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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only 29 133 were recruited (ATBC Cancer Prevention Study Group, 1994).

Continuing our previous research (Vartiainen *et al*, 1994) and analysing random population samples of Finnish subjects, we prospectively monitored mortality of 18 344 men (aged 25–64 years) through the National Death Register for a mean of 14.6 years. There were 91 suicides among 7649 smokers and 53 suicides among 10 695 non-smokers. In order to replicate the findings of Partonen *et al*, we classified cholesterol into the same three categories. Using the Cox model the relative risks were adjusted for identical variables except for carbohydrate intake. Among smokers the unadjusted risks (with 95% CIs) of suicide increased from 1.00 to 1.48 (0.63–3.47), and to 1.80 (0.75–4.31) with increasing cholesterol level. The relative hazards changed clearly after adjustment for covariates (1.00, 1.38, 1.62, respectively), but remained non-significant. In the report by Partonen *et al*, the relative risks did not change at all after adjustment for covariates, which we find surprising. We found no association between cholesterol and suicide in non-smokers.

Inconsistent findings between these two large longitudinal studies may have resulted from several confounding effects. First, 75% of the participants in the ATBC study were treated with alpha-tocopherol alone, beta-carotene alone, or both. It is possible, theoretically, that these antioxidants possess some unknown central nervous system effects. Second, the method of suicide may influence the cholesterol–suicide association. Our own findings implicate that very high serum total cholesterol is associated with the increased risk of violent, but not with non-violent suicide (Tanskanen *et al*, 2000). Third, it has been suggested that cholesterol is only a surrogate marker of changes in dietary polyunsaturated fatty acids, which have been linked to depression (Hibbeln & Salem, 1995) – one of the strongest risk factors for suicide. Probably various other factors also confound this controversial relationship.

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We read with interest the excellent large-scale prospective study reported by Partonen *et al* (1999). They found that low serum total cholesterol appears to be associated with low mood and suicide. However, others have reported conflicting results (McCallum *et al*, 1994). Weidner *et al* (1992) found that patients on a cholesterol-lowering diet were associated with reductions in depression if they were instructed to increase fish consumption. This implied that differences in the composition of polyunsaturated fatty acids (PUFAs) might explain the conflicting finding. The PUFAs are classified into two main groups: omega-3 (or n-3) of which the parent essential fatty acid is alpha-linolenic acid (C18:3n-3), and n-6, of which the parent essential acid is linoleic acid (C18:2n-6). Maes *et al* (1999) found that major depression is associated with: significantly decreased total n-3 fatty acids; increased monounsaturated fatty acids and C22:5n3 proportions and increased C20:4n6/C20:5n3 and C22:5n6/C22:6n3 ratios; lower C22:4n6, C20:5n3 and C22:5n3 fractions in phospholipids; lower C18:3n3, C20:5n3 and total n3 fatty acids, and higher C20:4n6/C20:5n3 and n6/n3 ratios in cholesteryl esters; and lower serum concentrations of phospholipids and cholesteryl esters. These findings are consistent and have shown well-established positive correlation between depression and coronary artery disease. Many studies have documented evidence of hypothalamic–pituitary–adrenocortical axis hyperactivity within medication-free patients with major depression, including hypercortisolaemia (Raadsheer *et al*, 1994). Hypercortisolaemia can induce hypercholesterolaemia, hypertriglyceridaemia and hypertension. These are well known to be predisposing factors of cardiovascular disease. If low serum cholesterol concentrations were linked to increased depression, it would be difficult to interpret the correlation between depression and coronary artery disease. The relationship between cholesterol and depression may not be specific enough.

Maes, M., Christophe, A., Delanghe, J., *et al* (1999) Lowered omega-3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Research*, **85**, 275–291.

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Authors' reply: We analysed data from the ATBC Cancer Prevention Study, which was a primary prevention trial to test whether alpha-tocopherol and beta-carotene supplements would reduce the incidence of lung and other cancers (ATBC Cancer Prevention Study Group, 1994). Smokers were recruited from the total population of elderly men and assessed for eligibility. A previous diagnosis of cancer, current severe angina with exertion, chronic renal insufficiency, cirrhosis of the liver, alcohol dependence, or a disorder limiting participation in the long-term trial were grounds for exclusion.

We concluded that low serum total cholesterol appeared to be associated with low mood. We also found that low serum total cholesterol predicted, after adjusting for risk factors, the occurrence of conditions indicative of poor outcome, such as hospitalisation owing to major depressive disorder and death from suicide. Findings were similar for violent deaths exclusive of suicide. Trial supplementation had no effect

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