combinations of drugs and high-dose dual-action antidepressants.

We feel it necessary to point out that in our clinical experience therapeutic efficacy in resistant depression necessitates enhancement of noradrenergic neurotransmission. Drugs that increase noradrenergic neurotransmission have been shown to enhance drive, motivation and vigilance and it is clear that these are significantly impaired in those with severe depressive disorders and perhaps even more so in those with treatment-resistant depression (Weiss *et al*, 1995/1996).

Many of the 'older' antidepressants (tricyclics and monoamine oxidase inhibitors) are effective in treatment-resistant depression provided they are prescribed at sufficiently high doses; however, this incurs significant risks to the patient and is not a strategy that can be safely used on an outpatient basis because of the need to monitor antidepressant blood levels closely in order to avoid serious side-effects (Hodgkiss *et al*, 1995).

Venlafaxine displays differential effects according to dose. At low therapeutic doses it preferentially enhances serotonergic neurotransmission, whereas at higher doses it also enhances noradrenergic neurotransmission. Clinically, this is borne out to some extent by its pattern of side-effects; nausea and anxiety at low doses and an increase in blood pressure at high doses (Danjou & Hackett, 1995).

Danjou, P. & Hackett, D. (1995) Safety and tolerance profile of venlafaxine. *International Journal of Psychopharmacology*, **10** (suppl. 2), 15–20.

Hodgkiss, A. D., McCarthy, P. T., Sulke, A. N., *et al* (1995) High dose tertiary amine tricyclic antidepressants in the treatment of severe refractory depression. The central role of plasma concentration estimations. *Human Psychopharmacology*, **10**, 407–415.

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

Weiss, J. M., Demetrikopoulo, K. & West, C. H. K. (1995/1996) Hypothesis linking the noradrenergic and dopaminergic systems in depression. *Depression*, **3**, 225–245.

G. S. Malhi, A. E. Farmer National Unit for Affective Disorders, Maudsley Hospital, Denmark Hill, London SE5 8AZ

Pharmacokinetics of clozapine

Author's reply: We appreciate Dr Swift's (1999) interest in our research (Kurz *et al*, 1998). The letter posed two questions: first, is there a relationship between plasma level variability and clinical deterioration? Second, what are the causes for plasma level variability?

The first question cannot be answered from our study, as we have only included patients into the drug-monitoring programme who were on clozapine for at least 25 weeks. Relapse among patients on medication was rarely seen and did not lead to withdrawal from clozapine (Kurz *et al*, 1996). Our sample, therefore, clearly consists of positively selected patients concerning their psychopathology. On the other hand, both the in- and the out-patient course of treatment was followed. There is a lack of long-term studies on pharmacokinetics in psychopathologically stable patients. In such patients, the variability of plasma levels was not followed by changes in psychopathology.

The causes for intra-individual variations in antipsychotic plasma levels are manifold and are discussed extensively in our paper. A lack of compliance concerning drug intake is a very important issue in this respect. However, even in studies with controlled drug intake or depot medication, moderate to high inter- and intra-individual variations in plasma levels have been found. It should be pointed out that in our sample no patient showed any plasma level below measurable values, and those patients who showed high intra-individual coefficients of variation usually had only one markedly aberrant plasma level during the investigation period. This means that all patients had adequate therapeutic levels most of the time. This suggests good compliance. We are convinced that one of the main causes for stability in these patients was the treatment setting of the drug-monitoring programme that provided a good therapeutic alliance with high motivational support.

We cannot definitively answer the question of whether regular assessment of plasma levels is useful in all patients on clozapine maintenance treatment. The crucial finding in our study is that patients will remain stable *despite* a fluctuation in plasma levels, and clinicians should not worry if single plasma level measurements are within a reasonably large range of variation.

Kurz, M., Hummer, M., Oberbauer, H., *et al* (1996) Termination of clozapine treatment. *Schizophrenia Research*, **18**, 125

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

Swift, G. (1999) Pharmacokinetics of clozapine (letter). *British Journal of Psychiatry*, **175**, 288.

