



<b>Title</b>	<b>Economic evaluation of midazolam–droperidol combination, versus droperidol or olanzapine for the management of acute agitation in the emergency department: A within-trial analysis</b>
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# Economic Evaluation of Midazolam–Droperidol Combination, Versus Droperidol or Olanzapine for the Management of Acute Agitation in the Emergency Department: A Within-Trial Analysis

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## Abstract

**Background** The combination of midazolam and droperidol has proven superior to droperidol or olanzapine monotherapy in the management of acute agitation in emergency departments (EDs).

**Objective** This is the first economic analysis to evaluate the cost–benefit and cost effectiveness of the midazolam–droperidol combination compared with droperidol or olanzapine for the management of acute agitation in EDs.

**Methods** This analysis used data derived from a randomised, controlled, double-blind clinical trial conducted in two metropolitan Australian EDs between October 2014 and August 2015. The economic evaluation was from the perspective of Australian public hospital EDs. The main outcomes included agitation management time and the agitation-free time gained. Sensitivity analyses were undertaken.

**Results** The midazolam–droperidol combination was the least costly regimen (Australian dollars [AU\$]46.25 per

patient) compared with the droperidol and olanzapine groups (AU\$92.18 and AU\$110.45 per patient, respectively). The main cost driver for all groups was the cost of the labour required during the initial adequate sedation. The combination afforded an additional 10–13 min of mean agitation-free time gained, which can be translated to additional savings of AU\$31.24–42.60 per patient compared with the droperidol and olanzapine groups. The benefit–cost ratio for the midazolam–droperidol combination was 12.2:1.0, or AU\$122,000 in total benefit for every AU\$10,000 spent on management of acute agitation. Sensitivity analyses over key variables indicated these results were robust.

**Conclusions** The midazolam–droperidol combination may be a cost-saving and dominant cost-effective regimen for the treatment of acute agitation in EDs as it is more effective and less costly than either droperidol or olanzapine monotherapy.

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### Key Points For Decision Makers

The combination of midazolam and droperidol is more effective and cost saving than droperidol or olanzapine monotherapy in managing acute agitation in the emergency department (ED).

The rapid effect of the midazolam–droperidol combination could allow clinical and security staff to spend less time restraining agitated patients, leading to a reduced burden on personnel requirements in EDs.

## 1 Introduction

Aggression or acute agitation caused by alcohol or illicit drug intoxication with or without underlying mental illness is a common occurrence in emergency departments (EDs) [1–3]. Patients presenting with acute agitation in the ED often require more intensive resources for their management than do general medical patients [4, 5].

The recommended standard approach to managing acute agitation in EDs is early verbal de-escalation followed by the use of sedative medications and mechanical restraint if verbal de-escalation fails [6–8]. Existing guidelines recommend at least five staff (e.g. two nurses, one doctor and two security staff) should be available during the process of restraint and sedation to ensure the procedure can be performed safely and effectively [1, 7–9]. Given the labour-intensive nature of the management, a prolonged period of agitation places substantial strain on the human resources of EDs and is costly to the hospital.

Benzodiazepines (e.g. midazolam, diazepam) or antipsychotics (e.g. droperidol, olanzapine) are commonly used for sedation in EDs to manage acute agitation [10–13]. A recent systematic review concluded that a combination regimen (i.e. benzodiazepines and antipsychotics in combination) is associated with more rapid sedation and fewer adverse events (AEs) than benzodiazepine monotherapy [14]. While a number of trials have demonstrated that antipsychotics are at least as effective as benzodiazepine monotherapy [11, 13], clinical data comparing the use of antipsychotics alone versus combination regimens are lacking.

A multicentre randomised controlled trial (RCT) comparing the efficacy and safety of the midazolam–droperidol combination with that of droperidol or olanzapine monotherapy was recently reported [15]. The trial indicated that the midazolam–droperidol combination is superior to both droperidol and olanzapine monotherapy and that

safety profiles are comparable. However, whether this combination regimen is more cost saving is unknown. For the purpose of this study, the primary analysis is a cost–benefit analysis. The secondary analysis is a cost–effectiveness analysis that explores the effectiveness (i.e. agitation-free time gained) of the midazolam–droperidol combination versus droperidol or olanzapine monotherapy for the management of acute agitation in EDs.

