British Journal of Psychiatry (1996), **169** (suppl. 31), 21–30

Schizophrenia, Violence, Clozapine and Risperidone: a Review

THE SPECIAL HOSPITALS' TREATMENT RESISTANT SCHIZOPHRENIA RESEARCH GROUP

The association between schizophrenia and violence

There is no longer much doubt that there is a small but real association between psychosis and violence directed at others, as well as between psychosis and self-directed violence, including suicide. Schizophrenia and the affective psychoses appear to have a similar order of association with suicide (Caldwell & Gottesman, 1990), but schizophrenia is more likely to be associated with serious other-directed violence. The evidence for the effect of schizophrenia comes from three main directions. There are two substantial cross-sectional USA community studies (Swanson *et al*, 1990; Link *et al*, 1992), respectively showing a significant quantitative association between schizophrenia and violence. Comparative studies of illness and offending careers (Lindqvist & Allebeck, 1990; Hodgins, 1992; Coid *et al*, 1993; Taylor, 1993; Wessely *et al*, 1994), all show different patterns of violent offending by people with schizophrenia compared with those without a psychotic illness, the 1993 studies confirming that the onset of violence is almost invariably after the onset of illness. The third type of evidence is from phenomenology. Taylor (1985) and Link & Stueve (1994) have shown a strong association between delusions and serious violence, the former demonstrating a specific effect of acting on delusions. (For a more extended discussion see Taylor, 1995.)

Johnstone *et al* (1986) found that nearly 20% of a sample of people presenting to hospital in their first episode of schizophrenia had threatened the lives of others, but in over half of the cases the illness had already been evident for over a year (Humphreys *et al*, 1992). Even at this stage, there thus could have been an opportunity for intervention. When serious violence leads to criminal charges it is rare for someone with schizophrenia not already to be well known to psychiatric services (Taylor & Gunn, 1984). A seriously violent offence often occurs within a few months of discharge from hospital treatment (Taylor, 1993), usually discharge with professional staff agreement (Hafner & Boker, 1973). People with schizophrenia are probably as susceptible to many of the non-illness factors associated with anti-social violence as healthy people, including poverty, low social status and unemployment, but there is also an additional specific association between the illness and violence (Wessely *et al*, 1994).

All this suggests that much violence by people with schizophrenia ought to be preventable. What, then have been the barriers to this? Are they failures of compliance with treatment on the part of the patient, failures on the part of psychiatrists, or true resistance to medication? Undoubtedly lack of treatment compliance is a problem for some violent patients, but others fail to improve even in highly controlled therapeutic environments, suggesting that treatment resistance in its physical, organic sense can be a serious problem for such patients.

Use of conventional antipsychotic drugs in the management of violence associated with schizophrenia

Antipsychotic medication is just one part of the satisfactory management of schizophrenia and any violence associated with it (Taylor *et al*, 1993), but it is a very important part. Christison *et al* (1991) reviewed all published double-blind controlled studies of treatments consistently shown to be superior to placebo for schizophrenia and delivered in the context of resistance to 'traditional' neuroleptics. There had been very little consideration of the impact on violence in this context but the reviewers recognised a distinction between 'aggressive outbursts' (aggression is a broader term than violence) in response to psychotic phenomena, needing specific antipsychotic treatment, and

'refractory impulsive aggression', which appears relatively autonomous from characteristic symptoms of psychosis, and perhaps best helped using adjunctive carbamazepine. The Royal College of Psychiatrists (Thompson, 1994) has offered subsequent practical guidance, acknowledging that the theoretical basis for some of it remains slight.

Use of clozapine or risperidone among patients with schizophrenia who are violent: the current literature

Almost no research has been done on the use of clozapine or risperidone with patients who are violent. This may reflect a diffidence both to treat with more risky and demanding treatments, and to research patients who are regarded by many as least able to give real consent and most likely to be litigious. Certainly there is at least one study of clozapine that explicitly excluded such patients (Conley *et al*, 1988). There are no reports of the use of risperidone specifically for this group.

Balassa *et al* (1971) conducted the first survey of the impact of clozapine on aggressive acts. Although they found reduction in explosive, aggressive and self-harming behaviour (86%), it is perhaps worth describing the sample in more detail. Seventeen people with mental retardation, six with defect-state schizophrenia, 10 with 'psychopathy', six with post-traumatic 'psychosyndromes' and three with epilepsy made up the total of 42 subjects. The mean daily dose was 21.7 mg, and the outcome measures not defined.

Maier (1992) described the use of clozapine with 25 men with a schizophrenic illness in an in-patient forensic psychiatry facility in the USA. They were there because of at least one extremely dangerous act, mostly personal violence. At least three months on high doses of each of at least two different neuroleptics had failed to produce remission of symptoms. On clozapine, 17 patients improved clinically, 13 of these sufficiently to be discharged or transferred to lesser security. Two patients had to be moved to a higher level of security, five patients had adverse physical responses and one patient abused the clozapine by taking repeated overdoses and inducing seizures. It is apparent, however, that in this small series of patients, no problem emerged with clozapine that could not be managed, and the majority of the patients benefited. The further important observation was made that not only were positive *and* negative symptoms of schizophrenia improved, but that in two cases thought to have an additional personality disorder this also substantially improved. This latter apparent improvement may in part have followed from a substantial increase noted in both staff and patient optimism and attitudes to treatment more generally. Ebrahim *et al* (1994) examined a subgroup of 27 offender patients with a US state hospital, using a similar definition of previous treatment resistance. With clozapine they noted that 70% of the patients improved on both positive and negative symptoms of schizophrenia, and that, specifically, there was a diminution in 'aggressiveness' – not further defined. Buckley *et* al (1995) went so far as to suggest a specific antiaggressive effect for clozapine in a small sample of patients studied. The violent group (8 men and 3 women) showed a significant reduction in number and length of seclusion, or restraint episodes. They required higher doses of clozapine than the non-violent, but showed a similar state of symptomatic improvement after treatment, according to BPRS scores. This would seem to indicate symptom mediation of violence, but they insist that the magnitude of reduction in aggression scores in some but not all patients was in excess of symptom reduction.

