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Management of Treatment Resistant Schizophrenia Unresponsive to Clozapine

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A recent challenge in schizophrenia has been the management of patients who have failed to respond not only to standard therapeutic regimes but also to trials of atypical neuroleptics such as clozapine and risperidone. This article focuses on the further psychological and pharmacological management of such patients.

Reasons for an inadequate response to clozapine

While clozapine may be effective to some degree in up to 70% of patients with treatment refractory schizophrenia, some will fail to benefit. A follow-up study of patients treated for up to 12 years found that between 47 and 63% were unimproved (Povlsen *et al*, 1985). The management of this problem is best considered in the light of the reason for clozapine failure. A thorough reassessment of the case is often helpful, both to identify particular target symptoms and behaviours in need of modification, but also more fundamentally to review the diagnosis. Our experience is that a significant proportion of patients with refractory schizophrenia have a considerable (and hitherto unrecognised) affective component. This has implications for treatment with antidepressants, lithium and ECT, as adjuncts to either standard neuroleptics or, more rarely, clozapine (see below).

Comorbid drug use

Another important diagnostic issue is that of comorbid drug abuse, which may be associated with an earlier onset of the schizophrenic illness, increased positive symptomatology, a greater risk of relapse, poor compliance, violent behaviour and a forensic history (Breakey *et al*, 1974; Tsuang *et al*, 1982; Negrete *et al*, 1986; Buckley *et al*, 1994; Mulvey, 1994; Linszen *et al*, 1994; Smith & Hucker, 1994). This complication may be relatively common in samples of patients with neuroleptic unresponsive schizophrenia. Of the last 50 such patients (mean age 33.1, s.d. 9.2) admitted to our service, 16 (32%) had a history of past or current alcohol or substance use. The corresponding figure in a sample of 118 patients (mean age 34.0, s.d. 10.7) with treatment resistant schizophrenia or schizoaffective disorder, studied by Buckley *et al* (1994) was 25%.

These patients are increasingly a focus of research (Duke *et al*, 1994; Linszen *et al*, 1994; Smith & Hucker, 1994) but the dynamic between continuing schizophrenic symptoms, neuroleptic side-effects and a patient's self-medication with illicit drugs remains unclear (Schneier & Siris, 1987; Duke *et al*, 1991). If there is this dual diagnosis, then not only may a specialist drug service be helpful but also the symptomatology seems to be rather different, with more dysphoria and frank post-psychotic depression (Siris *et al*, 1991). Nevertheless, the clinical response to clozapine in patients with comorbid substance use may be equivalent to that in patients without such a problem (Buckley *et al*, 1994). Siris *et al* (1991) suggested that an adjunctive antidepressant may be helpful in the chronically dysphoric schizophrenic drug abuser.

Poor compliance

Noncompliance (direct and indirect) can be either overt or covert. Psychiatrists accept that this is a perennial problem, occurring in up to 50% of patients with schizophrenia prescribed antipsychotic medication (Babiker, 1986; Bebbington, 1995). Mann (1986) estimated that around a third of schizophrenic out-patients fail to comply accurately with their medication, and even higher figures have been reported for those maintained solely on oral medication. Even among in-patients, figures for noncompliance of between 10 and 30% have been reported.

Poor adherence to the treatment regime is as much an issue with clozapine as it is with other oral preparations. In a study of clozapine plasma levels

and response, Potkin *et al* (1994) found some extremely low levels, suggestive of covert non-compliance. This was despite the fact that the patients had consented to participate in the study and would, therefore, be considered relatively cooperative (Bowen & Barnes, 1994). The presence of side-effects such as hypersalivation may be a rough and ready way of judging whether a patient is taking clozapine, but plasma drug levels are more reliable and informative. With in-patients, one simple strategy to minimise poor compliance is to present the tablets crushed. On our unit all patients receive clozapine crushed from the start. This is principally to avoid the problems associated with the possible abrupt but covert onset of either compliance or noncompliance at a later stage, when the dose has reached the therapeutic range.

One difficult situation that arises is when a patient, known to be refractory to all antipsychotic medication except clozapine, stops taking clozapine and relapses.