## 2 Methods

### 2.1 Study Design, Setting and Population

This economic evaluation was conducted from the Australian public hospital ED perspective. Clinical outcomes and resource utilisation were obtained from an RCT [15] (Australian and New Zealand Clinical Trials Registry identifier: ACTRN12614000980639) undertaken in the ED of two metropolitan public hospitals in Melbourne, Australia, from October 2014 to August 2015.

Patients were eligible for inclusion in the trial if they were aged 18–65 years and required intravenous sedation for acute agitation. A total of 349 patients were randomised to an intravenous bolus of midazolam 5 mg–droperidol 5 mg combination or droperidol 10 mg or olanzapine 10 mg [15]. Two additional doses were administered if required: midazolam 5 mg, droperidol 5 mg or olanzapine 5 mg, respectively. If adequate sedation was not achieved 5 min after the two additional doses, additional open-label sedative medication(s) could be administered at the doctor's discretion.

This economic analysis was approved by the Melbourne Health Human Research Ethics Committees. Reporting of this analysis followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [16].

### 2.2 Outcome Measurement

The clinical outcome was adequate sedation, which was defined as a score < 2 based on a 6-point, validated Acute Arousal Scale [17] (5 = highly aroused, violent toward self, others, or property; 4 = highly aroused and possibly distressed or fearful; 3 = moderately aroused, agitated, more vocal, unreasonable, or hostile; 2 = mildly aroused, pacing, willing to talk reasonably; 1 = settled, minimal agitation; 0 = asleep).

In the RCT, the time required to achieve the initial adequate sedation, the need for and frequency of re-sedation within 60 min after achieving the initial adequate sedation and sedation AEs were assessed [15]. When a patient required re-sedation within 60 min after achieving the initial adequate sedation, frequency of re-sedation,

mean duration of clinical and security staff attendance, dose and medication used were recorded. Overall, 22 patients required re-sedation within 60 min after achieving the initial adequate sedation. The mean duration of clinical and security staff attendance for one re-sedation episode was 27 min. A total of 14 patients experienced airway obstruction: seven with the midazolam–droperidol combination, three with droperidol and four with olanzapine.

Two primary outcome measurements were used in the current economic evaluation: agitation management time (i.e. time required to achieve initial adequate sedation + number of re-sedations  $\times$  27 min) (Table 1) and the agitation-free time gained. In the RCT, the maximum time required to manage an episode of agitation was 185 min (proximately >3 h); therefore, we assumed that all episodes of agitation can be managed within 3.5 h (i.e. 210 min). For that reason, agitation-free time gained was calculated as 210 min minus the agitation management time for the patient.

### 2.3 Assumptions

The following assumptions were made when measuring the cost of management:

1. The cost of consumables (e.g. intravenous line, tubing and oxygen) were identical for all three regimens.
2. All patients required the attendance of five staff (one ED doctor; two senior ED registered nurses [RNs]—one grade 2 RN with at least 5 years of experience and one grade 3 RN, usually a floor coordinator; and two security staff) to administer the sedative medication from initial drug administration until adequate sedation and during each re-sedation episode.
3. If airway obstruction occurred, only one episode of airway management was required throughout the sedation period for each patient.
4. No additional pathology, imaging or monitoring tests were required as a consequence of sedation.

### 2.4 Measurement of Costs

The costs of management related to the use of the sedative medication, consumables and personnel to manage the acute agitation and the airway; the savings resulted from the decrease in human resource utilisation (i.e. agitation-free time gained).

#### 2.4.1 Cost of Management

A bottom-up approach was used to calculate the mean costs by tracing the actual use of resources and medications for each patient recruited [18]. Discounting was not applied because of the short duration of the ED presentations. All costs were expressed in Australian dollars (AU\$) for the financial year 2015–2016.

We took a conservative approach by focusing on the cost of management incurred during the initial adequate sedation, the re-sedation and the airway management. The direct medical costs of managing agitation do not include non-agitation management costs such as costs related to other underlying medical or psychiatric problems and costs for the entire ED length of stay (LOS). Estimated unit costs used are listed in Table 2.

