Pharmacovigilance in Hospice/Palliative Care: Net Effect of Haloperidol for Delirium

Gregory B. Crawford, MBBS, MPHC, MD, FRACGP, FAChPM,[1,2]
Meera Agar M, MBBS, PhD, FRACP, FAChPM,[3,4]
Stephen J. Quinn, B Math, MMath, PhD,[5]
Jane Phillips, RN, PhD,[6]
Caroline Litster, BSocSc (Hons),[3]
Natasha Michael, MBChB, FAChPM, MRCP, MRCGP, MSc,[7]
Matthew Doogue, MBChB, FRACP,[8]
Debra Rowett, BPharm,[9]
David C. Currow, MPH, FRACP[3]

Abstract

Introduction: Prescribing practice in hospice/palliative care is largely extrapolated from other areas of clinical practice, with few studies of net medication effects (benefits and harms) in hospice/palliative care to guide prescribing decisions. Hospice/palliative care patients differ in multiple ways from better studied participant groups, hence the applicability of studies in other participant groups is uncertain. Haloperidol, a butyrophenone derivative and dopamine antagonist, is commonly prescribed for nausea, vomiting, and delirium in hospice/palliative care. Its frequent use in delirium occurs despite little evidence of the effect of antipsychotics on the untreated course of delirium. The aim of this study was to examine the immediate and short-term clinical benefits and harms of haloperidol for delirium in hospice/palliative care patients.
Method: A consecutive cohort of participants from 14 centers across four countries who had haloperidol commenced for delirium were recruited. Data were collected at three time points: baseline, 48 hours (clinical benefits), and day 10 (clinical harms). Investigators were also able to report clinical harms at any time up to 14 days after it was commenced.
Results: Of the 119 participants included, the average dose was 2.1 mg per 24 hours; 42 of 106 (35.2%) reported benefit at 48 hours. Harm was reported in 14 of 119 (12%) at 10 days, the most frequent being somnolence ($n = 11$) and urinary retention ($n = 6$). Seven participants had their medication ceased due to harms (2 for somnolence and 2 for rigidity). Approximately half (55/119) were still being treated with haloperidol after 10 days.
Conclusion: Overall, 1 in 3 participants gained net clinical benefit at 10 days.

Introduction

Delirium is a common and distressing symptom for many patients and families as the end of life approaches[1,2] and if no reversible factors are present, is an indicator of poor prognosis.

Haloperidol is a butyrophenone derivative and dopamine antagonist. It is commonly prescribed for nausea, vomiting, and delirium in hospice/palliative care.[3–5] Its use in delirium occurs despite little placebo controlled evidence that antipsychotic medication changes the natural history of delirium. Although open label studies or randomized trials comparing two antipsychotics have shown improvement of delirium scores over time,[2] this may relate to the natural history of delirium, which is to resolve over time as precipitants are treated and reversed. The three studies[6–8] with placebo arms have methodological problems (inadequately powered, inadequate allocation concealment).

Current international guidelines suggest targeted use of antipsychotics for severe behavioral disturbance in delirium

[1]Discipline of Medicine, University of Adelaide, Adelaide, Australia.
[2]Central Adelaide Local Health Network, Adelaide, Australia.
[3]Discipline of Palliative and Supportive Services, [5]Flinders Clinical Effectiveness, Flinders University, Adelaide, Australia.
[4]Department of Palliative Care, Braeside Hospital, HammondCare, Sydney, New South Wales, Australia.
[6]School of Nursing, The University of Notre Dame, Australia, Darlinghurst, New South Wales. Australia.
[7]Department of Cancer Experiences Research Peter MacCallum Cancer Centre Melbourne, Australia.
[8]Department of Clinical Pharmacology, Flinders Medical Centre, Bedford Park, South Australia, Australia.
[9]Repatriation General Hospital. Daw Park, Adelaide, Australia.
Accepted June 21, 2013.

with cautious dosing and close monitoring.[9] The potential harms of haloperidol include: central effects (sedation, insomnia, restlessness, anxiety, euphoria, confusion, urinary incontinence, grand mal seizures); cardiovascular effects (tachycardia, hypotension, conduction irregularities); and extrapyramidal effects (akathisia, dystonia, and persistent tardive dyskinesia).[5] More rarely, haloperidol has been reported to cause neuroleptic malignant syndrome and hematological abnormalities including leucopenia, leucocytosis, and anemia. Although widely prescribed, the benefits and harms of haloperidol for delirium have not been well quantified in hospice/palliative care patients.

