Cost-effectiveness of Midazolam versus Haloperidol versus Olanzapine for the Management of Acute Agitation in the Accident and Emergency Department

Running title: Cost-effectiveness of Intramuscular Sedatives

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Abstract

Objectives

A multicentre randomised controlled trial (RCT) in Hong Kong accident and emergency (A&E) departments concluded that intramuscular olanzapine is noninferior to the haloperidol and midazolam, in terms of efficacy and safety, for the management of acutely agitated patients in A&E setting. Determining their comparative cost-effectiveness will further provide an economic perspective to inform the choice of sedative in this setting.

Methods

This analysis used data from a RCT conducted in Hong Kong A&E departments between December 2014 and September 2019. A within-trial cost-effectiveness analysis comparing the three sedatives was conducted, from the A&E perspective and a within-trial time horizon, using a decision-analytic model. Sensitivity analyses were also undertaken.

Results

In the base-case analysis, median total management cost associated with intramuscular midazolam, haloperidol and olanzapine were HKD 1958.9 (USD 251.1), HKD 2504.5 (USD 321.1), and HKD 2467.6 (USD 316.4) respectively. Agitation management labour cost was the main cost driver, whereas drug costs contributed the least. Midazolam dominated over haloperidol and olanzapine. Probabilistic sensitivity analyses supported that midazolam remains dominant more than 95% of the time and revealed no clear difference in the cost-effectiveness of intramuscular olanzapine versus haloperidol (ICER 667.16; 95% CI -770.89, 685.90).

Conclusions

Intramuscular midazolam is the dominant cost-effective treatment for the management of acute agitation in the A&E setting. Intramuscular olanzapine could be considered as an alternative to intramuscular haloperidol as there is no clear difference in cost-effectiveness, and their adverse effect profile should be considered when choosing between them.

Highlights

- No studies had evaluated the cost-effectiveness of intramuscular sedatives for acute agitation in the emergency setting. While previous studies had investigated the economics of sedative use in psychiatric ward or chronic management of mental illnesses, the focus in these settings commonly lies in prolonged sedation and long-term care and cost implications, which are less applicable to the emergency setting.
- We conducted a within-trial cost-effectiveness analysis comparing intramuscular midazolam, olanzapine and haloperidol in the emergency setting using data from a multicentre RCT in six A&E departments in Hong Kong. We found that labour cost accounted for a significant portion of total agitation management cost in the emergency setting whereas drug cost is relatively negligible. Intramuscular midazolam is the dominant treatment, whereas sensitivity analyses revealed no clear difference in the cost-effectiveness of intramuscular olanzapine versus haloperidol.
- While intramuscular midazolam is the dominant treatment, in cases where benzodiazepines is less desirable, intramuscular olanzapine is preferred over haloperidol, as there is no clear difference in cost-effectiveness between them but intramuscular olanzapine has a more favourable adverse effect profile. These findings support formulary decisions on introducing or broadening the use of intramuscular olanzapine for acute agitation in the emergency department, particularly in the Hong Kong healthcare setting.

Introduction

Acute agitation, a state of "excessive motor or verbal activity",(1) is a commonly encountered presentation in hospital accident and emergency (A&E) departments. The management of acutely agitated patients is challenging(2) and uses a disproportionate amount of A&E resources.(3) When verbal de-escalation, mechanical restraint techniques and/or sedation using oral medication fail or are not appropriate, rapid tranquilisation using intramuscular sedative drugs is advised.(4) Such management aims to provide rapid control of symptoms with minimal side-effects, thereby preventing symptom escalation and ensuring the safety of the patient and healthcare providers.(1, 2)

Commonly used drug classes administered via intramuscular route are benzodiazepines (e.g. lorazepam, midazolam) and first- and second-generation antipsychotics (e.g. haloperidol, olanzapine).(2) Numerous agents are available for rapid tranquillisation in emergency settings, but head-to-head comparison among these agents for acute agitation in randomized clinical trials (RCT) are lacking, as a result no "clear superiority for any one agent" in acutely agitated patients has been demonstrated.(4) On the other hand, a meta-analysis of randomised controlled trials by Kishi et al. conducted in predominantly psychiatric settings concluded that intramuscular olanzapine is preferred over haloperidol in patients with chronic mental disorders as it is equally as effective and associated with fewer side-effects.(5) Yet, a study looking at prescribing patterns in Hong Kong A&E departments concluded intramuscular haloperidol was the most frequently used agent (46.8%), followed by midazolam (33.9%).(6) While the use of the newer, atypical antipsychotic olanzapine was common in the United States, (7) its use remained relatively uncommon in Hong Kong and other regions of the world. As such, a cost-effectiveness analysis comparing these intramuscular sedatives in terms of healthcare resource utilisation and agitation management costs

involved will provide a useful financial comparison to inform the choice of sedative for management of acute agitation in the A&E setting.

In Hong Kong, public hospitals are managed by the Hospital Authority (HA), a statutory body that provides public health services to Hong Kong's citizens. The region's health economy is dominated by the public sector, with 90% of the public health expenditure, which is mainly subsidised by the government through tax revenues, going towards the HA.(8) In recent years, the high and rising demand for A&E services, as well as the rapidly growing and ageing population in Hong Kong have led to increased pressure on healthcare resources. Between 2008 and 2018 the number of A&E presentations classified as "urgent", "emergency" or "critical" increased by 27%,(9) underlining the importance of using the available A&E resources as efficiently as possible. A cost-effectiveness analysis comparing various treatment options for acute agitation, which is routinely managed in A&E departments, may help inform the choice of sedative used and facilitate the allocation of A&E resources.

Methods

This economic analysis took an A&E costing perspective and within-trial time horizon, using data from an RCT conducted in the Accident and Emergency (A&E) departments of six public hospitals in Hong Kong (ClinicalTrials.gov identifier: NCT0230118).(10) The clinical outcomes, including the time required to achieve adequate sedation and whether re-dosing of the sedative drug was required, were obtained from the RCT. The RCT concluded that intramuscular olanzapine is noninferior to haloperidol and midazolam, in terms of efficacy and safety and should be considered when treating the acutely agitated patient, and is currently the only multicentre RCT comparing the three intramuscular sedatives for acute agitation management in the emergency setting. The study was approved by Institutional Review Board or Clinical Research Ethics Committee at each of the study sites. Data on each patient's investigations were extracted from electronic patient records retrospectively. A top-down costing approach was used, analysing the costs of expected individual treatment components and services in order to determine the overall cost for each study arm of the RCT.(11) Baseline characteristics of the study population were the same as that reported in the RCT. (11) Reporting of this analysis followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.(12)

Model structure and outcomes

A within-trial cost-effectiveness analysis was implemented by constructing a decision-analytic model using a decision tree, comparing the 3 alternative sedatives (IM midazolam 5mg, IM haloperidol 5mg and IM olanzapine 5mg) simulating 11 possible outcomes for each drug, depending on whether the patients achieved successful sedation by 10, 20, 30, 45 and 60 minutes after administration of the sedative drug, and whether re-dosing with sedative drug was required at any time during the sedation process (Figure 1). In line with the RCT, successful sedation was

defined as an agitation score of ≤ 2 on the 6-point agitation scale. "Not sedated" patients were re-evaluated at the subsequent time point. Agitation-free time gained was used as a metric for effectiveness in the cost-effectiveness analyses, which was defined as 150 minutes minus the recorded time to sedation, based on the observation that all agitated patients were managed within 150 minutes in the RCT. The decision tree and the probabilities of the occurrence of the individual branch outcomes were calculated from the results of the RCT. Data on the clinical outcomes and the probabilities of occurrence are summarised in Supplementary Table 1.

