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A Prospective Study of the Safety and Effectiveness of Droperidol in Elderly Patients for Prehospital Acute Behavioural Disturbance

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Abstract

Study objective: Acute behavioural disturbance in the elderly (≥65 years) is a significant issue for emergency medical services with increasing prevalence of dementia and aging populations. We investigated the prehospital safety and effectiveness of droperidol in the elderly with acute behavioural disturbance.

Methods: This was a prehospital prospective observational one-year study of elderly patients with acute behavioural disturbance. The primary outcome was proportion of adverse events (airway intervention, oxygen saturation<90% and/or respiratory rate[RR]<12, systolic blood pressure<90mmHg, sedation assessment tool score of −3 and dystonic reactions). Secondary outcomes included time to sedation, additional sedation, proportion with successful sedation.

Results: There were 149 patients (males 78[52%], median age 78years;65-101years) presenting on 162 occasions. Dementia was the commonest cause (107/164 [65%]) of acute behavioural disturbance. There were six adverse events in five patients (5/162 [3%];95% confidence interval[CI]:1-7%). Three had hypotension, one with associated hypoxia (80%); and two had respiratory adverse effects (RR,10 [no hypoxia] and hypoxia [80%] which required oxygen). Median time to sedation was 19min (Interquartile range:12-29min). Additional sedation was given in 2/162 patients during ambulance transfer and 16/162 within an hour of hospital arrival; 24/162 (15%) failed to sedate in the ambulance; 16 subsequently settled in ED and 8/24 received additional sedation. 123/162 (76%) patients successfully sedated, without

adverse effects or additional sedation. 114/162 (70%) patients received 5mg, 46 (29%) received two doses of 5mg and two patients (1%) received three doses.

Conclusions: Droperidol appeared to be safe and effective for prehospital sedation of acute behavioural disturbance in elderly patients.

Key words: Prehospital, elderly, acute behavioural disturbance, chemical sedation

Introduction

Acute behavioural disturbance in the elderly (≥ 65 y) is an increasing problem in our healthcare system.[1,2] This is due to the increasing elderly population with increasing frequency of dementia[3] and acute medical illness associated with an aging population. Patients with acute behavioural disturbance occur from the prehospital environment[4] with emergency medical services through to the emergency department (ED)[5,6], hospital wards[7] and also within nursing homes[8]. Recommendations on the management of the behavioural aspects of dementia and acute medical illness stress the importance of non-pharmacological interventions[2,9]. If pharmacological management is required, antipsychotics are preferred over benzodiazepines, based on evidence from randomised controlled trials of both the typical and atypical antipsychotics[10,11]. There is less evidence for the effectiveness of benzodiazepines and their adverse effect profile in the elderly limits their use to short term management of dementia symptoms,[11] or as a second line agent if antipsychotics are not tolerated[12]. Although recommended first line, both classes of antipsychotic drugs have adverse effects. Black box warnings from the Federal Drug Administration have been issued for the atypical (2005) and typical (2008) antipsychotics.[1] These warnings relate to the use of haloperidol, droperidol, risperidone, olanzapine, aripiprazole and quetiapine.

Acute behavioural disturbance in the elderly is increasing in both the prehospital and ED setting. Unfortunately, most studies investigating the pharmacological management of acute behavioural disturbance either exclude elderly patients[13,14] or

include only a small number of older patients[4,15-18]. This means that recommendations from these studies on the acute management of behavioural disturbance in the elderly age group are difficult to make. There is one small study of 49 elderly patients (>65 years) with acute behavioural disturbance, which suggested that droperidol was safe and effective in the elderly.[5] Over half of the patients were given an initial dose of 10mg (dose commonly used in <65 years) and the adverse effect profile was 10%, not dissimilar to all adults receiving droperidol.[18] A recent review of the acute agitated ED patient[6] suggested that elderly patients should be administered lower doses with slower titration of either a typical or atypical antipsychotic agents, as first line agents. The authors also suggested that the use of benzodiazepines, even single use, should be avoided because of adverse outcomes.

We have previously published a prehospital study examining the management of acute behavioural disturbance, comparing droperidol and midazolam, when our state based ambulance service changed to intramuscular droperidol in 2016.[4] The majority were adults 16 to 64 years, because patients at the extremes of ages were either not studied (<16 years) or less well represented (≥65 years), so additional data is required. Once the change to droperidol was completed, auditing of the safety and effectiveness of droperidol was commenced in these two age groups.