Much of the prescribing practice in hospice/palliative care has been extrapolated from related areas of clinical practice with populations that are more readily studied. Due to limited available evidence, an international initiative was commenced in 2011 to improve clinicians' understanding of the net clinical effects of key medicines used in hospice/palliative care and to further inform prescribing in this important area of patient care.[10] Building this evidence base is an extension of the Phase 3 and 4 studies that have been carried out by the Australian Palliative Care Clinical Studies Collaborative (PaCCSC).[11]

Prospective data collection at agreed time points, using standardized measures of clinical harms and benefits, for medications that are frequently prescribed for symptom control in hospice/palliative care patients can provide important information. This is information specific to the clinical context of hospice/palliative care and cannot be provided by studying other patient populations. This method of rapid reporting allows immediate and short-term net clinical effects (benefits and harms) to be systematically studied during routine care.

A new pragmatic tool for pharmacovigilance was created[12] using secure Web-based technology, deidentified and unreidentifiable data, and a small number of set fields focusing on a single medication for a single indication (even if there are multiple indications for that medication in hospice/palliative care). By aggregating data from a large number of centers each of whom have provided data from a small number of consecutive participants who were commenced on haloperidol for delirium as part of routine clinical care, the evidence base of the real-world net effectiveness of this medication can be established. This process minimizes the work involved for individual clinicians, and represents a wide range of clinical settings and service delivery models.

Methods

The aim of this study was to describe the net clinical effect (i.e., the overall risk and benefit) of haloperidol when prescribed for delirium in a consecutive, prospective cohort of hospice/palliative care patients. All participating sites received ethical waivers (as the work falls under quality assurance, quality improvement, performance monitoring, clinical audit study type) or approval for low risk research depending on each site's Human Research Ethic Committee's assessment of this work. This meant that patients and/or family members did not need to be approached or consent provided for the study to proceed.

The study methods have been described in detail previously.[10] An expert committee defined prespecified clinical benefit and harm fields based on the available literature relating to the use of haloperidol for delirium (Table 1). The National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI CTCAE) Likert scales for grading effects were used.[13] Nonidentifying demographic and clinical data were entered *pro forma* using a 128-bit encrypted Web portal (www.caresearch.com.au). Participants were consecutive patients at participating clinical sites started on haloperidol as part of routine clinical care for delirium.

Data were recorded at three set time points: baseline (the index symptom and symptoms that could reflect harm): 48 hours (index symptom (delirium) response), and 10 days (harms) after commencing haloperidol. The NCI criteria for delirium ask the clinician to rate overall severity of the symptoms but also impact on activities of daily living and other impacts (such as threats of harm to self or others; Table 2). This approach was chosen as the intention was to quantify the degree of impact from a symptom perspective and to align the assessment approaches of benefits and harms.

Overall benefit was defined as a 1-point reduction in the NCI CTCAE (for example severe to moderate, moderate to mild, mild to none) (Table 2). Harms were attributed to haloperidol if the criteria for NCI CTCAE were greater than a baseline measurement at or before day 10 for that individual participant. For harms rated as 3 or greater on the NCI CTCAE criteria, data were collected on the Naranjo Score. This is a questionnaire designed to determine the attribution of an adverse drug reaction being due to the drug itself rather than other factors. In the hospice/palliative care setting only question 2, which explores the timing of the adverse events in relation to the medication being commenced, is reported.[14] Functional status was recorded using the Australian modified Karnofsky Performance Scale and comorbidities assessed using the Charlson Comorbidity Index.[15,16]

Statistical methods

Univariable logistic regression model for each outcome on key clinical and demographic parameters was undertaken, clustering over site to account for correlated readings. Additionally, logistic regression was performed for each outcome on each pair of key parameters and their product term to identify possible subgroups that were associated with outcomes. We used multiple imputation to account for missing data, with 20 resamples drawn. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). No adjustment was made for multiple comparisons as the results are considered to be hypothesis generating. A p value less than 0.05 (two-tailed) is considered statistically significant. Data were imported into Excel (Microsoft, Seattle, WA). All analyses were performed in STATA SE version 12.1 (StataCorp, College Station, TX).

