Evaluation of effectiveness of randomized clinical trials in alternative medicine

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Abstract:

This paper is an attempt to evaluate effectiveness of randomized clinical trials in alternative medicine. People are living longer than ever before but several chronic diseases such as hypertension, arthritis, diabetes, malignancies and HIV/AIDS are increasing. Modern Medicine does not provide satisfactory solution of these diseases and is expensive. Therefore, non-traditional treatment is being encouraged which includes herbal medicine, homeopathy, naturopathy, acupuncture, therapeutic massage, ayurvedic and chinese medicine. The support to this concept comes out from the published figures which show that more herbs are being imported in advanced countries like USA, UK and Canada. We concluded after meta analysis that randomized clinical trials are ineffective in alternative medicine to evaluate the response of different remedies.

Key Words:

Randomized clinical trials, Alternative medicine.

Introduction

Controlled trials are usually carried out to prove the therapeutic effectiveness and safety of a drug or procedure before being used in clinical practice. These clinical trials help to achieve many objectives such as:

I. Search of appropriate dosage regime.
II. Choice of formulation.
III. Choice of Route of Administration.
IV. Clinical indication.
V. Comparison with existing medicines.
VI. Drug interactions.

Complimentary or alternative medicines are the medicines which are considered to be active for the treatment of certain diseases but most of them have not been studied for their pharmacological activity and safety on scientific basis and even some of them are not considered to be drugs on this basis.

Need of complementary medicines:

Four main factors are involved to create the need of complementary or alternative medicines at present and are leading to reject modern medicines

1) Health care is going to be expensive because of reduced insurance coverage, constrain on access to care and costs of prescriptions and services.

2) Alternative medicines suit the new approach of the people, according to which they are becoming increasingly interested in preventing strategies and holistic approach to health, such as eating a nutritionally sound diet, maintaining fitness and reduced stress.

3) Awareness and occurrence of adverse drug reactions have led to rejection of modern medicines by a segment of the public.

4) People are living longer than ever before and chronic diseases such as arthritis, diabetes, malignancies, and HIV/AIDS are on the rise. Modern medicine could not provide satisfactory solution of these diseases and conventional prescription drugs used to treat these conditions are often expensive and because at least a portion of this cost may not be reimbursed by insurance carriers, so consumers are paying more from themselves.

Therefore non traditional treatment is being encouraged which comprises complementary or alternative medicine and includes herbal medicine, homeopathy, naturopathy, acupuncture, therapeutic massage, ayurvedic medicine and traditional Chinese medicine.
Importance of Complementary or Alternative medicines:-

An article published in 1997 shows that $3.24 billion were spent by Americans on herbs\(^1\), another article published in 1999 presents that $4.3 billion were spent by this country on herbs\(^2\). In 1998 Eisenberg\(^3\) and his colleagues presented a study which suggested that approximately 42% of adult American in the general population had used one or more alternative medicines. Two more studies confirm rising rates of alternative medicine even for more narrowly defined subsets of general patient population. A study focusing on health maintenance organization found that 40% of the patients surveyed had used herbal remedies to treat or prevent health conditions\(^4\). While a study using the cross section of patients in the rural south found that 44% had used one or more alternative medicine approaches during the year preceding the study\(^5\). Use of complementary medicine, including herbs, appears to be even more widespread among other groups of patients, for example, a recent study found that the 60% of elderly Hispanic and non-Hispanic white patients had used herbal remedies\(^6\). Another study reported a similar higher percentage of alternative medicine use for patients with HIV/AIDS, that is 68%\(^7\).

Consideration of factors which may be involved in failure of controlled clinical trials for Complementary or Alternative medicine:-

1) **Limited research;** Primary research is still limited in alternative medicine. Even in United state, scientific study of herbs and their medicinal effects does not go beyond last quarter of last century. Much of the information that is available is anecdotal and largely unscientific not having been subject to the same rigorous control and replicate studies as are mandated for modern drugs. Lack of profitability may be a cause of loose interest of researchers in alternative medicine.

2) **Lacks of rules and regulation:** Manufacturer of alternative medicine like Herb manufacturer are not held to the same standard as are the manufacturer of pharmaceuticals. They are not required by law to demonstrate the safety, efficacy or quality of their products in most of European countries and United State. They remain unregulated. Some voluntarily adhere to GMPS and make every effort to produce a quality product, whiles other do not care for it. This cause poor and irregular quality.

