Current Research on Complementary and Alternative Medicine (CAM) in the Treatment of Anxiety Disorders: An Evidence-Based Review

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Chapter 31

Current research on complementary and alternative medicine (CAM) in the treatment of anxiety disorders: an evidence-based review

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Abstract

Complementary and alternative medicine (CAM) encompasses a wide range of different *non-mainstream* therapies that have been increasingly used for treatment or adjunctive treatment of various ailments with anxiety/anxiety disorders being one of the commonly CAM (self)medicated conditions. Thousands of published papers refer to use of CAM in various psychiatric disorders or in healthy or medically ill patients with mood or anxiety difficulties. In this chapter we focus specifically on clinically diagnosed (in line with the standard criteria) anxiety disorders and overview evidence of efficacy/safety of a range of CAM modalities: biologically-based therapies (typically herbal preparations and less so nutraceuticals); manipulative and body-based therapies (acupuncture, aerobic exercise, massage, therapeutic touch, repetitive transcranial magnetic stimulation, balneotherapy and others); mind-body therapies (yoga, morita therapy, tai chi, reiki, Chinese cognitive therapy, religious and spiritual interventions, relaxation, mediation and mindfulness-based interventions); and alternative medical systems (Ayurveda, homeopathy). We focus exclusively on randomized controlled trials and attempt to evaluate the existing body of evidence in the same manner that is applied to mainstream treatments.

Key words: Complementary and alternative medicine, anxiety disorders, randomized controlled trials, systematic reviews/meta-analyses, evidence based medicine

Introduction

Assessing *complementary and alternative medicine* (CAM) in treatment of anxiety disorders is linked to several dilemmas. One is related to terminology and definition of CAM. While the words *complementary* or *alternative* are self-understandable, the term CAM is typically used to address "*therapies that lie outside the spectrum of traditional, science-based clinical medicine and surgery*"(1). Within the paradigm of Evidence Based Medicine (EBM), decisions about therapeutic interventions should be based on critical assessment of evidence, where *evidence* (*scientific evidence*) means empirical observations supporting a certain claim/theory, and *quality evidence* means empirical observations that leave little uncertainty (because consistent, direct, unbiased, precise) about the direction and size of the effect of an intervention (2). However, the distinction between CAM and *conventional* is not only about scientific background. Definition by the National Center for Complementary and Alternative Medicine (NCCAM; since 2014 National Center for Complementary and Integrative Health; NCCIH), USA (3, p. 19) recognizes that the boundaries between CAM and the "*dominant (health) system*" are not always sharp or fixed, and that CAM "*encompasses resources, health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the dominant health system of a particular society or culture in a given historical period. CAM includes such resources perceived by their users as associated with positive health outcomes."* (3). Hence, reasons for defining a treatment as CAM are not only scientific, but also political, social and conceptual (4). Simply said, a CAM method would be any "*non-mainstream practice*" (5) aimed at achieving a beneficial health outcome. Within the present context, *mainstream* pertains to the usual allopathic Western practice whose knowledge-base derives from science. The EBM approach enables translation of seemingly incommeasurable concepts into the (scientific) language of proof and evidence - the discovery of artemisin, an antimalaric is a prominent example (6). Moreover, it classifies treatments as either supported by evidence or not; all other distinctions (e.g., conventional vs. CAM) are only of secondary relevance (7). Consequently, one could doubt whether, for example,

virtual reality or well-being therapy, each addressed in other chapters of this book, should be (due to this fact) considered mainstream or CAM, or whether otherwise mainstream psychiatric interventions being evaluated for further indication in anxiety disorders should be considered as such, or as CAM (on the account of thus far scarce evidence). For a practical purpose of defining a framework of this chapter, we considered all interventions *not* listed as recommended treatments for anxiety disorders in respective professional guidelines (e.g., 8-15) as CAM, except those with a recognized use (*mainstream*) in other psychiatric/neurological or medical conditions, or in treatment of anxiety disorders but with a new mode of implementation, e.g., cognitive behavioral therapy (CBT) *via* internet or smartphones. Surveys (16, 17) have identified more than 100 different CAM practices. We address them using the classification proposed by NCCAM (NCCIH) (3), i.e., as: a) biologically-based therapies (e.g., "folk medicine", diet-based therapies, natural products); b) mind-body interventions (e.g., meditation, relaxation, hypnosis, Tai Chi, Qi gong); c) manipulative and body-based methods (e.g., chiropractic, osteopathy, massage, movement therapies); d) alternative medical systems (e.g., Ayurveda, homeopathy, traditional healers); e) energy therapies (e.g., light therapy, magnetic fields) and others.

