Original Paper

The Impact of Patient Treatment Preferences on the Interpretation of Randomised Controlled Trials

K. McPherson[1] and A. Britton[1,2]

[1]Cancer and Public Health Unit; and [2]Health Promotion Research Unit, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT, U.K.

Reliable information about aggregate main treatment effects in cancer research comes from randomised controlled trials (RCTs). The possibility of important interactions, such as between treatment preferences and their effects, is necessarily subordinated in the quest for evidence about main treatment effects. If patient preferences can influence the effectiveness of treatments, for which there is some indirect evidence, then those estimates of the treatment's main organic effects from unblind RCTs might be wrong. RCTs clearly disallow patient choice and it is, therefore, important to know the extent of any preference effects in order to interpret the RCT evidence. It may be important to know whether they exist, and where and by how much they affect outcome. It is argued that measuring these effects reliably is methodologically difficult, and will require massive trials each directed at measuring one particular preference effect. Such effects have a slightly fanciful image, particularly in cancer treatment, and may be transient. Given the current uncertainties about their true nature and plausible biological mechanisms, the accumulated evidence is unlikely to provide sufficient justification for investing in such trials, given other current priorities. © 1999 Published by Elsevier Science Ltd. All rights reserved.

INTRODUCTION

CANCER TREATMENTS and their accompanying side-effects may arouse strong preferences and dislikes among their recipients. It therefore follows that recruitment into the essential evaluation of treatments, by randomised controlled trials (RCTs), may be problematic. Such experimental research is vital, however, to distinguish the relative merits of cancer treatments. Many large RCTs are successfully conducted in this field worldwide and, more importantly, comparable trials are combined together in meta-analyses to provide statistically reliable estimates of the effects of treatment for cancer.

The patients who participate in such research for the scientific benefit of others may none the less still hold particular beliefs, and have a preference for one of the treatments under investigation. If such patients are knowingly randomised to the treatment arm they want, might this in itself enhance the outcome for them? If preferences can influence the effectiveness of treatments through psychological pathways (or perhaps separately through better compliance) then unblinded

RCTs may wrongly attribute effects solely to a treatment's physiological/pharmacological properties. To interpret the RCT evidence base for cancer treatment it is often important to determine whether any preference effects exist and, if so, by how much they affect outcome. In this paper, we explore the extent and the importance of this phenomenon.

CAN PREFERENCE FOR TREATMENT INFLUENCE OUTCOME?

It is important to clarify at the outset that in this discussion 'preference effects' will refer to the associated belief in the healing properties of a particular treatment and its consequences for outcome. This is possibly more difficult to understand than, for example, a preference for dosage regimen or predicted side-effects of certain treatments. A preference for either mastectomy or lumpectomy for breast cancer; or prostatectomy or watchful waiting for cancer of the prostate, will be based on important attributable aspects of outcome for each treatment which are known to be different. Such matters are clearly separate from the attributable effects of preference itself on therapeutic outcome, possibly as a consequence of patients' belief. The existence of preferences

for a particular treatment can readily be studied, but their possible attributable effect remains poorly understood. We are also not concerned here with the generalisability of results from clinical trials where only certain kinds of patients agree to participate [1], although this is clearly important too.

There has been much written on the attitudes, beliefs and state of minds of cancer patients and their subsequent outcome; some literature supporting a holistic interaction between psychology and organic effects [2, 3] and other research refuting the link [4]. Indeed, the notion of any separate effects of psychology and physiology on the healing process is alien to many, but here the separation is made simply to distinguish two possible mechanisms that may have different implications for therapeutic policy. Broadly, the distinction may be important if treatment preferences are themselves transient as opposed to the physiological effects of treatment, which are less likely to be. Other papers in this issue explore the literature further. Outside cancer research, there is abundant evidence for the placebo effect [5–7]. Patients who believe they are being given effective treatment can show physical improvement, over and above the natural history of their condition.

Irrefutable, direct evidence for preference effects, in cancer and elsewhere, is sparse—largely because the ability to measure such effects is compromised by their very nature. Firstly, one can, of course, never randomise between patients' enthusiasm for a treatment and them hating the whole idea of it.* Secondly, the serious possibility of confounding is almost always present. People who tend to prefer something may be different in other ways (which could plausibly be related to prognosis) from those who do not. For this reason, randomisation would be essential to determine preference effects, and at the same time impossible. Thirdly, where people have strong preferences the possibility of randomising between competing treatments is limited anyway, by lack of enthusiasm for randomisation. Fourthly, detecting possibly small effect modifications of preferences is always difficult because of power considerations; small or large interactions on relatively small main effects can only be estimated with any precision using very large numbers.

