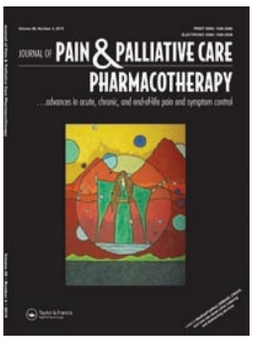

Taylor & Francis
Taylor & Francis Group

Journal of Pain & Palliative Care Pharmacotherapy

ISSN: 1536-0288 (Print) 1536-0539 (Online) Journal homepage: http://www.tandfonline.com/loi/ippc20

Using Neuroleptics to Treat Delirium in Dying Cancer Patients at a Cancer Center in Saudi Arabia

Mohammad Zafir Al-Shahri, Mahmoud Yassin Sroor, Wael Ali Ghareeb, Enas Noshy Aboulela & Wael Edesa

To cite this article: Mohammad Zafir Al-Shahri, Mahmoud Yassin Sroor, Wael Ali Ghareeb, Enas Noshy Aboulela & Wael Edesa (2015) Using Neuroleptics to Treat Delirium in Dying Cancer Patients at a Cancer Center in Saudi Arabia, Journal of Pain & Palliative Care Pharmacotherapy, 29:4, 365-369

To link to this article: http://dx.doi.org/10.3109/15360288.2015.1101638

Published online: 14 Dec 2015.

Journal of Pain & Palliative Care Pharmacotherapy. 2015;29:365–369.

ISSN: 1536-0288 print / 1536-0539 online
DOI: 10.3109/15360288.2015.1101638

Taylor & Francis
Taylor & Francis Group

REPORT

Using Neuroleptics to Treat Delirium in Dying Cancer Patients at a Cancer Center in Saudi Arabia

Mohammad Zafir Al-Shahri, Mahmoud Yassin Sroor, Wael Ali Ghareeb, Enas Noshy Aboulela, and Wael Edesa

ABSTRACT

Neuroleptics are commonly used for treating delirium as a common problem in terminally ill cancer patients. However, prescribing patterns are believed to substantially vary among health professionals. The aim of this study is to determine the pattern of prescribing neuroleptics for treating delirium in cancer patients dying in a palliative care unit in Saudi Arabia. We reviewed the medical records of adults with advanced cancer who died in the palliative care unit over 23 months. In addition to patients' demographics, data collection included the pattern of prescribing neuroleptics for the treatment of delirium during the last week of life. For the 271 patients included (57.6% females), the median age was 54 years. Although 62% of patients were on around-the-clock (ATC) neuroleptics to treat delirium, about two thirds of these were requiring rescue doses (PRN [pro re nata]) as well. The ATC neuroleptics included haloperidol alone (89.3%), levomepromazine alone (2.4%), or both (8.3%). All neuroleptics were administered via the parenteral route. On average, the maximum daily doses of the ATC neuroleptics were 4 mg for haloperidol and 15.5 mg for levomepromazine. Patients with primary or metastatic brain cancers were less likely to be on neuroleptics ($P < .0001$). The authors conclude that in their palliative care unit, haloperidol is by far the most commonly used neuroleptic, followed by levomepromazine, to treat the common problem of delirium in patients dying with advanced cancer. The generally low doses of neuroleptics required may be attributed to several factors in this population, including cultural motives.

KEYWORDS cancer, delirium, end of life, palliative care

INTRODUCTION

Delirium is a common problem in the terminally ill and may affect up to 10% of children and 88% of adults dying with advanced cancer.[1–3] It is associated with significant morbidity and mortality and, hence, considered a palliative care emergency.[4,5] The deleterious effects of delirium on patients include inability to communicate normally, incapacity in decision-making, disturbance in functional status, and poor quality of life.[6] Furthermore, family caregivers and health care providers caring for patients with hyperactive delirium are at risk of experiencing psychological distress.[7–11] The risk of developing delirium in cancer patients increases with age, history of previous cognitive failure, dementia, drug toxicity, and metabolic aberrations.[12–17]

In addition to nonpharmacological measures, the medications commonly used in treating delirium include haloperidol, risperidone, quetiapine, chlorpromazine, olanzapine, and levomepromazine.[18] Benzodiazepines are used when sedation is desired, such as in cases refractory to neuroleptics and in patients with increased risk of seizures.[14,19,20] The limited literature describing the pattern of neuroleptic prescription in the palliative care setting suggests the presence of substantial variability in the prescription patterns among health professionals.[21–23] This paper aims at exploring the pattern of prescribing neuroleptics for treating delirium in cancer patients dying in a tertiary palliative care unit in Saudi Arabia.