This book explicitly addresses anxiety disorders in line with the DSM 5 criteria (excludes obsessive-compulsive disorder [OCD] and post-traumatic stress disorder [PTSD]). This chapter includes reference to relevant publications on the topic where anxiety disorders were diagnosed in line with the accepted *mainstream* criteria that were in place at a given time period (e.g., previous editions of DSM). To be in line with the general concept of the entire book, the potential of CAM specifically in OCD or PTSD is not addressed, but studies comprising mixed patient populations with different anxiety disorders, including OCD or PTSD are considered. Level of anxiety is increased in different situational contexts, physiological (e.g., pregnancy) and medical conditions (e.g., malignancy, cardiovascular disorders). Even a brief search of Medline discloses a number of publications on the use of CAM to "relieve anxiety" in such settings - a recent systematic review (18)

addressed randomized controlled trials (RCTs) of CAM in pregnant women reaching certain cut-off scores on anxiety rating scales but none of the participants was actually diagnosed with *anxiety disorder due to another medical condition* (18); another one identified 19 RCTs of transcendental meditation in trait anxiety (19): in students, prison inmates, veterans, prison staff, patients with hypertension etc., but again, participants were not actually diagnosed with any *anxiety disorder*. This chapter focuses on evidence pertaining to the use of CAM for treatment of specifically *anxiety disorders* and not for relief of anxiety in otherwise healthy subjects or in medically ill patients. While this might be objected having in mind the concept of complementary and integrative health (20) that implies the use of CAM to improve the outcomes of *mainstream* treatments in any diseased condition, or to contribute to disease prevention and/or improvement of wellbeing (i.e., CAM as a part of a holistic approach) (20), we find the settings were anxiety is the only or the primary disorder to be more appropriate for detecting the potential of CAM procedures for its treatment as their main effect (not confounded or obscured by possible effects on the other primary underlying condition). In 2013, Jonas et al. (21) provided a comprehensive overview of the "evolution of CAM in the USA", evolution of terminology related to CAM and its conceptual perception and a "switch" in stakeholders' reasoning resulting in a "*shift from questions such as 'What is CAM?' or even 'Does this CAM work?' to questions such as 'How can we use this CAM practice to improve clinical outcomes, reduce overall health-related expenditures or increase worker productivity and quality of life*'" (21). We take a "step back" and primarily address the question "Does this CAM work?" for treatment of anxiety disorders looking for evidence in the EBM sense.

The NHIS surveys show a clear increasing trend in the use of CAM and anxiety and depression appear to be among 5-6 conditions for which CAM methods are most frequently used by adults and children (3-4% of participants reported using CAM for anxiety or depression) (22). In reverse, a large survey in 25 countries reported a 1-year prevalence of CAM use among patients with an anxiety disorder diagnosed in line with DSM 4 to be 3.9%; moreover, in those with high

disease severity, the prevalence was 7.2% for CAM use, 1.4% for only CAM use and 5.9% for CAM combined with other care (23). History of psychiatry is rich with examples of treatments that, at certain times, were considered scientifically *unsound* (by the actual criteria), but were subsequently accepted as *mainstream* only to be eventually discarded (24). In the meantime, understanding of the nature (biology) of psychiatric disorders has enormously evolved (although still being far from complete) and so is the understanding of the mechanisms through which the *mainstream* (or intended to be-) treatments exert their effects, this fact giving them the image of *scientifically-based*. This kind of knowledge is missing for most of the CAM treatments in most of the situations (20, 24) however the EBM methodology does not necessarily require understanding of the underlying mechanisms. Here we overview the body of evidence on efficacy/safety of CAM treatments for anxiety disorders using the established EBM principles that are standardly employed to evaluate the *mainstream* interventions. Considering the ever-growing number of publications on CAM (now counted in hundreds of thousands, 21, 25), many of which pertain to anxiety disorders, a selection had to be made so this overview is far from exhaustive. In this process, we reasoned as follows: a) RCTs have the highest potential to accurately (unbiasedly) identify treatment effects. As a starting point, we searched PubMed/Medline and Cochrane databases to identify systematic reviews of RCTs pertaining to treatment of anxiety disorders (diagnosed as explained) published between 2000 and January 15, 2019, and selected those reporting on the use of CAM (defined as explained). Where indicated by the systematic reviews, we further searched individual RCTs. We provided numerical data when we deemed it informative to support claims about treatment (non)effects. We considered it unfeasible to list other numerical data (interested readers are directed to the cited literature), in part due to their practical irrelevance and in part due to the fact that the area is dynamically changing and new data might have arisen in the meantime; b) we attempted to evaluate quality of evidence, i.e., the level of (un)certainty about the effect (or lack of it) suggested for individual treatments (how likely it is that the provided estimate hits the true "population effect"). While there

are widely used tools to evaluate quality (risk of bias) of RCTs (e.g., Cochrane collaboration tool, RoB 2.0; https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool) or of systematic reviews (e.g., updated AMSTAR tool; https://amstar.ca/), and overall quality of evidence (e.g., GRADE; https://cebgrade.mcmaster.ca/), we did not systematically employ any of them, but implemented key criteria contained in these tools, as outlined in Table 1; c) consequently, although this approach is sometimes used in evaluation of the *mainstream* treatments (e.g., 27), we disregarded evaluations of "post- vs. pre-" effect sizes since they cannot distinguish the treatment effect from chance, natural course of the disease or regression to the mean.

Biologically-based therapies

NCAM/NCCIH explicitly excludes vitamins and minerals from this subgroup of CAM, and the term refers typically to various herbal preparations (3, 5). Several systematic reviews addressing CAM, however, included also a reference to "nutraceuticals" or "diet" (e.g., 32-34). Some of the herbal preparations typically addressed as CAM have a long-standing medicinal use in the Western World related to *anxiety*, and some of them have a specific regulatory status. European Medicines Agency (EMA) and its Committee on Herbal Medicinal Products (HMPC) recognize a regulatory pathway of *traditional use registration* for herbal drugs - herbal drug/medicinal plant and preparations thereof need to be in human use for more than 30 years, data (generally, only bibliographic) are needed to support safety and *plausible* efficacy, and products are intended to be used without medical supervision (i.e., for self-medication or over-the-counter use) (35).

