BRITISH JOURNAL OF PSYCHIATRY (1999), 174 (suppl. 38), 34–43

Critical analysis and comparison of the side-effect and safety profiles of the new antipsychotics*

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The conventional antipsychotic drugs are associated with a wide range of unwanted effects (Barnes & Guy Edwards, 1993; Guy Edwards & Barnes, 1993). These side-effects represent part of the burden of patients given antipsychotic medication, affect compliance with treatment, and contribute to the prescribing clinician's weighing-up of the risks and benefits of a particular antipsychotic in an individual case. The conventional drugs show differences in their side-effect profiles, particularly with regard to sedation and extrapyramidal problems, and it is probably a reasonable generalisation to state that these have largely governed clinicians' choice. The newer 'atypical' antipsychotics (such as clozapine, risperidone, sertindole, olanzapine, quetiapine and amisulpride) are less liable to cause extrapyramidal symptoms than the conventional antipsychotics. However, this advantage is greater for some of the new drugs than for others, and their safety profiles also differ in other key respects. Thus, in terms of side-effects and safety, each of these newer drugs must be evaluated individually.

The range of side-effects associated with the new antipsychotics overlaps with those of the conventional drugs, with problems such as sedation, dysphoria, sexual dysfunction, weight gain, adverse endocrine effects, autonomic and cardiovascular effects, anticholinergic effects and seizures, in addition to the extrapyramidal phenomena (Owens, 1996). Here we shall discuss frequency of occurrence and clinical impact of selected key problems. One limitation of a critical comparison of the side-effects of the new antipsychotics is that it depends upon the results of clinical studies conducted at diverse sites, and in patient samples with different characteristics. Further, the investigators will have used different treatment regimes and assessment instruments, although in the major controlled studies of the new antipsychotics there has been greater uniformity of choice of rating scales for both symptoms and extrapyramidal side-effects. Nevertheless, the rating scales commonly used for the assessment of other side-effects, such as the UKU (Lingjaerde *et al*, 1987), were originally designed to reflect the profile of adverse effects with conventional drugs. Lastly, few trials have directly compared the side-effect profiles of new drugs in the same patient population. In the standard efficacy studies, comparing a new drug against a standard conventional drug, the choice of the latter has generally been limited to haloperidol, or occasionally chlorpromazine.

Clozapine remains a special case, in that it is licensed for use in patients who have proved unresponsive to, or tolerant of conventional antipsychotic medication. It is for treatment intolerance that the other new drugs have competing claims for benefit. For none of the new drugs is there more than tentative evidence of benefit in therapy-resistant cases. Thus, the risk–benefit balance when prescribing clozapine for treatment-resistant patients differs from that which might apply when considering treatment because of intolerance to side-effects.

AGRANULOCYTOSIS

Agranulocytosis is relatively rare with conventional antipsychotics, with a reported prevalence between 1/700 and 1/200 000. This complication tends to occur during the first three months of treatment, and may be more common with high dosage (Guy Edwards & Barnes, 1993). The aetiology is not fully understood, but toxic depression of the bone marrow may be responsible (Pisciotta, 1978). It may occur in patients of any age, but the risk is greater in the elderly. Fever and infection may be the only symptoms, or a patient may be clinically asymptomatic when the condition is detected by haematological monitoring (Jurivich *et al*, 1987; Grohmann *et al*, 1989).

So far, there are no reports of clinically-relevant haematological toxicity affecting the use of risperidone, sertindole, olanzapine, amisulpride or quetiapine (Casey, 1996; Arvanitis *et al*, 1997). But clozapine has an increased risk of agranulocytosis (defined as a reduction in the absolute neutrophil count to below 500 mm^3) compared with conventional drugs, although with an incidence worldwide that is less than 0.8% (Umbricht & Kane, 1996*b*). Over 80% of cases occur in the first three months of treatment (Owens, 1996), the median duration before the development of agranulocytosis being 60 days. No relationship with dosage has been found, but women and the elderly seem to be more at risk, and lower neutrophil counts before the initiation of clozapine treatment may also increase the risk (Alvir *et al*, 1993; Owens, 1996). Those patients developing agranulocytosis usually show recovery within 4–21 days of stopping clozapine.

A detailed study of over 6000 patients treated with clozapine in the UK and Ireland found that 2.9% developed neutropenia and 0.8% developed agranulocytosis, with a peak incidence of both disorders in the first 6–18 weeks of treatment. Fatal agranulocytosis occurred in 0.03% (Atkin *et al*, 1996).

MOVEMENT DISORDER

The extrapyramidal side-effects (EPS), such as Parkinsonism, akathisia and dystonia, are common and disabling and accompanied by subjective discomfort and distress. They can adversely influence compliance with treatment, and confound the clinical assessment of the mental state because of the overlap between the features of these movement disorders and the symptoms of the schizophrenic illness. Furthermore, anticholinergic drugs, which are prescribed to prevent or treat EPS, have their own unwanted effects, including possibly the antagonism of the therapeutic action of antipsychotic drugs (Barnes & McPhillips, 1996). Thus, a lower liability for EPS is a clear advantage for an antipsychotic agent. The new antipsychotics have been shown to be less likely than conventional antipsychotics to cause such

*__Author's note:__ During the interval between completion of this paper and its publication, the availability of sertindole was voluntarily suspended by the manufacturer, Lundbeck Ltd, because of concerns about cardiotoxicity.

problems: clozapine (Gerlach & Peacock, 1995; Kurz *et al*, 1995), remoxipride (Chouinard, 1990; Lewander *et al*, 1990), risperidone (Bollen *et al*, 1992; Chouinard *et al*, 1993; Marder & Meibach, 1994; Peuskens, 1995), sertindole (Tamminga *et al*, 1997), olanzapine (Beasley *et al*, 1996*b*), quetiapine (Arvanitis *et al*, 1997) and amisulpride (Coukell *et al*, 1996).

