

Tools for comparative evaluation of the effect of drug and non-drug medical treatments

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Abstract

Today a physically or mentally ill patient and his physician often have to make a choice between a drug-treatment and a non-drug treatment or alternative solution. Unfortunately the methods used for evaluation of treatment effect in biomedicine on the one hand and psychotherapy and CAM (complementary and alternative medicine) on the other are often very different. To compare the therapeutic effects of the different treatment modalities and their relative values, we need to look at Number Needed to Treat (NNT), total Number Needed to Harm (NNH), Therapeutic Value (TV=NNH/NNT), Extra Survival Time (ΔT), Improved Global Quality of Life (ΔQOL), Quality Adjusted Life Years (QALY= $\Delta T \times \Delta QOL$) and qualitative evaluations of indirect benefit and harm. We conclude that in spite of the qualitative evaluation often being colored by values and preferences, only this kind of evaluation can include the total impact of a treatment of the whole patient's life and destiny, making the qualitative evaluation at least as important as the quantitative. During the last decade comparisons of the treatment values (TV) of mental illness have documented that non-drug therapies could in fact also be the cure of choice. The next decade will show if physical illnesses like cancer also in general are better treated with non-drug scientific holistic medicine and other scientific CAM treatments.

Keywords: Integrative medicine, complementary and alternative medicine, evaluation.

Introduction

The science of medicine developed from holistic medicine of Hippocrates, which according to the Corpus Hippocraticum was founded in Greece at the island of Cos 300 BCE (1). Today this medicine has developed into biomedicine, using pharmacologically active drugs with the alternative of psychotherapy and CAM (i.e. homeopathy (2), clinical holistic medicine (3-7)), where pharmacologically active drugs are not used in the intervention. The Corpus Hippocraticum

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documents that holistic medicine focused on consciousness and rehabilitation of human character and purpose of life; the use of pharmacologically active drugs was extremely rare. Herbs and oils were used on the skin, bodywork was normal, and occasionally the patients were ritually cleansed though smoking and similar procedures also known from Native American medicine. CAM today integrates the medical systems of many premodern cultures (8) and has developed mainly into two trends, the less scientific “orthomolecular medicine” using natural often symbolic remedies and the scientific CAM combining conversational therapy and bodywork in a mindful, philosophical frame (9-15). Independently of the use of herbs and other remedies, CAM is basically using the placebo effect (16): a direct and indirect interaction with the patient’s consciousness to develop self-insight, consciousness living, human character, talents and purpose of life (17). CAM and psychotherapy can be grouped into the concept of consciousness-based medicine (18).

The many different modalities of treatment in modern medicine have made it difficult to compare the therapeutic outcomes and the value of the different medical systems. The largest methodological problem has been to compare the positive and negative effects of drug- and non-drug treatments.

A biomedical drug needs to be tested against placebo so the placebo control is mandatory in the documentation of the therapeutic value of a drug (19). The fundamental idea in this test is double blinding of physician and patient, where both do not know who gets the active drug. Most unfortunately many drugs have been developed to boost the placebo effect though the patient’s clear sensation of getting an active drug, which has led to the development of drugs with many side effects, like the antidepressant drugs for example. When drugs are compared to placebo it is necessary to use active placebo drugs that has a similar adverse-effect profile in order not to destroy the blinding and induce bias (19,20). We know from active-placebo controlled studies that all antidepressant drugs in use today work, because they boost the placebo because of their many adverse effects (20), so the active placebo control is of utmost importance. It is also important that the study is a long-term study, of at least one year, as short-term effects in principle are without clinical interest (i.e. if

a drug relieves the psychosis or depression only for hours or weeks).

When it comes to documentation of the positive and negative effects of non-drug placebo cures it has no meaning at all to test them against placebo drugs. Here we need another control to be able to objectively measure the treatment effects. The solution has been to use the patients as their own control. This control is actually the optimal control, if we are sure that the patients for a sufficient period of time have been stably chronically ill and is cured by the CAM-treatment with healing that lasts for a sufficient period of time for us to be sure that the diseases is cured (21).