3) **Absence of Nomenclature:** Common nomenclature is absent for herbs or plant origin medicines. For example, scientific name of garlic is *Allium sativum* which is used as antilipidemic, antimicrobial, antiasthmatic and anti-inflammatory and its common names which are found in literature are ail, allium camphor of the poor, da-suan, knoblauch, lasuan, nector of the gods, poor man's treacle rustic trickle and stinking rose. Similarly scientific name of yohimbe is paunystalia yohimbe which is used as an aphrodisiac and hallucinogenic, and its common name in literature are aphroden, corynine, yohimbe, querbrachine, yohimbehe, yohimbe, yohimbine. This makes the transfer of information difficult among the scientific community.

4) **Lack of uniform Quality:** Chemical analysis of the sample labeled as the plant or herbal product, but purchased from various suppliers or outlets has revealed wide variation in the quality and chemical contents. The manner in which such products are grown, harvested, processed and stored also affects the strength and quality of the product as do many other factors. Since this industry lack regulation, some herb may be manufactured with dosage standardized to their active chemical component while others not. In practical term, this means that a patient taking a herbal product made by one manufacturer may receive a much higher or lower dose of the active chemical than another patient taking the same herb, made by different manufacturer. This can make the controlled clinical trial difficult or can produce confusing results.

5) **Pharmacokinetic Variation:** As already discussed, most of the alternative or complimentary medicines do not yet have standardized dosage, nor do manufacturers always produce the preparation of constant strength. Most of the alternative procedures like acupuncture do not have proper and standard measurement scales for dosage. Crude herb or plant material itself may vary in chemical composition from one batch of the plant to another or even from plant to plant. Disagreement among trained persons who prescribe alternative or complimentary medicine about dose is common. Most of the time the decision about dosage depend upon the use of part of the plant or herb being used, its strength, the route of administration and personal perception of prescriber without uniform recommendations. All these facts produce pharmacokinetic variations among the patients. Logically different rates and extent of absorption, variable distribution and elimination and different biotransformation and bioavailabilities of these drugs exist in different patients. This phenomenon becomes further serious as consensus on appropriate dosage for various age groups, weight of the patients, sex and various health conditions does not yet exist.
No recommendations for dosage, indications or contraindications or precautions exist for pediatric, geriatric and pregnant patients. Current research is insufficient to allow safe generalization. Therefore to establish efficacy of such drugs by comparing them with standard modern drugs, is almost impossible.

6) **Potential toxicity:** Incorrect use of many plants or their products or herbs is potentially toxic. For example a herb may be safe and effective when used topically in the amount specified but may be highly toxic if taken orally. Some herbs contain potent liver toxins, systemic toxins, carcinogens, mutagens or teratogens. Toxicity of these drugs in pediatric, geriatric and pregnant patients is largely not determined. Use of different toxic substances during commercial preparations of alternative medicines may contaminate them and can enhance their toxicity. Many of the toxic effects of these medicines have yet to be determined, both because of insufficient research and because no law requires that adverse effects from these drugs be reported. Safety of the patients who will be recruited for clinical trials of these medicines will be questionable.

7) **Lack of training:** Variable training of those who will be involved in clinical trials of alternative medicine, will be required because standard of education and the knowledge of those who give these medicines to the patient, is not up to the requirement.

8) **Absence of correlation with biological markers and prognostic parameters:** Complementary or Alternative medicines do not have correlation with biological markers and prognostic parameters. For example, Tamoxifen which is an antiestrogen, is used in breast cancer and is indicated for the ER- positive patients\(^8\), which means a correlation has been established between ER-status and treatment; which has proved to improve the outcome of therapeutic effort in these patients. Similarly blood culture can help therapeutic outcome and avoid unnecessary toxicity if non specific antibiotic is given. Such correlation of treatment with diagnostic and prognostic parameters does not exist in alternative or complementary medicines and therefore individualization of treatment is not possible which logically increases expenses and time consumption, decreases therapeutic response and produces undue toxicities.

9) **Absence of drug monitoring:** Certain drugs require continuous monitoring. Serum levels of these drugs are periodically checked to avoid their toxicities and to evaluate response failure. For example sensitive plasma digoxin assays are available at most medical centres\(^9\). Similarly, Lithium levels are monitored especially in condition that causes volume depletions\(^10\). The monitoring of drug levels in complimentary or alternative drug has not been established as yet.