Cost calculation

Expected costs for the individual treatment outcomes of the model were calculated and weighted by the probability of the respective outcome occurring. The cumulative weighted costs of the three respective treatment options were then compared in order to calculate the incremental cost and identify the least costly treatment.(13) All costs were in Hong Kong Dollars (HKD) for the financial year 2019-2020. Main results were also presented in US Dollars (USD) at the linked exchange rate of HKD 7.80 to 1 USD.(14)

Direct medical costs included drug costs, as well as any diagnostic and monitoring tests required. In addition to the study drugs, drug costs also included open-label sedatives used. Direct non-medical costs comprised the salaries of the staff required for the management of an acutely agitated patient, as well as administrative overhead costs of HKD 200 per case.(15) The drug acquisition costs were obtained from the Queen Mary Hospital (QMH) A&E department. Costs of diagnostic and monitoring tests were obtained from the Hospital Authority (HA) Gazette(16). The labour costs were calculated using HA hourly staff salaries. Staff costs were related to the management of the agitation until the patient was adequately sedated.

The occurrence of adverse events was rare as reported in the RCT (4.8%, n=8, only one of which was serious and unlikely to be related to the study drug) and the cost of their management was deemed negligible, as staff attendance is already accounted for in the agitation management costs. All costs were from the perspective of A&E departments. Costs obtained from QMH are representative of the costs of all A&E departments of public hospitals in Hong Kong as drug contracts are negotiated in a centralised manner. Given the short treatment duration, no discounting was applied.

Assumptions

Several assumptions were made about the management of acute agitation in A&E departments. Since the actual time of staff attendance was not recorded, the time to adequate sedation was used to estimate the staffing required for each patient. In a small number of patients (n=6) the sedation was not documented until the end. These patients were reviewed case by case and the time to sedation was estimated from the given data, the A&E staff notes and the patient records, using a method consistent to all cases affected.(17)

Based on local practice of participating sites, it was assumed that on average one resident doctor, three nurses, one of whom an advanced practice nurse, and one health care assistant were required to attend an acutely agitated patient. This includes applying physical restraint and providing the necessary sedatives. For patients enrolled in the trial who received the sedative on the emergency ward rather than in the A&E department (n=11) or were transferred to an emergency ward immediately after injection of the sedative (n=2), the staff required for the management was assumed to be the same as in A&E and the data was processed in the same way as that of patients treated within the A&E department. Staff costs were calculated per minute of agitation. An additional analysis assuming fixed staff costs was also conducted (Supplementary Table 5).

All tests performed were assumed to have been done as part of investigating the patient's presenting agitation. Although some investigations included may not be related to the agitation itself or to the sedatives used, all of them were included in order to ensure consistency of the data collection and minimise bias.(18) Tests not directly indicated for acute agitation management are likely to be evenly distributed across the three treatment groups. All patients were required to have an 12-lead electrocardiogram done as part of the RCT documentation, therefore this cost was not included in the analysis as it applied to all patients. For olanzapine, the only cost data available was for a 10mg dose. The drug acquisition cost for a 5mg dose was assumed to be half the cost of a 10mg dose. An additional analysis costing olanzapine as per 10mg vials was conducted as well (Supplementary Table 5).

Cost-effectiveness analysis

A cost-effectiveness analyses comparing the three sedative regimens was conducted. As cost data distributions, especially for pathology and radiology costs were skewed, the analyses was conducted using both median costs (reported in main analysis) and mean costs (reported in supplementary analysis). The incremental cost effectiveness ratio (ICER), defined as the additional cost of management in HKD per minute of agitation-free time gained, was calculated by dividing the difference in the total cost of management by the difference in agitation-free time gained of the drugs in comparison.

The median agitation-free time gained associated with each treatment was multiplied by the agitation management labour cost per minute (HKD 29.3/min or USD 3.8/min) to determine the economic benefits (resulted from reduction in agitation time) associated with each treatment. The benefit-cost ratios (ratio of economic benefits over total management cost) among treatments was also reported.

Sensitivity analyses

One-way sensitivity analyses were carried out to investigate the impact of potential fluctuation in drug price and healthcare costs, as well as uncertainty in sedation effects and need for redosing, on cost-effectiveness of the investigated treatments. For the purpose of sensitivity analyses, pathology and radiology costs were assumed to be the same for all patients who underwent these tests, and the probability of patients requiring these tests depend on the treatment received. Probability of requiring a redose of the sedative drug were considered at the treatment level rather than the individual patient's level. Essential variables and their ranges of variation (Supplementary Table 2) were obtained from the RCT data and chosen based on consideration of practical relevance.

Probabilistic sensitivity analysis was also carried out to assess the uncertainty in the cost-effectiveness estimates, and to evaluate the robustness of conclusions. Monte Carlo simulation with 100,000 iterations was carried out using TreeAge Pro 2020 (TreeAge Software, Williamstown, MA, USA). The type and parameters of the distributions used in the model are detailed in Supplementary Table 2. In this analysis, it is assumed that the time-to-sedation associated with each drug follows a gamma distribution. The mean time-to-sedation is allowed to vary and follows a normal distribution with mean and standard deviation derived from the RCT data. Subsequently, the probabilities of being sedated at 10, 20, 30, 45, 60 minutes, as well as the expected agitation management time and agitation-free time gained, were calculated accordingly from the time-to-sedation distribution. Probability of redosing was assumed to be different for each drug, and follows a beta-distribution with parameters derived from the RCT data.

Results

Overall costs

In the base case analysis, midazolam was associated with the lowest median total treatment costs (HKD 1958.9, USD 251.1, Table 1). The low drug cost associated with midazolam (HKD 10.7, USD 1.3 vs. HKD 30.5, USD 3.9 for haloperidol and HKD 76.1, USD 9.8 for olanzapine) contributed to this, as well as the costs for pathology and agitation management being lowest for the midazolam group. The lower management costs resulted from the shorter median agitation management time for midazolam patients compared to the two other drugs (21 minutes for midazolam vs. 33 minutes for haloperidol and olanzapine). Overall, midazolam was 28% less costly than haloperidol and 26% less costly than olanzapine. The total and proportional median costs for the three treatment groups are shown in Table 1.

Despite high drug acquisition costs of olanzapine (HKD 55, USD 7.1 per 5mg olanzapine vs. HKD 6.5, USD 0.8 and HKD 21, USD 2.7 for 5mg midazolam and 5mg haloperidol respectively), the median total treatment cost with olanzapine was slightly lower than the cost of haloperidol treatment (HKD 2467.6, USD 316.4 vs. HKD 2504.5, USD 321.1).

We observed that costs distributions were highly skewed especially for pathology and investigational costs, since more than half of the patients did not undergo any laboratory tests and thus had zero cost, whereas those who required laboratory tests could incur significant pathology/radiology costs. As such, median treatment costs were reported as the main analyses. Mean treatment costs were also reported in Supplementary Tables 3 and 4.

Cost of management

Labour costs that incurred during the management of the agitated patient and their sedation contributed to a major proportion (~30-40% in the base case, >70% when excluding investigational costs) to the overall management cost, whereas sedative drug cost contributed only a minimal proportion (~0.5-3% in the base case, <10% when excluding investigational costs) (Figure 2).

