Variability in Human Drug Response
G.T. Tucker, Editor

Placebo Response

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ABSTRACT

The placebo is defined in medicine as an inactive substance or preparation given to satisfy the patient's symbolic need for drug therapy, and used in controlled studies to determine the efficacy of medicinal substances. In clinical trials it is used as a way of separating the therapeutic effects intrinsic in the pharmacological properties of the active substance from the non-specific effects attendant on giving a medication. Such placebo effects can be quite substantial as is seen in the literature on antidepressants. It is easy to confuse a placebo response with natural remission, in a condition in which natural fluctuations occur.

In practical terms the placebo should resemble the active treatment as closely as possible. This also allows an estimate to be made of the adverse reactions associated with the active compound. Occasionally the unwanted effects of an active drug can unblind the investigator and patient so that "active" placebos may be needed. Placebos are perfectly ethical in clinical trials as they enable a true measure of efficacy to be obtained.

The placebo response is not a fixed entity but depends on many factors including the patient, the doctor, the doctor-patient relationship, and factors in society.

Key words: placebo, ethics, natural remission, placebo responders.

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INTRODUCTION

Mindful that this is a symposium on variability in drug response, I shall be somewhat selective about the areas of placebo response to be discussed. There is a large literature on the placebo, both as a control in clinical trials and as a therapy in its own right. It is also only part of the wider issue of non-specific aspects of treatment [1,2]. In the former capacity the properties of the placebo were discussed in great detail from the 1950's onwards, and when the whole concept of the controlled clinical trial was introduced, first in the United Kingdom and then more widely.

I will draw attention to two main areas of relevance to this meeting. Firstly, there is the contrast between the concept of placebo as the inner control in which case the response is required to be as small as possible and placebo as an active therapy when it is hoped that the response will be large and clinically significant [3]. The second area that I shall focus on is the confounding of placebo response i.e. apparent therapeutic improvement following the administration of dummy medication and spontaneous remission i.e. an improvement in the illness for which the placebo has been administered. I will use the topic of antidepressant medication to illustrate these various points.

DEFINITION

The word placebo goes back for centuries [4]. It means 'I shall please', the first-person singular future tense of the Latin verb placere, meaning 'to please' [5]. The word entered the English language in about the 12^{th} century as the name commonly given to the Vespers for the Dead. A century or two later, the term placebo began to take on secular constructs but was predominantly used in an unflattering manner indicative of opprobrium. For example, there is a character named that in Chaucer's Canterbury Tales who was a servile sycophant. Another reference is to professional mourners hired as substitutes for members of the family to sing placebos at the bier of the deceased.

The first definition in medicine appeared in 1785 in Motherby's New Medical Dictionary where it was defined as 'a common place method or medicine'. In the next edition 10 years later, the description also included the words 'calculated to amuse for a time, rather than for any other purpose'. Then the implication was added that the placebo is both inert and harmless, devoid of effect. This is often taken as the popular definition although placebos can both induce harm and can certainly produce worthwhile therapeutic effects. A well-known dictionary (Dorland) includes the definition: an inactive substance or preparation given to satisfy the patient's symbolic need for drug therapy, and used in controlled studies to determine the efficacy of medicinal substances.

PLACEBO IN CLINICAL TRIALS

The most widely used research context for placebo is in clinical trials [6]. In this technology, a therapeutic procedure is evaluated in terms of its 'true' efficacy. This is taken to mean that the medication may have therapeutic effects intrinsic in its pharmacological properties. The use of the placebo is to separate by subtraction so called 'non-specific factors' which can produce a therapeutic improvement and yet are not intrinsic or characteristic of the therapeutic procedure tried [6]. In the simplest statistical terms, a linear equation is constructed comprising the mean value for the sample plus an element related to the placebo effect plus an element related to the specific therapeutic effect of the test agent or procedure plus a factor relating to error. The placebo is assumed to have the same elements except for the characteristic therapeutic effects. By subtraction, therefore, the efficacy of the test procedure or agent can be established. Of course, there are many assumptions in the model, not least of which is that it is a linear model with no interaction between the various elements. In

particular, it is assumed that the therapeutic effect adds to the placebo effect and yet this is by no means a self-evident assumption (Figure 1).

