PLACEBOS AND OTHER COMPARATIVE TREATMENTS

C.R.B. JOYCE

Medical Department, CIBA-GEIGY Limited, Basel, Switzerland

Introduction

Most contributions to the present series of articles about the methodology of clinical trials have an unusual title, an unusual approach to the problem, or both. In comparison, the placebo question may look hackneyed and faded. For example, several aspects of the relationship between placebos and clinical investigation have been reviewed, in a recent series of articles for the *European Journal of Clinical Pharmacology* (Dollery, 1979; Lasagna, 1979; Wilhelmsen, 1979; Feinstein, 1980; Joyce, 1980; Sherry, 1980) as well as in a report in the same journal on a conference entitled 'The Scientific and Ethical Basis of the Clinical Evaluation of Medicines' (Report, 1980). Almost all these papers, especially that by Feinstein (1980), contain useful comments and are worth reading. However, a number of predominantly continental authors, including at least one Professor of Criminal Law, have vigorously attacked the laboriously established principles of the clinical trial on ethical grounds (see Burkhardt & Kienle, 1978, 1981, for a review of their position). However, because many bad trials have been carried out, it does not mean that clinical trials are intrinsically unethical; because, in some, placebo may have been incorrectly used it does not follow that the use of placebo is never permissible. One may also suggest that part of the problem, at least, arises from identification of national law with universal ethics: because, in one country, an investigator may theoretically stand in peril of conviction for 'wilful and knowing homicide' (Burkhardt & Kienle, 1981) he is not necessarily in practical danger of eternal damnation.

Science is, of course, not the only standard for behaviour, especially in medicine. Where there is an apparent conflict between science and ethics, the conflict must be resolved as satisfactorily as possible. Sometimes this may require that the law be changed (Laurence, 1981). If there were no overlap between the initial assumptions or the respective methods of argument (the respective methods of investigation are clearly different), such matters would have to be decided by individual prejudice alone. But this appears not to be necessary; scientific as well as ethical arguments seek to be logical, though they

seldom share all the same premises (Vere, 1981). Some contributions to the debate seem to have been neither very scientific nor very logical. I shall try to be both, and ethical as well, in reaching the conclusion that an explicit description of the exercise of common sense or (if this be too much to ask) of logic may be a better guide for the behaviour of not entirely wicked men and women than is frequently allowed. The necessary and, I hope, sufficiently explicit description is to be found in the final section.

Placebos cannot be discussed in complete independence of other major pillars of the controlled clinical trial: the comparison of treatments, appropriate methods of allocation to treatment and blind evaluation (not necessarily blind conduct) of the trial. The use of placebos is not always essential, but reliance on the other principles can less frequently be avoided. And if, for 'placebo', is substituted the concept of 'the best appropriate comparative treatment', all four principles become fully interlocking and equally indispensable. In what follows, the other three are therefore also referred to either explicitly or implicitly at times. As Feinstein (1980) has pointed out, many criticisms of controlled trials are confused about their target: 'attacks on placebo controls may really be directed at randomization, doubleblinding, concurrent comparison, or some other component of the evaluation process'.

A useful working definition of placebo can be adapted from Shapiro (1978); it begs no questions at the outset. 'A placebo is any component of a therapy' (or 'control in experimental studies') 'that is without specific activity for the condition being treated . . . or being evaluated'.

Three basic assumptions must be made about clinical trials before considering frequently advanced criticisms, medical and ethical, of the use of placebos and listing circumstances in which the use of placebos is justifiable, essential, unnecessary or impossible.

Basic assumptions

1. The purpose of a clinical trial resembles that of any scientific experiment: to provide valid, generalis-

able and efficiently-obtained information (Mosteller, 1981). The information obtained should also be useful, non-trivial, and not obtainable by other means.

2. Patients or experimental subjects, diseases and environmental factors all fluctuate. Such fluctuations are only in part predictable, controllable or measureable. Their effects may be large and may augment or diminish each other as well as the effects of experimental treatments under investigation, and may place limits upon the degree of generalisability that is possible.
3. Such complex relationships reinforce the general need for the question to which an answer is desired to be specified very carefully; only thus can an appropriate design be chosen.

The use of placebos is attacked for medical or ethical reasons.