Here we investigate the safety and effectiveness of droperidol in the prehospital setting for elderly patients with acute behavioural disturbance.

Materials and Methods

Study Design and Setting

This is a prospective observational study of the safety and effectiveness of droperidol for elderly patients (≥65 years) with acute behavioural disturbance in the prehospital environment. It is part of a quality assurance monitoring program of patients managed by the Queensland state ambulance service with acute behavioural disturbance, after midazolam was replaced with intramuscular droperidol in November 2016. The state of Queensland has a population of five million people of which 15% or approximately 735,000 are aged 65 years and above. The study has ethical approval as a low or negligible risk study from the Brisbane Metro South Human Research Ethics Committee and the Queensland Ambulance Service, and included ambulance attendance for the whole state, urban and rural. Consent was waived by the ethics committees because patients with acute behavioural disturbance are frequently impaired and cannot give informed consent in the context of requiring immediate emergency medical treatment under the provision of duty of care.

Selection of Patients

Patients ≥65 years who were attended by the state ambulance service and thought to have acute behavioural disturbance were eligible for the study. Data were collected for the one-year period between July 2017 and June 2018. The severity of acute behavioural disturbance for study inclusion was based on having a sedation assessment tool (SAT) score of ≥2 (Figure 1)[19]. The SAT score was introduced in

2012 and its use is now compulsory for the assessment and management of acute behavioural disturbance by the ambulance service. The decision to include a patient in the study was made by the attending paramedic at the time of patient attendance. Exclusion criteria included successful verbal de-escalation or any known adverse or potential reaction to droperidol e.g. Parkinson's disease.

Interventions

A drug treatment protocol for droperidol developed by the ambulance service for the management of acute behavioural disturbance was introduced in November 2016 (supplemental materials online only). It is based on published research on the safety and effectiveness of droperidol in the ED.[5,18] For patients ≥65 years with acute behavioural disturbance and a SAT score ≥2, it recommends an initial intramuscular dose of 5 mg droperidol, followed by one repeat dose of 5 mg after 15 minutes, if the patient is not sedated. This is half the standard adult dose. Successful sedation is defined as a SAT score decreasing by 2 or more, or a SAT score decreasing to zero.[18]

Data collection

A purpose designed audit form (supplemental materials online only) was used for data collection.[4,20] It includes patient demographic information, ambulance case data, suspected cause of acute behavioural disturbance, SAT scores, droperidol administration details and vital signs, including airway intervention. Information from the audit form and the standard electronic ambulance report form (required on all cases) is then entered into a Microsoft Excel datasheet. Additional information to

confirm the cause of the acute behavioural disturbance, subsequent ED additional sedation and dystonic reactions (in ED or subsequent ED visits within the week of droperidol administration) were extracted from the ED medical record and/or discharge summary.

Outcomes Measures and Analysis

The primary outcome for the study was the proportion of patients with adverse events.[4,20] Adverse events included: airway obstruction requiring any airway manoeuvre from simple chin lift/jaw thrust through to either an insertion of a laryngeal mask airway or endotracheal intubation; oxygen saturations <90% on room air and/or respiratory rate <12 per minute; hypotension (systolic blood pressure <90 mmHg); a SAT score of minus 3 (equates to a Glasgow Coma Score of 3); and dystonic reactions. Secondary outcomes were time to sedation, defined as the time of drug administration until the SAT score decreased by two points or more, or decreased to zero; requirement for additional sedation after successful sedation, either in the ambulance or in the first hour after ED arrival; number of injuries to the patient or ambulance staff; number of patients who failed to sedate (as defined above) in the ambulance; and successful sedation defined as the proportion of patients who were sedated, had no adverse effects and did not require additional sedation. The time to sedation in this study was changed from our previous adult study[4] in which the time from arrival of the ambulance at the patient was used, rather than the time from drug administration. The reason for this was that paramedics attending patients ≥65 years

with acute behavioural disturbance were spending lengthy periods of time de-escalating patients, in an attempt to avoid administering parenteral medications.

