

Review

The evidence base of complementary and alternative therapies in depression

A.F. Thachil ^{*}, R. Mohan ¹, D. Bhugra ²

Kings College London, Section of Cultural Psychiatry, HSRD, PO: 25, Institute of Psychiatry, DeCrespigny Park, London SE5 8AF, UK

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Abstract

Background: Depression is one of the leading indications for using Complementary and Alternative Medicine (CAM). This paper reviews the evidence of efficacy of different types of CAM in depression with the aim of identifying the highest level of evidence.

Methods: We conducted literature searches restricted to the English language for studies on CAM as monotherapy in depression. All papers were reviewed by two researchers and the evidence was ranked according to a widely referenced hierarchy of evidence.

Results: 19 papers formed the final review. We found Grade 1 evidence on the use of St. John's wort, Tryptophan/5-Hydroxytryptophan, S-adenosyl methionine, Folate, Inositol, Acupuncture and Exercise in Depressive disorders, none of which was conclusively positive. We found RCTs at the Grade 2 level on the use of Saffron (Herbal medicine), Complex Homoeopathy and Relaxation training in Depressive disorders, all of which showed inconclusive results. Other RCTs yielded unequivocally negative results. Studies below this level yielded inconclusive or negative results.

Limitations: Searches were restricted to the English language. Our list of CAM approaches may not have been comprehensive. We excluded studies on the use of CAM as an adjunctive treatment and this review aimed to identify only the highest level of evidence.

Conclusions: None of the CAM studies show evidence of efficacy in depression according to the hierarchy of evidence. The RCT model and the principles underlying many types of CAM are dissonant, making its application in the evaluation of those types of CAM difficult. The hierarchy of evidence we used has limited utility in grading trials of CAM.

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Keywords: CAM; Complementary therapy; Depression; Depressive disorders; Evidence; Hierarchy of evidence

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* Corresponding author. Tel.: +44 207 837 8888x5615; fax: +44 207 277 1462.

E-mail addresses: afthachil@yahoo.co.uk (A.F. Thachil), spharom@iop.kcl.ac (R. Mohan), d.bhugra@iop.kcl.ac.uk (D. Bhugra).

¹ Tel.: +44 207 848 0048; fax: +44 207 277 1462.

² Tel.: +44 207 848 0047; fax: +44 207 277 1462.

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1. Introduction

The last decade has witnessed a significant growth of interest in Complementary and Alternative Medicine (CAM) worldwide. In the UK, about 1 in 10 of the adult population consults a CAM practitioner every year, and 90% of these contacts happen outside the National Health Service (NHS) (Thomas et al., 2001). In 1998, 40% of the respondents of a national survey in the United States had used at least one such therapy in the previous 1 year (Astin, 1998). In 1996, it was estimated that almost half of Australian adults used complementary medicines in the past year and a fifth consulted complementary practitioners (MacLennan et al., 1996). 42% of 115 Danish psychiatric in-patients had used Complementary and Alternative Medicine (CAM) at least once during the course of their illness (Raben and Aggernaes, 1991).

Depression is one of the 10 most frequent indications for using CAM (Astin, 1998; Kessler et al., 2001). Depression is a significant cause of morbidity and mortality world-wide, imposing a range of costs on individuals, families and communities and accounting for a sizeable proportion of the global burden of disease and

disability (Scott and Dickey, 2003). Taking the disability component of burden alone, depression is the leading cause of disability in both sexes and across all ages, accounting for almost 12% of all disability (The World Health Report, 2001). A major problem is that much of depression is under-diagnosed and under-treated, and compliance with antidepressants is often low (Davidson et al., 1999; Kendrick, 2000), a fact that assumes significance given the prevalence of CAM use by those who are depressed. The 3 most widely used CAM approaches in depression are Relaxation, Exercise and Herbal remedies (Astin, 1998).

Some of the reasons for the use of CAM include the relatively lower incidence of adverse effects, perceived effectiveness, the desire for egalitarian relationships with medical practitioners, a holistic approach to the individual's problems and dissatisfaction with conventional healthcare (Ernst and White, 2000; Razali and Najib, 2000; Astin, 1998). However, despite this upsurge in the number of CAM consultations, providers of conventional healthcare have failed to address the issue. The United Kingdom Department of Health (DOH) has published an Information Pack on CAM (DOH, 2001) for Primary Care Groups (PCGs) which deals with 6 therapies;

Acupuncture, Aromatherapy, Chiropractic, Homeopathy, Hypnotherapy and Osteopathy. This has in part been responsible for several of these therapies being made accessible to patients by PCGs and the UK Department of Health funding several CAM research projects, as per the recommendations of the House of Lords Select Committee on CAM (House of Lords, 2000). However, this list is based on popularity and currently available evidence of efficacy. This is still a positive step, as it can provide impetus for further research into these approaches, but this may mean that those therapies that are not listed may be neglected in research.

Given their frequent use, CAM approaches warrant the same level of evaluation as conventional treatments. Service users, planners, general practitioners and mental health professionals need to be informed about which treatments are effective, which are not, and which ones have been adequately evaluated. With this goal in mind, we aimed to review studies that looked at the efficacy of different types of CAM in Depressive disorders among adult patients, with the specific aim of identifying the highest level of available evidence for each of these CAM approaches. For this purpose, we used a hierarchy of evidence which is one of the most widely used frameworks for ranking research-based clinical knowledge, and underpins many health policy and management decisions (Gray Muir, 1997). The reviewed research was graded according to the levels of this hierarchy.

