An Open Trial Comparing Haloperidol with Olanzapine for the Treatment of Delirium in Palliative and Hospice Center Cancer Patients

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Abstract

This study compared the efficacy between haloperidol and olanzapine to treat the delirious syndromes in the palliative and hospice center cancer patients. Patients those received hospice and palliative care, with an advanced cancer, and met the DSM-IV criteria for delirium were recruited. They were administered the DRS-c and CGI-S at the time point of T_0,T_1,T_2,T_3 during 1 week. 16 patients (M:F=9:7; mean age ± SD=61.13 ± 16.5) in olanzapine group and 14 patients (M:F=4:10; mean age ± SD=68 ± 12.14) in haloperidol group were recruited. In both groups there was significant difference in scores of DRS-c and CGI-S across time periods (haloperidol group: DRS-c: at T_1, p=0.008; at T_2, p=0.044; at T_3, p=0.043 and CGI-S: at T_1, p=0.012; olanzapine group: DRS-c: at T_3, p=0.042 and CGI-S: at T_1, p=0.040). However, comparison of the scores of DRS-c and CGI-S across time periods between two groups showed no statistical difference. The results showed that the delirium improved in both groups but no statistic difference comparing both groups. Therefore, olanzapine might be a useful alternative to haloperidol in the treatment of delirium in advanced cancer patients. (J Intern Med Taiwan 2008; 19: 346-354)

Key Words ： Olanzapine, Haloperidol, Delirium, Advanced cancer patients, Palliative and hospice care

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Introduction

Delirium, also called acute confusional state, is a global brain dysfunction characterized by alterations in the state of consciousness and attention associated with cognitive (e.g., amnesia), behavioral (e.g., agitation), and perceptive (e.g., hallucination) disturbances[1]. Delirium is also one of the most common neuropsychiatric complications at the end stage of life, particularly in patients with advanced cancer[2].

Among those cancer patients needing psychiatric evaluation, delirium is the second most frequent diagnosis (17%), only exceeded by adjustment disorder[3]. The incidence of delirium is 25~85% in hospitalized cancer/AIDS patients[2,4,5], and 65~85% in terminally ill patients[6,7]. Eventually, up to 83% of patients develop delirium in their final days, and 10% to 30% of them may require palliative terminal sedation[6,8]. It is associated with high morbidity and mortality, and therapy is often suboptimal[2]. Recognized risk factors for delirium include advanced age[9,10], prior cognitive impairment[9,11], illness severity[11,12], and burden of comorbidity. It is proposed that causative factors induce a failure of high energy metabolism at an inter- and intra-neuronal level resulting in a cholinergic/ dopaminergic imbalance[13].

Based on the previous studies, the standard approach to manage delirium in the medically ill, even in those with advanced cancer, includes a search for underlying causes, a correction of those factors, and the management of the symptoms of delirium[14]. The management of the symptoms of delirium involves the use of both non-pharmacological and pharmacological interventions. Non-pharmacological or supportive intervention alone is often not effective in controlling the symptoms of delirium, and symptomatic treatment with neuroleptics or antipsychotic medications is necessary[14,15]. Delirium identified on admission to a Palliative Care Unit may be reversible in almost 50% of cases through adopting a suitable therapeutic approach.

However, in palliative care the etiology of delirium is usually multifactorial. Organ failure[6] and delirium-inducing medications such as opioids[13] are frequently implicated. Reversal of the etiology in the terminally ill may not always be possible. Palliation of the symptoms is a feasible clinical goal. Therefore, finding some useful way to treat advanced cancer patients with delirium, thereby relieve the delirious patients' suffering and improve the quality of life at the end of life demand immediate attention for our clinicians.

