advanced than many other ACT services? What intervals and outcome measures reliably assess ACT interventions? In our opinion, two years is a relatively short period to adequately engage, treat and initiate significant rehabilitation of a person with severe mental illness. We owe it to our clients to enhance their quality of life by sustaining the merits of PACT into the 21st century. Prospective longitudinal research may still identify elements crucial to advancing lessons of the past to the future.

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Drug treatment for resistant depression

On the basis of a four-week study carried out in 122 patients suffering from treatment-resistant depression, Poirier & Boyer (1999) claimed that "venlafaxine showed some evidence of superiority to paroxetine in this difficult-to-treat population". Careful analysis of their results, however, suggests that evidence supporting this assertion can be improved.

First, it should be noted that the design of the study was inherently biased in favour of venlafaxine since, in both treatment groups, two-thirds of included patients had proved to be "resistant" to a selective serotonin reuptake inhibitor (SSRI). In spite of this, no significant differences were observed between venlafaxine and paroxetine for the primary efficacy variable (defined as the change in total Hamilton Depression Rating Scale (HAM–D) score between day 0 and day 28) in either the observed case analysis (-11.1 and -10.2 respectively; $P=0.55$) or the last-observation-carried-forward (LOCF) analysis ($P=0.70$, intention-to-treat).

Furthermore, there was no significant difference between the two treatments with respect to the response rates (>50% decrease from baseline in HAM–D score and a Clinical Global Impression (CGI) improvement score of 1 or 2) following the more robust LOCF analysis, although for the observed case analysis the difference just achieved significance ($P=0.044$).

Second, CGI severity and improvement scores improved over time following both treatments. Although there was no significant difference between the two groups, the trend was clearly in favour of paroxetine.

Finally, it should be noted that the dose titration for paroxetine was very rapid (30 mg as early as on Day 5) and neither optimal nor consistent with the manufacturer's recommendations. This rapid titration could have contributed to the high incidence of adverse events found in the paroxetine-treated group (63% of patients treated with paroxetine compared with 69% of those given venlafaxine). In addition, it appears that the comparison was not performed at equivalent doses for both antidepressants; the mean daily dose of venlafaxine was 269 mg/day (i.e. 44 mg/day more than the maximal daily dose recommended by the manufacturer in ambulatory patients) *v.* 36.3 mg for paroxetine, which is not the maximal dose for this agent.

To sum up, the authors emphasis on a fairly marginal significance emerging from a subsidiary analysis of a secondary efficacy parameter seems disproportionate.

Poirier, M.-F. & Boyer, P. (1999) Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *British Journal of Psychiatry*, **175**, 12–16.

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Author's reply: We do not consider that our study was "inherently biased in favour of venlafaxine" for three main reasons:

(a) The proportion of two-thirds of patients included in each group who were previously resistant to treatment with an SSRI is a realistic picture of what is observed in everyday practice, since the prescription of an SSRI is now the predominant one in any type of depression.

(b) Two-thirds of the patients included in the venlafaxine (a serotonin and noradrenaline reuptake inhibitor) group were previously resistant to tricyclic antidepressant drugs, which also act on noradrenaline and serotonin. The bias in favour of venlafaxine is in the same proportion as the bias in favour of paroxetine.

(c) There is no clear evidence that a patient resistant to an SSRI must not be switched to another SSRI. Not all SSRIs are the same, and the consistent pharmacological differences between these drugs authorise our point of view for such a switch.

What is more, Dr Daniels' opinion, that when a patient is resistant to an SSRI subsequent treatment with paroxetine (another SSRI) should be avoided, is likely to be incorrect as in our study, a significant number of patients previously resistant to an SSRI afterwards responded to treatment with paroxetine.

The fact that no significant differences were observed between venlafaxine and paroxetine with respect to the mean HAM–D change, both in the observed-case and in the LOCF analyses, was fully recognised in our report. The main differences we reported between the two drugs was in remission rate – an important criterion for prediction of future outcome.

Finally, regarding the dosages of the drugs used, at the time the study protocol was designed, paroxetine dosage (including dose titration) was not very clear in terms of regulatory recommendations (in France at least) and it was not possible to recommend a dosage of paroxetine as high as 40 mg/day. This can be seen as too low now, in the light of subsequent research on the dose–response relationship for paroxetine.

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Cholesterol, depression and suicide

In a recent study low serum total cholesterol was associated with an increased risk of suicide (Partonen *et al*, 1999). However, the study population was a special subgroup, since the subjects were older male smokers. In addition, the final trial participants were very selected, since the target population included approximately 283 000 subjects, but

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