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.

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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.

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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.

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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

neuronal circuits utilise glutamate for neurotransmission. We are continuing to measure these metabolites in a 1.5 cm^3 volume encompassing the left anterior cingulate with MRS at 4.0 Tesla in healthy volunteers and never-treated patients with schizophrenia. The comments by Feinberg & Guazzelli regarding dreaming prompted us to examine our 4.0 Tesla MRS data with respect to the sleep/wake state of the healthy volunteer control subjects. In total, 15 healthy volunteers have been scanned to date. Of these subjects, two could not be reached. Each of the remaining subjects were asked whether they had slept during the spectroscopy study. Of these subjects, six remembered sleeping at some point during the study, six did not sleep, one person could not remember. Comparison of metabolite levels (mean (s.d.)) between subjects who remembered sleeping (n=6) and those who did not sleep (n=6) showed a significant increase in glutamine levels (9.9 (2.7) *v.* 6.1 (1.7), P=0.02) in subjects who remembered sleeping, using a two-tailed t-test. The relative glutamine increase in the subjects who reported that they were asleep was comparable to the increase previously observed in patients with schizophrenia (Bartha *et al*, 1997).

Since it is highly likely that subjects who were sleeping during data acquisition were dreaming, the increased levels of glutamine in these subjects may be due to increased glutamatergic activity in the anterior cingulate, part of the basal ganglia–thalamocortical circuit implicated by Feinberg & Guazzelli in schizophrenia. The similarity of findings between healthy subjects who were likely to be dreaming and patients with schizophrenia highlights the need for further investigation of these regions in schizophrenia.

Bartha, R., Williamson, P. C., Drost, D. J., *et al* (1997) Measurement of glutamate and glutamine in the medial prefrontal cortex of never-treated schizophrenic patients and healthy controls using proton magnetic resonance spectroscopy. *Archives of General Psychiatry*, **95**, 464–473.

Feinberg, I. & Guazzelli, M. (1999) Schizophrenia – a disorder of the corollary discharge systems that integrate the motor systems of thought with the sensory systems of consciousness. *British Journal of Psychiatry*, **174**, 196–204.

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Quick rating of depressed mood

Sir: I would like to comment on McKenzie & Marks' (1999) claims about some characteristics of their rating scale.

First, test–retest reliability was assessed by comparing self-rated single item (D1P) on its own with ratings presented in the Fear Questionnaire, one given immediately after the other. Although assessments were made at six different visits, repeated measures analysis was not used.

As the bias introduced seems substantial (e.g. lack of random order, recall, practice) the resulting distortion of estimates may be large. Additionally, the construct's time instability means that the range included the whole spectrum of values, resulting in a further inflation of Pearson's r. It is not surprising that Pearson's r was unity or near unity at each visit.

Second, they indicate that Pearson's $r=-0.54$ between D1P at discharge, and self-rated percentage improvement has predictive merit. However, 71% of the variability in self-rated percentage improvement is unexplained by D1P at discharge, and the reduction in errors of prediction is only 16% when using this information. They also conclude that pre-treatment D1P scores predict a binary category (drop-outs with low mood given as referral reason/otherwise) by referring to different means: 6.7 (drop-outs) and 3.7 (non-drop-outs). However, most pre-treatment D1P scores will not predict membership to either subset simply because of the substantial distribution overlap (s.d.=1.83 and 2.47, respectively). The positive skewness of non-drop-outs would not invalidate the latter statement as it did not seem to have seriously violated the t-test's assumptions. I conclude that D1P's predictive validity is rather low.

Third, concurrent validity was assessed by comparing D1P with D1C (same item completed by clinician), the 21-item Beck Depression Inventory (BDI), and a 'true' depression factor in the BDI (factor analysis). However, the authors used Pearson's r, a technique that does not measure agreement.

They also report a regression line with an intercept of 1.07 and a slope of 0.71, and claim interval correspondence between the BDI and D1P. Interestingly, as these values indicate no equivalence (i.e. intercept not 0, slope not 1) it could be concluded that there is lack of agreement between the scales. However, this argument is flawed because measurement error is not considered. As linear regression does not often give single values for error, it is difficult to assess comparability using this technique.

It is unfortunate that the authors have not used appropriate methods to assess agreement between measurement instruments, such as the well-known techniques proposed by Altman & Bland (1983).

Altman, D. G. & Bland, J. M. (1983) Measurement in medicine: the analysis of method comparison studies. *Statistician*, **32**, 307–317.

McKenzie, N. & Marks, I. (1999) Quick rating of depressed mood in patients with anxiety disorders. *British Journal of Psychiatry*, **174**, 266–269.

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Authors' reply: Marchevsky noted Altman & Bland's (1983) suggestions to compare two methods of measurement. These have some merit but do not change our conclusions.

Test–retest reliability was studied by comparing the D1P on its own and as one of 23 questions embedded within the Fear Questionnaire; presented at the same time were problems and targets, work/social adjustment and the Compulsion Checklist (Marks, 1986). Apart from the Compulsion Checklist all the items were rated on a nine-point scale. The order in which the two D1P modes and the other scales were rated varied (albeit non-randomly) across subjects. It thus seems unlikely that there were order effects, or that bias was introduced by practice or recall, since that would require recall of one among nearly 40 similar ratings. Not only Pearson's r but also Cohen's kappa, a chance-corrected measure of agreement, showed values close to unity.

Dr Marchevsky questions the use of Pearson's r and beta from linear regression. These equal one another (0.71 in the instance he quoted). One might debate how much an r measure of association also measures agreement. However, that r represents the degree to which variability in one