Results

The clinical and demographic data of the study subjects are shown in Table 1. Data were available for 119 participants from 14 hospice/palliative care sites in four countries between February 2012 and August 2012. Clinical sites were drawn from consultative services, ambulatory clinics and specialist inpatient hospice/palliative care units, reflecting the scope of current specialist palliative care practice in the participating countries.

Table 1. Baseline Clinical and Demographic Data

	n (%)	Median	Range	Mean	SD
Age	118 (99)	75	34–99	73.2	12.8
Gender (male)	70 (59)				
Australian-modified Karnofsky Performance Status Score	119 (100)	30	10–60	32	12.2
Charlson Comorbidity Index score	119 (100)	6	0–14	5.7	3.2
Body mass index	102 (86)	24	17–37	24.7	4.7
C-reactive protein	40 (34)	86.7	2–317	108	95.3
Calculated creatinine clearance	71 (60)	56	7–760	78.8	120.8
National Cancer Institute Common Toxicity Grading for Delirium	119 (100)	2	1–4	2.2	0
Primary life-limiting illness					
Cancer	105 (88)				
End-stage renal disease	1 (1)				
End-stage cardiac disease	5 (4)				
End-stage respiratory disease	0				
End-stage hepatic disease	0				
AIDS	0				
Neurodegenerative disease	2 (2)				
Other	6 (5)				
Baseline adverse events	n (%)[a]	Severity[b] median (range)			
Akathisia	13 (11)	1 (1–3)			
Gait change	11 (9)	2 (1–3)			
Rigidity	7 (6)	1 (1–3)			
Somnolence	49 (41)	2 (1–3)			
Tremor	11 (9)	1 (1–3)			
Dizziness	6 (5)	1 (1–2)			
Urinary retention	9 (8)	2 (1–3)			
Other	2 (2)	2.5 (2—3)			

[a]Patients could have more than one harm.
[b]National Cancer Institute's Common Toxicity Criteria Adverse Events (NCI CTC AE).
Other harms: postural hypotension (1); myoclonus (1).
SD, standard deviation.

The majority of participants had cancer. Participants received an average of 2.1 mg of haloperidol per 24 hours (standard deviation [SD] 1.6; median, 2 mg; range, 0.5–8.0) in parenteral or oral forms.

At 48 hours, 10 people had died and overall benefit was reported in 42 of 106 participants (35.2%; CI 26.6%–44.0%) of participants with recorded scores. (Table 3, Figs. 1 and 2). At the end of the study, a total of 52 people had died and 55 of 67 were still on regular haloperidol.

A total of 14 of 57 participants (24.6%; CI 13.0%–36.1%; Table 3) experienced 29 harms up to and including day 10 (Table 4). The most frequently encountered harms were

Table 2. Outcomes at Forty-Eight Hours after Commencing Haloperidol for Delirium in Palliative Care Patients ($n = 119$[a])

			NCI CTC AE delirium score[b] at baseline (T_0) before commencing haloperidol			
		Subtotals	*1* *27*	*2* *37*	*3* *47*	*4* *3*
NCI CTC AE[b] delirium score at 48 hours (T_1) after commencing haloperidol	0	12[c]	**7**	**4**	**1**	**0**
	1	29	12	**13**	**4**	**0**
	2	33	5	16	**11**	**1**
	3	27	0	2	24	**1**
	4	3	0	0	3	0
	5	10[d]	3	2	4	1