We hypothesised that many of these therapies would not meet the criteria for the best evidence i.e. levels 1 or 2 of the hierarchy of evidence (Table 2).

2. Methods

We conducted computerized literature searches to identify all studies related to the use of CAM as monotherapy in Depressive disorders. The following databases were searched—MEDLINE (literature from 1966–June 2005), EMBASE (literature from 1980–June 2005), AMED (Allied and Complementary Medicine, literature from 1985–June 2005), PSYCINFO (1974–June 2005), the Cochrane Complementary Medicine field and the Cochrane Library (up to June 2005). Age restrictions were not applied. The search terms were Complementary Medicine, Complementary Therapy, Alternative Medicine, Alternative Therapy, Depression and Depressive Disorder. We combined these individually with Systematic Review, Meta-analysis, RCT, Case-control study, Cohort study, Open study, Case series and Case study for each search. Subsequently we also searched for individual therapies by name, combined with Systematic Review, Meta-analysis, RCT, Case-control study, Cohort study,

Open study, Case series and Case study as search terms. We also hand searched for cross-referenced articles and books. The searches were restricted to publications in the English language.

We obtained the list of CAM approaches from diverse sources—textbooks, primers and guides in the area (Ernst et al., 2001; Micozzi, 2005), the DOH information pack (DOH, 2001), and CAM databases and discussions. We supplemented this search with interviews with CAM practitioners in London and other cities in the UK, to identify various forms of CAM. The final list included 55 Complementary and Alternative Therapies (Table 1).

Studies that investigated the use of CAM as an adjunct to conventional treatment were excluded from the review, since we focussed on CAM as monotherapy. We also excluded studies that evaluated a combination of two or more CAM approaches as the primary therapeutic intervention. Studies on subjects younger than 18 years were excluded from the review. Studies that addressed depressive states outside ICD (International Classification of Diseases) and DSM (Diagnostic and Statistical Manual of Mental Disorders) based diagnoses of depressive disorders were excluded to ensure homogeneity.

Table 1
List of complementary and alternative therapies

1. Acupuncture	28. Laughter
2. Acupressure	29. Manipulation
3. Alexander technique	30. Massage
4. Art therapy	31. Meditation
5. Ayurveda	32. Movement therapy
6. Bach flower remedies	33. Music therapy
7. Balneology	34. Naturopathy
8. Chelation therapy	35. New age healing
8. Chiropractic	36. Nutritional therapy
9. Colonic hydro therapy	37. Osteopathy
10. Colour therapy	38. Oxygen therapy
11. Cranio-sacral therapy	39. Pilates
12. Cranial osteopathy	40. Polarity
13. Crystal healing	41. Pranic healing
14. Dance therapy	42. Qigong
15. Energy	43. Reflexology
16. Essential oils	44. Reiki
17. Exercise	45. Relaxation
18. Folk medicine	46. Rolfing
19. Gerson therapy	47. Shiatsu
20. Healing	48. Siddha
21. Hellerwork	49. Spiritual healing
22. Herbal medicine	50. Therapeutic touch
23. Homeopathy	51. Traditional healing
24. Hydro therapy	52. Traditional Chinese medicine
25. Hypnosis	53. Tragerwork
26. Kampo	54. Unani
27. Kinesiology	55. Yoga

Two researchers independently reviewed the citations retrieved from the search. One of these was the retrieving researcher. We identified potentially relevant abstracts, obtained the original articles and reapplied the inclusion and exclusion criteria. They were then critically appraised independently by each researcher for the methodology and the level of evidence, and were then ranked according to the hierarchy of evidence (Table 2). The appraisal included assessment of sampling methods, randomisation, blinding, statistical analyses, outcome measures, duration of follow-up, monitoring of side effects and criteria used in systematic reviews. Disagreements were resolved by discussion. For those therapies where evidence at a particular level was available, we did not search for evidence below that level e.g. where systematic reviews or randomised controlled trials were available, we did not search further for evidence at lower levels, which was lower in the hierarchy of evidence.

3. Results

We identified 59 studies that evaluated the use of CAM in depressive disorders. Of these, we excluded 12 systematic reviews since they pre-dated the latest in that particular CAM; one systematic review because it studied anxiety in depressed patients, and 12 papers since they were non-systematic reviews or commentaries. Besides these, 16 more papers were excluded as they had either one or more of the following methodological problems: they (i) evaluated the use of CAM as an adjunct to conventional therapy, (ii) evaluated the use of a combination of complementary therapies, (iii) did not use operationalized (ICD or DSM) diagnoses of depression, (iv) studied samples with mixed diagnoses (v) evaluated the use of CAM in subjects under 18 years, (vi) contained little information about the methodology; and (vii) did not have definite outcome measures. 19 papers formed the final review and are shown in Table 3.

Table 2
Hierarchy of evidence

Grade 1	Strong evidence from at least 1 systematic review of multiple well designed randomised controlled trials.
Grade 2	Strong evidence from at least 1 properly designed randomised controlled trial of appropriate size.
Grade 3	Evidence from well-designed trials without randomisation, single group pre-post, cohort, time series or matched case-controlled studies.
Grade 4	Evidence from well-designed, non-experimental studies from more than one centre or research group.
Grade 5	Opinions of respected authorities, based on clinical evidence, descriptive studies or reports of expert committees.

