sherpa.ac.uk/id/publication/16060>.

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The published version of this article can be found at the following citation:

Ng JY, Jain A. Complementary and alternative medicine mention and recommendations in guidelines for anxiety: A systematic review and quality assessment. Psychiatry Research. 2022 Jan 10:114388. <https://doi.org/10.1016/j.psychres.2022.114388>.

Highlights

- Complementary and alternative medicine (CAM) use is prevalent among patients diagnosed with anxiety.
- An assessment of CAM recommendations in anxiety practice guidelines is absent.
- CAM recommendations were present in slightly more than half of all eligible guidelines.
- Quality of CAM recommendations varied within and across guidelines.
- A gap exists as the majority of guidelines do not provide CAM recommendations.

Abstract

Background: Up to 43% of patients with anxiety disorders (ADS) use complementary and alternative medicine (CAM), however, many healthcare providers receive little training on this topic. Clinical practice guidelines (CPGs) are relied upon to guide decision-making, especially with respect to topics less familiar to healthcare providers. In the present study, we identified the quantity and assessed the quality of CAM recommendations in CPGs for the treatment and/or management of ADS.

Methods: MEDLINE, EMBASE, and CINAHL were systematically searched from 2009 to April 2020 to identify eligible CPGs. In addition, the Guidelines International Network and the National Center for Complementary and Integrative Health websites were also searched. Eligible CPGs containing CAM recommendations were evaluated using AGREE II.

Results: Eleven CPGs were eligible, of which six made CAM recommendations. Average scaled domain percentages for these six CPGs from highest to lowest were as follows (% overall, % CAM): clarity and presentation (83.3%, 73.6%); scope and purpose (77.8%, 76.4%); editorial independence (69.4%, 36.8%); stakeholder involvement (55.6%, 31.9%); rigour of development (53.1%, 46.9%); and applicability (43.8%, 29.2%).

Conclusions: A need exists to improve the quality of CAM recommendations in anxiety CPGs through insight from AGREE II and other CPG development resources.

Keywords: Anxiety; anxiety disorders; complementary and alternative medicine; AGREE II; clinical practice guideline

Abbreviations

ADS: anxiety disorders

AGREE II: Appraisal of Guidelines for Research & Evaluation II

CAM: complementary and alternative medicine

CBT: cognitive behavioural treatment

CPG: clinical practice guideline

GAD: generalized anxiety disorder

NCCIH: National Center for Complementary and Integrative Health

PICO: Patients, Intervention, Comparison and Outcomes

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SSRIs: selective serotonin reuptake inhibitors

1. Background

Anxiety disorders (ADS) are the most common type of mental illnesses with a global prevalence ranging from 4.8 to 10.9% in 2017 (Thibaut, 2017). ADS are defined by hyperarousal, debilitating fear, and excessive worry, and are diagnosed using the Diagnostic and Statistical Manual of Mental Disorders 5 (American Psychiatric Association 2013), and the International Statistical Classification of Diseases and Related Health Problems 11 (World Health Organization 2018). ADS can have debilitating physical manifestations, including muscle tension and headaches (Peres et al., 2017). They can also negatively impact treatment outcomes of frequently associated comorbidities, such as type 2 diabetes mellitus (Bickett and Tapp, 2016 Sep; 241). A range of therapies are used to treat/manage ADS, including psychosocial treatments and pharmaceutical medications, with the most common being cognitive behavioural treatment (CBT) and selective serotonin reuptake inhibitors (SSRIs), from each category respectively (World Health Organization 2018). CBT and SSRIs are often used in combination (World Health Organization 2018). Although conventional medication is effective for treating ADS, the associated side-effects often result in issues relating to medication adherence (Sansone and Sansone, 2012). As a result, patients with ADS also commonly turn to complementary and alternative medicine (CAM), which they believe may be a milder form of treatment with fewer side-effects (Teo et al., 2016). “Complementary medicine” is defined as the use of a non-mainstream practice together with conventional medicine, while “alternative medicine” is defined as the use of non-mainstream practice in place of conventional medicine [(National Institutes of Health, National Centre for Complementary and Integrative Health (NCCIH) 2016, Ng et al., 2016)].

It has been found that approximately 43% of patients with ADS use CAM (Bystritsky et al., 2012). Common CAM therapies used for the treatment and/or management of ADS include

herbal medicine, acupuncture, and mind-body practices (Bystritsky et al., 2012). Although the mechanism of action for active ingredients in many herbal medicines is unclear, some research suggests that they can help reduce ADS symptoms by modulating neuronal pathways in the brain, including the noradrenergic and glutamatergic pathways (Liu et al., 2015). Acupuncture has been proposed to induce activation of opioid receptors and increase endogenous opioid peptides, thereby resulting in an analgesic effect (Kawakita and Okada, 2014, Lee et al., 2019). Mind-body practices, such as yoga and meditation, are associated with reduced stress, which can decrease anxiety (Gothe et al., 2019). Despite the popularity of CAM use among patients with ADS, clinicians generally lack training and education about the safe and effective use of these therapies (Patel et al., 2017). Patients also rarely disclose the use of CAM to their healthcare provider, believing that they may either be faced with judgement or lack of knowledge on the provider's part (Foley et al., 2019, Ng et al., 2020). Lack of knowledge about a patient's CAM use, however, can result in adverse events from herb-drug interactions, or reduce the efficacy of conventional treatment regimens (Frenkel and Cohen, 2014).

One way in which healthcare providers can gain knowledge surrounding therapies that they lack familiarity with is through consulting evidence-based clinical practice guidelines (CPGs). These documents are relied on by healthcare professionals to diagnose, treat, and manage various conditions, such as ADS. CPGs also serve as a basis for informed and shared decision-making between clinicians and patients, which may ultimately improve treatment adherence and patient outcomes. To our knowledge, no past research has systematically identified the quantity nor assessed the quality of CAM recommendations in CPGs for the treatment and/or management of ADS, thus, this is the purpose of the present study.