10) **Profit to the sponsor:** In the United State, clinical trials are to demonstrate the safety, efficacy, and reliability of a drug, are expensive and time consuming. Currently the drug approval process takes anywhere from eight years to as many as eighteen years, with cost in the hundreds of million of dollars. Because of the great expense, manufacturers typically want to patent their products in order to recover their investment and make a profit. However, naturally occurring products such as herbs cannot be patented. Hence, no economic incentives exists and to date US Pharmaceutical manufacturers have pursued only limited research on whole plants or their crude extracts.

### Development of a clinical trial:-

1) A scientific basis is required before considering a drug for clinical trial. This scientific basis is extracted from the information present in the literature and from the data of experiments.

2) The observational studies in an important epidemiological tool and in pharmaceutical medicine, it can provide information about its clinical efficacy and safety. In these circumstances the side effects are distinguished from untoward effects of the disease being treated, of other concomitant disorders and of those caused by other medicines taken by the patients or by other cohort of patients, necessary and helpful to develop a remedy.

### Problems during designing and conduct of randomized controlled trials or alternative medicines:-

1) **Insufficient information:**

Insufficient scientific information like lack of knowledge about absorption, distribution, metabolism, elimination and drug interactions of trial drug (complementary medicine) can lead to poor designing of clinical trial, the results cannot be explained and logically related and may give rise to the ethical issues.

2) **Patient compliance:**

Patient compliance is adherence of the patients to the schedule
and poor compliance confounds the interpretation of the efficacy and safety of the drug. Patient compliance for complimentary or alternative medicine is poor because:

a) Patient’s believe on medicine is found to be increasing or decreasing in relation to the intensity of the disease which can reflect on the compliance.

b) Unexpected side effects may reduce the interest in the drug(s).

c) Unknown drug interactions.

d) Most of the complimentary or alternative medicines are slow acting, therefore persistence sign and symptoms of the disease may lead to loss of patient interest in the treatment.

During the course of trial, compliance may be improved or assessed directly;

i) By observing the patients taking their drugs.

ii) By taking blood or urine or other biological samples to measure parent drug or metabolites.

iii) By including a biological marker in the medicine that is non toxic, inert, chemically stable and easily detectable in biological fluid.

iv) By making spot checks on the patients at home.

The application of second and third strategies have questionable application in case of complimentary medicines trials because techniques for the measurements of particular drug or it’s metabolite or biological marker is must for this purpose.

3) Experimental Error:

Following points are important in this regard.

a) Equipments used for the measurement of clinical efficacy and safety end points should be sensitive enough. Sometimes efficacy and safety end points may be biological markers. Complementary medicine or it’s metabolites may interrupt the results giving false high or low values of tests. For example if LDL reduction is the efficacy end point of a study then complementary medicine can interrupt the chemical reactions of it’s measurement, if prior extensive studies are not carried out.

b) Drug interactions are also important. During trial design option of the drugs which do not interfere the results and are taken by the patients to reduce their symptoms or for the concurrent diseases, is always considered. For example a patient may use insulin for diabetes during a clinical trial carried out on Dementia provided the studies have shown absence of any pharmacokinetic or pharmacodynamic interaction of insulin and the study drug. However lack of information about drug interactions of a complementary drug may give false results.

c) A complementary medicine can have certain features associated with its administration. For example it may be required to heat or may be asked to dissolve in milk before it’s oral administration. A comparator drug may not have such limitations. Therefore blindness can not be retained.

4) Clinical trial medicines:

a) Manufacturing: Complementary medicine may be a herb or part of a plant or homeopathic medicine. There is a possibility of variable quality. For example different samples may contain variable concentration of active ingredients or other components. This may give non uniform dissolution, unpredictable serum levels and variable half life. All these factors may disturb the clinical response. Therefore uneven results are expected in clinical trials which can not be explained on scientific ground. Similarly supply of the medicine relative to the demand may also be questionable, during clinical trial especially of a complementary medicine. For example if trial medicine is obtained from a seasonal plant, its continuous supply throughout the trial may be troublesome. If this drug is stored, the possible degradation of its active ingredients may produce unreliable results. The presence of degraded products may give rise adverse effects or toxic reactions.

b) Storage: Effects of environmental factors like moisture, temperature, sunlight are also important on drugs. Stability of most of the drugs is investigated before their clinical use. Lack of studies on such aspects of alternate medicines may disturb the clinical response and can produce invalid data.

c) Comparative Medicine; In case of controlled trial, the two drugs used in double blind studies must be similar in shape, colour and size. If complementary medicine is a herb or some liquid or part of a plant with certain dose then it is impossible to create a placebo or choose a comparator
of similar shape, colour and size. The blindness is difficult to maintain in such circumstances.

