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Study Protocol

A naturalistic study of herbal medicine for self-reported depression and/or anxiety a protocol

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ABSTRACT

Background: Mental health conditions including anxiety and depression account for around 8% of the global disease burden. Anxiety and depression often coexist and impose a high individual and social burden. Patients with mental and behavioural conditions may be at increased risk of co-morbidities and are often high health-care utilisers. Herbal medicine is estimated to be used by up to 80% of the worlds population, and by 22% of Australian women seeking care for depression. The holistic and tailored treatment approach offered by practitioners of herbal medicine is difficult to capture in randomised controlled trials and as such there is a paucity of research demonstrating the outcomes of real-life practice. This project aims to address this gap with a whole practice, observational model.
Methods: The study will employ a naturalistic observational design. Two-hundred patient participants will be recruited to be treated by 15 clinician participants from different naturopathic clinics. The observed changes in anxiety and depression symptoms of patients will be documented across three consultations using validated patient-reported outcome measures (SF-36, DASS-21, GHQ-28 and POMS-2).
Discussion: Clinical studies investigating the efficacy of individualised herbal medicine treatment as prescribed by a naturopath are rare. Our study attempts to fill this gap with a longitudinal observation of individualised care as practiced by naturopaths in Australia; to offer valuable insights into the effectiveness of individualised herbal medicine practice and provide contextualisation of data currently focused on individual herbal medicines in specific conditions.
Trial Registration: Australian and New Zealand Clinical Trials Registry: ACTRN12616000010493

1. Introduction

Mental health conditions including anxiety and depression affects one in nine Australians.[1] Anxiety is a distressing, unpleasant emotional state of nervous unease extending beyond that of a normal physiological stress adaptation response.[2] Depression involves feelings of sadness and/or a loss of interest in activities once enjoyed.[3] Anxiety and depression often (but not always) coexist, impacting wellbeing, personal relationships, career and productivity and collectively impose a high individual and social burden.[4] In 2014–2015 four million Australians reported having a mental or behavioural condition, of which the most common were anxiety-related conditions followed by mood disorders including depression[1] affecting their wellbeing, personal relationships, career and productivity.[5]

In addition to the specific disease burden of anxiety and depression, patients with depression may also be at higher risk of other negative health behaviours or risk factors – for example patients with depression are more likely to use alcohol or other recreational drugs (often in an attempt to treatassociated anxiety symptoms); are more likely to become heavy smokers, and are more likely to neglect their own health, increasing the risk of co-morbidities.[6] For these reasons, people suffering depression and/or anxiety are often high health care utilisers[7] contributing to significant indirect medical and productivity costs.[8] Depression and anxiety are conditions which also significantly impact qulaity of life. Of those with a psychological disability, 40% report profound levels of core lifestyle limitation with a wide range of coexisting health conditions and impairments [9]. In 2014–2015, 8.4% of working age people with a mental or behavioural condition were unemployed, compared 3.7% of working age people without these conditions.[10] For these reasons, main countries (including Australia[11]) have identified these conditions as priority areas for treatment.

In addition to conventional treatments, complementary medicines (those products and services not considered part of

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conventional health care delivery) have also been commonly used to treat mental health conditions.[12] Herbal medicines in particular have been investigated individually for their efficacy in anxiety and depression. In anxiety, for example, Chamomile (*Matricaria recutita*) significantly reduced anxiety symptoms as well as being very well tolerated with no increase in adverse events at higher doses, compared with placebo[13]; Echinacea significantly decreased anxiety over time (3 days)[14]; Gotu kola significantly reduced the amplitude of the startle response[15] and reduced anxiety by 26%[16]; and Passionflower significantly reduced anxiety symptoms in three clinical trials.[17–19] Unfortunately, many herbal medicine studies in this condition have been short term, open-label, and/or poorly report their findings.[20] However, some herbal medicines (Kava being a notable case) have good evidence of clinically efficacy,[21] with very low incidence of adverse effects.[22]

Individual herbs have also been investigated for their antidepressant effects. A number of meta-analyses on St. John's wort either in comparison to selective serotonin reuptake inhibitors (SSRI) or placebo and have found it to be significantly better than placebo and of similar efficacy to many conventional antidepressant medication.[23,24] Smaller studies have identified other options, such as Saffron, which demonstrated significant improvement of depression over placebo using either stamen[25] or petal[26] and equivalent effects to imipramine[27] with stigma and fluoxetine with petal[28] and stigma.[29]