Chiles *et al* (1994) raised an important question in relation to patients showing only partial response to clozapine, such that continued detention in an institution would remain necessary – if there is insufficient improvement to lead to discharge can the expense of continuing the medication be justified? People in this series were not technically offender patients, but many were violent or provocative in the in-patient setting. One hundred and fifteen of 139 patients offered clozapine completed at least 12 weeks on it with resultant significant group changes in the number of seclusion episodes, and the mean length of seclusion for the remaining episodes. As a cost effectiveness commentary these are important observations, since it may be inferred that considerable savings on staffing required for seclusion or restraint may be achieved.

Use of clozapine or risperidone among compulsorily detained or exceptionally dangerous patients

Theoretical advantages of clozapine or risperidone for the patient with schizophrenia who is violent

As presently understood, clozapine and risperidone seem to have a broadly similar range of action in the central nervous system. It is to be presumed likely that, insofar as they lower the risk of violence, the main effect is on symptom mediated violence;

https://doi.org/10.1192/S0007125000298589 Published online by Cambridge University Press

enhanced symptom reduction would thus equate with enhanced reduction in at least more serious, delusionally driven violence. This will be difficult to test as this sort of violence tends to have a low base rate. The effect of these two neuroleptics on the serotonergic system may offer an additional potential mechanism; however, it is drugs that block the $5HT_{1A}$ receptors that appear to have selective anti-aggressive effects, at least in animals (Miczak *et al*, 1994), while it is thought that it is the $5HT_2$ or $5HT_3$ receptors that are blocked or desensitised by clozapine or risperidone (Meltzer, 1991).

Two sets of clinical observations led to testable hypotheses that clozapine may offer a special advantage to the person with schizophrenia who is violent, the first to do with its effect on emotional indifference and the other on concurrent substance abuse.

Gerlach & Peacock (1994) compared 100 people with schizophrenia on clozapine with 100 on the more exclusively dopaminergic neuroleptics and observed significantly less 'emotional indifference' as well as less depression, less akathisia and fewer sexual side-effects. It is always difficult to be sure how far similar sounding concepts have real similarities, but it may be worth noting that emotional indifference to the victim was one of the key features distinguishing between the seriously violent attacks of psychotic men, who denied positive or negative feelings for their victims at the time of the attack, and non-psychotic men in a criminal sample (Taylor, 1993).

Although there is a rather mixed picture of the relationship between schizophrenia, substance abuse and violence, no clinician dare disregard the use of alcohol or illicit substance by people with a psychosis. Tardiff & Sweillam (1980) in a hospital sample and Virkkunen (1974), Hafner & Boker (1973) and Taylor (1993) in the schizophrenia subgroup of offender samples found an inverse relationship between alcohol use and violent acts, but Lindqvist & Allebeck (1990) found a positive association. Perhaps of most importance is that in a large community sample (Swanson *et al*, 1990) alcohol and illicit substance abuse greatly increased the risk of self-reported and generally less serious violence over a 12 month period.

It is a common clinical impression, at least in forensic psychiatric practice, that people with schizophrenia who do use self-chosen drugs – the commonest in Britain being alcohol or marijuana, although crack cocaine has been gaining ground – do so for self-medication rather than as a form of primary substance abuse. Buckley *et al* (1994) found that a substantial minority (25%) of a sample of people with treatment resistant schizophrenia used or abused drugs, mainly alcohol or marijuana. Not only were these patients as responsive to clozapine as the non-abusers, but only four of the 23 substance abusing patients returned to their substance abuse during the first six months of treatment desite having opportunities to do so. Further anecdotal reports, including a multi-drug using schizophrenic patient (Albanese *et al*, 1994) and a cocaine abuser (Yovell & Opler, 1994) have suggested similar conclusions.

Risks of clozapine or risperidone use in a population at high risk for concurrent gross brain disorder

Although the risk of seizures for risperidone is low, clozapine carries an increased risk of inducing seizures, which appears to be dose related (Haller & Binder, 1990). At 600 mg clozapine daily it is as high as 5%. It might be expected that pre-prescription epilepsy or other brain disorder might increase the risk. One retrospective study (Povlsen *et al*, 1985) and one small study in a public sector hospital in the USA (Wilson & Claussen, 1994) tend to bear this out.

There is some evidence to suggest that those people with schizophrenia who are also violent may be disproportionately likely to have overt abnormalities of brain structure or function, but there has been little systematic study in this area. A pilot study of multiple measures of cerebral structure and function among patients in one special hospital showed evidence of gross brain damage on MRI in all six schizophrenic men examined, none of whom had an organic syndrome as part of their diagnostic cluster and for two of whom neither CT scan nor EEG had hinted at problems; only psychometry had been suggestive (Chesterman *et al*, 1994). A multiple measure study is underway of 40 predominantly delusional and 40 mixed symptom men with schizophrenia and 40 men without any evidence of psychosis, resident in the hospital because of their violence potential. According to traditional views it may be that the epileptogenic potential of clozapine could even be advantageous in fit-prone violent schizophrenics. Landolt (1958) noted the association between 'forced normalisation' of the EEG in patients with both temporal lobe epilepsy and schizophrenia-like psychosis when the patients were at their most psychotic, and a 'deterioration'

in the EEG as the psychosis improved. Davison & Bagley (1969) discussed possible mechanisms to explain this, which they regarded as more than a crude biological antagonism between fits and psychosis, and the psychosis as not simply a toxic effect of the anticonvulsant drugs. At any rate, it appears to be safe and effective to treat patients with clozapine and anticonvulsants simultaneously, in particular valproate (Kando *et al*, 1994). There is now some clinical experience of this in the English special hospitals and the comparable Scottish State Hospital which would tend to confirm that the combination is safe and effective. More systematic study in this area is, however, needed.