Dr. Mohammad Zafir Al-Shahri is with the King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. Drs. Mahmoud Yassin Sroor, Wael Ali Ghareeb, Enas Noshy Aboulela, and Wael Edesa are with the King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia and the Faculty of Medicine, Cairo University, Cairo, Egypt.

Address correspondence to: Dr. Mohammad Zafir Al-Shahri, King Faisal Specialist Hospital and Research Center, Oncology Centre, MBC 64, P. O. Box 3354, Riyadh 11211, Saudi Arabia (E-mail: alshahri_m@yahoo.com).

METHODS

This study is part of a larger research project designed to explore the prescription patterns during the last week of life for cancer patients dying in the palliative care unit at King Faisal Specialist Hospital and Research Center, Riyadh (KFSHRC-R). The study is approved by the research approving authority in the hospital. We reviewed the electronic medical records of adults with advanced cancer who died in the palliative care unit over a 23-month period ending December 2011. In addition to patients' demographics, data collection included the pattern of neuroleptic prescribing for the treatment of delirium in the last week of life. In case a patient was on more than one neuroleptic during the last 7 days of life for treating delirium, the latest medication was considered active and the previous one omitted. However, if more than one neuroleptic continued to be administered concomitantly, both were included in data collection.

The Statistical Package for the Social Sciences (SPSS) version 17 (SPSS, Chicago, IL, USA) was used for analyzing the data. In addition to descriptive statistics, continuous variables were compared using Student's *t* test or analysis of variance as appropriate, and the categorical variables were compared using the chi-square test. *P* value of less than .05 is considered significant and the means are presented ±1 standard deviation.

RESULTS

A total of 271 adult patients, with a median age of 54 years and female preponderance (57.6%), died in the palliative care unit during the study period. All patients died with either metastatic (90%) or locally extensive (10%) disease, and the most common cancer types were gastrointestinal (29.2%), gynecological (13.7%), breast (13.3%), and head and neck (12.2%). Table 1 shows patients' demographics in more details.

Of all patients who were receiving neuroleptics for delirium ($n = 208$), 106 (51%) received both around-the-clock (ATC) and rescue doses on as-needed basis (PRN [pro re nata]), 62 (29.8%) solely received ATC medication, and 40 (19.2%) received only PRN neuroleptics. The prescribed ATC neuroleptics included either haloperidol alone (89.3%), levomepromazine alone (2.4%), or both drugs administered concomitantly (8.3%). On the other hand, 146 (53.9%) patients of the total sample were on PRN neuroleptics. Of these, 137 (93.8%) were prescribed haloperidol, 2 (1.4%) were prescribed levomepromazine, and 7 (4.8%) were prescribed both drugs simultaneously. Figure 1 summarizes the pattern of constancy (ATC versus PRN) of the neuroleptics prescribed.

TABLE 1. Patients' demographics

Characteristic		Frequency	%
Age (in years)			
Median	54		
Mean	54.7		
Standard deviation	15.5		
Range	18–94		
Sex			
Male		115	42.4
Female		156	57.6
Cancer type			
Gastrointestinal		79	29.2
Gynecological		37	13.7
Breast		36	13.3
Head and neck		33	12.2
Hematological		20	7.4
Bone and soft tissue		19	7.0
Genitourinary		17	6.3
Lung		8	3.0
Others		22	8.1
Cancer stage			
Metastatic		244	90
Locally advanced		27	10
Total		271	100

All patients who were on ATC haloperidol ($n = 159$) were receiving the drug via the parenteral route, mostly subcutaneously (60.4%). The drug was administered as a continuous infusion in most of the cases (86.2%). During the last week of life, the maximum daily dose of the ATC haloperidol ranged between 0.5 and 15 mg, with a median of 3 mg and a mean of 4.0 ± 3.2 mg. For 83.6% of patients on ATC haloperidol, the administration of the drug continued until the time of death.