2. Methods

2.1. Approach

Using standard methods (Higgins and Green, 2011) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Moher et al., 2009) we conducted a systematic review to capture CPGs for the treatment and/or management of ADS. A protocol was registered with PROSPERO, registration number CRD42020182224. Eligible CPGs found to contain CAM recommendations were evaluated twice using the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument (Brouwers et al., 2010); once for the overall CPG and once for the CAM sections of the CPG. AGREE II is a validated instrument consisting of 23 items categorized into six domains that each capture a unique dimension of CPG quality: scope and purpose (overall aim of the CPG and target population), stakeholder involvement (extent to which the CPG was developed by and represents appropriate stakeholders), rigour of development (process used to synthesize evidence and formulate recommendations), clarity and presentation (language, organization, and format of CPG), applicability (barriers to implementation and strategies to improve uptake), and editorial independence (influence of bias and competing interests). Each item is rated on a 7-point Likert scale, with a score of 1 indicating that the item or concept is very poorly reported, and a score of 7 indicating that the quality of reporting is exceptional and all criteria of the item has been met.

2.2. Eligibility criteria

A Population, Intervention, Comparison, and Outcomes (PICO) framework was used to develop the criteria for CPG eligibility. Eligible populations included adults aged 18 years and older with ADS. For the purpose of this study, CPGs must have focused on the topic of ADS, including either generalized anxiety disorder (GAD), social anxiety disorder, anxiety

disorder due to another medical condition, or unspecified anxiety disorder. CPGs were not excluded if they mentioned other mental health disorders, such as post-traumatic stress disorder or obsessive-compulsive disorder, however, only recommendations pertaining to ADS are reported in this review. The interventions included the treatment and/or management of ADS. With respect to comparisons, CPGs were assessed for the quality of ADS recommendations. The outcomes were the calculated scores based on the format and content of CPGs using the AGREE II instrument. Additional criteria included that CPGs must be developed by non-profit organizations (i.e. disease-specific foundations, academic institutions, government agencies, or professional associations), and published between 2009 and April 2020 in the English language. Exclusively consensus-based CPGs were also excluded as they are generally not designed to be assessed using the AGREE II instrument. If CPGs were not publicly available or accessible through our library system, we obtained them through McMaster University's interlibrary loan system. Other forms of publications, such as consensus statements, abstracts, protocols, conferences proceedings, or editorials were ineligible, along with primary articles that evaluated existing treatments for ADS. Additional ineligible criteria included articles focusing on the curriculum, education, training, research, professional certification, or performance of ADS.

2.3. Searching and screening

MEDLINE, EMBASE, and CINAHL were searched on April 17, 2020 from 2009 to April 15, 2020 inclusive. Commonly used keywords and indexed headings relating to ADS were included in the search strategies executed, with a sample being provided in Supplementary File 1. The Guidelines International Network (GIN) [<https://www.g-i-n.net/>] was also searched using the eligibility criteria and keywords including “anxiety.” Finally, we hand-searched the list of CPGs on the National Center for Complementary and Integrative Health

(NCCIH) website [<https://www.nccih.nih.gov/health/providers/clinicalpractice>]. AJ and another research assistant screened titles and abstracts, then full-texts, from all sources to assess items for eligibility. JYN reviewed the screenings to standardize the screening process, and aided in resolving any discrepancies through discussion.

2.4. Data extraction and analysis

The data extracted and summarized from each CPG included the following: date of publication, country of first author, type of publishing organization (academic institutions, government agencies, disease-specific foundations, or professional associations or societies), and mention of CAM. Additional information from CPGs that mentioned CAM was extracted, including the types of CAM mentioned, CAM recommendations, CAM funding sources, and if the CPG development panel included CAM providers. Data was also extracted from each developer's website to ensure that all CPG development and implementation resources were identified.

2.5. Guideline quality assessment

JYN, AJ, and another research assistant participated in a pilot test which involved applying the AGREE II instrument to three separate CPGs, then discussing and resolving any score discrepancies. AJ and the other research assistant then independently and in duplicate evaluated eligible CPGs containing CAM recommendations twice using AGREE II: once for the overall CPG and once for the CAM sections of the CPG. The AGREE II questions were modified for the CAM sections of each CPG and can be found in Supplementary File 2. Discrepancies between the scores were reviewed by JYN and resolved following discussion. Averages were taken for all 23 items of a single CPG by a single appraisal and used to calculate average appraisal scores for the overall CPG and the CAM sections of the CPGs.

Average overall assessments were then calculated by averaging each appraiser's "overall guideline assessment" score for each CPG. The quality of the eligible CPGs was assessed by next calculating the scaled domain percentages as described in the AGREE II instrument user manual (Brouwers et al., 2010). Scaled domain percentages were calculated for each of the six domains by taking the total of the two appraisers' individual scores for the domain, scaling it to the minimum and maximum potential score for that domain, and then converting it into a percentage. These scaled domain percentages were then used to compare CPGs to inform whether or not the CPG should be recommended, recommended with modifications, or not recommended.

3. Results

3.1. Search results (Fig. 1)

Searches retrieved 712 articles, of which 610 were unique following deduplication and 597 were eliminated based on title/abstract screening. Of the remaining 13 full-text articles considered, we excluded one summary document and one consensus-based CPG. The remaining 11 evidence-based CPGs were deemed eligible [(Gautam et al., 2020, Reddy et al., 2020, Mazza et al., 2019, Andrews et al., 2018, Gautam et al., 2017, Gurney et al., 2017, Lim et al., 2015, Howell et al., 2013, Bandelow et al., 2012, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]; six CPGs made mention of CAM and provided recommendations [(Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, Gautam et al., 2017, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)].