From Gray Muir (1997).

The studies we found will be discussed under the corresponding levels of evidence.

4. Grade 1 evidence

Our search found Grade 1 evidence on the use of St. John's wort, a herbal medicine, a number of Nutritional Therapy approaches, Acupuncture and Exercise in Depressive disorders. None of this evidence was unequivocally positive. Where the results tended towards the positive, the evidence was not sufficiently conclusive as to indicate clear benefit.

4.1. *Hypericum perforatum* (St. John's Wort)

We found Grade 1 evidence for the use of *Hypericum Perforatum* (St. John's Wort) in depressive disorders (Linde et al., 2005). However, results of placebo-controlled trials showed marked heterogeneity. In trials restricted to patients with major depression, the combined response rate ratio (RR) for hypericum extracts compared with placebo from six larger trials was 1.15 (95% confidence interval, 1.02–1.29) and from six smaller trials was 2.06 (95% CI, 1.65 to 2.59). In trials not restricted to patients with major depression, the RR from six larger trials was 1.71 (95% CI, 1.40–2.09) and from five smaller trials was 6.13 (95% CI, 3.63 to 10.38). Compared with selective serotonin reuptake inhibitors (SSRIs) and tri- or tetracyclic antidepressants, respectively, RRs were 0.98 (95% CI, 0.85–1.12; six trials) and 1.03 (95% CI, 0.93–1.14; seven trials). Patients given St. John's wort dropped out of trials due to adverse effects less frequently than those given older antidepressants (Odds Ratio: 0.25; 95% CI, 0.14–0.45). Patients given St. John's wort dropped out of trials due to adverse effects less frequently than those given SSRIs, but this difference was not statistically significant (OR: 0.60, 95% CI, 0.31–1.15).

4.2. *Tryptophan/5-Hydroxytryptophan*

We found Grade 1 evidence indicating some benefit from Nutritional Therapy in Depression, with Tryptophan/5-Hydroxytryptophan (Shaw et al., 2002). A systematic review found only 2 trials, out of 108 extracted from literature, to be of sufficient quality to meet the inclusion criteria. They involved a total of 64 patients and the available evidence suggests these substances were better than placebo at alleviating depression (Peto Odds Ratio 4.10; 95% confidence interval 1.28–13.15; RD 0.36; NNT 2.78). However, the evidence was of insufficient quality to be conclusive. The possible

Table 3
Highest level of evidence for CAM approaches in depressive disorders

Type of CAM	Author/year	Type/description	Outcome	Level of evidence
Herbal Medicine—St. John's wort (<i>Hypericum perforatum</i>)	Linde et al., 2005	Systematic review of 35 RCTs.	Minimal beneficial effect, with a Response Rate ratio (RR) of 1.15; (95% CI, 1.02–1.29) over placebo in 6 larger trials and 2.06 in 6 smaller trials (95% CI, 1.65–2.59).	Grade 1, equivocal.
Nutritional therapy—Tryptophan and 5-hydroxy-tryptophan for depression.	Shaw et al., 2002	Systematic review and meta-analysis of 2 RCTs.	Significant effect over placebo (Peto odds ratio 4.10; 95% CI 1.28–13.15; RD 0.36; NNT 2.78), but sample size small (64), duration short (10 weeks) and data insufficient to evaluate adverse effects.	Grade 1, equivocal.
Nutritional therapy—S-adenosyl methionine (SAME) in depression.	Bressa, 1994	Meta-analysis	Greater response rate with SAME compared to placebo (global effect size 27–38% depending on definition of response), antidepressant effect comparable to standard tricyclics. Most studies were methodologically flawed and brief in duration (<6 weeks).	Grade 1, equivocal.
Acupuncture	Smith and Hay, 2004	Systematic review and meta-analysis of 7 RCTs.	Results from 5 trials included in the meta-analysis showed no difference in the reduction in the severity of depression compared to medication (WMD 0.53, 95% CI –1.42 to 2.47). Evidence insufficient to determine the efficacy of acupuncture vs. medication due to the poor methodological quality of the trials.	Grade 1, equivocal.
Exercise	Lawlor and Hopker, 2001	Systematic review and meta-analysis of 14 RCTs.	Standardised mean difference in effect size –1.1 (95% CI, –1.5 to –0.6) over no treatment. No statistically significant difference in effect size over cognitive therapy. All studies had important methodological weaknesses.	Grade 1, equivocal.
Nutritional therapy—Folate for depression.	Taylor et al., 2003	Systematic review and meta-analysis of 3 RCTs.	No significant benefit when used instead of antidepressant. Significant effect with folate augmentation (avg. reduction in HDRS scores of 2.65 points, 95% CI 0.38–4.93; NNT for 50% reduction in HDRS scores=5).	Grade 1, equivocal.
Nutritional therapy—Inositol for depression.	Taylor et al., 2004	Systematic review and meta-analysis of 4 RCTs.	The pooled estimate of effect (SMD –0.08, 95% CI –0.45 to 0.30) was consistent with both a presence and absence of therapeutic benefit. Trials were short term and the total sample size (141) was small.	Grade 1, equivocal.
Herbal Medicine— <i>Crocus sativus</i> L. (Saffron) in mild to moderate depression.	Noorbala et al., 2005	RCT	Both Crocus and Fluoxetine groups showed a significant improvement over the 6 weeks of treatment ($P<0.0001$). Crocus was found to have an effect similar to Fluoxetine ($F=0.13$, $df=1$, $P=0.71$). Sample size was small (40).	Grade 2, inconclusive.
Herbal Medicine— <i>Crocus sativus</i> L. (Saffron) in mild to moderate depression	Akhondzadeh et al., 2004	RCT	Both Crocus and Imipramine groups showed significant improvement over the 6 weeks of treatment ($P<0.0001$). The difference between the two was not significant as indicated by the effect of group, the between-subjects factor ($F=2.91$, $df=1$, $P=0.09$). Sample size was small (30).	Grade 2, inconclusive.
Complex Homeopathy—Neurapas balance, a combination of St. John's wort, passion flower and valerian extracts in mild depression.	Urlea-Schön et al., 2003	RCT	More effective than placebo ($P<0.0001$) with regard to improvement in the primary outcome criterion HAMD ₂₁ , which decreased from 12.59 (S.D. 1.39) to 6.81 (S.D. 3.75) in the neurapas group and from 12.47 (S.D. 1.40) to 12.79 (S.D. 2.46) in the placebo group. Sample size was small (67).	Grade 2, inconclusive.