Due to the fact that many of the investigational tests done may not be directly linked to the sedative chosen and varied notably among the individual patients, a cost comparison excluding these investigational costs may be of interest. When pathology and radiology costs are excluded, midazolam remains as the least costly option with a cost saving of HKD 379.3 (USD 48.6) vs. haloperidol and HKD 431.2 (USD 55.3) vs. olanzapine (Table 2).

Cost-effectiveness analysis

Considering the relative effectiveness of the three treatments, midazolam was more effective than haloperidol and olanzapine, as reflected by an additional agitation-free time gained of 12.32 and 12.37 minutes when midazolam was used compared to haloperidol and olanzapine respectively. This resulted in additional economic benefits (due to reduction in agitation time) of HKD 361.3 (USD 46.3) and HKD 362.8 (USD 46.5) respectively. The net benefit-cost ratios were 1.93:1 for midazolam, 1.37:1 for haloperidol and 1.39:1 for olanzapine.

Midazolam was shown to be the most cost-effective among the three treatments. On the other hand, the cost-effectiveness of haloperidol versus olanzapine was less clear. In the base case, the ICER of olanzapine compared with haloperidol was HKD 727.69. Haloperidol was associated with an additional HKD 727.7 (USD 93.3) per minute of agitation-free time gained. Yet, when costs for investigational tests were excluded, haloperidol dominated over olanzapine with a slightly lower

cost (HKD 1203.3 vs 1255.2, USD 154.3 vs 160.9) and slightly higher effectiveness (116.76 vs 116.70 minutes of agitation-free time gained) than olanzapine.

In the case where only patients with underlying mental illness at the time of A&E admission were included, midazolam remained the dominant treatment. Olanzapine had a lower median cost (HKD 2268.72 vs 2501.30, USD 290.9 vs 320.7) and slightly lower effectiveness (117.11 vs 117.35 minutes of agitation-free time gained) compared to haloperidol. The ICER of olanzapine compared to haloperidol was HKD 982.52 (USD 126.0) per minute of agitation-free time gained.

Sensitivity analyses

Probabilistic sensitivity analyses supported the robustness of the results against variations in time to sedation, probability of redosing or investigational tests, and costs. While midazolam remained dominant among the three treatments in more than 95% of the iterations at various hypothetical willingness-to-pay thresholds (Figure 3), there was no considerable difference in the cost-effectiveness between olanzapine and haloperidol (Table 3). Midazolam was associated with the lowest management cost and highest effectiveness, while differences between olanzapine and haloperidol were minimal (Table 3).

One-way sensitivity analyses also revealed that midazolam remains dominant, regardless of variations in costs, time to sedation, and probability of redosing or investigational tests (Supplementary Figures 2A & B). On the other hand, cost-effectiveness of haloperidol versus olanzapine varied significantly as pathology and radiology costs fluctuate, such that neither were consistently dominant. The probabilities of requiring pathology or radiology tests, pathology and radiology costs and drug costs contributed to the greatest variation in ICER when haloperidol and olanzapine were compared (Supplementary Figure 2C).

Discussion

To our knowledge, this is the first multi-centre pharmacoeconomic study evaluating sedative drugs and the management of acute agitation specifically in the A&E setting. Similar economic evaluations of agitation management have been conducted in A&E departments of Australian hospitals, where they found that intravenous midazolam was 3.8% less costly than intravenous droperidol for managing acute agitation in the emergency department. (19) Other studies looking at the economics of sedative use have been conducted in the hospital ward and psychiatric setting,(20) where the focus commonly lies on prolonged sedation,(21) the treatment of chronic mental illnesses and long-term care and cost implications.(22) Due to the differences in measured outcomes and perceived acceptable time to adequate sedation in different clinical contexts, the results of these studies are less generalisable to the A&E setting.

Similar to previous studies,(13, 23) our analyses showed that drug acquisition costs only contribute to a small part of the overall agitation management cost, whereby a major proportion is attributed to labour costs, which is directly proportional to the time to sedation. Even for the most expensive drug (i.e. olanzapine) in this study, labour cost was shown to be 10 times the drug cost incurred in the overall agitation management process. In contrast, a drug with shorter time to sedation not only reduce labour cost incurred, but also brings practical benefits by reducing patient's disturbances to other patients and staff in the A&E department, which could not be accounted for economically. As such, when making decisions in the formulary management context regarding intramuscular sedatives for agitation management in the A&E setting, the effectiveness and adverse event profile is considered a greater consideration, compared to additional drug acquisition costs, which is considered relatively negligible.

Midazolam was the least costly treatment option, which can be mainly attributed to its faster average time to sedation and thus a much lower agitation management labour cost compared to antipsychotics. It was also the most effective sedative option as it was associated with the most agitation-free time gained. As such, midazolam was shown to be dominant strategy economically. Despite this, previous studies reported that the use of midazolam and other benzodiazepines is associated with undesirable adverse effects including over-sedation(24) and respiratory distress(25, 26), requiring additional monitoring of respiratory function and prolonging total length of hospital stay. Indeed, particularly in patients with suspected underlying psychoses, the use of antipsychotics for rapid sedation is generally preferred in practice over benzodiazepines to prevent over-sedating the patient and preserve the opportunity for psychiatric follow up and assessment, following the initial management. Furthermore, our previous randomised clinical trial had shown that intravenous olanzapine as an adjunct to midazolam can further reduce time to sedation compared with midazolam alone.(27) Hence, despite midazolam being the dominant treatment economically, it is still valuable to determine, from an economic point of view, whether olanzapine could be recommended as an alternative to haloperidol.

While haloperidol was reported to be the most commonly used sedative for the management of acute agitation in Hong Kong,(6) yet as a first-generation antipsychotic, it is associated with adverse effects including QT prolongation, dystonia and extrapyramidal symptoms. Although the occurrence of adverse events was relatively uncommon in the RCT (4.8%), these adverse effects would carry significant management cost when they do occur. Indeed, a meta-analysis of randomised controlled trials (RCT) concluded that intramuscular olanzapine is preferred over haloperidol as it is equally as effective and associated with fewer side-effects.

In our base-case analyses, we showed that olanzapine was associated with a slightly lower total management cost compared to haloperidol (HKD 2467.6, USD 316.4 vs. HKD 2504.5, USD 321.1). However, sensitivity analyses revealed that the cost-effectiveness of olanzapine compared to haloperidol varied significantly as pathology and radiology costs varied. Despite a higher drug cost for olanzapine than haloperidol, there is no clear difference in cost-effectiveness of olanzapine versus haloperidol after considering potential inter-patient variability in pathology and radiology costs. Considering this and the more favourable adverse effect profile and convenient once-daily dosing of olanzapine compared to haloperidol, there is potential for a more wide-spread use of olanzapine in the management of acute agitation.