The costs per initial adequate sedation were categorised as labour costs or medication costs. Labour costs were calculated by multiplying the time required to achieve initial adequate sedation by the sum of the average hourly wages of five hospital staff involved in the sedation process (see Sect. 2.3). The mean hourly wages of ED doctors with different years of experience (varying from year 1 to 6), and the mean hourly wages for grade 2 RNs (year 5–10) were used. Hourly wages for security staff were obtained from the hospital human resources department, hourly wages for ED doctors were obtained from the Australian Medical Association Victoria [19, 20] and hourly wages for RNs were obtained from the Australian Nursing and Midwifery Federation [21]. Medication costs were the mean costs of medications to achieve initial adequate

**Table 1** Mean agitation management time using midazolam–droperidol combination, droperidol or olanzapine monotherapy

Outcomes	Mean agitation management time (SD), min		
	Midazolam–droperidol ( $n = 118$ )	Droperidol ( $n = 111$ )	Olanzapine ( $n = 120$ )
Sedated with no re-sedation	9.6 (14.7)	20.2 (25.7)	22.2 (30.1)
Sedated with one re-sedation	35 (7.0)	34 (0.7)	62 (24.8)
Sedated with two re-sedation	–	74 (16.5)	83 (36.7)
Sedated with three re-sedation	92 <sup>a</sup>	–	88 <sup>a</sup>
Overall	11.7 (17.3)	22.1 (27.1)	25.6 (33.0)

SD standard deviation

<sup>a</sup> Only one case with three re-sedation events within 60 min after initial sedation; actual time was reported and no SD could be calculated

sedation, which included both study medications and other open-label sedative medications. Medication acquisition costs were obtained from the Australian Health Purchasing Victoria Catalogue 2012-058 [22]. The doses administered were rounded up and costed to the nearest vial size to account for wastage.

The costs of sedation with re-sedation were calculated by adding the cost of initial adequate sedation and the cost of re-sedation according to the number of re-sedations required. The cost per re-sedation was calculated by adding the labour costs and the medication costs associated with one re-sedation. The labour cost was calculated by multiplying the mean time required to re-sedate the patient (i.e. 27 min) by the sum of the average hourly wages of five hospital staff. Adjusted medication costs were based on the probabilities of each medication used for re-sedation within 60 min after achieving initial adequate sedation.

For patients requiring airway management, additional costs were added to the total cost of managing the acute agitation. The added cost of one airway management was

the sum of the labour cost and the cost of consumables [i.e. oropharyngeal airway (OPA) or nasopharyngeal airway (NPA)]. The labour cost was calculated by multiplying the estimated time for one airway management (i.e. 30 min) by the sum of the average hourly rate of one ED doctor and one grade 3 RN. The time per airway management was estimated based on the experiential knowledge of the ED consultants and senior ED nurses, who have extensive experience in managing airway compromise requiring airway adjuncts.

## 2.5 Cost–Benefit Analysis

As cost–benefit analyses express both inputs and consequences of different regimens in monetary units [23], agitation-free time gained was multiplied with total cost of the response team per minute (i.e. AU\$2.84/min) to measure the economic benefits gained. Benefit–cost ratios for all three sedation regimens were calculated by dividing the economic benefits by the management costs.

**Table 2** Estimated unit costs

Items	Description	Unit costs (AU\$)
Labour costs	ED doctor (per minute)	0.84
	ED RN grade 2 (per minute)	0.52
	ED RN grade 3 (per minute)	0.59
	Security staff (per minute)	0.44
	Total cost of response team (per minute) <sup>a</sup>	2.84
Medication costs	Midazolam 5 mg/5 ml	0.23
	Droperidol 2.5 mg/ml	4.54
	Olanzapine 10 mg	20.22
	Water for injection 10 ml	0.12
Cost of re-sedation within 60 min after achieving initial adequate sedation	ED doctor time (27 min) <sup>b</sup>	22.97
	Two security staff time (27 min) <sup>b</sup>	23.76
	One grade 2 RN (27 min) <sup>b</sup>	14.24
	One grade 3 RN (27 min) <sup>b</sup>	15.98
	Adjusted medication costs <sup>c</sup>	6.46
Cost of airway management	Total cost of one re-sedation	83.41
	ED doctor time (30 min)	25.32
	Grade 3 RN time (30 min)	17.62
	Consumable costs (NPA, OPA)	4.63 <sup>d</sup>
	Total cost of one airway management	47.56

Costs are presented in Australian dollars, year 2015–2016 values

ED emergency department, NPA nasopharyngeal airways, OPA oropharyngeal airways, RN registered nurse

