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Benchmarking benzodiazepines and antipsychotics in the last 24 hours of life

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Abstract

Aim To document benzodiazepines and antipsychotics (BDZ/APS) given to patients in the last 24 hours of life to establish normal prescribing patterns in hospices across New Zealand (NZ).

Methods A cross-sectional benchmarking design with retrospective chart review was carried out across 14 NZ hospices. Data (n=351) on medication use and dosages was analysed for inter-hospice variability. Analysis was shared with participating hospices for reflection.

Results There are significant differences in how these predominantly sedative medications are used within hospices in NZ, though the reasons for this cannot be commented on in this study. Diagnosis, place of death and use of the Liverpool Care Pathway influence how medications are used.

Conclusion NZ hospices are willing to submit data to enable the description of usual medication use in NZ, and have established that variations in prescribing and administration exist. This enables self reflection on the variations and the establishment of an ongoing benchmarking exercise.

The use of benzodiazepines and antipsychotic (phenothiazines and butyrophenones) medication in the final 24 hours of life is common within palliative medicine. These medications are used for a variety of indications, including nausea, delirium, anxiety, dyspnoea and seizures. However they are often grouped together as 'sedative' medications, regardless of the intent with which they are being used, as a side effect for most of these can be a degree of sedation.

Sedative drugs can be used as part of a targeted treatment to lower a patient's consciousness in a titrated, proportional way for relief from intolerable and refractory symptoms. This specific use is known as palliative sedative therapy (PST), terminal sedation or palliative sedation.

Many ethical questions and controversy surround the use of PST but it has general acceptance within palliative medicine as an infrequently used end-of-life treatment option. Detailed guidelines are now available from the US and Europe,[1,2] which includes the call for a regular review of practice for the purposes of improving quality of care (p921).[1]

However BDZ/APS are frequently used at the end of life for many different and often much less clearly defined indications, including anxiolysis and terminal restlessness.[3] For this latter indication, prescribing and administration practices may vary widely, and has both advocates and critics.[4–7]

Where there is no universally agreed best practice, benchmarking is useful in enabling sometimes isolated health care providers ensure their practice is compatible with that of their colleagues[8,9] and may help improve practice.[10]

'Normal' prescribing of BDZ/APS in NZ is not well documented although there are some guidelines.[11,12] Given this possible variation, hospices in NZ volunteered to submit data to establish a benchmarking cycle of these medications at the end of life in NZ. In this context, the benchmark is not against a standard or a centre of excellence, but rather it establishes a range and distribution of practice within which a hospice can orientate and understand its own practice.

This is the third cycle for benchmarking medication at the end of life, with data on opioid use previously published.[13]

Method

Study design—A cross-sectional design with retrospective chart review was used. All hospices with inpatient beds (n=18) identified through the Hospice New Zealand (HNZ) website were invited to take part with a written invitation. An open invitation was also circulated to all hospices through the HNZ e-mail list.. The written invitation included a document outlining the aims of the study and instructions on how to complete the electronic data collection template.

Hospices were asked to undertake a retrospective review of notes and drug charts of consecutive patients who died under their care in February and March 2008. The expectation was that this would provide at least 20 patients for each unit, recognising some small hospices would not meet this goal, and larger hospices would exceed it.

For admission to the study patients had to be under hospice care for at least the last 24 hours of their life and be 18 years or older. An accurate record of medications administered had to be available, which for many hospice teams confined the suitable patient pool to patients who had died in their Inpatient Unit (IPU).

The study variables were age, gender, diagnosis (coded using the UK palliative care minimum data set[14] with the addition of Melanoma as a specific diagnosis), use of the Liverpool Care Pathway (LCP) and place of death (Inpatient Unit (IPU), Aged Residential Care (ARC), public hospital or home).

The template allowed for documentation of each medication used, the route of administration, and the total amount of medication administered in the 24 hours before death. For continuous subcutaneous medication or long-acting medication which was either started or changed during the last 24 hours, pro-rata calculation was used to ascertain the actual dosage delivered. Other medications given for symptom management and any comments thought to be relevant were also recorded.