Thus, the fact that strong evidence for preference effects does not exist should not be taken as evidence that they do not. Such effects are often regarded as fanciful and demonstrating that they do, or do not, exist is extremely difficult [8]. It is simply naïve to believe that because there is not much evidence for them, they are, therefore, either rare or implausible.

Given our current state of knowledge on the link between psychogenic factors and physical response, combined with the growing debate on the possible biological pathways for such effects [9, 10], believing in the healing properties of a particular treatment may sometimes itself enhance the body's response. The placebo effect is, after all, well studied but poorly understood. Clearly, not all patients may exhibit such psychological phenomena to the same degree, and of course, some will not at all. Moreover patients may themselves, for all sorts of reasons, have diametrically opposed, but strong, preferences.

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* This is the main circumstance in epidemiology where randomisation is not logically possible, as opposed to simply ethically undesirable. Randomising between heavy cigarette smoking and abstinence, for example, is possible in principle but not remotely justifiable ethically. To randomise between genuine beliefs is simply a contradiction in terms.

THE USE OF RANDOMISED TRIALS IN CANCER TREATMENT EVALUATION

The most reliable evidence for treatment effects comes from the RCTs. In theory, by randomising patients between a treatment and a control, the average biological effects, uncontaminated by all confounding, can be estimated by comparing the mean responses between the two groups. Ideally, to minimise bias, patients and their assessors should be unaware of which treatment arm they are randomised to: the so-called double-blind RCT. When two drugs are under investigation, blinding can be achieved by the use of identically coloured pills or 'dummy' medicines, and so on. However blinding may be impossible, particularly for cancer treatments. How can a blind comparison be made between, say, tamoxifen, radiotherapy and chemotherapy, unless the competing treatments can be made to seem alike? Many of the most influential and often cited RCTs in cancer research are (perforce) not blinded [11–13]. Even in supposedly blind trials patients may correctly 'guess' which arm they are in due to the treatment regimen or side-effects [14]. Hence, many cancer RCTs are susceptible to the possible effects of patient preference.

THE THEORETICAL EXTENT OF PATIENT PREFERENCE EFFECTS

In the absence of much empirical evidence, patient preference effects can be investigated by means of a very simple theoretical method. Imagine two treatments for some condition designated by A and B. Let us assume that, with regard to the purely physiological effect, A benefits on average a proportion (P) of eligible people, and B a higher proportion $(P + x)$. Thus, taking an example where measured outcome is 5-year survival from diagnosis of cancer, if P is 0.50 and x is 0.10, then on average 60% would be alive at 5 years on treatment B and 50% on treatment A.

Assume also that having a preference for A bestows an extra average advantage (preference effect) for treatment A of an amount y, to $P + y$ and alternatively a preference for B of a similar amount y (for simplicity) to $P + x + y$ for treatment B. Conversely of those who prefer A, only $P + x - y$ will be affected if given treatment B, and of those who prefer treatment B, $P - y$ will benefit if given A. These are postulated average interaction effects for patients among whom these treatments would be appropriate, and this simple model allows for a preference interaction even if the main effect (x) of the new treatment B is zero. These effects are summarised in Table 1.

If the proportion of the eligible population who prefer treatment A is α, while β prefer B and γ are indifferent, then we require that $(\alpha + \beta + \gamma) = 1$. More complicated models could be imagined in which the effects of preferences were multiplicative, graded, different for each treatment and/or asymmetric, but since these effects are poorly understood we want to investigate the simplest possible theoretical effects.

Table 1. *Proportion of people who benefit from treatment*

Postulated treatment effects if:	Indifferent	Prefer A	Prefer B
On treatment A	P	$P + y$	$P - y$
On treatment B	$P + x$	$P + x - y$	$P + x + y$

It can be shown (by subtracting the estimated mean effect in group A from that in group B) that the best estimate for the attributable effect of treatment B over treatment A in a large well-conducted randomised comparison will be:

$$x + 2y(\beta - \alpha)$$

This is different from x (the true 'physiological' effects) by an amount equal to $2y(\beta - \alpha)$ (the preference component in this trial). Hence such trials will only estimate the main treatment effect correctly either if y is zero (no effect of preference) or if $\beta = \alpha$ (an equal proportion prefer A as B). It is important to remember that for simplicity we have assumed that the preference advantages are equal for both treatments (a value of 'y' is added to, or subtracted from, both). A more complicated model would be needed to incorporate graded or changing preferences. Also here the effects of random variation are ignored, and in general, therefore, distinguishing reliably between x and y will require very large trials. In practice, of course, this may be difficult to achieve as those with strong preferences are likely to seek treatment elsewhere.