<sup>a</sup> Response team consists of one ED doctor, one ED RN grade 2, one RN grade 3 (floor coordinator) and two security staff

<sup>b</sup> Average time for one security alert for a re-sedation episode

<sup>c</sup> Adjusted medication costs are calculated based on the probabilities of each medication (midazolam, droperidol, olanzapine, ketamine) being used for re-sedation within 60 min

<sup>d</sup> The mean cost of the unit price for NPA and OPA

## 2.6 Cost-Effectiveness Analysis

In this study, the cost-effectiveness analysis compared different sedation regimens in terms of cost per minute of agitation-free time gained. The incremental cost-effectiveness ratio (ICER) is the difference in the cost of management between the comparators (e.g. midazolam–droperidol and droperidol) divided by the difference in their effectiveness (i.e. agitation-free time gained). A positive ICER implies the sedation regimen increased agitation-free time gained at a certain cost; the ICER will be important for policy makers to make decisions based on the willingness-to-pay value [24]. Whilst a negative numerator (cheaper cost) and a positive denominator (e.g. more agitation-free time gained) imply the intervention is more effective at a lower cost (i.e. a dominant strategy), the ICER will not be calculated [24, 25].

## 2.7 Sensitivity Analyses

The robustness of the result was assessed using both one-way and two-way sensitivity analyses to examine the uncertainty surrounding key variables. These analyses included changes in the drug-acquisition costs, mean initial adequate sedation medication and labour costs, mean duration of staff attendance during re-sedation, probabilities of the need for re-sedation, costs of consumables, and duration of airway management. The variables and ranges of variation are shown in Table 3. All analyses were performed using TreeAge Pro 2015, R1.0. (TreeAge Software, Williamstown, MA, USA).

Two-way sensitivity analysis was performed to examine the worst- and the best-case scenarios based on the variation of the mean agitation-free time gained and the mean total management costs. An alternative scenario, with the ideal number of staff members (i.e. seven staff) involved in both initial sedation and re-sedation was also evaluated.

## 2.8 Statistical Analysis

The sample size was calculated based on the primary endpoints of the RCT rather than the economic evaluation [15]. In the RCT, of the 361 patients enrolled, only a small number (12; 3% of the total) were excluded for either missing the primary endpoint or for repeated enrolment. Hence, only cases with complete data were included in the analysis, which should have little impact on the accuracy of the results. As cost data distribution are positively skewed [23, 26], some studies reported median and interquartile range values [27, 28]. However, the provision of information about mean costs is more helpful to policy makers, who require information on the total cost of implementing a strategy by multiplying the mean costs by the total number of patients [26]. Therefore, mean costs and 95% confidence intervals (CIs) are reported.

## 3 Results

### 3.1 Base-Case Analysis

The midazolam–droperidol combination was found to be more cost saving than droperidol or olanzapine monotherapy; it is also a dominant regimen, i.e. it was cheaper and more effective. The overall mean cost of management with the midazolam–droperidol combination was AU\$46.25 (95% CI 36.77–55.74) per patient compared with AU\$92.18 (95% CI 76.66–107.70) per patient with droperidol and AU\$110.45 (95% CI 91.51–129.39) per patient with olanzapine (Table 4). Despite the higher costs of re-sedation and airway management with the midazolam–droperidol combination, the overall mean cost of this combination regimen was 50 and 58% lower than that of droperidol or olanzapine monotherapy, respectively (Table 4). The main cost driver for all groups was the labour costs required during the initial adequate sedation (Fig. 1).

In terms of improved effectiveness, the mean agitation-free time gained with the midazolam–droperidol combination was 199 (95% CI 196–202) min compared with 188 (95% CI 183–193) min with droperidol and 184 (95% CI 179–190) min with olanzapine (Table 6). This additional agitation-free time gained resulted in additional economic benefits of AU\$31.24 and AU\$42.60 per patient (Table 5), respectively.

Overall, the total economic benefits of the midazolam–droperidol combination compared with droperidol and olanzapine was AU\$77.17 and AU\$106.80 per patient, respectively. The net benefit–cost ratio for the midazolam–droperidol combination was 12.2:1.0 (Table 5), equivalent to AU\$122,000 cost savings for every AU\$10,000 spent on the management of acute agitation with this combination.

