Correspondence

EDITED BY LOUISE HOWARD

Do SSRIs affect personality traits?

Sir: Ekselius & von Knorring (1999) concluded that significant effects on personality traits are seen in depressed patients treated with selective serotonin reuptake inhibitors (SSRIs). It is possible that modulation of neurotransmitter systems affects personality traits. However, it is far-fetched to derive such conclusions from this study. First, personality assessment by a single self-rating is inadequate. Second, while in a state of depression severe enough to warrant antidepressant medication is not the best time to assess personality. Third, all the items in the scale used by Ekselius & von Knorring to assess personality are affected in depression. Ideally, this issue can be studied only in subjects who have no mental illness but do have personality problems. They should have a comprehensive assessment of personality and mood at baseline and at follow-up. There should also be control groups on placebo and/or on other antidepressant drugs.

Ekselius, L. & von Knorring, L. (1999) Changes in personality traits during treatment with sertraline or citalopram. *British Journal of Psychiatry*, **174**, 444–448.

K. S. Gracious Medway Hospital, Gillingham, Kent ME7 5NY

Authors' reply: It is easy to agree that, ideally, the effect of SSRIs on personality traits should be studied in subjects who have personality problems but no mental illness. However, conclusions can also be derived from other sources. We had three good reasons to believe that the results of our study could be interpreted as an effect of SSRIs on personality traits. First, in an earlier study by Perris *et al* (1979), in-patients suffering from depressive syndromes completed the Karolinska Scales of Personality (KSP) (Schalling *et al*, 1987) during depression and when recovered after treatment with tricyclic antidepressants or electroconvulsive therapy. Twelve out of 15 scales remained stable. The only significant changes concerned components of anxiety and social desirability. Thus, it is not true that all items in the scales are affected in depression. Instead, the KSP scales are fairly independent of the state of the subject. Second, in our study (Ekselius & von Knorring, 1999), changes in the depressive symptomatology, assessed by means of the Montgomery–Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979), explained no more than 0–8.4% of the changes seen in any separate personality scale. Third, the results are in line with those of Knutson *et al* (1998) who demonstrated, in healthy volunteers, that relative to placebo, SSRI administration changed personality traits and reduced focal indices of hostility.

Ekselius, L. & von Knorring, L. (1999) Changes in personality traits during treatment with sertraline or citalopram. *British Journal of Psychiatry*, **174**, 444–448.

Knutson, B., Wolkowitz, O. M., Cole, S. W., et al (1998) Selective alteration of personality and social behavior by serotonergic intervention. *American Journal of Psychiatry*, **155**, 373–379.

Montgomery, S. & Åsberg, M. (1979) A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, **134**, 382–389.

Perris, C., Eisemann, M., Eriksson, U., et al (1979) Variations in self-assessment of personality characteristics in depressed patients with special reference to aspects of aggression. *Psychiatrica Clinica*, **12**, 209–215.

Schalling, D., Åsberg, M., Edman, G., et al (1987) Temperament traits associated with platelet MAO activity. *Acta Psychiatrica Scandinavica*, **76**, 172–182.

L. von Knorring, L. Ekselius Department of Neuroscience, Psychiatry, University Hospital, SE-751, 85 Uppsala, Sweden

Lipid supplementation in schizophrenia

Sir: We read with interest the excellent editorial by Walker *et al* (1999). However, the analogy of adrenoleukodystrophy (ALD) and schizophrenia is questionable. We would like to focus on some aspects that could be misinterpreted.

First, in ALD, prior to suggesting a dietary treatment, the causal relationship between accumulation of very long chain fatty acids (VLCFAs) and clinical symptoms had been clearly defined. ALD leads to large zones of demyelination through the accumulation of VLCFAs with a chain length of 24 or more predominantly in the adrenal cortex and the white matter of the central nervous system. Based on this pathogenetic mechanism, attempts were made to lower the levels of VLCFAs in patient tissues. In contrast, in the studies of cerebral lipid metabolism in patients with schizophrenia, there is a plethora of sometimes contradictory findings and no cause of the disorder relating to lipid metabolism has as yet been firmly established. Therefore, Walker *et al*'s suggestion that supplementation with polyunsaturated fatty acids (PUFAs) will "help to relieve schizophrenia", seems overly enthusiastic.