One of the most common traditional systems of herbal medicine is western herbal medicine, which bases its roots on European and North American historical practice. Herbal medicine is estimated to be used by up to four billion people (80% of the world's population)[30] with approximately 10% of the Australian population regularly consulting with a naturopath or herbalist.[31] Further, approximately 22% of women seeking care for depression consult with a naturopath or herbalist.[32] Herbalists and naturopaths work within a holistic framework, placing the patient in a social and environmental context,[33] using individualised herbal medicine prescriptions often in conjunction with dietary and lifestyle advice. The emphasis is placed on treating the underlying causes of health problems and maintaining or improving the general health status of the patient.[33]

A large body of evidence exploring the effectiveness of herbal medicines from the western herbal medicine tradition has focused on singular herbs and their constituents. However, the individualised approach emphasised in most forms of practitioner-based herbalism[34] in which patients receive tailored prescriptions comprising a mixture of herbs, has rarely been explored. Differentiating the whole-of-practice of herbal medicine from the individual herbs prescribed and combined is critical to examining the real-world impact of herbal medicine practice.[35] The role of the herbalist in using a holistic and tailored approach to treating patients is an essential component of traditional herbal medicine. The impact of this paucity of evidence should not be understated, particularly in relation to policy development and implementation. For example, this gap has already been identified in the Australian setting, with the Commonwealth government suggesting withdrawal of private health insurance rebates for herbalists due to the paucity of evidence for benefit of herbal medicine practice, suggesting that it could not be assumed that evidence for individual herbal medicines would translate to evidence for herbal medicine practice.[36]

However, while the need to conduct more rigorous research on individualised heral medicine practice the nature of herbal medicine practice itself often makes it difficult to investigate via conventional randomised controlled trials, where it is often challenging to capture the complexities of holistic clinical practice, such as an individualised approach to prescribing, addressing the underlying causes of disease in addition to presenting symptoms, an emphasis on disease prevention as well as the enhancement of vitality and well-being.[37] To address the evidence gap, but to ensure that the results accurately reflect what occurs in clinical practice, this project uses a novel whole practice observational model to reflect the clinical realities of practice in real world settings.

2. Methods

2.1. Objectives

The primary objective of this study is to evaluate individualised herbal medicine treatment of self-reported anxiety and/or depression improve clinical outcomes (as measured by the SF-36, DASS-21, GHQ-28 and POMS-2) in patients with a self-reported anxiety and/or depression. Prescription patters of herbal medicines will also be evaluated to inform future studies.

Secondary objectives are to explore the feasibility of the naturopathic and herbal medicine communities to become more actively involved in the research process. The project will seek stakeholder engagement of naturopathic and western herbal medicine practitioners throughout Australia as the practitioners administering the intervention and objective measures.

2.2. Study design

The study will be a naturalistic observational exploration of naturopathic consultations using individualised herbal medicine for self-reported anxiety and depression. This study will be observing and documenting the effects of individualised herbalism rather than individual herbal therapies.

As this is an observation study with a single group only, and fully open label no randomisation will occur – all participants will receive treatment based upon the clinical assessment of their treating clinician. No blinding will occur during the intervention but will occur during the analysis.

There will be one main centre for this trial (Herbs on the Hill at Mater Hill, Brisbane), which has a governance agreement with UTS and all relevant insurances, all prescriptions will be dispensed from the main centre with prescriptions delivered to study participants directly by post where the consultation occurred at another location. However, data will be collected from multiple degree-trained naturopathic clinicians around Australia, who have signed a governance agreement and completed training in data collection for the study.

2.3. Intervention

Participation in the study will include three consultations occurring over a period to be decided by the treating practitioner and the patient, based on clinical circumstances. This is to ensure the intervention reflects real-world practice. Individualised herbal medicines are to be prescribed for the client as they would be in the regular/normal Naturopathic consultation as if the participant were they not in the study. The prescription could be either a tincture or tablet or combination drawn from a common practitioner-only range of products in naturopathic dispensaries in Australia. In this way, this study will document treatment as it occurs in natural practice, at the discretion of the practitioner (note: these will be included as variables).