During the psychotic episode they may refuse to take oral medication, and the intramuscular administration of standard neuroleptics is unlikely to be of benefit. The reasons for refusing to restart clozapine may include a lack of insight into the need for treatment, uncertainty about the benefits in relation to their perception of the potential hazards of clozapine and the severity of their illness, or a particular fear of phlebotomy. If the last is the main stumbling block, then other drug treatments requiring blood tests, such as lithium or an anti-convulsant, are also excluded.

In such a situation, there are two possible therapeutic options, both of which require careful consideration by the clinical team. Both require the patient to be detained under a Section of the Mental Health Act (1983) and to have had a second opinion from the Mental Health Act Commission regarding the planned treatment. The first is to give clozapine and take the necessary blood samples despite the patient's reluctance. The prevailing view is that if both the stated conditions are fulfilled, and the haematological monitoring is part of a treatment programme, then this is permissible, although ultimately the decision of the responsible clinician. The second option is to give a course of ECT to gain a temporary improvement, which may be capitalised on to restart clozapine (Safferman & Munne, 1992; Green *et al*, 1994). Our experience of both these options is that they can be effective when nothing else has worked, but the possible benefits need to be weighed against the potential risks, which include damage to the therapeutic relationship with staff.

A proportion of patients will comply poorly with clozapine after discharge from hospital. Meltzer (1992) reported an incidence of noncompliance of 19% in his clinic, two-thirds of which occurred within the first three months. There is no easy solution to this problem, which in our experience can be encountered even in patients who admit they have derived more benefit from the drug than any previous prescription. It seems to be a particular problem where side-effects are intolerable, or the psychotic symptoms themselves are in some way pleasurable or rewarding. Plasma levels of the drug may be helpful in as much as they alert the clinician to the problem and, in this patient group, the prospect of incipient relapse.

Psychological approaches to address non-compliance

A major reason for noncompliance with clozapine, as with other medication, is denial of illness, a denial that may be inevitable when delusional beliefs are held with complete conviction. Cognitive–behavioural therapy (CBT) may be effective in helping patients to take an objective position with respect to their psychotic experiences, enabling them to re-attribute them from a delusional explanation to an 'illness' explanation. At this point the subject of medication to treat the illness becomes a meaningful one for discussion, and education about the illness and medication becomes feasible. Even where it is not possible to change the patient's lack of insight, we have found that it may be possible to achieve compliance by adopting a purely pragmatic approach, exploring the advantages and disadvantages of taking the prescribed medicine. In order to adopt the required neutrality with respect to medication that this approach requires, it is better for the therapist to be someone other than the prescribing doctor or key worker who may, in those roles, be required to persuade/instruct the patient to take medication.

A common problem encountered in medication compliance work is that the patient does not accurately recall what it was like when he was ill or when he discontinued his medication, so the advantages of being on medication cannot be appreciated. Before an appropriate cost–benefit analysis can be conducted this information must be obtained from case notes or from people who knew the patient during these times, and this information must be accepted by the patient. This aspect of the work can take many weeks to achieve. It sometimes happens that when the cost–benefit analysis is done the patient agrees that he is better on medication, but his rationale for taking it is

quite different from that of the prescribing doctor (for example, "The medication keeps away the poisonous dust that muddles my mind"). Although we are always careful to explain why we believe the medication to be useful, we do not demand acceptance of this explanation, rather we stress our agreement about the end result of medication being beneficial.

A major factor in compliance with medication is the quality of the relationship with the mental health care workers. For example, it is our impression that some patients who deny illness will nevertheless take the medication prescribed if they trust the doctor and clinical team looking after them and believe that they are knowledgeable and have the patient's best interests at heart. This would imply that modification of negative beliefs about the clinical team would improve the chances of medication compliance: this hypothesis is currently the subject of a research project we are conducting.

