

The use of benzodiazepines in palliative care

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Background: Benzodiazepines are widely used in palliative care, but few studies have attempted to study their use. **Aim:** To determine the frequency and nature of benzodiazepine prescribing in a palliative care setting. **Method:** The notes of a consecutive series of 100 patients who had died or been discharged from the hospice were studied. Demographic, illness and prescription data were noted. The indication for the administration of benzodiazepines, their effectiveness and any adverse effects were recorded. **Results:** Notes were found on 93 patients. Some 54 (58%) were prescribed benzodiazepines either by the hospice or their General Practitioner. Younger patients and those on opioids or anti-psychotics were more likely to be prescribed benzodiazepines. Most administration of benzodiazepines occurred within the last three weeks of life in response to symptoms of anxiety or less specific distress. **Conclusions:** A relatively high proportion of patients was prescribed benzodiazepines. The role of benzodiazepines at different stages of palliative care merits further study. *Palliative Medicine* 2006; **20**: 407–412

Key words: anxiety; benzodiazepines; depression; palliative care

Background

Prescribing medication to alleviate distressing symptoms is a core aspect of palliative care. The extensive use of opioids, which are subject to legislative controls and tend to be used sparingly in other settings, has become a defining characteristic in this area of practice. Benzodiazepines are another class of drugs extensively used in palliative care.

Benzodiazepines, although widely prescribed in both general and hospital practice 20 years ago, are now subject to tighter controls similar to, though not as stringent as, those applied to opioids.¹ This is mainly due to their high potential for producing dependence. Such concerns are much lower in a population with advanced disease. The high levels of psychological morbidity in this population, together with the apparent effectiveness of benzodiazepines in relieving short term anxiety have led, anecdotally at least, to high levels of use in a palliative care setting. However, the use of benzodiazepines is not without risk. These drugs can worsen confusion and lead to increased rates of falls.² The potential for dependence if given for longer than a few weeks exists, and their use can make accurate assessment of depression,³ or the psychological management of anxiety,⁴ more difficult.

There are only a few studies describing the prescribing practices in palliative medicine. Drummond *et al.*, sent

questionnaires to hospices in Australia asking about the frequency of use of a number of drugs.⁵ A total of 36% of hospices reported using subcutaneous midazolam and rather more used midazolam with other medications in syringe drivers. Curtis and Walsh have described the prescribing habits of an outpatient palliative care service in the USA.⁶ Some 21% of patients were taking hypnotic medication, and 4% were taking anti-anxiety medication, though it is not clear if any patients were taking both medications. Hoskin and Hanks reported on the medication received by 158 patients at the Royal Marsden Hospital, a specialist oncology hospital.⁷ A total of 39% were prescribed anxiolytic drugs, presumably benzodiazepines, although this was not further described. Most recently, Sykes and Thorns reviewed the use of sedative drugs, including benzodiazepines, in the last week of life and found that 82% of patients received midazolam on at least one occasion.⁸ Building on this work, we aimed to explore more widely the use of benzodiazepines in our unit.

Aim

The aim of the study was to describe the numbers and characteristics of our patients who were prescribed benzodiazepines and other psychotropic medication. We attempted to identify the indications for administering benzodiazepines together with an assessment of the level of information recorded in the patients' notes as to the indication for the administration, the effectiveness of the medication and what record was kept of adverse effects.

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Method

Patients who had been cared for by St Christopher's Hospice were studied. The hospice has up to 48 inpatients and approximately 500 home care patients at any one time. Starting from a cut-off date of 30 September 2002, we identified the previous 100 patients who had ended their hospice care, whether as in-patients or at home. This largely consisted of patients who had died, but also included those who had been discharged from the service. The information gathered from the notes and drug charts can be divided into four categories:

- i) Patient information, including demographic details, diagnosis, source of referral and presence of a past psychiatric history.
- ii) Drug information, including administration of benzodiazepines, opiate analgesics, anti-psychotics and anti-depressants.
- iii) For those prescribed benzodiazepines, the main indication and frequency were noted together with evidence from the notes of effectiveness.
- iv) Based on the first documented administration of a benzodiazepine, the time from entry into palliative care to administration, and from administration to death was calculated.