2.4. Participants and recruitment

2.4.1. Clinicians

Naturopaths with a minimum of a degree qualification, and who have experience in treating clients with anxiety and

depression, will be eligible to participate in this study. Clinicians will be recruited at professional seminars and conferences and with posts on professional social media discussion pages. Clinicians will be responsible for screening for inclusion criteria and obtaining informed consent, they will also collect the data across the consultations and forward this to the lead researcher for collation.

2.4.2. Patients

Patient participants will be recruited by regular clinic promotion channels which may include referrals from other health professionals (General Medical Practitioners, Psychologists) and by advertising in medical and complementary medicine clinics in Australia as well as website and social media Facebook posts. Participants need to be aged between 18 and 65 years, who self-present to a Naturopathic clinic for treatment of anxiety and/or depression and will be screened for their eligibility in their initial consultation.

2.5. Inclusion criteria

Clinician inclusion criteria have been described above (degree qualified naturopathic practitioners who have experience treating anxiety and/or depression)

Patient inclusion criteria comprise any person, male or female, aged 18–65 who self-present to a Naturopathic clinic for treatment of anxiety and/or depression. No formal diagnosis of anxiety/depression is required, but anxiety and/or depression must be the patient's main reason for scheduling the clinical visit. Participants will be included if they comply with the study criteria and are willing to both provide written informed consent. Participants need to be fluent at reading and writing English

2.6. Exclusion criteria

Non-English speakers will be excluded.

Patients will be advised that participation in the study will require any prescription to be herbal in nature, rather than having a broad range of ingestible medicines often used in naturopathy (e.g., vitamin supplements, homoeopathy, etc.). If patients do not want their treatment to be restricted, they can continue treatment with their naturopathic practitioner, but will not be enrolled in the study.

2.7. Concomitant care

Participants are permitted to continue with any other treatments which commenced prior to the commencement of the study but discouraged from commencing new treatment options for the duration of the study, unless urgently required. All treatments, including those provided by the clinicians in this study and from outside this study will be documented. Clinicians are permitted to provide participants with additional advice with regards to lifestyle, stress management and general wellbeing according to general naturopathic theory but cannot provide ingestible medicines other than the herbal prescription.

2.8. Sample size

Sample size of 200 participants was chosen as a naturalistic observation and considered feasible over a 3-year recruitment period. Without a previous effect size, it was not possible to determine the effect size and therefore sample size calculations are not possible, power calculation as the purpose to recruit as many as possible within the study periods. However, this data will be used as the foundation for future power calculations.

2.9. Recruitment

The participant may present with self-identified anxiety or depression, or the clinician may assess anxiety or depression as being the underlying cause of the participant's presentation. The recruitment phase will be for 36 months, where approximately 200 adults (no specific ratio, and dependent on ability to recruit, ages 18–65) will be recruited. No specific culture, race or socio-economic group will be targeted or restricted from recruitment. The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all inclusion criteria and none of the exclusion criteria. The participant will receive a study enrolment number and this will be documented in the participant's record and on all study documents.

2.10. Ethical issues

This protocol has been approved by the Ethics Committee of University of Technology Sydney (HREC approval 2014000809) and is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616000010493).

There is some risk to participants of inconvenience and harm. As in the case of any intervention using agents which pharmacokinetically and pharmacodynamically alter the physiological workings of the body and/or has a biological effect, negative reactions can occur, hence the study is not without risk. These risks are reduced by virtue of the herbal medicine being prescribed by an experienced professional as opposed to a person self-selecting and self-prescribing herbal medicine from a self-serve store like a health food shop, supermarket or pharmacy. These risks are also reduced by ensuring the herbal medicine products are of the highest quality available so that the clinician-researcher can be assured the herbal medicine they are prescribing is the herbal medicine the participant is receiving. There is also the risk of excluding specific nutritional supplement treatments for the course of the study, the participant may not receive the optimum treatment available from consulting a Naturopath.

2.11. Outcome measures

Each of the four measures are to be completed by each patient participant at Baseline, 1st follow-up and 2nd follow-up. As this is an observational, hypothesis generating study, rather than an interventional study, we are monitoring treatment for three sessions. The follow-up session time-points remain at the discretion of the clinician and patients, based on clinical need, as we are observing naturalistic practice. These individualised herbal formulas are intended to be prescribed to meet the needs of the unique clinical presentations of each participant, and as such identifying the clinical effects of the specific herbs prescribed in this case is not aligned with the study aims and we have not planned a sub analysis. However, if we identify some consistency in the herbs prescribed, a post hoc subanalyses will be considered should there be sufficient consistency in treatment to support statistically valid analysis.