It is our common observation that a patient who is resistant to all interventions on a busy acute ward can become generally better engaged, and more compliant with medication, within a period of transfer to our medium stay unit. The task of the team is then to ensure that this compliance is continued after discharge from the unit. Taking medication may be seen as part of the role of being an in-patient but incompatible with that of community resident. A number of patients will argue that medication equates with being ill, and so being well must equate with no medication, and therefore discharge, which equates with being well, must equate with stopping medication. It is clearly necessary to break this line of reasoning if compliance after discharge is to be achieved, and we have found that this is best done by education within a CBT framework.

The unit is highly staffed and there is time to explore a patient's knowledge and beliefs about their illness and its treatment. A trusting relationship with a key worker can be developed, within which there is education about the role of medication and the need to continue it when well. The team also seeks to broaden the focus of care so that the patient perceives medication as only one aspect of a treatment and rehabilitation programme.

Inadequate duration of treatment with clozapine

It is important not to abandon a trial of clozapine prematurely as some patients may have a delayed response. Fitton & Benfield (1993) reviewed the relevant studies and concluded that a six-week treatment period was probably inadequate to attain the maximum therapeutic benefit. They considered that six to 12 months of treatment might be necessary before it was appropriate to discontinue clozapine on the basis of insufficient response. Meltzer (1992) concluded that a therapeutic response to clozapine would be seen in 30% of treatment-resistant schizophrenic in-patients within the first six weeks, but a further 20% would respond by three months of treatment and an additional 10–20% would respond by the end of six months. Such a view would seem to hold true for improvement in both psychopathology and social functioning, according to the results of recent, uncontrolled studies of patients with chronic schizophrenia (Wilson, 1992; Johnson *et al*, 1994).

Breier *et al* (1993) in their descriptive study of clozapine treated patients over the first year of treatment, found that the great majority of patients (17 out of 18) who were going to meet the criteria for response had done so by four months. However, whereas the BPRS scores had reached a plateau at six months in the responders, the quality of life rating showed no improvement at six months but a trend by 12 months. This suggests that perseverance with clozapine is warranted even if the initial improvement is not immediately translated into better global function.

Inadequate dosage

A number of studies have looked at plasma levels of clozapine to examine any correlation with response. The initial studies did not support the idea of a threshold level for the drug to be effective. However, more recently, several studies using a fixed dose, prospective design have all found more or less similar threshold levels for response, around 450 ng/ml (Perry *et al*, 1991; Meltzer, 1992; Potkin *et al*, 1994). Potkin *et al* found that 60% of patients above this level had responded at four weeks as opposed to 8% of those below it. At this point in the trial half the patients were randomly allocated to a doubling of the clozapine dose, from 400 to 800 mg a day. Of the patients who had been below the plasma threshold level on the lower dose, a third achieved this level in the second part of the study: 25% of these patients improved as opposed to 9.5% of the patients who remained below the threshold level.

Plasma levels may be particularly relevant in patients also receiving medication that can induce hepatic metabolic enzymes and thus lower clozapine levels (Miller, 1991).

Adverse effects

Poor compliance may be related to intolerance of side-effects, particularly sedation and excessive salivation. Many patients have found clozapine-induced hypersalivation to be particularly ignominious, and been distressed by finding their pillow soaked in saliva in the morning. The mechanism is unknown, and the problem is often difficult to treat, although there are reports of successful treatment with amitriptyline (Copp *et al*, 1991) and clonidine (Grabowski, 1992). Enuresis is another embarrassing problem, seen early in treatment. Patients can be reassured that this is usually transient (Warner *et al*, 1994).

One serious side-effect of clozapine is the development of seizures. The incidence of clozapine related fits has been variously estimated at between 0.8 and 20% (Welch *et al*, 1994). The reasons for this wide range across patient samples include differences in patient selection, the drug doses used and the duration of treatment. Pacia & Devinsky (1994) reviewed clozapine-related seizures in over 5000 patients monitored during the first six months after the drug was introduced in the United States, and found an incidence of 1.3%. Such seizures were found in those receiving low doses in the titration phase and administered high doses during the maintenance phase. Rechallenge with clozapine, usually attempted under anticonvulsant cover, at reduced dosage or with more gradual dose increase, was generally successful. The cumulative incidence of seizures over time is likely to be greater, and has been estimated at 10% over 10 years of therapy (Devinsky *et al*, 1991).

