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Benzodiazepines in schizophrenia

Is there a trend towards long-term prescribing?

AIMS AND METHOD

We sought to determine the prevalence of long-term benzodiazepine prescribing in patients with schizophrenia occupying psychiatric rehabilitation beds. A cross-sectional survey was conducted in 11 National Health Service trusts.

RESULTS

Almost 10% of patients occupying rehabilitation beds had a diagnosis of schizophrenia and received long-term benzodiazepines in combination with one or more antipsychotics.

CLINICAL IMPLICATIONS

Our results are consistent with those of other authors and show that benzodiazepines are frequently used in the long-term in patients with schizophrenia despite a lack of open acknowledgement of this practice and a paucity of objective data to support its efficacy.

With a move away from using the sedative side-effects of antipsychotic drugs to control acute behavioural disturbance in the setting of mental illness, the use of benzodiazepines in this context has increased as they sedate effectively with minimal risk of side-effects. The Royal College of Psychiatrists consensus statement on the use of high dose antipsychotics (Thompson, 1994) clearly states that benzodiazepines alone or in combination with standard doses of antipsychotics are the drugs of choice when rapid tranquillisation is required. The principle being applied here is 'when sedation is required, use a sedative'. A problem then arises because of the time lag between the administration of antipsychotic drugs and therapeutic effect (Keck *et al*, 1989). For some patients this can be several weeks and additional sedation is often required during this time. It is at this point that the use of benzodiazepines to control behavioural disturbance parallels their use to control anxiety symptoms. When does acute disturbance become chronic disturbance and is the use of benzodiazepines in the longer term ever justified? It is our informal impression that the use of benzodiazepines in the medium- or long-term in patients with a schizophrenic illness that is difficult to treat is increasing locally and we sought to survey this in a larger patient sample.

Method

Pharmacists belonging to the South East Thames Psychiatric Pharmacists Network (a branch of the UK Psychiatric Pharmacy Group) were asked to identify all patients cared for by their trust who:

(a) occupied a psychiatric rehabilitation bed on the 9 November 1998;

(b) had a diagnosis of schizophrenia;

(c) had been receiving a benzodiazepine for more than six weeks.

Patients prescribed as required (p.r.n.) benzodiazepines were included only if doses were administered at least three times weekly.

Prescription records and clinical notes were then used to obtain the following demographic and clinical information for each patient: age, gender; age at onset of illness; and doses and routes of administration of all prescribed psychotropic drugs. The total number of beds surveyed by each pharmacist was recorded.

Results

Data were received from 11 trusts, covering a total of 315 rehabilitation beds. Participating trusts are listed in the Acknowledgements.

Twenty-nine patients with a diagnosis of schizophrenia who had received a benzodiazepine for more than six weeks were identified, representing 9.2% of patients occupying these beds. Twenty-one (6.6%) received regular and eight (2.5%) p.r.n. benzodiazepines. The mean age of the patients was 40.7 years (range 21–68) and the mean age of illness onset 21.4 years (range 11–34).

The most commonly prescribed benzodiazepine was lorazepam (n=17), followed by diazepam (n=7), clonazepam (n=4) and temazepam (n=1). The mean daily dose

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of lorazepam was 2.9 mg (range 1–6 mg), diazepam 10.4 mg (2–20 mg) and clonazepam 1.7 mg (1–4 mg).

All 29 patients were prescribed at least one regular antipsychotic with 12 receiving two or more. Eight patients received clozapine (three in combination with other antipsychotics), 15 other atypical antipsychotics (two in combination), 15 oral typical antipsychotics (four in combination) and four depot preparations (all in combination). By using the maximum *British National Formulary* (BNF, 1999) dose as 100% and adding percentages for those patients prescribed more than one antipsychotic, the total prescribed dose of antipsychotic ranged from 33–216% (mean 92%) per patient. Eight patients were prescribed more than 100% of the BNF recommended dose.

Fifteen patients were prescribed other psychotropic medication, nine of whom received a mood stabiliser and six an antidepressant.

Discussion

Almost one in 10 patients occupying rehabilitation beds had a diagnosis of schizophrenia and received benzodiazepines in the medium- or long-term. Possible reasons for this include: inadequate response to antipsychotics alone; an 'antipsychotic sparing effect' of the benzodiazepine; poor review of the drug regime after a period of acute disturbance; misuse by patients; and, in the case of p.r.n. medication, inappropriate use by staff.

Inadequate response to antipsychotics

It is generally accepted that 30% of patients with schizophrenia respond poorly if at all to conventional antipsychotics and a third of this group respond poorly to clozapine (Kane, 1992). The patients in our sample occupied a long-term hospital bed, and there was a high prevalence of antipsychotic polypharmacy, use of antipsychotics in total doses of over 100% of the BNF maximum and co-prescription of other psychotropic drugs, indicating that their illness was not easy to control. Alternative strategies are clearly required for these patients.

