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Confusion over use of placebos in clinical trials

Better guidelines needed

See p 844

"Medicine the science" is gradually replacing "medicine the art," and demands for treatments to be evidence based have given the process a recent fillip.[1] The key to this transition has been the controlled clinical trial, which, for drugs at least, is now an essential component for assessing interventions. But the clinical trial is more than a scientific instrument, for in addition to meeting the needs of the scientist it must also satisfy licensing authorities, marketing departments, prescribers, consumers, ethicists, lawyers, and often all of these in many countries. With such diverse interests, disagreements over the design of trials are inevitable, and one area in which conflict arises is in the use of the placebo.

On page 844 of this week's journal Aspinall and Goodman, who have analysed trials of ondansetron for postoperative nausea and vomiting, argue that placebos have been used so excessively that patients have been deprived of effective treatment.[2] Similar concerns were raised last year about trials of non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, antidepressants, and ondansetron (when used for the treatment of nausea and vomiting induced by chemotherapy).[3] These allegations need addressing. Firstly, however, understanding of what determines the use of placebos is important.

Controlled clinical trials are designed to show whether a product has a pharmacological effect. Some trials seek evidence by using historical comparisons, some by comparing the product with no treatment, and others by showing a dose-response relation for the new drug. But proof is scientifically strongest if data come from trials that compare the new drug with a placebo,[4] with interventions given in a double blind fashion and in random order. Trial formats are not, however, fixed and designs vary during the development of drugs (for example, exploratory and confirmatory studies have different constraints) and in differing circumstances. Blindness is difficult if the product has features that cannot be masked, such as taste and smell. Use of a placebo would be unethical if it meant that life was endangered (for example, use of an adrenaline placebo for anaphylaxis) or symptoms were made intolerable. Advice on the use of placebo is inconsistent.

Ethical considerations have dominated advice about placebo, and the emergence of local research ethics committees has intensified this development. The committees' judgments influence whether trials happen, results are published, grants are awarded, and even drugs are licensed. In Britain committees have to choose between two essentially irreconcilable approaches. The Department of Health's guidelines ask ethics committees to scrutinise the design of trials, pointing out that if they find the research methodology poor, and so the study is without scientific value, they would be justified in rejecting the application.[5] Studies destined to produce unreliable results would be unethical; certainly, volunteers should not be put at risk or resources wasted in such trials. Conversely, since placebo controlled trials offer the greatest scientific rigour for assessing the efficacy of a drug,[4] applications for such trials, at least for new drugs, should clearly be received with encouragement.

Compare this with the recommendations of the declaration of Helsinki, which states that, far from being essential, the use of a placebo is unethical: "in any medical study, every patient—including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method."[6] Since placebos are, by their nature, inert this requirement seems to preclude the use of placebos entirely. (Incidentally, it seems also to preclude study of "active" experimental drugs since proof of their efficacy cannot come until the trial is completed.) If a placebo controlled trial is to take place then with few exceptions committees will insist that before subjects agree to take part (so before they give their informed consent) the implications of not receiving active treatment are made absolutely clear to them. In a similar vein, the use of a placebo when efficacy has already been established would almost certainly be viewed as unethical.

The licensing laws also influence the use of placebo, although their effect has been to favour placebo controls. In Europe this results more from what is not said than what is. No reference to placebos is made in the United Kingdom's Medicines Act 1968. European Union regulations state only that in some instances it may not be appropriate to use a placebo as a comparator and hence, by implication, that in most instances a placebo would be appropriate.[7] In both regulations, however, the granting of a licence depends on proof of the drug's effectiveness, and as comparison with a pharmacologically active product is not sought, in most circumstances the preferred comparator at the time of licensing is likely to be a placebo.