Descriptive statistics are used to report all primary and secondary outcomes. Continuous outcomes are reported as medians, interquartile ranges (IQRs) and ranges and dichotomous outcomes are reported with 95% confidence intervals (CI). All analysis was performed in GraphPad Prism 7.0d for Mac OS X (GraphPad Software, La Jolla California CA, U.S.A.; www.graphpad.com).

Results

We recruited 177 elderly patients over one-year who were administered droperidol for acute behavioural disturbance (Figure 2). Two (1%) patients did not have an audit form completed and thirteen (7%) patients were excluded, leaving 149 patients who presented on 162 occasions (six patients presented twice, two patients presented three times and one patient presented four times). Ten of the 13 exclusions were for acute behavioural disturbance not being the primary reason for presentation e.g. trauma, after review of the records (Figure 2). In all 13 cases other medications were administered e.g. opiates and/or benzodiazepines.

Of 149 patients, 78 (52%) were male with a median age of 78 years (IQR: 71 to 86 years; range: 65 to 101 years; Table 1). In almost two thirds of cases 107/164 [65%], dementia was the primary cause of acute behavioural disturbance. Nursing home residents accounted for 78/149 (52%) of patients. Police were in attendance on 67/162 (41%) occasions of acute behavioural disturbance (Table 1).

In total, there were six adverse events in five of 162 patients (3%; 95% CI: 1 to 7%). Three (2%) patients had hypotension (Table 2), two of which were asymptomatic and hypotension resolved spontaneously. The remaining patient with hypotension also had oxygen saturations of 80%, which was managed with intravenous fluid and oxygen to good effect. The fourth patient had a respiratory rate of 10 with oxygen saturation 97%, which resolved spontaneously. The remaining patient had oxygen saturation 88% with otherwise normal observations, which resolved with the addition of oxygen.

Of the five patients (all successfully sedated) who had an adverse event (Table 2), four patients received a single dose of 5 mg droperidol and the remaining patient received two doses of 5 mg (total 10 mg). There were no dystonic reactions.

The median time to sedation was 19 min (IQR: 12 to 29 min; range: 5 to 72 min). Two of 162 patients (1%; 95% CI: 0 to 4%) received additional sedation (droperidol 5 mg) once successfully sedated during the ambulance journey to hospital. Additional sedation in the first hour after arrival to hospital was required in 16 of 162 patients (10%; 95% CI: 6 to 16%). Additional sedation in the ED included further doses of droperidol, midazolam, diazepam, lorazepam and olanzapine. One patient required a ketamine infusion for aeromedical retrieval. There were no documented cases of injuries to ambulance staff or patients.

There were 24/162 patients (15%) who failed to sedate (SAT score did not decrease by 2 points or more, or the score did not decrease to zero) in the ambulance. Sixteen of 24 patients (67%) subsequently settled in the ED and did not receive additional sedation within the first hour of arrival. The remaining 8/24 patients (33%) received additional sedation in the first hour in ED. In total 123/162 patients (76%) were successfully sedated and did not have any adverse effects or require additional sedation (Figure 3).

Overall 114/162 patients (70%) received one dose, 46/162 (29%) received two doses and two patients (1%) received three doses of droperidol. No patient received ketamine in the prehospital setting. In total 141/162 patients (87%) were managed as

per ambulance protocol. In most patients receiving droperidol doses outside the protocol, this was because the attending ambulance officers thought the patient was under 65 years and they gave a higher initial dose.

Discussion

We have shown that the use of intramuscular droperidol for acute behavioural disturbance in the elderly is both safe and effective. The predominant cause of acute behavioural disturbance was dementia, with nursing home patients accounting for half of the presentations. The rate of adverse events was low with half resolving spontaneously with no prehospital intervention. When prehospital intervention was required, they were standard paramedic interventions with the administration of oxygen and/or intravenous fluid. No airway interventions were required. Over three-quarters of the patients were successfully sedated with a single dose of 5 mg droperidol without any adverse events.

We found that there appeared to be less adverse effects (3%) with droperidol in this elderly population, compared to other reported studies of droperidol use for acute behavioural disturbance in the prehospital and ED setting.[4,18,20,21] Previous studies were predominately of adults under the age of 65 years with adverse effects occurring in 5 to 13%[4,18,21] or in children occurring in 8%.[20] A study of 49 elderly patients with acute behavioural disturbance in the ED, reported a higher rate of adverse effects.[5] Five of the 49 patients (10%) had adverse effects: hypotension (2), over-sedation (2) and both in one. Two patients received a single dose of 10mg droperidol, one received droperidol and midazolam (10mg + 10mg) and one received midazolam (5mg and haloperidol 2.5mg).[5] Our study supports a lower dose of 5mg droperidol as monotherapy is likely to be safer in the elderly, and just as effective.