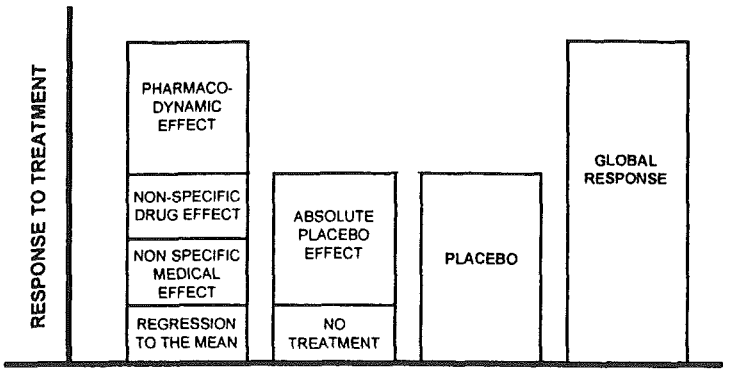

Figure 1. The placebo effect in the overall response to a treatment. The global response is the pharmacodynamic effect plus the placebo effect, which is itself the result of the 'absolute placebo effect' and the effect of regression to the mean. The absolute placebo effect includes the non-specific effect of the drug and the non-specific effect of the medical act. The effects presented in the figure are arbitrary and do not represent any specific drug.
(Reproduced with permission from Garcia-Alonso *et al.* 1988 [14])

Placebos are used in clinical trials whenever this is ethically justifiable; this is generally speaking when either the condition to be treated is fairly trivial and certainly not life threatening or when there is no established treatment for the condition. In this way patient is not deprived of potential benefit. However, wherever possible, in particular within the regulatory context, placebo is to be preferred as it gives the opportunity to measure the true intrinsic therapeutic effect of the test agent. If a presumed active drug is used as comparison, a failure to differentiate it from the test agent may mean that both agents are effective, both agents are ineffective, or that the test system was insensitive.

One problem in such clinical trials is the fact that an effect attributable to placebo can often be quite substantial. This can be evidenced in two ways. Firstly, there may be an improvement across all subjects showing up as a mean effect. An example is an improvement in Hamilton depression scores with an antidepressant. However, the placebo group may also improve across time. The second way is to look at people attaining a certain criteria of response say, 50% diminution in a rating scale or an operational outcome such as discharge from hospital. However, the number of placebo patients meeting this criterion can be quite substantial. In most antidepressant trials it can be 35-50% and even higher in trials of anxiolytics or of psychotherapeutic procedures. The problem with the placebo response is most acute where the efficacy of the test procedure is incomplete, either due to only partial efficacy or to the inclusion in the sample of patients who do not respond to the treatment for whatever reason. Often, however, the reason for treatment – unresponsiveness is never discovered. For

example, it is well established that only about 70% of schizophrenic patients treated with the older typical antipsychotic drugs show a response. The characteristics of non-response, apart from compliance problems, is quite unclear. Pharmacokinetic factors seem inadequate to explain the difference.

Consequent upon this the efficacy of a compound may have a fairly narrow window in which to be detected. Typically, with a placebo response at 35% and a drug response of 70%, efficacy can usually be established within fairly large-scale trials. However, if the placebo response rate moves up to 50%, it is almost impossible to establish efficacy in a formal comparison.

Placebo response versus natural remission

This topic is surprisingly neglected, few commentators having discussed it in any detail. However, the usual design of the double blind placebo controlled study does not differentiate between these two factors. To do this a no treatment arm needs to be included. This is not common although there has been a relatively large number of psychotherapy trials, which have a no treatment group, usually, a "wait-list" group that is later randomised into treatment.

The reason why this is important relates to the natural history of diseases and the methods of determination of patients coming to treatment. Many conditions are chronic and fluctuating or they may be relapsing conditions with natural remissions. The patient tends to come to notice or for treatment when his condition has worsened either due to spontaneous fluctuations in severity (i.e. we don't know why) or to some extraneous factors such as nutrition, stress etc. With a naturally fluctuating condition then regression to the mean is likely to be manifest as an improvement in the condition [8] (Figure 2). Only in some conditions is it likely that