Sometimes it is decided to elect for double dummy technique or to mask the identity of the marked compitor and to stimulate the appearance of the new medicine. In doing so it must be realised that the absorption characteristic might be changed (for example by a shellac coating). Same problem may be faced in case of complementary medicine.

d) **Presentation:** Variability in the analysis of different samples may cause non uniform presentation.

e) **Transportation:** The transportation of medicines to investigating centres especially abroad is also important to consider. The stability of the drug can not be ignored in this regard. If complementary medicine is a herb or fresh plant product, its transportation, distribution and handling may require especial arrangement which should be different from other drugs. Time consumed from collection of a particular drug upto handling it to the patients and its use, is important in such cases because it may effect the activity of main ingredients and degraded products may alter the response. This aspect of these drugs requires extensive studies. Clinical study designs without considering these facts may produce invalid results.

5) **Designing of Clinical Trials:**

a) **Patientpopulation:** Target population is the population which is expected to use a particular drug. A drug is tested in carefully and narrowly defined groups which are expected from this population. Process of selection of target population is same for the complementary medicine as well as for other medicines. However unique situations can not be overlooked. For example if a complementary medicine has shown good results in rheumatoid arthritis, an investigator may be reluctant to enter young women in the study with active disease and expose them to a therapy for many months which has shown response but has not been proved to be effective through controlled trials on the scientific basis and its disease modifying ability has not been established. Similarly if an alternative or complementary medicine has shown its effect in meningitis, then an investigator can not take risk to treat the patient by such drug because any delay in response or lack of response may cause death or permanent disability. The literature contains examples of the medicine which have shown great promise in small, highly selected population of subjects but have failed to confer therapeutic benefits when used in the more heterogeneous population in clinical practice.

b) **Selection of Placebo:** It is difficult to select in most of the clinical trials designed for alternative medicine. For example in case of Acupuncture.

c) **Selection of Parallel or Crossover design:** This requires especial attention in this case. Following are important considerations if parallel design is selected for complementary or alternative medicines.

i) There will be more robust to trial violation (missed visits, missing data etc.). It is natural, sometimes due to lack of confidence on trial medicine or sometimes due to slow response of the drug in recruited patients.

ii) Variability of data obtained is likely to be large because of two main reasons. First, certain precautions are advised during treatment with herbal or plant origin medicines. For example diet is strictly controlled during treatment with herbal medicine which is difficult to be followed by patients and therefore data obtained from those patients, who will not follow the precautions strictly will add variability. A good example is ‘Ephedra’ which is used in Chinese medicine to treat asthma, bronchitis, headache, pulmonary congestion and joint pain. This drug can not be used with coffee, cola, red bull and tea. Patients either do not use this drug or do not follow the precaution. They can not resist the habit of coffee or cola or red bull or tea and try to hide the fact that they are not following the precaution. Therefore the data becomes unreliable and variable. Second, different composition of alternative medicines can make the data further variable because as already discussed, most of the alternative or complementary medicines do not yet have standardized dosage, nor do manufacturer always produce the preparations of consistent strength.

iii) Large number of patients are required because data is expected to be variable.

iv) Waxing and waning of disease can be tolerated in parallel design which makes this design suitable for complementsary medicines.

v) Carry over of periodic effects are insignificant in parallel study design which is better for complementary or alternative medicines because their pharmocokinetic data is still not available in most of the cases which is required to evaluate these effects.
Similarly following are important considerations if cross over design is selected for complementary or alternative medicines,

a) Variability of data is likely to be smaller in case of cross over design for modern medicines but variability of data is likely to be larger in case of cross over design for complementary or alternative medicine. A major factor is that insufficient informations are present about pharmacokinetic of these drugs. Therefore carry over effects or the effects from the first period which are not worn off at the time of conducting the second period and are usually determined by half life and elimination of the drug, can interrupt the data.

b) Stability of the disease is mandatory in case of carry over design. However baseline at each carry over must be similar. Will it be possible in case of complementary or alternative medicine? This requires experimentation.

c) Periodic effects or the order in which one treatment occurs in a sequence compared with another, influences the response to early treatment, may confound the interpretation of the cross over studies. This factor can not be overlooked in complementary medicine trials.