If seizures occur, then the advice of the Clozaril Monitoring Service (CPMS) is that clozapine should be stopped for 24 hours and then restarted at 50% of the dose. Welch *et al* (1994) looked at a group of patients who had developed fits while receiving clozapine. They managed to avoid further seizures in this sample by titrating the dose against electroencephalogram (EEG) findings.

If the problem seems to have been either one of individual patient susceptibility or related to a high maintenance dose, then anticonvulsant cover is probably indicated. Sodium valproate is the choice of anticonvulsant in this situation, as carbamazepine is contraindicated because of its potential for causing agranulocytosis. Phenytoin is also inadvisable as it induces the hepatic metabolism of clozapine, leading to a decrease in the plasma level (Kando *et al*, 1994). Although it has sometimes been suggested that patients receiving a daily dose of more than 500 mg a day should have anticonvulsant cover routinely, the CPMS do not recommend this practice. It is perhaps better to make a clinical decision based on the individual patient, their history, and whether they are receiving any other threshold lowering drug concurrently (Toth & Frankenberg, 1994).

Adjunctive treatments

Antidepressants

Depressive symptomatology is a common accompaniment of schizophrenia, as are its consequences such as deliberate self-harm. Depression influences the level of social functioning which the patient achieves and not to recognise it might be to see treatment nonresponsive schizophrenia where schizophrenia is lying side by side with depression. Research in the area of intercurrent and post-psychotic depression has been predicated on the assumption that depressive symptoms may represent a reaction to the experience of being psychotic, be part of the core symptomatology of the condition, or a misinterpretation of negative symptoms or drug side-effects (Hirsch *et al*, 1990). However, researchers looking carefully at the phenomenology of schizophrenic depression find themselves able to distinguish it not only from medication side-effects but also from negative symptomatology (Siris *et al*, 1988; Kibel *et al*, 1993).

Koreen *et al* (1993) followed 60 first-episode patients with schizophrenia for up to five years. When psychotic, 26% were also depressed, but when in remission, only 4% were depressed. Of those who were depressed when psychotic, the depressive symptomatology lifted with the resolution of the psychosis in 98%. This issue has been further examined by the same group in a placebo-controlled, follow-up trial of imipramine in 24 schizophrenic or schizoaffective patients with postpsychotic depression that had initally proved responsive to the antidepressant (Siris *et al*, 1994). These investigators found that those subsequently receiving placebo were significantly more likely to suffer either depressive or psychotic relapse within the one year follow-up period. This suggests that depressive features might form part of the core symptomatology of schizophrenia and that antidepressants may prevent psychotic relapse. While this is an intriguing proposal, the mixed diagnoses of the group under study should be noted. Nevertheless, where depressive symptoms are persistent in patients with schizophrenia, a six week trial of an adjunctive antidepressant should be considered (Siris, 1993). Unfortunately, there are no systematic

research findings to guide the clinician to a particular class of antidepressant drug.

Carbamazepine

Carbamazepine appears to be a useful adjunctive treatment in schizophrenia. However, there is as yet no consensus as to which patients may benefit, either by indices of organicity or by virtue of specific psychopathological symptoms.

There have been about a dozen trials of carbamazepine in schizophrenic patients. These have been of varying design and quality, and of these only four have been double-blind placebo-controlled trials. Numbers have ranged from an early negative trial involving only two patients (Stevens *et al*, 1979) to a study sample of 43 patients (Klein *et al*, 1984). Nine studies in the English language literature have been reviewed by Schulz *et al* (1990). EEGs were carried out in only six of these investigations, and in only three were patients recruited with abnormal EEGs. Two studies used patients with normal EEGs and only one study contained a mixed sample, finding that the two groups did not show a differential response to carbamazepine. The other studies are those of Wetterling (1987), an open trial of carbamazepine as adjunctive treatment in chronic schizophrenics in a long-stay ward, which showed improvement in the BPRS items excitement and tension; as well as two trials of carbamazepine as monotherapy (Sramek *et al*, 1988; Carpenter *et al*, 1991) neither of which support this as a viable treatment option.

