Amitriptyline: still efficacious, but at what cost?†

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In this month's *Journal* two leading researchers make the claim that amitriptyline is still the 'leading antidepressant' after 40 years of research. This claim might appear surprising, considering that amitriptyline is now seldom used as a first-line antidepressant in this country due to its perceived adverse event profile (Martin *et al*, 1997), and hardly used at all in countries where patients contribute to the costs of their own health care. If such an all-encompassing claim were made by a company for one of its own products, it is likely that it would be contested by other companies at the Prescription Medicines Code of Practice Authority. Robust evidence is therefore needed to support it. Can it really be true that no advances have been made in the pharmacotherapy of depression in all that time?

Barbui & Hotopf's meta-analysis (2001, this issue) has replicated, using all available randomised controlled trials (RCTs), Andersen's (1998) findings in in-patient studies – that amitriptyline has a small efficacy advantage over all other antidepressants, including the other tricyclics and heterocyclics. To do this they included all RCTs identified by an exhaustive search in which amitriptyline was one of the treatments. This strategy has the advantage of comprehensiveness and therefore gives maximum statistical power. However, while it is crucial to trial design, randomisation is not the only quality indicator. The strategy of including all RCTs ignores other threats to the validity of the findings of the primary studies. The authors note, for example, that nine trials were open studies and four were only single-blind. No explicit diagnosis of depression or severity criteria were used as entry criteria in 34% of the studies and only 36% of trials used operationally defined diagnostic criteria. Only 70% of the studies used what the authors refer to as 'valid and reliable' outcome measures. One should not conclude from this that current RCTs of antidepressants are poorly designed. The earliest study included in the meta-analysis is from 1962 – at least 20 years before the industry brought in good clinical research practice to improve the design and conduct of clinical trials. Those trials published after 1980 were of demonstrably higher quality, but in this analysis no weighting is given for these quality differences.

The results are structured into four types, two for efficacy and two for adverse events. On the efficacy side it appears that there was no statistical excess of patients who were classified as responders in the amitriptyline group over the comparators. The number needed to treat (NNT) to get one extra responder compared with all antidepressants was 42 and compared with selective serotonin reuptake inhibitors (SSRIs) it was 34.5. There was a significant difference in the final mean depression score but such continuously distributed variables are difficult to place in clinical context. The efficacy advantage of amitriptyline therefore appears to be marginal in these analyses.

There was no difference in drop-out rates between amitriptyline and other compounds, but there was a difference in reported side-effects with a number needed to harm (NNH) of 7.4, the most significant difference in the study. The fact that the tolerability disadvantage of amitriptyline does not translate into excess drop-out rates is not surprising, since patients drop out of clinical trials for many reasons unrelated to treatment type, thus obscuring differences between them. A recent RCT in UK primary care (Thompson *et al*, 2000) showed that fluoxetine had a significant advantage over dothiepin (which is similar to amitriptyline in side-effects) in adherence using highly reliable measures.

So what are we to make of these results? They imply that if I, as a psychiatrist, treat a patient with some unspecified kind of depressive condition (possibly varying from mild sub-clinical symptoms to severe psychotic depression) I am unlikely to see much extra effectiveness by choosing amitriptyline over another antidepressant, even an SSRI. In fact I will need to treat 42 patients with amitriptyline to find one extra responder after 4–6 weeks. Out of those 42 patients, between five and six would have an adverse event that they would not have suffered if they had been taking one of the comparator treatments, which include other tricyclics as well as newer compounds. If I were a general practitioner the findings would be meaningless, since none of the studies was carried out in my health care setting on representative samples of primary care patients. Indeed, given that one of my main objectives as a doctor is to 'first do no harm' I might be concerned that by far the largest difference between amitriptyline and other treatments is in its capacity to cause adverse events.

It is possible that the flaws in the primary research studies introduced a conservative bias in the outcome of the meta-analysis and that amitriptyline is really much more effective than the comparators – but this would be speculation. If we ignore these methodological flaws for a moment and accept the efficacy advantage of amitriptyline as real then we might ask what causes it. There are broadly two possibilities. Amitriptyline is highly sedative compared to many of the comparators and will therefore score well on the sleep disturbance items of outcome scales. This alone might account for much of the difference in both efficacy and side-effects. However, it is also a dual-acting reuptake inhibitor acting at both serotonergic and noradrenergic synapses, and there is a growing, but still early, literature to suggest that this might convey an efficacy advantage regardless of sedative side-effects (Clerc *et al*, 1994; Wheatley *et al*, 1998).

We cannot really ignore the methodological flaws of some of the primary research. In any form of study the quantity of primary data is important to gain statistical power, but the quality of that data is also important. This applies equally to meta-analysis, where the primary data is the individual RCT, as to brain scans or blood tests. Surely it is inappropriate to include studies which are so flawed that they are now only of historical interest.

†See pp. 129–144, this issue.

https://doi.org/10.1192/bjp.178.2.99 Published online by Cambridge University Press

Although it may be the case that amitriptyline has a real, but small, efficacy advantage I would argue that the clinical case for using it as first-line treatment is not made by this study. As a doctor, the evidence presented leads me away from that conclusion – as it would if I were a patient. However, there is a separate set of arguments about cost effectiveness that are often made by public health doctors, health economists and health care managers that require different kinds of evidence. These arguments run as follows: 'there is insufficient evidence for a difference in either beneficial or harmful outcomes of treatment with different antidepressants to justify using anything but the cheapest available drug – amitriptyline'. At a population level these arguments have more force than suggestions that amitriptyline is the best choice for the individual patient since, they argue, cheaper drugs leave more money available for other aspects of care. The cost effectiveness of antidepressants is currently being investigated in the UK primary care context in an RCT in Southampton. At present however, the only evidence is from the USA (Simon *et al*, 1996, 1999). The results suggest that the costs of acquiring antidepressants are only a small part of the total cost of treating depression, so that the differences in costs between the cheapest and the most expensive drugs, while not trivial, are not critical either. We wait to see if the same is true in the UK context.

At present, it would seem reasonable to make the choice of treatments by tailoring it to individual patients' needs and wishes. This means allowing the patient to make an informed choice after giving them information about all the available treatment alternatives including evidence-based psychological treatments such as problem-solving therapy, cognitive therapy or interpersonal therapy. We know that this seldom happens in practice (Thompson, 2000). The almost total unavailability of such treatments within the National Health Service is a much more pressing issue for depression services in primary and secondary care than the acquisition costs of individual drugs. Given what we know about the tremendous physical health (Ormel *et al*, 1999) and economic (Wells *et al*, 1999) problems caused by depression, the doctor's aim should be to help every patient with depression to recover and stay well – at any reasonable cost.

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(First received 17 July 2000, final revision 17 July 2000, accepted 19 July 2000)

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https://doi.org/10.1192/bjp.178.2.99 Published online by Cambridge University Press