3.2. Guideline characteristics (Table 1)

The 11 eligible CPGs were published between 2011 and 2020 inclusive, and originated from India (n=3), the United Kingdom (n=3), Australia (n=2), Canada (n=1), Singapore (n=1), and the United States (n=1). These CPGs were developed by professional associations (n=8), academic institutions (n=2), and an international agency (n=1). The 11 eligible CPGs discussed GAD (n=7), panic disorder (n=6), social anxiety disorder (n=5), obsessive-compulsive disorder (n=4), phobias (n=4), post-traumatic stress disorder (n=4), unspecified anxiety disorder (n=3), depression (n=2), and anxiety disorder due to another medical condition (n=1). Six of the 11 eligible CPGs made CAM recommendations including the following: applied relaxation (n=4), meditation (n=2), yoga (n=2), alternative therapies (n=1), and vitamins (A, C, and E) (n=1). No CPGs included CAM providers as part of their development panel or received CAM funding sources. A summary of the CAM recommendations for the treatment of ADS is presented in Fig. 2 for the benefit of clinicians and researchers (see Table 1).

3.3. Average appraisal scores and average overall assessments: overall guideline (Table 2)

Across the six evaluated CPGs, average appraisal scores on the seven-point Likert scale ranged from 2.7 to 6.3 (1 equals strongly disagree, and 7 equals strongly agree on each item). Three CPGs achieved or exceeded an average appraisal score of 6.0, while the other three CPGs had average appraisal scores below 4.0. The average overall assessments for each of the six CPGs were between 2.5 (lowest) and 6.0 (highest). Three CPGs achieved or exceeded an average overall assessment of 5.5, while the other three CPGs had average overall assessments below 4.0 (see Table 2).

3.4. Average appraisal scores and average overall assessments: CAM sections (Table 2)

Among the six evaluated CPGs, average appraisal scores on the seven-point Likert scale for CAM sections ranged from 2.3 to 5.6 (1 equals strongly disagree, and 7 equals strongly agree on each item). Three CPGs achieved an average appraisal score between 4.0 and 6.0, while the other three CPGs had average appraisal scores below 4.0. The average overall assessments for each of the six CPGs were between 2.0 (lowest) and 5.0 (highest). Two CPGs achieved an average overall assessment of 5.0, while the other four CPGs had average overall assessments below 4.0.

3.5. Overall recommendations regarding use of guidelines: overall guideline (Table 3)

Between the six evaluated CPGs, both appraisers recommended three CPGs. Both appraisers agreed on their overall recommendations for four out of six CPGs, which included two “No”s (Gautam et al., 2020, Gautam et al., 2017), and two “Yes”s [(National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]. The appraisers did not agree on two of six CPGs, of which one was rated by the appraisers as “Yes” and “Yes with modifications” (Andrews et al., 2018), and the other was rated as “Yes with modifications” and “No” (Reddy et al., 2020) (see Table 3).

3.6. Overall recommendations regarding use of guidelines: CAM sections (Table 3)

Between the six evaluated CPGs, both appraisers agreed on and did not recommend two CPGs based on the CAM section scores (Gautam et al., 2020, Gautam et al., 2017). The appraisers did not agree on four of six CPGs, of which two were rated by two appraisers as “Yes” and “Yes with modifications” [(National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)], and the others

were rated by two appraisers as “Yes with modifications” and “No” (Reddy et al., 2020, Andrews et al., 2018).

3.7. Scaled domain percentage quality assessment (Table 4)

The scaled domain percentages of the overall CPGs for each AGREE II domain ranged between 30.6% to 100.0% for scope and purpose, 13.9% to 94.4% for stakeholder involvement, 14.6% to 90.6% for rigour of development, 52.8% to 100.0% for clarity of presentation, 4.2% to 70.8% for applicability, and 8.3% to 95.8% for editorial independence. The scaled domain percentages of the CAM sections for each AGREE II domain ranged between 30.6% to 97.2% for scope and purpose, 5.6% to 69.4% for stakeholder involvement, 10.4% to 82.3% for rigour of development, 52.8% to 100.0% for clarity of presentation, 4.2% to 58.3% for applicability, and 8.3% to 66.7% for editorial independence (see Table 4).

3.8. Scope and purpose

The objectives, health questions, and the identified populations to whom the CPGs were applied, were well-defined in all of the CPGs except one (Gautam et al., 2020) in both the overall CPG and CAM sections. The authors clearly identified the health intent, outcomes and interventions, along with the target population characteristics in all but one CPG (Gautam et al., 2020), in which the intended population was not specified.

3.9. Stakeholder involvement

Half of the evaluated overall CPGs included relevant members in the CPG development group with well-detailed characteristics of each member, including their expertise, geographical location, and institution [(Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE)

2011)]. The same three CPG developer groups also sought the views and preferences of the target populations and clearly defined the target users, while the other three did not (Gautam et al., 2020, Reddy et al., 2020, Gautam et al., 2017). In contrast, no CPG development group included relevant CAM experts [(Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, Gautam et al., 2017, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]. Only one CPG (Andrews et al., 2018) sought the views and preferences of the target CAM population and thoroughly explained the method used to obtain the information. Three CPGs clearly defined the target CAM users and explanations on how the CAM sections may be implemented [(Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)], while others lacked this information (Gautam et al., 2020, Reddy et al., 2020, Gautam et al., 2017).