### 3.2 Sensitivity Analyses

One-way sensitivity analyses indicated that the conclusion of this evaluation was not sensitive to the variation of all the parameters at the range shown in Table 3. For two-way sensitivity and alternative scenario analysis (Table 7), the midazolam–droperidol combination remained the most cost-saving (Table 5) and the dominant regimen (Table 6).

## 4 Discussion

This is the first analysis to evaluate the cost–benefit and cost effectiveness of managing acute agitation in EDs with a midazolam–droperidol combination compared with either droperidol or olanzapine monotherapy. Importantly, because much less time is required to manage one acute

**Table 3** Variation range for variables investigated in one-way sensitivity analyses

Variables	Base case	Variation range		Source of range
		Low	High	
Cost of midazolam 5 mg	0.23	0.02	0.44	Base case value $\pm 90\%$
Cost of droperidol 2.5 mg	4.54	0.45	8.60	Base case value $\pm 90\%$
Cost of olanzapine 10 mg	20.22	2.02	38.40	Base case value $\pm 90\%$
Mean initial adequate sedation medication cost				
Midazolam–droperidol	9.74	9.24	10.24	95% CI of the mean value
Droperidol	27.47	25.66	29.27	95% CI of the mean value
Olanzapine	35.30	32.84	37.75	95% CI of the mean value
Mean initial adequate sedation labour cost				
Midazolam–droperidol	27.35	19.82	34.87	95% CI of the mean value
Droperidol	57.43	43.83	71.02	95% CI of the mean value
Olanzapine	63.17	47.88	78.45	95% CI of the mean value
Mean duration of clinical staff attendance during re-sedation (min)	27	11.6	42.4	$\pm SD$ (15.4 min)
Probabilities of sedated with no re-sedation (%)				
Midazolam–droperidol	94.1	89.8	98.3	95% CI of the base case
Droperidol	95.5	91.6	99.3	95% CI of the base case
Olanzapine	91.7	86.7	96.6	95% CI of the base case
Probabilities of sedated with one re-sedation (%)				
Midazolam–droperidol	5.1	1.1	9.0	95% CI of the base case
Droperidol	1.8	0 <sup>a</sup>	4.2	95% CI of the base case
Olanzapine	5.0	1.1	8.9	95% CI of the base case
Probabilities of sedated with two re-sedation (%)				
Midazolam–droperidol	0	0	30	Base-case value +30% <sup>b</sup>
Droperidol	2.7	0 <sup>a</sup>	5.7	95% CI of the base case
Olanzapine	2.5	0 <sup>a</sup>	5.3	95% CI of the base case
Duration of airway management (min)	30	15	45	Base-case value $\pm 50\%$
Cost of consumables for airway management	4.63	2.32	9.26	Base-case value $\pm 50\%$

Costs are presented in Australian dollars, year 2015–2016 values

CI confidence interval, RCT randomised controlled trial, SD standard deviation

<sup>a</sup> Given the negative values for the lower bound of the 95% CI, zero was used to enable modelling

<sup>b</sup> No case was observed in the RCT and 30% was used to enable modelling

agitation presentation, the midazolam–droperidol combination was more effective and cost saving than droperidol and olanzapine monotherapies. This provides pivotal information to guide the use of these regimens in the ED setting for the management of acute agitation. Sensitivity analyses confirmed the robustness of the results across a broad range of variations.

In a tertiary-care ED with approximately 450 episodes of sedation for acute agitation (security database, unpublished data, based on the experience of the Royal Melbourne Hospital in 2014), the total annual mean cost to manage these patients would be approximately AU\$21,000 with the midazolam–droperidol combination compared with nearly AU\$42,000 with droperidol and AU\$50,000 with olanzapine. Furthermore, as the midazolam–

droperidol combination increased the agitation-free time gained by approximately 50%, this will result in further cost savings of AU\$14,058 and AU\$19,170, respectively. Thus, the midazolam–droperidol combination could generate a total annual cost savings of nearly AU\$35,000 and AU\$48,000, respectively.