We acknowledge several limitations for this economic evaluation. Firstly, the time horizon of this study is limited to the duration of stay in the A&E department due to the underlying RCT data. As such, the economic evaluation focused on the A&E perspective and might not be generalisable to the broader perspective of the public sector as a whole. Nevertheless, this study provided data on cost-effectiveness of intramuscular sedatives in an emergency setting in which patients often present with undifferentiated agitation, where evidence remains limited, and A&E resource utilisation is an important consideration for formulary decisions especially in Hong Kong. Further studies could evaluate the costs associated with not only the A&E stay but also the inpatient/outpatient episodes following. Secondly, this study did not differentiate between patients with or without underlying psychiatric disorder and/or substance abuse and their medication history, which may potentially affect their agitation management time and hence the labour costs involved. However, the baseline characteristics of the study population showed that these patients were distributed equally across the study groups. Thirdly, the cost of management was estimated based on a single RCT in the Hong Kong A&E setting. Results may be less generalizable to other settings

and further economic evaluations on the cost-effectiveness of different sedative regimens in the A&E setting may be needed. Fourth, adverse effects of the study drugs and the costs associated with their management were not considered in this economic analysis. Yet, such costs was deemed negligible in the general case since the occurrence of adverse events in the RCT was uncommon (4.8%, n=8, only one of which was serious and unlikely to be related to the study drug), and related costs for staff attendance was already accounted for in the agitation management labour costs. Fifth, combination therapy of an antipsychotic followed by a benzodiazepine, which is also often used in initial management of acutely psychotic patient, has not been investigated and can be further studied. Sixth, results may not be generalizable to settings where the A&E length of stay is much longer as the A&E department in Hong Kong, where the patient turnover rate is high.

Conclusions

From an economic point of view, our analysis concludes that intramuscular midazolam is the dominant strategy for the management of acute agitation of unknown aetiology in the A&E department. Sedation using the currently rarely used intramuscular olanzapine could be considered as an alternative to intramuscular haloperidol, especially when there is underlying psychoses, since (i) there is no clear difference in cost-effectiveness of intramuscular olanzapine compared to haloperidol, (ii) olanzapine carries a more favourable adverse effect profile with more convenient once-daily dosing, and (iii) drug costs only accounts for a small portion of the overall management costs compared to labour costs and the drug acquisition cost of generic intramuscular olanzapine may continue to be more competitive in the future.

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Table 1. Proportional costs incurred in the management of acute agitation in A&E setting using midazolam, haloperidol and olanzapine

	Midazolam			Haloperidol			Olanzapine		
Sedation within	**Prop.***	**Cost/patient (HKD)** ***Median (IQR)***	**Prop. cost# (HKD)**	**Prop.***	**Cost/patient (HKD)** ***Median (IQR)***	**Prop. cost# (HKD)**	**Prop.***	**Cost/patient (HKD)** ***Median (IQR)***	**Prop. cost# (HKD)**
10 min									
Redosing	3.6%	733.8 (620.1-847.6)	26.2	3.5%	1387.8 (961.6-1814.1)	48.7	7.4%	3176.5 (2132.3-4275.0)	235.3
No redosing	42.9%	1817.3 (499.8-3352.3)	778.9	15.8%	3229.3 (1094.3-4304.3)	509.9	22.2%	628.3 (548.3-4155.8)	139.6
20 min									
Redosing	7.1%	1932.2 (1448.4-2424.0)	138.0	5.3%	828.7 (818.2-908.7)	43.6	5.6%	2901.7 (1899.2-4946.2)	161.2
No redosing	21.4%	1888.7 (793.2-2898.2)	404.7	12.3%	2388.3 (2351.3-3795.7)	293.3	24.1%	2241.7 (1146.7-3731.7)	539.7
30 min									
Redosing	1.8%	957.3 (957.3-957.3)	17.1	0.0%	-	-	3.7%	3520.3 (2355.2-4685.5)	130.4
No redosing	10.7%	1086.5 (1086.5-1671.5)	116.4	22.8%	1406.0 (1101.0-3206.0)	320.7	11.1%	1302.5 (1135.0-3277.3)	144.7
45 min									
Redosing	1.8%	5602.3 (5602.3-5602.3)	100.0	7.0%	2262.0 (1562.0-3352.0)	158.7	0.0%	-	0.00
No redosing	1.8%	2809.2 (2809.2-2809.2)	50.2	10.5%	3924.7 (2081.6-5279.3)	413.1	5.6%	2815.0 (2195.0-3047.5)	156.4
60 min									
Redosing	3.6%	3891.8 (2946.1-4837.4)	139.0	8.8%	3990.8 (2002.0-5232.0)	350.1	3.7%	4390.0 (3620.0-5160.0)	162.6
No redosing	0.0%	-	-	5.3%	3381.0 (3205.0-3779.3)	178.0	3.7%	3765.8 (2743.8-4787.9)	139.5
Not sedated at 60 min	5.4%	3516.6 (2759.5-4009.8)	188.4	8.8%	2148.7 (2031.3-2870.7)	188.5	13.0%	5078.0 (3776.4-6050.8)	658.3
Median cost per patient in HKD (USD)			**1958.9 (251.1)**			**2504.5 (321.1)**			**2467.6 (316.4)**

*proportion of patients with outcome of interest (treatment branch)

#proportional cost of outcome of interest (treatment branch) in HKD

Table 2. Results of cost-effectiveness analyses (base-case, alternative scenario, subgroup analyses)

Scenario	Median cost (HKD) / patient	Effectiveness (min)	Economic benefit (HKD)	Benefit-cost ratio	ICER (ref: midazolam)	ICER (ref: haloperidol)
Base case						
Midazolam	1958.9	129.07	3785.7	1.93	(Ref)	Dominant
Haloperidol	2504.6	116.76	3424.4	1.37	Dominated	(Ref)
Olanzapine	2467.6	116.70	3422.9	1.39	Dominated	727.69
Alternative scenario – excluding investigational costs (pathology and radiology)						
Midazolam	824.0	129.07	3785.7	4.59	(Ref)	Dominant
Haloperidol	1203.3	116.76	3424.4	2.85	Dominated	(Ref)
Olanzapine	1255.2	116.70	3422.9	2.73	Dominated	Dominated
Subgroup analysis - Patients with underlying mental illness						
Midazolam	1922.06	129.66	3802.92	1.98	(Ref)	Dominant
Haloperidol	2501.30	117.35	3441.81	1.38	Dominated	(Ref)
Olanzapine	2268.72	117.11	3434.87	1.51	Dominated	982.52

ICER: Incremental cost-effectiveness ratio.

Economic benefits refer to the cost savings as a result of reduction in agitation time (clinical outcome) associated with different treatments.

Table 3. Results of probabilistic sensitivity analysis for the cost-effectiveness of the treatments investigated

Treatment	Cost (HKD) / patient	Effectiveness (min)	Economic benefit (HKD)	Benefit-cost ratio
Midazolam	2,358.53 (1,470.54-3,665.47)	129.30 (124.90-133.69)	3,792.34 (3,663.28-3,921.07)	1.70 (1.03-2.60)
Haloperidol	2,802.07 (1,874.33-4,150.74)	117.40 (112.58-122.22)	3,443.23 (3,302.03-3,584.58)	1.28 (0.83-1.85)
Olanzapine	2,917.83 (1,906.52-4,394.20)	117.64 (109.40-125.91)	3,450.45 (3,208.70-3,692.99)	1.24 (0.77-1.85)

Treatment	ICER	A was dominant (% of iterations)	B was dominant (% of iterations)	Neither were dominant (% of iterations)
Midazolam (A) vs Haloperidol (B)	-38.79 (-94.02 to 10.52)	95.209	0.005	4.786
Midazolam (A) vs Olanzapine (B)	-53.59 (-152.69 to 3.89)	96.835	0.205	2.960
Olanzapine (A) vs Haloperidol (B)	667.16 (-770.89 to 685.90)	26.560	39.432	34.008

All values refer to mean (95% confidence interval) from the results of a Monte Carlo simulation.

ICER: Incremental cost-effectiveness ratio

Economic benefits refer to the cost savings as a result of reduction in agitation time (clinical outcome) associated with different treatments.