M. Kurz University Clinics, Department of Biological Psychiatry, Anichstrasse 35, A-6020 Innsbruck, Austria

Olanzapine and tardive dyskinesia

Sir: A recent article reported that annual tardive dyskinesia (TD) risk is significantly lower for olanzapine (0.52%) than for haloperidol (7.45%) (Beasley *et al*, 1999).

One alternative hypothesis that could account for the low reported risk for olanzapine is that the Abnormal Involuntary Movement Scale (AIMS) measurements as implemented could have been insensitive to detect true TD. AIMS training, interrater reliability, and quality monitoring procedures are not described. Assay of sensitivity for the AIMS assessments as implemented in this study to detect true TD may be available, in that TD prevalence as assessed by the AIMS at baseline could be compared with previous TD prevalence studies of patients with equivalent antipsychotic exposure. However, current TD prevalence determined on baseline AIMS examination is not reported (as distinct from historical but not current TD or from exclusion from incidence analysis because of not completing two assessments after baseline).

Alternative hypotheses for the high risk observed in the haloperidol group also are possible. Previous research on patients at similar risk because of similar 10–15 years of previous TD-free antipsychotic exposure suggests that the risk of new cases of TD on continued conventional antipsychotic is only 3% annually (Glazer *et al*, 1993). There are only five cases of TD in the haloperidol group – could some of these be false positives? The report indicates that some cases of withdrawal dyskinesia may still be contained in the data set, despite exclusion of the first six weeks of data. The Schooler–Kane criteria specified that persistent TD should not be diagnosed until 12 weeks after medication change (Schooler & Kane, 1982). Inspection of Fig. 1 suggests that some of the haloperidol cases occurred between week 6 and week 12. Analysis excluding this interval would be of interest. Another possible source of false positive TD cases could be pseudoparkinsonism or akathisia, which can be mistaken for TD (Munetz & Cornes, 1983; Cummings &

Wirshing, 1989); perhaps particularly unless emphasis is laid on training and monitoring AIMS examiners. Pseudoparkinsonism and akathisia would be expected to be more common on haloperidol.

Further studies comparing the TD risk of atypical and conventional antipsychotic medications are needed.

Beasley, C. M., Deliva, M. A., Tamura, R. N., *et al* (1999) Randomised double-blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long-term treatment with olanzapine or haloperidol. *British Journal of Psychiatry*, **174**, 23–30.

Cummings, J. L. & Wirshing, W. C. (1989) Recognition and differential diagnosis of tardive dyskinesia. *International Journal of Psychiatry in Medicine*, **19**, 133–144.

Glazer, W. M., Morgenstern, H. & Doucette, J. T. (1993) Predicting the long-term risk of tardive dyskinesia in outpatients maintained on neuroleptic medications. *Journal of Clinical Psychiatry*, **54**, 133–139.

Munetz, M. R. & Cornes, C. L. (1983) Distinguishing akathisia and tardive dyskinesia: a review of the literature. *Journal of Clinical Psychopharmacology*, **3**, 343–350.

Schooler, N. R. & Kane, J. M. (1982) Research diagnoses for tardive dyskinesia. *Archives of General Psychiatry*, **39**, 486–487.

S. W. Woods Department of Psychiatry, Yale University School of Medicine, 34 Park Street, Room B38, New Haven, CT 06519, USA

Author's reply: We appreciate the opportunity to respond to several interesting points raised by Dr Woods in his letter regarding our recent article (Beasley *et al*, 1999).

Dr Woods suggests the possibility that the reported difference in rates of development of tardive dyskinesia (TD) may have been due to the insensitivity of the assay procedure (periodic administration of the Abnormal Involuntary Movement Scale (AIMS)) to "true TD". The letter further suggests that this may have been due to the lack of systematic rater training and/or lack of interrater reliability. It is true that raters were not trained systematically nor was interrater reliability evaluated. However, for these hypotheses to be tenable, the insensitivity would have been selective for the olanzapine treatment group. Low interrater reliability is generally believed to increase variability in a random fashion and thereby create a situation where differences are more difficult to detect owing to this source random error. Further, with the haloperidol treatment group, there was clearly substantial sensitivity with our assay procedure as discussed and addressed at length in our article.