[a]Missing data = 5.
[b]NCI CTC AE National Cancer Institute Common Toxicity Criteria Adverse Events–delirium scale: 0, None; 1, Mild acute confusional state; 2, Moderate and acute confusional state limiting instrumental activities of daily living (ADL); 3, Severe and acute confusional state limiting self-care ADLs. Hospitalization indicated; 4, Life-threatening consequences; threats of self harm or harm to others; hospitalization indicated; 5, Death.
Delirium score: improved, $n = 42$ (36.8%) of whom 12[c] (10.5%) had a total resolution of delirium; unchanged, n = 52(45.6%); worsened, $n = 20$ (17.5%) of whom 10[d] (8.8%) died within 48 hours of commencing haloperidol. (A further 42 were dead by day 10 and a further 10 people by day 14).

Table 3. Net Clinical Effects (Individual Patients)

Benefit/s n, % *(95% CI)* *(1-point NCI reduction in delirium score over baseline)*[a]	*Harm(s)* n, % *(95% CI)* *(1-point NCI increase in any toxicity score over baseline)*[b]	*Action following harm(s)*[c]	n *(%)*
Yes $n=42$ (38.5% CI 29.2%, 47.8%)	No $n=13$ (52.0% CI 31.0%, 73.0%)	Medication added (1), dose reduction (1)	2 (2)
	Yes $n=4$ (16.0% CI 0.6%, 31.4%)	Cessation	1 (1)
		Dose reduction	0
		No change to medication	2 (2)
		Medication to treat toxicity added	1 (1)
		Other	0
		No action	0
	Missing $n=8$ (32.0% CI 12.3%, 51.6%)		
	Died $n=17$		
No $n=62$ (56.8% CI 47.4%, 66.3%)	No $n=23$ (57.5% CI 41.5%, 73.5%)	Ceased (1), no change (1), other (1)	3 (3)
	Yes $n=9$ (22.5% CI 9.0%, 36.0%)	Cessation	2 (2)
		Dose reduction	1 (1)
		No change to medication	5 (4)
		Medication to treat toxicity added	2 (2)
		Other	1 (1)
		No action	0
	Missing $n=8$ (20.0% CI 7.0%, 33.0%)		
	Died n = 22		
Missing $n=5$ (4.6% CI 0.6%, 8.6%)	No $n=2$ (66.7% CI −76.8%, 210.0%)		
	Yes $n=1$ (33.3% CI −11.0.1%, 176.8%)	No change to medication	1 (1)
	Died $n=2$		
Died $n=10$			

[a]Reported at 48 hours.
[b]Reported up until 10 days.
[c]A person may have more than one action.
National Cancer Institutes' Common Toxicity Criteria for Adverse Events (NCI CTC AE); CI, confidence interval.

somnolence (11; 9%) and urinary retention (6; 5%). Seven participants had their medication ceased for harms of whom two had somnolence and two had rigidity.

In the logistic regression analyses, the Karnofsky score moderated the relationship between Charlson Comorbidity Index (CCI) and benefit from haloperidol. The higher the Karnofsky score the stronger the association between worsening comorbidity (higher CCI) and poorer response. For those with a median Karnofsky score of 30, subjects were approximately 12% less likely to benefit with each one point increase in CCI (OR = 0.88; CI 0.77 1.00; $p=0.043$). For someone with a Karnofsky score of 60, subjects were approximately 39% less likely to benefit with each point increase in CCI (OR = 0.63; CI 0.43 0.99; $p=0.02$). All other univariable and interaction analyses did not contain terms that were significant.

Discussion

Approximately 1 in 3 participants experienced benefit at 48 hours. Approximately 1 in 15 participants stopped haloperidol due to harms, 4 of which were graded 4. By using a multicenter, multinational, rapid, prospective design to reflect actual clinical practice, this study helps to understand the actual performance of medications in hospice/palliative care. The participants were mostly elderly (mean age, 73 years) and of poor physical functional status (mean AKPS 32). They had multiple comorbidities (CCI mean 5.7) prior to commencing treatment for delirium. Despite this clinical setting, haloperidol was relatively well tolerated in the immediate and short term. Of those with a documented harm, few were treated by a reduction in the dose or cessation of the medication.

