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Pragmatic research issues for herbal medicines

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ABSTRACT

Traditional medicines is the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, used in maintenance of health and in prevention, diagnosis, improvement or treatment of physical or mental illness. Herbal therapies are not an integral part of conventional care although they are still used by patients in their health care management. In developed countries generally herbs are considered as dietary supplement and removed from medical scene. These medicines need to be subjected to rigorous research to establish their effectiveness and safety. Clearly defined treatments are required and should be recorded in a manner that enables other suitably trained researchers to reproduce them reliably. Quality control of herbal products is also a prerequisite of credible clinical trials. Clinical trials can be designed to be either pragmatic or explanatory both pragmatic and explanatory randomized controlled trials have a useful role to play in the evaluation of health care interventions. Pragmatic trials are designed to ûnd out about how effective a treatment actually is in routine, everyday practice. Explanatory trials are designed to ûnd out whether a treatment has any efficacy (usually compared with placebo) under ideal, experimental conditions. Both have a place in our repertoire of research methods. In this paper I have described the key steps in undertaking a pragmatic trial, and describe some differences from an explanatory trial. My focus will be on the parallel-arm design, although the principles can be applied to other types of study. I have explored some of the strengths and weaknesses of pragmatic trials. Methodological strategies for investigating the herbal interventions and the issues regarding appropriate patient selection, comparisons group, treatment protocol, sample size, Referral, recruitment and randomization, outcomes, reporting and dissemination.

KEYWORDS

Herbal medicines;
Explanatory trials;
Pragmatic trials;
Traditional medicines.

INTRODUCTION[1-5]

Herbal medicine is now considered a very popular form of remedy even though its therapeutic efficacy needs to be investigated. Herbal medicines are closer to conventional drugs than other complementary and alternative medicine (CAM) approaches[1]. The wide-spread use of herbal medicines suggests, though does

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not assure, the safety and efficacy of these medicines. In many countries herbal medicines are even prescribed by doctors alongside modern drugs and dispensed or supplied primarily by pharmacists. Herbal Medicines consist of many chemical constituents with complex pharmacological effects on the body. The lack of pharmacological and clinical data on the majority of herbal medicinal products is a major impediment to the integration of herbal medicines into conventional medical practices[2,3]. There is a common misconception among consumers that because herbal remedies are "natural", then they must automatically be safe to take. On contrast, many of natural products from plant species are poisonous and toxic to many organs. For instance, the Rhubarb plant is a nutritious vegetable, but the leaves from the Rhubarb plant, if eaten could cause someone to go into convulsions or possibly even die. This example reveals the importance of self-education when it comes to knowing which herbs are good or bad for you. Combinations of herbs can also negatively interact with each others. Taking a herbal supplement that boosts your energy for example, such as Ginseng or ephedra in large amounts could cause heart palpitations. If there herbs were taken while consuming large amount of caffeine, it would cause heart palpitations which can lead to much more serious problems and even a heart attack. Another serious example is kidney stones. In most cases, natural lemon juice can be used to treat kidney stones. However, there is individual variation and it will not work for many cases. The most common type of kidney stone is a calcium stone - about 80% of people who get kidney stones get this type and the lemon juice works wonderfully to dissolve these types of stones. If however, you have kidney stones that are one of the other three types; the lemon juice remedy may not work for you at all[4,5].

TRADITIONAL MEDICAL SYSTEMS (TMS)[6-13]

For centuries traditional medical systems (TMS) were the primary medical system in the countries of origin, and now nevertheless the present dominance of the Western scientific medical model, citizens and healthcaregivers are starting to rely and trust TMS substituting conventional scientifically proved therapies with unconventional ones. Generally cultural rooted ness enduring and widespread use of TMS may indicate safety, but not the efficacy of the treatments especially in herbal medicines where tradition is almost completely based on remedies containing active principles at very low and ultra low concentrations, or relying on magical-energetic properties of sun, moon, etc[6-8]. Long-term use of medicinal herbs enables a process of selection but limited and only partial, of short and medium-term safe remedies, that however does not match with modern issues relatives to the interferences with synthetic drugs. Treatment selection is often limited because of the multiple meaning of efficacy in relation to pathology and diseases in different cultures[9-10]. The transfer of a medical concept to a new country may be really misleading and lead to deep modifications of its medical-therapeutic and cultural essence, especially if a remedy is part of a TMS, and modifications follow adaptation to local conditions and cultural habits. These modifications may deeply vary in extension, but probably years or just moths after migration a TMS can have absorbed cultural influences form the host country[11-13].