Medication is often a component of delirium management and haloperidol remains the drug of first choice. However, the side effects of haloperidol for the treatment of the symptoms of delirium include the development of extrapyramidal symptoms (EPS), tardive dyskinesia (TD), and neuroleptic malignancy syndrome (NMS)[16]. The effect of haloperidol may be challenged by the newer second-generation antipsychotics such as risperidone, olanzapine, quetiapine and etc. Olanzapine has been studied in a series of case reports that have examined its utility in the management of delirium[7,17,18,19]. Breitbart et al. conducted a prospective trial of olanzapine for the treatment of delirium in a sample of 79 hospitalized cancer patients who met DSM-IV criteria for a diagnosis of delirium and were rated systemically with the Memorial Delirium Assessment Scale (MDAS) as a measure status. The result was that 57 patients had a complete resolution of their delirium with olanzapine therapy, with no extrapyramidal side effects, and 30% experienced sedation (usually not severe enough to interrupt treatment). Although several factors were found to be significantly associated with a poor response to olanzapine treatment for delirium, including age more than 70 years, a history of dementia, cancer spread to the central nervous system, and hypoxia as delirium etiologies, "hypoactive" delirium, and delirium of "severe" intensity (i.e., MDAS > 23)[5]. Olanzapine is well tolerated and associated with an improvement in psychiatric symptoms, although it

demonstrates a lack of EPS and minimal sedative, hypotensive, and anticholinergic side effects in the dose range used in older adults[20].

On the basis of the previous research, we wish to figure out the efficacy between olanzapine, a second-generation antipsychotic, and haloperidol, a first-generation antipsychotic, for the treatment of delirium in advanced cancer patients. Meanwhile, we look forward to explore other useful alternative antipsychotic to relieve the delirious symptoms.

Materials and Methods

Ethical Considerations

This study was undertaken in the guidelines on good clinical practice. The The-Zzer Study Group for Human Medical Research Foundation approved the study protocol. Informed consent was required for participation in this study.

Study Design and Objectives

This was a prospective randomized-controlled, clinical trial study. All the participants after being recruited should be followed for one week. This study aim was to compare the efficacy between haloperidol and olanzapine in treating the delirious advanced cancer patients in the hospice and palliative care center. The patients were recruited from August 2003 through April 2004.

Participants

All patients were recruited from the hospice and palliative care center of Mackay Memorial Hospital, a 2060-bed, general and teaching hospital in Taipei, Taiwan. The care center is one of the biggest hospice and palliative care centers in the world (63-beds). All patients were referred from the hospice and palliative care center to the consultation-liaison psychiatry service for an evaluation of mental status change.

Patients who had past histories of psychiatric disorders, who were in a coma, who could not swallow oral medication, and who had been treated with neuroleptic agents within 4 weeks prior to the enrollment, were excluded from this study. They were required to have received hospice and palliative care, in an advanced cancer, and to have met the Diagnostic and Statistical Manual of Mental Disorders (4th ed.) criteria for delirium1. Patients provided written informed consent before admission to this study. However, considering the condition of consciousness or no capacity to sing informed consent for participants, consent was singed by their relatives or closed family members.

Measurements and Procedures

The participants were met the Diagnostic and Statistical Manual of Mental Disorders (4th ed.) criteria for delirium while they were consulted to the psychiatric service. Afterwards, they all administered the Delirium Rating Scale-Chinese (DRS-c), which was translated from the Delirium Rating Scale (DRS)[21] and the validity and reliability of DRS-c were examined in 2001 by Chuang Y.M. and et al[22] and Clinical Global Impression-Severity (CGI-S)[23] at their admission to the study by the study assessor. The baseline assessments were marked as T_0.

The Delirium Rating Scale (DRS) which had 10 items and each item had a four-point scale (from 0 to 3) except item 6,8,10 had five-point scale (from 0 to 4) has been shown to be a valid instrument for identifying and grading the severity of delirium in patients admitted to a general hospital for medical or surgical treatment[24]. The total scores of DRS-c ranged from 0 to 33[21].

CGI was a three-item scale used to assess treatment response in psychiatric patients. They are severity of illness, global improvement, and efficacy index. Item 1 was rated on a seven-point scale (1=normal to 7=extremely ill), item 2 on a seven-point scale (1=very much improved to 7=very much worse), and item 3 on a four-point scale (from "none" to "outweighs therapeutic effect"). The severity of illness item required the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical expe-

rience, a patient was assessed on severity of mental illness at the time of rating according to: normal (not at all ill), borderline mentally ill, mildly ill, moderately ill, markedly ill, severely ill, or extremely ill. Clinical Global Impression-Severity (CGI-S) was been chosen to assess the psychiatric condition of the participants in this study, and the scores of CGI-S ranged from 1 to 7 [23].