The templates were collated, and the initial analysis shared with the contributing hospices for comment and correction. The final analysis was returned to each hospice containing their own analysed data, enabling them to compare medications and dosages used with the rest of NZ.

Analysis—Data was anonymised by allocating each hospice a number, and entered into PASW (Previously SPSS) Version 18.0 for statistical analyses. This included descriptive analysis, then analysis of variance looking for differences in practice between hospices. A log transformation of the dosage data was used to more approximate a normal distribution, and to exclude 'nil' dosages from the calculation of median dosages. A Haloperidol Equivalent Daily Dosage (HEDD) as described by Hui[15] was used to combine haloperidol and levomepromazine (Nozinan™) as a single dosage figure. (HEDD=total haloperidol dosage (mg) by any route + oral levomepromazine dosage (mg) × 8/300 + parenteral levomepromazine dosage (mg) × 8/100.)

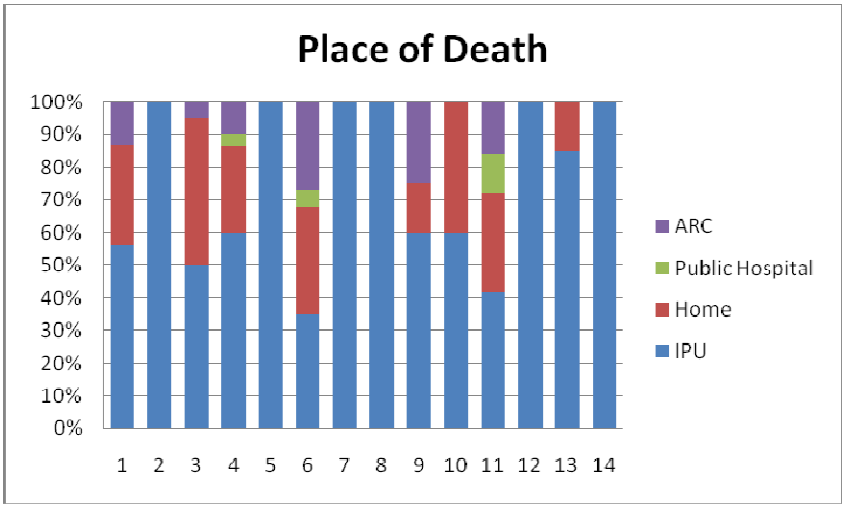
To facilitate an easy visual comparison between hospices, a drug 'footprint' was devised for both benzodiazepines and antipsychotics which records the percentage of patients in each hospice receiving a particular medication or no medication. Only the occurrence of use is displayed, regardless of the frequency or dosage of each medication administered to a patient.

Ethics—A certificate of approval was obtained from the New Zealand Health and Disability Ethics Committee (Central Regional Ethics Committee). Further ethical approval was not required for this retrospective study.

Results

Fourteen hospices across rural and urban NZ contributed data on 351 patients. There were 181 males and 170 females, with a mean age of 70 (range 21–96). 64 patients died at home, 6 in a public hospital, 251 within a hospice inpatient unit and 30 in an ARC setting. (Figure 1).

Figure 1. Percentages of patient data for each place of death over 14 hospices



302 patients (86%) died of cancer-related diseases and 49 (14%) died of non-malignant disease. The most common cancers were gastrointestinal (24%), lung (17%), prostate and breast (both 7%) and melanoma (6%), while notable non-malignant diseases included chronic respiratory disease (4%) and heart failure (3%).

Benzodiazepines included midazolam, clonazepam, and flunitrazepam, with single uses of diazepam and lorazepam. Antipsychotics were commonly haloperidol and levomepromazine. Quetiapine and risperidone were used infrequently. Phenobarbitone was used once. Separate footprints for benzodiazepines and for antipsychotics have been generated (Figures 2 and 3).

Seventy-five percent of patients overall received a benzodiazepine. Midazolam was the most commonly used, although flunitrazepam was preferred at one hospice. The percentage of patients in each hospice receiving either midazolam or flunitrazepam in the last 24 hours of their life varied from 40%–87%. If any benzodiazepine was included, percentages ranged from 45%–93% (Figure 2).