3.10. Rigour of development

Developers from half of the evaluated CPGs described the strategy used to search for evidence in detail [(Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]. The same three CPGs also clearly defined the criteria used for selecting evidence, and highlighted the strengths and weaknesses of the body of evidence. Similarly, the three CPGs [(Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)] thoroughly described the methods used for formulating recommendations and the outcomes of the recommendation development process. Potential health benefits were always considered in formulating the recommendations, while side effects were considered in all except one CPG (Reddy et al., 2020). All but one CPG (Gautam et al., 2017) included explicit links between the evidence

and recommendations. Some CPGs failed to explicitly state that they were externally reviewed by experts prior to publication (Gautam et al., 2020, Reddy et al., 2020, Gautam et al., 2017), while the other three clearly declared a statement and process for conducting the external review [(Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]. Half of the six CPGs did not include a statement or a procedure for updating the recommendations (Gautam et al., 2020, Reddy et al., 2020, Gautam et al., 2017). One CPG vaguely outlined a method of updating the CPG but did not explicitly state when it would be updated (Andrews et al., 2018). Two CPGs included both a statement that they will be updated and outlined a methodology for doing so [(National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]. With regard to the CAM section evaluations, developers from half of the six CPGs described in detail the strategy used to search for evidence [(Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]. The same three CPGs also clearly defined the criteria used for selecting CAM evidence and highlighted its strengths and weaknesses. Similarly, the three CPGs [(Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)] described the methods used for formulating recommendations and the outcomes of the recommendation development process. Some potential health benefits were considered in formulating the CAM recommendations in all CPGs; side effects were considered in all but one CPG (Reddy et al., 2020). All but one CPG (Gautam et al., 2017) included explicit links between the evidence and CAM recommendations. All CPGs failed to explicitly state that they were externally reviewed by CAM experts prior to publication [(Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, Gautam et al., 2017, National Collaborating Centre for Mental Health (NICE) 2011,

National Collaborating Centre for Mental Health (NICE) 2011)]. Half of the six CPGs did not include a statement or a procedure for updating the CAM sections (Gautam et al., 2020, Reddy et al., 2020, Gautam et al., 2017), while one CPG vaguely outlined a method of updating the CPG but did not explicitly state when it would be updated (Andrews et al., 2018). Two CPGs included a statement that CAM sections will be updated and outlined a methodology for doing so [(National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)].

3.11. Clarity of presentation

The recommendations in all the overall CPGs, except one (Gautam et al., 2020), were specific and unambiguous; one CPG did not include caveats or identification of the relevant population (Gautam et al., 2020). Similarly, all CPGs except one (Gautam et al., 2020) included different options for the management or treatment of ADS. The key recommendations in all six CPGs were easily identifiable and grouped together. With regard to the CAM section evaluations, three CPGs included specific and unambiguous CAM recommendations [(Reddy et al., 2020, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)], while the recommendations in three CPGs were somewhat ambiguous (Gautam et al., 2020, Andrews et al., 2018, Gautam et al., 2017). Two of the six CPGs also lacked different CAM options for the management of ADS (Gautam et al., 2020, Andrews et al., 2018), while the other four included numerous CAM options. The key CAM recommendations in all six CPGs were generally easily identifiable and summarized (Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, Gautam et al., 2017, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011).

3.12. Applicability

Three of the six CPGs generally discussed facilitators and barriers to the implementation of the overall recommendations [(Reddy et al., 2020, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]. The same three CPGs included some advice and/or tools on how the overall recommendations can be put into practice, though some elements such as how-to manuals were missing at the time of assessment. Similarly, three CPGs [(Reddy et al., 2020, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)] considered the potential resource implications of implementing the overall recommendations. Two CPGs (Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011) provided some monitoring and auditing criteria, however, descriptions of measuring such criteria were lacking. With regards to the CAM sections, two CPGs discussed some facilitators and barriers to implementations of the CAM recommendations (Reddy et al., 2020, National Collaborating Centre for Mental Health (NICE) 2011), while the other CPGs did not include such information. Only one CPG briefly included advice and/or tools on how the CAM recommendations could be put into practice (National Collaborating Centre for Mental Health (NICE) 2011). The potential resource implications of implementing the CAM recommendations were only sought in two CPGs [(National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)], while no CAM sections presented monitoring and/or auditing criteria.

3.13. Editorial independence

Five of the six overall CPGs reported a funding source [(Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)], while only one of those five

CPGs stated that the funding source did not influence the content of the CPG (Reddy et al., 2020). Similarly, the same five CPGs declared competing interests, and reported how the competing interests were identified and could influence the recommendations, albeit sometimes vaguely [(Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]. Pertaining to the CAM sections, five CPGs reported a non-CAM funding source [(Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)], while only one of those five CPGs stated that the funding source did not influence the content of the CPG (Reddy et al., 2020). No CPGs included CAM experts in their guideline development group [(Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, Gautam et al., 2017, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)].

4. Discussion

ADS are the most common mental illnesses globally (Thibaut, 2017) with their treatment typically including psychosocial treatments, such as CBT, and pharmaceutical therapies, such as SSRIs – which may be used alone or in combination with each other (World Health Organization 2018). The use of CAM is also popular among patients with ADS due to fewer perceived side-effects in comparison to pharmaceutical medications (Teo et al., 2016, Bystritsky et al., 2012). Despite the high prevalence of CAM use for ADS, no studies have identified the quantity and/or assessed quality of CAM recommendations in CPGs for the treatment and/or management of ADS, which is the objective of our present study.