Parkinsonism

Drug-induced Parkinsonism is characterised by muscle rigidity, tremor, impaired postural reflexes, seborrhoea of the face and excess salivation. In addition to the limitations on mobility, the patient suffers from decreased and slowed mental activity (Casey, 1996). The bradykinesia component, comprising features such as a lack of facial expression, paucity of gesture, and slow monotonous speech, may be mistaken for retarded depression or negative symptoms of schizophrenia.

Clozapine

In the landmark, multi-centre study of Kane *et al* (1988), which established that clozapine was a superior antipsychotic for severely ill patients with schizophrenia unresponsive to neuroleptics, EPS ratings were significantly lower in those patients treated with clozapine over six weeks, even though the patients with whom they were compared had received a combination of chlorpromazine and benztropine. Gerlach & Peacock (1995) found that patients with chronic schizophrenia treated with clozapine for an average of five years exhibited fewer signs of Parkinsonism, such as hypokinesia, rigidity and tremor, than patients receiving long-term treatment with conventional antipsychotics. Overall, 33 out of 100 clozapine-treated patients (33%) showed bradykinesia, compared with 61% of those receiving conventional antipsychotics, even though 63% of the latter group were also prescribed anticholinergic medication. Kurz *et al* (1995) reported on the EPS developing in 92 patients receiving their initial 12 weeks of treatment with clozapine, and 59 patients receiving haloperidol: the cumulative incidence rates for both tremor and bradykinesia were lower in the clozapine-treated group (24% and 22% respectively) than in the haloperidol group (39% and 48%) (although only the latter difference was statistically significant).

Risperidone

To investigate the efficacy and safety of risperidone, the major controlled trials adopted an innovative design: after a short wash-out period, a fixed dose of haloperidol was tested against multiple fixed doses of risperidone. A single daily dose of haloperidol, either 10 or 20 mg, was compared with a range of risperidone doses of 1–16 mg/day across the various studies (see Mortimer & Barnes, 1996). The large multi-centre studies of Chouinard *et al* (1993) and Marder & Meibach (1994) both found an optimum therapeutic dose of 6 mg/day of risperidone to be superior to haloperidol (20 mg/daily) in terms of EPS. For example, in the study by Marder & Meibach (1994), in 338 moderately symptomatic schizophrenic in-patients, anticholinergic medication was withdrawn on entry into the study, and the increase in EPS in the group treated with 6 mg/day of risperidone was not significantly different from that observed in the placebo group. Furthermore, the proportion of patients receiving anticholinergic medication to tackle emergent EPS did not differ significantly between the placebo group (18%) and those receiving risperidone 6 mg/day (20%). The figures for the highest dose of risperidone (16 mg/day) and haloperidol 20 mg/day were significantly higher than for placebo: 39% and 47% respectively. The relatively high level of EPS in the placebo group may be due to carry-over effects from previous medication, which would be greater with short wash-out periods of a week or less (Kerwin, 1994).

Song (1997) carried out a meta-analysis of double-blind randomised, controlled trials of risperidone and concluded that within the optimum daily dose range of 4–8 mg, fewer extrapyramidal problems are seen than with conventional antipsychotics (mainly haloperidol), and they are associated with significantly less use of concomitant antiparkinsonian medication. However, at higher doses it would seem that this advantage is lost (Chouinard *et al*, 1993; Marder & Meibach, 1994). In some studies comparing similar doses of risperidone and haloperidol, the severity of EPS has not differed significantly between treatment groups (Claus *et al*, 1992; Ceskova & Svestka, 1996), although the use of anticholinergic drugs was significantly lower in those receiving risperidone. Overall, these data suggest that the propensity of risperidone to cause EPS depends on the dose. Here it differs from clozapine, increased dosage of which is not associated with a greater risk of extrapyramidal effects.

A few clinical studies have compared risperidone and clozapine directly. In a sample of patients with a previous lack of response to, or intolerance of, conventional antipsychotics, Daniel *et al* (1996) found that risperidone (1–10 mg/day) produced equivalent benefit to clozapine (75–800 mg), but required more anticholinergic medication (benztropine) to be used. In a study of non-treatment-resistant patients randomised to risperidone 4 mg, risperidone 8 mg, or clozapine 400 mg/day, Klieser *et al* (1995) found no significant difference between the two treatment groups in ratings on the Simpson & Angus (1970) scale. However, while none of the clozapine patients required antiparkinsonian medication, two patients receiving risperidone were treated with biperiden for 'acute dyskinesia'. These findings highlight the need for direct comparison of the various new antipsychotics in carefully controlled trials, in both treatment-refractory and non-treatment-refractory patients, to gain an understanding of their relative therapeutic benefits and side-effect profiles.