A psychiatric specialist determined whether the necessary of the patients to receive antipsychotic treatment, based on clinical grounds. If the patients needed to have antipsychotic, they were separated randomly to an olanzapine group or a haloperidol group, with a starting dose of olanzapine 5 mg per day at 6:00 PM by oral use or haloperidol 5 mg per day at 6:00 PM by oral use. The dosages should be titrated by the psychiatric specialist who was the same one to determine the patients should use the antipsychotic after 24 hours (T_1), if the patient's condition did not improve. At 48 hours (T_2) and 1 week (T_3) after giving the first dose of antipsychotic, the DRS-c and CGI-S were re-administered to evaluate the difference between the two groups. The maximum doses were 15 mg of olanzapine per day and 15 mg of haloperidol per day by oral use. When the patients required an adjunctive psychotropic therapy for acute symptoms, they were given Midazolam by intramuscular injection, as needed. The side effects of olanzapine and haloperidol were observed and recorded on the chart by the clinicians in the hospice and palliative care center and the assessor of this study without formal instruments.

Assessment

In this study there was just one assessor, whose background was both a nurse and a counseling psychologist, to do all the assessment. Before the study, this assessor had extensive training about the pharmaco-dynamic effect and the side effects of the antipsychotic. This assessor was also trained how to measure the DRS-c and CGI-S and followed standard procedure. The baseline screening and assessment were completed within 24 hours after the patient was recruited. Besides, the assessor was blind to what kind of antipsychotic the patients received when she assessed the following DRS-C and CGI-S and the side effect of both groups cross time periods.

Statistical Analysis

Statistical analysis was performed by use of the SPSS 12.0 for Windows (SPSS Inc., Chicago, USA) program. Tests for normal distribution revealed that the data did not conform to normal distribution. Therefore, nonparametric statistical methods were applied to all data except sex. The independent sample t-test was performed to analyze sex. The Mann-Whitney U test was used to analyze the comparative efficacy of olanzapine group and haloperidol group. The Wilcoxon signed rank test was used to measure the efficacy intra the both groups. Tests were two-tailed with a significance level of 0.05.

Results

At the end of the study, there were total 16 patients (9 males and 7 females) recruited in the olanzapine group and 14 patients (4 males and 10 females) in the haloperidol group. The mean age of the participants in both groups had no statistical significance (mean ± SD: 61.13 ± 16.5 years, ranging from 23 to 80 for the olanzapine group, and 68 ± 12.14 years, ranging from 39 to 87 years for the haloperidol group, p=0.270). There was no significant difference between the two groups in sex (p=0.124) either. The

Table 1.The characteristics of two groups

	Olanzapine group	Haloperidol group	P-value
Sex			
Male	9	4	0.124
Female	7	10	
Age			
Mean age	61.13	68.00	0.270
SD	16.50	12.14	
Range	23-80	39-87	

Table 2. The Mann-Whitney U test comparing scores on the DRS-c and CGI-S at different time period in both groups

	Olanzapine group	Haloperidol group	P-value
T_0			
Number	16	14	
DRS-c(SD)	17.56(5.18)	16.50(4.70)	0.646
CGI-S(SD)	5.00(1.03)	4.5(1.02)	0.190
T_1			
Number	14	14	
DRS-c(SD)	14.29(4.55)	11.93(3.81)	0.204
CGI-S(SD)	4.07(1.21)	3.57(0.65)	0.358
T_2			
Number	10	14	
DRS-c(SD)	14.90(3.48)	13.00(5.02)	0.332
CGI-S(SD)	4.10(1.20)	3.79(0.89)	0.594
T_3			
Number	5	7	
DRS-c(SD)	10.60(3.65)	12.29(5.59)	0.568
CGI-S(SD)	3.60(0.55)	3.57(0.98)	1.000

characteristics of two groups were shown in Table 1.

At T_0, scores of DRS-c and CGI-S between the two groups had no significant difference statistically (mean ± SD of DRS-c: 17.56 ± 5.18 for the olanzapine group and 16.5 ± 4.70 for the haloperidol group, p=0.646; mean ± SD of CGI-S: 5.0 ± 1.03 for the olanzapine group and 4.5 ± 1.02 for the haloperidol group, p=0.190). At other time periods during this study, there was no statistical significant difference comparing between two groups about the scores of DRS-c and CGI-S, either. The comparison of scores on the DRS-c and CGI-S at different time period in both groups examined by the Mann-Whitney U test was showed in Table 2.