Benzodiazepines are prescribed in schizophrenia for a variety of reasons including: as hypnotics; to alleviate the side-effects of neuroleptics such as akathisia and tardive dyskinesia; to treat comorbid anxiety considered unrelated to the primary diagnosis and to treat core psychotic symptoms including negative symptoms (Lingjaerde, 1991). They possess some pharmacological effects that may, theoretically, be beneficial in patients with psychotic illness. Benzodiazepines facilitate γ-aminobutyric acid (GABA) transmission and GABA inhibits some dopamine pathways. It has been postulated that the resultant effect is similar to that achieved by neuroleptics, but via a different route (Easton & Janicak, 1991). Benzodiazepines block stress activation in the meso-prefronto-cortical tracts, a pathway which has few dopamine receptors. Wolkowitz *et al* (1992) postulate that this is the mechanism for augmentation of antipsychotic response in those individuals with schizophrenia who are sensitive to stress.

There are many reports of benzodiazepines usefully augmenting antipsychotic response when given in standard doses, although negative reports also exist. Wolkowitz & Pickar (1991) reviewed the literature in this area and concluded that 30–50% of patients respond favourably to the combination, although only a few in a very striking way. Those with more severe psychosis, motor disturbance or anxiety symptoms may respond preferentially and improvement may be seen across the whole range of psychotic symptoms including hallucinations, delusions, thought disorder and negative symptoms. Some patients were noted to respond within 24 hours. Virtually all the literature describes only the acute phase of treatment, with follow-up data beyond eight weeks rarely available. One exception to this is the study by Wolkowitz *et al* (1992), where five of seven patients who initially responded to alprazolam augmentation, showed sustained improvement after 37 months.

There is a suggestion that the tribenzodiazepines (estazolam, alprazolam and the closely related clonazepam) may be superior to the other benzodiazepines in augmenting neuroleptic response (Wolkowitz & Pickar, 1991). Some authors, however, recommended avoiding these high potency benzodiazepines and state a preference for diazepam or chlordiazepoxide stating that their longer half-lives are likely to lead to less risk of withdrawal psychosis secondary to non-adherence (Christison *et al*, 1991). This is speculative rather than proven. The issue of 'which benzodiazepine' is particularly important as diazepam and lorazepam are the benzodiazepines most frequently used for rapid tranquillisation (Pilowsky *et al*, 1992) and therefore, by default, the most likely to be prescribed on a chronic basis. This is confirmed by our findings.

Antipsychotic sparing effect

Pecknold (1993), surveyed 149 out-patients diagnosed as suffering from schizophrenia and found that 41% received both antipsychotics and benzodiazepines on a chronic basis. Those patients receiving combined antipsychotics and benzodiazepines received a lower overall dose of antipsychotic than the group receiving antipsychotics alone. This may be due to an antipsychotic sparing effect of the benzodiazepine or simply to the fact that the cohort receiving benzodiazepines were less ill. We did not survey antipsychotic doses in those patients with schizophrenia who did not receive benzodiazepines and so cannot confirm this finding.

Diazepam has been shown to be superior to placebo and as effective as fluphenazine in aborting prodromal symptoms of relapse in patients with schizophrenia who were otherwise medication free (Carpenter *et al*, 1999). That is, an antipsychotic sparing effect has been demonstrated in these circumstances. It is well recognised that ongoing antipsychotic medication does not guarantee that the patient will be relapse free and it is possible, although not proven, that benzodiazepines may have a similar protective effect in patients

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receiving antipsychotics who begin to decompensate, thus sparing them from exposure to increased doses of antipsychotics.

There are reports of both tolerance developing to the antipsychotic effect of benzodiazepines, and rebound psychosis on withdrawal (Wolkowitz *et al*, 1992) where for some patients more severe symptoms than those that were initially present before benzodiazepines were prescribed become apparent. This could be interpreted by prescribers as a benzodiazepine withdrawal reaction or, alternatively, as benzodiazepines having a true antipsychotic effect which when removed precipitates relapse.

Poor review of the drug regime

This may be in the form of failing to discontinue benzodiazepines after a period of acute disturbance, or failing to use a more effective antipsychotic (i.e. clozapine) where it is indicated. Most of the respondents reported a small number of patients who fulfilled our criteria and there was not a striking difference in prevalence rates between trusts. It seems unlikely that a similar proportion of patients in each trust would have their prescription review neglected in the same way. Our data does not allow further discussion of this point.

Misuse by patients

Dependence is potentially a major problem when benzodiazepines are used to treat anxiety spectrum disorders and although some authors express the opinion that such problems are less likely in patients with schizophrenia (Wolkowitz & Pickar, 1991), a survey by Hawley *et al* (1994) which identified 6% (10 times the prevalence rate for schizophrenia) of hospital benzodiazepine-dependence clinic attendees as suffering from schizophrenia would not support this view. Benzodiazepines should always be used with caution in those with a history of drug or alcohol misuse.

Inappropriate use by staff

Over a quarter of patients who were receiving benzodiazepines had p.r.n. prescriptions which were administered at least three times a week. It is possible that staff resorted to medication too easily and that using de-escalation techniques such as talking down, one to one attention or 'time-out' may have reduced the need for p.r.n. Again, our data does not allow further discussion of this point.

Implications

The results of this survey are in line with those of Pecknold (1993) and Hawley *et al* (1994) and show that a substantial proportion of patients with schizophrenia receive benzodiazepines in the long-term. It is time to openly acknowledge this practice and gather objective data to evaluate its efficacy and risks.

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