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# Patient and physician preferences: impact on treatment effectiveness*

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**ABSTRACT** – The greater reliability of randomised controlled trials (RCTs) over non-randomised studies to objectively assess efficacy and/or safety of new therapeutic interventions is one of the main paradigms which sustains the evidence-based decision process in clinical practice. This assumption is primarily based on the hypothesis that randomisation, and particularly blinding procedure, drastically reduces the potential bias related to the preferences of patients and physicians. However, from non-randomised studies to double-blind, placebo-controlled RCTs, the preferences of patients and physicians can impact the evaluation of treatment effectiveness. Both internal validity and external validity of RCTs are impacted by various biases related to patient and physician preferences. Thus, influence of patient and physician expectations on trial outcomes might be much less trivial than expected, both in open-label and double-blind, placebo-controlled, randomised trials. Accordingly, it might be interesting to systematically collect information about patient preferences before randomisation, using dedicated questionnaires, in order to be able to evaluate the impact of non-preferred allocation on trial results.

**Key words:** antiepileptic drugs, clinical trials, placebo, preferences

The evidence-based decision process, which gradually became predominant in clinical practice over the last 20 years, has been built on several methodological paradigms. These include the greater reliability of randomised controlled trials (RCTs) over non-randomised studies to objectively assess efficacy and/or safety of new therapeutic interventions (Sackett *et al*., 1996). This assumption is primarily based on

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the hypothesis that randomisation, and particularly blinding procedure, drastically reduces the potential bias related to patient and physician preferences. However, influence of patient and physician expectations on trial outcomes might be much less trivial than expected, both in open-label and double-blind, placebo-controlled, randomised trials.

## Why randomise patients?

Randomisation is usually viewed as a prerequisite for a trial to achieve a high level of internal validity, which supports the scientific accuracy of the study conclusion. Randomising patients between intervention and control arms allows one to estimate the mean intervention effect by comparing the main outcome measure between groups and by minimising confounders. It is thus generally assumed that, in comparison to RCTs, non-randomised studies lead to overestimation of the effect of intervention (Colditz *et al*., 1989; Schulz *et al*., 1995). The limited internal validity of non-randomised studies is considered to be mostly related to the impact of patient and/or physician preferences on treatment evaluation. The risk of selection bias and unbalanced groups is thus easily recognisable when the physician can select the study arm according to its own subjective evaluation of potential benefit and/or risk of both the studied intervention and its control. However, it is important to note that the risk of efficacy overestimation in observational studies may be less pronounced than intuitively considered. It has been suggested that discrepancies between observational studies and RCTs might be small, if important confounding factors are controlled for (MacLehose *et al*., 2000). In particular, the role of blinding outcome assessment or the use of an outcome which is not susceptible to bias, increases the methodological quality of a non-randomised study (MacLehose *et al*., 2000). Interestingly, these factors relate to the magnitude of patient and/or physician preferences, reinforcing the issue of their impact on evaluations of therapeutic interventions. However, in the absence of clear difference between high quality observational studies and open-label randomised trials (MacLehose *et al*., 2000), the exact impact of randomisation on preference-related bias remains an open question.

## What is the magnitude of preference-intervention interactions in open-label RCTs?

Despite randomisation, patient and/or physician preferences can impact efficacy evaluation in several ways. Both internal validity and external validity of the study can be affected. Patients allocated to the preferred intervention could be more motivated in participating in the study, more compliant, and could expect better outcome, a situation which might favour treatment effect. In contrast, patients allocated to the non-preferred intervention could experience "resentful demoralisation", which might lead to worse outcome through poor compliance, inaccurate reports during follow-up, decreased expectancy of good outcome, increased rates of drop-out, and nocebo effect (King *et al*., 2005b).