Under reasonable assumptions on y and on $\beta - \alpha$ [15], by how much might RCTs wrongly estimate main treatment effects if the true nature of any preference effect is, as usual, poorly understood? Consider the size of the difference in the proportions preferring the two treatments: if 35% prefer treatment B and 60% treatment A, the difference is 25%, i.e. $(\beta - \alpha) = -0.25$. In this model if the average 'physiological' effect of B over A (that is x) is 10% (let the effect of A alone be arbitrarily 50%) and if the preference advantage (that is y) is 5% then the actual treatment effects will look like this (Table 2).

If these values are ever appropriate then simple substitution will indicate that a fair RCT will be 25% 'out', that is in this case: $2y(\beta - \alpha)$ is 25% of x. That is x (the 'physiological' effect) will be estimated as $\frac{3}{4}x$, or if 60% prefer B and 35% A, that is $(\beta - \alpha) = 0.25$, then the unbiased RCT estimate will be $1\frac{1}{4}x$. Either way these results would be wrong, as the estimated effect will be attributed to the treatment alone, but will, in reality, reflect in part the (possibly changing) distribution and extent of (usually unknown) preference effects.

If the difference in the proportions who prefer A or B is 50% then the size of the 'bias' from a randomised comparison rises itself to 50%, for these hypothetical values of $x = 10\%$ and $y = 5\%$. If, however, y is only 1% then the 'biases' in the results of RCTs will be reduced to 5% for a 25% difference in proportions with contrasting preferences, and 10% for a 50% difference. However, if y is 10% (that is the role of preference is more profound than the physiological treatment effects) then the trials will be respectively 50 and 100% 'out', on average (that is the treatment effect will be estimated as $1\frac{1}{2}$ or $2x$). This is potentially important if such large differences in the prevalence of preferences are shown to be plausible.

Consider an unblind or poorly blinded trial (in the sense that patients might well be able to tell which treatment they are on) comparing placebo with a supposedly active new treatment, where the benefits are highly biologically plausible, but which in fact has no additional physiological benefit. The difference in the prevalence of preferences might be large, with 90% preferring the new 'active' treatment, because of its biological plausibility, with perhaps 5% preferring the control and 5% being indifferent. If this argument is sensible then '$\beta - \alpha$' becomes 0.85 and hence, if the preference effect remains as much as 5%, the 'bias' is 8.5% in absolute terms. Consequently, if the natural history is such that 50% 'survive' anyway, such a trial would suggest that treatment improved this to 58.5%, but only while such strong preferences exist.

This raises concern for cancer treatments which have been evaluated in many enormous unblind trials (and meta-analyses) with highly significant estimated benefits of approximately 10% improvement on the conventional treatment. These treatments are now offered on the essentially unquestioned assumption that they act through stable, general (and plausible) physiological processes. Preference effects may, however, not be stable, and certainly will not be general, and hence we ought to be in a better position to know which mechanism is dominant before making strong recommendations based on large meta-analyses of unblind trials. Clearly, such analyses give the most reliable, and clearly unbiased, assessment of treatment efficacy, but they do not distinguish or identify the mechanism of the effect. That is usually inferred from the biology—but that inference could be wrong, when other plausible, possibly unexpected, mechanisms exist.

IMPLICATIONS

The implications of these arguments are important in our interpretation of evidence of new treatments. In cancer trials, the latest treatments were often regarded as a new hope for patients with serious diseases that often were not readily amenable to current treatments. The new treatments sometimes receive much media attention and speculation. Although Chalmers shows that new treatments are just as likely to be worse, as better, than their predecessors [16], such a finding is unlikely to be widely absorbed or accepted either by enthusiastic clinicians or by their anxious patients. Hence, a proportion of patients might be always inclined to strongly prefer the new treatment to the conventional or placebo. If this were true, then the estimated benefit of a new treatment may actually be partly attributable to a psychological belief in its efficacy, rather than solely to its straightforward physiological or pharmacological mechanism. If new treatments are favoured over established ones for cancers with poor prognosis (50% 5-year survival for example), then the new treatments may gain in apparent effectiveness, even if they have no additional straightforward physiological benefit. In the absence of clear evidence (as opposed to belief) for the mechanisms involved it would be unusual for the apparently least plausible mechanism (patient preference) to be attributed with the effect.