There is little high-quality evidence available to guide the management of delirium in hospice/palliative care patients, particularly as people with this condition approach the end of their lives.[16] Systematic reviews have identified only a small number of studies, with a paucity of literature relating to the setting of people recognized to be approaching the end of life. However the findings of this study are consistent with systematic reviews.[18–20] Haloperidol is still recommended as the first-line agent in delirium management.[16] Of note, the doses reported by Campbell et al.[18] were much greater than those received by participants in this study (mean, 6.5 mg per 24 hours compared with 2.1 mg per 24 hours).

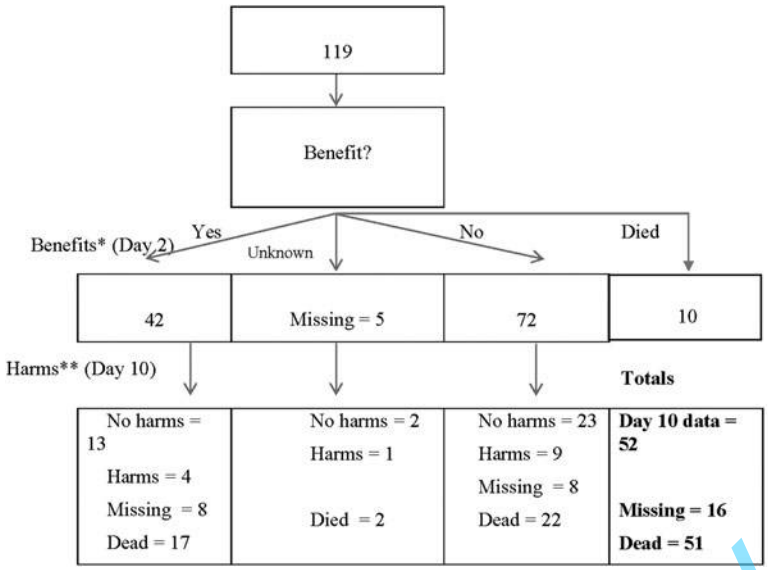

FIG. 1. Participant flow for the use of haloperidol in palliative care for delirium (n = 119; 14 sites; 4 countries). *Benefit is defined as ≥ 1-point reduction on the National Cancer Institutes' Common Toxicity Criteria for Adverse Events (NCI CTC AE) for delirium. **Harms are defined as ≥ 1-point increase over baseline for relevant NCE CTC AE score.

An important change to the first of these pharmacovigilance studies[12] was that harm was measured at baseline in addition to T_1 and T_2 and only worsening over baseline is reported. There were high baseline rates of somnolence 49 (41%), akathisia 13(11%), gait change 11(9%), and rigidity 7(6%) that may otherwise have been attributed to haloperidol.

Limitations

This study addresses only immediate and short-term harms. Harms of prolonged haloperidol administration such as some of the extrapyramidal effects will not be detected. Consistency of interpretation and measurement is a challenge for multicenter studies. This study also relies on clinicians recognizing delirium and utilizing a rating scale that only quantifies symptoms and some clinical impacts; rather than a detailed delirium scale with established psychometric properties. NCI CTCAE is conceived as a high-level screening tool for a wide range of symptoms and data are not available on its correlation with diagnostic tools for delirium. A project officer provided continuing e-mail updates and an information stream about the study to provide a central point of liaison for participating sites (Australia, New Zealand, Canada, and the United Kingdom).

