The ethics of continuation studies in dementia

John M. Kellett

At least one ethical committee is not prepared to approve open continuation studies of treatments for dementia. The author considers that such studies are an ethical necessity if patients are to give six months of their illness to trying out what may be placebo. The reasons for this conflict are discussed. In particular, it is suggested that such studies contribute real scientific information.

Ethics committees have a particular responsibility for supervising research into patients who are not competent to give consent, and should consider both the carer and the patient involved in drug trial studies. Hirsch & Spence (1995) explored some of the ethical issues surrounding research on mentally incapable patients. An overemphasis on scientific validity can lead to paradoxical judgements when considering the ethics of continuation studies.

When a carer and his or her patient with dementia consent to take part in a study on Alzheimer's disease, one factor in this decision is the possible beneficial outcome for the patient from the treatment. As there is no benchmark drug for comparison, all current trials must have a placebo arm. Usually, only a minority of patients will find themselves in this group. However, carers may prefer a study where all patients can try the active preparation if it appears to be of benefit. Indeed it has been argued that in the past, this was a necessary part of any study in order to satisfy ethical requirements.

The ethics committee at St George's Hospital take a different view. They consider that no one should take a drug of unproven efficacy except in a situation where that efficacy can be established (i.e. under double-blind conditions). They argue that until a drug has been proven to be effective, the null hypothesis should hold sway. Under these circumstances, if a patient appears to benefit, whether on an active drug or on placebo, he may be allowed to continue the treatment unchanged. If the patient fails to benefit, he should stop the treatment and be entered on another double-blind study, ignoring the fact that his health may have declined in score such that he may no longer qualify for a trial. The reasonable assumption that the active drug might have some points in its favour if a company is ready to invest millions of pounds on an active trial is dismissed.

The justifiable desires of patients to try an active drug are sidelined in the interest of worthless scientific scepticism. Even if one were to accept St George's scheme as a means of preserving hope, it would leave the researchers in the unenviable position of having to be untruthful to patients about the contents of their medication and would make it impractical to continue the blind study into the continuation phase. Their view would be defendable if there was substantial doubt about the risk of side-effects, the condition was relatively stable and not lethal and other effective remedies were available. These conditions would, for example, apply to a trial of an antidepressant for mild depression. The same committee has often expressed the view that the results of the trial should be available before the start of the continuation phase, a most unlikely event when recruitment into trials may continue for a year or more, and premature analysis would invalidate the results.

The conditions mentioned above do not apply to Alzheimer's' disease. The remorselessly progressive nature of the illness is such that a patient is unlikely to fulfil the entry criteria to another study after six months on placebo, and after the rejection of tacrine by the Committee on Safety of Medicines there is no approved effective alternative treatment available. Surgeons may be right to avoid the temptation of relieving doubt by diving into the acute abdomen because the consequences of misjudgement are profound. However, the side-effects of most current cholinergic drugs (unlike tacrine) are, at the most, unpleasant rather than life-threatening, while the relief accorded to carers and their patients that they are trying the most effective remedy is immense. I would argue that this would justify the continuation of an ineffective remedy, let alone the more effective second generation remedies. The case for allowing patients to take remedies before their efficacy has been fully

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established is strong, not least because their condition is closely observed, unlike self-medication with patent remedies.

There are, however, two more arguments for continuation studies which are often overlooked. Whether or not the drug produces an immediate improvement, the critical question remains its effect on the course of the disease. A patient sample who have been on placebo for six months and then start the active preparation can be compared with those who have been on the active preparation throughout, thereby allowing one to judge whether they catch up (i.e. the drug has no effect on the course) or not. An important question can be answered provided double-blind randomisation is maintained, although it could be argued that this would only justify continuation studies lasting three months. The second scientific justification is the need to monitor later side-effects which, though unlikely, need to be established before a drug is released for continuous use over the five-year course of a case of dementia.

One might suggest that a continuation open label study after a double-blind placebo controlled study on patients with Alzheimer's disease is an ethical necessity and not an ethical transgression.

Reference

HIRSCH, S. & SPENCE, S. (1995) Ethical approaches to researching the mentally incapable patient. *Psychiatric Bulletin*, **19**, 414–416.

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Shoes and souls

Mani Rajagopalan

I would love to be in your shoes;
Asking me questions I can't understand,
Telling me things I won't hear,
And soaking my brain with neuroleptic fluids.

How would you know what it's like?
To talk to people you cannot see
To listen to voices you don't want to hear
And to hate people you know you love?

Would you care enough to stay silent,
And listen to the anguish of a troubled soul?
To share the myriad feelings within me,
And to walk with me out of this hell?

But then you have your own concerns;
Dopamine receptors are far more fascinating,
And I'm just a case report on your CV,
I would love to be in your shoes.

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