Up to 39% of patients at each hospice received more than one benzodiazepine, with a median of 5%. The combination of benzodiazepines was always midazolam and clonazepam apart from two instances of midazolam and flunitrazepam.

Figure 2. Benzodiazepine footprint

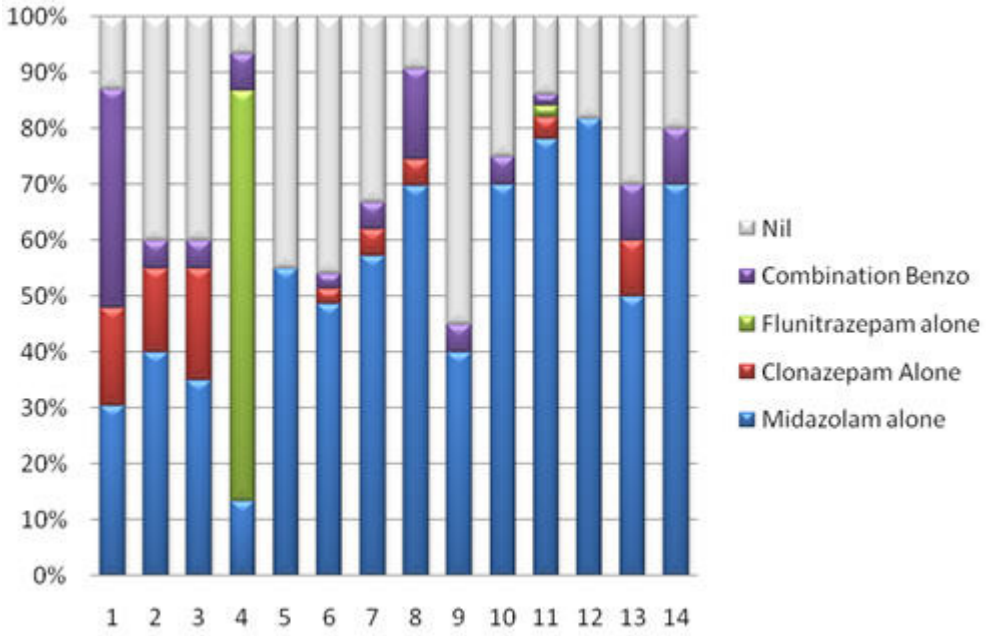
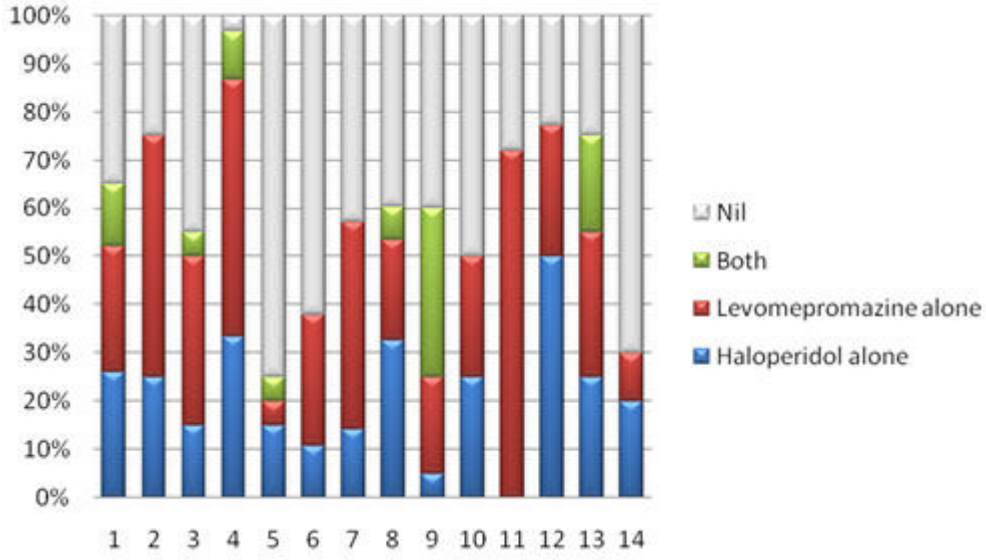


Figure 3. Antipsychotic footprint



Overall 62% of patients received an antipsychotic, with levomepromazine used more frequently than haloperidol (147 vs 94 patients). There was a range in the incidence of the use of any antipsychotic from 30% up to 97% between hospices (Figure 3). Up to 35% of patients at a hospice received the combination of both haloperidol and levomepromazine with a median of 2.5%.

