Pilot Study of Lemborexant for Insomnia in Cancer Patients with Delirium

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Abstract
Delirium occurs very frequently in cancer patients. Insomnia is a symptom of delirium. Lemborexant is a drug that regulates sleep–wake rhythms without causing extrapyramidal symptoms. Based on its ability to improve sleep, lemborexant is expected to have efficacy for insomnia with delirium. The purpose of this study was to determine the efficacy of lemborexant for insomnia in cancer patients with delirium. A retrospective observational study was conducted between July 2020 and February 2021. Fourteen patients (six females; mean age, 69 years) were included. Lemborexant was effective in 11 of 14 (78.6%) patients. Of 14 patients, 10 had hyperactive delirium. Lemborexant might have similar efficacy for insomnia with and without delirium when compared with previous studies. The efficacy rate of lemborexant was 70% for patients with insomnia and hyperactive delirium. This study might lead to dose reductions of antipsychotic medications and fewer extrapyramidal symptoms in cancer patients with delirium.

Keywords: cancer patients; delirium; insomnia; lemborexant; orexin receptor antagonist

Introduction
Delirium occurs in ~40%1 of hospitalized cancer patients requiring a palliative care consultation and in 90%2 of patients at the end of life. Disturbance of sleep–wake rhythm (DSWR) occurs in 97%3 of patients with delirium. DSWR, which includes insomnia, is considered a symptom of delirium in the World Health Organization’s International Statistical Classification of Diseases and Related Health Problems, 11th Revision.4 The relationship between delirium and insomnia involves several mechanisms. DSWR increases levels of inflammatory cytokines,5 which are correlated with delirium.6,7 Inflammatory cytokines cause decreased rapid eye movement sleep (REMS).8 Impaired REMS is associated with delirium.9 Benzodiazepines and Z-drugs, drugs whose names often begin with Z, are commonly used for insomnia. They are risk factors for delirium.2 These drugs decrease REMS10 and should be avoided in patients with insomnia at high risk for delirium, including cancer patients. Treatment of insomnia that does not rely on benzodiazepines or Z-drugs and does not cause delirium is needed.

Lemborexant is a dual orexin receptor antagonist that works on orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R). Lemborexant is indicated for the treatment of insomnia. It has been shown to be safer and more efficacious than zolpidem, the most frequently used sleep medication, in a global phase III study.11 Lemborexant promotes sleep without decreasing the amount of REMS.12 Lemborexant might be effective for insomnia without worsening delirium, but there are no studies evaluating this
| Patient | Age (years) | Gender | Cancer type | Insomnia type | Delirium type | Therapy type | Psychotropic drug | Dose (mg/day) | Efficacy | Overall evaluation | Add | PRO | Additional use | AE |
|---------|-------------|--------|-------------|---------------|---------------|--------------|------------------|---------------|----------|------------------|------|-----|---------------|----|
| 1       | 53          | F      | HM          | Maintain      | Hypo          | Add          | Trazodone, haloperidol | 5            | 5        | Effective         | Good | No  | No            |    |
| 2       | 55          | F      | HBP         | Initiate      | Hyper         | Add          | Asenapine       | 5            | 5        | Effective         | Good | No  | No            |    |
| 3       | 82          | M      | Lung        | Maintain      | Hyper         | Switch       | Trazodone, risperidone | 5            | 5        | Effective         | Good | No  | No            |    |
| 4       | 75          | F      | Lung        | Initiate      | Hyper         | Switch       | Zolpidem, suvorexant, olanzapine | 5            | 5        | Effective         | Good | No  | No            |    |
| 5       | 83          | M      | Urological  | N/A           | Hypo          | Add          | Haloperidol     | 5            | 5        | Effective         | Good | No  | No            |    |
| 6       | 67          | F      | HM          | N/A           | Hypo          | Switch       | Hydroxyzine, risperidone | 2.5          | 5        | Effective         | Good | No  | No            |    |
| 7       | 61          | F      | HM          | N/A           | Hyper         | Add          | Hydroxyzine, asenapine, haloperidol, chlorpromazine, quetiapine, Haloperidol | 2.5          | 2.5     | Ineffective       | Not good | Yes | Liver dysfunction |    |
| 8       | 79          | M      | HBP         | Initiate      | Hyper         | Switch       | Zolpidem, chlorpromazine, quetiapine, Haloperidol | 2.5          | 5        | Ineffective       | Good |     |               |    |
| 9       | 78          | M      | HBP         | Initiate      | Hyper         | Switch       | Chlorpromazine, quetiapine, Haloperidol | 5            | 5        | Ineffective       | Not good | No  | No            |    |
| 10      | 55          | M      | Colorectal  | Initiate      | Hyper         | Add          | Chlorpromazine, quetiapine, Haloperidol | 5            | 5        | Ineffective       | Not good | No  | No            |    |
| 11      | 79          | M      | HBP         | Initiate      | Hyper         | Switch       | Trazodone, chlorpromazine, quetiapine | 5            | 5        | Effective         | Good | No  | No            |    |
| 12      | 73          | M      | Head/neck   | Initiate/maintain | Hyper         | Switch       | Chlorpromazine, quetiapine | 5            | 5        | Effective         | Good | No  | No            |    |
| 13      | 53          | M      | HBP         | Initiate      | Hyper         | Add          | Hydroxyzine, chlorpromazine, haloperidol | 5            | 5        | Effective         | Good | No  | No            |    |
| 14      | 73          | F      | Sarcoma     | Maintain      | Hyper         | Add          | Trazodone, etizolam, chlorpromazine | 5            | 5        | Effective         | Good | No  | No            |    |