Lavender (*Lavandula angustifolia*) preparations

Background. HMPC has adopted two community herbal monographs (36, 37) pertaining to *Lavandula angustifolia* Miller and ***traditional use*** of preparations for "*relief of mild symptoms of mental stress and exhaustion and to aid sleep*": lavender flower (*L. angustifolia*, *flos*) comminuted substance to be used for preparation of tea or as a tincture; and essential oil obtained by steam

distillation from the flowering tops (*L. angustifolia, aetheroleum*), to be used orally or as a bath additive. There appears to be no RCTs evaluating Lavender tea, tincture or baths in treatment of anxiety disorders (38, 39). On the other hand, an industrially sponsored oral product containing an active substance defined as "lavender essential oil obtained by steam distillation" (Silexan®, WS® 1265) (40) is likely the most comprehensively evaluated herbal preparation for treatment of anxiety disorders. The product (80 mg soft gelatin capsules) has been approved (*traditional use*) in Germany (40), Sweden (41) and several other EU and non-EU European countries for "relief of mild anxiety" (e.g. Sweden) or "treatment of restlessness accompanying anxious mood" (Germany) (80 mg capsule once daily). The development of the product is outlined in an "umbrella" review (40) and is addressed in several other targeted reviews/meta-analyses (42-45). Silexan was evaluated in RCTs in patients with generalized anxiety disorder (GAD) (DSM 5 300.02), anxiety disorder not otherwise specified (DSM 4 300.00; ICD-10 F41.9), restlessness and agitation (ICD-10 R45.1) or mixed anxiety and depressive disorder (ICD-10 F41.2) (Table 2). The latter 3 conditions are referred to as "subsyndromal anxiety disorder" – patients meet some but not all criteria for diagnosis of GAD (44).

Efficacy. GAD. In one (46) large, multicentric low-risk of bias 10-week double-blind RCT Silexan 80 mg qd was superior to placebo and tended to be superior to paroxetine 20 mg qd in respect to Hamilton Anxiety rating scale (HAM-A) score reduction at the end of treatment, proportion of responders (≥50% score reduction), but not in proportion of remitters, while Silexan 160 mg qd was superior based on all outcomes (Table 2). No withdrawal difficulties were observed during a subsequent week after abrupt Silexan withdrawal/paroxetine taper (47). Another 10-week identically designed/conducted multicentric unpublished double blind trial (Table 2) was indicated in the reviews (43, 44). In this trial Silexan 80 mg qd was not superior to placebo (Table 2) (44). The third (48) double-blind, multicentric 6-week trial compared Silexan 80 mg qd to lorazepam 0.5 mg qd. Although non-inferiority was claimed for Silexan (48), it suffered several limitations (Table 2)

leaving high uncertainty about efficacy of Silexan. No withdrawal symptoms were observed in either arm over a 2-week taper (48). Subsyndromal anxiety disorder". Three identically designed (Silexan 80 mg qd) multicentric, double-blind 10-week placebo-controlled low risk of bias RCTs (49-51) were conducted in these conditions (Table 2). Data were also analyzed jointly in a meta-analysis (45). Silexan was formally superior to placebo in all 3 trials regarding HAM-A reduction, in 2/3 regarding response rates (numerically better in the third trial) and in 1/3 regarding remission rates (numerically better in other two trials) (Table 2; 45). Differences vs. placebo were rather large in the first trial (49) and smaller and similar in the other two (50, 51) (Table 2), hence quite some heterogeneity was observed (45). However, all effects were in the same direction (Table 2, 45).

Safety. Adverse events (AEs) monitoring and reporting was adequate (regulatory trials). In none of the individual trials or joint analyses was incidence of "any AE" higher with Silexan (10 to 160 mg/day) than with placebo. The only AE observed more commonly with Silexan was eructation (40, 42-51). Targeted studies in healthy subjects demonstrated no effect of Silexan (160 mg qd over 11 or 28 days) on the activity of CYP1A2, CYP2C9, CYP2C19 or CYP3A4 (relevant in metabolism of *mainstream* treatments) and no pharmacokinetic interactions with oral contraception (40). Studies are underway to evaluate the impact of Silexan on driving ability (vs. placebo and lorazepam) in healthy subjects (https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-001101-14/DE).

Conclusion. Safety and tolerability of this particular product over 2-3 months of use is well documented. One additional large multicentric low risk of bias trial would be needed to demonstrate its efficacy in initial short-term treatment of GAD. There is no data on long(er)-term treatment, attainment/maintenance of response/remission; hence utility of this product as a monotreatment for GAD is unknown. There is moderate evidence of efficacy of Silexan 80 mg qd for short-term treatment in patients with "subsyndromal anxiety disorder", but the size of the effect is uncertain. There is no data on long(er)-term treatment.