European regulators spell out what they want from applicants in booklets on the design of trials[8,9] (one, published 1994, came into effect in June 1995[8]; the other is still in draft form[9]). Neither, however, addresses the position of placebos except to note that the placebo is a legitimate comparator and

to emphasise that "scientifically, efficacy is most convincingly established by demonstrating superiority to placebo in a placebo-controlled trial."[8] Equivalent guidelines produced by the Food and Drug Administration are more detailed. Exceptions are respected (as, for example, in trials of antibiotics where existing treatments prolong life) but, for the most part (and treatments for depression, anxiety, pain, heart failure, and hypertension are examples), when considering the licensing of a new drug the administration clearly prefers data from clinical trials comparing the effect of the product with that of a placebo.[10 11]

The value of placebo controlled trials to the drugs industry, consumers, clinicians, and administrators in the health service add yet further dimensions. Industry has to comply with the regulatory authorities' rulings, and in many respects it is in the company's interests to compare the new product with only a placebo. By carefully selecting the researchers, companies can use such trials to familiarise opinion formers with their new products. And, of course, at the launch of a new product the last thing a company wants is a study showing that its product is less effective than the competition. In contrast, consumers, clinicians, and administrators would be keen to discover how the efficacy of the new drug compares with established treatment.[12] For this, placebo controlled studies are unhelpful.

Confusion over the use of placebos in clinical trials needs resolving. When a new drug is being developed every effort must be made to determine whether the product is effective in the condition for which it will be used. Studies should be rigorously controlled, and in many circumstances the most reliable indication of the drug's effectiveness will come from trials directly comparing the product with a placebo. Well designed placebo controlled clinical trials will be needed for each clinical end point and, once efficacy is established for these, research should switch to comparisons with conventional products. Manufacturers have a responsibility to ensure that data on efficacy are collected as efficiently and as quickly as possible. There is no place for a myriad of small, poorly conceived, placebo controlled studies that can offer little real advance. Drug companies, which alone have data on the trials being undertaken, are the only group that can curb such practices.

Relying on public scrutiny introduces too much delay as such duplication may not be evident for years, when the results of the various studies are eventually published. Licensing authorities should standardise and make explicit their requirements for placebo controlled studies. Finally, the blanket Helsinki recommendations, which undermine the use of placebos generally, need revision.

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Pregnancy in women with cystic fibrosis

Outcomes for mother and baby have much improved

The first successful pregnancy in a woman with cystic fibrosis was reported in 1960—at a time when the median survival of children with the disease was less than 10 years.[1] The patient died six weeks after delivery, and the authors concluded that "cystic fibrosis is seriously complicated by pregnancy." Since then reports have documented a gradual change from high fetal loss and maternal death due to cor pulmonale and respiratory failure to a good chance of a successful full term delivery of healthy infants to mothers whose overall health may be little changed.[2-5] Sadly, this outcome is not available to patients whose health is poor or to those few women who have been sterilised or warned not to conceive.

How, then, in the late 1990s should doctors approach the issues of fertility, contraception, and pregnancy in their women patients with cystic fibrosis? No reliable data are available on fertility rates in these women. Puberty and the establishment of regular menstruation are often delayed, and women with severe disease may develop secondary amenorrhoea due to undernutrition.[6]

The cervical mucus is thicker in women with cystic fibrosis, but this seems not to bar conception, and reliable contraception is important for all women. In our experience oral contraceptives are the most widely used method. Sex steroids are fat soluble and so their absorption might be impaired, but pharmacokinetic studies have shown therapeutic concentrations after standard doses and a medium dose (30 μg oestrogen) combined pill should be the first choice.[7] Additional barrier methods should be used during courses of oral or intravenous antibiotics as these may further reduce absorption.

One recent projection suggested that 4% of women with cystic fibrosis become pregnant each year (North American Cystic Fibrosis Foundation's national patient registry, 1992). Whenever possible, pregnancy should be planned and couples should have access to genetic counselling. The man should be offered testing to determine his carrier status. If he is a carrier chorionic villus sampling should be considered since the risks of the couple conceiving an infant with cystic fibrosis are 1 in 2 and they may wish to consider selective termination in the first trimester.

Women with severe disease have to recognise that they may be unable to complete a pregnancy, and that their premature death might leave a motherless child. Even relatively healthy women may not wish to take these risks, and counselling may be needed to help them cope with difficult decisions. Some women will choose to terminate their pregnancy, but general anaesthesia may be hazardous when lung function is impaired. Regional or spinal anaesthesia is used in some centres, but termination may also be performed medically with mifepristone and prostaglandin.[8 9]