Risks from other concurrent treatments

It is recommended both for clozapine and for risperidone that the dose is built up slowly, but for some violent patients it is essential to gain rapid control at least of arousal. Thus, the main potential value for clozapine or risperidone in the context of violence is likely to be for the more stable psychotic patients with persistent and disabling symptoms that may not only lead to violence, but probably the most serious violence (Taylor, 1985). Two cases have been reported, however, in which clozapine was successfully introduced for more acutely disturbed people – by using it at the end of a course of ECT which was effective, but only transiently so (Green *et al*, 1994). Both patients were women, who are less responsive to clozapine than men (Lieberman *et al*, 1994). The women in Green's report had been intractably ill in spite of a variety of vigorous treatments for 21 and 24 years respectively, the first delusional, agitated and highly assaultive and the second mute and catatonic, with weight loss.

Neuroleptics may be prescribed with a range of other drugs which have sedative properties for the person who has schizophrenia and is violent, with some justification for expecting that even if the psychosis is medication resistant the violence may be temporarily limited. However minimal the specific antipsychotic effect, and whatever the ideals of a complete wash-out of other medication before starting clozapine or risperidone, it is difficult to persuade clinical practitioners, and particularly nursing staff in minute to minute contact with a repetitively assaultive patient that has already killed, that he should have a period without medication, but it can and has been done. Lieberman *et al* (1994) suggest restricting sedative medication to amylobarbitone or chloral. Apparent disinhibition has, however, occasionally been reported with such drugs (Karson *et al*, 1982; Dietch & Jennings, 1988). People who are violent, then, are probably disproportionately likely to remain on other neuroleptics or drugs thought to assist control of their violence while they try clozapine or risperidone. There is almost no information on drug interactions with risperidone. Concurrent use of carbamazepine or some antidepressants with clozapine, may lead to an increased risk of agranulocytosis, while concurrent use of lithium, may increase the risk of neuroleptic malignant syndrome (Pope *et al*, 1986).

Risks of abrupt discontinuance of clozapine or risperidone

It is rarely clinically wise to discontinue psychotropic medications abruptly, but in a few cases there are real dangers in doing so. There is as yet no evidence that sudden cessation of risperidone causes potentially dangerous complications, but equally there is no evidence that such a practice would be necessary. Clozapine potentially leaves patients much more vulnerable because in the face of a falling white blood cell count it is necessary to stop it at once. A rapid deterioration of mental state, such that the psychosis may appear worse even than the pre-treatment state, has been documented in these circumstances (Ekblom *et al*, 1984; Perenyi *et al*, 1985; Eklund, 1987; Borison *et al*, 1988), although probably it is more usual that the effects are less dramatic (Lieberman *et al*, 1989). De Leon *et al* (1994) demonstrated effective use of trihexiphenidyl with lorazepam over two weeks after clozapine withdrawal which had precipitated, in a woman who had continued to be medication-resistant, an agitated state with behaviour threatening to self and others, and suggested that its use for a man in similar circumstances had been preventive. A particularly worrying case of abrupt withdrawal in a patient with an established violence history is described later in this text.

Consent to treatment for clozapine or risperidone

Seriously violent people with a psychosis are more likely than others to be compulsorily detained in hospital, with the implication that they are receiving treatment against their will. Also common is a concern that, as they were generally not fully responsible for their violent act or acts, that their lack of mental capacity must necessarily apply across all other decisions, including those about specific treatment. There is, however, legal recognition in common law countries, like Britain and the

USA, that mental capacity is not an absolute. A patient may, for example, be sufficiently impaired in judgement over the decision whether to come into hospital to require compulsory detention, but still adequately competent to decide on specific treatments once there. This is enshrined in statute in Britain within the mental health legislation. In most respects clozapine and risperidone, for consent purposes, would be treated as any other drug given for mental disorder. Generally fully informed consent is necessary and under all circumstances should be sought. If necessary, however, these medications may be given without explicit consent for up to three months to patients who have been compulsorily detained for *treatment*. Thereafter, the psychiatrist legally responsible for the patient's care must either document that valid consent has been obtained from the patient to continue *or* must, in England and Wales, call in an independent doctor, appointed by a special body – The Mental Health Act Commission – to approve, or not, the treatment plan. The procedure is set out in the Mental Health Act 1983. (Scotland and Northern Ireland follow similar principles but under different legislation (Gunn *et al*, 1993).) A difficulty arises with clozapine because of the requirement that the patient has a regular blood test if treatment is to continue. In ordinary circumstances if anyone insisted on proceeding with the test in the absence of the patient's consent this could constitute 'battery', and leave the person taking blood liable to a civil suit. The Mental Health Act Commission (1993) has, however, recognised that safe treatment with clozapine includes regular monitoring. After setting out the complexities of expert legal advice obtained, the Commission advises ". . . if clozapine was authorised either by a Responsible Medical Officer or by the certificate of a Section 58 Appointed Doctor, the administration of the medicine should include the authority for the necessary monitoring". The extent to which in reality monitoring can be enforced if the patient is not consenting, and the effect on the wider therapeutic alliance between patient and clinical team if this is attempted, are clearly factors which will need to be taken into account in reaching a decision on how to proceed.

