original papers

Psychiatric Bulletin (2003), **27**, 14–16

JATINDER J. S. BAINS AND OLAV B. NIELSSEN

Combining depot antipsychotic medications with novel antipsychotics in forensic patients: a practice in search of a principle

OBJECTIVE
We observed a pattern of combining depot antipsychotic medication with the newer 'atypical' antipsychotics in forensic patients. We aimed to determine the prevalence and rationale for such 'combination therapy'.

METHOD
The medical records of forensic patients in 3 forensic hospitals in New South Wales, Australia, were reviewed and the responsible psychiatrists asked to explain the rationale for treatment of those patients on combination therapy.

RESULTS
Twenty-two per cent of the forensic patient population were receiving combination therapy. The reasons given for combination therapy were the presence of treatment-resistant illness, to ensure adherence to at least part of the treatment and to assist transfer to lower security units.

CONCLUSIONS
Such a high prevalence of a practice that is discouraged and without theoretical justification is a cause for concern. It appeared to reflect the practical difficulties of managing forensic patients.

Forensic patients in New South Wales are either unfit to be tried, have been found not guilty of a serious offence on the grounds of mental illness or have been transferred to hospital because their illness could not be adequately managed in the mainstream prison setting. Most have schizophrenia, often complicated by substance abuse and antisocial conduct.

The authors observed that each of the five psychiatrists attending the maximum-security prison hospital had independently prescribed combinations of the more recently available atypical medications, olanzapine and risperidone, in combination with the conventional antipsychotic medications available in slow-release preparations given by injection. The treatment decisions were independent, and there was little review of each other's prescribing practices. Other centres have reported similar patterns of prescribing in treatment-resistant patients (Norrie & Hustig, 1998).

Several reasons were proposed for the decisions to prescribe a combination treatment. First, forensic patients are often prescribed medication against their will, and thus the use of atypical antipsychotics may be seen as a way of minimising distressing side-effects and also reducing the risk of developing tardive dyskinesia (by allowing the use of lower net doses of depot antipsychotic) (Umbricht & Kane, 1996; Brecher, 1996). Second, forensic patients are more often treatment-resistant (Beck *et al*, 1997), and a combination of medications may have been prescribed in the hope that this would provide a wider spectrum of efficacy. Third, many forensic patients have a history of poor compliance with treatment (Young *et al*, 1986). It has been observed that some patients do not take oral medication in tablet form even in the strictly-supervised setting of a maximum-security hospital. Fourth, in the community, mentally disordered offenders are often non-compliant with oral antipsychotics (Duncan & Rogers, 1998), and this (in combination with substance abuse) has been associated with prediction of serious violent acts in this population (Swartz *et al*, 1998). These factors may help to explain the considerable resistance to the transfer of forensic patients to lower-security settings in New South Wales. Treatment with depot medication has been seen as a secure form of treatment, more likely to result in a patient being accepted and approved for transfer to such a setting.

Method

Long Bay Hospital is a 90-bed maximum-security psychiatric hospital built in 1985 in the grounds of the largest prison complex in New South Wales. The forensic wards of Cumberland and Morisset Psychiatric Hospitals have 24 beds each, described as medium-security, and they usually accept forensic patients from the more secure setting.

The medical records of patients in all three hospitals were reviewed, with particular note being taken of diagnosis, duration of illness and the antipsychotic medication prescribed. For each patient receiving a combination therapy, the responsible psychiatrist was asked to complete a brief questionnaire to explain the reasons for giving this medication. For comparison, data were also collected from a group of 40 treatment-resistant patients living in three supervised group homes in the community.

Results

There were 60 forensic patients in Long Bay Prison Hospital at the time of the survey, all of whom were male, as female forensic patients are located elsewhere. There was a total of 45 forensic patients in the lower-security units of Cumberland and Morisset Hospitals (including 4 female patients). The total sample size was

https://doi.org/10.1192/pb.27.1.14 Published online by Cambridge University Press

