TECHNICAL COMMENTARY

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Herbal medicines

Introduction

Herbal medicines have been suggested as a potential alternative treatment which may positively contribute to the treatment of schizophrenia. Herbal therapies can include traditional Chinese medicines and Indian ayurvedic therapy, as well as more common medicines such as Gingko Biloba.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found three reviews that met inclusion criteria[3-5].

- Moderate to low quality evidence suggests chlorpromazine may be more effective than Dang gui cheng qi tang for global state.
- Moderate to low quality evidence suggests wendon decoction may improve global state more than no treatment, but when compared to antipsychotics, there were no differences in global or mental state. However, there were fewer extrapyramidal and insomnia side effects with wendon decoction.
- Low quality evidence is unable to determine any benefit of ayurvedic herbal therapies over placebo or chlorpromazine.

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Agarwal V, Abhijnhan A, Raviraj P

Ayurvedic medicine for schizophrenia

Cochrane Database of Systematic Reviews 2007; 4: Art. No.: CD006867. DOI: 10.1002/14651858.CD006867.

View review abstract online

Comparison 1	**Brahmyadiyoga with or without tagara vs. placebo.**
Summary of evidence	**Low quality evidence (very small samples, imprecise, direct) is unable to determine any benefit of ayurvedic herbs over placebo.**

Mental state

Assessed using ayurvedic assessment or Multiphasic Questionnaire (MPQ)

Interventions included either brahmyadiyoga (12g/day for 30 days, then 16g/day for 45 days) or 8g/day brahmyadiyoga plus tagara for 1 month, then 12g/day brahmyadiyoga plus tagara for a second month.

Improved mental state with brahmyadiyoga over placebo using Ayurvedic assessment;

1 RCT, N = 68, RR 0.56, 95%CI 0.36 to 0.88, p = 0.011, NNT 4, 95%CI 3 to 12

Authors state that the overall change observed among the two groups was of no clinical significance; the use of brahmyadiyoga or tagara had no significant effect on mental state when assessed by standardised tools (MPQ).

Behaviour

Assessed using the Fergus Falls Behaviour Rating Scale

No significant difference between brahmyadiyoga and placebo;

1 RCT, N = 43, WMD 1.14, 95%CI -1.63 to 3.91, p = 0.42

Leaving the study early

No significant difference between brahmyadiyoga and placebo;

2 RCTs, N = 120, RR 0.77, 95%CI 0.37 to 1.62, p = 0.49, Q = 0.74, p = 0.39, I^2 = 0

No significant difference between tagara and placebo;

1 RCT, N = 68, RR 1.0, 95%CI 0.39 to 2.54, p = 1.0

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Risks	Authors report that none of the adverse effects were significant between groups, although numbers are small and confidence intervals wide. There was a trend for an increased risk of vomiting and nausea following brahmyadiyoga (N = 43, RR = 13.13, *p* = 0.07).
Consistency in results‡	Unable to assess 1 RCT, consistent for leaving the study early.
Precision in results§	Imprecise
Directness of results‖	Direct
Comparison 2	**Brahmyadiyoga with or without tagara vs. antipsychotic chlorpromazine.**
Summary of evidence	**Low quality evidence (very small samples, imprecise, direct) is unable to determine any benefit of ayurvedic herbs over chlorpromazine.**
Mental state and psychological assessment **Assessed using ayurvedic assessment or Multiphasic Questionnaire (MPQ)**	
Interventions included brahmyadiyoga (12g/day for 30 days, then 16g/day for 45 days) or 8g/day brahmyadiyoga plus tagara for 1 month, then 12g/day brahmyadiyoga plus tagara for 2nd month. *Ayurvedic assessment found greater improvement with chlorpromazine;* 1 RCT, N = 45, RR 1.82, 95%CI 1.11 to 2.98, *p* = 0.018 One further RCT found a similar trend association (*p* = 0.06) using MPQ. 1 study favoured chlorpromazine over tagara for improving mental state, when using MPQ assessment.	
Behaviour **Assessed using The Fergus Falls behaviour rating scale**	
No significant differences between brahmyadiyoga and chlorpromazine; 1 RCT, N = 45, RR 3.50, 95%CI -0.18 to 7.18, *p* = 0.062	
Leaving the study early	
No significant differences between brahmyadiyoga and chlorpromazine; 2 RCTs, N = 120, RR 0.91, 95%CI 0.42 to 1.97, *p* = 0.81, Q = 0.11, *p* = 0.74, I^2 = 0 *No significant differences between tagara and chlorpromazine;* 1 RCT, N = 68, RR 1.00, 95%CI 0.39 to 2.54, *p* = 1.00	
Risks	No significant differences were reported between groups. There was a