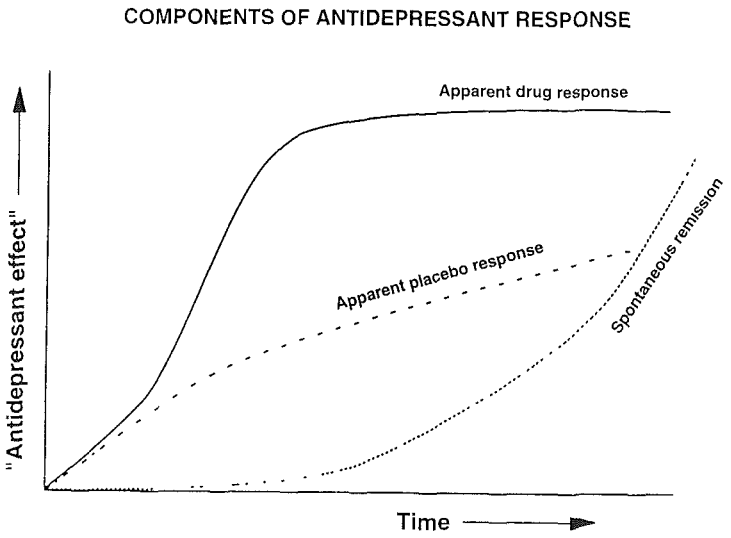

Figure 2.

the condition will progress to include increasing severity, morbidity and even death. In many disorders the severity will tend to lessen as time goes on. This means that a proportion, sometimes a substantial proportion, of what appears to be a placebo response is in fact a natural remission and is not related to the administration of medication. A sophisticated discussion regarding drug-placebo differences in onset of response concluded that antidepressant drugs may convert a percentage of non-responders (to placebo) to responders [9].

In statistical terms in clinical trials this natural remission is not a real problem because it should apply equally to both active treatment and placebo groups, providing true random allocation to treatment has been effected. However, it is a problem in trying to estimate the placebo response.

SOME PRACTICAL CONSIDERATIONS

Placebos in clinical trials should be as sufficiently closely matched to the active treatment that it is impossible for both the patient and the doctor to distinguish between them. There are anecdotal stories about placebos differing in some subtle way from the active medication and one can be sure that if there is some way of distinguishing then patients with infinite ingenuity will find those ways. Therefore, the colour, size, weight etc of placebo in a controlled trial is fixed by the formulation parameters of the active treatment (Table 1).

Table 1.
Minimal specifications to manufacturers of capsules or tablets to be used in a comparative trial

1. To match perfectly* for:
   (a) Shape
   (b) Size
   (c) *Surface* colour
   (d) *Surface* texture
   (e) Weight
2. To match as closely as possible for:
   (a) Taste on licking
   (b) Taste on chewing
   (c) *Internal* colour
   (d) *Internal* texture
   (e) Smell
   (f) Specific gravity
3. To bear no external distinguishing signs, and to be put up in containers free of identifying marks. The containers for each treatment should be packed in separate boxes labelled with the identity of their contents.

* Samples must be indistinguishable to a panel of four judges.
(From Joyce, 1968)

(Reproduced with permission from Joyce CRB, 1982 [6]

The placebo concept should be included in all areas of therapeutic endeavour. It has been used in surgery where sham operations may be performed consisting of anaesthesia and

incision of the skin. Foods or complete diets that look alike but differ in their composition can be used in dietetics. In acupuncture placebo points can be used which are not related to the traditional acupuncture points. In electroconvulsive therapy a series of studies was carried out which used anaesthesia, muscle relaxation, positioning of the electrodes but no actual shock. And, of course, it can be used in psychotherapy in some form [10].

The need for placebos to be indistinguishable from active treatment is because of the tendency for placebos to be regarded as being in some sense weaker or less credible or applied in a less enthusiastic manner than therapies believed to have intrinsic activity. At a minimum the placebo controls should be equivalent on major recognised common factors which might include expectancy of improvement, credibility of rationale, credibility of the actual procedures meeting the demand for improvement and the attention, enthusiasm, effort and perceived belief in treatment procedures and commitment to client improvement in the therapist him /or herself. As will be mentioned later, these factors are important in maximising placebo response but also maximising response to active medication as well.

ADVERSE REACTIONS

Although placebos are incorporated into comparative studies in order to control primarily for efficacy issues, they are also invaluable in providing a controlled database for unwanted effects and safety aspects. In that controlled environment, the differential elicitation of unwanted effects can be carried out and significances sought between the incidence and prevalence of such unwanted effects in the placebo and active treatment groups. The placebo may appear to give rise to such adverse effects ("nocebo" effects) [11] for four main reasons.