In the olanzapine group, there were significant difference at T_3 comparing the scores of DRS-c across different time periods (p=0.042), whereas the CGI-S scores across time periods showed statistical difference at T_1 (p=0.040). In the haloperidol group, the DRS-c scores had a significant improvement across time periods (at T_1, p=0.008; at T_2, p=0.044; at T_3, p=0.043), whereas the CGI-S scores also had a significant difference at T_1 (p=0.012). The comparison of scores on the DRS-c and CGI-S across time periods intra the haloperidol group and intra the olanzapine group was examined by Wilcoxon Signed Rank Test shown in Table 3.

Table 3. The Wilcoxon signed rank test comparing scores on the DRS-c and CGI-S in olanzapine group and haloperidol group across time period

	T_1- T_0	T_2- T_0	T_3- T_0
Olanzapine group	N=14	N=10	N=5
P-value			
DRS-c	0.181	0.165	0.042*
CGI-S	0.040*	0.123	0.066
Haloperidol group	N=14	N=14	N=7
P-value			
DRS-c	0.008*	0.044*	0.043*
CGI-S	0.012*	0.062	0.102

*P-value <0.05

However, the comparison of scores on the DRS-c across time periods between two groups showed no statistical difference (at T_1, p=0.123; at T_2, p=0.240; at T_3, p=0.414), as did the CGI-S (at T_1, p=0.581; at T_2, p=1.000; at T_3, p=0.618). The comparison of scores on the DRS-c and CGI-S across time periods between the two groups analyzed by Mann-Whitney U test.

As the dosage, olanzapine 5 mg per day by oral use was found in most participants, except one patient whose dose was titrated to 15 mg per day at T_1, another two whose dose increased to 10 mg per day at T_2, and another one whose dose titrate to 10 mg per day at T_3 due to uncontrolled delirious symptoms. Most patients in the haloperidol group had also 5 mg per day by oral use, except for four patients, two whose dose was titrated to 10 mg per day at T_2, and the other two whose dose was titrated to10 mg per day at T_3. During this study, midazolam by intramuscular injection, as needed was chosen as an adjunctive psychotropic therapy for acute disturbing symptoms. The dosage and frequency of Midazolam by in-

tramuscular injection across time periods were found no significant difference statistically (at T_0, p=1.000; at T_1, p=0.593; at T_2, p=0.192; at T_3, p=0.315). As the side effect of both neuroleptics such as EPS, no formal instruments for evaluation were used in this study. However, no significant finding was found in the clinical record or by the observation of the assessor during the study.

Discussion

Management of delirium of those patients in the hospice and palliative care center whose comorbidities render the physician reluctant to administer haloperidol could be problematic for considering the adverse effects. Recent studies had explored the safety and efficacy of second-generation antipsychotics in the management of delirium outside the hospice and palliative care center[5,7,17,18,25-27]. Meanwhile, in our previous case report19, we also found serial cases who suffered delirium with treatment of olanzapine, a second generation antipsychotics, is useful and efficacy. Consequently, in this study, we compared haloperidol and olazapine with oral use in treating delirium of advanced cancer patients in the hospice and palliative care center. The DRS-c was chosen to measure the severity of delirium and the Chinese version was already translated and the validity and reliability were done[22].

In this study, we found olanzapine is as efficacy as haloperidol in reducing delirious symptoms in advanced cancer patients. From the result shown above, there were some advantages in this study showed as followed. First, this is a pilot prospective randomized control study. All patients were free of previous psychiatric diagnoses, and didn't use any type of psychiatric agents for at least 4 weeks prior to admission in this study. Second, this is also the first report using an Asian Hospice and Palliative Care center that replicated the results of Western studies. Third, this study provides a new standpoint for treating delirium in terminal cancer patients to enhance their quality of life at the end of their life.