(continued on next page)

Table 3 (continued)

Type of CAM	Author/year	Type/description	Outcome	Level of evidence
Relaxation therapy	Murphy et al., 1995	RCT	Both the relaxation and CBT groups had significantly better BDI scores ($P < 0.01$) than the tricyclic group post-treatment. 73% of the relaxation group improved to set BDI criteria post-treatment compared to 82% for CBT and 29% for tricyclics. The study had several methodological drawbacks, including small sample size (37).	Grade 2, inconclusive.
Nutritional therapy—Docosahexaenoic acid (DHA, an omega-3 fatty acid) in major depression.	Marangell et al., 2003	RCT	Response (defined as $\geq 50\%$ reduction in MADRS scores) rates were 27.8% in the DHA group and 23.5% in the placebo group, the difference between which did not reach statistical significance.	Grade 2, negative.
Nutritional therapy—Tyrosine for depression.	Gelenberg et al., 1990	RCT	No evidence that tyrosine had antidepressant activity. Sample size small (65) and study duration short (4 weeks).	Grade 2, negative.
Herbal Medicine— <i>Lavandula angustifolia</i> Mill. Tincture in mild to moderate depression.	Akhondzadeh et al., 2003	RCT	Less effective than Imipramine in mild to moderate depression ($F = 13.16$, $df = 1$, $P = 0.001$), though a combination of Imipramine and <i>Lavandula</i> was more effective than Imipramine alone ($F = 20.83$, $df = 1$, $P < 0.0001$). Sample size was small (45).	Grade 2, negative.
Music therapy in major and minor depression	Hanser and Thompson, 1994	Open-label RCT	Participants in both music intervention groups showed significant improvements on all measures at 8 weeks compared to wait list controls, with the improvements being maintained at 9 month follow-up ($P < 0.05$). The sample was small (30), not representative of the general population and double-blind conditions were lacking.	Grade 3, inconclusive.
Yoga (Sudarshan Kriya)	Janakiramiah et al., 2000	Open-label RCT	Remission (HDRS ≤ 7) rates were 67%, compared to 93% in ECT group and 73% in tricyclic group, at the end of 4 weeks. Sample size was small (45) and double-blind conditions lacking.	Grade 3, negative.
Movement therapy in major depression	Stewart et al., 1994	Randomized, open, single group, uncontrolled study	5 of 12 patients with Major Depression showed reduction in depression scores on movement therapy days compared to days without therapy ($P < 0.05$). The study had serious methodological limitations.	Grade 3, inconclusive.
Aromatherapy massage in major depression	Okamoto et al., 2005	Non-randomized, open, single-group, uncontrolled study.	HAMD scores in the 5 patients with mild depression improved from 14.8 (S.D. 2.39) to 8.8 (S.D. 3.63) ($P = 0.039$). The study had serious methodological limitations.	Grade 3, inconclusive.
Traditional Chinese Medicine in melancholia	Wu et al., 1999	Case series ($n = 40$)	19 cured, 16 improved, 5 failed, with total effective rate of 87.5%	Grade 5, positive.

association between these substances and the potentially fatal Eosinophilia–Myalgia Syndrome has not been elucidated.

4.3. *S*-adenosyl methionine

We also found Grade 1 evidence for another Nutritional Therapy approach, with *S*-adenosyl methio-

nine (SAME) (Bressa, 1994), indicating that it may be of some benefit in Depression. The only systematic review and meta-analysis of the studies on SAME, though not recent (1994), showed a greater response rate when compared with placebo, with a global effect size ranging from 27% to 38% depending on the definition of response. The meta-analysis of 6 RCTs found that 70% of subjects showed some response to SAME, compared

with 30% for placebo. Furthermore, pooling of data from 7 trials comparing SAME with standard tricyclics found no difference indicating a comparable antidepressant effect. However, most studies were methodologically flawed and brief in duration (<6 weeks). SAME was well tolerated and caused few side-effects. Reliable comparisons to SSRIs are not available.