therefore 105. The mean age was 36 years (range 20–77 years, s.d. 11.3). Schizophrenia was the most common diagnosis (*n*=96, 91.4%). Other diagnoses were schizoaffective disorder (*n*=3, 2.9%), delusional disorder (*n*=1, 1%), bipolar mood disorder (*n*=1, 1%), depression (*n*=1, 1%), severe personality disorder (*n*=1, 1%), epilepsy (*n*=1, 1%) and post-head injury syndrome (*n*=1, 1%). The diagnosis of substance abuse usually related to behaviour prior to admission, and was not often cited as a current diagnosis because the length of time spent in custody usually precluded recent drug use. The mean duration of illness, taken from the first recorded contact with psychiatric services where known, was 12.28 years (range 1–42 years, s.d. 9.37). There was little difference in length of diagnosis in patients receiving combinations of oral atypical antipsychotics and conventional depot antipsychotics (mean 10.21 years. s.d. 6.39), and patients not receiving such a combination (mean 12.33 years, s.d. 10.15).

Fifty-two per cent of patients (*n*=55) were receiving atypical antipsychotics, of which 35 (63.6%) were receiving olanzapine, 13 (23.6%) were receiving risperidone and 7 (12.7%) were receiving clozapine (Table 1). The mean doses were: olanzapine 17.6 mg per day, risperidone 4.7 mg per day and clozapine 387 mg per day, respectively. Far fewer patients were receiving oral forms of other antipsychotic medications (*n*=19, 18.1%).

Half the patients (*n*=52) were receiving depot antipsychotics, of whom 30 (57.7%) were receiving zuclopenthixol (mean dose 225 mg 2-weekly, range 50–600 mg every 2 weeks), 14 (26.9%) were receiving haloperidol (mean dose 68 mg 2-weekly, range 12.5–200 mg every 2 weeks), 6 (11.5%) were receiving flupenthixol (mean dose 60 mg 2-weekly, range 40–100 mg every 2 weeks) and 2 (3.8%) patients were receiving fluphenazine (mean dose 37.5 mg 2-weekly, ranges 25–50 mg every 2 weeks) (Table 2).

Twenty-three patients (22%) were receiving a combination of oral atypical and depot conventional antipsychotics. This compared with only 10 (9.5%) patients receiving oral conventional and depot conventional antipsychotics. Of those patients on combination therapy, only one was receiving a maximum (or as in this case, greater than maximum) dose of depot conventional antipsychotic, as defined by the *British National Formulary* (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2001).

The reasons cited for the use of depot preparations in addition to atypical antipsychotics (more than one could be given) were: treatment-resistance (*n*=20, 87%), a history of non-compliance with medication (*n*=14, 61%) and to assist in transfer to a lower-security unit (*n*=7, 30%). Only consultants at the maximum-security unit cited the reason as assisting the transfer to a lower-security unit. The objective of reducing the potential side-effects of treatment, with depot medications through seeking a lower net dose of depot by giving part of the treatment as an oral atypical antipsychotic, was not cited as a reason for combination therapy.

The reasons given for not prescribing clozapine to patients receiving combinations of other drugs were the resistance of patients to taking clozapine and the likelihood that they would not persist with oral medication or comply with the requirement of regular blood counts. Several of the patients had been treated with clozapine without success or had treatment withdrawn because of a haematological complication.

Table 1. Atypical antipsychotics prescribed (*n*=55)

Atypical antipsychotic	Mean dose (mg/d)	*n* (%)
Olanzapine	17.6	35 (63.6%)
Risperidone	4.7	13 (23.6%)
Clozapine	387	7 (12.7%)

Table 2. Depot antipsychotics prescribed (*n*=52)

Depot antipsychotic	Mean dose (mg/2-weekly)	Range (mg/2-weekly)	*n* (%)
Zuclopenthixol	225	50–600	30 (57.7%)
Haloperidol	68	12.5–200	14 (26.9%)
Flupenthixol	60	40–100	6 (11.5%)
Fluphenazine	37.5	25–50	2 (3.8%)

Eight (20%) of the community sample (*n*=40) were receiving a combination of depot medication and atypical antipsychotics. Thirteen (32.5%) were receiving depot antipsychotic medication and five (12.5%) were receiving clozapine. Treatment-resistance was cited as the reason for prescribing combination therapy for all of the patients in the community sample, with unreliable adherence to treatment cited as a reason for combination therapy in only two of those patients.