The magnitude of the impact of patient preference on intervention outcomes has been evaluated using two methodological approaches. The first one is a partial preference design in which the patients without strong preferences are randomised, whereas those with strong preferences are given a choice (Brewin and Bradley, 1989). An important limitation of this design is that uncontrolled confounders in the non-randomised groups might impact the outcome (Preference Collaborative Review Group, 2008). The second approach consists of using standard RCTs in which patient preferences are recorded before randomisation but after patients have given consent to participate in the study (Torgerson *et al*., 1996). In this approach, the allocation remains defined by randomisation results and is not modified by patient preferences. However, the impact of potential pre-randomisation preferences on study results can be analysed.

Both approaches have provided conflicting results (King *et al*., 2005a; Preference Collaborative Review Group, 2008). In a meta-analysis which pooled 32 RCTs evaluating various pathologies and interventions using both previously described designs, King and colleagues showed that differences in outcome across trials between randomised and preference groups were generally small, suggesting that preferences might not substantially interfere with the internal validity of RCTs (King *et al*., 2005a). When baseline differences for the primary outcome were ignored, only 5 of the 46 comparisons were statistically significant, all of which favoured the preference arm. However, analysis of standardised effect sizes after accounting for baseline differences in the primary outcome variable between randomisation and preference groups showed that net effect sizes were small, and even clustered around zero for the studies with the largest sample sizes (King *et al*., 2005a). In contrast, another meta-analysis using a different methodology demonstrated a significant impact of patient preferences on treatment effect (Preference Collaborative Review Group, 2008). In order to avoid the potential impact of uncontrolled confounders in non-randomised groups, the study was restricted to trials including information about patient preferences, but

using a classic randomisation process. Furthermore, to improve homogeneity, only eight musculoskeletal trials were included in the primary analysis. Finally, individual patient data ($n$=1,594) were available in this study. Comparisons of effect sizes were performed between three groups: patients randomised to their preferred treatment, patients randomised to their non-preferred treatment, and patients who were indifferent to the intervention allocation. Patients randomised to their preferred treatment demonstrated a significantly greater effect size than those who were indifferent to the intervention allocation (effect size=0.162 [0.011; 0.314]; $p$=0.036) (Preference Collaborative Review Group, 2008). However, no significant difference was observed between patients randomised to their non-preferred treatment and the two other groups.

These two meta-analyses also provided information about potential mechanisms underlying the impact of preferences. Interestingly, these data challenge the common view that "resentful demoralisation" and associated lack of compliance account for reduced treatment effect in patients not receiving their preference. Indeed, the greatest compliance to the study protocol was observed in the patients who did not receive their preference (Preference Collaborative Review Group, 2008). Compliance was thus significantly increased in this group in comparison with patients who were indifferent (odds ratio: 1.70 [1.08; 2.69]; $p$=0.02), whereas a non-significant trend in the same direction was observed between these patients and those who received their preference (odds ratio: 1.26 [0.82; 1.94], $p$=0.29) (Preference Collaborative Review Group, 2008).

Overall, although the magnitude of this bias remains disputable, patient preferences seem to be associated with treatment effect in RCTs. Accordingly, it might be interesting to systematically collect information about patient preferences before randomisation, in order to be able to evaluate the impact of non-preferred allocation on trial results (Torgerson *et al*., 1996). Unfortunately, none of the trials included in these meta-analyses evaluated antiepileptic intervention, making it difficult to translate the above findings to antiepileptic drug (AED) trials.

## Is blinding the ultimate answer?

The gold standard to limit the impact of patient and physician preferences on intervention outcomes in RCTs is double-blind design. For both patients and physicians remaining blinded to the allocated intervention, their preferences are usually considered to be reduced to insignificant levels in double-blind RCTs (Schulz and Grimes, 2002). However, as further discussed below, several non-pharmacological factors that impact efficacy evaluation in double-blind studies might be related to patient and/or physician preferences, especially in epilepsy trials.