Medical reasons offered for rejecting placebos

Clinicians may still occasionally be heard to object to placebos for one or more of the following reasons:

1. *That they are inactive, or at least ineffective.*

The pure placebo should certainly be inactive in a pharmacological sense by definition. Recent evidence has confirmed reports that endorphin release is increased following the administration of placebos (Goldstein & Grevert, 1978). There is thus a pharmacological basis for the activity of placebos; which are certainly not ineffective. An extensive literature documents the phenomenology of the placebo (Beecher, 1959; Joyce, 1959; Lasagna *et al.*, 1954), as well as the frequency with which all kinds of measure (physiological and psychological) may change following its administration.

The frequently reported statement (often attributed to Beecher, 1959) that there is a 35% 'placebo effect' is actually an over-simplification. The frequency may well vary from 0 to 100% depending upon the definition of effect, the kind and number of subjects, the indication, external and internal circumstances and many other factors.

2. *That placebos are not used in 'real life'.*

This is only true in the sense that they are seldom called placebos. Unfortunately (or perhaps not), placebos are in fact frequently used in real clinical life. Pure placebos are sometimes deliberately used, but the placebo is more often 'impure', i.e., a drug with one or more pharmacological effects for none of which, however, is it given in the case in question. On still other occasions, placebos are given because the doctor believes innocently that they are drugs with

relevant pharmacological activity. The error occurs because the remedy has not been subjected to adequate clinical trial and its inefficacy has therefore not been shown in the relevant indication.

3. *That controlled trials, including those using placebos, often fail to demonstrate differences that 'everyone knows' (Batterman & Grossman, 1955) are real.*

True treatment differences are rather more likely to show up in a well-controlled trial than they are in real life, where the absence of controls is likely to allow unmeasured variation of many kinds to swamp the differences of interest. A good trial differs from ordinary medicine only in that it collects data in an orderly fashion. Any trial that distorts the practice of medicine in other ways than this is likely to be a bad trial. The objection is therefore an argument against (bad) trials, not against the use of placebos.

4. *That in 1981 there is at least one better treatment for most conditions than placebo.*

This point is valid; especially if partial responses to treatment rather than full success are considered to represent adequate outcomes. It is a main reason why the scope of this article covers the subject of comparative treatments in general.

Ethical objections to the use of placebo

1. *That individuals are put at risk in order to acquire theoretical benefit for an often unspecified group of patients.*

The Tokyo Declaration is clear that no individual may be placed in a trial if the investigator knows that potential risk to him or her outweighs potential benefit. The investigator should possess the information necessary to make this judgement at the outset; if not, he should obtain all the information available. He should make the judgement for each patient separately and explicitly.

The objection can be also met in a different way. Science proceeds (at the moment) by the method of falsification. Contemporary statistical methods usually test the Null-Hypothesis, and not the alternative. Some anxiety felt by lawyers and others probably arises from a belief that the physician's undertaking to try to improve the patient's state is broken if that individual participates in a trial to test the assumption that there is no difference between treated groups. But there is really no conflict. The Null-Hypothesis is seldom of interest to the physician when he treats an individual. His intention is that each patient shall benefit, no matter which

treatment he receives. Whether individual benefit has accrued is decided by comparing different moments in the history of the individual; such a 'historical' comparison is minimally scientific, but it is ethical and relevant. The hypothesis about differences between treatments, on the other hand, is tested by comparing whole groups at the same moment in time. This is scientific and, because it does not interfere with the requirements of the individual, it is also ethical.

2. *That there is almost always some evidence that at least one treatment has an advantage, or a smaller disadvantage; when this is so, all patients should be given the treatment known to be better.*

The argument might be acceptable if the evidence in question satisfied current criteria and if these met the approval of all parties. The problem arises because they do not, and it must therefore be tackled in a different way. The argument that a single paper claiming superiority for one treatment justifies its prescription for all patients is clearly false. Otherwise the publication of two trials with opposite results would allow all patients given either treatment to sue the investigator (or their physician even if they are not participating in a trial) because everyone had been deprived of the best available treatment. But the publication of one properly controlled investigation, showing a difference between the proposed treatments, is not sufficient ground for neglecting to perform further controlled trials. Early investigations may be thoroughly contradicted by later ones. This is not infrequently the case.

3. *That comparative trials are often badly designed and produce no useful information (i.e., they do not answer the question; or the question itself was badly framed).*

To this there is a short answer: a badly designed trial is always unethical (Sackett, 1975).