Figure 1. Midazolam branch of the decision-analysis model depicting the management of acute agitation. The haloperidol and olanzapine arms have the same tree branches. Sedated means adequate sedation was achieved by the given time point after administration of sedative drug. Adequate sedation was defined as an agitation score ≤ 2 on the 6-point scale described above. Re-dosing means re-dosing with sedative drug was required at any time during the sedation process.

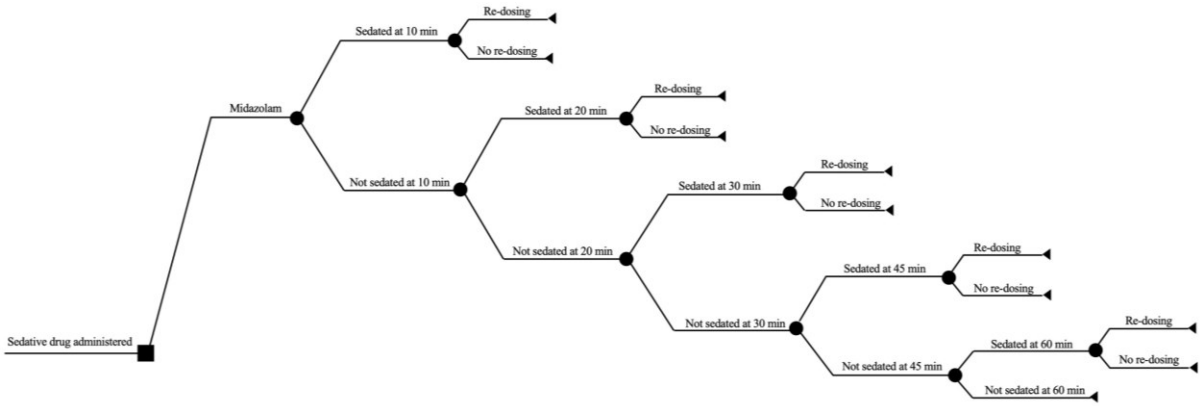


Figure 2. Cost components involved in the management of acute agitation in the A&E department for the base-case. All costs are in Hong Kong Dollars for the financial year 2019-2020.

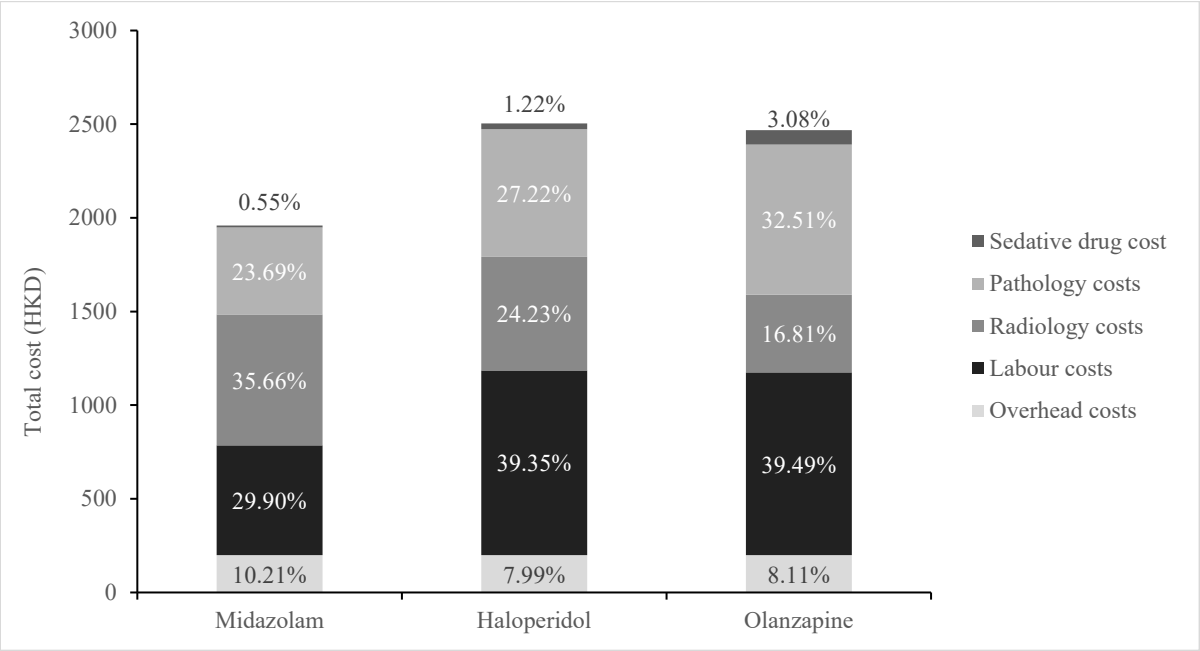
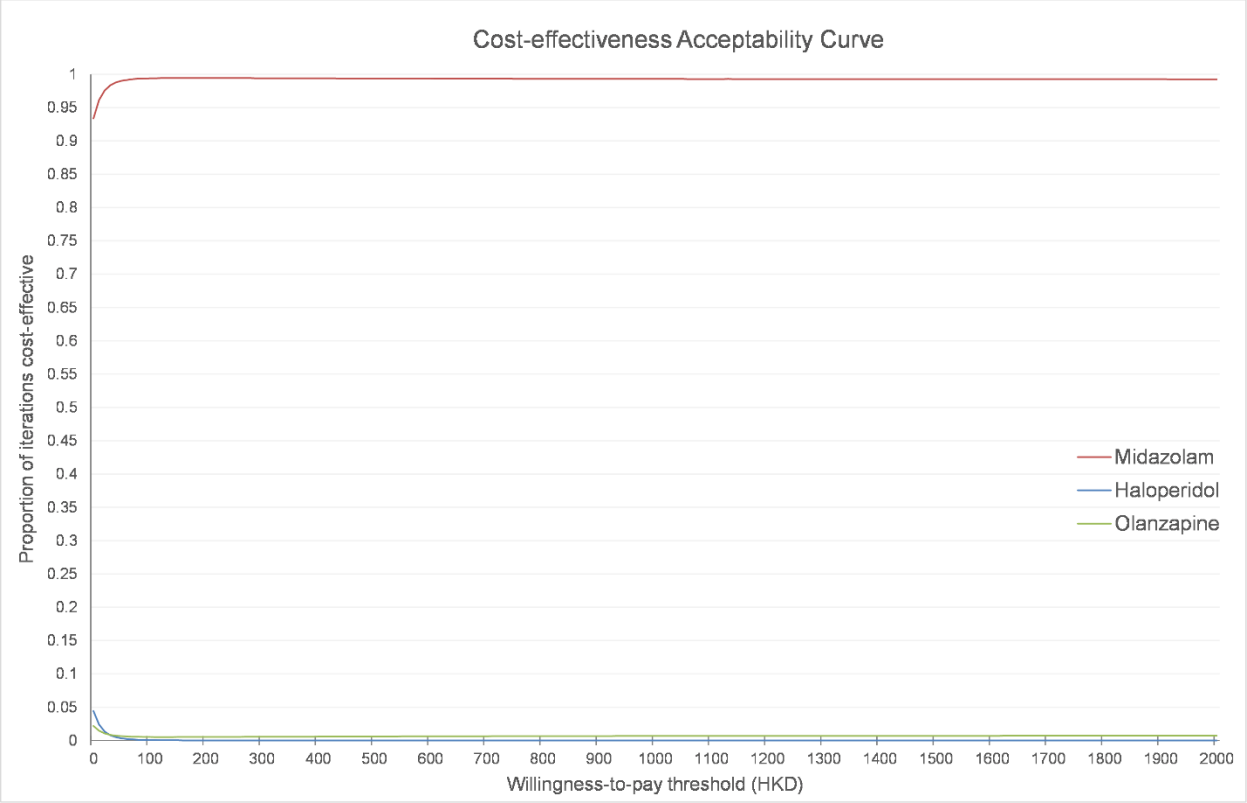


Figure 3. Cost-effectiveness acceptability curve of the treatments investigated



Based on results of probabilistic sensitivity analysis with Monte Carlo simulation of 100000 iterations

Supplementary Appendix

Supplementary Table 1. Clinical outcomes and probabilities of occurrence.