Generalizability

Clinical sites were drawn from consultative services, ambulatory clinics and specialist inpatient hospice/palliative care units, reflecting the scope of current specialist palliative

TABLE 4. HARMS ENCOUNTERED FROM BASELINE TO TEN DAYS ($n = 119$)[a]

	Harms				*Response to toxicity*				
					Change in medications			*Additional actions*	
	Benefit/s Yes n = *42*[a]	*Benefit/s No* n = *62*[a]	n *(%) harms*[b]	*Severity median (range)*[c]	*Medication ceased* n = *3*	*Dose reduced* n = *1*	*No change in medication* n = *7*	*Medication to treat toxicity added* n = *3*	*Other* n = *1*
Akathisia	1	2 (2)	1 (1)	2 (2–4)	1	—	—	3	1
Gait change	1	1 (1)	1 (1)	3 (3)		—	2	—	0
Rigidity	0	2 (2)	—	3.5 (2–5)	2	—	—	1	0
Somnolence	3	7 (6)	3 (3)	2 (1–4)	2	—	6	3	1
Tremor	0	2 (2)	—	3 (2–4)	1		1	1	—
Dizziness	0	—	—	—	—		—	—	—
Urinary retention	2	3 (3)	2 (2)	2 (1–3)	—	1	3	1	1
Other[d]	2	1 (1)	2 (2)	2 (2–3)	1	1	2	1	0

[a]Missing $n = 15$ (see Table 3 for explanation).
[b]Participants can have more than one harm but can also have more than one response.
[c]National Cancer Institute's Common Toxicity Criteria Adverse Events (NCI CTC AE).
[d]Other harms: dyskinetic jaw/tongue/lip movements (1), depression (1), myoclonic jerks (1), postural hypotension (1), urinary retention 1(1) *n* (%) 2 (2) severity 1 no change in medications.

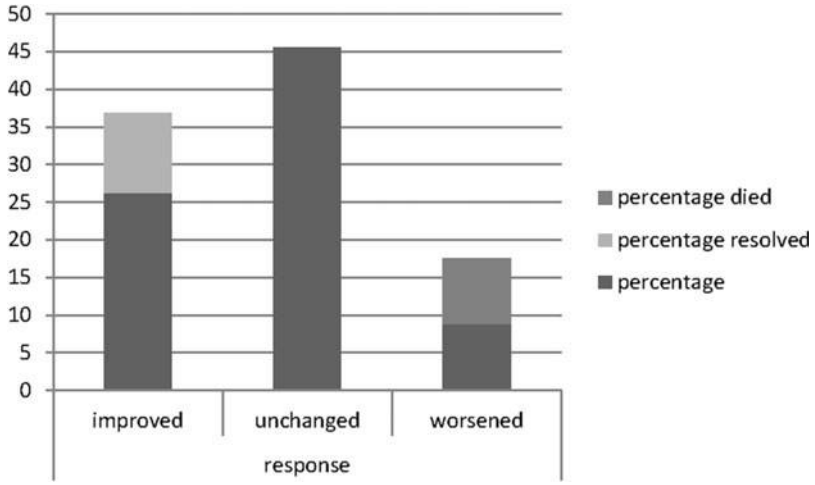

FIG. 2. Response at 48 hours to haloperidol for delirium in a palliatve care population.

care practice in the participating countries. The age range of participants (mean age of 73 years) and predominance of malignant diagnoses (88%) represents current referral patterns for many services.

This study demonstrates that when haloperidol is used for delirium, where the mean dose was 2.1 mg per 24 hours, it is relatively well tolerated, with relatively few immediate and short term side-effects. An adequately powered, multi-site, parallel arm Phase 3 double-blinded, randomized, placebo-controlled trial evaluating the additional net benefit of haloperidol in treating delirium in hospice/palliative care patients is nearing completion of accrual.

Acknowledgments

Thanks go to all the clinicians and the clinical units who have contributed to this program, Mr. Zac Vandersman and Ms. Caroline Litster. Participating units include: Sunshine Coast Hospital & Health Service, Braeside Hospital, Calvary Mater Newcastle, Sacred Heart Hospice, St. Vincent's Sydney, Calvary Healthcare, Greenwich Hospital, Wolper Private Hospital, Peter MacCallum Cancer Institute, St. Vincent's Hospital (Melbourne), Barwon Health, Royal Melbourne Hospital, Calvary North Adelaide, Southern Adelaide Palliative Services, Grey Nuns Hospital Edmonton, Canada, Leeds Teaching Hospitals NHS Trust, England UK, Haven of Hope Hospital, Hong Kong.