As noted in the letter, the comparison of baseline prevalence of TD detected in our study and the estimates of point prevalence for TD in the population of patients suffering from schizophrenia and with demographic characteristics similar to those of our research sample affords a method to judge the validity of our assay procedure for TD. The percentage of patients identified as having TD at baseline in our study population (defined as meeting Schooler–Kane criteria or having a history of TD recorded on their charts) was 28.8%. Kane *et al* (1988) found a point of prevalence of 23.4% across three sites. Additional studies and reviews suggest a prevalence of about 20% among patients with schizophrenia (Kane *et al*, 1980; Kane & Smith, 1982). Our baseline prevalence and the point prevalence of TD cited in the literature are comparable, suggesting at least good reliability between investigators conducting our study and the raters generating the point prevalence data in the literature described above. If the point prevalence data cited in the literature are accepted as accurately describing the point prevalence of "true TD", the concordance also suggests the validity of the ratings of our investigators.

We have acknowledged that cases identified during the initial six-week examination period may have been identified because of confounding of withdrawal phenomena. The possibility also exists that AIMS ratings were confounded by akathisia and/or parkinsonism. Dr Woods suggests that an analysis excluding that initial study period would be useful. Although not displayed graphically, such an analysis was included in Tables 1 and 3 and indicates a clear difference between olanzapine treatment and haloperidol treatment. Also, although the data were not included in the article, Barnes Akathisia Scale (Barnes, 1989) and Simpson–Angus Scale (Simpson & Angus, 1970) scores correlated poorly with the AIMS scores in our study.

We believe that we cautioned the readers of our article not to accept the absolute rate of development of TD found in our study as necessarily valid. However, the relative differences between rates of development of TD during olanzapine and haloperidol treatments in these large samples of patients would appear well established and valid.

We agree that further studies of the incidence and rate of development of TD in patients treated with typical compared with atypical antipsychotics is warranted. It would be useful to standardise frequency of observation and optimise validity and relativity of assay methods.

Barnes, T. R. E. (1989) A rating for drug-induced akathisia. *British Journal of Psychiatry*, **154**, 672–676.

Beasley, C. M., Deliva, M. A., Tamura, R. N., *et al* (1999) Randomised double-blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long-term treatment with olanzapine or haloperidol. *British Journal of Psychiatry*, **174**, 23–30.

Kane, J., Wegner, J., Stenzler, S., *et al* (1980) The prevalence of presumed tardive dyskinesia in psychiatry inpatients and outpatients. *Psychopharmacology*, **69**, 274–251.

— **& Smith, J. M. (1982)** Tardive dyskinesia: prevalence, incidence and risk factors, 1959 to 1979. *Archives of General Psychiatry*, **39**, 473–481.

—, **Woerner, M. & Lieberman, J. (1988)** Tardive dyskinesia: prevalence, incidence, and risk factors. *Journal of Clinical Psychopharmacology*, **8** (suppl.), 52S–56S.

Simpson, G. M. & Angus, J. W. S. (1970) A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica*, **21** (suppl.), SII–SI9.

C. M. Beasley Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA

Atypical antipsychotics and neuroleptic malignant syndrome

Sir: We were interested to read the article by Barnes & McPhillips (1999), particularly the paragraph about neuroleptic malignant syndrome (NMS) in which it was suggested that the newer atypicals (sertindole, olanzapine and quetiapine) have not been associated with NMS.

We are sorry to note that this is not the case. Presumably since the above article went to press, there have been at least two case reports of NMS in association with olanzapine (Filice *et al*, 1998; Burkhard *et al*, 1999) in which olanzapine was the only neuroleptic used. With regard to quetiapine we are informed (Zeneca, personal communication, 1998) that their internal safety database has established possible and definite cases of NMS associated with quetiapine usage.

Although the atypicals have been rightly celebrated for their efficacy and side-effect profiles, any drug whose mechanism of action involves the blockade and down-regulation of central dopamine receptors should be regarded as a potential cause of NMS. Clinicians should maintain as great a vigilance with the atypical neuroleptics as with the older, traditional ones.