2.12. Profile of mood states form (POMS-2)

The POMS assesses transient, distinct mood states using an adjective checklist consisting of 65 items usually taking between 3 and 7 minutes to complete.[38] This has been updated to the POMS 2 providing a quick assessment of transient, fluctuating feelings, and enduring affect states, its sensitivity to change makes the assessment ideal for treatment monitoring and evaluation, as well as clinical trials.[39]

2.13. Depression and Anxiety Stress Scale 21 (DASS-21)

The Dass-21 is a short form of the original[40] 42-item self-report measure of depression, anxiety, and stress. The utility of the short-form version is supported by normative data based on a large sample[41] facilitating measurement of change in state over time on the three dimensions of depression, anxiety and stress.[42]

2.14. Short Form 36 Quality of Life Scale (SF-36)

Constructed to survey health status the SF-36 was designed for use in clinical practice and research for self-administration by persons over 14 years of age in five to ten minutes.[43] The SF-36 assesses eight health concepts: physical functioning; role limitations due to physical problems; social functioning; bodily pain; general mental health (psychological distress and well-being); role limitations due to emotional problems; vitality (energy and fatigue); general health perceptions,[43] as well as a measure of health transition or change.[44]

2.15. General Health Questionnaire – 28 (GHQ-28)

Developed in 1978 by Goldberg,[45] as a measure of emotional distress in medical settings. Divided into four subscales: somatic symptoms; anxiety/insomnia; social dysfunction, and severe depression each consisting of seven items. The GHQ-28 is a widely used and validated screening tool for emotional distress and possible psychiatric morbidity, takes around 5 minutes to complete, assessing a client's current state and whether that differs from their usual state.[46]

2.16. Participant case history

Demographic and health history information is to be collected for each patient participant, including Health history (history of anxiety/depression diagnosis), health service utilisation (time since last medical visit), and other concurrent treatments.

2.17. Safety assessments

A Data Safety and Monitoring Committee will be established to assist with monitoring and reporting. This Committee will consist of four persons with: medical expertise, statistical expertise and clinical expertise in individualised herbal medicine prescription for patients with anxiety and mild to moderate depression. This Committee will be independent of the research team. This Committee will review researcher monitoring and reporting procedures, and will provide guidance when adverse events do occur. The University of Technology Sydney Human Research Ethics Committee will also monitor safety and review, with regular reporting by researchers.

2.18. Data collection and management

Both practitioner participants and patient participants enrolled in the study is allocated a code to facilitate blinding during data analysis.

The initial consultation will follow the same process as any other consultation with the respective clinician-researcher, including a relevant case history and treatment plan, lasting approximately one hour in duration. The treatment plan/prescription can include lifestyle, stress management and general wellbeing advice along with herbal medicines with the form and dosage at the clinician-researcher discretion. Prescriptions are not to include specific nutrients. Once the consultation is complete the patient participant completes all four measures (SF-36, DASS-21, GHQ-28 and POMS-2).

Table 1
Enrolment, Intervention and Assessment

Interventions	Visit 1 (1 h)	Visit 2 (30 min)	Visit 3 (30 min)
Informed consent	√		
Inclusion/Exclusion	√		
Participant history	√		
Clinical assessment	√	√	√
SF-36	√	√	√
DASS-21	√	√	√
GHQ-28	√	√	√
POMS-2	√	√	√
Adverse event assessment		√	√

The participant returns after a time period determined by the clinician-researcher for the first follow-up visit (ideally 2 weeks) where their progress is assessed as per a regular consultation of approximately 30 minutes duration. The clinician-researcher assesses the suitability of the formulation based upon their clinical assessment of the progress of the participant and adjusts the herbal medicine treatment as they see fit. Once the consultation is complete the participant completes the standard sociodemographic form as well as all four measures (SF-36, DASS-21, GHQ-28 and POMS-2). The participant returns as above for a third consultation and the process is repeated. At each of the three consultations the participant pays the regular consultation fee while the herbal prescription is provided at no cost to the participant as consideration for various inconveniences such as the requirement to complete the four measures at each consultation and the delay in being prescribed nutritional supplements.

