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21 and 27 years old (all pregnancies went to term). She became pregnant again at the age of 31 and since she was treated with numerous drugs with possible teratogenic effect, abortion was recommended. The early termination of this pregnancy was successfully achieved by aspiration alone during the tenth week. Abortion was immediately followed by a manic episode with psychotic features which resolved with conventional treatment. Mrs A. experienced a fifth pregnancy at the age of 33 (to term, Caesarean section) which was associated with a manic episode with psychotic features. At the age of 35 she experienced a sixth pregnancy which stopped spontaneously at the tenth week. This spontaneous abortion was followed by a manic state. At the age of 36 she experienced a seventh pregnancy (to term) which was followed by a manic episode with psychotic features. Delivery was followed by a marked decrease in peripheral oestrogen. Peripheral oestrogen crosses the blood–brain barrier and modulates various systems of neurotransmission, especially dopaminergic transmission (Fink *et al*, 1996), and the oestrogen decrease has been hypothesised as being a precipitating factor of puerperal psychosis in predisposed individuals (Deuchar & Brockington, 1998).

The occurrence of both puerperal psychotic mania and abortion-associated psychotic mania in the same person suggests an individual predisposition, and a single aetiological mechanism can be hypothesised: abortion (spontaneous or induced) during the first trimester is followed by a marked decrease in oestrogen levels (Blazar *et al*, 1980) and the termination of all seven pregnancies was simultaneously associated with both the occurrence of acute psychotic mania and a decrease in oestrogen levels consistent with a modification of the brain oestrogen environment. This suggests that the oestrogen withdrawal hypothesis may be relevant in psychoses occurring after pregnancies that are not going to term.

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Mirtazapine withdrawal causing hypomania

Sir: Although a number of studies have reported the development of hypomania following discontinuation of antidepressant therapy (e.g. Mirin *et al*, 1981; Hartmann, 1990; Landry & Roy, 1997), this has not yet been reported for the relatively new noradrenergic and specific serotonergic antidepressant, mirtazapine.

A 65-year-old woman was commenced on mirtazapine 30 mg nocte owing to symptoms of depressed mood with diurnal variation (worse in the morning), intermittent suicidal ideation, disrupted sleep pattern, poor concentration, lack of motivation and general anhedonia. Although she derived little benefit from the medication, she remained on it for a period of five weeks at which point of her own accord, she decided to discontinue it abruptly at a time when her suicidal ideation was particularly marked. Within two days of stopping the drug, she felt dramatically better and became quite elated and mildly disinhibited, with pressure of speech, increased energy levels and a reduced need for sleep. She adopted a youthful style of dress and demeanour and offered one of the authors small gifts. At no point during this time, however, did she develop flight of ideas or any psychotic symptoms. She continues to be mildly hypomanic six weeks after drug withdrawal.

This woman had a long history of recurrent anxiety and depressive episodes. She had previously suffered a mild degree of hypomania following commencement of paroxetine in July 1998 but there is no other history of hypomania. Prior to commencing mirtazapine, she had been treated unsuccessfully with sertraline in doses up to 100 mg daily (she was unwilling to increase the dose further because of side-effects and lack of efficacy). Although hypomania has been noted to have occurred following mirtazapine augmentation of sertraline (Soutullo *et al*, 1998), the symptoms of hypomania only occurred in this case immediately after discontinuation of the mirtazapine and the two drugs were never given concurrently.

Mechanisms proposed to explain this withdrawal phenomenon previously noted with other classes of antidepressant include 'cholinergic overdrive' (Dilsaver & Greden, 1984) and noradrenergic hyperactivity (Charney *et al*, 1982), although the true reason for its occurrence remains unclear. This further report of the same phenomenon with one of the newer classes of antidepressant serves to highlight the need for further research in this area.

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Drug therapy in treatment-resistant depression

Sir: We commend the study by Poirier & Boyer (1999), comparing the efficacy of venlafaxine and paroxetine in people with treatment-resistant depression as this is a difficult sub-population in which to conduct research. However, we were dismayed that there was no discussion as to why venlafaxine should be superior to paroxetine, a finding that is indeed supported by our clinical experience in managing people with treatment-resistant depression.

The majority of our referrals with treatment-resistant depression have usually been prescribed adequate doses of tricyclic antidepressants, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors during the course of their illness. It is our practice to use augmentation strategies,

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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 out-patient 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).

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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.

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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 &