Eight studies have been carried out on chronically unwell patients, some of the studies recruiting from long-stay institutions. It is therefore perhaps promising that most of these studies reported a positive result. There is very little consistency as to the nature of the patients' improvement. Of those trials which demonstrated a benefit in the treatment period, two studies reported a general but non-specific decrease in BPRS score, two reported a decline in schizophrenic or 'psychotic' features, three showed a lessening of affective disturbance, and three studies reported a reduction in violent or aggressive behaviour, or a lessening of withdrawal/autistic features and an improved engagement with those around them (Schulz *et al*, 1990).

The design of clinical trials in this area has been influenced by the idea of a syndrome of episodic dyscontrol (Maletzky, 1973), a category in which to place unprovoked aggressive behaviour accompanied by quasi-epileptic phenomena and non-specific abnormalities on the EEG, usually involving the temporal lobe. It has been reported that carbamazepine is effective in treating such patients (Stone *et al*, 1986). Many of the trials of carbamazepine in schizophrenia have recruited violent patients. Of the nine studies reviewed by Schulz, four were of patients specifically labelled as violent and one recruited cases with an 'excited' psychosis. The common opinion that carbamazepine may be uniquely suitable for those schizophrenics with behavioural disturbance and an abnormal EEG may be partly a reflection of the assumptions which lay beneath the original studies in this area.

Carbamazepine is a powerful inducer of the hepatic microsomal enzyme oxidation system, and several studies have demonstrated that carbamazepine lowers plasma neuroleptic concentrations, estimated variously at 50% (Kahn *et al*, 1990), 60% (Arana *et al*, 1986) and 50–80% (Jann *et* al, 1989). In addition, and along with other anticonvulsants, it is highly protein-bound and can therefore alter the free fraction of other administered drugs. Unfortunately, and almost without exception, the studies carried out to date have not controlled for the effect of carbamazepine on the clinical effect of co-administered neuroleptics.

The summarised findings of the trials seem to be that schizophrenics with or without EEG abnormalities, and with or without a history of affective or behavioural disturbance, may benefit, and that they may do so in variety of ways, but the most likely outcome is a non-specific improvement in rapport and social adjustment. If a patient is to continue on clozapine then carbamazepine cannot be prescribed because of the potential haematological side-effects of both drugs but the clinician can turn to sodium valproate. There is very little in the way of trial work with sodium valproate in schizophrenia, but if one places any credence on the suggested modes of action for carbamazepine, then valproate should be reasonable alternative. One difference is that valproate does not lower levels of co-administered neuroleptics, in fact it is said to modestly increase plasma haloperidol levels (Centorrino *et al*, 1994).

Lithium

Several clinical studies have tested the value of lithium augmentation of both conventional neuroleptics (Small *et al*, 1975; Growe *et al*, 1979; Carmen *et al*, 1981) and clozapine. In the Northwick Park Functional Psychosis Study, Johnstone *et al* (1988) compared treatment with pimozide and lithium, and found that lithium was effective only in reducing

elevated mood. Lerner *et al* (1988) found that adjunctive lithium was helpful only in those patients with schizophrenia who had higher scores for depression on the BPRS. A British special hospital sample of in-patients with treatment resistant schizophrenia did not benefit from the addition of lithium (Collins *et al*, 1991). Similarly, Wilson (1993) having excluded all those with affective symptomatology from the schizophrenic sample under study, found that the lithium augmentation of haloperidol was ineffective. Van Kammen *et al* (1985) pre-treated half their group of schizophrenics with lithium and then gave them all d-amphetamine. They found that those pre-treated with lithium had lower activation-euphoria ratings on the BPRS but that they were no less psychotic.

Lithium has also been added to clozapine, and Bryois & Ferrero (1993) reported a series of 11 patients who had responded to this combination. Five of the patients were diagnosed as having schizophrenia, and five as schizoaffective. However, a note of caution should be sounded with the clozapine/lithium combination, which has been reported to cause an encephalopathy. The advice of those who have experimented with the combination is that such complications are unlikely to occur when the plasma lithium level is kept below 0.5 mmol/l and that the adverse effects will reverse on stopping treatment. Such a combination would however be a last resort and should only be attempted in hospital.