In addition to the benefit of cost savings, using the midazolam–droperidol combination was also associated with additional agitation-free time gained. The published literature on agitation in the ED reports that these episodes are more likely to occur in the evening or overnight, which coincides with periods of minimal or reduced staffing [1, 29]. Liberating a team of healthcare staff for that amount of time would have the potential to enhance ED patient flow. In a busy overnight shift, where it is possible

**Table 4** Mean costs of management using midazolam–droperidol combination, droperidol or olanzapine monotherapy

Outcomes at time points	Midazolam–droperidol			Droperidol			Olanzapine		
	Proportion (%)	Cost/pt	Proportional cost <sup>a</sup>	Proportion (%)	Cost/pt	Proportional cost <sup>a</sup>	Proportion (%)	Cost/pt	Proportional cost <sup>a</sup>
Sedated with no re-sedation									
No airway obstruction	89.0	37.08	33.00	92.8	84.90	78.78	90.0	98.47	88.62
Airway obstruction	5.1	84.64	4.30	2.7	132.46	3.58	1.7	146.03	2.43
Sedated with one re-sedation									
No airway obstruction	4.3	120.31	5.10	1.8	168.13	3.03	4.2	181.70	7.57
Airway obstruction	0.8	167.87	1.42	0	215.69	0	0.8	229.26	1.91
Sedated with two re-sedation									
No airway obstruction	0	203.53	0	2.7	251.35	6.79	2.5	264.92	6.62
Airway obstruction	0	251.09	0	0	298.91	0	0	312.48	0
Sedated with three re-sedation									
No airway obstruction	0.8	286.76	2.43	0	334.58	0	0	348.15	0
Airway obstruction	0	334.32	0	0	382.14	0	0.8	395.71	3.30
Mean (95% CI) costs of management per pt			46.25 (36.77–55.74)			92.18 (76.66–107.70)			110.45 (91.51–129.39)

Costs are presented in Australian dollars, year 2015–2016 values

CI confidence interval, pt patient

<sup>a</sup> The cost per patient was determined within each outcome, then multiplied by the proportion of patients, for the eight possible outcomes to get the proportional cost

<sup>b</sup> The proportional costs for each outcome were summed to give the mean cost per patient for each regimen

to have up to eight episodes of acute agitation (Royal Melbourne Hospital security database, unpublished data, based on the experience of the Royal Melbourne Hospital in 2014), using the midazolam–droperidol combination to manage these patients will amount to a substantial decrease in staff workload.

The cost-effectiveness analysis also revealed that the midazolam–droperidol combination is the dominant regimen, being less costly and more effective than the other two monotherapy regimens. Decision making should be straightforward. Hence, the ICER is of little value in this situation because the additional gain is not obtained with additional costs.

Despite the resource implications, only one published cost-minimisation analysis has evaluated the costs of managing acute agitation in the ED [27]. However, that study did not consider the differences in frequency of re-sedation within 60 min and AE rates between the

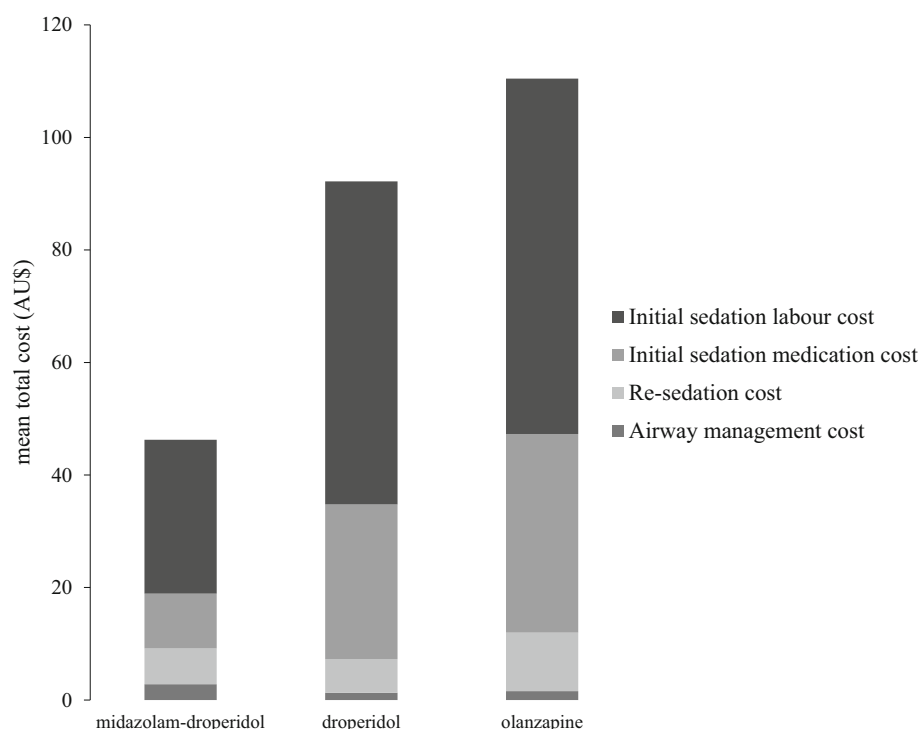
droperidol and the midazolam regimens. Consequently, direct comparison is not possible.