Outcomes at time points	Midazolam arm n = 56		Haloperidol arm n = 57		Olanzapine arm n = 54	
Sedated at 10 min	n = 26	46.43%	n = 11	19.30%	n = 16	29.63%
Re-dosing	n = 2	7.69%	n = 2	18.18%	n = 4	18.75%
No re-dosing	n = 24	92.31%	n = 9	81.82%	n = 13	81.25%
Not sedated	n = 30	53.57%	n = 46	80.70%	n = 38	70.37%
Sedated at 20 min	n = 42	75.00%	n = 21	36.84%	n = 32	59.26%
Re-dosing	n = 6	14.29%	n = 5	23.81%	n = 6	18.75%
No re-dosing	n = 36	85.71%	n = 16	76.19%	n = 26	81.25%
Not sedated	n = 14	25.00%	n = 36	63.16%	n = 22	40.74%
Sedated at 30 min	n = 49	87.50%	n = 34	59.65%	n = 40	74.07%
Re-dosing	n = 7	14.29%	n = 5	14.71%	n = 8	20.00%
No re-dosing	n = 42	85.71%	n = 29	85.29%	n = 32	80.00%
Not sedated	n = 7	12.50%	n = 23	40.35%	n = 14	25.93%
Sedated at 45 min	n = 51	91.07%	n = 44	77.19%	n = 43	79.63%
Re-dosing	n = 8	15.69%	n = 10	22.73%	n = 8	18.60%
No re-dosing	n = 43	84.31%	n = 34	77.27%	n = 35	81.40%
Not sedated	n = 5	8.93%	n = 13	22.81%	n = 11	20.37%
Sedated at 60 min	n = 53	94.64%	n = 52	91.23%	n = 47	87.04%
Re-dosing	n = 10	18.87%	n = 15	28.85%	n = 10	21.28%
No re-dosing	n = 43	81.13%	n = 37	71.15%	n = 37	78.72%
Not sedated	n = 3	5.36%	n = 5	8.77%	n = 7	12.96%

Sedated at given time point means adequate sedation was achieved by the given time point after administration of sedative drug. Adequate sedation was defined as an agitation score ≤ 2 on the 6-point scale described above. Re-dosing means re-dosing with sedative drug was required at any time during the sedation process.

Supplementary Table 2. Variables investigated in one-way and probabilistic sensitivity analyses

Variable	Base case	One-way sensitivity analyses		Probabilistic sensitivity analyses				Source of range
		Variation range		Distribution	Mean	Median	Standard deviation	
		Lower	Upper					
Drug costs								
Midazolam 5mg (HKD/vial)	6.5	3.25	13	Log-normal	6.92	6.5	-	50%-200% of base case
Haloperidol 5mg (HKD/vial)	21	10.5	42	Log-normal	22.36	21	-	
Olanzapine 5mg (HKD/vial)	55	27.5	110	Log-normal	58.55	55	-	
Other drugs (HKD)	21.95	10.975	43.9	Log-normal	23.37	21.95	-	
Labour costs (HKD/min of agitation)	29.33	14.665	58.66	Log-normal	31.22	29.33	-	50%-200% of base case
Overhead costs (HKD)	200	100	400	Log-normal	212.90	200	-	
Pathology costs (HKD)	2050	160	4740	Gamma	2154.75	-	1042.98	Data from RCT
Radiology costs (HKD)	1400	210	2105	Gamma	1215.75	-	534.73	Data from RCT
Mean time to sedation (min)								
Midazolam	20.70	16.29	25.10	Normal	20.70	-	2.25	Data from RCT (variation range based on 95% CI)
Haloperidol	32.61	27.81	37.41	Normal	32.61	-	2.45	
Olanzapine	32.35	24.08	40.63	Normal	32.35	-	4.22	
Probabilities of requiring redosing (%)								
Midazolam	23.21	12.16	34.27	Beta	39.40	-	37.51	Data from RCT (variation range based on 95% CI)
Haloperidol	29.82	17.95	41.70	Beta	30.14	-	23.43	
Olanzapine	29.63	17.45	41.81	Beta	23.75	-	17.90	
Probabilities of requiring pathology test (%)								
Midazolam	44.64	31.62	57.66	Beta	44.64	-	6.64	Data from RCT (variation range based on 95% CI)
Haloperidol	45.61	32.68	58.54	Beta	45.61	-	6.60	
Olanzapine	51.85	38.52	65.18	Beta	51.85	-	6.80	
Probabilities of requiring radiology test (%)								
Midazolam	46.43	33.37	59.49	Beta	46.43	-	6.66	Data from RCT (variation range based on 95% CI)
Haloperidol	50.88	37.90	63.86	Beta	50.88	-	6.62	
Olanzapine	46.30	33.00	59.60	Beta	46.30	-	6.80	

Other drugs refer to cost of diazepam occasionally given as an extra sedative. CI: confidence interval. Specific parameters for different distributions were derived from the given mean, median or standard deviation.

Supplementary Table 3. Proportional costs incurred in the management of acute agitation in A&E setting using midazolam, haloperidol and olanzapine, using mean costs

	Midazolam			Haloperidol			Olanzapine		
Sedation within	**Prop.***	**Cost/patient (HKD)** ***Mean (SD)***	**Prop. cost# (HKD)**	**Prop.***	**Cost/patient (HKD)** ***Mean (SD)***	**Prop. cost# (HKD)**	**Prop.***	**Cost/patient (HKD)** ***Mean (SD)***	**Prop. cost# (HKD)**
10 min									
Redosing	3.6%	733.8 (321.7)	26.2	3.5%	1387.8 (1205.6)	48.7	7.4%	3230.9 (1995.0)	239.3
No redosing	42.9%	2105.7 (1651.3)	902.5	15.8%	3007.7 (2002.9)	474.9	22.2%	2139.2 (1969.1)	475.4
20 min									
Redosing	7.1%	1940.3 (963.0)	138.6	5.3%	875.0 (99.0)	46.1	5.6%	3596.3 (3105.8)	199.8
No redosing	21.4%	2248.3 (1681.4)	481.8	12.3%	2918.2 (1381.0)	358.4	24.1%	2393.6 (1408.5)	576.2
30 min									
Redosing	1.8%	957.3 (-)	17.1	0.0%	-	0.0	3.7%	3520.3 (3295.6)	130.4
No redosing	10.7%	1712.1 (1266.3)	183.4	22.8%	2474.1 (1797.6)	564.3	11.1%	2190.5 (1519.5)	243.4
45 min									
Redosing	1.8%	5602.3 (-)	100.0	7.0%	2652.0 (1410.6)	186.1	0.0%	-	0.0
No redosing	1.8%	2809.2 (-)	50.2	10.5%	3996.8 (2326.3)	420.7	5.6%	2556.7 (881.4)	142.0
60 min									
Redosing	3.6%	3891.8 (2674.6)	139.0	8.8%	4000.2 (2073.5)	350.9	3.7%	4390.0 (2177.9)	162.6
No redosing	0.0%	-	0.0	5.3%	3529.2 (588.5)	185.7	3.7%	3765.8 (2890.9)	139.5
Not sedated at 60 min	5.4%	3340.7 (1259.6)	179.0	8.8%	2800.7 (1248.3)	245.7	13.0%	4819.0 (1678.0)	624.7
Mean cost per patient in HKD (USD)			**2217.7 (284.3)**			**2881.4 (369.4)**			**2933.3 (376.1)**