The conclusion of these studies seems to be that lithium can be used to treat affective symptoms in schizophrenia but it is not an effective treatment for treatment resistant schizophrenia.

ECT

During the 1980s there were three, double-blind studies of electroconvulsive therapy (ECT) in schizophrenia, comparing neuroleptic medication alone with neuroleptics in combination with ECT. In each study there was a more rapid recovery in the group receiving ECT, but the additional benefit had been lost by the follow-up assessment at 12 weeks or later (Taylor & Fleminger, 1980; Brandon *et al*, 1985; Abraham & Kulhara, 1987). The findings suggested that affective symptoms did not respond over and above psychotic symptoms, and that a good response to ECT was associated with a short duration of illness. The latter has been used to argue that adjunctive ECT is unlikely to have a role in the treatment of chronic, treatment resistant schizophrenia (Salzman, 1980; Janakiramaiah *et al*, 1982). However, the findings from a number of single case reports and small studies suggest some benefit from adjunctive ECT in a proportion of patients with treatment resistant schizophrenia (Friedel, 1986; Milstein *et al*, 1990; Safferman & Munne, 1992); Gujavarty *et al* (1987) reported an improvement in seven of eight treatment resistant patients with "positive symptom psychosis". Friedel (1986) treated nine such patients with either unilateral or bilateral ECT and found that eight responded, with those with bilateral ECT being slower to relapse. Sajatovic & Meltzer (1993) gave ECT in combination with loxapine to nine patients with diagnoses of either schizophrenia or schizoaffective disorder, of whom five improved, mainly in their reports of positive symptoms. In a retrospective study, Milstein *et al* (1990) reported improvement in 60 (55%) of 100 treatment resistant patients. These studies provide little guidance on possible predictors of response to ECT, though the presence of affective features may predict a better outcome in such patients (Meltzer, 1992).

If a treatment resistant patient were to show an impressive response to ECT, the question raised would be how to maintain the improvement. Although there are a few case reports of maintenance ECT (Kramer, 1990) clinicians and patients are likely to be loathe to embark upon such a regime in ignorance of the long-term effects, although Fink (1979) did not consider that it posed any special risk. The possibility that ECT might hasten the onset of response to clozapine or enhance the therapeutic effects has not been addressed in any published research. Fink (1990) has suggested that the combined use of ECT and clozapine should be considered earlier rather than later, particularly as the full benefits from clozapine may be delayed by up to one year. However, on the basis of the current evidence, ECT should probably be used only as a last resort, after pharmacological treatments have been systematically assessed (Meltzer, 1992).

Cognitive–behavioural therapy

Psychological treatments are particularly important for patients who are medication resistant since even when optimal medication regimes have been achieved, significant residual symptoms are the norm. Psychoanalytical therapies are generally considered to be inappropriate for the symptoms of schizophrenia but the recent development in the use of cognitive–behavioural techniques to modify delusions and hallucinations (Fowler *et al*, 1995; Chadwick *et al*, 1996; Haddock & Slade, 1996) offers an adjunctive treatment that we have found

to be effective for a number of our patients, in reducing the distress and adverse effects of their residual symptoms and in giving them some measure of control over them when they recur.

A core feature of CBT with schizophrenia is the promotion of insight within a normalising rationale (Kingdon & Turkington, 1994). Where there is distress associated with the symptoms, as in paranoia, the gaining of insight may of itself result in a reduction of that distress, and improved insight also open up the possibility of applying other CBT techniques. The CBT techniques used with our patients may range from the purely practical suggestion of using a Sony Walkman or wax earplug to control the voices (Nelson *et al*, 1991) to more cognitive techniques to modify the delusions and hallucinations (Fowler *et al*, 1995; Nelson, 1995).