4) Dosage; Following are important consideration in this regard,

a) **Dose selection**: complementary medicine has lack of standardization. Therfore the dose which can be investigated for desired therapeutic response in a controlled clinical trial may not have practical importance for further use. Since batch to batch variation in active ingredients in these drugs have been noted, so confusing data may be produced by a long clinical trial. Meta analysis of different studies may be impossible. Further more the lack of pharmacokinetic data for these drugs in relation to body size, efficacy of the metabolising and excretory pathways, race, age, state of disease, can further add to confusion in the data.

b) **Dosing schedule**: Dose selection in exploratory studies requires a knowledge of pharmacology, toxicology, metabolism and kinetics in animal and man. By the end of dose running programme studies, following can be defined.

i) The therapeutic dose range in the core population who will frequently receive the drugs. This is difficult in complementary medicine due to lack of standardization and therefore, requires to decide either the dose range is adjusted according to active ingredient of the drug or total weight of the drug. This is another confusing factor.

ii) The minimum effective dose, maintenance dose and the dose which is tolerated in the majority of the defined population. This is also difficult to decide for complementary medicine through clinical trials which is again due to lack of uniform quality or quantity of active ingredient and other components. Some unique procedures make it further impossible like Acupuncture.

iii) The therapeutic dose range at risk groups, for example, in elderly or hepatically impaired or renal failure patients. It requires an extensive study of complementary or alternative medicine. However lack of research in these medicines, does not allow to determine the therapeutic dose range in at risk groups presently, in most of the cases. In these patients drug interaction becomes most important which is again an area of poor investigation in complementary or alternative medicine.

Dose selection for phase I or II studies depends upon a number of factors.

I) The duration of action against primary efficacy end points.

II) The pharmacokinetic characteristics of the parent compound and any active metabolites in particular the area under curve, the clearance, the plasma half life and the bioavailability of formulations.

III) Difference between intermediate dose can be investigated by considering primary end point responses. In case of complementary medicines, the major factors that are lack of standardization, pharmacodynamic and pharmacokinetic characteristic of other components of drugs and their interactions with each other and lack of procedure for determination of pharmacokinetic parameters of drug, can not help dose selection for phase II and III studies.

5. **Investigation of Dose-Response relationship**: Dose-response relationship is determined by dose titration studies which involves starting patients at a predetermined dose which is increased until desired therapeutic effects are achieved. Two factors complicate the interpretation of such studies which are dose increase and the increased duration of exposure. However knowledge about mechanism of action and pharmacokinetic parameters helps to resolve these complications to a great extent. Most of the complementary
or alternative medicines follow mysterious mechanism of action. Sometimes they are combination of a number of active ingredients and pharmacokinetic details of each ingredient and their mutual interaction is difficult to work out. Therefore the results of dose titration studies are expected to be further complicated in case of such medicines. Sheiner and his colleagues have suggested modification of the design, for example inclusion of randomly assigned placebo arm for the duration of the study and the analysis that is the use of parametric patient-specific dose-response model\textsuperscript{11}. However both of these considerations can face practical difficulties in case of complementary or alternative medicines.

6) Concurrent medications; Concurrent medications can be used by the patients who enter into the clinical trials, either for the conditions for which the test drug is being evaluated or for unrelated conditions. The decision to continue concurrent medicines, to reduce their doses or to stop them, entirely depends upon the person who is going to prescribe the alternative or complementary medicines. It is important to consider that enough information is required to support the decision in this regard because withdrawal of treatment may pose an ethical problem for many conditions, for example, mild hypertension, chronic arthritis, irritable bowel syndrome, but it will not be acceptable in others, for example epilepsy, severe heart failure. The phenomena of synergism or antagonism and the adverse effects of the drugs are also important to consider at this stage.

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