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# PHARMAC and availability of pharmaceuticals - and response

In his editorial,[1] Professor Menkes makes a number of points to which we would like to respond. We support the principle of obtaining pharmaceuticals at the best possible price and of prescribing in a way to get the best health outcome for the money available. We agree that it is in nobody's interest for expensive but ineffective treatments to be sanctioned. However, we question whether PHARMAC adopts a systematic unbiased approach to reckoning cost effectiveness in pharmaceuticals. There is evidence that a number of pharmacological agents, discussed in the article,[2] which are available in most other countries, are useful in depression when treatment resistance or side effects occur and it is the fact that these data seem to be selectively noted or ignored by PHARMAC that we have difficulty with. There are also some specific points to which we would like to respond.

Firstly, on the basis of other studies of drug treatment data which apparently show that drug sponsorship has affected the interpretation and also in some cases the data, Professor Menkes casts doubt on company sponsored trial data and presumably, by implication, the meta-analysis of Thase.[3] However, he finds no fault in this particular meta-analysis and does not criticise interpretation of the data. Since there are no other data available on this subject, for reasons which we discussed in our article, we find this approach unhelpful.

Secondly, Professor Menkes specifically criticises the study by Poirier and Boyer[4] of venlafaxine versus paroxetine in treatment resistant depression stating that it "unfortunately does not specify what proportion of patients failed to respond to SSRIs during the index episode". In fact, the paper quite clearly specifies that in the venlafaxine group 66% of patients previously failed to respond to an SSRI and in the paroxetine group 65% had failed to respond to an SSRO. This is comparable with the number of patients that have previously failed to respond to a tricyclic antidepressant in each group. His assertion that it would be unsurprising that SSRI non-responders tend not to respond when challenged with another SSRI is not supported by the data or our clinical experience. Open trials quite clearly show that the response rate to a second SSRI in the presence of non-response to a first SSRI is approximately 50%[3] and the strategy of switching from one SSRI to another is commonly clinically used.

Furthermore the pharmacological profile of venlafaxine is similar to that of some tricylic antidepressants, making this, in our opinion, a very fair comparison. Indeed, this is a trial of a novel strategy (venlafaxine) versus a commonly used strategy (switching to a second SSRI). The suggestion that venlafaxine be compared with the novel strategy of augmentation of SSRI with reboxetine (which is not funded in New Zealand) seems to us to be far more open to methodological criticism.

Finally we would like to draw the attention of readers to a forthcoming meta-analysis of venlafaxine[5] which adds to the data suggesting that this may be more effective than SSRIs in the treatment of depression. Once again this is drug company sponsored. Readers, PHARMAC and Professor Menkes can decide whether to evaluate the data

critically or simply to dismiss it on the grounds that it may be affected by this sponsorship.

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2. Porter RJ, Mulder RT. Inadequate availability of pharmacological treatment for affective disorders in New Zealand. NZ Med J 2002; 115: 78-81.
3. Thase ME. Citalopram treatment of fluoxetine nonresponders. J Clin Psychiatry 2001; 62: 683-7.
4. Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. Br J Psychiatry 1999; 175: 12-6.
5. Smith D, Dempster C, Glanville J et al. The efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry. In press.

## Response

I am pleased that Porter and Mulder agree that pharmaceuticals be obtained at the best possible price and used in a way which maximizes health outcomes -- this is entirely in line with PHARMAC's operating principles.[1] However, they question whether PHARMAC adopts a systematic unbiased approach in reckoning cost effectiveness, based on the agency's decision not to purchase certain drugs available in other countries. Of course in themselves such decisions can hardly be taken to indicate bias. The real issue is whether these decisions are reasonable given the evident cost-effectiveness of venlafaxine and the other drugs in question. Since a drug's cost-effectiveness is calculated as a ratio of benefit to cost, any treatment can become 'not worth it' if the supplier demands too high a price.

The argument boils down to a simple question: are new drugs such as venlafaxine worth what the companies want to charge, given the existing drugs budget and the competing priorities both within and without psychiatry? Thus far, it would seem that PHARMAC's calculations have yet to justify purchase of venlafaxine, but the potential usefulness of this and other agents in treatment of resistant mental disorders has left them on an 'investment list' prompting continuing negotiations with suppliers. Looking back over PHARMAC's history, the same arguments previously unfolded with regard to purchase of branded SSRIs and atypical antipsychotics. In both cases, good evidence has become available vindicating PHARMAC's hard-nosed purchasing policy. In both cases, enormous price differentials (one to two orders of magnitude) relative to conventional treatments effectively prohibited the unrestricted availability of the branded drugs -- the additional benefits simply were not worth it. In both cases, targetting the new drugs' availability to those most likely to benefit was both clinically and fiscally sensible. Unfortunately, awareness of this simple point was obscured,

*inter alia*, the very effective lobbying and marketing strategies of the pharmaceutical companies concerned, and by the rhetoric of a number of indignant prescribers.

Because PHARMAC has been given responsibility for judiciously allocating scarce resourcing it is inevitable that hard decisions will need to be made, and that some prescribers and their patients will be frustrated. If Porter and Mulder have constructive suggestions for affordable improvements to PHARMAC's methods of economic analysis,[2] or ways to make ends meet such as how to increase revenue or to reduce the prices demanded by suppliers, then their suggestions will be welcome. Meanwhile they should not be surprised if PHARMAC's efforts to avoid bias lead to an apparent, often frustrating, resistance to focused lobbying. Such lobbying reflects both dedication and the individualism which is part of our clinical medical culture,[3] and which inevitably collides with the utilitarian ethos of government agencies.

Just because a study is funded by a drug company does not make it worthless but is cause for healthy scepticism. Thus I seem to be somewhat more sceptical than Porter and Mulder regarding the RCT of venlafaxine versus paroxetine in refractory depression.[4] I am grateful to my Canterbury colleagues for bringing to my attention the proportion of patients who failed to respond to SSRIs during the index episode in that study. However, concern remains when a single sponsored RCT is relied upon to make important funding decisions. This is particularly true given very recent evidence from a large (n=168) RCT confirming that more than 50% of chronically depressed SSRI or tricyclic non-responders improve significantly when crossed over to the alternate antidepressant class,[5] suggesting a cheap alternative for many patients who might otherwise receive vanlafaxine.

Porter and Mulder also take issue with my 'implied' scepticism about sponsored meta-analysis, such as the one by Thase et al,[6] and find my approach unhelpful since "there are no other data available on this subject." I am indeed sceptical about that meta-analysis, specifically because other data apparently do exist and have been excluded from the analysis, probably on the basis of publication bias.[7] As Porter and Mulder note in their original article[8] "...Reputable journals are extremely careful about the review and publication of studies with possible conflicts of interest and we have no reason to suppose that the British Journal of Psychiatry is any different in this regard." Exactly so, and it is fascinating to note recent concerns about the links between Wyeth (the manufacturer of venlafaxine) and the editor of the British Journal of Psychiatry, in which the aforementioned meta-analysis appeared.[9]

Venlafaxine will, I predict, shortly become available in New Zealand, but since the price demanded by Wyeth is many times that of the generic SSRI and tricyclic alternatives, its availability may sensibly be restricted to use in a specific population of patients refractory to both conventional antidepressant classes. The net economic impact of venlafaxine is difficult to anticipate, partly due to externalized costs of depression and its treatment, but also because the majority of pharmacoeconomic analyses may suffer from sponsorship bias, sometimes with embarrassing transparency.[10]

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