*proportion of patients with outcome of interest (treatment branch)

#proportional cost of outcome of interest (treatment branch) in HKD

Supplementary Table 4. Results of cost-effectiveness analyses (base-case, alternative scenario) using mean costs

Scenario	Mean cost (HKD) / patient	Effectiveness (min)	Economic benefit (HKD)	Benefit-cost ratio	ICER (ref: midazolam)	ICER (ref: haloperidol)
Base case						
Midazolam	2217.7	129.07	3785.7	1.71	(Ref)	Dominant
Haloperidol	2881.4	116.76	3424.4	1.19	Dominated	(Ref)
Olanzapine	2933.3	116.70	3422.9	1.17	Dominated	Dominated
Alternative scenario – excluding investigational costs (pathology and radiology)						
Midazolam	817.1	129.07	3785.7	4.63	(Ref)	Dominant
Haloperidol	1185.9	116.76	3424.4	2.89	Dominated	(Ref)
Olanzapine	1222.1	116.70	3422.9	2.80	Dominated	Dominated
Subgroup analysis - Patients with underlying mental illness						
Midazolam	2314.65	129.66	3802.92	1.64	(Ref)	Dominant
Haloperidol	2798.14	117.35	3441.81	1.23	Dominated	(Ref)
Olanzapine	2869.27	117.11	3434.87	1.20	Dominated	Dominated

Supplementary Table 5. Results of cost-effectiveness analyses for additional costing scenarios.

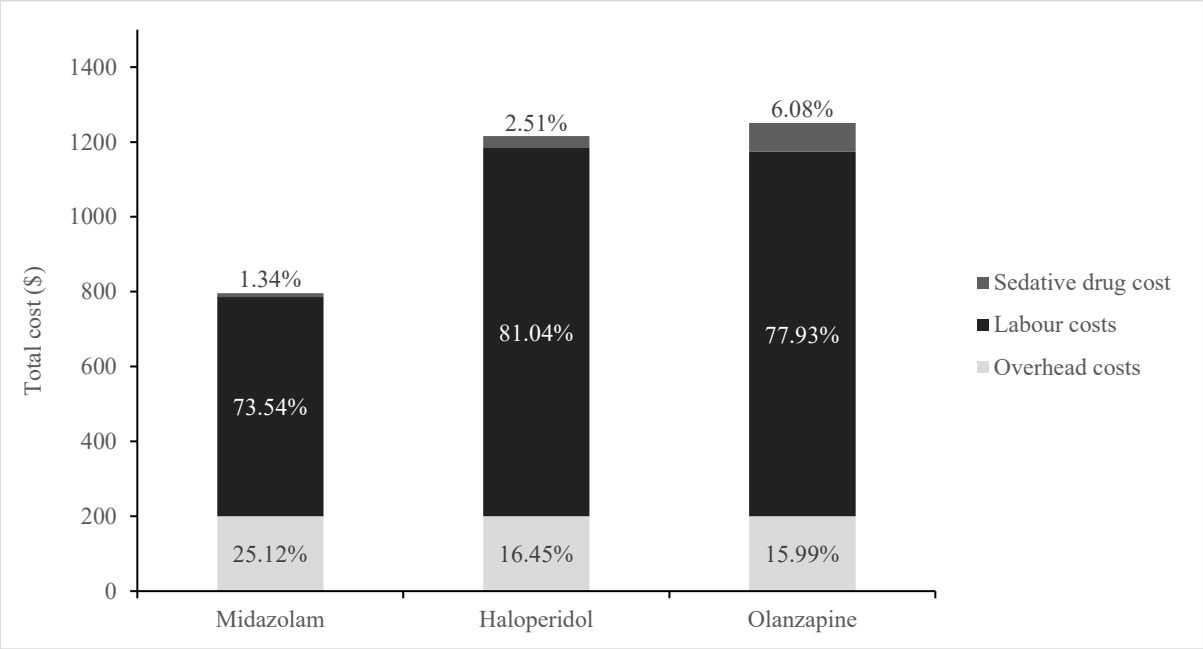
Scenario	Median cost (HKD) / patient	Effectiveness (min)	Economic benefit (HKD)	Benefit-cost ratio	ICER (ref: midazolam)	ICER (ref: haloperidol)
Costing olanzapine as per 10mg vials						
Midazolam	1958.9	129.07	3785.7	1.93	(Ref)	Dominant
Haloperidol	2504.5	116.76	3424.4	1.37	Dominated	(Ref)
Olanzapine	2540.9	116.70	3422.9	1.35	Dominated	Dominated
Assuming fixed staff costs (HKD 1760, USD 225.6)						
Midazolam	3133.3	129.07	3785.7	1.21	(Ref)	Dominant
Haloperidol	3290.7	116.76	3424.4	1.04	Dominated	(Ref)
Olanzapine	3197.2	116.70	3422.9	1.07	Dominated	1840.83

Scenario	Mean cost (HKD) / patient	Effectiveness (min)	Economic benefit (HKD)	Benefit-cost ratio	ICER (ref: midazolam)	ICER (ref: haloperidol)
Costing olanzapine as per 10mg vials						
Midazolam	2217.7	129.07	3785.66	1.71	(Ref)	Dominant
Haloperidol	2881.4	116.76	3424.43	1.19	Dominated	(Ref)
Olanzapine	3004.6	116.70	3422.94	1.14	Dominated	Dominated
Assuming fixed staff costs (HKD 1760, USD 225.6)						
Midazolam	3370.6	129.07	3785.66	1.12	(Ref)	Dominant
Haloperidol	3684.8	116.76	3424.43	0.93	Dominated	(Ref)
Olanzapine	3744.3	116.70	3422.94	0.91	Dominated	Dominated