Sertindole

The design common to many of the clinical trials of risperidone, using a single, fixed dose of haloperidol as the comparison treatment for a range of risperidone doses, attracted the comment that the dose of 20 mg haloperidol might be judged as above the optimum dose for the treatment of acute psychotic episodes for the majority of patients (Kane, 1994). A refinement of the design was to compare multiple fixed doses of both a new and a conventional drug. This was adopted in a multi-centre study testing sertindole in schizophrenia: three doses of the drug (12, 20 and 24 mg/day) were compared with three doses of haloperidol (4, 8 and 16 mg/day) and placebo (Tamminga *et al*, 1997). All doses of sertindole produced improvement in Parkinsonism ratings on the Simpson & Angus (1970) Scale, while all doses of haloperidol produced worsening ratings. Parkinsonism ratings for the three doses of sertindole were significantly lower than for all doses of haloperidol, and not significantly different from those of placebo. These data do not suggest any relationship between Parkinsonism and sertindole dose within the range tested in these clinical studies.

https://doi.org/10.1192/S0007125000298097 Published online by Cambridge University Press

Olanzapine

Similar findings have been reported for olanzapine. Beasley *et al* (1996*b*) compared three dose ranges of olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/day) with a single dose range of haloperidol (15±2.5 mg/day) and placebo. Patients were started on the middle dose within their assigned range, but the prescribing clinician could adjust the dose up or down as indicated. Simpson & Angus Scale ratings of Parkinsonism improved in the placebo group and in all three olanzapine dosage groups, but worsened significantly in the patients receiving haloperidol. This was despite the administration of significantly more antiparkinsonian medication (benztropine) to the haloperidol group compared with all the other treatment groups.

Quetiapine

Clinical studies with quetiapine have also indicated a low liability for Parkinsonism, with no relationship to dose within the therapeutic range (Arvanitis *et al*, 1997; Small *et al*, 1997). Arvanitis *et al* compared quetiapine in five doses (75, 150, 300, 600 and 750 mg/day) with haloperidol (12 mg/day) and placebo. During the study, Parkinsonism improved for all treatment groups except the haloperidol group. The incidence of Parkinsonism was 29% for those patients receiving haloperidol, 10% for the placebo-treated patients, and 4–8% for the quetiapine groups. This was despite the use of antiparkinsonian medication (benztropine) in 48% of the haloperidol-treated group, compared with only 14% of the placebo group and 12% of the quetiapine groups.

Amisulpride

The findings of clinical studies with amisulpride suggest that it produces EPS related to dose, although the relative likelihood of such problems is low within the recommended dose range, at least in comparison with conventional antipsychotics (Coukell *et al*, 1996; Freeman, 1997). At low dosages (300 mg/day or less), the incidence of Parkinsonism would seem to be similar to that in placebo-treated (Boyer *et al*, 1995; Loo *et al*, 1997). Speller *et al* (1997) compared amisulpride and haloperidol over one year, using a low-dose paradigm, in a sample of older, long-term inpatients. They found no significant difference in Parkinsonism between the two treatment groups at the end of the study, but the use of anticholinergic agents was significantly higher in the haloperidol group.

Akathisia

Neuroleptic-induced akathisia, characterised by mental unease and motor restlessness, is a distressing condition with an incidence of 20–45% (Barnes, 1992). The subjective discomfort experienced by patients with akathisia can prompt refusal of medication. Insomnia can be a problem for a minority of patients, who cannot lie comfortably in bed and are driven to pace around purposelessly. Although the subjective experience and restless movements have been clearly described, the condition often goes unrecognised, or is misdiagnosed as agitation or psychotic excitement.

Clozapine

Clinical studies with the new antipsychotics have generally found them to have a lower liability to cause akathisia. Chengappa *et al* (1994) reported a rate of 7% for akathisia in 29 patients treated with clozapine. The comparative study of clozapine and haloperidol by Kurz *et al* (1995) found an incidence of 6% for akathisia in the clozapine-treated patients, compared with 32% for the haloperidol group. Wirshing *et al* (1990) found that changing from a conventional antipsychotic to clozapine was effective in a case of apparently treatment-resistant akathisia. Further, Linazasoro *et al* (1993) described nocturnal akathisia in a small sample of patients with Parkinson's disease receiving levodopa; the condition improved dramatically with the addition of clozapine in relatively low dosage. Nevertheless, some investigators have found the prevalence and severity of akathisia with clozapine to be similar to that with conventional antipsychotics (Claghorn *et al*, 1987; Cohen *et al*, 1991). Umbricht & Kane (1996*b*) attribute these discrepant findings to a carry-over effect from previous medication, as the prevalence of akathisia appears to fall as clozapine treatment continues (Safferman *et al*, 1993).

Risperidone

The findings of the clinical studies with risperidone, cited above, suggest that in the optimum dose range of 4–8 mg/day, it results in a significantly lower incidence of akathisia than does haloperidol (Moller, 1996). These studies tended not to use a specific rating instrument for akathisia, but rather, items relating to akathisia within scales for extrapyramidal problems (Chouinard *et al*, 1980) and general side-effects.

Sertindole

In the seven-arm sertindole study (Tamminga *et al*, 1997), akathisia was assessed using a specific rating scale for akathisia (Barnes, 1989). The condition was present in 12% of those patients receiving placebo, while the figures reported for the three sertindole doses, of 12, 20 and 24 mg/day, were 12%, 3% and 10% respectively. The corresponding figures for haloperidol were 27%, 37% and 33%, which were significantly higher than those for placebo. The anticholinergic medication administered was 20% or less, and did not differ between the groups on the three doses of sertindole and on placebo. The figures were significantly higher with haloperidol, between 40 and 50% for all three groups.