If delivery of drugs can be enforced on clinical grounds, this is not an option for researchers. Notwithstanding the potential for indirect harm through the bias in the knowledge base that may result from refusal of research subjects, it is not possible to include patients who are clearly, even forcibly refusing participation in a trial of clozapine or risperidone, or any other drug. A greater dilemma comes for those patients who do not seem able to consent but are not refusing. Automatic exclusion from research participation for the whole class of detained or violent patients can only be to their disadvantage. It would not be impossible, however, to envisage a system of additional safeguards for this group, to enable them to have the chance of participation. In England and Wales, further involvement of the Mental Health Act Commission, notwithstanding the need for guidance from an ethical committee too, might be helpful for those whose competence for treatment decisions is in question. Ethics committees alone might set the safeguards in other circumstances, acknowledging that it is probably unethical to deprive patients of the opportunity to participate in properly designed and conducted trials merely because they are detained or violent. In this case many uncertainties remain about the use of clozapine or risperidone for patients with seriously violent propensities, and it is arguable that most of these can only now be resolved by systematic study of these patients; other patients are not satisfactory surrogates.

Compliance with treatment, and its exceptional importance among the potentially dangerous person with schizophrenia

If it has once been established that a major factor in causing a piece of antisocial behaviour is a mental disorder, and particularly when there is a clear link between symptoms and violence, it is of manifest importance not only to gain control of those symptoms but also to maintain it. The importance of the treatment that achieves this is even greater if, on abrupt cessation, there is a risk of rebound into violence as well as psychosis. Neither clozapine nor risperidone are available as depot preparations, nor at least in the case of clozapine likely to be, and so maintenance depends heavily on the motivation and compliance of the patient. Given the possibly devastating effects of abrupt cessation of clozapine, it would thus be valuable in some cases to have a system for regular independent verification that the patient is continuing to ingest the pills. Additional repeated blood tests are likely to be both impractical and unacceptable to the patient, perhaps putting at risk the compliance that he has. The independent verification would have to be through detection of metabolites in some painlessly and easily provided body fluid – saliva, sweat or urine – and sufficiently simple that lay hostel staff would be able to conduct the test in conjunction with the patient.

On the positive side, there is some evidence that clozapine and risperidone are likely to be more acceptable to patients than the more conventional neuroleptics, partly because of the lower chance of dystonia and akathisia, and possibly additionally through a greater sense of wellbeing (Buckley *et al*, 1994). This is partly borne out in the one truly long-term follow-up study (Lindstrom, 1988). In a retrospective study of 96 patients followed for 13 years, only seven had discontinued the drug through lack of compliance, and this in a previously difficult and unresponsive group. Schmauss *et al* (1989) did not comment on compliance, but did confirm that, among women with schizophrenia, after seven to eight years of treatment with clozapine, only mild parkinsonism and akathisia were evident in a minority, and no tardive dyskinesia. Weight gain and salivation were distressing, but not a bar to continuing treatment for this group. One third had EEG abnormalities.

Patient compliance may be particularly poor in an offender group, partly because of learned attitudes to authority figures and psychiatric services (Bowden, 1978), partly because of generally chaotic lifestyles, and partly because offending can be directly linked to sudden disruption of treatment if an individual is arrested or confined to a police cell or jail. Violence does not cease to be a problem just because a person is in custody. Even given compliance, little is known about the risk of medication resistance developing to clozapine or risperidone in the longer term. One case of relapse is known in a special hospital patient for whom compliance was certain and treatment with clozapine had been very effective for two years (Shubsachs, Marlborough House Sub-Regional Secure Unit, personal communication).

English special hospitals and the special treatment issues

Overview of the patient population

Each patient admitted to one of the special hospitals (Ashworth, Broadmoor, Rampton) must have a mental disorder according to the International Classification of Diseases (World Health Organization, 1978, 1992), be compulsorily detainable under the Mental Health Act 1983, and pose a serious and imminent danger to others. Serious self-harm is also common. The vast majority have been convicted of a serious criminal offence, with an average over the last eight years of less than 10% admitted under civil provisions of the Act, and over two-thirds of the total having been regarded as dangerous enough at the time of their Court appearance to have attracted Home Office restrictions on discharge from hospital (Maden *et al*, 1993). Nearly two-thirds of the patients have schizophrenia.

Practical clinical experience of 'treatment resistance'

The average length of stay in a special hospital for a patient with a psychotic illness is about eight and a half years. A few remain after 25 years. Dell & Robertson (1988) studied men in a Broadmoor sample between 1982 and 1984. Among the 127 sampled with psychosis, insufficient improvement in mental state was the commonest first reason for continued detention (75%). The extent of their treatment is not clear, but the figures given for treatment current to the study suggest 40% receiving less than the equivalent of 300 mg of chlorpromazine and only just over one-third doses in excess of 600 mg equivalents.

Maden *et al* (1993) presented a similarly gloomy picture of patients resident for more than 12 months in any of the three hospitals. The clinical teams were likely to rate persistent symptoms as an obstacle to progress, here with an emphasis on treatment resistance ($n=102$; 35% of *all* patients; i.e. not exclusively those with a psychosis) rather than non-compliance ($n=39$; 13%). The presumption must therefore be of medication resistance in over 50% of psychotic patients. More specifically, positive symptoms of psychosis were rated as virtually unchanged in 73% of the 153 men and 28 women, with psychoses and negative symptoms unchanged in 50%. Clinical staff predicted deterioration over the next five years for over 90%.

Use of clozapine and risperidone in the special hospitals to date

Background prescribing

Fraser & Hepple (1993) completed a one day census of prescription habits as documented on prescription cards in Broadmoor Hospital in February 1991. These were compared with practices described in much earlier studies of general psychiatric populations in the UK (variously in Newcastle, Oxford, Malvern and Birmingham); they appeared little different overall. This predated the introduction of clozapine and risperidone at Broadmoor.