About three-quarters of patients receiving levomepromazine were administered 12.5 mg or less in 24 hours (74%), 13% received over 25 mg.

Dosage of medications—Table 1 shows the range, median and mean for dosages of the five principal medications.

Table 1. Dosage descriptors

Medication	Range (mg)	Median (mg)	Geometric mean (mg)
Midazolam	1–118	15	20.7
Flunitrazepam	0.5–96	12	20.5
Clonazepam	0.125–5	1	1.3
Haloperidol	0.1–10	2.5	2.73
Levomepromazine	0.1–275	12.5	21

When comparing dosages across patients who died in the different hospice IPUs, there is a significant variation between the 14 institutions in midazolam and HEDD dosages (Table 2).

Table 2. ANOVA using hospice as dependant factor

Variables		df	F value	P value
Midazolam	All deaths	208	1.971	0.025
	Deaths in IPU	156	1.880	0.037
HEDD	All deaths	219	4.203	<0.001
	Deaths in IPU	162	1.916	0.032

HEDD=haloperidol equivalent daily dosage; IPU=Inpatient Unit; df=degrees of freedom.

Table 3. (Bivariate) comparisons of midazolam dosage

Midazolam	Geometric mean Midaz (mg)	N	df	F value	P value
IPU death	14.8	157			
			208	7.950	0.005
Death not in IPU	9.8	52			
Male	13.1	106			
			208	0.050	0.823
Female	13.6	103			
Malignant (IPU)	15.2	135			
			156	0.847	0.359
Non-malignant (IPU)	12.5	22			
Died on LCP*	15.3	46			
			156	10.824	0.001
Died off LCP*	9.5	24			
Died in IPU using LCP	15.8	70			
			156	0.643	0.424
Died in IPU not using LCP	14.0	87			

*Includes only hospices using the LCP; LPU=Liverpool Care Pathway; IPU=Inpatient Unit; df=degrees of freedom.

Some of this variation will come from the significant difference in the dose of midazolam used by patients dying in an IPU when compared with dying in places other than an IPU, (Table 3), however when considering just patients who died in IPUs, there is still a significant difference between hospices. To take this variation out of the analyses, most analyses will use data just from patients dying in IPUs.

When looking at IPU patients, there is a difference in midazolam dose between those on the LCP and those not on the LCP. However hospices that used the LCP were not using different dosages of midazolam overall. Diagnosis in IPU patients (malignant vs non-malignant) did not alter the dosage of midazolam, and gender for all patients did not alter the dosage.

Table 4. (Bivariate) comparisons of haloperidol equivalent daily dosage (HEDD)

HEDD	Geometric mean HEDD	N	df	F value	Significance
IPU death	1.42 mg	163	219	6.342	0.013
Death not in IPU	0.99 mg	57			
Male (all)	1.28 mg	108	219	0.053	0.819
Female (all)	1.32 mg	112			
Malignant(all)	1.34 mg	193	219	7.736	0.189
Non-malignant (all)	1.03 mg	27			
Died on LCP*	1.82 mg	72	137	13.006	<0.001
Died off LCP*	1.03 mg	66			
IPU in LCP hospice	1.64 mg	92	162	5.298	0.023
IPU in non-LCP hospice	1.18 mg	71			

*Includes only hospices using the LCP; IPU=Inpatient Unit; df=degrees of freedom.

Using the HEDD, patients dying outside the IPU received a lower mean dose of antipsychotics (Table 3). Comparison again showed significant differences between the 14 hospices in the use of antipsychotics (Table 1), which remained when only those who died in an IPU were analysed. In hospices that used the LCP, patients who died on the LCP received a higher mean dose of antipsychotic than those who were not on the LCP.