Our estimates of labour costs were built on the assumption that three ED clinicians and two security staff would attend a security alert during both an initial and a re-sedation episode. Ideally, seven staff should be available during the process of restraint and sedation: one security staff member for each limb and one senior ED nurse for the head (to prevent the patient from biting and to ensure the patient's airway is not compromised), and another ED nurse to prepare medication for the ED doctor to administer [7]. In situations involving seven staff, this would further add to the economic advantage of using the midazolam–droperidol combination.

The current evaluation suggests that airway obstruction had limited impact on resource utilisation because of the overall low rate of occurrence. Midazolam is associated with an increased risk of respiratory complications that



**Fig. 1** Composition of different mean cost components in overall management of acute agitation in emergency departments. Costs are presented in Australian dollars, year 2015–2016 values



**Table 5** Results of two-way analyses (base-, worst- and best-case scenario) for cost–benefit analysis

Scenario	Mean costs of management per patient	Economic benefits	Incremental economic benefits	Benefit–cost ratio
Base case <sup>a</sup>				
Midazolam–droperidol	46.25 (36.77–55.74)	565.16 (556.64–573.68)	–	12.2:1.0
Droperidol	92.18 (76.66–107.70)	533.92 (519.72–548.12)	–31.24	5.8:1.0
Olanzapine	110.45 (91.51–129.39)	522.56 (508.36–539.60)	–42.60	4.7:1.0
Worst case				
Midazolam–droperidol	55.74	556.64	–	10.0:1.0
Droperidol	76.66	548.12	–8.52	7.2:1.0
Olanzapine	91.51	539.60	–17.04	5.9:1.0
Best case				
Midazolam–droperidol	36.77	573.68	–	15.6:1.0
Droperidol	107.70	519.72	–53.96	4.8:1.0
Olanzapine	129.39	508.36	–65.32	3.9:1.0

Costs are presented in Australian dollars, year 2015–2016 values

Economic benefits = mean agitation-free time gained (min) × total cost of response team (AU\$2.84) per minute; negative sign indicates that the midazolam–droperidol combination generated greater economic benefits

<sup>a</sup> Mean (95% confidence interval)

may lead to intubation [10, 13], whereas droperidol raises concerns of QT prolongation and Torsades de Pointes (TdP) [30]. It was not possible to estimate the impact of intubation and TdP in the current within-trial analysis as no patient experienced these AEs in the RCT [15]. As the midazolam–droperidol combination reduced the need for high-dose midazolam or droperidol monotherapy, and

subsequently reduced the risk of these severe AEs, the rare incidence of these AEs and the associated costs were unlikely to change the conclusions of this study. Similarly, other minor AEs such as hypotension and oxygen desaturation were not considered in this evaluation because those AEs were assumed to be self-limiting and would not have a significant impact on resource utilisation.

**Table 6** Results of two-way analyses (base-, worst- and best-case scenario) for cost-effectiveness analysis

Scenario	Mean costs of management per patient	Incremental cost	Effectiveness (mean agitation-free time gained, min)	Incremental effectiveness (min)	ICER
Base case <sup>a</sup>					
Midazolam–droperidol	46.25 (36.77–55.74)	–	199 (196–202)	–	Dominant
Droperidol	92.18 (76.66–107.70)	45.93	188 (183–193)	–11	Dominated
Olanzapine	110.45 (91.51–129.39)	64.20	184 (179–190)	–15	Dominated
Worst case					
Midazolam–droperidol	55.74	–	196	–	Dominant
Droperidol	76.66	20.92	193	–3	Dominated
Olanzapine	91.51	35.77	190	–6	Dominated
Best case					
Midazolam–droperidol	36.77	–	202	–	Dominant
Droperidol	107.70	70.93	183	–19	Dominated
Olanzapine	129.39	92.62	179	–23	Dominated