4. *That the use of placebo is deceitful (Saber & Reece, 1979).*

This objection presupposes that placebos are without effect and that the physician has no intention of benefiting his patient. The first point has already been dealt with: if the second is valid, the physician is unethical whether he uses placebo or not. The promise to improve can be met by the use of a placebo (but see below), as the derivation of the word itself implies. The physician should not enter a patient into a trial at all, if he feels certain that he already knows the best treatment for that individual. If the physician feels certain that he knows the best treatment for most patients likely to enter the trial, he should not take part in it himself. If he is honestly unable to

decide which treatment is best for a given patient he should himself carry out a trial: if necessary, upon the single patient in question—a situation for which experimental designs exist (Chassan, 1960, 1961). In the circumstances described, it is not more (or less) ethical to give one treatment than another. The theoretical but unknown benefit of either treatment may be offset by an equally unknown risk; or *vice versa*.

It should be clear by now that if the purpose of a particular trial can be better met by taking in a second active treatment, this should indeed be used instead of a placebo. If, however, this is not so, the use of placebo is not merely permissible, but compulsory. The fact that a placebo *will* be used, but not *when* it will be used, can sometimes be communicated to the patient before his or her consent is given. There is a danger, however, that giving this information may weaken the treatment effect. If, in the judgement of the physician, there is such a danger, the information should not be given.

'Invasive placebo treatment is unlikely ever to be justified' (Altman, 1980). However, invasive placebos have been illuminatingly used to define the benefit of some surgical procedures, and it seems best to keep an open mind on the matter, bearing the patient's best interests within it.

We can now define the circumstances in which the use of placebo is not merely justified but an ethical necessity.

When is the use of a comparative treatment not only justifiable but essential?

1. A comparative treatment is always necessary; however, it is sometimes maintained, especially when the condition is said to be 'objective' or the end-point 'hard', that a placebo, even if feasible and permissible, is unnecessary (Ritter, 1980). As has already been pointed out above, placebo has strong and remarkable effects on some very hard end-points. If doubt about the efficacy or toxicity of the proposed standard treatment still lingers at the outset, a placebo will be needed to set it at rest. This may even be true of antibiotics, especially in prophylactic trials (Hill *et al.*, 1981).

2. Placebo will have to be used if the intention is to measure non-specific effects (such as the influence of the physician's training, the patient's expectations, etc.) that would otherwise be attributed to the treatment. This can only be achieved if a placebo-treated is compared with a no-treatment group. This is unnecessary, however, if it is only desired to control for non-specific effects without actually measuring them.

3. Placebo will be necessary if information about the relative usefulness of the trial as a whole is sought. Measures of placebo reaction as well as of

compliance can be used not only as covariates in the analysis (Joyce, 1962), but to decide whether the results of the trial are to be accepted or rejected as a whole (Coronary Drug Project Group, 1981). Liljestrand's (1981) point that a trial must be based upon a large sample, if there are either many placebo reactors or many whose compliance with the treatment regime is low, may be put in different terms. If placebo reaction rate is high or compliance low, or both, a trial is either impossible or not worth doing, for the treatment will not be worth using. Whether there are exceptions to this dogma will depend upon the definition of 'high', 'low' and 'worth'.

4. Placebo provides psychological support before the trial proper begins (e.g., during wash-out of previous treatments). Its use also allows the maintenance of effect to be studied after treatment withdrawal (e.g. during a follow-up period; Stunkard *et al.*, 1980).

5. Especially, but not only, in painful conditions, placebo may sometimes work faster than known analgesics (Evans, 1981).

6. If drug supplies are limited, or if confidence in a treatment previously thought useful collapses, and (in either case) there is no alternative active treatment, the use of placebo will be essential.

When is the use of placebos or other comparative treatments unnecessary or impossible?

1. There are circumstances in which it is difficult or impossible to design an adequate control treatment. These include studies of acupuncture, bio-feedback, autogenic training, behaviour therapy and other unorthodox remedies that are beginning to attract serious scientific attention: but there are sometimes similar problems in less controversial areas. In a remarkable study of the utility of insulating the newborn, Cross and his colleagues felt so sure of their treatment that they were able to accept 'interference'

by nursing staff to 'protect' their patients even though the effect of this variable was unbalanced (Chaput de Saintonge *et al.*, 1979).