4.4. Acupuncture

A Cochrane systematic review and meta-analysis of 7 RCTs on Acupuncture (Smith and Hay, 2004) produced equivocal results. The results from 5 trials (409 participants) included in the meta-analysis showed no difference in the reduction in the severity of depression (HAM-D) compared to medication (WMD 0.53, 95% CI –1.42 to 2.47). 4 trials (375 participants) reported on improvement in depression as an outcome (RR 1.20, 95% CI 0.94–1.51), again showing no differences between groups. However, the evidence was insufficient to determine the efficacy of acupuncture vs. medication due to the poor methodological quality and reporting of these trials. There was insufficient data to demonstrate whether acupuncture is more effective than a wait-list control, non-specific or sham acupuncture control, or whether acupuncture plus medication is more effective than acupuncture plus placebo.

4.5. Exercise

We found Grade 1 evidence pertaining to the effectiveness of exercise in depression (Lawlor and Hopker, 2001). However, this evidence is inconclusive. All 14 studies included in the systematic review had important methodological weaknesses. The participants in most studies were community volunteers i.e. not clinical populations, and diagnosis depended on their score on the Beck Depression Inventory. When compared with no treatment, exercise reduced symptoms of depression (standardised mean difference in effect size –1.1 (95% confidence interval –1.5 to –0.6); weighted mean difference in Beck depression inventory –7.3 (–10.0 to –4.6)). The effect size was significantly greater in those trials with shorter follow up and in two trials reported only as conference abstracts. The effect of exercise was similar to that of cognitive therapy (standardised mean difference –0.3; 95% confidence interval –0.7 to 0.1).

4.6. Folate

A systematic review on the effectiveness of folate in the treatment of depression found only one trial (out of

the 3 included), which evaluated the use of folate as monotherapy (Taylor et al., 2003). Two studies involving 151 people assessed the use of folate in addition to other treatment and found that adding folate reduced Hamilton Depression Rating Scale scores on average by a further 2.65 points (95% confidence interval 0.38 to 4.93). One study involving 96 people assessed the use of folate instead of the antidepressant trazodone and did not find a significant benefit from its use.

4.7. Inositol

A systematic review to determine the effectiveness of inositol in treating depression identified four trials, with a total of 141 participants (Taylor et al., 2004). All were short-term trials of double-blind design. In one trial, inositol was used as monotherapy. In the other studies it was used in addition to conventional antidepressant agents. The pooled estimate of effect (SMD –0.08, 95% CI –0.45 to 0.30) was consistent with both a presence and absence of benefit. Thus, there was no clear evidence of therapeutic benefit.

5. Grade 2 evidence

We found RCTs conforming to Grade 2 criteria as the highest level of available evidence on the effectiveness of Saffron (herbal medicine), homoeopathy, and relaxation training in Depressive disorders, all of which showed inconclusive results. We also found RCTs evaluating some nutritional therapy and herbal medicine approaches that showed conclusively negative results. These were in addition to those RCTs evaluating CAM approaches that had Grade 1 evidence.

5.1. Saffron

Two well-designed RCTs from the same research group compared the effectiveness of the herb Saffron (*Crocus sativus* L.) against standard antidepressants in mild to moderate depression, diagnosed according to the Structured Clinical Interview for DSM-IV. In the first (Noorbala et al., 2005), both Saffron and Fluoxetine groups showed a significant improvement over the 6 weeks of treatment ($P < 0.0001$). Crocus was found to have an effect similar to Fluoxetine ($F = 0.13$, $df = 1$, $P = 0.71$). However, the sample size was small (40). In the second (Akhondzadeh et al., 2004), both Saffron and Imipramine groups showed a significant improvement in the HAM-D over the 6 weeks of treatment ($P < 0.0001$). The difference between the two was not significant as indicated by the effect of group, the between-subjects

factor ($F=2.91$, $df=1$, $P=0.09$). Sample size (30) was smaller than in the first trial.

5.2. Homoeopathy

Another RCT studied the effectiveness of Neurapas balance, a complex homoeopathic remedy, which is a combination of St. John's wort, passion flower and valerian extracts, in 67 adult patients with mild depressive disorders according to ICD-10. The patients had a baseline Hamilton Rating Scale for Depression (HAM_{D21}) score of between 10 and 17 (Urlea-Schön et al., 2003). The trial duration was 6 weeks. Neurapas was found to be more effective than placebo ($P<0.0001$) with regard to improvement of the primary outcome criterion HAM_{D21}, which decreased from 12.59 (S.D. 1.39) to 6.81 (S.D. 3.75) in the neurapas group and from 12.47 (S.D. 1.40) to 12.79 (S.D. 2.46) in the placebo group. Sample size was small (67).

5.3. Relaxation training

Another RCT with a small sample (37) of patients with DSM-IV moderate depression, compared relaxation training, cognitive-behavioural therapy and tricyclic antidepressants (Murphy et al., 1995). This produced evidence in favour of relaxation training, with 73% of the relaxation group improving to set BDI criteria post-treatment, compared to 82% for CBT and 29% for tricyclics. Both the relaxation and CBT groups had significantly better BDI scores ($P<0.01$) than the pharmacological treatment post-treatment. However, the results need to be interpreted with caution because of the sample size, lack of control for the effects of attention from professionals (in the relaxation and CBT groups) and reported non-compliance in the medication group.