*aBased on symptoms reported by the patient and nursing observations in the medical record.
*bRefers to whether psychotropic medication was added or not.
HBP, hepatobiliary or pancreatic; HM, hematological; hyper, hyperactive type; hypo, hypoactive type; N/A, not available; PRO, patient reported outcome.
Methods

This study involved a retrospective chart review to evaluate the efficacy of lemborexant for insomnia in cancer patients with delirium. It was conducted at the National Cancer Center Hospital (NCCH) in Tokyo, Japan.

Eligibility criteria included (1) being diagnosed cancer and delirium, (2) being managed with scheduled antipsychotics for delirium by a psycho-oncologist, (3) age of 20 years old or older, (4) being prescribed lemborexant for insomnia from July 2020 to February 2021, (5) insufficient effect on delirium (i.e., having insomnia and other symptoms that meet diagnostic criterion for delirium) with antipsychotics before scheduled doses of lemborexant, and (6) availability of documented patient’s reported outcome (PRO) regarding the efficacy for insomnia.

We collected the following data: background (age, gender, cancer type, insomnia type, and delirium type), baseline laboratory data before administration, PRO (effective or ineffective), psychotropic drug use, lemborexant dose, lemborexant administration (switch, switching from a previously administered psychotropic drug, or add, as an addition to psychotropic drugs), and adverse events (AEs).

The diagnosis and classification of delirium in the medical records were made by psycho-oncologists according to the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (fifth edition, DSM-5). For this study, another psycho-oncologist confirmed the diagnosis and classification of delirium based on medical records according to DSM-5 criteria. All patients were receiving antipsychotic medications.

Evaluations of PRO were determined by two psycho-oncologists and a psychiatric nurse specialist who used medical records to identify the best PRO within five days of the first prescription of lemborexant for each patient. To minimize the effect of decreasing delirium over time, we matched the duration of drug administration for delirium reported in previous studies. PRO was classified as effective if the patient made statements such as “I slept well.” PRO was classified as ineffective if there was no patient assessment of “I slept well” during the observation period, the patient continued to complain of insomnia, additional psychotropic medication was used, or the patient clearly had insomnia based on nursing records. If the three experts disagreed, PRO was classified as ineffective.

This study was approved by our institutional review board. Opt-out information was published on the NCCH website.

Analysis

Descriptive statistics were used to analyze the demographic data and compare the characteristics of patients in the effective and ineffective groups. Fisher’s exact test was used to assess the determinants of efficacy of lemborexant for depression.