In contradistinction to the pattern of benzodiazepine administration, hospices using the LCP were using a higher median dosage of antipsychotics than those who had not adopted the LCP. Again neither diagnosis nor gender made a significant difference to the dosage of antipsychotic for IPU deaths.

Discussion

The purpose of this study is to provide data for hospices to reflect on their own practice in the context of NZ. The importance of having national data is demonstrated by Claessens'[16] comprehensive review of the international literature on palliative sedation, which notes the inconsistencies in definitions of sedation, and significant variations in prevalence, indications and dosages across the literature.

Variations in practice occur between countries,[17] between centres in the same country,[18] and within the same centre over time.[19,20] The interpretation and comparison of studies is therefore difficult as they are reporting on different patient populations, with variations in staff training, skills and resources and in the context of different cultural practices and priorities.[21,22] Because of this, the usefulness or validity of applying this literature directly to NZ is questionable, other than demonstrating the potential scope of variation in the use of these medications.

This collection of data has demonstrated significant differences in medications (both benzodiazepines and antipsychotics) being used across the country. The footprints give an idea of the different frequencies of medication use, which are not amenable to statistical analyses because of the small numbers from each hospice. However, they do provide a useful start for reflection by each hospice on how their prescribing sits compared to their peers'. The dosage data is robust enough for analyses, and this is discussed below.

As a country, the frequency of benzodiazepine use in NZ is as high as any international reports.[23] The footprint for benzodiazepines shows the predominant use of midazolam as the first line benzodiazepine at the end of life, which is in line with international recommendations.[1,24] The dosages are skewed as expected towards the lower amounts.

In NZ small doses of a benzodiazepine are often used for anxiolysis or to treat terminal restlessness. How significant these dosages are in lowering consciousness significantly over the 24 hours is debatable. Sykes and Thorns[25] arbitrarily called a midazolam dosage of over 10 mg in 24 hours 'sedative', which would apply to 60% of NZ patients receiving midazolam. This is a similar percentage to that recorded in a UK hospice by Stephenson.[19] Seventeen percent of patients on midazolam (10% of the total patient pool) received doses above 30 mg. When the intent is lowering of consciousness, recommendations for PST start at 0.4 mg/hr (10 mg/day) and are expected to reach as high as 20 mg/hr (480 mg/day).[26]

Midazolam dosages did not correlate to diagnosis, unlike opioid dosages which are higher in malignant disease.[13] Patients dying in IPUs received higher mean dosages of midazolam. An assumption can be made that those dying in IPUs have higher symptom burdens and more complex needs than those dying elsewhere, but this remains an assumption.

Patients on the LCP tended to have higher dosages of midazolam, but as there was no difference in dosages between hospices that used the LCP and those that did not, it is likely that the differing dosages are a function of the disease trajectory (less rapid and more expected) of patients who are started on the LCP, rather than an effect of the LCP per se. The fact that the introduction of the LCP has no effect on the mean

dosage of midazolam used in a hospice is supportive of the idea that the LCP is not a change in practice for hospices, but rather incorporates existing practice.

The variation between hospices of midazolam dosages is not explained, and may provoke some reflection and discussion amongst hospices. There is no clear reason for variations in midazolam dosages in the literature, although it is recognised that individual responses to these medications vary widely, particularly in the presence of renal and hepatic failure. Morita[27] investigated causes for the variations in midazolam dose, but the identified factors of icterus, age, pre-exposure to midazolam and length of sedation only accounted for 36% of variation.

The use of flunitrazepam was quite confined at the time of the study, and appears less frequently in the literature. Bioequivalence may be about 5 to 10 times the potency of midazolam, with a longer half life.[28,29] Although it is a hypnotic it may also have a very useful role as an anxiolytic in a palliative care setting, and perhaps as a respiratory depressant.[28,30,31] European guidelines recommend starting with a bolus of 1–2 mg, then 0.2–0.5 mg/hr[2].