Olanzapine

In the five-arm, placebo-controlled trial comparing olanzapine and haloperidol (Beasley *et al*, 1996*b*) the same akathisia scale was used, and showed an improvement in ratings in all olanzapine treatment groups compared with baseline, while the placebo and haloperidol groups showed a minimal worsening in ratings. While the evidence suggests that the propensity of olanzapine to cause akathisia is low (Beasley *et al*, 1996*a*; Tollefson *et al*, 1997*a*), Beasley *et al* (1996*b*) noted that agitation, nervousness and anxiety were among the most common treatment effects of olanzapine, and concluded that the cause might be drug-related. One possibility is that they reflect the subjective experience of akathisia of an intensity insufficient to provoke the characteristic restless movements that would allow a more confident diagnosis (Halstead *et al*, 1994). This is an issue that applies to the interpretation of non-specific symptoms of psychomotor activation and subjective dysphoria in clinical trials with all the new antipsychotics. For example, summarising the side-effects of risperidone, an article in *Drugs and Therapeutics Bulletin* (Anon, 1993) concluded that agitation, anxiety and insomnia were less common with risperidone than with haloperidol. These symptoms may partly reflect the

https://doi.org/10.1192/S0007125000298097 Published online by Cambridge University Press

subjective component of drug-induced akathisia in some cases.

Quetiapine

In the seven-arm study comparing quetiapine with placebo and haloperidol (Arvanitis *et al*, 1997), the Simpson & Angus Scale for EPS was modified to include an akathisia item. No statistical analysis of the results was reported, but no more than 2% of patients in any of the quetiapine-treated groups were judged to be exhibiting akathisia, compared with 10% of the placebo-treated group and 15% of those patients receiving haloperidol. A study comparing high- and low-dose quetiapine with placebo (Small *et al*, 1997), again using the Barnes Akathisia Rating Scale, found no difference in change scores between the three treatment groups.

Amisulpride

Akathisia would appear to be relatively infrequent with amisulpride. Loo *et al* (1997) found no difference in akathisia scores between low-dose amisulpride and placebo. Coukell *et al* (1996) cited a one-year tolerability study of amisulpride (200–1200 mg/day) or haloperidol (5–30 mg/day), which revealed no differences in akathisia incidence between the two drug groups.

Tardive dyskinesia

There is some evidence to suggest that those patients who exhibit acute EPS may be at greater risk of developing tardive dyskinesia (Umbricht & Kane, 1996*a*). This raises the hope that new drugs with a lower liability for acute EPS may be associated with a lower incidence of tardive dyskinesia over time. The paucity of reported cases in the literature of tardive dyskinesia developing in association with clozapine led Umbricht & Kane (1996*b*) to the view that if the condition does occur with clozapine, the incidence is significantly lower than with conventional drugs. Furthermore, preliminary data point to a lower risk of tardive dyskinesia with risperidone and olanzapine (Brecher, 1996; Tollefson *et al*, 1997*b*). However, the relatively short-term trials conducted so far do not allow any confident predictions regarding the risk of tardive dyskinesia with maintenance treatment by new and conventional drugs at optimal doses.

In a sample of patients receiving stable doses of clozapine monotherapy, Chengappa *et al* (1994) found evidence that it ameliorated tardive dyskinesia which had developed during previous treatment with conventional antipsychotics. Indeed, evidence is accumulating for the efficacy of clozapine as a treatment for tardive dyskinesia in some cases (Lamberti & Bellnier, 1993; Factor & Friedman, 1997).

CARDIAC EFFECTS

Pulse rate, blood pressure, orthostatic hypotension

All antipsychotic drugs produce antimuscarinic effects to a greater or lesser degree. These effects often remit with time. The main cardiovascular antimuscarinic effect is dose-related tachycardia, which rarely causes clinically-relevant symptoms within therapeutic dose ranges. Olanzapine, which has a low affinity for muscarinic receptors, is reported to produce no changes in heart rate compared with placebo, whereas clozapine, the most potently anticholinergic of the new drugs, produces the most pronounced tachycardia. Nevertheless, while quetiapine has virtually no muscarinic activity, tachycardia is a recognised side-effect. Risperidone and sertindole produce similar antimuscarinic effects to haloperidol (Casey, 1997).

Postural hypotension, caused by α_1-adrenoceptor blockade, has been reported with new drugs such as sertindole and quetiapine (Casey, 1997), but appears no more common with atypical drugs than with some conventional antipsychotic drugs. The problem is frequently seen with clozapine, although it rarely produces syncope or necessitates discontinuation of the drug. Allergic reactions to antipsychotics may be associated with hypertension but these are uncommon and, again, no more likely with atypical antipsychotics than with conventional drugs. More seriously, allergic myocarditis has been reported in association with clozapine, but appears to be very rare (Meeker *et al*, 1992; Jensen & Gotzsche, 1994; Lilleng *et al*, 1995).