Data were analysed using the Statistical Package for the Social Sciences (SPSS – v. 11.0). The χ^2 test was used for categorical variables and the Student's *t*-test for continuous variables. All P values were two-sided and a 5% significance level was used.

Results

The notes of 93 of the 100 patients identified were available. A total of 45% were male and the median age at referral to the hospice was 73 years. Just under one-third had been referred from primary care; the remainder came from local hospitals or other hospices. All patients had cancer, with gastro-intestinal (27%), lung (23%) and breast (12%) cancers being the most common. Some 23% of patients had a past psychiatric history recorded in the notes and 21% spent some time as an inpatient in the hospice.

Table 1 shows the results in both those prescribed and not prescribed benzodiazepines.

Of 93 patients, 54 (58%) had evidence of being administered benzodiazepines during their time in palliative care. Of these, eight were already being prescribed benzodiazepines on referral to the hospice and two had benzodiazepines solely in a syringe driver – almost all of the patients who did have benzodiazepines in a driver had previously been administered the medication either orally

or by injection. The median age of those prescribed benzodiazepines was 70 years as opposed to 80 years in those not prescribed benzodiazepines. There were no differences between male and female, different malignancies, or whether or not there was documented evidence of metastases. A past psychiatric history was no more common in those patients administered benzodiazepines (23%) compared to the others (22%). Patients with a period as an inpatient in the hospice, and those administered opiates and anti-psychotics were more likely to have been administered benzodiazepines.

Of the 46 patients commenced on benzodiazepines during their palliative care stay, 16 were prescribed a second benzodiazepine, six a third benzodiazepine and one patient a fourth benzodiazepine. Of those already taking benzodiazepines at the time of referral, one was prescribed three further benzodiazepines. In this group, a total of 69 separate benzodiazepine prescriptions were administered. Of these 69 prescriptions, 45 were on an 'as required basis', 19 regular and five via syringe driver. On more than four occasions, 22/45 'as required' prescriptions were administered and 14/19 regular prescriptions were administered for more than one week.

In 54/69 (78%) patients, an indication was recorded. Knowing exactly why these drugs were used is difficult as many clinical terms were used. These terms have been collected into broad categories in the table but there will be many areas of overlap, not least because on many occasions multiple reasons were given. Anxiety/agitation was the most common reason, accounting for more than one-third of prescriptions. Midazolam was the benzodiazepine most often used, followed by lorazepam and temazepam. In 70% of cases, we were able to find an entry identifying staff perception of effectiveness, almost always positively.

There was a wide variation in the timing of administration of benzodiazepines and the period from administration to death. The median time from referral to administration was 57 days out of a median hospice stay of 83 days. The median time from administration to death was 18 days. The point of first administration of benzodiazepines is shown in Figure 1.

Discussion

We examined the notes of patients who had been under the care of a large hospice in London. The characteristics of the patients appear to make them representative of patients receiving palliative care in the UK. Some 58% had documented evidence of having received benzodiazepines whilst under the care of the hospice. This is lower than the figure found in the previous study from our unit,⁸ and as no relevant procedural changes have occurred in the meanwhile, this is presumably as a result of