HERBAL MEDICINES TODAY[14-19]

The World Health Organization (WHO) estimates that 4 billion people, 80% of the world population, presently use herbal medicine for some aspect of primary health care. Herbal medicine is a major component in all indigenous peoples' traditional medicine and a common element in Ayurvedic, homeopathic, naturopathic and traditional oriental. WHO notes that of 119 plant-derived pharmaceutical medicines, about 74% are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native cultures[14]. Major pharmaceutical companies are currently conducting extensive research on plant materials gathered from the rain forests and other places for their potential medicinal value. Rather than using a whole plant, pharmacologists identify, isolate, extract, and synthesize individual components, thus capturing the active properties. This can create problems, however. In addition to active ingredients, plants contain minerals, vitamins, volatile oils, glycosides, alkaloids, bioflavanoids, and other substances that are important in supporting a particular herb's medicinal properties. These elements also provide an important natural safeguard Isolated or synthesized active compounds can become toxic in rela-

tively small doses; it usually takes a much greater amount of a whole herb, with all of its components, to reach a toxic level. Herbs *are* medicines, however, and they can have powerful effects. Substances derived from the plants remain the basis for a large proportion of the commercial medications used today for the treatment of heart disease, high blood pressure, pain, asthma, and other problems[15-17]. There are over 750,000 plants on earth. Relatively speaking, only a very few of the healing herbs have been studied scientifically. And because modern pharmacology looks for one active ingredient and seeks to isolate it to the exclusion of all the others, most of the research that is done on plants continues to focus on identifying and isolating active ingredients, rather than studying the medicinal properties of whole plants. Herbalists, however, consider that the power of a plant lies in the interaction of all its ingredients. Plants used as medicines offer synergistic interactions between ingredients both known and unknown[18,19].

WHAT "PRAGMATIC" MEANS...[20,21]

Pragmatism emphasizes the practical problems experienced by people, the research questions posited, and the consequences of inquiry. In pragmatic science, the goal is to develop knowledge that can be used to improve a situation[20,21].

WHY RESEARCH INTO EFFECTIVENESS OF HERBAL MEDICINES IS IMPORTANT?[22,23]

Herbal products have always been an important part of the public's healthcare around the world. The herbal products may have many ingredients, often with varying concentrations of the therapeutic compounds between products and between different batches of the same product. The issue of quality control and the selection of appropriate dosage regimens have been emphasized[22]. A single formulation and dosage form with maintained consistency in multiple batches should be used throughout the different stages of the clinical trials. Although traditional complementary medicine and its practitioners have not demanded clinical trials such clinical trials are a requirement for modern scientists. As the use of herbal products rises, clinical investigation of these practices becomes increasingly important. This is because once the efficacy is proven, alternative treatments can be endorsed. Difficulties abound in determining efficacy due to the variety of methods used to compare different therapies and lack of comprehension of the model of holistic medicine[23].

PRAGMATIC STUDIES IN TRADITIONAL MEDICINE[24-26]

Clinical trials can be designed to be either pragmatic or explanatory. Pragmatic Trials (PT) are designed to find out about how effective a treatment actually is in everyday practice. Explanatory trials are designed to ûnd out whether a treatment has any efficacy (usually compared with placebo) under ideal, experimental conditions. PT answers questions about the overall effectiveness of an intervention, and cannot study the contributions of its different components. Pragmatic trials are used with the aim of providing the evidence that will help policy makers, practitioners or patients make choices between two interventions[24,25]. They help deûne the best use of limited resources. The infrastructure for research in traditional medicine is significantly less developed than that for conventional medicine. However, there is now an increasing demand that the safety and efficacy of traditional medicine be determined, so that it can be considered by the public[26].

KEY STEPS IN CONDUCTING A PRAGMATIC TRIAL[27-35]

Satisfactory research question

The study design should be appropriate according deûned research question. Such trials gives idea about the overall effectiveness of an intervention, and cannot study the contributions of its different components. It includes the contribution of the therapeutic relationship, patient's expectations, and any speciûc therapy that is used generally compare the effect of another treatment, not with a placebo as in explanatory trial. The main aim is providing the evidence that will help to make choices between two interventions.

An ideal patient group

In pragmatic trials, the participating volunteer's are representative of the wider population, so that your re-

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sults can be generalized. Because of larger population one must set wide inclusion criteria, so that patients are not excluded if, for example, they have other medical conditions, or are taking medication. .As it is a a trial of complementary medicine, bear in mind that not all patients will be interested, nor will all physicians in their role as gate-keepers be willing to refer patients. So one must identify an define therapeutic niche for the therapy. For example, it would be sensible to choose a condition where conventional treatment is often unsatisfactory, like low back pain or irritable bowel syndrome, so that patients and their doctors are willing to consider an alternative approach. These are complex issues that need to be clariûed during the design process, preferable with small pilot studies.