In medication resistant patients, where delusions are often held with complete conviction, direct modification of the delusional system may be impossible and in some cases, especially where delusions are important to self-esteem, complete modification may be undesirable. In these cases, we have found that partial modification within the delusional system may be both possible and effective. With partial modification only particular aspects of the delusional system are targeted, specifically those aspects that are resulting in problems for the patient, and the rest of the system is left intact.

A particular feature of our treatment resistant population is the difficulty in engaging the patient in therapy, and the therapist may have to spend many sessions building up trust and rapport before any CBT techniques can be used. However, this time is well spent as some patients may make substantial progress once therapy can be progressed. As yet we have not been able to determine which factors, if any, are predictive of positive response to CBT in our patient population, but our experience is that providing the patient will agree to meet with the therapist then there is nearly always something beneficial that can be achieved from these sessions.

Benzodiazepines

Benzodiazepines are commonly administered as co-treatment with an antipsychotic in both in-patients (Baldessarini *et al*, 1995) and out-patients (Pecknold, 1993) with schizophrenia. Clinicians prescribe benzodiazepines as adjuncts to antipsychotic medication in treatment resistant schizophrenia for three main indications. First, benzodiazepines may be used to treat the anxiety and distress related to specific symptoms or environmental stress. By reducing a patient's level of anxiety, agitation and expressed hostility, to say nothing of a possible beneficial effect on neuroleptic-induced akathisia, benzodiazepines may facilitate engagement with the therapeutic programme on the ward. Secondly, they may be used to produce sedation in a disturbed, excited patient. The motivation to use benzodiazepines in this circumstance may be partly to avoid the adverse effects that would be associated with additional antipsychotic medication. Thirdly, the aim may be to achieve an enhanced antipsychotic effect.

Overall, although the majority of studies of adjunctive benzodiazepines in patients with chronic schizophrenia published in the last 20 years have reported some clinical benefit, the results are inconclusive (Lingjaerde *et al*, 1982; Wolkowitz & Pickar, 1991; Johns & Thompson, 1995). Those studies reporting a positive response have tended to find it only in a proportion of cases, usually occurring within the first two to three weeks, and with some tolerance to the beneficial effects over subsequent weeks. The improvement seen has not been restricted to a reduction in anxiety. Rather, improvement has been noted across a range of mental state phenomena, including anxiety, positive psychotic symptoms, tension, hostility and excitement and, possibly, negative symptoms (Wolkowitz *et al*, 1990; Csernansky *et al*, 1988). No reliable clinical predictors of response to benzodiazepines have emerged, although a relatively consistent finding has been a more favourable outcome in those patients presenting with prominent psychotic or anxiety symptoms, or high levels of motor tension, agitation, or retardation (Wolkowitz & Pickar, 1991; Johns & Thompson, 1995).

Several authors have called attention to the potential risks of prescribing benzodiazepines for people with treatment-refractory schizophrenia, including the development of dependency and a rebound worsening of symptoms on drug withdrawal, as well as side-effects such as sedation, ataxia and memory impairment (Nestoros *et al*, 1983; Chouinard, 1988; Wolkowitz *et al*, 1992). There is also the risk of disinhibition with aggressive, impulsive behaviour. We have recently observed discrete episodes of sexually-disinhibited behaviour in two in-patients with treatment resistant schizophrenia, in clear association with the administration of a single, modest dose of a benzodiazepine.

With regard to drug interactions of particular significance in this group of patients, problems may arise from co-administration with clozapine.

Potentially fatal instances of orthostatic and cardiorespiratory dysregulation reported in patients receiving clozapine have been attributed to the concomitant administration of benzodiazepines (Sassim & Grohmann, 1988; Grohmann *et al*, 1989). However, it has been suggested that such problems may also occur, unpredictably, with clozapine as monotherapy (Bredbacka *et al*, 1993).

In summary, there is some evidence that benzodiazepine augmentation of antipsychotic medication can produce some benefit, but there is a marked interindividual variability, the improvements seen may be relatively short-lived, and there are recognised hazards associated with their use. For these reasons, and because of the potential problem of dependence, benzodiazepines should generally be given as short-term trials. The relevant literature provides little guidance for clinicians on dosage or choice of drug, or predictors of response.

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