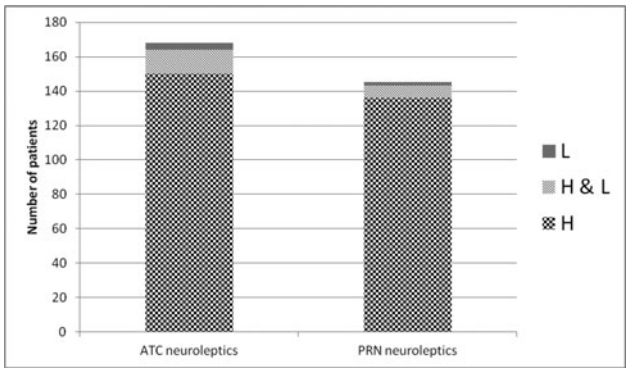

FIGURE 1. The pattern of constancy of the neuroleptics prescribed. ATC = around-the-clock; PRN = pro re nata (as needed); H = haloperidol; L = levomepromazine; H & L = concurrently prescribed H & L.

TABLE 2. Comparing the prescription patterns of haloperidol and levomepromazine

	Haloperidol		Levomepromazine	
Prescription	ATC	PRN	ATC	PRN
Patients: *n* (% of total sample)	159 (58.7)	143 (52.8)	18 (6.6)	9 (3.3)
Highest dose (mg)				
Median	3	1	9.4	3.125
Mean	4.0	1.4	15.5	5.2
SD	3.2	0.86	18.3	3.1
Range	0.5–15	0.5–5	3.125–75	3.125–12.5
Route of administration: *n* (%)				
IV	63 (39.6)	100 (69.9)	9 (50)	4 (44.4)
SC	96 (60.4)	43 (30.1)	9 (50)	5 (55.6)

ATC = around-the-clock; PRN = pro re nata (as needed); IV = intravenous; SC = subcutaneous.

All patients who were on PRN haloperidol ($n = 143$) were receiving the drug via the parenteral route, mostly intravenously (69.9%). In most of the cases (86.7%), the drug was ordered as every 4 hours PRN. The PRN dose of haloperidol ranged between 0.5 and 5 mg, with a median of 1 mg and a mean of 1.4 ± 0.86 mg. The lapse between the last dose of PRN haloperidol and the time of death ranged widely from 1 to 157 hours, with a median of 39 hours and a mean of 49.8 ± 41.4 hours.

In the 18 patients who were receiving levomepromazine ATC, the administration of the drug was equally divided between the subcutaneous and intravenous routes. The daily dose was most commonly divided in either three ($n = 9$; 50%) or two ($n = 7$; 38.9%) doses. During the last week of life, the maximum daily dose of the ATC levomepromazine ranged between 3.125 and 75 mg, with a median of 9.4 mg and a mean of 15.5 ± 18.3 mg. Only one patient continued to receive the drug as a continuous infusion until death. For the remaining patients, the median time between the last dose received and the time of death was 8 hours, with a mean of 10.7 ± 10.4 hours.

As few as 9 (3.3%) patients were prescribed PRN levomepromazine in doses ranging between 3.125 and 12.5 mg, with a median of 3.125 mg and a mean of 5.2 ± 3.1 mg. The PRN levomepromazine dosing frequency was mostly ordered at 4-hourly (55.6%) or 6-hourly (22.2%) intervals. The median time between the last dose of PRN levomepromazine administered and the time of death was 12 hours, with a mean of 33 ± 35.8 hours. Table 2 compares the prescription pattern of the two neuroleptics used.

Patient characteristics such as age, sex, type, or extent of cancer were not found to be associated with being on ATC neuroleptics or otherwise. Neither did those characteristics show significant associations with the dose of the neuroleptics nor the time lapse between the last dose of the neuroleptic given and the time of death. Patients with brain primary or metastatic cancers were less likely to be on neuroleptics ($P < .0001$).

DISCUSSION

The wide variability in the prevalence of delirium in palliative care patients may be attributed to various factors including variation in diagnostic methods, types of settings, proximity to the time of death, and the subtype of delirium being studied.[3] Previous studies in palliative care settings elsewhere have suggested that hypoactive delirium is usually more common (68%–86%) than agitated delirium.[5,24,25] It is not possible to identify the subtypes of delirium in our data. It is noteworthy that in our setting, delirium of any type is routinely diagnosed and treated by the palliative care physicians without any input from psychiatrists. The proportion of patients on ATC neuroleptics for treating delirium in our sample (62%) is not far from the prevalence of delirium reported by Lam et al. (58.8%) in a comparable setting and patient population.[24] The higher prevalence reported by Lawlor et al. (88%) was limited to patients in their final hours of life [4].