Kava Kava (*Piper methysticum*) preparations

Background. The use of Kava Kava (preparations of Kava rhizomes; *Piper methysiticum* G. Forst., rhizome) in treatment of anxiety/anxious disorders is likely the most controversial topic in the setting of herbal (CAM) preparations for anxiety and has been addressed and debated in numerous reviews/meta-analyses (e.g., 26, 32-34, 52-60). In part, the topic is intertwined with the topic of recreational/ceremonial and traditional medicinal (for various ailments, including anxiety) consumption of Kava beverage (maceration of grounded dried peeled rhizome in water and coconut milk) originating in Polynesia, Melanesia and Micronesia, with a tradition of over 2000 years (61). In 2016, The Food and Agriculture Organization of the United Nations World Health Organization (FAO) comprehensively evaluated the use of this beverage to conclude that excessive consumption might have unwanted acute and transitory but also potentially long-term health effects, and that thus it should be limited in extent (61). In part, it was prompted by observations related to industrially manufactured food/dietary supplements (dried tableted extracts or liquid extracts frequently obtained using organic solvents) in the Western countries which, at some point, were associated with a signal of hepatotoxicity resulting in withdrawal/ban of these products throughout most of the EU (except the homeopathic ones). In Germany, approval was revoked by the medicines agency, but based on a court decision in one of the German federal states ethanolic extracts were later re-introduced to market (62). In 2017 HMPC provided Assessment report on *Piper methysticum* stating that there **was not sufficient** evidence of "*plausible* efficacy and documented safety" that would justify a Community Herbal monograph on *Piper methysticum* preparations as either **well-established** use or **traditional use** herbal products (62) for treatment of anxiety/stress-related disorders: an exhaustive review was provided on phytopharmaceutical, manufacturing, non-clinical pharmacological/toxicological aspects and clinical data (overall more than 1700 publications). The following key points were emphasized (62): a) a variety of preparations (different extraction methods; isolated or synthetic components) were used in analytical, non-clinical and clinical studies; b) non-clinical toxicology/safety pharmacology studies

yielded variable results, indicating hepatotoxicity or increased incidence of hepatoblastoma for some specific preparations, likely not applicable to others, and a lack of adequate reproductive and developmental toxicity studies; c) clinical studies varied in duration, dosage (based on kavalactones), type of extract, patient population and outcome measures. Table 3 summarizes RCTs of Kava preparations "in anxiety" identified by HMPC to illustrate their clinical heterogeneity.

Efficacy. Two meta-analyses are commonly used to substantiate efficacy of Kava extracts – one by Cochrane Collaboration (53) and one that included only studies with the extract WS1490 (likely based on acetonic or ethanolic extraction) (54). The first one (53) included 7 RCTs vs. placebo (trials No 1, 6, 11-14 in Table 3, and one additional 8-week trial of WS1490 70 mg tid, n=20, vs. placebo, n=20, in "climacteric syndrome, HAM-A >18") (53, 62). Based on 197 patients on Kava and 183 on placebo, a pooled estimate (weighted mean difference, WMD) of difference (Kava-placebo) in HAM-A reduction at the end of treatment was 3.85 (95%CI 0.05 to 7.66) by random-effects method. However, τ^2=19.89 and I^2=78% (53) call for caution in interpretation. For example: a) without the "climacteric syndrome" trial (6 trials), WMD is 2.36 (95%CI -0.79 to 5.51); z=1.47, p=0.142, τ^2=10.59, I^2=69% (no effect); b) with all 7 trials but using the Hartung-Knapp-Sidik-Jonkman (HKSJ) correction recommended with small number of trials/small trials, the 95%CI for WMD extends from -1.81 to 9.47, t=1.660, p=0.147 (no effect) and without the "climacteric syndrome" trial, it extends from -1.79 to 6.50, t=1.467, p=0.202 (no effect); b) based on all 7 trials, 95% prediction interval for Kava-Placebo difference extends from -8.59 to 16.3 (from Kava substantially worse to substantially better) and the range of effects (WMD$\pm 2\tau$) is -5.02 to 12.72. The published pooled effect, hence, should be carefully interpreted. The second meta-analysis was based on individual patient data (54) and included the same trials as the previous one (53), except for the trial No 1 in Table 3 (overall, 180 on WS1490 and 165 on placebo), to conclude superiority in terms of HAM-A reduction (reported WMD 5.94, 95%CI -0.86 to 12.8; p=0.074). A few points: a) re-calculation on study summary data for the purpose of this chapter indicated: WMD=4.96, 95%CI 1.14 to 8.77, z=2.547,