## Patient and physician preferences and representation of the included population

The methodological quality of a clinical trial is not only defined by its internal validity but also by its external validity. The latter refers to the confidence with which an investigator expects the results of his study to generalise to other contexts (Cook and Campbell, 1979). The external validity of RCTs is directly related to the comparability of the recruited and targeted populations. Patient recruitment is largely influenced by both patient and physician preferences. Thus, the magnitude of the preference of the tested intervention, and in particular, concerns to blindly receive placebo, can alter patient recruitment. In paediatric epilepsy trials, the reluctance of parents to enrol their affected child in double-blind RCTs is well known (Shinnar and Pellock, 2005). This issue might expose the risk of evaluating AEDs in highly selected children suffering from very severe epilepsy, not reflecting the target population of the trial. Similarly, it has been hypothesized that the dramatic increase in the number of licensed AEDs available for patients with uncontrolled epilepsy has modified both patient and physician preference, resulting in recruiting patients at a later stage of refractoriness in phase III regulatory trials. However, this concern is not evidence-based. Although some data are lacking, to formally exclude this hypothesis, patient characteristics, in terms of epilepsy severity, have not been significantly modified over the last 25 years (Rheims *et al*., 2011).

Importantly, the impact of patient and/or physician reluctance to be recruited and/or recruitment of patients into double-blind RCTs is not restricted to external validity, but can also affect internal validity. Indeed, selection of patients suffering from very severe epilepsy might favour regression-to-the-mean effect. In epilepsy trials, the latter corresponds to spontaneous variation of seizure frequency; extreme on the first measure (typically during baseline), to average on a second measurement (typically during the overall double-blind period) (Barnett *et al*., 2005). This phenomenon might be of particular importance for children enrolled in placebo-controlled RCTs and has partly been related to the lower treatment effect observed in paediatric trials in comparison with adult trials (Rheims *et al*., 2008).

## Patient and physician preferences, placebo effect, and RCT outcomes

Placebo is still often used in clinical trials performed in patients with epilepsy. In fact, all AEDs are required to demonstrate superior efficacy to placebo as add-on therapy in patients with drug-resistant epilepsy (Marson and Williamson, 2009). Several issues relate to the use of a placebo group (Finniss *et al*., 2010). Among them, the consequences of the patient's wish to receive the active intervention and not the placebo are important, and can be viewed as the greatest preference factor impacting treatment efficacy in double-blind studies.

Over the years, the response to placebo has been increasingly scrutinised. Indeed, a progressive modification of the response to placebo in RCTs has been observed in several diseases. In epilepsy trials, it was shown that responder rate to placebo has gradually increased over the years, virtually doubling between 1989 and 2009 (Rheims *et al*., 2011). Importantly, a parallel increase in response to active medication has also been observed (Guekht *et al*., 2010; Rheims *et al*., 2011). As a result, the effect size, measured as the relative risk for being a 50% responder, was decreased, though this trend did not reach statistical significance (Rheims *et al*., 2011). An increase in placebo response over the years has also been reported for other conditions (Sysko and Walsh, 2007; Gallahan *et al*., 2010), particularly for major depressive disorder (Walsh *et al*., 2002; Stolk *et al*., 2003).

During a double-blind, placebo-controlled trial, the response to placebo is influenced by several factors. Its typical determinants are the regression-to-the-mean effect, the Hawthorne effect, and what may be referred to as "the placebo effect *per se*". However, it appears difficult to formally separate the Hawthorne effect and "placebo effect *per se*". The Hawthorne effect relates to a specific context-related effect, namely that of being included in the trial with informed-consent procedures and medical and nursing care (Adair, 1984). On the other hand, it is usually considered that "*the placebo effect is a genuine psychobiological event attributable to the overall therapeutic context*" (Finniss *et al*., 2010). In other words, both aspects, Hawthorne and placebo effects, refer to the impact of the patient/clinician relationship on therapeutic interventions, and it may be that both share similar underlying mechanisms.

