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Clinical research on traditional drugs and food items—the potential of comparative effectiveness research for interdisciplinary research

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ABSTRACT

Ethnopharmacological relevance: In the traditional context, herbs are often used as herbal whole system therapies, however, most clinical trials included highly selected patients and applied standardized treatment protocols with the aim to exclude as much bias as possible. These studies have contributed important information on the efficacy of herbal medicine extracts; however, their results are only marginally helpful to understand the value of herbal medicine and food items in a more traditional usual care context.

Methods: The new development of comparative effectiveness research (CER) will be introduced and synergies with ethnopharmacology will be outlined.

Results: CER provides great opportunities for guiding researchers and clinicians in improving management of disease. CER compares two or more health interventions in order to determine which of these options works best for which types of patients in settings that are similar to those in which the intervention will be used in practice. CER uses a broad spectrum of methodologies including randomized pragmatic trials that can also be applied to herbal whole system therapies. Ethnopharmacological research can provide highly relevant information for CER including data on characteristics of typical patients as well as traditional usage including methods of collection, extraction, and preparation. Recommendations for future research on traditional herbal medicine and food items are (1) a systematic cooperation between ethnopharmacology and clinical researchers and (2) a call for more CER on traditional herbal medicines and food items.

Conclusion: Multiple stakeholders, including ethnopharmacologists, should cooperate to identify relevant study questions as well share their knowledge to determine the optimal placement of a clinical trial in the efficacy–effectiveness–continuum.

1. Traditional herbal pharmacotherapy and food as complex interventions

When studying the use of traditional medicine in ethnic groups, one common observation is that herbal whole system therapies are often used to prevent and treat diseases as well as that food ingredients (e.g. spices such as curcumin) play an important role.

Herbal whole system therapies are multi-component or complex interventions that often include multiple herbs, along with other treatments like exercise and diet (Zick et al., 2009). This is similar for food. According to the European Food Safety Authority (EFSA) (2013) supplements are concentrated sources of nutrients or other substances with a nutritional or physiological effect, whose purpose is to supplement the normal diet.

Most claims for food supplements are not based on strictly pharmacological approaches, but on epidemiological observations or in vitro experiments (Visioli, 2012). Research on nutrition is difficult and food items as well as herbs can be used in different settings and from a pharmaceutical point of view even using a single herb could be seen as a complex intervention. The different ingredients of an herb or a food item may act additively or synergistically, and this action will be even more complex in a formula that consists of different herbs or food that contains different food items. In herbs the traditional settings in which often even individualized herbal formulae are combined with other interventions can be viewed as the most complex context. Chinese medicine serves as a good example. The delivery of Chinese herbal medicine usually involves herbal formulae that may range in the number of ingredients from a single herb to complex formulae of over 20 ingredients (Flower et al., 2012). Furthermore, the combination with multiple other interventions

Abbreviations: CER, Comparative effectiveness research

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such as diet advice, acupuncture, and qigong is common. The evaluation of herbal whole system interventions can address a number of different research questions from aspects such as patient's experience while using herbs up to the specific effect of single ingredients (Flower et al., 2012). Because complex interventions including medication, but also nutritional elements are also often applied in conventional medicine, (e.g. cardiovascular rehabilitation) the UK Medical Research Council (Craig et al., 2008) has developed guidance on how to design research phases for complex interventions. Those recommendations include paying attention to model validity/best practice as well as allowing some flexibility in the treatment protocol, and could be transferred to herbal whole system therapies as well as to nutrition.

2. Reverse research strategy

Contemporary clinical research, especially drug research, follows a clear hierarchical research strategy from phase I to phase IV trials, ensuring that efficacy is established before effectiveness is evaluated. For traditional treatments, which have been widely available before the clinical research paradigm has been implemented, a reverse research strategy has been suggested (Fonnebo et al., 2007). According to these suggestions, having knowledge about the context of usage and the safety of an intervention is necessary to design more relevant studies on comparative effectiveness and component efficacy. Furthermore, using a strategy that generates evidence on comparative effectiveness before determining component efficacy will help to focus on treatments that have relevance for practice and a potential for integration into health care while saving research resources. (Witt et al., 2012a) This could be also applied to research on food items.