1. The placebo may not itself be totally inactive. For example, colouring matter on a capsule has been known to induce allergic or hypersensitivity reactions.
2. The illness itself may develop or even worsen and this is attributed to adverse effects of the medication.
3. The attempt to withdraw the medication may be followed by apparent discontinuation effects and this is well known to happen with long-term administration of placebos as well.
4. The method of administration may itself have some adverse effects even though the drug to be administered or the procedure to be given itself has no intrinsic dangers.
5. Previous administration of a similar but active preparation may have caused adverse effects [12].

Despite all of this a comparison between placebo and active drug groups provides the most accurate estimate of the adverse effects of the active medication. However, as the database for such clinical trials rarely exceeds 2000 patients per group, only relatively common adverse effects can be quantified in this way. Beyond that, one must rely on the inaccurate and often rather suspect methods such as spontaneous reporting and post marketing surveillance.

A complicating factor in drug-placebo comparisons with antidepressants is the unblinding of both patients and investigator by the detection of adverse effects of the antidepressant. The use, of so-called "active" placebos to mimic side effects of medication has been advocated as a solution [13].

ETHICS OF PLACEBO STUDIES [6]

The problem of placebos in clinical trials relates to the therapeutic studies only. In non-therapeutic studies, administration of the active medication when there is no therapeutic reason pre-empts any considerations that the placebo might be unethical. Indeed, it could be argued that failure to incorporate a placebo when one is exposing a non-patient to some tests, drug or procedure is itself unethical. With clinical trials, however, the need for a placebo requires careful consideration and may indeed vary from institution to institution [14]. In my own hospital, quite severely ill patients are referred to us, as a post graduate centre, and the use of placebo is less frequently justified than in primary care settings. The other factor to take into account is how well established the efficacy of a comparative study procedure is, not merely in the literature but within the context of the setting in which the study is to be carried out. If the investigators with their patients and selection procedures in that institution have consistent effects for a comparative substance then the use of the placebo is less necessary. The use of very low doses of a drug as a placebo is an unsatisfactory solution to this problem as it is still a placebo. In my experience, patients are surprisingly willing to accept that they may be given a dummy medication and do understand that a response may still be forthcoming to that "sugar pill".

THE PLACEBO RESPONSE

The problem of differentiating this from natural remission has been described earlier. The question of the time cause of the placebo response is usually that it shows a similar pattern to that of active medication. This may be somewhat belated compared with the active medication. The question of the further outcome in patients who have responded to placebo has been little addressed but there is some evidence, at least with antidepressant medication that the placebo response may not persist, particularly in the more chronically ill patients. This does seem to be reasonable. In other words, if natural remission takes place then the condition does not recur but if it is a chronic condition then the placebo response (wears off). A major question concerns the factors that govern placebo response and whether these are the same as those that govern response to an active medication. Firstly, of course, it should not be possible for the patient to determine whether or not they have taken an active medication. This is the goal of the double blind controlled trial but this can be vitiated by the obvious subjective effects of some medications. Secondly, the placebo response may not be sustained [15] (Figure 3).

The factors that govern the response to placebo are as follows:

The patient – there are important correlations between patient personality traits such as introversion/extraversion and "neuroticism" and drug response. The personality dimensions can influence response to active medication and can also influence quite profoundly response to placebos. The personality dimension that has been emphasised is suggestibility although in the present day usage of untried medications, the term gullibility might be more appropriate. The response of otherwise quite sensible people to claims for therapeutic efficacy of compounds

which are unlikely to be active beggars belief. I do not want to get embroiled in whole question of homeopathic medicine but the pharmacology and rationale of such treatments is so obscure that one is forced to conclude that it is one of the most powerful sets of placebo responses available.