p=0.011, τ^2=16.09, I^2=74%; b) with HKSJ correction, 95%CI -1.05 to 10.97, t=2.122, p=0.087 (no effect); b) without "climacteric" trial and with HKSJ correction (5 RCTs, 160 WA1490, 145 placebo), WMD=3.41, 95%CI -0.73 to 7.55, τ^2=6.25, I^2=56.1%, t=2.287, p=0.084 (no effect); c) with all 6 trials, range of effects from -3.1 to 12.98, 95%PI from -7.14 to 17.3; d) the largest trial with WS1490 (No 5 in Table 3) was not included as it used Anxiety Status Inventory: reduction in scores were somewhat higher with WS1490 (n=71) than with placebo (n=70) but not significantly (63). The meta-analysis (54) reported also a strong effect of WS1490 based on proportion of responders (reduction in HAM-A ≥50%) - pooled OR=3.30, 95%CI 2.09-5.22. Recalculation based on summary data, without the "climacteric syndrome trial" and including the largest trial (63; response= reduction in ASI >5 score points), with HKSJ correction gives Mantel-Haenszel RR=1.47, 95%CI 1.10-1.97, t=3.379, p=0.02, τ^2=0.017, I^2=22.4%, and 95%PI extending from 0.90 to 2.37 indicating, still, some uncertainty. We previously (26) addressed RCTs of Kava vs. placebo to point-out meaninglessness of pooled estimates due to clinical and statistical heterogeneity (even after adjustment for baseline symptom scores and trial duration) resulting in high uncertainty about the existence of an effect (but also non-existence of a mild effect), and pointing-out also that the trial with active comparators (No 4 in Table 3) lacked assay sensitivity, while active controls were likely sub-dosed. Joint analysis of three small trials in DSM 4 GAD patients (trials 1-3 in Table 3) (same investigators) indicated no difference between Kava and placebo in terms of HAM-A reduction over 4-8 weeks and proportion of responders (numerically higher with placebo: 14/30, 47% vs. 9/28, 32%) (64). One recent meta-analysis (60) included 3 RCTs of Kava vs. placebo in exclusively GAD patients (trials 1, 7 and 9, period 1, in Table 3) to conclude "*promising evidence…suggesting Kava….to be an effective treatment in GAD*". This conclusion was based on a total of 63 patients on Kava, 67 on placebo over 1-6 weeks of treatment, with standardized mean difference in HAM-A reduction of 0.59 (95%CI -0.57 to 1.75) (tends to favor Kava), with τ^2=0.93 and I^2=89% (60) – an apparently non-conservative interpretation of data.

Safety. In all trials and observational studies (62), Kava extracts were well tolerated with no indication of withdrawal difficulties or any relevant adverse effects (62). The *hepatotoxicity* signal, however, is real and should not be neglected (65). Some observations suggest that the risk might be associated with products based on organic solvents, doses and duration of use that by far exceed those seen in studies related to anxiety, or also with individual subject characteristics (61, 62, 65).
Conclusion. The issue of the risk of serious liver damage associated with Kava products needs to be resolved by mechanistic and epidemiological studies. Evaluation of efficacy is perplexed by heterogeneity of products, doses, dosing regiments, patient characteristics, and trial durations. A biological rationale exists, but the currently existing RCTs should be viewed as a (cumulative) proof-of-concept material suggesting (albeit with some uncertainty) that Kava-Kava extracts (as a therapeutic principle, not a specific product) might have a mild-moderate effect in terms of reducing the level of anxiety in the initial short-term treatment in patients with anxiety disorders. A judgement on utility of this "therapeutic principle" in treatment of anxiety disorders is impossible – since no data of this kind exists. In 2015, a protocol of a two-site (in Australia) double-blind placebo-controlled 16-week RCT was published (66): it was to include non-treated DSM 5 GAD patients (HAM-A ≥18), randomized to 2x120 mg/day of kavalactones (tableted aqueous dry extract of a high-quality noble *Borogu* cultivar) (n=105) or placebo (n=105). According to the trial site (https://clinicaltrials.gov/ct2/show/NCT02219880, accessed January 29, 2019), recruitment has been completed (total N=178), but no results are yet available.

Other herbal products

Systematic reviews published over the past 10 years (e.g., 26, 33, 34, 58, 59, 67-70) have identified a range of herbal preparations evaluated mostly in one or two RCTs in anxiety disorders. Some of the addressed medicinal plants [e.g., Passion flower (*Passiflora incarnata* L., *herba*), Valerian (essential oil: *Valeriana officinalis* L., *aetheroleum*; or root: *Valeriana officinalis* L*., radix*), Hawthorn leaf and flower (*Crataegus spp., folium cum flore*) and California poppy (*Eschscholzia californica* Cham.,

herba)] have Community herbal monographs justifying ***traditional use*** for "relief of mild symptoms of mental stress" and/or "to aid sleep" within EU. Data addressed here were identified in the mentioned systematic reviews.

Crataegus+ Eschscholzia. In one 12-week multicentric low risk of bias (assessed previously, 26) RCT in DSM 3 R GAD patients, 2x2 tablets a day of 75 mg *Crataegus* extract+20 mg of *Eschscholtzia* extract+75 mg elemental magnesium (n=130) resulted in a significantly greater HAM-A reduction (difference=-1.7; 95%CI -1.8 to -1.6) and greater proportion of responders (RR=1.41; 95%CI 1.04-1.93) than placebo (n=134). One additional similar trial would be needed to confirm ability of this product to reduce anxiety in initial short-term treatment of GAD.

Table 4 summarizes body of evidence on several other herbal preparations classified, based on criteria in Table 1 (size, duration, bias, design issues, precision), as those for which data could be considered as an "early proof-of-concept" justifying further research (Chamomile, Ginkgo biloba and a specific mix of herbal extracts); those for which data are inconclusive (do not demonstrate but do not exclude a possible effect) (*Passiflora, Galphimia, Echium amoneum*, cannabidiol and a specific Chinese herbal mix) and those for which data strongly suggest no effect (St. John's Wort extract, a specific Korean herbal mix).