Most traditional herbs have been widely used without systematic knowledge about their usage, safety, effectiveness, and efficacy. However, research on them has grown substantially over the last two decades. The methodological quality of previous herbal medicine studies has often been criticized. This critique has encouraged subsequent studies to emphasize the rigor exemplified by very standardized treatment protocols, thus excluding as much bias as possible. These studies have contributed important information on the efficacy of herbal medicine extracts; however, their results are only marginally helpful to understand the value of herbal medicine in a more traditional usual care context. These rigorous studies are typically characterized by tight inclusion criteria that result in highly selected study populations; the treatment protocols are standardized, and study settings are experimental. Consequently, the majority of previous clinical trials have assessed the efficacy of single herbs or herbal formulations rather than their effectiveness. This is different with research on food items; because of the complexity of nutrition based-settings and long-term administration of food items, randomized placebo-controlled trials are much more difficult to apply (Visioli, 2012).

3. Efficacy and effectiveness

What is the difference between efficacy and effectiveness? "Efficacy" refers to "the extent to which a specific intervention is beneficial under ideal conditions," whereas, "effectiveness"' is a measure of the extent to which an intervention, when deployed in the field in routine circumstances, does what it is intended to do for a specific population (Last et al., 2001).

From an ethnopharmacological perspective, it is important that the context of the usage of herbal medicines (e.g. methods of collection, extraction, and preparation) that is used in a clinical trial is similar to that used by the ethnic group. Such replication supports the use of traditional empirical knowledge, and ensures more relevance of the research results. Knowing the context also respects that research ideas on traditional herbal medicine emerge from positive experience in clinical practice, which highlights the need for high quality field research, as well as field studies, systematic expert surveys and observational studies.

The idea that clinical research in medicine should provide more relevance for clinical decision-making by generating data on the comparative effectiveness of interventions has received broad and prominent attention (Conway and Clancy, 2009). This discussion has resulted in a newly defined research strategy known as "comparative effectiveness research" (CER) (Institute of Medicine, 2009). The conduct and reporting of CER promises to help clinicians, payers, patients and other stakeholders make better and more informed decisions (Sullivan et al., 2013).

4. Comparative effectiveness research

CER addresses the effectiveness of interventions in the everyday practice setting, and also includes trials that compare real-world whole systems of health care. According to the Institute of Medicine, CER is defined as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels" (Institute of Medicine, 2009). Key aspects that characterize CER include : (1) the capacity of its results to inform specific clinical decisions; (2) its comparison of two or more health interventions (such as a therapy, medication, or other treatment) in order to determine which of these options works best for which types of patients; (3) studies conducted with typical patients and in settings that are similar to those in which the intervention will be used in practice (Institute of Medicine, 2009).

A further key aspect of CER is the requirement to include stakeholders (VanLare et al., 2010) such as patients, physicians, and payers in the identification of research questions, in the design and implementation of studies, and in the evaluation and dissemination of study results. By seriously considering stakeholders' input, CER has the potential to produce results that inform clinical and health policy decision-making. Furthermore, it can re-shape stakeholders' attitudes about research and regulatory authorities.

CER uses a broad spectrum of research methods that include retrospective analyses of electronic health records as well as pragmatic trials (Tunis et al., 2010).

5. Electronic health records

The costs of clinical trials make it impossible to evaluate all clinical questions in randomized trials and data available in electronic health records have great potential to facilitate CER (Katzan and Rudick, 2012). Clinical informatics and structured accessible secure data captured through electronic health records systems provide mechanisms through which electronic health records can facilitate CER (Miriovsky et al., 2012). There are challenges and opportunities when using electronic health records which include: the substantial level of effort to establish and sustain data sharing partnerships; the importance of understanding the strengths and limitations of clinical informatics tools, platforms, and models that have emerged to enable