Clozapine

Prescription of clozapine started in Rampton Hospital in January 1990, and four and 12 months

Table 1
Use of clozapine in the English special hospitals, January 1990–December 1994

	Ashworth *n* (%)[1]	Broadmoor *n* (%)	Rampton *n* (%)	Total *n* (%)
No. of resident patients on clozapine December 1994	28	19	46	93
Months of use	55	46	60	
No. of patients ever on clozapine	55	58	88	201[2]
No. of patients transferred or discharged on clozapine	6 (11)	5 (9)	17 (19)	28 (14)
No. of clozapine stopped due to decreased white cell count	4 (7)	1 (2)	4 (5)	9 (40)
No. stopped for other reasons	17 (31)	33 (57)	21 (24)	71 (40)
Average daily maintenance dose (see text for definition)	NK	NK	(*n*=60) 473 mg	

1. Percentages refer to the number in the subgroups in relation to the number ever on clozapine.
2. Approximate total of patients with schizophrenia or similar psychosis over similar time period – 1612.

later in Ashworth Hospital and Broadmoor Hospitals respectively. (At Carstairs State Hospital in Scotland clozapine has been in use since June 1990.) There had thus been considerable clinical experience by the end of 1994 (see Table 1). It is not certain how many patients were truly eligible, but during the same time period just over 1600 patients were resident at some time under the legal category of mental illness, which here means mainly schizophrenia, and the Dell & Robertson (1988) and Maden *et al* (1993) studies just described are suggestive of widespread treatment resistance.

The 201 patients given clozapine thus represented in the order of 12% of the potentially available population.

The progress of people on clozapine is under more detailed study, but, in brief, just 4–5% of patients (nine in total) have had to stop clozapine abruptly because of a falling white cell count, not significantly different from the published risk for other patient groups. Some 40% of patients have had to discontinue clozapine for other reasons, including relapse, lack of efficacy, tachycardia or refusal to comply with the blood test. Twenty-eight (14%) of the patients improved sufficiently to be transferred or discharged from special hospital, most after long pre-clozapine residence; a figure likely to be an underestimate of success as the discharge process can be very protracted.

An average daily dose was calculated on the following basis: only those on a steady dose for three months or more were included; if there were more than one such period on a steady dose but the dose was different the longer period was used for the 'maintenance dose' calculation.

Although there were some patients who reached or exceeded the 600 mg threshold, the average of just over 470 mg reflects fairly well the order of dosage which was in common use at Rampton Hospital. Data from the other hospitals are less complete because of the more recent implementation of comparable pharmacy records systems. The lower overall use of clozapine at the other hospitals reflects in part the different lengths of time for which doctors there have been prescribing it, but in part too that clozapine appears to be in less favour at Ashworth, and Broadmoor. In Broadmoor the proportion of patients with schizophrenia is higher than at the other two. It is not possible yet to account for the apparently lower success rates at Ashworth and Broadmoor among clozapine users; research data on illness careers are still under collection.

One of the greatest concerns in treating the psychosis of people whose illness has at least in part driven that violence is the risk of rebound psychosis following abrupt cessation of clozapine. There are a number of research reports of this (Ekblom *et al*, 1984; Perenyi *et al*, 1985; Eklund, 1987; Borison *et al*, 1988), and some clinical experience within the high security services. For those who progress to the community there is the added concern that a sudden decision to stop taking medication may be neither medically led nor detected rapidly enough to limit rebound. The numbers of patients in special hospital who have to stop clozapine abruptly are small. It will take years to provide a satisfactory indication of whether such risk, as feared, is accompanied by risk of return of exacerbation of violence. In the meantime, guidance must include a recommendation that if sudden cessation must or does occur, consequent treatment planning must include contingencies for increasing nursing and/or care staff availability. A case example serves to illustrate why.

Case history

An 18-year-old woman, with a three year history of schizophrenia was admitted to the State Hospital,

Carstairs after two years of persistent verbal aggression and physical violence in a range of settings and in spite of a range of physical and psychological treatments. Over the next two months staff were assaulted on six occasions, each attack psychotically driven. At the time of admission to the State Hospital her medication was zuclopenthixol decanoate 600 mg weekly, chlorpromazine 1200 mg daily, carbamazepine 1200 mg daily and procyclidine 10 mg daily. The depot medication and carbamazepine was discontinued over six weeks and she was started on clozapine a week later. The dose was increased from 50 mg to 400 mg over 14 weeks, but improvement started after two. Her hallucinations and delusions persisted, but she was much less agitated, and no longer required the 'buffer zone' of 12–15 feet between her and others for safety. She started to engage in ordinary social behaviours, she could concentrate on activities and she was often seen smiling.

Three months after starting clozapine, routine screening showed a falling white cell count. Her clozapine was stopped immediately. Within 48 hours her mental state had become much worse than it had been before clozapine. She had a slight pyrexia, and tachycardia and increased blood pressure. She was grossly thought disordered, speaking in word salad, and hallucinated; and there was organic quality to her state for 14 days. She could or would not eat or drink unaided, and lost weight in spite of continuous care. Her violence re-emerged on day 14 with head banging and renewed assaults. She required two or three trained nurses with her at all times. It took six months of various other medications and finally ECT before she regained her pre-clozapine mental state.

Risperidone

Risperidone prescription in the special hospitals, as elsewhere, has considerably post-dated the use of clozapine, but there is also growing experience (see Table 2). Based on similar calculations as those for clozapine the rate of use overall is very similar. Broadmoor Hospital uses proportionately more risperidone than clozapine.