The second problem relates to fatty acid therapy itself. In ALD, dietary therapy is based on the observation that monounsaturated fatty acids, such as oleic acid, can interfere with the elongation of saturated fatty acids, possibly by competing for a microsomal elongating enzyme system. Erucic acid (22:1 n-9), a component of rapeseed oil, has an even greater effect. A 4:1 mixture of glyceryl trioleate and trierucate referred to as Lorenzo oil reduces the plasma levels of VLCFAs of ALD patients. Most interestingly, however, Lorenzo oil therapy results at the same time in a marked reduction in plasma levels of n-3 and n-6 PUFAs (Moser *et al*, 1992). Thus, the dietary therapy in ALD results in exactly that change in lipids that is now suggested to represent a causal factor for schizophrenia. It is this change which, according to Walker *et al*, should be reversed by supplementation.

Third, the clinical efficacy of Lorenzo oil does not warrant high-flown expectations for PUFA supplementation in schizophrenia. Lorenzo oil does not have a significant effect on the rate of progression of childhood ALD (Moser *et al*, 1992) and it was questioned whether it was taken up at all in brain tissue (Poulos *et al*, 1994). Furthermore, an unanticipated effect on platelet count limited its use (Zinkham *et al*, 1993).

The editorial conveys optimism about the potential clinical efficacy of PUFA supplementation in schizophrenia. The analogy

with Lorenzo oil therapy in ALD is deficient at best. In view of the complexities of fatty acid metabolism, more detailed studies are essential. Especially since "nutripharms are 'naturally' appealing to the general public" (Walker *et al*, 1999), one should be careful not to generate another "prematurely amplified hope" (Moser, 1993).

Moser, H.W. (1993) Lorenzo oil therapy for adrenoleukodystrophy: a prematurely amplified hope. *Annals of Neurology*, **34**, 121–122.

—, Moser, A. B., Smith, K. D., *et al* (1992) Adrenoleukodystrophy: phenotypic variability and implications for therapy. *Journal of Inherited Metabolic Disorders*, **15**, 645–664.

Poulos, A., Gibson, R., Sharp, P., *et al* (1994) Very long chain fatty acids in X-linked adrenoleukodystrophy brain after treatment with Lorenzo's oil. *Annals of Neurology*, **36**, 741–746.

Walker, N. P., Fox, H. C. & Whalley, L. J. (1999) Lipids and schizophrenia. *British Journal of Psychiatry*, **174**, 101–104.

Zinkham, W. H., Kickler, T., Borel, M. S., *et al* (1993) Lorenzo's oil and thrombocytopenia in patients with adrenoleukodystrophy. *New England Journal of Medicine*, **328**, 1126–1127.

I. Maurer, H.-P. Volz Department of Psychiatry, Friedrich-Schiller University Jena, Philosophenweg 3, 07740 Jena, Germany

Authors' reply: Drs Maurer & Volz offer a helpful overview of ALD, however they take our analogy between schizophrenia and ALD too literally. We aimed to emphasise by example the potential impact of abnormal lipid metabolism on brain function.

The purpose of our editorial was to review the evidence for and against a role of altered lipid handling in schizophrenia. We acknowledge that this is inconclusive but we argue that there is sufficient consistency to make further hypothesis-testing worthwhile. It is true that it would be premature to claim a breakthrough in the treatment of schizophrenia in spite of encouraging case reports (Puri *et al*, 1998), but it is not premature to postulate.

Puri, B. K., Steiner, R. & Richardson, A. J. (1998) Sustained remission of positive and negative symptoms of schizophrenia following treatment with eicosapentaenoic acid. *Archives of General Psychiatry*, **55**, 188–189.

N. P. Walker, H. C. Fox, L. J. Walley Department of Mental Health, University of Aberdeen, Clinical Research Centre, Royal Cornhill Hospital, Cornhill Road, Aberdeen AB25 2ZH

Pharmacokinetics of clozapine

Sir: The paper by Kurz *et al* (1998) attempted to fill a long-neglected gap in our knowledge of the pharmacokinetics of clozapine and has important implications for clinicians who use clozapine levels as a means of optimising therapy. An early paper by Thorup & Fog (1977) had suggested that intra-patient variability was marked in some patients, but that study had serious methodological flaws. Following Kurz's study we now know that patients on stable doses of clozapine may show considerable variability without clinical deterioration.