Table 2. Descriptive Statistics of Patients’ Clinical Characteristics by Group

|                      | Effective | Ineffective | Total | p    |
|----------------------|-----------|-------------|-------|------|
| Age                  |           |             |       |      |
| ≥70 Years            | 142.3%    | 71.4%       | 8     | 1.000|
| <70 Years            | 35.7%     | 7.1%        | 6     |      |
| Gender               |           |             |       |      |
| Male                 | 28.6%     | 0.0%        | 4     | 1.000|
| Female               | 35.7%     | 7.1%        | 6     |      |
| Cancer type          |           |             |       |      |
| HBP                  | 21.4%     | 14.3%       | 3     | 5    |
| HM                   | 14.3%     | 7.1%        | 2     | 3    |
| Lung                 | 14.3%     | 0.0%        | 2     | 2    |
| Other                | 21.4%     | 0.0%        | 3     | 3    |
| Insomnia type        |           |             |       |      |
| Maintain             | 28.6%     | 0.0%        | 4     | 4    |
| Initiate             | 42.9%     | 14.3%       | 6     | 8    |
| Delirium type        |           |             |       |      |
| Hyperactive          | 50.0%     | 21.4%       | 10    | 0.506|
| Hypoactive           | 28.6%     | 0.0%        | 4     |      |
| Method               |           |             |       |      |
| Add                  | 42.9%     | 7.1%        | 7     | 7.1%|
| Switch               | 35.7%     | 14.3%       | 7     |      |
| Psychotropic drug    |           |             |       |      |
| Haloperidol          | 21.4%     | 14.3%       | 4     |      |
| Risperidone          | 14.3%     | 0.0%        | 2     |      |
| Chlorpromazine       | 35.7%     | 7.1%        | 6     |      |
| Olanzapine           | 7.1%      | 0.0%        | 1     |      |
| Asenapine            | 7.1%      | 7.1%        | 2     |      |
| Quetiapine           | 21.4%     | 0.0%        | 3     |      |
| Zolpidem             | 21.4%     | 0.0%        | 3     |      |
| Suvorexant           | 7.1%      | 0.0%        | 1     |      |
| Trazodone            | 28.6%     | 0.0%        | 4     |      |
| Hydroxyzine          | 14.3%     | 7.1%        | 3     |      |
| AE                   |           |             |       |      |
| Yes                  | 0.0%      | 7.1%        | 1     | 0.214|
| No                   | 78.6%     | 14.3%       | 13    |      |
| Laboratory data at baseline |       |             |       |      |
| Alb ≥mean            | 42.9%     | 0.0%        | 6     | 0.209|
| AST ≥mean            | 35.7%     | 21.4%       | 8     | 0.539|
| ALT ≥mean            | 28.6%     | 14.3%       | 6     | 1.000|
| ALP ≥mean            | 50.0%     | 0.0%        | 7     |      |
| Bil ≥mean            | 64.3%     | 14.3%       | 11    |      |
| Cre ≥mean            | 35.7%     | 7.1%        | 6     | 1.000|
| eGFR ≥60 mL/min/1.73 m² | 28.6% | 0.0% | 4 | 0.506 |

*Each drug was used in combination with other psychotropic drugs.

**Mean value was calculated from 14 patients’ values. Mean Alb value = 2.78 g/dL. Mean AST value = 25.4 IU/L. Mean ALT value = 26.2 IU/L. Mean ALP value = 142.3 IU/L. Mean Bil value = 0.51 mg/dL. Mean Cre value = 0.73 mg/dL. Alb, serum albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; Bil, total bilirubin; Cre, creatinine; eGFR, estimated glomerular filtration rate; HBP, hepatobiliary or pancreatic; HM, hematological.
insomnia in cancer patients with delirium. Statistical analysis was performed using JMP14 (SAS Institute, Cary, NC, USA). Statistical significance was set at $p < 0.05$.

**Results**

We included 14 cancer patients (6 females) in this retrospective analysis. Age ranged from 53 to 83 years (mean, 69.0 ± 11.4 years) (Table 1). Five patients had hepatobiliary pancreas cancer (35.7%) and three had hematological cancer (21.4%). Seven patients had difficulty falling asleep, three had difficulty maintaining sleep, one had both, and three were unsure. There were 10 patients (71.4%) with hyperactive delirium. The most common psychotropics were chlorpromazine in six patients (42.9%), haloperidol in five patients (35.7%), and trazodone in four patients (28.6%). Each drug was used in combination.