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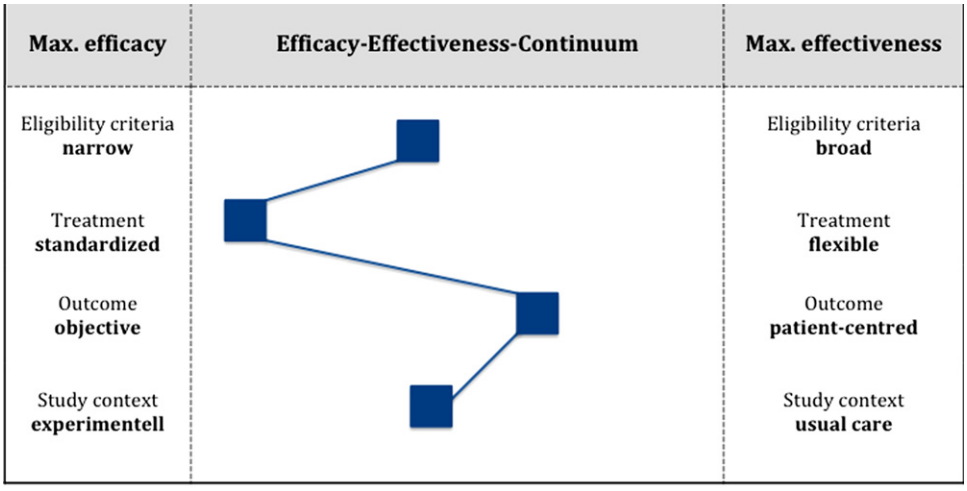
research with electronic health records; the need for rigorous methods to assess data validity, quality, and context for multisite studies; and emerging opportunities to achieve meaningful patient and consumer engagement and work collaboratively with multidisciplinary teams (Holve et al., 2012). However, information on traditional herbal therapies, food or even food supplements are usually not included in electronic health records. To make this clinical derived data more useful for CER on traditional herbs, food items/food supplements, but also to prevent drug interactions (e.g. with grapefruit juice or hypericum extract) adding this information to routine clinical data would be a big step forward.

6. The efficacy–effectiveness continuum in pragmatic trials

Pragmatic trials are randomized studies that address the effectiveness of interventions, by less restrictive patient selection, a more flexible treatment protocol and a focus on patient-centered outcome parameters (Zwarenstein et al., 2008). Pragmatic trials can be used to compare single interventions (e.g. single herbs) with another pharmaceutical intervention or a non-pharmaceutical intervention or to compare whole medical systems (e.g. a complex multicomponent Chinese medicine intervention with a complex multicomponent conventional medicine intervention) (Witt, 2011).

The characterization of a study as either more or less a study of efficacy or effectiveness derives from a consideration of several study dimensions including eligibility criteria, treatment protocols, outcomes, and the context of the study. Efficacy-oriented trials use narrow eligibility criteria, a standardized treatment protocol, objective outcome measures (e.g. laboratory parameters) and are performed in a well-controlled setting (e.g. university clinic). On the contrary, maximum effectiveness would be represented if these criteria were close to a usual care setting, meaning that typical patients – including those with comorbidities and co-medication – are recruited, treatments protocols are flexible, relevant patient-centered outcomes are used as main measures, and the context – including the qualification of providers – reflects a setting in which the treatment is usually performed (Witt et al., 2012b). It is important to note that there is no sharp distinction between efficacy and effectiveness trials. Rather these terms exist in a continuum and the site along this continuum may differ for different features of the trial design (Witt et al., 2012c).