Electrocardiogram (ECG) abnormalities

ECG abnormalities are relatively common in people receiving antipsychotics, occurring in around 25% (Thomas, 1994). Though most of these changes have previously been considered benign, there is increasing concern that prolongation of the QT interval might proceed to potentially fatal ventricular arrhythmias, particularly *torsades de pointes*. There is evidence that this arrhythmia occurs with other drugs that prolong the QT interval, such as the antihistamine terfenadine. The risks with this drug were only detected through extensive post-marketing surveillance (Josefson, 1997).

There is no consensus on the clinical significance of a prolonged QT interval related to treatment with antipsychotic medication. First, arrhythmias are rare, and other factors may be required to trigger an arrhythmia if the QT interval is prolonged (Zehender *et al*, 1991); such factors include electrolyte imbalances, coincident cardiac disease, prescribed and illicit drugs, stress, and extremes of emotion or physical exertion, including restraint procedures (Royal College of Psychiatrists, 1997).

Second, the QT interval as seen in the 12-lead ECG is an averaged measure of repolarisation across most of the ventricles. Repolarisation is itself a complex process, involving the passage of ions through several different ion channels. Preliminary evidence would suggest that different antipsychotic drugs affect different channels to differing degrees. Thus, different drugs may act in different ways upon the QT_c and some changes may be more hazardous than others.

Finally, even the rate-corrected QT interval is subject to diurnal fluctuation and to regional variation within the myocardium. QT_c, as determined by a single 12-lead ECG, may therefore be a misleading measure. For example, although the balance of cardiological opinion appears to be that the longer the QT_c, the greater the risk of arrhythmia, there are reports of drug-induced *torsades de pointes* occurring where the QT_c was within normal limits. Thus categorisation of the safety of drugs solely according to particular effects on QT_c may be simplistic.

Assessing the limited data available, members of all of the classes of the conventional antipsychotics have been reported to cause QT prolongation (Aunsholt, 1989; Lande *et al*, 1992; Thomas, 1994; Krahenbuhl *et al*, 1995). Warner *et al* (1996) found that a degree of QT_c (QT interval corrected for heart rate) prolongation (>420 ms) was significantly more common (23%) in a sample of 111 chronic in-patients with schizophrenia receiving various conventional antipsychotic drugs than in 42 age-matched, drug-free controls (2%). QT_c

https://doi.org/10.1192/S0007125000298097 Published online by Cambridge University Press

prolongation was also significantly more likely in those patients receiving mega-doses, that is, above 2000 mg chlorpromazine equivalents a day.

Some of the newer antipsychotics, such as risperidone and sertindole, also prolong the QT_c interval. In the case of olanzapine, an increase in QT_c over baseline was seen in 5% of treated patients, but the mean change was only 1.3 ms, not statistically significantly different from placebo. With quetiapine, mean QT_c increases of up to 8 ms have been seen, but there are no reported instances where the QT_c has exceeded 500 ms (Arvanitis *et al*, 1997).

In the case of sertindole, no untoward clinical consequences (specifically, no reports of serious arrhythmias) have yet been reported for sertindole administered within the therapeutic dose range, in clinical trials or in post-marketing monitoring (Ramirez *et al*, 1997; Anon, 1997). But Hale (1998) reported that two patients developed *torsades de pointes* after taking overdoses of more than 20 times the maximum recommended dose of the drug (although both made a full recovery). These patients were also receiving other medication, which was apparently implicated in the cause of the *torsades de pointes*: neither would have been eligible for the drug under the current summary of product characteristics.

The manufacturer recommends that sertindole be contra-indicated in those with pre-existing QT interval prolongation, those taking drugs known to affect the QT interval, and those with cardiac disease or uncorrected hypokalaemia. An ECG is recommended before treatment with sertindole and periodically thereafter. Where the QT interval exceeds 520 ms, the drug should be discontinued. There is continued concern regarding the potential for cardiotoxicity and life-threatening arrhythmias with sertindole, and a pan-European post-marketing study is collecting information on the safety profile of the drug under marketed conditions (Wehnert *et al*, 1997).

To summarise, questions remain about the clinical significance of QT interval prolongation with antipsychotic drugs, and the exact mechanism remains obscure. For the new drugs, the consequences may only become apparent after a period of widespread use in a broader population of patients than those participating in clinical trials. Clinicians should remain aware of the possibility of cardiac arrhythmias, particularly in those with pre-existing cardiac disease and in those taking other pro-arrhythmogenic drugs, including diuretics.

WEIGHT GAIN

All antipsychotics appear to cause weight gain, which has important implications for the general health of the patient, as obesity increases the risk of cardiovascular disease, diabetes and osteoarthritis. It may also affect compliance because patients worry about their appearance (Barnes & Guy Edwards, 1993). The mechanism of the weight gain is unknown. The serotonin antagonist activity of antipsychotic drugs may be relevant, as it causes increased oxidation of carbohydrate rather than fat, leading to stimulation of appetite and fat storage (Stanton, 1995). A mechanism involving increased appetite is consistent with a weight gain early in treatment which then stabilises. Physical underactivity may also make a contribution, though the problem appears to be greater with drugs least liable to cause EPS, such as the low-potency drugs and clozapine, than with drugs with a high liability for EPS. Heimberg *et al* (1995) reported that weight gain occurs with clozapine even after extensive pre-treatment with other antipsychotics. This suggests that the mechanism for weight gain with clozapine differs from that with conventional antipsychotic medication.