Lemborexant was administered in seven patients as a “switch” and seven patients as an “add.” It was effective in five of seven “switch” cases and in six of seven “add” cases. The distribution of delirium subtype was the same in both groups. Lemborexant was initiated at a dose between 2.5 and 5 mg per day. The maximum maintenance dose was 5 mg per day.

For 11 patients (78.6%), lemborexant was evaluated as effective; it was evaluated as ineffective for three patients (21.4%). The patient characteristics of the effective and ineffective groups were not significantly different (Table 2).

One patient (7.1%) discontinued lemborexant because of liver dysfunction. No other AEs occurred, including oversedation or extrapyramidal symptoms.

**Discussion**

In this study, we demonstrated that lemborexant was effective for insomnia in 11 of 14 cancer patients with delirium (78.6%). The efficacy rate of lemborexant 5 mg per day in adult patients with insomnia (mean age, 63.7 ± 6.8 years) in a previous study was 82.0%; the patient population and efficacy rate of the two studies seemed similar. Lemborexant might have similar efficacy in insomnia with and without delirium. Lemborexant had an efficacy rate of 70.0% for treating insomnia with hyperactive delirium. Improving sleep–wake rhythms in patients with delirium using lemborexant might lead to decreased delirium.

Antipsychotics are commonly used to treat delirium. However, several studies have suggested that antipsychotics are not beneficial; their use has been questioned. Anti-pyschotics have problems such as extrapyramidal symptoms and oversedation. Agitation is a common problem in delirium. When antipsychotic doses are increased to treat agitation, there is a risk of worsening extrapyramidal symptoms. Lemborexant is a drug that contributes to appropriate sleep–wake rhythms without extrapyramidal symptoms. This study might lead to reductions in antipsychotic dosage and extrapyramidal symptoms. Lemborexant might be useful when it is difficult to increase the dose of antipsychotics due to extrapyramidal symptoms or when a dose reduction is necessary.

The orexin system provides a reason to expect that lemborexant can be effective for insomnia without worsening delirium. The orexin system has recently become a focus of attention in the regulation of sleep–wake rhythms. Ox2R is known to be more important than Ox1R in the regulation of sleep–wake rhythms. Orexin receptors include Ox1R and Ox2R. Orexin-A and orexin-B are known agonists. Ox1R has a high affinity for orexin-A, and Ox2R has a similar affinity for both orexin-A and orexin-B. A previous study showed that orexin-A is elevated in the serum of patients with agitated delirium. Another recent study showed that Ox2R stimulation is associated with accelerated aggression in rodents. These findings suggest that orexin receptor antagonists might have efficacy for agitation, and that Ox2R is particularly important. Lemborexant has a high affinity for Ox2R.

Lemborexant was ineffective for three patients in this study. One patient requested discontinuation of lemborexant, another patient discontinued lemborexant due to liver dysfunction, and the third patient had an unspecified reason. The patient who experienced liver dysfunction had pancreatic cancer and was treated under the policy of best supportive care only; thus, liver dysfunction could have been due to the progression of the primary disease.

This study has several limitations. First, there are no clear criteria for dosing lemborexant. Patients for whom lemborexant was classified as ineffective did not reach the maximum dose of 10 mg per day. There is not enough information to determine whether the dose was insufficient or lemborexant was ineffective. Second, the state of delirium could not be assessed quantitatively using criteria such as the Memorial Delirium Assessment Scale or the Richmond Agitation-Sedation Scale; delirium could only be assessed according to DSM-5 criteria.

Third, lemborexant is efficacious in combination with other psychotropic drugs. This study might not be able to show the efficacy of lemborexant monotherapy. Fourth, due to the short observation period, the assessment of AEs during long-term administration might have been insufficient. Finally, this study was a single-center retrospective study with a small number of subjects. It might be difficult to generalize these results.

This study is the first to suggest that lemborexant is efficacious for treating insomnia in cancer patients with delirium. Despite some limitations, our findings suggest that lemborexant can be expected to have efficacy for insomnia in such patients. We hoped that decreased insomnia would be effective in decreasing delirium. We will conduct a prospective study to explore the efficacy of lemborexant as a novel therapy for delirium.