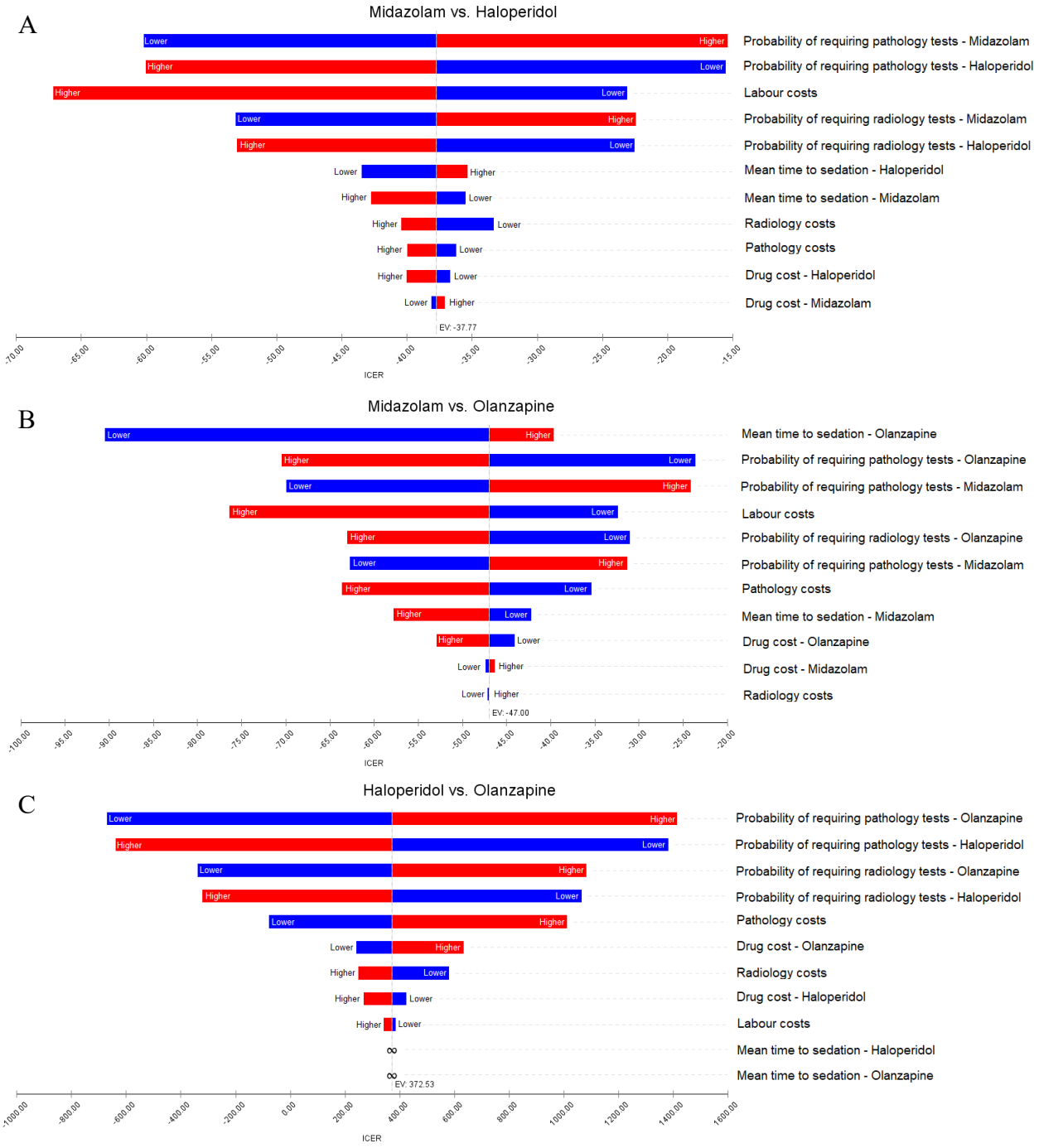
Supplementary Table 6. Pathology and radiology tests undergone by patients in each treatment group

Type of test	Number of patients undergone test (%)			p-value
	Midazolam (n=56)	Haloperidol (n=57)	Olanzapine (n=54)	
Electrocardiogram (ECG)	51 (91.1)	53 (93.0)	50 (92.6)	0.923
Liver and renal function test	24 (42.9)	25 (43.9)	25 (46.3)	0.933
Complete Blood Count (CBC)	24 (42.9)	26 (45.6)	27 (50.0)	0.751
Hemoglobin	8 (14.3)	7 (12.3)	9 (16.7)	0.805
PT/INR, APTT	10 (17.9)	8 (14.0)	9 (16.7)	0.853
Blood glucose (H'stix)	34 (60.7)	35 (61.4)	38 (70.4)	0.501
Random glucose	22 (39.3)	16 (28.1)	20 (37.0)	0.416
Blood gas	3 (5.4)	4 (7.0)	5 (9.3)	0.729
C-reactive protein	2 (3.6)	0 (0.0)	2 (3.7)	0.345
Thyroid function test	12 (21.4)	13 (22.8)	11 (20.4)	0.952
Amylase	4 (7.1)	3 (5.3)	7 (13.0)	0.315
Calcium phosphate (CaPO4)	12 (21.4)	12 (21.1)	12 (22.2)	0.988
Urate	0 (0.0)	1 (1.8)	1 (1.9)	0.599
Vitamin B12 & folate	0 (0.0)	2 (3.5)	0 (0.0)	0.142
Bone profile (ALP, Albumin, Calcium, Phosphate)	1 (1.8)	1 (1.8)	2 (3.7)	0.747
Albumin	8 (14.3)	9 (15.8)	10 (18.5)	0.830
Calcium	8 (14.3)	7 (12.3)	9 (16.7)	0.805
Calcium (albumin adjusted)	7 (12.5)	6 (10.5)	9 (16.7)	0.623
Phosphate	6 (10.7)	7 (12.3)	9 (16.7)	0.634
Cardiac enzymes (CK, LDH, AST)	0 (0.0)	1 (1.8)	2 (3.7)	0.343
Creatine Kinase (CK)	9 (16.1)	7 (12.3)	8 (14.8)	0.843
Lactate Dehydrogenase (LDH)	3 (5.4)	3 (5.3)	3 (5.6)	0.998
Troponins	5 (8.9)	3 (5.3)	4 (7.4)	0.750
Routine urine test	2 (3.6)	0 (0.0)	3 (5.6)	0.218
Urine toxicology test	14 (25.0)	12 (21.1)	11 (20.4)	0.818
Paracetamol	5 (8.9)	8 (14.0)	12 (22.2)	0.144
Ethanol	6 (10.7)	7 (12.3)	13 (24.1)	0.108
Salicylates	4 (7.1)	7 (12.3)	11 (20.4)	0.119
Lithium	1 (1.8)	0 (0.0)	1 (1.9)	0.592
Urine pregnancy test	2 (3.6)	6 (10.5)	0 (0.0)	0.030
Treponema pallidum (VDRL)	0 (0.0)	3 (5.3)	2 (3.7)	0.243
CT brain	14 (25.0)	25 (43.9)	19 (35.2)	0.109
X-ray chest	14 (25.0)	15 (26.3)	9 (16.7)	0.425
X-ray hand	1 (1.8)	0 (0.0)	0 (0.0)	0.369
X-ray face	0 (0.0)	1 (1.8)	0 (0.0)	0.379
X-ray Nose	0 (0.0)	1 (1.8)	0 (0.0)	0.379
X-ray Hip	1 (1.8)	0 (0.0)	0 (0.0)	0.369
X-ray Skull	2 (3.6)	0 (0.0)	0 (0.0)	0.135
X-ray L-spine	0 (0.0)	0 (0.0)	1 (1.9)	0.349
X-ray C-Spine	1 (1.8)	0 (0.0)	0 (0.0)	0.369

Supplementary Figure 1. Cost components involved in the management of acute agitation in the A&E department, excluding investigational (pathology and radiology) costs. All costs are in Hong Kong Dollars for the financial year 2019-2020.



Supplementary Figure 2. Results of one-way sensitivity analyses. Tornado diagrams showing variations in incremental cost-effectiveness ratio (ICER) as various costs and probabilities varied, comparing (A) midazolam vs haloperidol, (B) midazolam vs olanzapine, (C) haloperidol vs olanzapine



ICER: incremental cost-effectiveness ratio. This figure shows the variation in ICER when each input variable changes from the lower-end (blue) to the higher-end (red) of the variation range.