Clozapine may be particularly culpable, with at least two-thirds of patients gaining weight to a moderate to marked degree (Umbricht & Kane, 1996*b*). For example, Lamberti *et al* (1992) reported that almost half of 36 patients who were switched from their previous antipsychotic medication to clozapine gained 20 lb (9.1 kg) over the next year. Patients may continue to put on weight over the second and third years of clozapine treatment.

Weight gain is also a recognised problem with risperidone, sertindole and olanzapine. Casey (1996) noted that patients receiving these drugs in clinical studies gained an average of 1–4 kg in the first two months, and some will continue to gain weight subsequently. In a multi-centre study, weight gain occurred in all risperidone-treated groups across a range of doses from 1–16 mg/day (Peuskens, 1995). At doses of risperidone 8 mg/day and higher, the weight gain was significantly greater than that seen with haloperidol at 16 mg/day (Umbricht & Kane, 1996*b*). On long-term treatment with olanzapine, at starting doses of 10 mg/day or more, patients manifested an average gain of 12 kg over the next year, with 20% increasing their bodyweight by 7% or more from baseline, compared with 5% of patients treated with haloperidol (Casey, 1996; Beasley, 1997). With quetiapine, mean weight gains of 1.4–4.5 kg were observed over a six-week trial period (Arvanitis *et al*, 1997), which was a greater increase than that seen in the haloperidol or placebo groups. In another clinical trial of quetiapine lasting six weeks, Small and colleagues (1997) reported bodyweight pain of 7% or more in 25% of those in a high-dose group (250–750 mg/day).

SUBJECTIVE BURDEN

Patients often complain of subjective experiences of medication which are difficult to describe and quantify, and hence difficult to rate reliably. Non-specific complaints such as "feeling like a zombie" have been incorporated in the so-called 'neuroleptic-induced deficit syndrome' (Lader, 1993), which may partly reflect the psychological components of EPS. As yet, there is no agreed way to distinguish such symptoms from depressive features, the unrest of subtle akathisia, the mental aspects of drug-induced Parkinsonism, and negative symptoms of the psychotic illness itself. However, the implications for the tolerability of long-term therapy may be considerable (Barnes & McPhillips, 1995). Until comparative study designs include more detailed and refined assessments of subjective elements, confident statements about the relative impact of sedation and fatigue with atypical drugs will be impossible.

Sedation may be variously assessed by measures of excessive sleeping, difficulty in waking, daytime sleeping or daytime torpor. The use of such terms may reflect the inherent bias of clinical trials towards phenomena which can readily be measured objectively by direct observation or by simple questioning. Judged by these criteria, the sedation induced by atypical drugs appears comparable to that induced by low-potency antipsychotics, such as chlorpromazine. A summary of the side-effects of risperidone in the *Drug and Therapeutics Bulletin* (Anon, 1993) concluded that sedation occurs in about 25% of patients receiving risperidone, headache in 20% and nausea in 9%. The effect is usually attributed to blockade of central histamine and α-adrenergic receptors.

Owens (1996) has observed that a state of emotional dissociation, or ataraxy, was observed from the very outset when chlorpromazine was given to humans, and that the dissociation of the patient's emotions from the external world was then regarded as desirable as an acute effect. However, this phenomenon may be experienced as a distinct handicap in maintenance therapy. The poorly-circumscribed sensation of emotional dissociation is a subjective experience which may be unrelated to effects on sleep or sleepiness, but which is communicated as a state of fatigue, or tiredness. Such a report from a patient is often rated objectively in terms of a need to rest rather than by its subjective aspects.

The literature concerning patients' perceptions of their burden of illness and of the side-effects of medication is slight. But the patient's assessment of the benefits and disadvantages of treatment may be a crucial determinant of compliance with medication. Fleischhacker *et al* (1994) observed a lack of concordance between the burden of objectively-rated extrapyramidal symptoms and compliance with antipsychotic medication. By contrast, akathisia and subjective dysphoria, which are side-effects diagnosed by asking the patients about their subjective experience, may strongly predict future non-compliance (Van Putten & May, 1978; Awad & Hogan, 1994). A recent cross-sectional study reported better scores for subjective quality of life among in-patients maintained on clozapine and risperidone than in matched in-patients receiving conventional antipsychotic drugs (Franz *et al*, 1997). Such studies must be interpreted with great caution, as the factors which lead to patients being selected for atypical drug treatment may include intolerance to the adverse effects of conventional neuroleptics, and superior social performance. Prospective studies are required, in which patients are randomised to optimal treatment with either group of drugs.

SEXUAL FUNCTION

A general problem in assessing clinical trials in this area is that sexual side-effects are often not reported at all, or are assessed by a general enquiry about adverse effects rather than by employing a systematic rating instrument. Monteiro *et al* (1987) observed that most patients report side-effects only when asked directly and specifically, and not in response to simple questionnaires. What studies do exist refer far more frequently to sexual dysfunction in males (Barnes & Harvey, 1993), and rarely compare atypical drugs with conventional neuroleptics or placebo. Though most drug-induced sexual problems are reversible when the drug is discontinued, most patients are treated for long periods, so that unwanted effects in this area may represent a considerable burden. Moreover, the sufferer may only become aware of a problem after the acute illness has subsided and normal relationships are resumed during the maintenance phase of treatment.