The Australian Palliative Care Clinical Studies Collaborative is supported by funding from the Palliative Care Branch of the Australian Government's Department of Health and Ageing.

Author Disclosure Statement

No competing financial interests exist.

References

1. Leonard M, Agar M, Mason C, Lawlor P: Delirium issues in palliative care settings. J Psychosom Res 2008;65:289–298.
2. Breitbart W, Alici Y: Evidence-based treatment of delirium in patients with cancer. J Clin Oncol 2012;30:1206–1214.
3. Critchley P, Plach N, Grantham M, Marshall D, Taniguchi A, Latimer E, Jadad AR: Efficacy of haloperidol in the treatment of nausea and vomiting in the palliative patient: A systematic review. J Pain Symptom Manage 2001;22:631–634.
4. Fainsinger RL, Tapper M, Bruera E: A perspective on the management of delirium in terminally ill patients on a palliative care unit. J Palliat Care 1993;9:4–8.
5. Vella-Brincat J, Macleod AD. Haloperidol in palliative care. Palliat Med 2004;18:195–201.
6. Hu H, Deng W, Yang H: A prospective random control study comparison of olanzapine and haloperidol in senile delirium. Chongging Med J 2004;8:1234–1237.
7. Tahir TA, Eeles E, Karapareddy V, Muthuvelu P, Chapple S, Phillips B, et al: A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. J Psychosom Res 2010;69:485–490.
8. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, et al: Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med 2010;38:419–427.
9. National Institute for health and Clinical Excellence (NICE) Delirium: Diagnosis, prevention and management (Clinical guideline (CG)103:2010; http://guidance.nice.org.uk/CG103/Guidance/pdf/English) (Last accessed October 1, 2013).
10. Currow DC, Rowett D, Doogue M, To THM, Abernethy AP: An international initiative to create a collaborative for pharmacovigilance in hospice and palliative care clinical practice. J Palliat Med 2012;15:282–286.
11. Currow DC, Shelby-James TM, Agar M, Plummer J, Rowett D, Glare P, Spruyt O, Hardy J: Planning phase III multi-site clinical trials in palliative care: The role of consecutive cohort audits to identify potential participant populations. Support Care Cancer 2010;18:1571–1578.
12. Currow DC, Vella-Brincat J, Clark K, Fazekas B, Doogue M, Rowett D: Pharmacovigilance in hospice/palliative care. Rapid report of net clinical effect of metoclopramide. J Palliat Med 2012;15:1071–1075.
13. Anon. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, V4.0, DCTD, NCI, NIH, DHHS. http://ctep.cancer.gov/protocol Development/electronic_applications/ctc.htm (Last accessed May 28, 2009).
14. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt CJ: A method for estimating the probability of adverse drug reactions. Clin Pharmacol Therapeut 1981;30:239–245.

15. Abernethy AP, Shelby-James TM, Fazekas BS, Woods D, Currow DC: The Australian-modified Karnofsky Performance Status (AKPS) scale: A revised scale for contemporary palliative care clinical practice. BMC Palliat Care 2005;4:7.
16. Charlson ME, Pompei P, Ales KL, MacKenzie RC: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–383.
17. Candy B, Jackson KC, Jones L, Leurent B, Tookman A, King M: Drug therapy for delirium in terminally ill adult patients. Cochrane Database Syst Rev 2012;11(Nov 14): CD004770.
18. Campbell N, Boustani MA, Ayub A, Fox GC, Munger SL, Ott C, Guzman O, Farber M, Ademuyiwa A, Singh R: Pharmacological management of delirium in hospitalized adults: A systematic evidence review. J Gen Intern Med 2009;24(7):848–853.
19. Seitz DP, Gill SS, Lvan Zyl LT: Antipsychotics in the treatment of delirium. A systematic review J Clin Psychiatry 2007;68:11–21.
20. Lacasse H, Guévin J-F, Perreault MM, Williamson DR: Systematic review of antipsychotics for the treatment of hospital-associated delirium in medically or surgically ill patients Ann Pharmacother 2006;40):1966–1973.