In practice, we can use the time-span of a year before and after treatment. If the patient for one full year has had a low self-rated physical health due to permanent, chronic low-back pain and inability to work with nothing that has helped until now, but a CAM intervention then cures the pain in a month or two and thus brings the patients self-rated health from “low” back to “good” (a useful scale is found in (22)) and stays completely cured and well-functioning for another year, we have a positive response to the treatment. The self-assessed health has been shown to be a very simple and extremely important information with a predictive measure of health (3,4). In practice most seriously ill patients of the western world will see a biomedical physician first, who most often will prescribe a drug and therefore almost all chronic patients are patients that the drugs failed to cure. Randomizing the patients into two groups, one treated with drugs and another treated with CAM is therefore the optimal procedure, but not possible in practical life, since very few ill patients will accept not to be treated by the biomedical physician right away. As the NNT (Number Needed to Treat) often are 5 or more, most of the severely ill patients become chronic patients as times go by. Now they are open for entering CAM-studies, since these non-responders are now also control for the drug treatment that did not help them, which is important to notice.

If we want to compare drug- and non-drug therapy it is obvious that one could randomize between the two types of treatment and this has now been done in most psychiatric diseases (23-25). The studies have systematically documented the non-drug therapy is superior to the drugs. Unfortunately most

biomedical treatments for somatic illnesses have not been tested against non-drug treatment. The randomization into two groups, one receiving CAM and one receiving a drug is technically possible, but difficult in practice, as patients often have a materialistic philosophy of life making them want drugs, or a spiritual philosophy of life making them want to improve their health though the development of consciousness, quality of life, sense of coherence, character and self-insight. These patients cannot ethically be randomized into two such groups.

So we need realistic, practical, reliable tools for comparison between medical drugs and non-drug treatments. If we take cancer as an example, research in cancer treatment has suffered from very severe methodological problems. Ulrich Abel (26) showed in his critical review from 1992 that chemotherapy in advanced epithelial cancers (a group containing about 80% of all cancers, i.e. breast cancer) rather showed a negative effect on survival and quality of life than a positive effect (except for lung cancer where survival was prolonged with a mean of three month) (26). This finding did not lead to the intensive testing against active placebo or no treatment, that was necessary from a methodological point of view and new chemotherapeutic cures have since 1992 been tested by comparison to the old types, meaning that nobody today can tell if chemotherapy has therapeutic value for the patients, even if they are better than the old ones. The effects of CAM on advanced epithelial cancer have not been systematically investigated; but some studies indicate that CAM might be of therapeutic value to these patients (27-29). It is very likely that there actually are some efficient CAM-treatments for some cancer types and other illnesses that are ignored, because of lack of methodology and research.

We need conceptual and mathematical tools to be able to compare the different drug- and non-drug treatments using the data generated by different types of studies. In this paper we will therefore identify the tools needed for making a valid comparison of drug- and non-drug medical treatment.

Tools for comparative evaluation

In principle there are three different approaches to assess the positive and negative treatment effects: 1)

Assessing the therapeutic value from the Number Needed to Treat (NNT also called NNtB) to benefit and to harm (NNH also called NNtH) (30), 2) assessing the total outcome in quality-adjusted life-years (QALY-outcome) based on the improvement of global quality of life and the prolongation of life (31) and finally 3) estimating the total value of a treatment from a qualitative evaluation of direct and indirect benefits and harms. The three approaches are increasingly complex.

Many other measures have been suggested like the WHO's Healthy Life Years (HLY), but in these measures health is either not related to quality of life, making the measure of little interest for the patient, or closely related to quality of life, making it much more relevant to measure quality of life itself. The HLY seems to be preferred by the pharmaceutical industry as an argument for the use of drugs even when these drugs do not improve quality of life, and the questions is if WHO in recommending HLY instead of QALY is not working too closely together with the pharmaceutical industry to be able to objectively serve the patients best interest.