Loss of sexual drive is a relatively common problem, but assessment is confounded by the fact that patients with schizophrenia report generally decreased sexual activity, compared with controls (Aizenberg *et al*, 1995). Elevated plasma prolactin levels are thought to be a contributory factor, although clozapine does not elevate prolactin at any dose, and sertindole and olanzapine produce rises which are usually within the normal range (Casey, 1996). Similarly, the information available from clinical trials with quetiapine suggests that it does not induce hyperprolactinaemia. However, both amisulpride and risperidone cause a dose-related rise in prolactin, as seen with conventional antipsychotic drugs.

Male sexual dysfunction

The physiological bases of penile erection and of ejaculation are unclear. Alpha-adrenergic blockade may affect ejaculation and both muscarinic blockade and α-adrenergic blockade may interfere with penile erection (Barnes & Harvey, 1993). Of the new drugs, sertindole seems particularly prone to cause ejaculatory dysfunction, which is apparently distinct from the retrograde ejaculation typically seen with conventional drugs. Around 20% of men receiving this drug experience no or decreased ejaculate during treatment, although sperms are still produced, and there are no effects on libido, erection or orgasm. The effect reverses when the drug is discontinued (van Kammen *et al*, 1996).

The sexual effects of the new antipsychotics are seldom independently reported in detail. Nevertheless, the product information for olanzapine quotes erectile impotence in 0.7%, abnormal ejaculation in 0.2% and anorgasmia in less than 0.1% of male patients. These data compare favourably with those for haloperidol in direct comparative studies. Information from the same source suggests that priapism affects 0.1% of men treated with olanzapine. This complication has been reported with a large number of conventional neuroleptics but appears to be generally uncommon. Alpha-adrenergic blockade has been proposed as a cause, though it is also cited as a cause of erectile impotence (see above), and the explanation is likely to be complex (Barnes & Harvey, 1993).

Female sexual dysfunction

The pathophysiology of sexual dysfunction in women is even less well understood than in men. Further, women tend to be far less frequently represented in clinical trials than men. A variety of disorders have been tentatively attributed to serum prolactin elevation (a common effect of antipsychotic drugs), including loss of libido, dysmenorrhoea, menstrual irregularities and amenorrhoea, breast swelling and tenderness, and lactation. Most of the new drugs are reported to cause lower prolactin elevations than do conventional neuroleptics (see above), so such effects might be supposed to be less common (Casey, 1997). However, adequate data comparing actual side-effects of atypical drugs with placebo or with conventional antipsychotics are lacking.

Within the limitations of the available data, it seems that adverse effects on sexual function are no more common with atypical drugs than with conventional neuroleptics. An exception is the unexplained reduction in ejaculatory volume seen with sertindole, which is, however, reversible. Unwanted effects on sexual function are rarely declared by the patient as a sole reason for discontinuing therapy, though in the absence of adequate data, it is possible that some patients may decide not to comply with treatment in the long term for this reason.

MISCELLANEOUS SIDE-EFFECTS

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a rare but potentially lethal adverse effect that has been reported with most known antipsychotic drugs, including clozapine and risperidone among the new drugs (Umbricht & Kane, 1996*b*). There are, as yet, no reports of NMS in association with sertindole, quetiapine or olanzapine.

https://doi.org/10.1192/S0007125000298097 Published online by Cambridge University Press

Seizures

Antipsychotic medications are reported to increase the risk of epileptic seizures, though this has not been rigorously tested for most conventional antipsychotics. With clozapine, the risk is undoubtedly higher than with conventional antipsychotics, with a risk of seizure of around 1% in those treated at doses below 300 mg/day, 2.7% at doses between 300 and 599 mg/day and 4.4% at doses of 600 mg/day or greater (Umbricht & Kane, 1996*b*). While seizures clearly seem to be dose-related phenomena, our clinical experience suggests that the rate of increase of dose and amount of individual increments may also be relevant. Most patients who experience a tonic–clonic seizure are able to continue on clozapine after a dosage reduction, a gradual re-challenge or the addition of an anticonvulsant. Myoclonic seizures, manifesting as 'drop-attacks' without loss of consciousness, or progressing to generalised seizures, have also been reported with clozapine treatment (Devinsky & Pacia, 1994). Risperidone, olanzapine, quetiapine and sertindole have shown no increase in risk of seizures when compared with haloperidol or placebo.

Urinary incontinence with clozapine

Although an association has been noted between incontinence and various conventional antipsychotic drugs (Pollack *et al*, 1992), incontinence is not recognised as an established side-effect and no data are available regarding its frequency, severity or duration. With clozapine treatment, Kuchenhoff (1993) found enuresis in up to 2.4% of patients, while Merschel *et al* (1993) reported an incidence of 8.5%. Fuller *et al* (1996) investigated urinary incontinence in a sample of 57 treatment-refractory patients treated with clozapine (75–900 mg/day); 17 showed some evidence of it; and it was more likely in women and in those receiving concomitant treatment with a conventional antipsychotic. Warner *et al* (1994) assessed 12 patients established on a therapeutic dose of clozapine and found that five had experienced nocturnal incontinence, which occurred in the first three months of treatment and resolved spontaneously. Patients had been embarrassed by the problem, and reluctant to report it, so it was often unrecognised by clinical staff. Specific enquiry may be necessary to identify incontinence during the early phase of treatment, so that the problem can be discussed and reassurance provided.

