UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

March 4, 2022 Vol. 2, No. 8

Palliative Care Pharmacy Team:

Clinical Pharmacy Specialist:

Maria Felton Lowry, PharmD, BCPS, BCGP
Assistant Professor
University of Pittsburgh School of Pharmacy, Department of Pharmacy and Therapeutics
Palliative Care Clinical Pharmacy Specialist
UPMC Palliative and Supportive Institute

Cell: 412-627-8473
Office: 412-864-2899
Email: lowrymf@upmc.edu

If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Benzodiazepine Use for Delirium in Palliative Care

Background:

Delirium is a common symptom experienced by patients during hospitalization. The etiology of delirium as well as outcomes are different depending on patient-specific characteristics and situation. Delirium can be characterized as transient/reversible, possibly reversible, or irreversible depending on etiology. Medications, infection, metabolic disturbances, structural abnormalities along with a patient's comorbidities can precipitate or worsen delirium. In the case of hyperactive delirium, hyperactivity can range from restlessness to overt aggression. Palliation of delirium symptoms and reduction of delirium-related distress is desired and it likely the appropriate target for pharmacologic therapy. Pharmacologic therapy has not been associated with reduction of severity or length of delirium. Benzodiazepines have been shown to worsen transient delirium; they do, however have a role with certain types of delirium such as terminal delirium or delirium related to alcohol withdrawal.

Importance:

It is important to palliative care clinicians to be aware of the literature surrounding benzodiazepine use for delirium in our palliative care population.

The Literature:

JAMA Intern Med. 2017 Jan 1; 177(1):34-42.

Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial

Objective: To determine efficacy of risperidone or haloperidol vs. placebo in relieving target symptoms of delirium associated with distress in palliative care patients

Outcomes:

- Primary: mean group difference of delirium symptom score (Nursing Delirium Screen Scale (NuDESC): Severity range, 0-6) between baseline and day 3
- Secondary: delirium severity, midazolam use, extrapyramidal effects, sedation, and survival

Methods: double-blind, parallel arm, dose-titrated RCT ; intention to treat analysis

- 11 inpatient hospice or hospital PC services, patients with life-limiting illness, delirium, and delirium symptom score of 1 or more
- Age-adjusted titrated doses of PO risperidone, haloperidol, or placebo administered every 12 hours for 72 hours, based on symptoms of delirium with rescue SQ midazolam as required for severe distress or safety
- SQ midazolam 2.5mg every 2 hours was administered if patients scored 2 on the NuDESC item for "inappropriate behavior" or "illusions and hallucinations"

Results: n = 247; mean age 74.9 years, 88.3% with cancer

- Delirium score was higher in risperidone and haloperidol groups as compared to placebo
- More EPS in both active arms
- Participants in placebo group had better overall survival than haloperidol
- Average dose of midazolam required:

Study Day	Placebo	Haloperidol + Risperidone
1	13/75 (17.3%)	50/144 (34.7%)
2	11/68 (16.8%)	40/121 (33.1%)
3	9/66 (13.6%)	32/108 (29.6%)
Median dose	2.5mg	4mg haloperidol 2.5mg risperidone

Conclusion: In patients receiving palliative care, individualized management of delirium precipitants and supportive strategies result in lower scores and shorter duration of target distressing delirium symptoms than when risperidone or haloperidol are added

JAMA. 2017 Sep 19;318(11):1047-1056.

Effect of lorazepam with haloperidol vs haloperidol alone on agitated delirium in patients with advanced cancer receiving palliative care: a randomized clinical trial

Objective: To compare the effect of lorazepam vs placebo as an adjuvant to haloperidol for persistent agitation in patients with delirium in the setting of advanced cancer

Outcomes:

- Primary: Change in Richmond Agitation-Sedation Scale (RASS) Score: -5 unarousable to 4 very agitated/combative (baseline, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 hours), daily until discharge or death
- Secondary: rescue neuroleptic use, delirium recall, comfort (perceived by caregivers and nurses), communication capacity, delirium severity, adverse effects, discharge outcomes, and overall survival

Methods: Single center, double-blind, parallel-group, RCT

- Lorazepam (3mg) IV versus placebo in addition to haloperidol (2mg) IV upon onset of agitation episode

Results: n=90, mean age: 65 years

- Reduction in RASS scores at 8 hours
  - Lorazepam + haloperidol → -4.1 points
  - Placebo + haloperidol → -2.3 points
- Less rescue neuroleptics, greater perceived comfort in lorazepam + haloperidol group
- No difference in delirium-related distress or survival
- Hypokinesia was 19% in lorazepam + haloperidol vs. 27% in placebo + haloperidol group

Conclusion: the addition of lorazepam to haloperidol compared with haloperidol alone resulted in a significantly greater reduction in agitation at 8 hours

Bottom Line:

- Agar et al. results do not support use of antipsychotic, preferring placebo or benzodiazepine for patients with agitated delirium
- Hui et al. results show combination of lorazepam + haloperidol are more effective in reducing RASS score, although these patients are less able to communicate
- Difficult to tell if addition of benzodiazepine flipped patients from hyperactive delirium to hypoactive delirium…?
- When sedation is desired as part of goals of care in setting of serious illness and delirium is likely terminal, addition of benzodiazepine is beneficial to aid in reduction of agitation

Stay tuned for Grand Rounds this Spring!

CLINICAL PEARL: Patients with agitated, terminal delirium can be appropriate candidates for benzodiazepines