An example of a trial in which hypericum extract WS 5570 was compared to paroxetine in patients with moderate and severe episodes of unipolar major depression (Szegedi et al., 2005) is displayed in Fig. 1. This study excluded patients with other psychiatric and psychological disorders as well as patients with substance abuse and those who have not been responsive to treatment in previous episodes. The treatment was fully standardized: one drug with a fixed dosage that could be doubled after two weeks if symptoms did not decrease by at least 20%. The primary outcome was the Hamilton Depression (HAMD) scale, a well validated and widely accepted patient-centered outcome. However, HAMD has to be assessed by a trained psychologist or psychiatrist and is not commonly used in a usual care setting. The setting of the trial with 21 psychiatry outpatient centers reflects part of the German usual care setting, but still neglected general practitioners who often treat depression. To summarize, this trial falls more on the efficacy side of the efficacy–effectiveness–continuum, but it would not be difficult to push it more toward the effectiveness side (see Fig. 2). Not excluding patients with other psychological and psychiatric diseases (e.g. with the exception of psychotic diseases) and not using a HAMD cut-off point as inclusion criterion would result in a more heterogeneous study population that is closer to the typical population with depression. Including general practitioners in the treatment, and using a patient self-rated outcome would more closely reflect a usual care setting. However, the most significant change in the design would be to extend the treatment to all hypericum and paroxetine products available in German pharmacies, and to leave the decision on the product and dosage to the psychiatrist or general practitioner to fully reflect what happens in usual care.



Szegedi A et al (BMJ 2005). Patients 18-70 years of age with moderate to severe episodes of unipolar major depression and ≥22 on the Hamilton Depression scale (HAMD) were treated by 21 psychiatric outpatient centers in Germany over six weeks daily with 900 mg hypericium extract WS 5570 or 20 mg paroxetine, main endpoint was the HAMD after 42 days assessed by psychiatrist or psychologist, design was a randomized, controlled double-blinded study using a double dummy placebo.

Fig. 1. Placement in the efficacy–effectiveness–continuum, an example from clinical research on hypericum.

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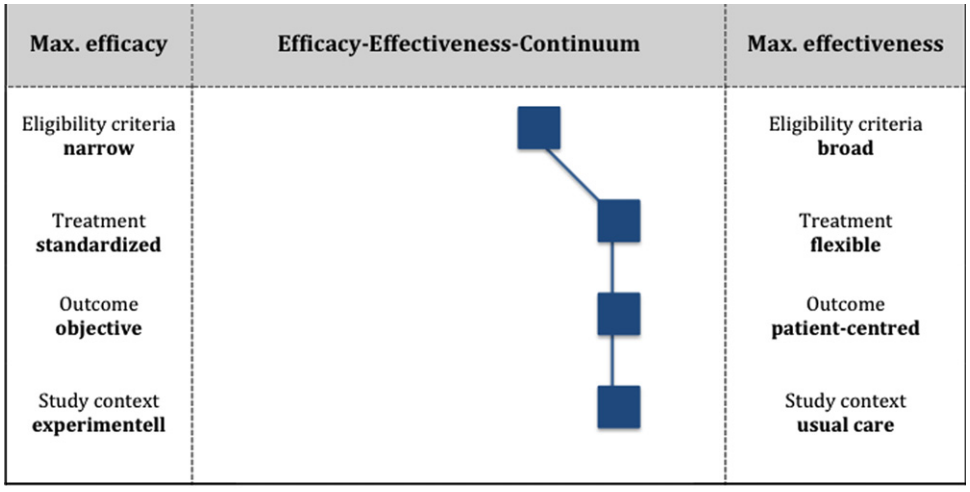

Fig. 2. Hypothetical effectiveness trial on hypericum.

In CER the decision where a study is placed within the efficacy–effectiveness–continuum is not a primary scientific question, it is a conscious decision that is based on extensive stakeholder involvement.

7. Pragmatic trials to compare whole medical systems

Pragmatic trials could also be used to compare individualized complex medical systems for a disease, for example, to compare Chinese medicine with conventional medicine (Witt et al., 2012b) or to compare Japanese Kampo medicine with conventional medicine (Watanabe et al., 2011). Furthermore, pragmatic trials provide good potential for the effectiveness evaluation of food items or food supplements in a randomized design, because compared to typical randomized controlled trials they allow to apply complex and individualized interventions in a more realistic setting.