According to previous studies[7,28], there was no consensus among experts on a first-line second-generation antipsychotic drug for delirium. But typically, high-potency neuroleptics like haloperidol were used as first-line treatment for delirium. Haloperidol, a first-generation antipsychotic, is the gold standard of antipsychotic drug therapy and the first drug choice for the control of the symptoms of delirium. Haloperidol is a dopamine antagonist of dopamine-2 receptors in the basal ganglia and of the limbic parts of the forebrain, which corrects the acetylcholine/dopamine systems imbalance[13]. The major disadvantages of the use of first-generation antipsychotics like haloperidol for the treatment of the symptoms of delirium include the development of extrapyramidal symptoms (EPS)[28], tardive dyskinesia(TD), and neuroleptic malignancy syndrome(NMS)[16]. EPS was likely to be more common in delirious patients, in part because delirium was more common in elderly and severe medically ill patients, who were more prone to EPS. Although no significant EPS was found in the haloperidol group from the medical record in this study, we still needed to pay more attention to advanced cancer patients when they use haloperidol.

Several second-generation antipsychotics such as risperidone, olanzapine and quetiaopine, with more variable dopamine D_2 antagonist properties and perhaps more specific dopamine blocking effects, which results in a lower incidence of extrapyramidal and related side effects, are now available and are being used clinically in the treatment of behavioral disturbances in dementia[25,29,30] and in the treatment of delirium in medically hospitalized patients[7,17,18,26,27]. Second-generation antipsychotics, might be useful in treating delirium because of their high affinity for dopamine receptors and their lower incidence EPS, compared with first-generation antipsychotics.

From review articles[4,28], Risperidone received a high second-line rating for delirium in elderly patients. Quetiapine received lower second-line ratings.

Although high-potency first-generation antipsychotics and olanzapine also received second-line ratings, there was no consensus on delirium in older patients[28]. As the dosage of second-generation antipsychotics, if an oral or feeding tube route is available, 0.25-0.5 mg of risperidone twice daily(mild to severe agitation)is a reasonable starting dose and it may increased up to 4 mg/day if symptoms fail to clear. As olanzapine, 2.5-5 mg at bedtime (mild to severe agitation) is a reasonable starting dose. This may increase to 20 mg/day if symptoms fail to clear. To quetiapine, 25-50 mg twice a day is a reasonable starting dose. This may be increased every 1-2 days to 100 mg twice a day if it is well tolerated. Up to 600 mg/day of quetiapine may be used. No matter risperidone, olanzapine or quetiapine, they may be discontinued without difficulty 7-10 days after patients return to baseline, with cleared sensorium and alleviation of delirium symptoms, particularly after reorganization of the sleep-wake cycle. As for haloperidol, the dosage of haloperidol is titrated to effect. In palliative care patients a useful regimen may be 0.5-1.5 mg orally (mild), 1.5-5 mg orally (severe) and 10 mg subcutaneously or intravenously (very severe). These doses may be repeated every 30-40 minutes until symptoms are alleviated. In this study, the treatment dosage of most patients in the olanzapine group is 5 mg and the dosage of most patients in the haloperidol group is also 5 mg. The dosage in this study is at the similar range comparing to previous studies.

In our study, we aimed to figure out whether haloperidol or olanzapine was better in treating advanced cancer patients in the hospice and palliative care center. From the pass researches, olanzapine was a thienobenzodiazepine compound related to clozapine, but olanzapine, unlike clozapine, was much less likely to decrease white blood cell counts. The common side effects reported with olanzapine include orthostatic hypotension, dry mouth, drowsiness, restlessness, and peripheral edema. Although we did not formally rate the EPS caused by antipsychotics in our study, neither one suffered EPS was noted from the medical record or observed by the assessor in this study. Among those side effects of olanzapine, the most common was sedation. It was useful in single doses at the beginning of the night to help with sleep-wake cycle disorders. One researcher had reported that muscarinic antagonist properties of olanzapine could played a role in worsening the delirium of some susceptible patients those who experienced a worsening of delirium with olanzapine were both older than 80 years and could have been particularly sensitive to the anti-muscarinic properties of olanzapine[5]. However, in this study, although there was only one patient aged 80, we didn't find the similar result in this patient comparing the previous study. Contrary, the scores of DRS-c in this patient had a trend to improve although there was no statistic significant difference. Olanzapine was as effective as haloperidol, which was the first choice for the delirium treatment of advanced cancer patients.