At Rampton Hospital, while fewer than 25% of patients so far have abandoned clozapine, over the shorter time period only about half of those prescribed risperidone are still taking it, and just two have successfully left the hospital. Calculated on the same basis as for clozapine, 27 risperidone patients at Rampton reached a 'maintenance' dose, at a mean of 7 mg.

At first sight the possibly poorer response to risperidone may not seem surprising in that as many as nine patients at Rampton Hospital had been on clozapine previously, as well as other neuroleptics, without benefit. Eight of the clozapine patients, however, had previously been on risperidone. Two of the most psychotic and assaultive patients – one man and one woman – had been on clozapine and risperidone simultaneously. In the woman's case doses of 500–600 mg of clozapine were sustained for 2–3 months, and in the man's 200–300 mg of clozapine, each with 8 mg of risperidone. In neither case was there either advantage or detectable adverse effect.

Future directions

An outline has been presented of the importance of clozapine or risperidone for some people with schizophrenia who are violent, and some of the special problems in such prescription for this group. Special hospital patients form a small, extreme subgroup of such people, who have generally failed in or been failed by other hospitals. For many, the only hope of a safe return to the community is treatment innovation and research.

Table 2
Use of risperidone in the English special hospitals, August 1993–December 1994

	Ashworth *n* (%)[1]	Broadmoor *n* (%)	Rampton *n* (%)	Total *n* (%)
No. of resident patients on risperidone December 1994	26	39	22	87
Months of use	NK	18	17	
No. of patients ever on risperidone	NK	54	43	97[2]
No. of patients transferred or discharged on risperidone	NK	0	2 (5)	2 (2)
No. of patients for whom risperidone stopped due to side-effects or failure to respond	NK	15 (28)	19 (44)	34 (35)
Average daily maintenance dose (see text for definition)	NK	NK	(*n*=27) 7 mg	

1. Percentages calculated as in table one, but excluding Ashworth.
2. Approximate total number of people with schizophrenia=1612, as before.

https://doi.org/10.1192/S0007125000298589 Published online by Cambridge University Press

A programme of research has been established involving each of the special hospitals. The preliminary goals were to generate the first clinical description of a total resident group, secondly to prepared integrated, detailed descriptions of clinical state, illness, treatment, social and offending careers of selected subsamples, and thirdly prepare hospitals, generally unused to clinical trials, for treatment research. An open study of the prescription of clozapine or risperidone has been established, in which decisions on prescription are made entirely by the patient's consultant psychiatrist, in conjunction with the clinical team, but research psychiatrists complete ratings of previous and base line states and, prospectively, any response. On this basis a preliminary report of a two year follow-up of patients prescribed clozapine in Rampton suggests that outcome is comparable to that in other patient groups (Delal *et al*, 1996). It is intended that the work will offer the ground work needed for going on to test variations in approaches to treatment, but also provide a database to enable systematic long-term follow-up of these patients.

Acknowledgements

Grateful thanks to the SHSA for funding the research workers, to Drs Isobel Campbell and Steven Novosel for detailed guidance on the case history, Sophie Davison for her translation of the Balassa paper, and Kim Fraser for additional information about his study; thanks to Nengi Charles and Christine Tonks for secretarial support for the project and paper.

References

ALBANESE, M. J., KHANTZIAN, E. J., MURPHY, S. L., *et al* (1994) Decreased substance use in chronically psychotic patients treated with clozapine. *American Journal of Psychiatry*, **151**, 780–781.

BALASSA, M., DEISENHAMMER, E. & SCHEVRER, H. (1971) Clozapine, ein nicht ketaleptogenes neuroleptikum, in der behandlung von verhaltensstorungen mit erregungszustanden. *Wiener Medizinische Wochenschrift*, **121**, 90–92.

BORISON, R. L., DIAMOND, B. L., SINHA, D., *et al* (1988) Clozapine withdrawal rebound psychosis. *Psychopharmacological Bulletin*, **24**, 260–263.

BOWDEN, P. (1978) Men remanded into custody for medical reports. *British Journal of Psychiatry*, **133**, 320–338.

BUCKLEY, P., THOMPSON, P., WAY, L., *et al* (1994) Substance abuse among patients with treatment resistant schizophrenia: characteristics and implications for clozapine therapy. *American Journal of Psychiatry*, **151**, 385–389.

———, BARTELL, J., DONERWORTH, K., *et al* (1995) Violence and schizophrenia: clozapine as a specific antiaggression agent. *Bulletin of the American Academy of Psychiatry and the Law*, **23**, 607–611.

CALDWELL, C. B. & GOTTESMAN, I. I. (1990) Schizophrenics kill themselves too: a review of risk factors for suicide. *Schizophrenia Bulletin*, **16**, 571–589.

CHESTERMAN, L. P., TAYLOR, P. J., COX, T., *et al* (1994) Multiple measures of cerebral state in dangerous mentally disordered inpatients. *Criminal Behaviour and Mental Health*, **4**, 228–239.

CHILES, J. A., DAVIDSON, P. & MCBRIDE, D. (1994) Effects of clozapine on use of seclusion and restraint at a state hospital. *Hospital and Community Psychiatry*, **45**, 269–271.

CHRISTISON, G. W., KIRCH, D. G. & WYATT, R. J. (1991) When symptoms persist: choosing among alternative somatic treatment for schizophrenia. *Schizophrenia Bulletin*, **17**, 217–245.

COID, B., LEWIS, S. W. & REVELEY, A. M. (1993) A twin study of psychosis and criminality. *British Journal of Psychiatry*, **163**, 87–92.

CONLEY, R. R., SCHULZ, S. C., BAKER, R. W., *et al* (1988) Clozapine efficacy in schizophrenic nonresponders. *Psychopharmacological Bulletin*, **24**, 269–274.