Discussion and conclusion

A review of the scientific literature revealed that combination therapy with atypical and conventional antipsychotics is not encouraged. The American Psychiatric Association's guidelines for the treatment of schizophrenia encourage monotherapy (American Psychiatric Association, 1997). The Royal College of Psychiatrists' Consensus Statement (Thompson, 1994) describes the practice of combining more than one antipsychotic as undesirable, although it may be occasionally acceptable in patients for whom it has been shown to be necessary from the experience of dealing with them for many years. Similarly, reviews of the management of treatment-resistant schizophrenia have usually recommended adequate trials of treatment with single antipsychotic medications, rather than combinations of antipsychotics (Pantelis & Barnes, 1996).

We found no publications reporting clinical trials of treatment with combinations of antipsychotic medication, although there are references to the practice as a strategy for managing treatment-resistant schizophrenia (Frankenburg, 1999; Norrie & Hustig, 1998; Daniel & Whitcomb, 1998). Weiden *et al* (1998) discuss combination therapy for patients with a high risk of non-compliance should depot medication be withdrawn, and

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who have only partially responded to treatment. In such a group, combination with atypicals was described as 'a practical way to augment the depot response'.

A possible benefit of combination therapy is that it may increase compliance with oral antipsychotic medication, as patients are more likely to become compliant with medication after their symptoms abate and insight develops. Moreover, the routine of taking regular medication may have developed through the use of combination therapy. Given these factors, it is possible that compliance with the oral antipsychotic may continue after the depot antipsychotic has been withdrawn. However, as far as we are aware, this assertion is not supported in the literature. The data did not support the assertion that combination therapy was used to reduce the distressing side-effects associated with typical antipsychotics in that none of the treating psychiatrists offered this as a rationale for treatment. Given this, and that only one of the patients on combination therapy was on a maximum dose of depot conventional antipsychotic, it may be that patients on combination therapy had not received an adequate trial of maximum-tolerated doses of depot antipsychotic.

The observation of widespread treatment with combinations of antipsychotic medication may reflect poor practice, as monotherapy is an agreed treatment goal for schizophrenia (American Psychiatric Association, 1997; Thompson, 1994). This is of particular concern as forensic patients are a vulnerable patient population. However, it is also recognised that forensic patients are more difficult to treat because of more severe, treatment-resistant illnesses, multiple diagnoses and a history of serious offending while psychotic. The survey reveals that in this group, compliance with treatment, severity of illness, treatment-resistance and transfer to lower-security settings are of particular concern to the treating psychiatrists. Although the community samples of severely treatment-resistant patients were not strictly comparable with the forensic patients, combination therapy was found to be as common in the community sample, and reflected an attempt to overcome treatment-resistance, rather than because of concern over non-compliance or dangerousness when untreated. This was supported by the finding that only a third of the community sample were receiving depot medication, compared with half of the forensic patients. A more representative estimate of Australian community practice is provided by a 1998 survey of 1034 patients prescribed antipsychotic medication within one area health service (Lambert & Singh, 2000). This survey found that 42% were receiving a depot preparation, but only 18% of those (7.6% of the total sample) were receiving a combination of depot and oral medication. The type of oral medication was not recorded.

Our survey has found that the prescription of oral atypical antipsychotic medications in combination with depot antipsychotic preparations is common, both in forensic patients and in a community sample, although for different reasons. The practice is discouraged and there is no published research to support such a combination on theoretical or practical grounds. However, this practice appears to be widespread because of the desire to attempt to overcome treatment-resistance and to assist management in lower-security settings. More generally, the practice probably reflects a deficiency in the range of treatment options currently available and the lack of a depot atypical antipsychotic.

Acknowledgements

We wish to thank Dr Peter Shea and Dr Andrew Walker at Morisset Hospital, and Dr Martin Patfield at Cumberland Hospital for their assistance in collecting the data.

Declaration of interest

Both J. B. and O. N. were employees of Long Bay Prison Hospital (Corrections Health Service) at the time the research was conducted. O. N. has received payment for lectures sponsored by GlaxoSmithKline and Janssen Cilag.

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***Jatinder J. S. Bains** Consultant Psychiatrist (Manly Hospital) and Lecturer in Psychiatry (Sydney University), East Wing, Manly Hospital, Darley Rd, NSW 2066, Australia, **Olav B. Nielssen** Consultant Psychiatrist, Corrections Health Service, Matraville, Australia

https://doi.org/10.1192/pb.27.1.14 Published online by Cambridge University Press