**Authors’ Contributions**

All authors contributed to study conception and design, data analysis, and article preparation.

**Acknowledgments**

We thank Asako Mitsui for data collection and all the patients involved in this study.

**Funding Information**

No funding was received for this article.

**Author Disclosure Statement**

No competing financial interests exist.
References

1. Elsayem AF, Bruera E, Valentine AD, et al.: Delirium frequency among advanced cancer patients presenting to an emergency department: A prospective, randomized, observational study. Cancer 2016;122:2918–2924.

2. Ogawa A, Okumura Y, Fujisawa D, et al.: Quality of care in hospitalized cancer patients before and after implementation of a systematic prevention program for delirium: The DELTA exploratory trial. Support Care Cancer 2019;27:557–565.

3. Meagher DJ, Moran M, Raju B, et al.: Phenomenology of delirium. Assessment of 100 adult cases using standardised measures. Br J Psychiatry 2007;190:135–141.

4. World Health Organization: The International Statistical Classification of Diseases and Health Related Problems, ICD-11. https://icd.who.int/browse11/l-m/en/#http://id.who .int/icd/entity/897917531 (Last accessed January 25, 2022).

5. Mullington JM, Simpson NS, Meier-Ewert HK, et al.: Sleep loss and inflammation. Best Pract Res Clin Endocrinol Metab 2010;24:775–784.

6. Hoogland IC, Houbolt C, van Westerloo DJ, et al.: Systemic inflammation and microglial activation: Systematic review of animal experiments. J Neuroinflammation 2015;12:114.

7. Liu X, Yu Y, Zhu S: Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. PLoS One 2018;13: e0195659.

8. Mullington J, Korth C, Hermann DM, et al.: Dose-dependent effects of endotoxin on human sleep. Am J Physiol Regul Integr Comp Physiol 2000;278:R947–R955.

9. Trompeo AC, Vidi Y, Locane MD, et al.: Sleep disturbances in the critically ill patients: Role of delirium and sedative agents. Minerva Anestesiol 2011;77:604–612.

10. Mazza M, Losurdo A, Testani E, et al.: Polysomnographic findings in a cohort of chronic insomnia patients with benzodiazepine abuse. J Clin Sleep Med 2014;10:35–42.

11. Rosenberg R, Murphy P, Zammit G, et al.: Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: A phase 3 randomized clinical trial. JAMA Netw Open 2019;2:e1918254.

12. Beuckmann CT, Ueno T, Nakagawa M, et al.: Preclinical in vivo characterization of lemborexant (E2006), a novel dual orexin receptor antagonist for sleep/wake regulation. Sleep 2019;42:zs2076.

13. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-5 (R)). Washington, DC: American Psychiatric Association, 2013, pp. 596–602.

14. Neufeld KJ, Yue J, Robinson TN, et al.: Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: A systematic review and meta-analysis. J Am Geriatr Soc 2016;64:705–714.

15. Hui D, Dev R, Bruera E: Neuroleptics in the management of delirium in patients with advanced cancer. Curr Opin Support Palliat Care 2016;10:316–323.

16. Hui D, De La Rosa A, Wilson A, et al.: Neuroleptic strategies for terminal agitation in patients with cancer and delirium at an acute palliative care unit: A single-centre, double-blind, parallel-group, randomised trial. Lancet Oncol 2020;21:989–998.

17. Yamanaka A, Tabuchi S, Tsunematsu T, et al.: Orexin directly excites orexin neurons through orexin 2 receptor. J Neurosci 2010;30:12642–12652.

18. Sakurai T, Amemiya A, Ishii M, et al.: Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 1998;92:573–585.

19. Vilke GM, Mash DC, Pardo M, et al.: EXCITATION study: Unexplained in-custody deaths: Evaluating biomarkers of stress and agitation. J Forensic Leg Med 2019;66:100–106.

20. Flanigan ME, Aleyasin H, Li L, et al.: Orexin signaling in GABAergic lateral habenula neurons modulates aggressive behavior in male mice. Nat Neurosci 2020;23:638–650.

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