<u>Nutrients/nutraceuticals</u>

Systematic reviews found no RCTs evaluating lysine or lysine-arginine (33, 34), *N*-acetylcyteine, tryptophan, folate or dehydroepiandrosterone (32) supplementation in anxiety disorders. Two reviews (34, 75) identified two small (each N=21) 4-week treatment, 1-week wash-out double-blind cross-over RCTs of inositol (12 g/day) including patients with DSM 3-R or DSM 4 *panic disorder with or without agoraphobia* (76, 77): in the first trial comparison was vs. placebo, in the 2nd trial vs. fluvoxamine (50-150 mg/day). The first one (76) reported greater reduction of the number of panic attacks vs. placebo, the second one (77) reported no difference vs. fluvoxamine. Both used inappropriate way of data analysis (number of attacks as a continuous variable, instead as Poisson

event rates; analysis not accounting for period effect), the 2nd trial lacked assay sensitivity. Data could be viewed as an early "proof-of-concept" (but with uncertainty).

Manipulative and body-based therapies

Acupuncture

Data is methodologically extremely variable (78). Recent systematic reviews identified 13 (79) and 6 RCTs (80) of various acupuncture procedures, none in patients diagnosed with anxiety disorders. One miniature (acupuncture n=7, sham n=6) 4-week double blind low-risk of bias RCT in ICD-10 GAD patients (see 26) indicated a possible anxiolytic effect. A recent 5-week RCT in children with GAD indicated considerably greater HAM-A reduction in those treated with a specific acupuncture procedure (n=10) than in the waiting-list controls (n=10) (81). This small single-center trial is burdened with risk of various biases inherent to waiting-list controlled trials (see Table 1). One non-randomized 6-week, open-label Chinese trial (82) indicated closely similar CGI score reduction with specific Jin-3-needling therapy, western pharmacotherapy and combined treatment in GAD patients (N=86). Due to low quality and lack of assay sensitivity, the trial is uninformative. The "body of evidence" about acupuncture for anxiety disorders practically does not exist.

Exercise

Several reviews addressed aerobic exercise for "psychiatric symptoms/disorders" (e.g., 83-86) mixing RCTs in psychiatric patients (various diagnoses), medically ill or healthy subjects, all recognizing clinical heterogeneity (indications, exercise protocols, duration) and mostly high risk of bias in these trials. Two provided pooled estimates (83, 86) which, based on criteria of clinical heterogeneity, statistical heterogeneity and high risk of bias (Table 1) are uninformative. Nine RCTs identified in these reviews actually conducted in patients with anxiety disorders are summarized in Table 5: a) in addition to heterogeneity of exercise protocols, all trials were small resulting in imprecise estimates/(under)powered statistical tests; b) in panic disorder, one trial (88) indicated a

greater symptom improvement vs. pill placebo (but less then with chlomipramine) while another, by the same group (90), with a 2x2 factorial design indicated similar changes with exercise (plus paroxetine or pill placebo) vs. relaxation (plus paroxetine or pill placebo) and was, due to the choice of reference treatment actually inconclusive about exercise (non)effect; c) all other trials were inconclusive about exercise (non)effect due to risk of bias (performance, ascertainment, attrition) and/or lack of assay sensitivity (choice of control treatments). Overall, there is some indication (but with considerable uncertainty) that aerobic exercise as a concept might be anxiolytic in patients with anxiety disorders.

Other procedures

A Cochrane review in 2007 (96) found no controlled trials of *therapeutic touch* in patients with anxiety disorders. A more recent one (97) identified two small 4-week RCTs (total N=40) of *repetitive transcranial magnetic stimulation* (rTMS) vs. sham procedure in panic disorder patients indicating no differences in symptom reduction – trials do not indicate, but also do not exclude a possible rTMS effect. We previously (26) identified individual RCTs in GAD patients indicating (criteria in Table 1) an effect of a specific *balneotherapy* procedure (greater HAM-A reduction in an open-label 8-week trial vs. paroxetine 20 mg qd, N=237), and a possible effect of *Swedish massage*, of a specific *flotation in water* protocol and of *Chinese bloodletting*.

Mind-body therapies

A very recent scoping review of systematic reviews of CAM (98) concluded "moderate quality of evidence" (in the GRADE sense) supporting efficacy of CAM in anxiety: meditation, yoga and mindfulness-based stress reduction (MBSR). However, different reviews included different CAMs under the same names, e.g., mediation, or included yoga, reiki and similar interventions under "meditative therapies" (99). Moreover, very heterogeneous patients were included in these trials.

We therefore reviewed a number of systematic reviews to identified data pertaining specifically to trials in patients with anxiety disorders.

Yoga

Across reviews addressing yoga (99-103), only 5 RCTs were in patients diagnosed with anxiety disorders: a) 3 small high risk of bias trials from India; one 8-week vs. no treatment in "anxiety disorder" (N=45) indicating no difference regarding symptom severity; three 3-4-week trials vs. naturopathy (massage, acupressure, breathing), relaxation or breathing&relaxation, respectively in GAD, DSM 3 anxiety or "psychoneurosis", respectively (79 subjects total). One pooled estimate suggested lower anxiety scores with yoga (SMD -0.86; -1.56 to -0.15), but with I^2=50% (103). An appropriate estimate would include HKSJ correction for 95%CIs -2.39 to 0.67, t=-2.419, p=0.137 (no effect); b) one small Canadian high risk of bias 3-week trial vs. progressive relaxation in "snake anxiety" (N=40), indicating no difference and c) one small Brazilian 8 week trial in DSM 4 panic disorder vs. yoga + CBT indicating no difference. Based on criteria in Table 1, there is no relevant data on (non)effect of yoga in anxiety disorders.