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	trend for an increased risk of vomiting and nausea following brahmyadiyoga (p = 0.06).
Consistency in results	Unable to assess outcomes with 1 RCT, consistent for leaving the study early.
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**Ayurvedic treatment: a complex mixture of many herbs, combined with shodana (cleaning), shamana (palliative) satwawajayachikitsa (psychobehavioural therapy) vs. chlorpromazine plus adjunctive trihexyphenidyl HCl and diazepam, for side effects.**
Summary of evidence	**Low quality evidence (very small sample, imprecise, direct) is unable to determine any benefit of ayurvedic treatment over chlorpromazine.**
Leaving the study early	
No significant differences between groups; 1 RCT, N = 36, RR 0.67, 95%CI 0.13 to 3.53, p = 0.63	
Risks	Not reported
Consistency in results	Not applicable (1 RCT)
Precision in results	Imprecise
Directness of results	Direct

Deng H, Xu J

Wendan decoction (Traditional Chinese medicine) for schizophrenia

Cochrane Database of Systematic Reviews 2017; 6: CD012217

View review abstract online

Comparison 1	**Wendon decoction vs. no treatment or antipsychotics (chlorpromazine or risperidone).**

Summary of evidence	**Moderate to low quality evidence (small sample, consistent, precise, direct) suggests wendon decoction may result in greater improvement in global state when compared to no treatment.**
Global state	
Medium-sized effect of greater improvement with wendon decoction; 1 RCT, N = 72, RR = 0.53, 95%CI 0.39 to 0.73, $p < 0.05$ Authors report that the evidence is low quality.	
Comparison 2	**Wendon decoction vs. chlorpromazine or risperidone.**
Summary of evidence	**Moderate to low quality evidence (small to medium samples, consistent, imprecise, direct) suggests no differences between groups in global or mental state, but fewer extrapyramidal and insomnia side effects.**
Global state	
No significant differences between groups (PANSS < 50% reduction); Global state: 2 RCTs, N = 140, RR = 1.18, 95%CI 0.98 to 1.43, $p > 0.05$, $I^2 = 0\%$ Authors report that the evidence is moderate to low quality.	
Mental state	
No significant differences between groups; Mental state: 2 RCTs, N = 140, MD = 0.84, 95%CI -4.17 to 5.84, $p > 0.05$, $I^2 = 0\%$ Authors report that the evidence is low quality.	
Risks	*Large effect of fewer extrapyramidal side effects with wendon decoction;* 2 RCTs, N = 140, RR = 0.02, 95%CI 0.00 to 0.15, $p < 0.05$, $I^2 = 0\%$ *Medium-sized effect of less insomia with wendon decoction;* 2 RCTs, N = 140, RR = 0.23, 95%CI 0.11 to 0.50, $p < 0.05$, $I^2 = 0\%$ Authors report that the evidence is moderate to low quality.
Consistency in results	Consistent
Precision in results	Imprecise for comparison 2

Directness of results	Direct

Rathbone J, Zhang L, Zhang M, Xia J, Liu X, Yang Y

Chinese herbal medicine for schizophrenia

Cochrane Database of Systematic Reviews 2005; 4: Art. No.: CD003444. DOI: 10.1002/14651858.CD003444.pub2.

View review abstract online

Comparison 1	**Chinese herbal medicine alone (Dang gui cheng qi tang, mean dose - 50ml/twice daily up to max. 200ml/day) vs. antipsychotic chlorpromazine (any dose).**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, imprecise, direct) suggests chlorpromazine may be more effective than Dang gui cheng qi tang for global state, with no differences between groups in study attrition.**

Global state

Measured by 'no improvement or worse' global state

The chlorpromazine group showed a significant, large improvement in global state compared to those receiving Dang gui cheng qi tang after 20 days of treatment;

I RCT, N = 90, RR = 1.88, 95%CI 1.24 to 2.86, *p* = 0.0031, NNH 4, 95%CI = 2 to 14

Leaving the study early

There was no loss to follow up in either group by 20 days.

Risks	Not reported
Consistency in results	Not applicable (1 RCT)
Precision in results	Imprecise
Directness of results	Direct

Herbal medicines

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale**,** CI = Confidence Interval,) I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, MPQ = Multiphasic Questionnaire, N = number of participants, NNH = number needed to harm, NNT = number needed to treat, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, PSRS = Psychotic Symptom Rating Scale, Q = Q statistic for the test of heterogeneity, RCT = Randomised Controlled Trial, RR = relative risk, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, SMD = standardised mean difference, vs. = versus, WMD = weighted mean difference

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[6].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[6].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[6];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

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§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[8].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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