Table 1 Patient characteristics and prescribing information

	Total study population (<i>n</i> = 93)	New benzodiazepine prescribed (<i>n</i> = 46)	Not prescribed benzodiazepine (<i>n</i> = 39)	Statistics
Patient information				
Age				
Median (IQR)	73 (62–84)	70	80	$U = 567$, $P = 0.004$
Gender				
Male <i>n</i> (%)	36 (38%)	20 (43%)	16 (41%)	$\chi^2 = 0.05$, $df = 1$, $P = 0.82$
Referred by				
Primary care (<i>n</i>)	31 (33%)	14 (30%)	17 (44%)	$\chi^2 = 1.58$, $df = 1$, $P = 0.21$
Hospital (<i>n</i>)	54 (67%)	32 (70%)	22 (56%)	
Diagnosis				
Lung cancers (<i>n</i>)	18 (19%)	9 (20%)	9 (23%)	
GI cancers (<i>n</i>)	23 (25%)	13 (28%)	10 (26%)	
Breast cancers (<i>n</i>)	9 (10%)	6 (13%)	3 (8%)	
Prostate cancer (<i>n</i>)	4 (4%)	1 (2%)	3 (8%)	
Pancreas cancer (<i>n</i>)	4 (4%)	3 (7%)	1 (3%)	
Kidney/bladder cancer (<i>n</i>)	5 (5%)	1 (2%)	4 (10%)	
Gynaecological cancers (<i>n</i>)	5 (5%)	4 (9%)	1 (3%)	
Haematological cancers including lymphomas (<i>n</i>)	4 (4%)	2 (4%)	2 (5%)	
Others (<i>n</i>)	13 (14%)	7 (15%)	6 (15%)	
Metastatic disease documented (<i>n</i>)	56 (60%)	30 (65%)	26 (67%)	$\chi^2 = 0.02$, $df = 1$, $P = 0.89$
Past psychiatric history (<i>n</i>)	19 (20%)	11 (23%)	8 (21%)	$\chi^2 = 0.14$, $df = 1$, $P = 0.71$
Drug information				
Prescribed benzodiazepines	54/93 = 58%			
	8/93 prescribed benzodiazepines at time of referral 46/93 benzodiazepines commenced in palliative care (these 46 patients received prescriptions for 69 benzodiazepines)			
Benzodiazepine prescriptions for syringe driver (<i>n</i>)	5/69 (7%)			
Prescribed opioids (<i>n</i>)	78 (83%)	43 (93%)	27 (69%)	$\chi^2 = 8.5$, $df = 1$, $P = 0.003$
Prescribed anti-depressants (<i>n</i>)	26 (28%)	15 (33%)	9 (23%)	$\chi^2 = 0.95$, $df = 1$, $P = 0.33$
Prescribed anti-psychotics (<i>n</i>)	25 (28%)	18 (39%)	6 (15%)	$\chi^2 = 5.87$, $df = 1$, $P = 0.02$
Prescribing information				
Indication recorded (<i>n</i>)	54/69 (78%)			
Indication				
Anxiety/panic/restlessness (<i>n</i>)	25			
Sleep disturbance (<i>n</i>)	8			
Dyspnoea (<i>n</i>)	7			
Seizures (<i>n</i>)	1			
Distress	9			
Other	4			
Which benzodiazepine				
Midazolam	30			
Lorazepam	21			
Diazepam	4			
Temazepam	13			
Others	1			
Effectiveness recorded (<i>n</i>)	48/69 (70%)			

sampling variations. Conversely, it is higher than levels of benzodiazepine prescription previously reported elsewhere in a palliative care context, although it is not clear how closely comparable the populations were. It may reflect improving recognition of anxiety in palliative

care,^{9,10} and a corresponding increase in the use of anxiolytic medication.

Younger patients and those taking opioids were more likely to be prescribed benzodiazepines, but there was no link with a past history of mental illness. Other reports