2. There are also circumstances in which the use of a placebo does not allow additional information to be obtained. These are not uncommon and usually relate to difficulty in maintaining the blindness of the comparison owing to a characteristic and easily detectable effect of the active treatment. This may be either therapeutic (e.g., the lowering of blood-pressure in hypertension) or undesirable (e.g., the postural hypertension after some antipsychotics) but cannot be reproduced by an inactive placebo; and if the placebo is 'impure'—that is, has been concocted from active but presumably irrelevant ingredients—and also successfully imitates the treatment with which it is being compared, it is possible that it may be as effective. However, if this is not important; if the comparison is between rather than within groups and the participants have no opportunity to exchange experiences; or if the functions of therapist and evaluator can be separated so that the latter at least can remain blind, a placebo can still be used.

The maintenance of blindness may also not be feasible for physical rather than clinical reasons. It is still assumed far too often that external appearance is the only important factor (Gerner & Jarvik, 1981), but treatments may resemble each other insufficiently in more than one way (see Table 1, from Joyce, 1968).

Conclusion

The routine, unthinking inclusion of a group treated with placebo in a clinical trial is never justified, even if demanded by regulatory authorities or their guidelines. No two experiments are identical, nor should they be (or the second would bring no new knowledge). As always, the questions to which each experiment is intended to provide an answer should be posed with exquisite care before the hypothesis is

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

1. To match perfectly* for:	2. To match as closely as possible for:
(a) Shape	(a) Taste on licking
(b) Size	(b) Taste on chewing
(c) <i>Surface</i> colour	(c) <i>Internal</i> colour
(d) <i>Surface</i> texture	(d) <i>Internal</i> texture
(e) Weight	(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).

tested to destruction. Then the questions implicitly asked in this article in regard to the choice of treatment should be answered. They are four:

1. Does the trial design require at least one comparative treatment? (If the answer is no, we are not dealing with a clinical trial. However, the only possible control may sometimes be historical.)
2. Is an adequate comparative treatment feasible? (If the answer is no, the trial is impossible.)
3. What feasible treatment comparisons are essential? (If the answer does not include placebo, do not use placebo.)
4. Are the decisions taken with regard to choice of treatment ethical? (If the previous questions have been explicitly asked and responsibly answered, this question will often be redundant. But here as elsewhere a little redundancy is no bad thing.)

The reasons for each decision taken in designing a trial should be clearly spelled out before the trial begins; especially those decisions that have ethical implications (which means most of them). Then they can be legitimately stated in subsequent publication. This is not always done (Crosnier *et al.*, 1981).