Costs are presented in Australian dollars, year 2015–2016 values

ICER incremental cost-effectiveness ratio

<sup>a</sup> Mean (95% confidence interval)

**Table 7** Results of alternative scenario analysis

Alternative scenario <sup>a</sup>	Mean cost of management per patient	Incremental cost	Effectiveness <sup>b</sup>	Incremental effectiveness (min)	Economic benefits	Economic benefits difference	Benefit-cost ratio	ICER
Midazolam–droperidol	56.63 (44.47–68.80)	–	199 (196–202)	–	742.27	–	13.1:1	Dominant
Droperidol	111.87 (91.89–131.85)	55.24	188 (183–193)	–11	701.24	–41.03	6.3:1	Dominated
Olanzapine	133.21 (109.05–157.37)	76.58	184 (179–190)	–15	686.32	–55.95	5.2:1	Dominated

Costs are presented in Australian dollars, year 2015–2016 values; figures in parentheses are 95% confidence intervals

Economic benefits = mean agitation-free time gained (min) × total cost of response team (AU\$3.73) per minute; negative sign denotes the midazolam–droperidol combination generated greater economic benefits

ICER incremental cost-effectiveness ratio, RN registered nurse

<sup>a</sup> Seven staff case scenario (one doctor, one grade 3 RN, one grade 2 RN, and four security staff). Total cost of the response team: AU\$3.73/min

<sup>b</sup> Mean agitation-free time gained, min

We acknowledge several limitations in this study. First, the results of this study can only be interpreted in the context of acutely agitated patients in the ED setting, and the results cannot be generalised to psychiatric inpatients. Furthermore, estimates of the mean costs of management were based on data from only one RCT, and more economic evaluations on the cost–benefit and cost effectiveness of other sedative regimens for the management of acute agitation in EDs are warranted.

To understand the immediate impact of the combination regimen, our evaluation was confined to the initial adequate sedation stage. Thus, hospitalisation costs for the entire ED LOS were not considered. However, in the RCT

[15], we found that the ED LOS was not sensitive to the choice of sedation regimen. Patient disposition can be influenced by other non-sedation-related factors, including underlying medical comorbidities, availability of inpatient beds, time of the day, etc. [31]. Therefore, the exclusion of hospitalisation costs for the entire ED LOS would afford a more accurate measure of the efficiency of the different sedation regimens in managing the acute agitation.

Finally, the re-sedation rate after 60 min was not included in this analysis because the need for further sedation after 60 min is subject to a patient's risk of violent behaviour after the initial adequate sedation. Prolonged sedation is not the goal of acute agitation management.

However, taking such costs into account would likely have no important influence on the cost savings of the midazolam–droperidol combination because the cost of re-sedation was not the main cost driver.

## 5 Conclusions

The midazolam–droperidol combination may be more effective and less costly than both droperidol and olanzapine monotherapy. This study provides support, from an optimal use of resource perspective, for the use of the midazolam–droperidol combination over droperidol or olanzapine monotherapy in the management of acute agitation in the ED. The rapid sedative effect of the midazolam–droperidol combination could allow clinical and security staff to spend less time restraining agitated patients and lead to substantial cost savings and freeing up of precious ED personnel for other emergency cases.

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**Author contributions** All authors conceived and designed the study. CY managed collation of the data and entry into the study database. CY and AH undertook the data analysis. All authors contributed to interpretation of the results, drafting and revision of the manuscript. All authors take responsibility for the paper as a whole.

### Compliance with Ethical Standards

This study is part of the randomised controlled trial [15] (Australian and New Zealand Clinical Trials Registry identifier: ACTRN12614000980639). Human Research Ethics Committees (HRECs) at the Austin Health, Melbourne Health, St Vincent's Hospital and Monash University approved the trial (HREC reference, HREC/13/MH/363). Because of the level of agitation, informed consent was not possible, and waiver of consent was granted by the HRECs.

**Conflicts of interest** CY, AH, DT, JK, EWC and DK have no conflicts of interest.

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**Data availability statement** The dataset contains complete medical records for the sample. Data are available from the authors upon reasonable request and with permission of the HRECs and other relevant bodies.

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