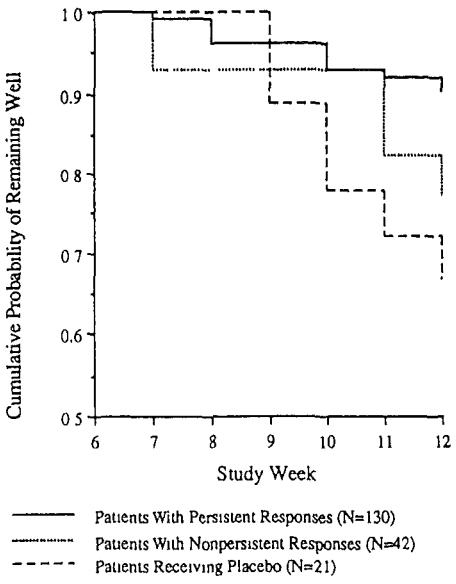

Figure 3. Cumulative probability of remaining well during study weeks 7-12 for patients with persistent and nonpersistent responses to drug treatment and for all patients receiving placebo (Reproduced with permission from Quitkin *et al.* 1993 [15])

Placebo responders among depressed patients include those who were apparently reacting to events or to life circumstances, those more recently becoming depressed and the less ill as assessed by standard rating scales [16] (Table 2).

The features in patients include motivation, expectation and experience but there is no clear type of individual who will respond to medication, rather response is individual, situation, complaint, and therapist influenced. This is so even for an interpersonal transaction such as psychotherapy [17]. Thus a patient may respond to all medication in one context, to another in another context, and be unresponsive in third context. It is also important to acknowledge the necessity for good information and it is also almost impossible to underestimate the ignorance that the average man in the street entertains concerning his or her bodily processes and their amenability to modification by therapy.

The doctor – the doctor's training, experience, susceptibility to suggestion himself, his scepticism and knowledge about medication will all influence the placebo response. Some

workers suggested that the effects of sedatives on patients depend on the personality type of the physician, particularly whether or not he was authoritarian in urging the patient to show response. His enthusiasm for the treatment is also important and therapists' expectations often predict outcome. The use of alternative medication together with standard procedures may also increase by an interactional placebo effect.

Table 2.
Variables that differentiate placebo responders from nonresponders

	Responders	Nonresponders
Clinical and diagnostic variables		
Endogenous subtype	Nonendogenous	Endogenous
Length of illness[1]	Shorter	Longer
Abusive disorders[2]	Present	Absent
Beck depression inventory items		
Reduced ability to work (no. 15)	None to slight	Marked
Worsened appearance (no. 14)	None to slight	Marked

1. Length of illness is defined as time in months since the first episode of depression
2. Abusive disorders refer to a history of alcohol or drug abuse
(Reproduced with permission from Fairchild *et al.* 1986 [16])

Doctor – patient relationship.

The relationship between the doctor and the patient is important in deciding whether a placebo response can occur. Some physicians are dictatorial, others are much more amenable to discussion with the patient of their needs and expectations, so called "concordance". Some doctors are better at communicating with their patients and are sensitive to the patients' psychosocial situation. The quality of communication is more important than quantity. It is also increasingly evident that patients need written material to take away with them as the anxiety and stress associated with a consultation militate against the proper assimilation of information regarding treatment. This is usually effected by information leaflets and so on.

Societal factors

The attitude of society to patients and doctors continuously alters [18]. We have recently seen a phase of anti-science together with anti-medicine. This is compounded by the necessity now in Western societies to ration health care for a variety of reasons not relevant here. Accordingly, society is exploring alternative methods of therapy, particularly those which are cheaper or which appear to carry few if any unwanted effects [19]. That the efficacy of many of these procedures is untried seems to escape the notice of Society, the media and politicians. The placebo effects which are intrinsic in this response have received very little attention. Group effects are also important, responses depending upon what other treatments are given in a group [20].

THE DRUG

In clinical trials placebo must match the active drug in all respects except the inclusion of the active constituent. However, with placebo response, a whole variety of factors may come into play. The size, shape, colour of the tablets or capsule, and the taste of the liquid formulation are all very important. In some countries injections have a much more powerful placebo effect than do oral medications. Children believe large tablets are more powerful than small ones because they contain more drug, whereas adults tend to think that small tablets must be more potent. There is even an anecdotal report that one anxious patient reported that his minor tranquilliser, formulated as a two coloured capsule, worked better if he swallowed it green end first!

EXCLUSION OF THE PLACEBO RESPONDERS

One practical implication of the placebo response is the widespread practice of trying to remove placebo responders from clinical trials. It is customary, particularly with chronic conditions, to have a "wash-out" period during which the patient can be recruited, various tests such as liver function test carried out and any current medication stopped and washed out of the system. This is obviously acceptable providing that any potential withdrawal reaction is either detected or the time frame is such that it will have concluded by the time that the trial proper starts.