Well-established evidence-based guidelines for treating delirium are still lacking.[26–28] Our data support the available literature reporting haloperidol to be widely recognized by palliative care specialists as the first-line drug for treating delirium.[23,27] Although our clinical practice occasionally involves prescribing other neuroleptics such as risperidone and olanzapine, our results have shown the second and only alternative in this sample to be levomepromazine. This is different from what Hui et al. have found in a similar setting in the United States where the alternative to haloperidol included olanzapine and chlorpromazine but not levomepromazine.[23] The usual practice in our unit is to switch to levomepromazine or another

neuroleptic only if haloperidol was deemed ineffective or contraindicated. However, the results of this study have shown that haloperidol and levomepromazine were inexplicably used concurrently in a small group of patients.

The daily dose of haloperidol required in our patients appeared to be similar to what was reported by Hui et al. but less than what had been reported by other studies involving cancer patients.[21–23] This may be attributed, in part, to the variability in settings and characteristics of patient populations. For instance, patients in the end-of-life phase are generally older in age, less hydrated, and more likely to have impaired organ function with possibility of requiring smaller neuroleptic doses. Furthermore, our patient population and their families often express their wishes to maintain the conscious level of patients as close to normal as possible for them to be able to perform prayers during such a critical phase of life. The finding that a significant proportion of our patients receiving ATC neuroleptics were also requiring rescue boluses may also be suggesting that our prescription pattern is rather conservative in terms of dosing. In our setting, we routinely start with low doses and increase the dosage slowly until the therapeutic objective is met. This may have contributed to the fact that the majority of patients continued to be on haloperidol until they died. This is not to say that adverse effects, including akathisia, are never encountered in our setting, but rather to emphasize the perceived rarity of such events when compared to what is reported in literature.[29]

A recent systematic review of the use of levomepromazine in palliative care emphasized the lack of high-quality literature on the subject.[30] Levomepromazine (methotrimeprazine) is a phenothiazine that had long been used as a second- or third-line drug for managing delirium in palliative care patients with variable effective dosing reaching up to 300 mg per day, even though the evidence supporting its use for this indication is weak.[31–33] Over years of use, we have found levomepromazine to be an effective and well-tolerated alternative to haloperidol, especially in patients with agitated delirium who usually require better sedation. The less likelihood of prescribing neuroleptics for treating delirium in our patients with primary or secondary brain tumors is due to the seizure-lowering potential of such drugs.[27,34] In such situations we tend to rely more on benzodiazipines when treating delirium.

Although the sample size of this study is reasonable, the retrospective design makes it difficult to draw tangible conclusions in terms of judging the quality of the current practice or suggesting alterations. Another limitation is the fact that delirium is being identified based merely on the documentation in patients' charts rather than on standardized diagnostic criteria. Furthermore, this study was limited to cancer patients dying in the palliative care unit and, as such, it is difficult to generalize the findings to cancer or noncancer patients dying in other units, let alone patients not yet in their final days of life.

CONCLUSION

Haloperidol is by far the most commonly used neuroleptic to treat the common problem of delirium in patients dying with advanced cancer in our palliative care unit. Levomepromazine rather than atypical antipsychotics is the second choice. The prescription pattern suggests conservative dosing for probably cultural motives. This study may be useful in analyzing the current situation in preparation for future prospective research investigating best approaches in managing this common problem in this patient population.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

[1] Combs D, Rice SA, Kopp LM. Incidence of delirium in children with cancer. *Pediatr Blood Cancer.* 2014;*61*:2094–2095.
[2] Massie MJ, Holland J, Glass E. Delirium in terminally ill cancer patients. *Am J Psychiatry.* 1983;*140*:1048–1050.
[3] Hosie A, Davidson PM, Agar M, Sanderson CR, Phillips J. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. *Palliat Med.* 2013;*27*:486–498.
[4] Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med.* 2000;*160*:786–794.
[5] Fang CK, Chen HW, Liu SI, et al. Prevalence, detection and treatment of delirium in terminal cancer inpatients: a prospective survey. *Jpn J Clin Oncol.* 2008;*38*:56–63.
[6] Leonard M, Agar M, Mason C, et al. Delirium issues in palliative care settings. *J Psychosom Res.* 2008;*65*:289–298.
[7] Brajtman S. The impact on the family of terminal restlessness and its management. *Palliat Med.* 2003;*17*:454–460.
[8] Namba M, Morita T, Imura C, et al. Terminal delirium: families' experience. *Palliat Med.* 2007;*21*:587–594.
[9] Morita T, Akechi T, Ikenaga M, et al. Terminal delirium: recommendations from bereaved families' experiences. *J Pain Symptom Manage.* 2007;*34*:579–589.
[10] Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics.* 2002;*43*:183–194.
[11] Partridge JS, Martin FC, Harari D, Dhesi JK. The delirium experience: what is the effect on patients, relatives and staff