Morita therapy

A Cochrane review (104) found 4 small Chinese high risk of bias 4-6 weeks RCTs: one in GAD (N=31 men), one in "anxiety" (N=86 women) (neither providing any numerical data) and 2 in social phobia, comparing Morita (n=19 or n=24) to pharmacological treatment ("unspecified" n=20 or alprazolam n=12, respectively). The pooled fixed-effect RR for "response" was reported=1.85, 95%CI 1.27-2.69 favoring Morita. An appropriate estimate would be random-effects with HKSJ correction=1.77, 95%CI 0.14-21.8, t=2.892, p=0.212 (no effect). Based on criteria in Table 1, there is no relevant data on (non)effect of Morita in anxiety disorders.

Tai Chi, Baduanjin mindfulness exercise, Chinese cognitive psychotherapy, reiki

A recent review (105) identified 1 high risk of bias Chinese 6-week trial in elderly with CCMD 3 "anxiety" treated with paroxetine+*Tai Chi* (n=16) vs. paroxetine (n=16), indicating greater HAM-A

reduction with combined treatment. Another review (106) identified one 12-week high risk of bias Chinese RCT in GAD of *Baduanjin mindfulness exercise* + pharmacological therapy vs. pharmacological therapy indicating greater improvement of symptoms. We previously (26) identified an open high risk of bias 24-week Chinese trial in CCMD 2-R GAD showing better symptoms scores with *Chinese psychotherapy* alone or combined with benzodiazepines vs. benzodiazepines alone (total N=131). With limitations due to small samples and high risk of bias, data indicate "add-on" effect of these procedures to pharmacological treatment. A recent Cochrane review (107) identified no RCTs of *reiki* in anxiety disorders.

Religious and spiritual interventions

Across 2 reviews (26, 108), two small high risk of bias 12-week RCTs in DSM 4 GAD were identified comparing a multifaith spiritual intervention to CBT (total N=22) indicating no difference, or to supportive psychotherapy (total N=23) indicating lower HAM-A scores and more responders at the end of treatment. With limitations due to high risk of bias and small samples, data indicate possible anxiolytic effect.

Relaxation

One review (109) identified only one 14-week RCT of *applied relaxation* (AR) in DSM 4 social phobia patients (110). In this otherwise high quality trial, comparison of relaxation (n=21) to wait-list controls (n=20) showing a markedly greater LSAS score reduction was partly compromised by the limitations inherent to wait-list controlled trials. In comparison to cognitive therapy (n=21), reduction of symptoms was significantly less with AR. Another review (111) included 16 RCTs of "good or acceptable quality" (111): 9 with AR (in GAD or panic disorder) and 7 with *mindfulness-based stress reduction* to conclude an overall "superiority of relaxation" in terms of high effect size (Hedges' g= around 0.62) (111). However (based on data from the review, 111): a) 5 trials evaluated AR in GAD, one (N=50) vs. wait-list showing no difference in symptoms after 12 weeks, and 4 vs. CBT over 6-12 weeks (N=172): random-effects *g*= 0.662, 95%CI (HKSJ correction) -0.1 to 1.42,

t=2.777, p=0.069, I^2=58% (no effect). Hence, data do not demonstrate (due to lack of assay sensitivity), but also do not exclude an effect of AR; b) 4 trials evaluated AR in panic disorder; in one 12-week trial, symptom reduction was greater with AR (n=16) than in wait-list controls (n=16), similar as with imipramine (n=16), but considerably less than with CBT (n=16) (112); in another 12-week trial, symptom reduction was similar for AR (n=19) and CBT (n=19); and in two 12-week trials (total N=48) vs. progressive relaxation or cognitive therapy, symptom reductions were in favor of AR, but not achieving statistical significance, g=0.60, 95%CI -1.64 to 2.84 (with HKSJ correction). Therefore, there is indication about the effect of AR, but also quite some uncertainty.

Mindfulness-based interventions (MBIs) and meditation

A considerable number of conceptually and methodologically variable systematic reviews/ meta-analyses have been published over the past 10 years addressing RCTs of MBIs and/or meditation for anxiety disorders/symptoms. One large review (113), for example, included trials with a "clinical diagnosis" (113) referring to mindfulness-based cognitive therapy (MBCT) or stress reduction (MBSR), mantra-based programs (e.g., transcendental or mantra mediation), but excluded acceptance and commitment therapy (ACT), dialectical behavior therapy (DBT), relaxation, spiritual treatments, trials with wait-list controls or "no treatment" controls; and considered all MBIs jointly and trials in all anxiety disorders and all treatment durations jointly. For MBIs vs. "non-specific controls" (any non-EBM-based treatment), based on 8 trials with 647 patients, pooled estimate for anxiety symptom scores reduction was (95%CI) from 0% to 44% greater reduction with MBIs("moderate strength of evidence for improvement"); based on 11 RCTs with 691 patients vs. "any EBM-based treatment" the estimate was from 39% less to 8% more symptom reduction (tends to favor EBM-based treatment) (113). For "mantra" (clinically standardized mantra meditation) (3 trials, 247 patients) vs. "non-specific controls" the difference was "0", and data vs. EBM-treatments were too few (both judged as insufficient for conclusions about (non)effects without considerable uncertainty) (113). Another recent large review (114) excluded ACT, DBT but also mantra, and