DAVISON, K. & BAGLEY, C. R. (1969) Schizophrenia-like psychoses associated with organic disorders of the central nervous system: a review of the literature. *Current Problems in Neuropsychiatry* (ed. R. N. Herrington). Ashford: Headley Brothers.

DELAL, B., LARKIN, E. & TAYLOR, P. J. (1996) A follow up study of the first 50 patients started on clozapine in Rampton Hospital (1990/1992). Presentation Rampton/SHSA Conference and in preparation for publication.

DELL, S. & ROBERTSON, G. (1988) *Sentenced to Hospital*. Maudsley Monograph Number 32. Oxford: Oxford University Press.

DIETCH, J. T. & JENNINGS, R. K. (1988) Aggressive dyscontrol in patients treated with benzodiazepines. *Journal of Clinical Psychiatry*, **49**, 184–188.

EBRAHIM, G. M., GIBLER, B., GACONO, C. B., *et al* (1994) Patient response to clozapine in a forensic psychiatric hospital. *Hospital and Community Psychiatry*, **45**, 271–273.

EKBLOM, B., ERIKSSON, K. & LINDSTROM, L. H. (1984) Supersensitivity psychosis in schizophrenic patients after sudden clozapine withdrawal. *Psychopharmacology*, **83**, 293–294.

EKLUND, K. (1987) Supersensitivity and clozapine withdrawal. *Psychopharmacology*, **91**, 135.

FRASER, K. & HEPPLE, J. (1993) Prescribing in a special hospital. *Journal of Forensic Psychiatry*, **3**, 311–320.

GERLACH, J. & PEACOCK, L. (1994) Motor and mental side-effects of clozapine. *Journal of Clinical Psychiatry*, **55** (Suppl), 107–109.

GREEN, A. I., ZALMA, A., BERMAN, I., *et al* (1994) Clozapine following ECT: a two-step treatment. *Journal of Clinical Psychiatry*, **55**, 388–389.

GUNN, J., BRISCOE, O., CARSON, D., *et al* (1993) The law, adult mental disorder, and the psychiatrist in England and Wales. In *Forensic Psychiatry: Clinical, Legal and Ethical Issues* (eds J. Gunn & P. J. Taylor), pp. 21–117. Oxford: Butterworth-Heinemann.

HALLER, E. & BINDER, R. L. (1990) Clozapine and seizures. *American Journal of Psychiatry*, **147**, 1069–1071.

HÄFNER, H. & BÖKER, W. (1973) *Crimes of Violence of Mentally Abnormal Offenders* (trans. H. Marshall, 1982). Cambridge: Cambridge University Press.

HODGINS, S. (1992) Mental disorder, intellectual deficiency and crime. *Archives of General Psychiatry*, **49**, 476–483.

HUMPHREYS, H. S., JOHNSTONE, E. C., MACMILLAN, J. F., *et al* (1992) Dangerous behaviour preceding first admission for schizophrenia. *British Journal of Psychiatry*, **161**, 501–505.

JOHNSTONE, E. C., CROW, T. J., JOHNSON, A. L., *et al* (1986) The Northwick Park study of first episodes of schizophrenia. *British Journal of Psychiatry*, **148**, 115–143.

KANDO, J. C., TOHEN, M., CASTILLO, P. H. J., *et al* (1994) Concurrent use of clozapine and valproate in affective and psychotic disorders. *Journal of Clinical Psychiatry*, **55**, 255–257.

KARSON, C. N., WEINBERGER, D. R., BIGELOW, L. B., *et al* (1982) Clonazepam treatment of chronic schizophrenia: negative results in a double-blind, placebo-controlled trial. *American Journal of Psychiatry*, **139**, 1627–1628.

LANDOLT, H. (1958) Serial electroencephalographic investigations during psychotic episodes in epileptic patients and during

schizophrenia attacks. In *Lectures on Epilepsy* (ed. A. M. Loventz de Haas), pp. 91–133. Amsterdam: Elsevier.

DE LEON, J., STENILLA, J. K., WHITE, A. O., *et al* (1994) Anticholinergics to treat clozapine withdrawal. *Journal of Clinical Psychiatry*, **55**, 119–120.

LIEBERMAN, J. A., KANE, J. M. & JOHNS, C. A. (1989) Clozapine: guidelines for clinical management. *Journal of Clinical Psychiatry*, **50**, 329–338.

———, SAFFERMAN, A. Z., POLLACK, S., *et al* (1994) Clinical effects of clozapine in chronic schizophrenia: response to treatment and prediction of outcome. *American Journal of Psychiatry*, **151**, 1744–1752.

LINDQVIST, P. & ALLEBECK, P. (1990) Schizophrenia and crime. A longitudinal follow-up of 644 schizophrenics in Stockholm. *British Journal of Psychiatry*, **157**, 345–350.

LINDSTROM, L. H. (1988) The effect of long term treatment with clozapine in schizophrenia: a retrospective study in 96 patients treated with clozapine for up to 13 years. *Acta Psychiatrica Scandinavica*, **77**, 524–529.

LINK, B., ANDREWS, H. & CULLEN, F. T. (1992) The violent and illegal behaviour of mental patients reconsidered. *American Sociological Review*, **57**, 275–292.

——— & STUEVE, A. (1994) Psychiatric symptoms and the violent/illegal behaviour of mental patients compared to community controls. In *Violence and Mental Disorder. Developments in Risk Assessment* (eds J. Monahan & H. Steadman). Chicago: University of Chicago Press.

MADEN, A., CURLE, C., MEUX, C., *et al* (1993) The treatment and security needs of patients in special hospitals. *Criminal Behaviour and Mental Health*, **3**, 290–306.

MAIER, G. J. (1992) The impact of clozapine on 25 forensic patients. *Bulletin of the American Academy of Psychiatry and the Law*, **20**, 297–307.