We identified 11 eligible CPGs published between 2011 and 2020 for the treatment and/or management of ADS, with only six CPGs making CAM recommendations [(Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, Gautam et al., 2017, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)]. Each CPG only recommended therapies from a few CAM categories, such as mind-body practices [(Gautam et al., 2020, Reddy et al., 2020, Gautam et al., 2017, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)] or nutritional practices such as vitamin supplements (Gautam et al., 2017). One CPG recommended the use of alternative therapies without providing additional details, examples, or guidance (Andrews et al., 2018). The scores obtained from the 23-item AGREE II instrument for these six evaluated CPGs also varied widely across each domain and indicated that the CPGs were of sub-optimal quality. With regards to the overall CPG, three CPGs achieved an average appraisal score and average overall assessment of 5.5 or higher [(Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)], while the other three CPGs received scores of 4.0 or lower (Gautam et al., 2020, Reddy et al., 2020, Gautam et al., 2017). Pertaining to the CAM sections, three CPGs achieved average appraisal scores between 4.0 and 6.0 [(Andrews et al., 2018, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)], while the other three CPGs had average appraisal scores below 4.0 (Gautam et al., 2020, Reddy et al., 2020, Gautam et al., 2017). Overall assessment scores for CAM sections were 5.0 for two CPGs [(National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)], and below 4.0 for the other four CPGs (Gautam et al., 2020, Reddy et al., 2020, Andrews et al., 2018, Gautam et al., 2017). The average scaled domain percentages for the overall CPGs, from highest to lowest, were:

clarity and presentation (83.3%), scope and purpose (77.8%), editorial independence (69.4%), stakeholder involvement (55.6%), rigour of development (53.1%), and applicability (43.8%). The average scaled domain percentages for the CAM sections of the CPGs were lower compared to the overall CPGs, and from highest to lowest, were: scope and purpose (76.4%), clarity and presentation (73.6%), rigour of development (46.9%), editorial independence (36.8%), stakeholder involvement (31.9%), and applicability (29.2%). The CPG that did not provide further details or guidance on alternative therapies scored less across all domains for the evaluation of CAM sections compared to the overall CPG (Andrews et al., 2018). The remaining five CPGs scored the same or less across AGREE II domains for CAM sections compared to overall CPGs [(Gautam et al., 2020, Reddy et al., 2020, Gautam et al., 2017, National Collaborating Centre for Mental Health (NICE) 2011, National Collaborating Centre for Mental Health (NICE) 2011)].

4.1. Comparative literature

Our findings of the sub-optimal quality of ADS CPGs are comparable to published studies assessing the quality of ADS CPGs. A systematic review evaluating the quality of CPGs for ADS in youth also reported low domain scores using AGREE II (Bennett et al., 2018). The study revealed that approximately 70% of the evaluated ADS CPGs for children may not be clinically valid as a result of weak development methods (Bennett et al., 2018). Additionally, a study assessing the quality of ADS CPGs developed by the Canadian Psychiatric Association also outlined the sub-optimal quality of the CPGs, with half of the average scaled domain percentages using the AGREE II instrument being below 60% (Middleton et al., 2019). Moreover, a study aiming to guide general practitioners in the management of ADS episodes evaluated the quality of ADS CPGs using AGREE II and determined that only two out of seven eligible CPGs achieved an overall score greater than 60% (Driot et al., 2017).

Similarly, a study evaluating the quality of ADS CPGs listed in the National Guideline Clearinghouse concluded that only one of two ADS CPGs achieved a score higher than 50% in three of the domains from the AGREE II instrument (Duda et al., 2017). This ultimately highlights a gap in high quality evidence-based CPGs for the treatment and/or management of ADS.

While to our knowledge, this is the first study to determine the quantity and assess the quality of CAM recommendations in CPGs for the treatment and/or management of ADS, our findings can also be compared to studies assessing CPGs of similar topics. One study evaluating the quantity and quality of CAM CPGs providing recommendations specific to herbal medicines, acupuncture, and spinal manipulation, reported similar results, with the order of domain scores from highest to lowest being clarity and presentation (85.3%), scope and purpose (83.3%), rigour of development (61.2%), editorial dependence (60.1%), stakeholder involvement (52.0%) to applicability (20.7%) (Ng et al., 2016). Another study evaluating the quantity and quality of CAM recommendations across CPGs for hypertension concluded that the domain scores varied in the order: scope and purpose (88.9%), clarity of presentation (88.9 %), stakeholder involvement (66.7%), applicability (60.4%), rigour of development (35.4%), and editorial independence (4.2%) (Ng and Gilotra, 2020 May 1). These averaged scaled percentages demonstrate that the variable and sub-optimal quality of ADS CPGs is consistent with existing literature and not unique. Moreover, two additional studies assessing the quantity of CAM recommendations in other health conditions, namely depression and lower back pain, found that the majority of eligible CPGs made CAM recommendations (Ng et al., 2020, Ng and Mohiuddin, 2020), which is unlike our findings with respect to ADS CPGs. Therefore, despite the fact that 43% of patients with ADS are

reported to use CAM (Bystritsky et al., 2012), there is a lack of high-quality CAM recommendations in CPGs relating to ADS.

4.2. Future directions and implications

Overall, this study revealed that few CPGs containing high-quality CAM recommendations for the treatment and/or management of ADS are available to support shared decision-making between healthcare providers and patients. The overall variability and sub-optimal quality of ADS CPGs may partly be explained by a lack of funding available to study CAM therapies (Fischer et al., 2014, Ernst et al., 2004, Nissen and Manderson, 2013) and negative attitudes from primary care providers towards CAM (Weisleder, 2010, Sharp et al., 2018, Offit, 2012). Despite the low quantity and quality of CAM recommendations in ADS CPGs, this category of therapies are utilized by over 40% of ADS patients (Bystritsky et al., 2012). With this in mind, healthcare providers, researchers, and CPG developers alike, should be aware of CAM therapies which may serve as a safe and effective option for patients with ADS. Ensuring the inclusion of evidence-based CAM recommendations in ADS CPGs, in tandem with clinician training and education about this category of therapies, may allow healthcare providers to provide care that better incorporates patients' views and preferences (Middleton et al., 2019), and increases the opportunities for patients to be involved in discussions that consider the weighing of risks and benefits of different treatment options pertinent to their own care (van der Weijden et al., 2013). To improve characteristics of CAM recommendations, developers may use the AGREE II instrument, which identifies criteria that constitute high-quality CPGs. Other frameworks and checklists that can assist developers, include the PANELVIEW Tool, and the Grading of Recommendations Assessment, Development and Evaluation Pro (GRADEpro) tool (Wiercioch et al., 2020, Gagliardi et al., 2015, Khodambashi and Nytrø, 2017). CPGs may further be improved by addressing the patient's preferences and needs for