Whatever the conditioning protocol and/or the disease in which response to placebo is studied, the psychosocial interactions between the patient, the clinician, and the treatment factor is paramount (Finniss *et al*., 2010). In particular, patient expectations of future therapeutic response exert a pivotal role. Using open-hidden study design, in which the treatment is given either in a routine clinical manner, including the psychosocial context surrounding treatment administration, or in a hidden manner without patient knowledge, it has been demonstrated that the context of substance delivery is an important part of treatment response (Finniss *et al*., 2010). These results have been related to patient expectations of treatment benefits, which are favoured when the treatment is delivered with verbal and contextual interactions. Furthermore, it has been shown that use of simple verbal cues to modulate patient expectations mediates placebo analgesic effects on experimental pain (Benedetti *et al*., 1999), placebo-induced changes in motor performance in Parkinson's disease (de la Fuente-Fernandez *et al*., 2001), or brain responses in patients with drug addiction (Volkow *et al*., 2003). Conversely, in the case of randomisation to placebo arm, it remains an open question as to whether the lack of efficacy or aggravation might result in nocebo effect in some patients.

Importantly, physician expectations also account for the placebo response. In a double-blind trial on post-operative dental pain, patients were separated into two groups which differed according to beliefs of the clinician (Gracely *et al*., 1985). Patients received fentanyl, naloxone or placebo and were informed that the administrated treatment would increase their pain (naloxone), decrease their pain (fentanyl), or have no effect (placebo). In contrast, the clinicians were randomised to two groups, in one of which they were told that there was no chance of being allocated to an active analgesic drug. Patient response to placebo significantly differed between the two groups of physicians, with lower response for clinicians who believed that patients could not receive an analgesic drug (Gracely *et al*., 1985).

Although these data converge to suggest that the higher the expectation, the greater the placebo response, the precise determinants of placebo response in epilepsy trials remain poorly understood. In particular, why has the response to placebo progressively increased over the years? One hypothesis might be that this observation should be interpreted as a methodological artefact rather than a true variation of the response to placebo. It has been speculated that the progressive increase in the number of study centres involved in each multicentre trial may have resulted in greater heterogeneity in the quality of clinical assessment (type of epilepsy syndrome and even epileptic nature of fits). However, other aspects could have an additional impact. The increasing complexity and intensity of monitoring procedures that are required for double-blind, placebo-controlled RCTs is likely to reinforce the Hawthorne effect, as suggested by the parallel increase of the responses to

placebo and active treatment in phase III epilepsy trials (Rheims *et al*., 2011). The relation between patient characteristics, their expectations, and the magnitude of the response to placebo also needs to be considered. Although the two-fold greater response to placebo observed in paediatric over adult epilepsy trials might be partly related to regression-to-the-mean effect (Rheims *et al*., 2008), greater expectations of children and their parents, compared to that of adults patients, might well have contributed to this finding. As suggested in placebo-controlled studies of an antimigraine agent, adolescents may have been more likely to believe that the treatment received was an effective pain-relieving medication, relative to adults (Rothner *et al*., 2006). A placebo effect by proxy might also be at stake in paediatric epilepsy trials, according to the important role of patients' parents in reporting seizures. This hypothesis was previously raised to account for the powerful placebo effect observed in children with developmental disabilities, and supported by the fact that this effect was greater in children with more hopeful parents (Sandler, 2005). While epilepsy trials were almost exclusively conducted in Western Europe, North America or Australia 20 years ago, multicentre studies now also involve centres from South America, Eastern Europe, or Asia. Interestingly, an unusual high response to placebo has recently been reported in some RCTs conducted in Asia (Lee *et al*., 2009; Xiao *et al*., 2009). However, whether the influence of cultural traditions on the view of health and medicine (Thompson, 2000), and consequently on expectations of AEDs, might result in variation of placebo and nocebo effects across countries, remains largely unknown.

## Conclusion

From non-randomised studies to double-blind, placebo-controlled RCTs, patient and physician preferences can impact the evaluation of treatment effectiveness. While primarily expected in open-label randomised studies, this bias is probably often underestimated in double-blind RCTs. The most appropriate way to deal with this important issue would be to systematically evaluate patient and physician preference throughout clinical trials, using dedicated questionnaires. □

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