8. Regulatory aspects of traditional herbal medicines and implications for CER

In contrast to traditional non-pharmaceutical interventions such as acupuncture, traditional herbal medicine in many countries is subject to drug research regulations, which have implications for CER. A recent systematic review (Hochman and McCormick, 2010) on conventional drug research published in high ranked medical journals showed that only a small number of drug trials compared real treatment alternatives. Performing placebo-controlled trials instead of CER has clear advantages for industry, because it is much easier to find a difference between the drug and a placebo than to determine non-inferiority or even superiority compared to another drug. In addition, much smaller samples are needed in placebo-controlled trials than in trials with active controls, a fact which has a direct influence on research costs. Furthermore, most study design of drug trials is still driven by regulatory agency requirements, requiring that the design aspects of outcome parameters and treatment protocol drive results more toward elements that characterize efficacy than effectiveness.

Overall, CER seems to be more suitable for phase IV studies than for studies before market approval. In those countries where clinical research on traditional medicines falls under the regulations governing pharmaceutical drug research, the absence of preclinical data (required to ensure safety prior to trial approval), makes it nearly impossible to perform real-life effectiveness studies on individualized complex herbal medicines.

9. Learning from practice

Recently developed guidelines for clinical research on Chinese herbal medicine (Flower et al., 2012) highlight that research ideas should emerge from positive experience in clinical practice. Clinical practice is complex and includes the characteristics of patients, characteristics of the interventions (incl. methods of collection, extraction, and preparation, etc), and a consensus on what best practice is. Data on these aspects can be determined by expert discussions, surveys, or observational studies. However, best practice for more traditional herbal medicine settings can differ from best practice in a more modern context. For example, Chinese herbal medicine used traditionally consisted of mainly herbal decoctions, whereas now, increasingly, concentrated herbal powders are used.

The need to know real life implementation is even more obvious for research on food items.

10. Contributions of ethnopharmacology to CER

Ethnopharmacological research can provide highly relevant information for CER in traditional herbal medicine and food. Ethnobotanical field surveys are a good method to identify the most promising plants and food items for future clinical research. Understanding the context also includes information on user and provider characteristics, as well as on relevant botanical information. However, because the research communities from ethnopharmacology and medical clinical research live in their own worlds, little knowledge exchange has taken place. Closer cooperation between those researchers who perform clinical research on traditional medicine and food items and ethnopharmacologists

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would be very promising. In the evaluation of traditional drugs and food items it is obvious that both scientific fields complement each other. Ethnopharmacology can provide data on the context and clinical research can design studies that take this traditional context into account. A general interdisciplinary research strategy with clear recommendations for both sides could guide future research. The inclusion of experts from each discipline when designing studies in either discipline will help to bridge the knowledge between them, and generate evidence in both fields that is more systematic, supports both research areas and will inform clinical-decision making.

The need for bridging between basic research and clinical research has been well established; the new development of translational research (the goal of which is to bring basic research from the "bench to the bedside") has been reflected in many recent research grants. However, presently, translational research addresses mainly the need to bridge between laboratory basic research and efficacy studies. Ethnopharmacology and CER have the potential to broaden this development of translational research. Field studies as well as observational studies on traditional contexts can inform both basic research and clinical research; and CER will help to translate knowledge from the bedside to the population level. Furthermore, combining knowledge on traditional contexts with data from population-based studies or electronic health records can even build a much more solid foundation to inform future basic research.

11. Recommendations for future research

11.1. (1) Systematic cooperation between ethnopharmacology and clinical research on traditional herbal medicines and food items to support clinical and health policy decision-making

Both the ethnopharmacology and the herbal medicine/food research communities should cultivate systematic knowledge exchange and develop mechanisms for interdisciplinary clinical research projects to produce results that are of relevance for decision makers. A general interdisciplinary research strategy with clear recommendations for both sides would be helpful to guide future research.

11.2. (2) More CER on traditional herbal medicines and food items

There is a need for more clinical studies that emphasize effectiveness over efficacy to support clinical and health policy decision-making. The study question, as well as the placement of the study in the efficacy–effectiveness–continuum, should be determined by involving multiple stakeholders including ethnopharmacologists. Furthermore, local and national regulations have to be taken into account when planning these trials. To reflect effectiveness, those studies should broaden the heterogeneity of study participants, and use research settings and treatment protocols that reflect usual care.

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