CAM treatments and involving them in the CPG development process (Middleton et al., 2019). CPGs assessed in this study also lacked patient resources, manuals, and patient versions of the CPGs, which can act as a barrier to the safe and effective uptake of CAM recommendations by patients. Additionally, one CPG only mentioned “alternative therapies” without providing any guidance or specific examples of CAM (Andrews et al., 2018) which does not provide clinicians with any direct guidance on how to guide their inquiring patients. To address this, researchers should be encouraged to conduct further research surrounding the integration of CAM recommendations in CPGs, involve patients in the development of CPGs, and incorporate their findings into patient-specific resources, such as patient handouts and patient-version CPGs (Légaré et al., 2011). Higher quality reporting of CAM recommendations in CPGs and providing patient resources may reduce harmful CAM use among patients, encourage patient disclosure of CAM use, increase clinicians’ knowledge about the risks and benefits of CAM, and ultimately promote shared decision-making to improve treatment outcomes for ADS and other medical conditions (Middleton et al., 2019, Légaré et al., 2011, Gärtner et al., 2019).

4.3. Strengths and limitations

One strength of the present review includes the fact that our study followed standard systematic review methods to identify CPGs for the treatment and/or management of ADS. Additionally, we assessed eligible CPGs containing CAM recommendations with the AGREE II instrument, which has been found to be both valid and reliable (Brouwers et al., 2010). While the AGREE II instrument recommends that CPGs be assessed by four independent appraisers, this study used two appraisers, which may be interpreted as a limitation. However, to mitigate this, an initial pilot test was conducted by JYN, AJ, and another research assistant on three separate CPGs to improve inter-rater reliability. Lastly,

only CPGs published in English were eligible for our study, however, it is acknowledged that CAM recommendations may be present in CPGs developed in non-English speaking countries. Many traditional systems of CAM originate from non-English-speaking countries, such as traditional Chinese medicine from China or Kampo medicine from Japan (Yuan et al., 2016). Thus, due to the integration of CAM into healthcare delivery systems (Gureje et al., 2015), CAM recommendations may be more prevalent in CPGs published in these regions in comparison to Western countries.

5. Conclusions

This systematic review identified six CPGs published since 2011 providing CAM recommendations for the treatment and/or management of ADS. Across these CPGs, recommendations included yoga, meditation, vitamins, and applied relaxation. The evaluation of these CPGs using the AGREE II instrument identified that the quality of CAM sections was lower than the overall CPGs. The scaled domain percentages were also generally lower for CAM sections, highlighting the need to improve the quality of CAM recommendations across this subset of CPGs. Given the high percentage of ADS patients who use CAM, a need exists to evaluate and include evidence-based CAM recommendations in this subset of CPGs. By doing so, researchers and CPG developers may better support informed and shared decision-making and bridge the gap between physician knowledge and patient preferences.

Declarations

Ethics approval and consent to participate

This study did not require ethics approval or consent to participate; it only involved a systematic review of the peer-reviewed literature.

Consent for publication

The authors consent to the publication of this manuscript.

Availability of data and materials

All relevant data are included in this manuscript.

Competing Interests

The authors declare that they have no competing interests.

Funding

JYN was awarded a Research Scholarship and an Entrance Scholarship from the Department of Health Research Methods, Evidence and Impact, Faculty of Health Sciences at McMaster University.

Authors' contributions

JYN: designed and conceptualized the study, collected and analysed data, co-drafted the manuscript, and gave final approval of the version to be published.

AJ: assisted with the collection and analysis of data, co-drafted the manuscript, and gave final approval of the version to be published.

Acknowledgements

We gratefully acknowledge Nandana Parakh for assisting with screening and data extraction.

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Figure Legend

Figure 1: PRISMA Diagram

Figure 2: Summary of CAM Recommendations in Clinical Practice Guidelines

Table Legend

Table 1: Characteristics of Eligible Guidelines

Table 2: Average Appraisal Scores and Average Overall Assessments of each Guideline