Hepatic transaminase rises

Abnormalities in liver function test have been associated with antipsychotics since their advent. Cholestatic jaundice has been reported mainly with older drugs, with a latent period of 2–4 weeks after their commencement. It may have been due to an impurity in the drug manufacture, as it is much less often reported now (Guy Edwards & Barnes, 1993). An hepatocellular disorder, resembling viral hepatitis in its effects on the liver, has been reported with a much wider variety of antipsychotics. This adverse effect is usually subclinical, abnormality being identified only on biochemical screening. In four safety studies, olanzapine produced transaminase rises in around 9% of those treated, a significantly greater proportion than affected by the reference drug haloperidol in comparative trials; the rise occurred in the first two weeks of treatment and peaked at four weeks. There were no clinical symptoms of liver dysfunction and the test results gradually returned to baseline in most cases (Beasley, 1997). Where olanzapine was discontinued, the transaminase returned to normal in every case. Risperidone, quetiapine and sertindole cause similar transaminase rises, but no more frequently than haloperidol (Casey, 1996; Arvanitis *et al*, 1997).

Thyroid hormone abnormalities

In two clinical trials (Arvanitis *et al*, 1997; Small *et al*, 1997), each lasting six weeks, quetiapine was found to produce dose-dependent decreases in thyroid hormone levels, particularly total and free T4 concentrations. However, there was no accompanying change in thyroid-stimulating hormone, and no clinical hypothyroidism was detected. In the seven-arm treatment trial (Arvanitis *et al*, 1997), these changes occurred within a few days of the commencement of quetiapine, but were not progressive over the course of the study. In the higher dose ranges, smaller decreases in total T3 and reverse T3 were also noted. The mechanism of the effect remains unclear. Long-term treatment data have not yet been published.

Nasal congestion

Nasal congestion has been reported to affect over 20% of those taking sertindole. The effect rarely provokes discontinuation of the drug (Casey, 1996).

CONCLUSIONS

To demonstrate the therapeutic and safety advantages of the new, so-called atypical, drugs over conventional antipsychotics, more sophisticated methodologies have been introduced into clinical assessment. In particular, atypical drugs have a different occupancy of the D_2 and other dopamine receptors, necessitating testing across a range of doses against conventional antipsychotics to ensure fair comparison of therapeutic and unwanted effects. This, in addition to ever-increasing safety requirements, means that the new drugs have undergone a level of evaluation and scrutiny beyond that applied to antipsychotic drugs in the past. Though criticism has been made of the shortcomings in study designs in this area, it is apparent that trial methods are in a state of continuing evolution. Further, given the time required to conduct and report a large multi-centre study, it is inevitable that current debate will sometimes concern outdated methodologies.

Regarding the choice facing clinicians, clozapine remains the only drug licensed for treatment resistance in schizophrenia. Its adverse effect profile is relatively well known, and its propensities to cause weight gain, hypotension, hypersalivation and seizures in the higher dose ranges appear as great as, if not greater than, those of conventional antipsychotics. Coupled with a liability to cause agranulocytosis, this formidable array of adverse effects is counterbalanced by a very low liability to cause EPS. Nevertheless, because of the disability caused by resistant schizophrenia, such a side-effect profile is accepted by many patients because of the unique opportunity of a response to treatment.

For patients who cannot tolerate adverse effects, notably EPS, risperidone, sertindole, quetiapine, olanzapine and amisulpride represent genuine alternatives to conventional drugs and to clozapine, being at least as affective as conventional antipsychotics, with a different adverse effect profile. Risperidone shows a low incidence of EPS within its optimum dosage range, and sertindole, quetiapine and olanzapine are largely free from such effects

across their suggested therapeutic dose ranges. However, these new drugs do have individual idiosyncratic adverse effects, such as the reduction in ejaculatory volume and the ECG changes seen with sertindole, the transient rise in liver transaminases seen with olanzapine and the changes in thyroid hormones observed with quetiapine. All the atypical drugs appear to cause appreciable weight gain, which may be through a different mechanism to that seen with conventional drugs.

An important limitation applies to the assessment of trials involving these drugs: different side-effects does not necessarily mean less burdensome side-effects. Even though the evidence points to better tolerance and acceptance of these new drugs by patients, the rating scales developed to assess conventional antipsychotics may fail to capture significant subjective domains of unwanted effects such as subjective dysphoria, sedation, long-term weight gain and effects on sexual function. The availability of atypical drugs for use in more patients should prompt the introduction of new instruments, or the modification of existing scales, to include ratings of subjective burden, for the assessment of adverse effects (Bhavnani & Levin, 1996). Without the results of long-term randomised comparative studies using such instruments, it is premature to assume that fewer EPS necessarily means improved quality of life or better compliance for the majority of patients. Nevertheless, if it can be demonstrated that the threat of tardive dyskinesia is appreciably reduced with such agents, the improved long-term risk–benefit balance would be relevant to clinicians' choice of antipsychotic for first-episode schizophrenia and use in early intervention. Though no serious, rare or delayed problems are apparent from the trials of atypical drugs conducted so far, such may yet be discovered.

DECLARATION OF INTEREST

Professor Tom Barnes has received lecture fees and travel grants from Eli Lilly. Dr Mike McPhillips has received no funding.

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https://doi.org/10.1192/S0007125000298097 Published online by Cambridge University Press

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https://doi.org/10.1192/S0007125000298097 Published online by Cambridge University Press