Number needed to treat (NNT)

The number of patients needed to be treated for one to be cured (or significantly benefited) is in principle the simplest concept of therapeutic value. If you treat 100 patients with syphilis with penicillin and 90 gets cured, and you treat 100 patients with syphilis with placebo and 50 gets cured, the $NNT = 100/40 = 2.5 \approx 3$ (32). The cure is about as efficient as it gets in biomedicine.

In many cases the outcome is not a cure, but only a much more modest improvement of a mental or somatic state. Here it is extremely important to chose a clinical significant improvement, in a dimension relevant for the patient: quality of life, self-assess physical or mental health, which is closely related to quality of life (34,35). A 20% improvement in some undefined behavioral measure, as it is often seen in studies of drug-treatments in mental illness, cannot be used as a base for a meaningful evaluation of a treatment for comparison with treatment alternatives.

Total number needed to harm (NNH_t)

If you treat 100 patients with syphilis with penicillin, and 10 gets clinically significant adverse effects, and you treat 100 patients with syphilis with placebo and 5 gets clinically significant adverse effects, the $NNH_t = 100/5 \cong 20$. The cure is about as safe as any biomedical cure. A simple way to find total NNH_t is to add all the NNH_t s from the treatment (calculated by using the inverted sum of the inverted NNH_t s). For a critical discussion of this approach, see (30).

Therapeutic value ($TV = NNH_t / NNT$)

If you treat 100 patients with syphilis with penicillin, and you have $NNT = 2.5$ and $NNH_t = 100$, the therapeutic value will be $TV = NNH_t / NNT = 20 / 2.5 = 8$. This is a fine number, and you should be happy to use this treatment both as physician as well as a patient. Similarly, when we treat 100 patients with a chronic, low self-assessed mental health with non-drug therapy, 57 of these are cured, and no patient harm (4), giving $NNT = 2$ and $NNH_t > 100$; $TV = NNH_t / NNT = 100 / 2 = 50$. The TV-numbers from non-drug therapy are normally ranging from 10-50, while many drugs have a TV of 0.1-10 (30). If a drug TV-value falls below 1 it should, as a rule, not be used as medicine, as it harms more as it benefits.

The therapeutic value allows for an immediate comparison of a drug- and a non-drug treatment; we have found that in general, when it comes to mental illnesses a non-drug treatment is often the cure of choice (30). A table of recommendations based on TVs is found in Table 1.

Extra survival time (ΔT)

If you treat 100 patients with syphilis with penicillin, and you prevent 1 from getting neurosyphilis and die 20 years before time, you add 20 years / 100 patients = 0.2 year to every patients life (mean). One patient in 100 having anaphylactic shock dies, but only one in a hundred gets this, so we can ignore the loss of survival time here.

Table 1. Treatment values (TV) needed for recommendation of medicine

$TV > 10$	Great medicine
$TV = 3-10$	Good medicine
$TV = 2$	Medicine almost without value, use with great care
$TV = 1$	Harms as much as it benefits and cannot be used as rational medicine
$TV < 1$	Harms more than it benefits and is not medicine

Improved global quality of life (ΔQOL)

The 40 patients cured are very happy; let us say their total quality of life is improved 20% (mean) for 30 years (mean). It is important to use a global measure, integrating all important aspects of quality of life, as the "health-related" QOL-measures are often measuring things very far from the patients experience of life as good or bad (33).