and what can be done to modify this? *Int J Geriatr Psychiatry*. 2013;*28*:804–812.
[12] Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med.* 1993;*119*:474–481.
[13] Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *JAMA.* 1990;*263*:1097–1101.
[14] Gaudreau J, Gagnon P, Roy M, Tremblay A. Psychoactive medications and risk of delirium in hospitalized cancer patients. *J Clin Oncol.* 2005;*23*:6712–6718.
[15] Levkoff SE, Evans DA, Lipzin B, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med.* 1992;*152*:334–340.
[16] Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA*. 1996;*275*:852–857.
[17] Ljubisavjevic V, Kelly B. Risk factors for development of delirium among oncology patients. *Gen Hosp Psychiatry.* 2003;*25*:345–352.
[18] Attard A, Ranjith G, Taylor D. Delirium and its treatment. *CNS Drugs.* 2008;*22*:631–644.
[19] Pandharipande P, Shintay A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care patients. *Anesthesiology.* 2006;*104*:21–26.
[20] Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C. A double-blind trial of haloperidol, chlorpromazine and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry.* 1996;*153*:231–237.
[21] Akechi T, Uchitomi Y, Okamura H, et al. Usage of haloperidol for delirium in cancer patients. *Support Care Cancer.* 1996;*4*:390–392.
[22] Olofsson SM, Weitzner MA, Valentine AD, Baile WF, Meyers CA. A retrospective study of the psychiatric management and outcome of delirium in the cancer patient. *Support Care Cancer.* 1996;*4*:351–357.
[23] Hui D, Reddy A, Palla S, Bruera E. Neuroleptic prescription pattern for delirium in patients with advanced cancer. *J Palliat Care.* 2011;*27*:141–147.
[24] Lam PT, Tse CY, Lee CH. Delirium in a palliative care unit. *Prog Palliat Care.* 2003;*13*:126–133.
[25] Spiller JA, Keen JC. Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care. *Palliat Med.* 2006;*20*:17–23.
[26] Grassi L, Caraceni A, Mitchell AJ, et al. Management of delirium in palliative care: a review. *Curr Psychiatry Rep*. 2015;*17*:550–558.
[27] Caraceni A, Simonetti F. Palliating delirium in patients with cancer. *Lancet Oncol.* 2009;*10*:164–172.
[28] Bush SH, Bruera E, Lawlor PG, et al. Clinical practice guidelines for delirium management: potential application in palliative care. *J Pain Symptom Manage.* 2014;*48*:249–258.
[29] Sachdev PS. Neuroleptic-induced movement disorders: an overview. *Psychiatr Clin North Am.* 2005;*28*:255–274.
[30] Dietz I, Schmitz A, Lampey I, Schulz C. Evidence for the use of Levomepromazine for symptom control in the palliative care setting: a systematic review. *BMC Palliat Care.* 2013; *12*:2.
[31] Breitbart W, Sparrow B. Management of delirium in the terminally ill. *Prog Palliat Care.* 1998;*6*:107–114.
[32] Fainsinger R, Young C. Cognitive failure in a terminally ill patient. *J Pain Symptom Manage.* 1991;*6*:492–494.
[33] Fainsinger R, Bruera E. Treatment of delirium in a terminally ill patient. *J Pain Symptom Manage.* 1992;*7*:54–56.
[34] Alldredge B. Seizures risk associated with psychotropic drugs: clinical and pharmacokinetic considerations. *Neurology.* 1999;*53*(Suppl 2):S68–S75.

RECEIVED: 11 August 2015
REVISED: 12 September 2015
ACCEPTED: 26 September 2015