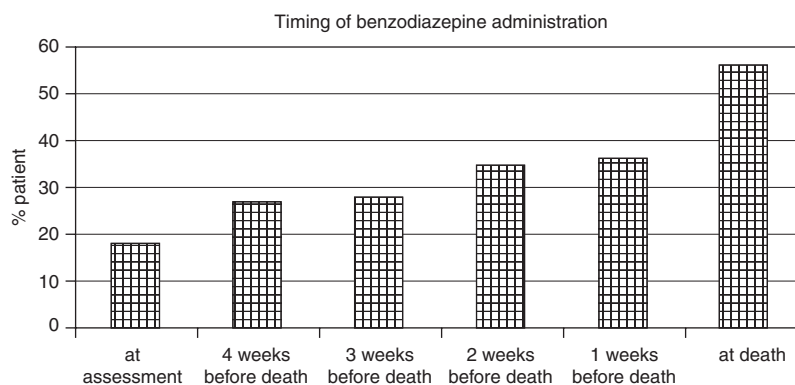


Figure 1 Timing of benzodiazepines administration

have suggested that younger patients are more likely to require opioid medication, often at higher doses.^{11,12} That younger patients were also more likely to be prescribed anti-psychotics is consistent with the observation that younger patients have, in general, more difficulty dealing with the symptoms of advanced disease.^{13–16} Given the characteristic age distribution of a palliative care population, however, it is not surprising that many of the patients prescribed benzodiazepines in our sample were elderly.

Only 9% of patients were taking benzodiazepines at the start of their hospice care, therefore the great majority of those who received benzodiazepines did so only while receiving specialist palliative care. But benzodiazepine treatment was concentrated in the last phase of life, with the drugs mostly being given for the first time within three weeks of death. There is, therefore, a strong association with advancing illness and deteriorating condition. The finding that benzodiazepines were more likely to be given to people who had needed admission rather than being able to remain at home suggests that these drugs were often part of a response to the more challenging symptoms encountered in a subset of patients towards the end of life.

The indications for which benzodiazepines were administered were given in about four out of five cases. It is possible that in some cases an indication was not given because despite the essential similarity of benzodiazepines as a drug class, particular indications are associated with particular agents, eg, temazepam as a hypnotic, or clonazepam as an anti-convulsant or as a treatment for neuropathic pain. Although terminology varied between staff, a diagnosis of anxiety or terminal restlessness was most likely to prompt the administration of benzodiazepine. However, there appears to be a group of 'distressed' patients who have a combination of pain, anxiety, breathlessness and sleep disturbance, who are prescribed a number of medications including benzodiazepines in an attempt to alleviate these symptoms. In the 70% of patients who had an outcome recorded for use, whatever

the indication, the desired effect was predominantly achieved.

Few patients were given benzodiazepines extensively. Only about a quarter (28%) of prescriptions were for regular oral administration, and 65% were 'as required' only. Half of the latter were actually administered on less than four occasions. The number of occasions when benzodiazepine was given via a syringe driver is perhaps lower than might have been expected given the popularity of this device in end of life care, this route accounting for only 7% of prescriptions. Nevertheless, the fact that 30 of 69 benzodiazepine prescriptions (43%) were for midazolam indicates that this class of drug was frequently indicated in situations where parenteral administration is appropriate, reinforcing the emphasis on the very final stages of life.

The advent of palliative care played an important role in widening the appropriate use of opioid analgesics. The relatively high level of benzodiazepine prescriptions in our study suggests that the same is happening here.

Protocols for the use of benzodiazepines in other healthcare settings emphasize the need for short courses, low doses and the avoidance of 'as required' prescriptions.^{17–19} There is little evidence for long term efficacy, but with a median stay under the hospice's care of just over three months, relatively few of our patient group could be said to have long term benzodiazepine use unless they had been taking this class of drug prior to hospice referral. Indeed, the fact that half of all benzodiazepine use was within the last three weeks of life and by a parenteral route implies that the patient group under consideration here is different from those with which usual guidance for benzodiazepine use is concerned. The relevance of benzodiazepine protocols to palliative care settings remains unclear.