electronically delivered treatments, and included trials in patients with clinical diagnoses or with anxiety symptom scores above certain levels and with any type of non-MBI controls. All anxiety trials (diagnosis, scores, duration) and all MBIs were considered jointly (114): a) based on 8 trials (472 patients) vs. no treatment, MBIs provided markedly greater symptom reduction (*d*=0.89; 0.62 to 1.17), but with much inconsistency (I^2=81%); b) based on 5 trials (374 patients) vs. non-EBM-based treatments, there appeared no difference (*d*=0.15; -0.16 to 0.46) and no inconsistency ; c) based on 5 trials (362 patients) vs. EBM-based treatments, difference tended to favor EBM (*d*=-0.18; -0.41 to 0.06) with mild inconsistency (I^2=38%). Another review focused specifically on MBCT in patients with a clinical diagnosis and found only one small trial (N=26) in social phobia indicating a better outcome with CBT vs. MBCT (115), while yet another focused on transcendental meditation (116) identified only one small trial (N=31) in "anxiety" finding no difference vs. muscle biofeedback or relaxation. A review focused on mindfulness and acceptance-base interventions for anxiety disorders (117) disregarded randomization and analyzed pre-post differences, which we consider inappropriate. Three recent reviews (118-120) included (among others, or exclusively) RCTs of mindfulness-based interventions in patients with clinical anxiety disorder diagnoses and enabled identification of RCTs by treatment, diagnosis and comparisons, one (118) exclusively regarding electronically delivered MBIs (internet, smartphones, recorded material), and two (119, 120) explicitly excluding such trials. All 3 reviews provided meta-analytical pooled estimates across a number of trials with considerable clinical (and statistical) heterogeneity. Using these 3 reviews, we identified all individual included trials: Table 6 outlines their characteristics sorted by the mode of delivery (electronic or "in person"). Overall, data suggest the following: a) major reviews/meta-analyses (across diagnoses and different treatment comparisons) (113, 114) support the view that, as a concept, MBIs may be useful in treatment of anxiety disorders; b) there is, however, a reasonable level of uncertainty about this effect: (i) no-treatment control/wait-list control groups may have inflated the effect; (ii) there is some inconsistency in comparisons vs. "non-EBM-based

treatments" – an indication of moderate superiority (113) but also of no relevant difference (114); (iii) and a consistent indication of inferiority vs. "EBM-based" treatments, which is particularly burdened with uncertainty since the number of RCTs is small and estimates are imprecise; c) in reality, the total number of individual RCTs is small with a limited number of patients, particularly when broken-down by mode of delivery-by-disorder-by-type of intervention-by type of the control (Table 6); d) not going into details about potential quality issues, data in Table 6 show that there are only 5 RCTs regarding "electronic delivery", quite clinically heterogeneous (diagnoses, treatments, controls): (i) only the two RCTs in GAD are similar enough as to justify a pooled estimate. In both trials MBI was superior to wait-list, but the pooled estimate (with HKSJ correction) extends from benefit to no benefit (Table 6) leaving still some uncertainty; the remaining 3 RCTs are too heterogeneous clinically and by results to justify data pooling; e) there are 8 "live" RCTs that are, actually, too heterogeneous clinically to justify pooled estimates (Table 6). Three comparisons vs. CBT (in "anxiety" and social anxiety disorder) suggest that MBI might be inferior to CBT (Table 6), two trials vs. wait-list suggest efficacy (GAD or combined different disorders) (Table 6), while 3 trials vs. "other, non-EBM-based treatments" do not (Table 6). Overall, therefore, while there might not be uncertainty about whether the concept generally "works" in anxiety disorder, there is quite some uncertainty about (non)existence and size of its effect in different anxiety disorders.

Alternative medical systems

Ayurveda

One dedicated systematic review (121) identified 5 RCTs of a herb *Ashwagandha* (*Withania somnifera*), but none in patients diagnosed with anxiety disorders. We previously identified (26) one overall low risk of bias 11-week RCT in GAD (N=102) indicating no difference in HAM-A reduction or response to an oral Ayurvedic preparation *Sarasvata choorna* vs. placebo; and one

small (4 weeks, total N=65) inconclusive (no assay sensitivity) trial of oral *Manasamitra Vataka* vs. benzodiazepines in GAD patients.

Homeopathy

We previously identified (26) one overall low risk of bias 10-week double blind placebo-controlled trial of homeopathy in GAD showing no difference in HAM-A reduction or response rate. Two dedicated reviews (122, 123) found no further published RCT of homeopathy in anxiety disorders.

Conclusion

A broad range of CAM modalities have been investigated in RCTs in anxiety disorders but to a considerably variable extent and with a considerable variability in trial quality and consistency of results. Some treatments considered as CAM (at this moment) do show a potential of possible utility in treatment of anxiety disorders, but so far none has been evaluated to the extent comparable to that of the *mainstream* treatments. Considering that the only reasonable "classification" of treatments is to those supported by evidence and those that (at the moment) are not, no lesser criteria should be in place for CAM than for *mainstream* treatments. There is a need for methodologically clear-cut and stringent larger clinical trials – meta-analytical estimates based on numerous small, heterogeneous trials are not likely to resolve the issue and the currently existing meta-analytical estimates in some cases appear to be overtly non-conservative.

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