5.4. Docosahexaenoic acid, tyrosine and Lavandula angustifolia Mill

RCTs conducted on the effectiveness of Docosahexaenoic acid (DHA, an omega-3 fatty acid) in major depression (Marangell et al., 2003), and Tyrosine (a naturally occurring amino acid and neurotransmitter precursor) in major depression (Gelenberg et al., 1990), both yielded unequivocally negative results. A small, preliminary RCT on the use of *L. angustifolia* Mill. Tincture, an herbal medication, in mild to moderate depression (Akhondzadeh et al., 2003); found that the preparation was unequivocally less effective than Imipramine. However, a combination of Imipramine and

Lavandula tincture was more effective than Imipramine alone ($F=20.83$, $df=1$, $P<0.0001$).

6. Grade 3 evidence

We found studies conforming to Grade 3 criteria as the highest level of available evidence on the effectiveness of Aromatherapy massage, Movement Therapy, Music Therapy and Yoga in Depressive disorders. These were in addition to those Grade 3 studies evaluating CAM approaches which had Grade 1 and 2 evidence.

It was not possible to draw firm conclusions from the results of these studies as all of them had significant methodological limitations.

6.1. Music therapy

An open RCT evaluated the effectiveness of Music Therapy in 30 older adults (aged 61–86 years) diagnosed with major or minor depressive disorder (Hanser and Thompson, 1994). They were randomly assigned to one of three 8-week conditions: a home-based program where participants learned music listening stress reduction techniques at weekly home visits by a music therapist, a self-administered program where participants applied these same techniques with moderate therapist intervention (a weekly telephone call), or a wait list control. After 8 weeks, the Geriatric Depression Scale scores of the 2 music groups were significantly better than those of the control group ($P<0.05$). These improvements were maintained over a 9-month follow-up period. The sample was small in size, not representative of the general population (only older adults, predominantly female and highly educated) and double-blind conditions were lacking. This result has not been replicated elsewhere.

6.2. Yoga (Sudarshan Kriya)

Another open RCT compared the relative antidepressant efficacy of Sudarshan Kriya Yoga (SKY) in depression with electroconvulsive therapy (ECT) and Imipramine (Janakiramaiah et al., 2000). Untreated melancholic depressives ($N=45$) were randomized equally into 3 treatment groups and followed up over 4 weeks. Significant reductions in scores on the Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HAM-D) occurred on successive occasions in all 3 groups. At week 3, the SKY group had higher scores than the ECT group but was not different from the Imipramine group. Remission (HAM-D score of 7 or less) rates at the end of the trial

were 93, 73 and 67% in the ECT, Imipramine and SKY groups, respectively. Due to the lack of double-blind conditions, small sample size and the short treatment period, the data is insufficient to judge the value of SKY for depression.

6.3. Movement therapy

In a small study (Stewart et al., 1994), 12 inpatients with Major Depression were randomly assigned to movement therapy sessions on 7 of 14 days. Five of them showed a reduction in depression scores on movement therapy days compared to days without therapy ($P < 0.05$). The study had several methodological drawbacks, including small sample size and lack of adequate controls.

6.4. Aromatherapy massage

In another small study (Okamoto et al., 2005), 5 patients aged 31–59 years with a single episode of DSM IV Mild Depression received a 30-min aromatherapy massage using essential oils of sweet orange, geranium and basil twice a week for 4 weeks. Patients were submitted to the 17-item Hamilton Depression Rating Scale (HAM) and Profile of Mood States (POMS) 1 week before the first session and 1 week after the last session. HAM score and the confusion–bewilderment (C–B) score, one of the subscales of POMS, improved from 14.8 ± 2.39 (Mean \pm S.D.) to 8.8 ± 3.63 ($P = 0.039$) and 62.2 ± 13.07 to 51.6 ± 8.05 ($P = 0.043$), respectively. The study had several methodological drawbacks, including small sample size, and the lack of blinding and controls.

7. Grade 4 and Grade 5 evidence

Though we found Grade 4 studies on CAM approaches in Depressive disorders, they did not amount to the highest level of evidence available on those CAM approaches. Grade 4 studies were found only for those CAM approaches which had Grades 1, 2 and 3 evidence. At Grade 5, we found a case series ($n = 40$) as the highest level of evidence on the use of Traditional Chinese Medicine (TCM) in melancholia (Wu et al., 1999). This reported 19 remissions, 16 reductions in severity and 5 non-responders, with a total effective rate of 87.5%.

8. Discussion

Though increasing numbers of trials are being undertaken in evaluating CAM approaches, there has

been little headway in using this evidence in providing health care (DOH, 2001; Thompson and Feder, 2005). This may be because the evidence for CAM effectiveness is viewed with scepticism. The sceptic may, however, point out that the available evidence is not conclusive enough. CAM treatments may be so different in terms of the individualisation of treatments, the integrity of practitioner–patient relationships, the use of healing rituals and the subtlety and long time frames of outcomes expected, that they defy standard research methods (Walach, 2001; Fabrega, 2002). This view has been disputed by several reviewers (Thompson and Feder, 2005; Vickers, 2001; Vickers et al., 1997), but remains open to debate. Our review was intended to be broad based, identifying the highest level of evidence available for each type of CAM in Depressive disorders.