Choice of comparator

If one have identified patient group, it would be easier to identify the control group, i.e. the reference group against whom relative change was measured. Unlike explanatory trial in pragmatic trial, it is not usually appropriate to use a placebo control and blinding, as these are likely to have a detrimental effect on the trial's ecological validity. Ideally, a comparison treatment is selected that is already credible in primary care, so that any differences can be easily found and can be easily interpreted.

Defined and adequate sample size

As described earlier such trials require larger population and so sample size is also large. Sometimes treatment may not be maximally effective in patients who are taking medication, for example. This variability between patients dilutes the treatment effect but does not undermine the credibility of a pragmatic trial. Also if someone is interested in long-term follow-up then a larger sample size would also be needed to cover losses through patients dropping out.

Treatment protocol

In pragmatic type of trials, one can easily grant the practitioners the freedom to treat the patients normally; it is easy to allow them to use complex and individual approaches for different patients. Also the variations which are permitted should be clearly defined. Also one should deûne what variations in treatment are permitted in the formal treatment protocol. There is a range of options here, from a very open protocol that allows wide ûexibility within a deûned framework, through to a tightly speciûed protocol that has been determined by consensus with experts. For complex interventions, ûrstly a handbook or manual is composed which deûnes the parameters for treatment. The aim here is to make sure the study protocol can be replicated, but at the same time is generalisable so that it is a reasonable match for routine practice

Referral, recruitment and randomization

In a pragmatic trial, if one want to set up referral procedures that are practical and relevant to real life choices. Perhaps you are exploring a potential role for your therapy in primary care and plan to utilize referrals from general practitioners Some trials use a patient database to retrospectively identify patients with the condition you are interested in, but have been diagnosed in the past. However, we do not yet know whether retrospective recruitment would reduce the generalisability of the trial. In other respects, recruitment and randomization are similar for pragmatic and explanatory trials.

Outcomes

The treatment must be recorded in a manner that enables other trained researchers to reproduce it reliably. This often requires objective endpoints. Herbal experts utilize a system of clinical observations which today might be considered obsolete and over subjective. Modern clinical trials insist on having data with hard endpoints that can be monitored. Thus there is a need to develop the means to objectively assess the subjective signs. In pragmatic studies choose a primary outcome that is relevant to everyday life, particularly one that measures the patient's function or quality of life. . Moreover, a pragmatic study is more likely to include long-term follow-up, since patients and policy makers will be very concerned about whether any beneûts are sustained. This has an additional advantage in studies of complementary medicine since patients' have reported that some changes takes place over a considerable period of time. Also changes resulting from complementary medicine are often broader than just to the primary Condition. Hence there may be a need to monitor outcomes across a wider spectrum, including changes to outlook, attitude and behavior.

Assessing the effects of individual differences

The first problem against the applicability of prag-

matic trial into complementary therapies including herbal medicine is that these are often very individualistic in approach and cannot always be standardized as a treatment for a large group of individuals. Moreover, the expectations and strong beliefs toward herbal medicine can influence the outcomes in trials. Baseline assessments of various psychological factors such as personality and mood must be carried out. These can be used as prognostic variables and can be used to check that randomization has produced comparable groups. The between treatment differences in outcomes due to expectations can be assessed by giving detailed information about the treatments prior to randomization and their expectations of effectiveness of each treatment assessed for example by means of VAS (visual analogue scale).

Reporting and dissemination

The reporting of clinical trials in general is improved by adhering to the CONSORT guidelines as well as guidelines for speciûc therapies, such as the STRICTA guidelines for acupuncture.In pragmatic trials full inervation is more complex than explanatory trials. In disseminating the results, should be made clear so that the pragmatic design found appropriate according to research question.

CONCLUSION

Pragmatic trials have an important place in the evaluation of health care interventions, but they answer different research questions. Pragmatic trials are useful in answering questions about how effective a therapy is when compared to some standard or accepted treatment. They also overcome some speciûc difficulties that can be encountered with explanatory trials of complementary therapies, for example when evaluating complex packages of care. Pragmatic trial results can be generalized to wider clinical settings where they can provide evidence of how well therapies might perform as alternatives or adjuncts to conventional interventions. They also can help facilitate decision-making about whether therapies should be utilized more widely. Whether conventional healthcare is prepared to accept complementary medicine or vice versa is debatable as one challenges the autonomy of the other. The specific effects of the therapies, how they should be used and delivered to optimum benefit, need to be established. Integrated Medicine. The Way Forward for the Next 5 Years (Foundation for Integrated Medicine 1997) proposed an examination of the research issues of efficacy, safety, biological plausibility, methodology, and funding.

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