Table 3: Overall Recommendations for Use of Appraised Guidelines

Table 4: Scaled Domain Percentages for Appraisers of Each Guideline

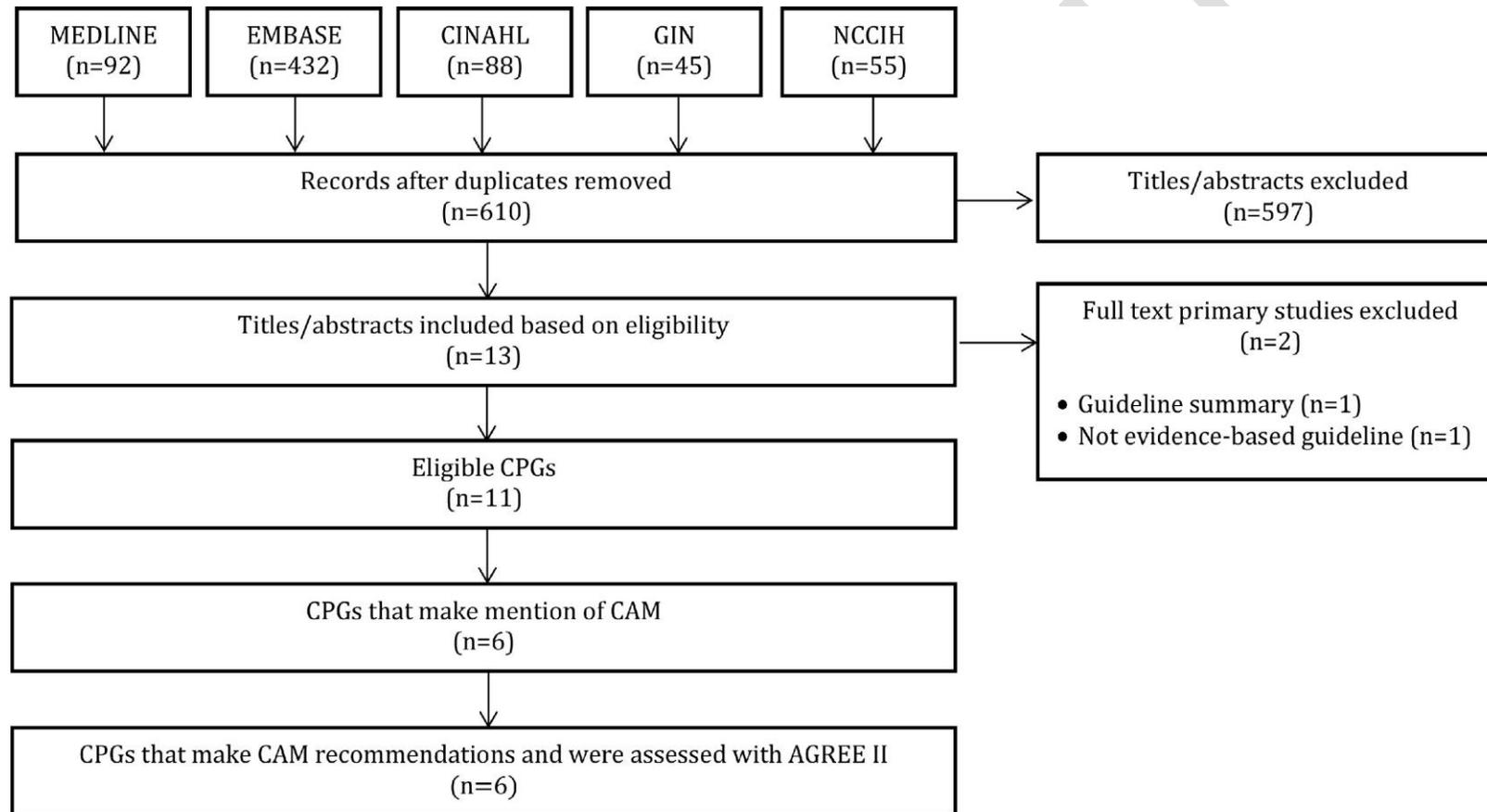
Supplementary Files

Supplementary File 1: MEDLINE Search Strategy for Anxiety Disorders Clinical Practice Guidelines Executed April 17, 2020

Supplementary File 2: Modified AGREE II Questions Used to Guide Scoring of CAM Sections of Each Guideline

Figures

Fig. 1. PRISMA Diagram



*List of Abbreviations: CAM = complementary and alternative medicine, CPG = clinical practice guideline, GIN = Guidelines International Network, NCCIH = National Center for Complementary and Integrative Health

Fig. 2. Summary of CAM Recommendations in Clinical Practice Guidelines

Guideline	CAM Therapy				
	Alternative Therapies ‡	Applied Relaxation	Meditation	Vitamins A, C, E	Yoga
Gautam et al. 2020 [22]	N/A	N/A	+	N/A	+
Reddy et al. 2020 [23]	N/A	+	N/A	N/A	N/A
Andrews et al. 2018* [25]	0	N/A	N/A	N/A	N/A
Gautam et al. 2017 [26]	N/A	+	+	+	+
NICE 2011** [31]	N/A	+	N/A	N/A	N/A
NICE 2011** [32]	N/A	+	N/A	N/A	N/A

Legend:
 +/green = recommendation for the therapy's use
 0/yellow = recommendation unclear/uncertain/conflicting
 N/A/grey = no recommendation provided
 * = Either average appraisal score or average overall assessment of 4.0 or higher for CAM section of CPG
 ** = Both average appraisal score and average overall assessment of 4.0 or higher for CAM section of CPG
 ‡ Note: Andrews et al. (2018) only refer to “alternative therapies” without providing additional details, examples, or guidance.

Tables

Table 1. Characteristics of Eligible Guidelines

Guideline	Country (First Author)	Developer	Mental Health Disorders Discussed	CAM Category	Guideline Topic
Gautam 2020 (Gautam et al., 2020)	India	Gautam Hospital and Institute of Behavioural Sciences	Unspecified anxiety disorder	Yoga, meditation	Yoga and alternative therapies for mental disorders
Reddy 2020 (Reddy et al., 2020)	India	National Institute of Mental Health and Neuro Sciences	GAD, panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder	Applied relaxation	Cognitive behavioural therapy for anxiety disorders
Mazza 2019 (Mazza et al., 2019)	Australia	Monash University	Unspecified anxiety disorder, post-traumatic stress disorder, depression	None	Diagnosing and managing work-related mental health conditions
Andrews 2018 (Andrews et al., 2018)	Australia	The Royal Australian and New Zealand College of Psychiatrists	GAD, panic disorder, social anxiety disorder	Alternative therapies	Pharmacological and alternative treatment of anxiety disorders
Gautam 2017 (Gautam et al., 2017)	India	Gautam Institute of Behavioural Sciences and Alternative Medicine	GAD, panic disorder	Yoga, meditation, applied relaxation, vitamins A, C, E	Management of anxiety disorders
Gurney 2017 (Gurney et al., 2017)	United States of America	The Department of Defence Center of Excellence for Trauma	Unspecified anxiety disorder	None	Treatment of anxiety
Lim 2015 (Lim et al., 2015)	Singapore	Ministry of Health: Singapore	GAD, panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder, post-	None	Management of anxiety disorders