9. Grade 1 evidence

We found systematic reviews and RCTs for 7 types of CAM i.e. Herbal Medicine–St. John’s wort (*Hypericum perforatum*), Nutritional Therapy–Tryptophan and 5-hydroxy-tryptophan, *S*-adenosyl methionine (SAME), Folate and Inositol, Acupuncture and Exercise. However, all of these noted important methodological drawbacks in the included RCTs. Though the quality of trials was highly variable, most of them had small sample sizes, short trial durations and poor monitoring of adverse events. In addition, many trials failed to describe the methods used to achieve randomisation, or to maintain allocation concealment. Successful blinding was often questionable in trials of acupuncture and exercise, and to a lesser extent, herbal medicine. Data regarding dropouts and withdrawals was scarce, especially in many of the older trials. Many older trials also lacked diagnostic precision. Intention-to-treat analyses were rare. The systematic reviews were also constrained by the fact that few trials among the large number of studies available were of sufficient quality to meet inclusion criteria. Many of these findings corroborate conclusions drawn by earlier researchers regarding the poor methodological quality of RCTs in CAM (Linde et al., 2001). It is therefore clear that despite the availability of systematic reviews and RCTs, these types of CAM have not conclusively demonstrated efficacy over placebo, let alone standard antidepressants.

10. Grade 2 evidence

We found 7 RCTs evaluating the efficacy of 4 types of CAM in depressive disorders. These included 4 RCTs which produced statistically positive results which

favoured the interventions—two on the Herbal medicine—*C. sativus* L. (Saffron) comparing it against fluoxetine and imipramine respectively, and one each on the Complex Homoeopathic remedy Neurapas balance (a combination of St. John’s wort, passion flower and valerian extracts), and Relaxation Therapy. However, the trials shared many of the methodological drawbacks discussed in the previous section. All had uniformly small sample sizes. The Relaxation Therapy trial relied exclusively on subjective scales to measure outcomes. Successful blinding was questionable in the trials of homoeopathic medicine and relaxation therapy, and to a lesser extent, herbal medicine. Information on power calculations were either insufficient for a critical appraisal or absent. Adequate reporting of adverse effects was restricted to the herbal medicine trials. In addition, none of the findings have been replicated in other trials or settings. It must be noted that the two RCTs on the Herbal medicine Saffron (which were from the same research group) had methodologically robust designs, but were hampered by their sample sizes.

The 3 remaining RCTs included the Nutritional interventions—Docosahexaenoic acid (DHA) and Tyrosine, and the Herbal medicine *L. angustifolia* Mill. Tincture, all of which, though sharing many of the same methodological drawbacks, produced statistically negative results with respect to their use as monotherapy in depression.

11. Grade 3 evidence

We found studies on 4 types of CAM—Music Therapy, Yoga (Sudarshan Kriya), Movement Therapy and Aromatherapy massage. All the studies had serious methodological limitations. All had small sample sizes and inadequate information on power calculations. All trials were open, as the nature of these interventions probably rendered blinding difficult. The issues raised by Walach (2001) and Fabrega (2002) with regard to the application of standard research methods to CAM are germane in this context. Blinding is difficult when an intervention such as Yoga is to be compared against a ‘placebo’ intervention, let alone an antidepressant. Such interventions can, in theory, be compared against similar interventions of the sham variety (the ‘placebo’ intervention) as has been done often in trials of acupuncture. However, in order to be a genuine placebo, the control procedure must be convincing, visible and should mimic, in all respects, apart from a physiological effect, the real active treatment. This has been found to be difficult even with sham acupuncture (White et al., 2003). A Cochrane systematic review has found that

differences between antidepressants and active placebos were small suggesting that unblinding effects may even inflate the efficacy of antidepressants in trials using inert placebos (Moncrieff et al., 2004).

This also raises issues regarding the utility of the hierarchy of evidence we used with respect to CAM trials. Where should a CAM trial, which was adequately randomized and controlled, but could not be blinded for the very reasons discussed earlier, be placed in the hierarchy of evidence, with its strict definitions of what constitutes each level? Here, the rating scale used as a measure of effectiveness in the National Service Framework for Mental Health in the United Kingdom (Table 4; Department of Health, 1999; quoted in Cooper, 2003), which draws on a ‘synthesis of evidence’ from research findings, and rated on a five-point ordinal scale according to their inferential power, appears to do better. This is related to the definitions of the respective levels of evidence being more pragmatic and hence, oriented to everyday clinical reality. The inclusion of the opinions of service users and carers under the umbrella of expert opinion, as Type V evidence, is representative of this and of relevance to CAM. However, the comparative strengths and utilities of each hierarchy are open to debate.

12. Grades 4 and 5 evidence

As mentioned earlier, the Grade 4 studies we found did not amount to the highest level of evidence available on those CAM approaches. At Grade 5, we found a case series of 40 cases on the use of Traditional Chinese Medicine in melancholia. This was the highest level of evidence available on the use of this particular CAM approach and was based on clinical impressions of what constituted remission and response. It also used an approach to the diagnosis of melancholia based on the traditions of Chinese medicine. Despite the obvious contradiction this presented to our stated focus on ICD/DSM depressive disorders, the evidence was included in the review as it was representative of a large body of case

Table 4

Rating scale used as a measure of effectiveness in the national service framework on mental health

Type I evidence	At least one good systematic review, including at least one randomised controlled trial.
Type II evidence	At least one good randomised, controlled trial.
Type III evidence	At least one well-designed intervention study without randomisation.
Type IV evidence	At least one well-designed observational study.
Type V evidence	Expert opinion, including the opinion of service users and carers.