Quality adjusted life years

$$(QALY = \Delta T \times \Delta QOL)$$

A normal quality of life (QOL) is empirically found in Denmark to be 70% of maximum (34,35). We can set death equal to a global QOL of 40%, as 40% seems to be the normal threshold for suicide at least judged from the data on schizophrenic patients (35). The QALY contribution from extra survival time in the penicillin example is 0.2 Year \times (70%-40%)QOL = 0.06 QALY. The QALY contribution from improved global quality of life when syphilis is cured is 30 Year \times (70%-50%)QOL = 30Y \times 0.20 QOL = 6 QALY. The total QALY contribution is thus 0.2 QALY + 6 QALY = 6.2 QALY.

This is six good year more (mean) for every patient. Again, this is an excellent number attached to a treatment with only minor and rare adverse effects, and you should be happy to use this treatment as physician as well as patient. If the QALY-outcome of a treatment comes close to zero or below zero (see table 2), it harms more than it benefit and should not be used. Interestingly, if global QOL below about 40% (54% was found to be the suicidal threshold)

(35) is calculated negative, even suicide and euthanasia can technically have a positive QALY-outcome for the patient. The QALY outcome of a drug- and a non-drug treatment can easily be compared.

Table 2. QALY outcome values needed for recommendation of medicine

Outcome >10 QALY:	Great medicine
Outcome =2-10 QALY:	Good medicine
Outcome =1 QALY:	Medicine almost without value, use with great care
Outcome =0 QALY:	Harms as much as it benefits and cannot be used as rational medicine
Outcome <0 QALY:	Harms more than it benefits and is not medicine

Qualitative evaluations of indirect benefit and harm

This is by far the most complicated way to evaluate the value of a treatment. The physician that follows the treatments at the venereal clinic will feel that he is doing a good job. But he is also giving patients the liberty to a rather free sexual life, as they can get cured for most of the STD (sexually transmitted disease) a wild life attracts. The day a frequent guest to the venereal clinic patient is diagnosed with HIV, the question is if the existence of cures for gonorrhea and syphilis inspired to unsafe sex, i.e. more frequent sex without use of preservatives. So there could be severe indirect effects of a treatment.

If you think about cancer, the choice of a CAM-treatment could prevent the patient from getting the surgery, i.e. in testicular cancer that in 98 of 100 cases could save his life. Even if the CAM-treatment is in itself completely harmless, the indirect harm could be highly significant. On the other hand, if the patient has a metastatic cancer in the uterus and chemotherapy are unlikely to help her, even if the chemotherapy does not shorten her life it could cost QOL, which is direct harm; being exhausted from chemotherapy could also prevent the patient from seeking CAM-treatment which might be able to help her induce spontaneous remission (36,37) and if there

is a fairly successful CAM-treatment this would be a clinically significant indirect harm.

Discussion

The problem with the qualitative evaluation of treatment effects is that it is highly sensitive to values and beliefs; quantitative science is on the other hand much too limited to catch the whole scene in order to give objective and final measures. The best solution seems to be to base decisions of treatments on a balanced analysis using both quantitative information about the therapeutic value, and the QALY outcome if an assessment exists, complemented with the different qualitative evaluations of the treatment. It might be that the whole situation is so complex, when it comes down to it, that even the patient's and the physician's intuition should have their say in the final synthesis of data.

The quantitative studies are normally not very long, but using a qualitative approach it is often possible to get an impression of a treatments impact and significance for the whole life-time, and these "impact on destiny" might very well be the most important dimension of evaluation.

Many mental and somatic diseases can be treated with drugs or with non-drug therapy. When a physician or patient is to choose a treatment alternative, it is important to compare the Number Needed to Treat, the Number Needed to Harm, the Therapeutic Value $TV = NNT_H / NNT$, outcome in survival time and global quality of life, integrated into the total measure of QALY-outcome, and finally a qualitative assessment is always needed as many important benefits and harms comes from indirect aspects of treatment.

The last 10 years research has favored non-drug therapy as a choice also for some mental illnesses (38) and it is important next that we address the somatic diseases like cancer and HIV to see whether drugs or non-drug treatment is the most valuable for the patient.

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