Guideline	Country (First Author)	Developer	Mental Health Disorders Discussed	CAM Category	Guideline Topic
			traumatic stress disorder		
Howell 2013 (Howell et al., 2013)	Canada	University Health Network; Lawrence Bloomberg Faculty of Nursing, University of Toronto	Anxiety disorders due to another condition	None	Screening, assessment, and supportive care of adults with cancer-related conditions
Bandelow 2012 (Bandelow et al., 2012)	United Kingdom	World Federation of Biological Psychiatry	GAD, panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder	None	Treatment of anxiety disorders
NICE 2011 (National Collaborating Centre for Mental Health (NICE) 2011)	United Kingdom	National Institution of Health and Care Excellence	GAD	Applied relaxation	Management of anxiety disorders
NICE 2011 (National Collaborating Centre for Mental Health (NICE) 2011)	United Kingdom	National Institution of Health and Care Excellence	GAD, panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, depression	Applied relaxation	Treatment of common mental health problems

Table 2. Average Appraisal Scores and Average Overall Assessments of Each Guideline

Guideline	Metric	Appraiser 1	Appraiser 2	Average	Standard Deviation
Gautam 2020 (Gautam et al., 2020) (Overall)	Appraisal Score	2.7	2.6	2.7	0.1
	Overall Assessment	3.0	3.0	3.0	0.0
Gautam 2020 (Gautam et al., 2020) (CAM section)	Appraisal Score	2.4	2.3	2.4	0.1
	Overall Assessment	3.0	3.0	3.0	0.0
Reddy 2020 (Reddy et al., 2020) (Overall)	Appraisal Score	4.1	3.6	3.8	0.4
	Overall Assessment	4.0	3.0	3.5	0.7
Reddy 2020 (Reddy et al., 2020) (CAM section)	Appraisal Score	3.6	3.1	3.3	0.4
	Overall Assessment	4.0	2.0	3.0	1.4
Andrews 2018 (Andrews et al., 2018) (Overall)	Appraisal Score	6.0	6.0	6.0	0.0
	Overall Assessment	6.0	5.0	5.5	0.7
Andrews 2018 (Andrews et al., 2018) (CAM section)	Appraisal Score	4.3	4.7	4.5	0.3
	Overall Assessment	3.0	4.0	3.5	0.7
Gautam 2017 (Gautam et al., 2017) (Overall)	Appraisal Score	2.8	2.6	2.7	0.1
	Overall Assessment	3.0	2.0	2.5	0.7
Gautam 2017 (Gautam et al., 2017) (CAM section)	Appraisal Score	2.4	2.2	2.3	0.1
	Overall Assessment	2.0	2.0	2.0	0.0
NICE 2011 (National Collaborating Centre for Mental Health (NICE) 2011) (Overall)	Appraisal Score	6.5	6.1	6.3	0.3
	Overall Assessment	6.0	6.0	6.0	0.0
NICE 2011 (National Collaborating Centre for Mental	Appraisal Score	5.1	5.5	5.3	0.3

Guideline	Metric	Appraiser 1	Appraiser 2	Average	Standard Deviation
Health (NICE) 2011) (CAM section)	Overall Assessment	5.0	5.0	5.0	0.0
NICE 2011 (National Collaborating Centre for Mental Health (NICE) 2011) (Overall)	Appraisal Score	6.5	6.0	6.3	0.4
	Overall Assessment	6.0	6.0	6.0	0.0
NICE 2011 (National Collaborating Centre for Mental Health (NICE) 2011) (CAM section)	Appraisal Score	5.5	5.7	5.6	0.1
	Overall Assessment	5.0	5.0	5.0	0.0

Table 3. Overall Recommendations for Use of Appraised Guidelines

Guideline	Overall Guideline		CAM Section	
	Appraiser 1	Appraiser 2	Appraiser 1	Appraiser 2
Gautam 2020 (Gautam et al., 2020)	No	No	No	No
Reddy 2020 (Reddy et al., 2020)	Yes with Modifications	No	Yes with Modifications	No
Andrews 2018 (Andrews et al., 2018)	Yes	Yes with Modifications	No	Yes with Modifications
Gautam 2017 (Gautam et al., 2017)	No	No	No	No
NICE 2011 (National Collaborating Centre for Mental Health (NICE) 2011)	Yes	Yes	Yes	Yes with Modifications
NICE 2011 (National Collaborating Centre for Mental Health (NICE) 2011)	Yes	Yes	Yes	Yes with Modifications

Table 4. Scaled Domain Percentages for Appraisers of Each Guideline

Guideline		Domain score (%)					
		Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial Independence
Gautam 2020 (Gautam et al., 2020)	Overall Guideline	30.6	16.7	21.9	52.8	4.2	75.0
	CAM Section	30.6	11.1	21.9	52.8	4.2	25.0
Reddy 2020 (Reddy et al., 2020)	Overall Guideline	80.6	19.4	21.9	86.1	39.6	95.8
	CAM Section	75.0	5.6	21.9	80.6	37.5	45.8
Andrews 2018 (Andrews et al., 2018)	Overall Guideline	100.0	94.4	80.2	91.7	62.5	79.2
	CAM Section	97.2	69.4	64.6	55.6	22.9	29.2
Gautam 2017 (Gautam et al., 2017)	Overall Guideline	61.1	13.9	14.6	75.0	16.7	8.3
	CAM Section	61.1	5.6	10.4	61.1	4.2	8.3
NICE 2011 (National Collaborating Centre for Mental Health (NICE) 2011)	Overall Guideline	97.2	94.4	89.6	100.0	70.8	79.2
	CAM Section	97.2	44.4	80.2	100.0	47.9	45.8
NICE 2011 (National Collaborating Centre)	Overall Guideline	97.2	94.4	90.6	94.4	68.8	79.2

Guideline		Domain score (%)					
		Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial Independence
for Mental Health (NICE) 2011)	CAM Section	97.2	55.6	82.3	91.7	58.3	66.7

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