As the limitations, we all known that the prevalence of delirium in advanced cancer patients was high, however, a limited amount of patients were able to be recruited in this study, due to the fact that some end-stage cancer patients couldn't take medication orally. In this study, enteral haloperidol was compared with olanzapine because during the experimental period, olanzapine was not available in parenteral form when we designed this study. And we wish to exclude differences attributable to administration route. Meanwhile, ethically, if the patients and their family members did not want to sign consents then those patients must be excluded, even though they were delirious. In Asia, in Taiwan, it was also difficult to recruit terminal patients into studies. Especially, on account of SARS(Severe Acute Respiratory Syndrome) broke out around July 2003, from August 2003 to April 2004 there were few patients admitted to hospital expect very ill, few cases could be recruited during that period. At the end of the study, there were only 16 patients (9 males and 7 females) recruited in the olan-

zapine group and 14 patients (4 males and 10 females) in the haloperidol group. This was might be the reason that why we found, unfortunately, so many dropouts in this study. The possible might because that due to the patients admitted during those days were so ill that they were found left the study due to death caused by the uncontrolled terminal cancer symptoms or transfer to other agency or leave hospital by the requirement of families (11 of 16 patients in the olanzapine group, and 7 of 14 patients in the haloperidol group).

This study was also limited as the followed. First, those patients included in this study were in different cancer stages and they also suffered from different kinds of cancer. Second, those patients had multiple physical disorders that were not correctable or reversible. Third, we didn't consider and ignored the drug-drug interaction between the various drugs that patients administered for their medical condition. Fourth, lack of formal assessment instrument to evaluate the extrapyramidal side effects or adverse side effects of haloperidol or olanzapine might also have influenced the final finding although we found no patients suffered EPS from the clinical record in this study or by the observe of the assessor. However, since this pilot trial was a small, open-label study, our findings were limited in terms of generalization.

From the above results, olanzapine and haloperidol were shown to be efficient in treating delirium in advanced cancer patients. Some patients in the olanzapine group experienced a sedative effect at T_2 and T_3, but no one had extrapyramidal side effects. We found that although haloperidol had faster effect in treating delirium of advanced cancer patients, olanzapine had the same affect at T_3. Comparisons of olanzapine and haloperidol for the treatment of delirium in advanced cancer patients revealed no significant differences in this study.

We conducted this study hoping to prove the hypothesis of previous studies that olanzapine treats delirium in cancer patients, since no similar data is available in Taiwan. The results were similar to those of prior studies, in that olanzapine may be a useful alternative to haloperidol in the treatment of delirium in elderly advanced cancer patients. The DRS is also a useful means of quantifying treatment responses in delirious elderly advanced cancer patients. Further research, particularly of a larger sample size and double-blind randomized control trial, will be needed to confirm our findings and expand clinicians' understanding of the optimal treatment interventions for delirium.

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使用Haloperidol與Olanzapine治療緩和安寧照護中心的癌症譫妄病人之療效比較

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摘 要

本研究旨在比較使用haloperidol與olanzapine治療緩和安寧照護中心的癌症譫妄病人之療效。病患必須符合(1)接受安寧緩和照顧(2)患有嚴重癌症(3)符合DSM-IV對譫妄的診斷準則者方可收案進入研究。在收案當下(T_0)，24小時後(T_1)，48小時後(T_2)及一個星期後(T_3)，病患接受DRS-c(中文譫妄量表)和CGI-S(臨床整體評估-嚴重性)的評估以比較兩種藥物對譫妄症狀的控制。Olanzapine組收案16人(男比女爲9：7；平均年齡爲61.13 ±16.5歲)。Haloperidol組收案14人(男比女爲2：5；平均年齡爲68 ±12.14歲)。在兩組組內我們發現在不同時間點的DRS-c及CGI-S值有顯著統計差異(haloperidol組：DRS-c：在24小時後(T_1)，p=0.008；在48小時後(T_2)，p=0.044；在一個星期後(T_3)，p=0.043且CGI-S：在24小時後(T_1)，p=0.012；olanzapine組：DRS-c：在一個星期後(T_3)，p=0.042且CGI-S：在24小時後(T_1)，p=0.040)，表示兩種藥物皆可對譫妄症狀有效控制。然而，比較兩組之間DRS-c及CGI-S值發現並無統計上顯著差異，表示兩種藥物對譫妄症狀的控制旗鼓相當。研究結果顯示haloperidol及olanzapine對病患的譫妄症狀皆有療效而且效果相當。因此，olanzapine可能可以成爲haloperidol在治療癌末譫妄病人的有效替代治療。