There is then a possible tendency for this process to increment, as evidence from each successive RCT may affect patient preferences, directly or indirectly [17]. Such a process might accrue more and more expensive (and possibly unpleasant) cancer treatments that are actually no better, in terms of the postulated physiological mechanism, than the original standard treatment. From a pragmatic standpoint, this may not matter; the patients with the particular preferences will fare better for psychological reasons. But in each increment of RCT the control might be the new treatment of

Table 2. *Proportion of people who benefit in this case*

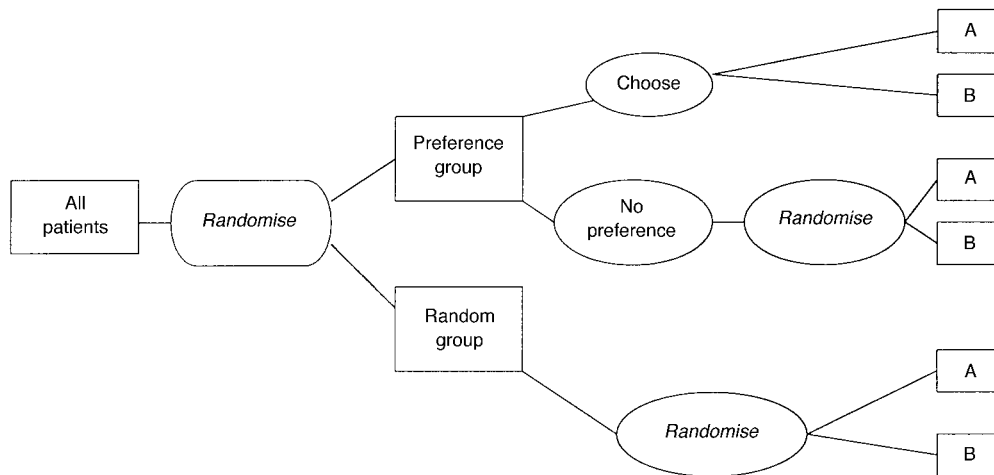| Postulated effects of treatment if:	Indifferent	Prefer A	Prefer B
On treatment A	50%	55%	45%
On treatment B	60%	55%	65%

Figure 1. Rücker's two-stage design.

2 years ago, which is no longer attracting the belief system (and its consequence) it did then. If the amount by which preferences can affect outcome ($2y$ above) is larger than the physiological effect of the new treatment (x above), then RCTs could wrongly attribute benefits, causing some new patients to suffer an overall disadvantage.

POSSIBLE SOLUTIONS

Several attempts have been made to design trials that will estimate the magnitude of preference effects. One such study design, proposed by Gerta Rucker, involves two stages of allocation [18]. The first stage randomises individuals into a 'preference group' or a 'random group'. In the second stage, those individuals in the 'preference group' who claim to prefer treatment A are allocated to receive treatment A, and likewise for treatment B. Those individuals in the 'preference group' who claim to have no preference are randomised to A or B. All patients in the 'random group' are randomised to A or B, regardless of preferences (Figure 1).

The treatment effect observed between A and B in the 'no preference' randomised arm of the 'preference group' can then be compared with the treatment effect observed between A and B in the 'random group' (where presumably some individuals had unrealised preferences) and an estimation can be made of the magnitude of preference effects in this study.

If people with strong preferences can ever be recruited into such a trial (Torgenson and colleagues [19], for example, demonstrate that it is possible, with limitations), the estimation of any preference effect remains complex. The problem is one of interpretation since, in this case, subtracting the means from the two randomised groups provides an estimate of a complex combined algebraic function of the main physiological effects and any preference effect (x and $2y$, respectively). Moreover sufficiently large trials that attempt to discern preference effects will require a formidable biological or clinical justification to obtain enough enthusiastic support.

Perhaps the first step should be the systematic documentation of the prevalence of individual preferences and an investigation of how they change with time and place. It should not be too onerous to set up a trial similar to the 'preference group' in Rucker's design (Figure 1). Under this design patients would be carefully and fully informed about the relevant scientific uncertainties and invited to choose their treatment. Those with little or no preference for treatment would be encouraged to accept randomisation. The systematic follow-up of such cohorts would offer the opportunity to establish through randomisation the physiological effects of treatment among those with no preference and to learn whether patients with apparently similar prognostic characteristics who actively choose their treatments have different outcomes from those predicted by randomisation. This design has been used in other areas of medicine [20], and could be used to investigate at least the plausibility of preference effects in cancer treatment.

There is a real 'catch 22' here. In order to reliably detect or refute the existence of preference effects in cancer treatment, a dedicated research effort is clearly required. Thus, the general plausibility and the possible importance of such effects has to be widely accepted among funders, clinicians and patients. Such effects, if real, are likely to be transitory and specific, because, in general, that is the nature of preferences themselves. The possible attributable effects of these preferences on outcome is furthermore regarded _prime facie_ as fanciful. But to deny their existence is simply not good enough, a classical Type III error. They may be very important indeed, and we could simply not know that, for all the goodwill in the world.

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