MELTZER, H. Y. (1991) The mechanism of action of novel antipsychotic drugs. *Schizophrenia Bulletin*, **17**, 263–287.

MENTAL HEALTH ACT COMMISSION (1993) Guidance on the administration of clozapine and other treatments requiring blood tests under the provisions of Part IV of the Mental Health Act. *Practice Note 1*. MHAC; Nottingham NG1 6BG.

MICZEK, K. A., WEERTS, E., HANEY, M., *et al* (1994) Neurobiological mechanisms controlling aggression preclinical developments for pharmacotherapeutic interventions. *Neuroscience and Behavioural Reviews*, **18**, 97–110.

PERENYI, A., KUNCZ, E. & BAGDY, G. (1985) Early relapse after sudden withdrawal or dose reduction of clozapine. *Psychopharmacology*, **86**, 244.

POPE, H. G., COLE, J. O., CHORAS, P. T., *et al* (1986) Apparent neuroleptic malignant syndrome with clozapine and lithium. *Journal of Nervous and Mental Disease*, **174**, 493–495.

POVLSEN, U. J., NORIGN, U., FOG, R., *et al* (1985) Tolerability and therapeutic effect of clozapine: a retrospective investigation of 216 patients treated with clozapine for up to twelve years. *Acta Psychiatrica Sandinavica*, **71**, 176–185.

SCHMAUSS, M., WOLFF, R., ERFURTH, A., *et al* (1989) Tolerability of long term clozapine treatment. *Psychopharmacology*, **99**, S105–S108.

SWANSON, J. W., HOLZER, C. E., GANJU, V. K., *et al* (1990) Violence and psychiatric disorder in the community: evidence from the Epidemiologic Catchment Area Surveys. *Hospital and Community Psychiatry*, **41**, 761–770.

TARDIFF, K. & SWEILLAM, A. (1980) Assault, suicide and mental illness. schizophrenia. *Archives of General Psychiatry*, **37**, 164–169.

TAYLOR, P. J. (1985) Motives for offending among violent and psychotic men. *British Journal of Psychiatry*, **147**, 491–498.

——— (1993) Schizophrenia and crime: distinctive patterns in association. In *Crime and Mental Disorder* (ed. S. Hodgins), pp. 63–85. Beverley Hills, CA: Sage.

——— (1995) Schizophrenia and the risk of violence. In *Schizophrenia* (eds S. Hirsch & D. Weinberger), pp. 163–183. Oxford: Blackwell Science.

——— & GUNN, J. (1984) Violence and psychosis. *British Medical Journal*, **288**, 1945–1949; **289**, 9–12.

———, ———, BROWNE, F. W. A., *et al* (1993) Principles of treatment for the mentally disordered offender. In *Forensic Psychiatry: Clinical, Legal and Ethical Issues* (eds J. Gunn & P. J. Taylor), pp. 646–690. Oxford: Butterworth Heinemann.

THOMPSON, C. (1994) The use of high dose antipsychotic medication. *British Journal of Psychiatry*, **164**, 448–458.

VIRKKUNEN, M. (1974) A. Observation on violence in schizophrenia; B. on arson committed by schizophrenics. *Acta Psychiatrica Scandinavica*, **50**, 145–160.

WESSELY, S. C., CASTLE, D., DOUGLAS, A. J., *et al* (1994) The criminal careers of incident cases of schizophrenia. *Psychological Medicine*, **24**, 483–502.

WILSON, W. H. & CLAUSSEN, A. M. (1994) Seizures associated with clozapine treatment in a state hospital. *Journal of Clinical Psychiatry*, **55**, 184–188.

WORLD HEALTH ORGANIZATION (1978) *Mental Disorders: Glossary and Guide to their Classification in Accordance with the Ninth Revision of the International Classification of Diseases*. Geneva: WHO.

——— (1992) *The Tenth Revision of the International Classification of Mental and Behavioural Disorders* (ICD–10). Geneva: WHO.

YOVELL, Y. & OPLER, L. A. (1994) Clozapine reverses cocaine craving in a treatment-resistant mentally ill chemical abuser: a case report and a hypothesis. *Journal of Clinical Psychiatry*, **55**, 591–592.

The special hospitals' treatment resistant schizophrenia research group: **Pamela J. Taylor** (Professor of Special Hospital Psychiatry, Institute of Psychiatry (IOP), London SE5 8AF); **Martin Butwell** (Research Data Manager, Broadmoor Hospital); **Colin Gray** (Consultant Forensic Psychiatrist State Hospital, Carstairs, Scotland); **Rachel Daly** (Senior Registrar (SR), UDMS of Guy's and St Thomas' Hospital, London and formerly Rampton Hospital); **Brian Delal** (Senior Research Registrar, Rampton Hospital); **Dana Ferraro** (Case Register Assistant, SHSA and IOP); **Robert Gibb** (Research SR, Ashworth Hospital); **Tracy Heads** (Research SR, Broadmoor Hospital); **Bernard Huckstep** (Chief Pharmacist, Rampton Hospital); **Emmet Larkin** (Academic Consultant Forensic Psychiatrist, Rampton Hospital and Sheffield University); **Morven Leese** (Statistician, IOP); **Girish Shetty** (Director of Medical Professional Development, Ashworth Hospital); **Mark Swinton** (Senior Lecturer, Liverpool University and Consultant Forensic Psychiatrist, Ashworth Hospital); **David Tidmarsh** (former Senior Lecturer IOP and Consultant Forensic Psychiatrist, Broadmoor Hospital); **Deborah Williams** (SR, Oxford rotation and formerly Rampton Hospital)

Correspondence: Professor Pamela J. Taylor, Professor of Special Hospital Psychiatry, Institute of Psychiatry, London SE5 8AF