All source data will be anonymised, with access to, and handling of, data restricted to delegated study staff who must comply with the requirements of the Data Protection Act 1998. Disclosure of confidential information can only be made during routine procedures such as monitoring and auditing by the study sponsor or in emergency situations such as when a compelling medical need arises (Table 1).[47]

2.19. Statistical methods

Analysis of data will be conducted with blinding to clinician-researcher allocations. Sample will be described using absolute and relative frequencies for categorical variables, and mean and standard deviation (or median and range) for continuous variables according to the data distribution. A repeated measures ANOVA will be used to measure the change in symptom scores across participants over the course of the study. Potential confounders (such as comorbidities, sociodemographics and health service utilisation) will be factored into analysis. Missing cases will be excluded in a repeated measures ANOVA. Effect sizes will be calculated to determine preliminary effects of individualised herbal medicine, or patterns of prescriptions. The influence of the herbal preparation itself, like provide details, patterns of herbal medicines? Data will be analysed using SPSS 23.0. Should some commonality in prescription patters be identified sub analyses will be undertaken to explore potential differences in clinical outcome based on specific herbal prescriptions

3. Discussion

Clinical studies investigating the use of individualised herbal medicine treatment as prescribed by a naturopath are rare,[35] and as a consequence it is difficult to assess the efficacy of this practice to inform policy development and healthcare decision-making. This study attempts to fill this knowledge gap by evaluating the practice of western herbal medicine across several locations and clinician-researchers within Australia. This may be better achieved

through other research methodologies such as naturalistic observation which may better capture real world practice.[48]

The lack of a comparator treatment and randomisation could be perceived as a limitation; however, provides the basis for answering the bigger question – does the clinical practice of western herbal medicine provide benefit? – through investigation and measurement of individualised treatment in a way which represents clinical reality. This approach is increasingly important as public health agencies place increasing emphasis on patient-centred outcomes and results.[48] The challenges involved in finding relevant placebo treatments in natural medicine which also lack activity is also significnt. Demonstrated by the complexities of providing a placebo in acupuncture where sham acupuncture has been devised to fill this role, although, its lack of effectiveness is far from clearly demonstrated[49] with nausea[50,51] and IBS[52] responding particularly well to sham acupuncture. Potential therapeutic effects from placebo were also identified by Sheehan and Atherton[53] where a herb was included in both the active and placebo formulae due to a concern that it was so distinctive in taste its absence would have been difficult to conceal. Berkovitz and coleagues[54] created a placebo which, although particularly indistinguishable from the individualise western herbal medicine treatment, could be potentially therapeutic, especially as the general beneficial therapeutic effects of bitters are becoming more widely understood and recognised as possessing not only gustatory but also extra-gustatory functions.[55,56]

This study will offer valuable insights into the effectiveness of individualised herbal medicine practice and provide contextualisation of data currently focused on individual herbs in specific conditions. It will also identify the herbs practitioners are actually using in their clinical practice and whether this aligns the available research on individual herbs. This study not only fills important research gaps but will also have real and practical relevance to clinical and patient communities. The experiences and challenges will provide valuable perspectives into the logistics of creating practitioner-based research networks, which may guide future researchers in this area.

The effectiveness of western herbal medicine practice in any condition is a major research gap making it difficult to develop policy or planning around herbal medicine practice, issues around professional regulation and development hinge on this clinical research.

Trial status

Recruitment commenced in March 2016, and the trials is expected to be completed by March 2019.

Conflict of interest

MediHerb Pty Ltd (Warwick Australia) has provided the herbal products to be prescribed by the individual clinician-researchers without charge but had/have no role in the design, conduct or analysis of the study. These herbal products will be dispensed at the HerbsontheHill dispensary in Brisbane Australia and posted to clients who had their consultation at one of the plenary centres.

JW and DC are naturopathic practitioners who have previously used extemporaneous herbal prescription in clinical practice for the treatment of anxiety and depression. The authors declare that they have no further competing interests.

Authors' contributions

JW conceived the study, designed the study protocol, and revised the manuscript. DC revised the study protocol and drafted the manuscript. All authors contributed to drafting the manuscript and have read and approved the final manuscript.

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