References

- ALTMAN, D.G. (1980). Statistics and ethics in medical research. *Br. med. J.*, **281**, 1267–1269.
- BATTERMAN, R.C. & GROSSMAN, A.J. (1955). Effectiveness of salicylamide as an analgesic and antirheumatic drug. Evaluation of the double blindfold technique for studying analgesic drugs. *J. Am. med. Ass.*, **159**, 1619–1622.
- BEECHER, H.K. (1959). *Measurement of subjective responses: quantitative effects of drugs*. New York: Oxford University Press.
- BURKHARDT, R. & KIENLE, G. (1978). Controlled clinical trials and medical ethics. *Lancet*, **ii**, 1356–1359.
- BURKHARDT, R. & KIENLE, G. (1981). Controlled trials—a social challenge. Comments on a recent controversy. *Eur. J. clin. Pharmacol.*, **20**, 311–317.
- CHAPUT DE SAINTONGE, D.M., CROSS, K.W., HATHORN, M.K.S., LEWIS, S.R. & STOTHERS, J.K. (1979). Hats for the newborn infant. *Br. med. J.*, **2**, 570–571.
- CHASSAN, J.B. (1960). Statistical inference and the single case in clinical design. *Psychiatry*, **23**, 173.
- CHASSAN, J.B. (1961). Stochastic models of the single case as the basis of clinical research design. *Behav. Sci.*, **6**, 42–50.
- CORONARY DRUG PROJECT RESEARCH GROUP (1980). Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. *New Engl. J. Med.*, **303**, 1038–1041.
- CROSNIER, J. & JUNGERS, P. (1981). Randomised placebo-controlled trial of hepatitis B surface antigen. *Lancet*, **i**, 797–800.
- DOLLERY, C.T. (1979). A bleak outlook for placebos (and for science). *Eur. J. clin. Pharmacol.*, **15**, 219–221.
- EVANS, F.J. (1981). The placebo response in pain control. *Psychopharmac Bull.*, **17**, 72–76.
- FEINSTEIN, A.R. (1980). Should placebo-controlled trials be abolished? *Eur. J. clin. Pharmacol.*, **17**, 1–4.
- GERNER, R.H. & JARVIK, L.F. (1981). Serious flaws in clinical drug trials. *Psychopharmac. Bull.*, **17**, 8–9.
- GOLDSTEIN, A. & GREVERT, P. (1978). Placebo analgesia, endorphins and naloxone. *Lancet*, **ii**, 1385.
- HILL, C., MAZAS, F., FLAMANT, R. & EVRARD, J. (1981). Prophylactic cefazolin versus placebo in total hip replacement. *Lancet*, **i**, 795–797.
- JOYCE, C.R.B. (1959). Consistent differences in individual reactions to drugs and dummies. *Br. J. Pharmacol.*, **14**, 512–521.
- JOYCE, C.R.B. (1962). Patient co-operation and the sensitivity of clinical trials. *J. chron. Dis.*, **15**, 1025–1036.
- JOYCE, C.R.B. (ed.) (1968). *Psychopharmacology: Dimensions and Perspectives*. London: Tavistock Publications.
- JOYCE, C.R.B. (1980). 'To please or not to please'. *Eur. J. clin. Pharmacol.*, **17**, 157–159.
- LASAGNA, L. (1979). Placebos and controlled clinical trials under attack. *Eur. J. clin. Pharmacol.*, **15**, 373–374.
- LASAGNA, L., MOSTELLER, F., von FELSINGER, J.M. & BEECHER, H.K. (1954). A study of the placebo response. *Am. J. Med.*, **16**, 770–779.
- LAURENCE, D.R. (1981). Reply (to Burkhardt, R & Kienle, G. (1981); see above). *Eur. J. clin. Pharmacol.*, **20**, 317–319.
- LILJESTRAND, Å. (1980). Significance of controlled clinical trials. *Eur. J. clin. Pharmacol.*, **18**, 209–211.
- MOSTELLER, F. (1981). Innovation and evaluation. *Science*, **211**, 881–886.

Some considerations felt to be important may appear to have been omitted: for example, the influence on ethical judgement of the severity of the condition. It is not possible to be exhaustive, but I hope that this point, like others, may in fact have been covered: the decision whether or not to use placebo should not rest upon the nature or the severity of the disease, but upon the necessity of benefiting the individual.

Finally, it is to be noted that neither the World Medical Assembly Declaration of Helsinki (1964; revised 1975), nor the CIOMS Guidelines (in press) for the implementation of the Declaration, especially in developing countries, make any reference to placebo at all.

Many friends and colleagues have criticised the personal opinions expressed in this paper. Theirs is the credit for any virtue it may have, but they are no more to blame for its undoubted weaknesses than if I had not consulted them at all.

- REPORT (1980). The scientific and ethical basis of the clinical evaluation of medicines. *Eur. J. clin. Pharmac.*, **18**, 129–134.
- RITTER, J.M. (1980). Placebo-controlled, double-blind clinical trials can impede medical progress. *Lancet*, **i**, 1126–1127.
- SABER, F. & REECE, R.D., (1979). Case study: The use of placebo and deception. *IRB*, June/July, 4–6.
- SACKETT, D.L. (1975). In *Platelets, Drugs and Thrombosis*, eds Hirsch, J., Kienle, J., Gallus, A.S. & Schoenbaum, E. Basel: Karger.
- SHAPIRO, A.K. (1978). In *Principles of Psychopharmacology*, eds Clark, W.G. & Del Giudice, J. New York: Academic Press.
- SHERRY, S. (1980). Frustrations with clinical trials. *Eur. J. clin. Pharmac.*, **17**, 79–80.
- STUNKARD, A.J., CRAIGHEAD, L.W. & O'BRIEN, R. (1980). Controlled trial of behaviour therapy, pharmacotherapy and their combination in the treatment of obesity. *Lancet*, **ii**, 1045–1047.
- VERE, D. (1981). Controlled clinical trials: the current ethical debate. *J. roy. Soc. Med.*, **74**, 85–88.
- WILHELMSEN, L. (1979). Ethics of clinical trials—the use of placebo. *Eur. J. clin. Pharmac.*, **16**, 295–297.