From the Department of Health (1999).

series on the use of Traditional Chinese Medicine in depression.

Despite the potential drawbacks of its standard RCT-based research methods with respect to CAM, the Cochrane Collaboration has facilitated CAM research. By March 2004, the Cochrane Collaboration had 145 completed reviews of randomised controlled trials of complementary and alternative therapies: a third showed a positive or possibly positive effect, although over half found insufficient evidence to make such judgments (Manheimer et al., 2004). However, the gold standard of evaluation remains the double blind, randomized controlled trial.

It is clear from our review that despite the availability of systematic reviews in 7 complementary therapies and RCTs in 12, these types of CAM have not conclusively demonstrated efficacy over placebo in depression. Some of the methodological problems in applying the RCT model to complementary therapies may partly explain this finding.

The application of the RCT model to many types of CAM is potentially fraught with difficulties. RCTs are specifically designed to cancel out the human factors (in particular the non-specific effects of the therapeutic relationship) and confounding variables (e.g. regression to the mean and patient variability). Many complementary therapies on the other hand intentionally involve non-specific elements, and depend on factors like individual resilience and changing patients' beliefs and behaviour. Obviously CAM is quite different from simply taking a pill. This makes their evaluation difficult though the difficulties are not insurmountable by pragmatic trial design (Walach, 2001). A further complication is that most CAM use occurs among patients with chronic diseases and relapsing dysfunction e.g. chronic pain, anxiety, chronic fatigue and chronic musculoskeletal problems (Astin, 1998) where conventional medicine is often unsatisfactory or relatively ineffective. In these areas it is difficult to establish clearly defined end-points by which to determine objective outcomes; they are also more difficult to evaluate using the conventional randomised controlled trial. Therefore the outcomes may be broader and less predictable than those standard trials generally account for (Walach, 2001).

However, many of these methodological problems are shared by complex interventions for chronic conditions in conventional health care (Campbell et al., 2000). Complex interventions are interventions, whether curative or preventative, comprising a number of separate elements, which seem essential to the proper functioning of the intervention although the 'active ingredient' of the intervention that is effective, is difficult

to specify (MRC, 2000). In response to the methodological difficulties that have arisen while evaluating such interventions, the Medical Research Council (MRC) has developed a framework to evaluate these complex interventions. It has been emphasized that this framework should not be read as an inflexible 'to do list', but rather as advice to apply to the extent to which it is relevant at a given stage of the project (MRC, 2000). In effect, this framework offers an approach to designing studies in keeping with the current levels of knowledge in the field, and encourages pragmatic and exploratory research designs as appropriate, an approach that appears particularly relevant to designing studies in CAM. Other responses to the difficulties encountered in CAM research have included pragmatic trial designs, nested qualitative studies, and the use of real world observational data to create an "evidence house" (Jonas, 2001). As discussed earlier, the existing systematic reviews have been constrained by the fact that few trials among the large number of studies available were of sufficient quality to meet inclusion criteria. Such pragmatic approaches may address that particular problem. However, the question remains whether complementary therapies will be shown to have effects of sufficient magnitude when larger trials with robust designs are carried out.

And then again, the growth in evidence on the clinical effectiveness of some complementary therapies in other conditions has not been matched by evidence of cost effectiveness. Complementary treatments present an additional healthcare cost in four out of the five rigorous cost effectiveness studies conducted in the UK (Canter et al., 2005). Though these studies are confined to acupuncture and spinal manipulation, they do raise an issue that CAM researchers in mental health will have to address soon, as health services find themselves with increasingly finite economic resources.

13. Limitations

This review was limited by the fact that the searches were restricted to the English language. It may be that significant research exists, outside the ambit of English language journals and western research models, of which we are unaware. Our focus on the use of CAM as monotherapy excluded studies that investigated the use of CAM as an adjunct to conventional treatment. We also excluded studies in which the primary therapeutic intervention under evaluation consisted of a combination of two or more complementary therapies. Research does exist that addresses these particular areas and it is possible that some of this evidence is relevant to the

treatment of depressive disorders. Despite our best efforts to ensure the inclusion of all CAM approaches, given the rich diversity of complementary therapies, it is possible that the list of CAM approaches we arrived at is not a comprehensive one. This again raises the possibility that we may have missed important research.

14. Conclusion

19 studies that used CAM as monotherapy in depression fulfilled the criteria set for inclusion in the final review. Systematic reviews formed the highest level of evidence in 7 complementary therapies and RCTs in 5. However, neither these nor those complementary therapies with lower levels of evidence have conclusively demonstrated efficacy over placebo in depression. All studies had significant methodological problems. The widely referenced hierarchy of evidence we used has limited utility in grading trials of CAM. Despite the drawbacks of its RCT based research model with respect to CAM, the Cochrane collaboration has facilitated CAM research. The RCT model and the principles underlying many types of CAM are dissonant, making its application in the evaluation of those types of CAM difficult. These methodological problems are similar to those encountered in the evaluation of complex interventions for chronic conditions in conventional health care. The MRC framework for the evaluation of such interventions can be used in CAM, as can pragmatic trial designs, nested qualitative studies and observational data. Unless CAM approaches are shown to have effects of sufficient magnitude in larger trials with robust designs, their utility in the treatment of depression remains limited. This information is of relevance to service users, planners, general practitioners and mental health professionals, given the increasing use of CAM by those who are depressed.

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