What implications does this have for clinicians? Generally, clozapine levels are used in patients who have only a partial response to clozapine, or who relapse after initially responding well. In view of Kurz *et al*'s findings, modifying the dose after checking a single clozapine level is now untenable. Measuring serial levels may be helpful in those patients who can be shown to have little variability, but these appear to be few and far between.

Kurz *et al* suggest that levels may also be useful in problem patients with levels of variability above 50%, in that these suggest poor compliance. This is a *non sequitur*. Coefficients of variability above 50% may represent poor compliance – so may coefficients below 50%. If we are to continue to use clozapine levels in problem patients, two questions need to be answered. First, is clinical deterioration related to fluctuations in clozapine levels in some patients? Second, what causes this variability?

In terms of the first point, Kurz *et al* have clearly shown that some patients will remain well, even when their levels vary widely. This may not apply to all patients: indeed, exclusion criteria are not specified in this study, but it seems likely that patients who did relapse during the course of the study were excluded for this reason. Checking regular levels in individual patients on clozapine should indicate whether or not they are sensitive to fluctuations.

The second question concerns the cause of the variability in levels. Pharmacokinetic variables are certainly one possibility. I suspect, however, that insufficient consideration has been given to the issue of compliance. Previous studies using various measures of compliance, including pill counts, clinician's estimates and interviews with patients, have assessed compliance in patients on antipsychotic medications at between 24 and 90% (Falloon *et al*, 1978; Buchanan, 1992). The wide range described probably reflects the different methods of assessment used. It is not clear how Kurtz *et al* attempted to ensure compliance, but direct questioning and clinician's judgement have generally been found to be unreliable (Cramer, 1991). If an in-patient group, whose medication was closely supervised, had much lower mean intra-individual coefficients of variation than those found by Kurz *et al*, the interpretation of variable plasma levels would be clearer and regular assessments would indeed become a useful guide in the management of problem patients.

Buchanan, A. (1992) A two-year prospective study of treatment compliance in patients with schizophrenia. *Psychological Medicine*, **22**, 787–797.

Cramer, J. A. (1991) Overview of methods to measure and enhance patient compliance. In *Patient Compliance in Medical Practise and Clinical Trials* (eds J. A. Cramer & I. A. Spiker). New York: Raven Press.

Falloon, I., Watt, D. C. & Shepherd, M. (1978) A comparative controlled trial of pimozide and fluphenazine decanoate in the continued treatment of schizophrenia. *Psychological Medicine*, **8**, 59–70.

Kurz, M., Hummer, M., Kemmler, G., *et al* (1998) Long-term pharmacokinetics of clozapine. *British Journal of Psychiatry*, **173**, 341–344.

Thorup, M. & Fog, R. (1977) Clozapine treatment of schizophrenic patients. *Acta Psychiatrica Scandinavica*, **55**, 123–126.

G. Swift Department of Psychiatry, Mater Misericordiae Hospital, University College Dublin, 63 Eccles Street, Dublin 7, Republic of Ireland

Medial prefrontal glutamine and dreaming

Sir: In their review article, Feinberg & Guazzelli (1999) proposed that malfunctioning corollary discharge and feed-forward systems in the brain could explain many of the symptoms of schizophrenia. Arguments were presented that implicated neuronal circuits involving the basal ganglia, thalamus and prefrontal cortex in this disease. Of particular interest to us were the parallels drawn between dreaming and psychosis.

Our group is using magnetic resonance spectroscopy (MRS) to study the limbic basal ganglia–thalamocortical circuit in subjects with schizophrenia. In a previous study, we found elevated levels of glutamine, a precursor and metabolite of the excitatory neurotransmitter glutamate, in never-treated patients with schizophrenia in the left medial prefrontal cortex, compared with healthy volunteers (Bartha *et al*, 1997). This is of note because the basal ganglia–thalamocortical