Of course there needs to be awareness of potential problems arising from benzodiazepine prescribing. Although in people with a short prognosis, concerns about dependence are much reduced, benzodiazepines have a number of adverse effects, including falls, drowsiness, dizziness and impaired cognitive function. Most

patients with advanced disease will have a number of risk factors for such symptoms, but recognizing and minimizing the role played by benzodiazepines is important. On the other hand, it must be acknowledged that benzodiazepines are only one of many medication-related causes for such events in the polypharmacy that is characteristic of palliative care. Although benzodiazepine use alone is associated with a heightened risk of falls, a much greater risk arises from use of multiple drug combinations.²⁰ Neither are benzodiazepines uniquely liable to precipitate falling in ill or elderly patients, the combined use of drugs with anti-cholinergic effects has been found to be a more important association with falling than benzodiazepines alone,¹⁷ and anti-depressants (whether tricyclics or SSRIs) and anti-convulsants are also associated with falls.²¹ Interestingly, opioid use alone appears not to be associated with falls.²¹

It might be argued that benzodiazepine prescribing represents a medicalization of distress, a 'quick fix' to deal with distress which might, if picked up early, have been tackled by listening to concerns, providing reassurance, and so on. We did not examine the extent to which our group received formal psychological support. Whether or not this is provided, there are some situations where the approach of death is so distressing that only pharmacological assistance appears practicable, although more research is needed on determining the relative appropriateness of drug and non-drug approaches at different stages in the patient's journey. Nonetheless, in patients who are well enough, psychotherapeutic approaches, such as cognitive behavioural therapy, are successful comparative to the use of drugs and can have an impact on anxiety in as little as one session,²² although still at the cost of greatly increased staff time compared with the use of drugs. In our unit, a study is currently under way to assess the practicability and effectiveness of providing cognitive behavioural therapy for anxious hospice patients at home.

A further concern is that benzodiazepine prescribing might be a response to symptoms of more serious underlying depressive and anxiety disorders. Depression is undoubtedly common in advanced disease,²³ and symptoms of anxiety are very common in depressive disorders. Anti-depressant prescriptions might be a more effective treatment, associated with different, though not necessarily fewer, adverse effects. The delay in onset of anti-depressant action can mean that some early use of a benzodiazepine may produce a more prompt therapeutic response for patients with a limited life expectancy.²⁴

It may be that in the palliative care environment the level of benzodiazepine prescribing we found is appropriate given the high levels of distress and symptoms in this population. Without firm evidence from randomized controlled trials, it is not possible to state an optimum level of prescribing. However, for at least half of our

group who received benzodiazepines, it is hard to see how such trials could be carried out or what would be the comparator. We have already reported on the range of sedative drugs used in this unit,⁸ and shown the lack of evidence for any effect on length of life. More subtle differences in action between benzodiazepines and anti-psychotics in a palliative care population would require further study, but the class differences in adverse effects are well known. Adverse effects of benzodiazepines were rarely noted in our sample, but whether this reflects a truly satisfactory result or simply a lack of recording cannot be stated.

This study has a number of limitations. We examined case notes and drug charts rather than patients – there were variations in the completeness of the notes, eg, in the area of past psychiatric history. In addition, although the clinical nurse specialists involved with the patients at home, work closely with prescribing doctors in primary care, it is possible that some patients were prescribed medications, including benzodiazepines, without the hospice being aware. The study was carried out in a single hospice and, thus, we are cautious of generalizing our results.

Conclusions

A total of 58% of patients under hospice care had been administered benzodiazepines, a higher figure than shown in other studies of palliative care populations. Younger patients and those prescribed opiates or anti-psychotics were more likely to be administered benzodiazepines. Half of the benzodiazepine use was concentrated in the last two to three weeks of life, with a major use of parenteral routes, suggesting a response to the symptoms of far advanced disease or the onset of dying. Although there were omissions, 70–80% of patients had a record of the indication for the drug and its effectiveness. A record of adverse effects was found much more rarely. Further studies are needed to evaluate the role of benzodiazepines in palliative care and, in particular, to assess the identification and treatment of depression and the use of non-pharmacological approaches to anxiety in this patient group.

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