Similarly to midazolam dosages, antipsychotic dosages varied between hospices. They have their own specific indications, perhaps more clearly defined than benzodiazepines.

Haloperidol is a major tranquilizer and not a sedative.[35] It is the drug of choice for delirium, which affects up to 85% of the hospice population in the last weeks of life,[15,32] and for nausea, which afflicts up to 70% of cancer patients in the last months of life.[33,34] For these common indications, there is a range of recommended dosages. When treating delirium, 0.5 mg to 2 mg every 2 to 12 hours is reasonable.[32] A US panel of end-of-life experts recommend a usual maximum dose of 3mg/day,[35] though there is some debate whether this is high enough.[15,36] When treating nausea, haloperidol is generally used in smaller dosages, commonly 0.5 mg to 3 mg in 24 hours.[33,34,36] For any indication in this study the dosages were not large, only 3% of patients who received haloperidol had a dose over 5 mg, the largest being 10 mg.

Levomepromazine, an older typical antipsychotic, also has dual indications. It was for some years widely used as a sedative medication with analgesic properties for restlessness in the terminally ill, but more recently has been used for its antiemetic effects in a much smaller dosage.[37,38]

Antipsychotic dosages for ambulant patients starting at 25–50 mg a day and increase up to 300 mg, while antiemetic dosages are as low as 2.5 mg a day and seldom above 25 mg a day. When using levomepromazine for its sedative properties, this would reasonably be within the range of 25 mg to 150 mg a day[11]. This study demonstrates that when levomepromazine is prescribed, for 87% it is at the primarily antiemetic range of 25 mg or less, though for 4% of patients it is at a significantly sedative dose of >50 mg.

When these two medications were combined as an HEDD, it was noted that there was a variation in dosage for IPU deaths amongst the hospices (p=0.032). It did not vary with diagnosis (p=0.643), but did with death on the LCP (p=0.002), and unlike benzodiazepines, dosages were generally higher in hospices that were using the LCP. (p=0.002; 1.2 vs 1.6 mg) Again, these variations are not immediately explainable. It

may be relevant that the LCP recommends haloperidol for nausea at the end of life, rather than metoclopramide which is otherwise a very commonly used antiemetic.

For these medications as a group, therefore, there is demonstrable variation of practice within NZ. Given international variations, and varying indications, this may be reasonable and expected, as long as practitioners within each community of practice are clinically astute and thoughtful in their practice. The onus is now on prescribers and those who administer and assess medication to reflect on what they do.

The dangers of uncritical use of sedative medication includes not recognising situations where more targeted intervention based on accurate diagnosis will alleviate symptoms, not recognising where non-pharmaceutical interventions may be more appropriate, or having insufficient communication between health professionals, the patient and the family regarding goals and unintended side effects of treatment.

Conclusion

A detailed analysis of this data was given back to the contributing hospices to enable practitioners and institutions to know and understand their current practice in the context of their peers. Participation in such a study is an indication of the need and willingness on the part of hospices to examine their practice, which in turn may increase the likelihood of changes in practice.[10]

It shows that in NZ, as internationally, prescription and administration of BDZ/APS medications is a complex process. Whereas analgesia is titrated against pain, resulting in reasonably uniform dosages across hospices, the use of antipsychotic and sedative medication is subject to greater variability and subjective assessment.

It is important for those both prescribing and administering to be aware of factors which may influence their behaviour in any given clinical situation. This includes their own personal beliefs, skills and training, the prevailing culture of their community of practice, and the wishes and preferences of those whom they are caring.

There is no correct medication or dosage that can be applied universally, and medication may not always be the best response to a given situation. Good communication with the patient and family, and within a multidisciplinary team, is essential.

The scope of this study does not extend to identifying those factors or investigating the reasons behind this variability. However, having received this data, hospices and practitioners can (and have) embarked on discussion and reflection on their own practices for the care of the dying, informed by the knowledge of their use of various psychoactive medications. Although anonymised, there is potential for discussion between self-identified hospices who wish to compare practice directly.

These discussions may or may or not result in change in practice, which will be shown in the next cycle of benchmarking.

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