However, it is often the practice to administer a placebo, single blind, during the week or two before the commencement of the trial proper. The patient is assessed before and after this period and if a response has occurred, defined in some specific way, that patient is then excluded from the study. Statistically, this results in an enriched sample and will bias the study in favour of the active medication, as the placebo responders will have been selected out. The use of this enrichment procedure is justified where it is essential to establish as soon as possible, i.e. in phase II trials that a putative therapeutic agent is in fact active. However, in later studies the efficacy of the active medication will be exaggerated and certainly when the medication is licensed and released, disappointment may be an inevitable outcome of this practical use.

PLACEBO MECHANISM

It might be thought that this section is redundant. After all, placebo will have an effect through a variety of non-specific factors but it is hard to envisage any specific mechanisms that would be common or could be common to all therapeutic procedures. Nevertheless, there have been some interesting approaches to searching for such common factors. An example is the use of naloxone in attempts to block the analgesic effect of placebo procedures which are believed to be releasing endorphins. Other mechanisms could be invoked, such as the production of other neurotransmitters like GABA to induce sedation and 5-HT to elevate mood. The development of antagonists and the use of more focused induction techniques for mood are an obvious way forward in this respect.

CONCLUSIONS

Placebo reactions need future further study and analysis in order to optimise not only their usage in selected areas, but also to optimise the use of active medications which incorporate a placebo response as an element. The wise physician uses his skills and personality to maximise the impact of the placebo effects in his therapeutic endeavours. The careful medical scientist goes to great pains to control the placebo response in order to evaluate the therapeutic effects as precisely as possible of his curative techniques such as medications.

REFERENCES

1. Turner JL, Gallimore R, Fox-Henning C. An annotated bibliography of placebo research. (Journal Supplement Abstract Service) Washington, DC: Amer Psych Assoc 1980.
2. Shepherd M, Sartorius N (eds.) Non-Specific Aspects of Treatment. Toronto: Hans Huber, 1989.
3. Grünbaum A. The placebo concept in medicine and psychiatry. Psychol Med 1986; 16:19-38.
4. Shapiro AK. A contribution to a history of the placebo effect. Behav Sci 1960;5:109-135.
5. Shapiro AK. Semantics of the placebo. Psychiat Quart 1968;653-696.
6. Joyce CRB. Placebos and other comparative treatments. Br J Clin Pharmac 1982;13:313-318.
7. Critelli JW, Neumann KF. The placebo. Amer Psychol 1984;39:32-39.
8. McDonald CJ, Mazzuca SA, Mc Cabe GP How much of the placebo 'effect' is really statistical regression? Stat Med 1983;2:417-426.
9. Stassen H H, Angst J. Delayed onset of action of antidepressants. CNS Drugs 1998;3:177-184.
10. Suedfeld P. The subtractive expectancy placebo procedure: a measure of non-specific factors in behavioural interventions. Behav Res Ther 1984;22:159-164.
11. Morgan PP. Ten words to adopt for 1986. Can Med Ass J 1985;133:1193.
12. Modestin J. Psychological components of psychopharmacological side effects. Bull Menninger Clinic 1985;49:29-36.
13. Moncrieff J, Wessely S, Hardy R. Meta-analysis of trials comparing antidepressants with active placebos. Br J Psychiat 1998;172:227-231.
14. Garcia-Alonso F, Guallar E, Bakke O.M. Use and abuse of placebo in phase III trials. Eur J Clin Pharmac 1998;54:101-105.
15. Quitkin FM *et al.* Further advice that a placebo response to antidepressants can be identified. Am J Psychiat 1993;150:566-570.
16. Fairchild CJ at al. Which depressions respond to placebo. Psychiat Res 1986;18:217-226.
17. Frank JD. Therapeutic components of psychotherapy. J Nerv Ment Dis 1974;159:325-342.
18. Glyn JR, Heymann TD. Factors that influence patients in Sri Lanka in their choice between Ayurvedic and Western medicine. Br Med J 1985;291:470-472.

19. Coakley DV, McKenna GW .Safety of faith healing. Lancet 1986;I:444.
20. Nowlis V, Nowlis HH. Office of Naval Research Tech Rep Proj NR 1953:144-060:5400.

Discussion: Placebo response

A. Breckenridge:

I assume that even within psychiatric disease, there is a hierarchy of conditions where the placebo response may be more obvious than others. For example, I would imagine that in anxiety and depression you would get a bigger placebo response than in schizophrenia. Is that correct?

M. Lader:

That is not necessarily true. One of the conditions which had a very gratifyingly low placebo response was obsessive-compulsive disorder. As the medications for treating it became available, and more patients were being treated, the placebo response rate went up. But the placebo response is more related to severity than the actual diagnosis of the condition, and it is also related to the natural fluctuation in the illness. Psychiatric conditions are notorious for their fluctuation; and for the fact that people come to notice, not just because of worsening of the severity, but because of social factors as well.

M.M. Reidenberg:

In the development process of a new drug, one would try to select patients whose history is such that you will show the biggest difference from the placebo to get the drug registered. Then one is also selecting patients that are progressively less representative of the total population with the disease. And the difference between the efficacy in the clinical trials and the efficacy in the real world will get bigger as we learn more about placebo response, and whatever the condition is one is developing the drug for. Are there ways that we ought to handle this, so as not to exaggerate the potential benefit of a drug as we use it?

M. Lader:

The most obvious way is the exclusion of the placebo responders. Very often a study will have a placebo run-in period of one to two weeks. Any patient who improves by 20-40% on the rating scale is then excluded from randomisation. If the placebo responders are taken out, the sample is enriched with an artificial high measure of the effectiveness. The other particular problem in psychiatry is the co-morbidity. In anxiety disorders, there is something like 60-70% co-morbidity of disorders with social phobia. If these people are excluded, a measure of the drug efficacy in a 'pure' population is obtained, whereas in practice co-morbidity is the norm. I would like to see realistic studies (I do not mean natural history studies, and just giving the drug out) that recruit patients who have got co-morbidity. I think that probably just reflects the inchoate nature of psychiatric classification.

E.A. Kalso:

We have been looking at the effectiveness of anti-depressants in the chronic pain syndrome, and the amount of adverse events with the placebo is quite striking. The chronic pain syndrome is seen as a somatising syndrome. I was wondering whether our patients are especially prone to being strong placebo responders, and whether you are aware of any studies where a symptom check-list, for example, had been used in order to predict placebo responders.

M. Lader:
When a patient is in pain, depression is a very important adjunct, and a depressed patient will complain more severely of pain. It is unclear why they should particularly respond to placebo, but certainly within depressed patients who are not in pain, there is a high placebo response rate.

E.A. Kalso:
We have also seen that other adverse effects, which have nothing to do with depression or pain, are very frequent in the placebo group.

M. Lader:
It is probably something to do with the sensitisation of the patient's bodily symptoms. They become introspective, they pick a bodily change very easily. Panic disorder patients do the same, and therefore any spontaneous physical feeling will be magnified into a complaint.

E.A. Kalso:
Should we use the placebo also in the clinic, in order to find out in which patients we should use the real drug, and in which the placebo does the same?

M. Lader:
It would depend on the condition and on the particular patient. If a patient is believed to be over-responding to their minimal symptoms, then it might be worth trying the placebo. But I would only do it with the permission of the patient. There is occasionally a place for it. With the sort of patients I see, they have had placebos, usually it is a low dose of a drug given by the primary care practitioner.

J. Urquhart:
This discussion on placebo response, reminds me of what was a seminal court case in the history of American drug regulation in 1909. A drug company made an anti-cancer drug and made elaborate claims on the label for its efficacy. The then new FDA moved against him for mislabelling. It went up to the U.S. Supreme Court and Justice Oliver Wendell Holmes junior, who was a great American jurist, ruled for the majority and said that "As everyone knows, drug efficacy is a question of opinion, not of scientific fact. Therefore the claims on the label were protected by the First Amendment protection for freedom of speech". When you get into all these intricacies, if we should exclude placebo responders and so on, I wonder if Justice Holmes was not right.

M. Lader:
When I was on the UK regulatory authority, one of the great problems we had to address was homeopathy. Is the homeopathic remedy really a remedy or is it just an extremely elaborate, well-structured placebo response?