The only adverse effects in our study were hypotension and over-sedation. Many past concerns about droperidol have been about extrapyramidal side-effects and QT prolongation. In our previous prehospital study of adult patients administered droperidol, over-sedation and hypotension were also the major adverse effects, with no dystonic reactions. In a larger ED study, 7 of 1402 patients (0.5%) administered droperidol had an extrapyramidal side-effect.[18] Extrapyramidal side-effects did occur in paediatric patients, with two of 102 paediatric patients (2%) having dystonic reactions in a similar prehospital cohort, both occurring 2 or more hours after administration.[20] Based on our study and previous cohorts,[4,18,20] extrapyramidal side-effects are unlikely to occur in the elderly with a single parenteral dose of droperidol, but are more common in younger populations.

There is significant controversy regarding the risk of QT prolongation with droperidol use in all age groups.[22-24] Despite the black box warning in the United States[24] and small uncontrolled studies in the past suggesting droperidol causes QT prolongation,[25] a recent Cochrane review of droperidol for psychosis-induced agitation and aggression did not support an association.[26] Cardiovascular arrhythmias did not occur any more frequently with droperidol, compared to placebo, midazolam or olanzapine.[26] In addition, a previous study of over one thousand patients administered droperidol found no association between droperidol and QT prolongation.[18] No arrhythmias occurred in our study, but an ECG was not available in the majority of patients so the QT interval was not assessed. An ECG is not a mandatory requirement

in the ED following the administration of droperidol, and in this prehospital study it was not possible to obtain an ECG in the cohort once they were admitted to the ED.

An important limitation of our study is that the outcomes are not generalisable to other settings, most importantly to inpatient settings and nursing homes. We have shown that a single dose of 5 mg, with a repeat dose in a limited number of cases, results in effective and safe sedation in the elderly. In no way does this translate to repeated doses or dosing for more than 6 h being associated with minimal adverse effects. This approach is reasonable to allow the initial assessment in the acutely medically unwell elderly patient, or isolated crises in dementia patients. This is both important for prehospital services and ED staff.

Another limitation of the study is that there was no control or comparison arm. However, the previous before and after study demonstrated a much higher adverse event rate in adult patients when mainly midazolam was used, compared to droperidol. It is likely that benzodiazepines would be associated with a similarly high rate of adverse effects in the elderly. A larger study may increase our confidence in the adverse event rate of 3%, but this is highly unlikely to be greater than the adverse event rate in adult patients (5 to 13%[4,18,21]) or the adverse event rate with benzodiazepines, based on the 95% confidence intervals of 1 to 7% in this study.

Our study increases our understanding of the safety and effectiveness of droperidol in the acute prehospital environment. It suggests that a lower dose of 5 mg droperidol in

the elderly is appropriate, safe and associated with an acceptable proportion of patients being rapidly sedated.

Table 1. Baseline characteristics

Demographics/Characteristics	**Number[a]**	**%**
Age, median (IQR, range), years	78 (71-86, 65-101)	
Male	78	52
ABD reason[b]		
Acute medical causes[c]	26	16
Alcohol	15	9
Dementia	98	60
Dementia and acute medical causes[c]	9	6
Mental illness	9	6
Self harm	6	4
THC intoxication	1	1
Baseline Sedation Assessment Score		
3	76	47
2	86	53
Nursing home resident	78	52
Police on scene	67	41
Reported use of handcuffs by police	8	5

[a]149 patients presented on 162 occasions

[b]Patients could have more than one reason for their ABD (acute behavioral disturbance)

[c]Includes postictal states, sepsis, pneumonia, stroke, scalp laceration, acute coronary syndrome and hypoglycaemia

Table 2. Adverse events

Age/Sex	Dose[a]	ABD cause	Adverse event(s)	Details/Management
76 Male	5 mg	Dementia	BPs<90 (88/54)	Spontaneously resolved, no IVF
87 Female	10 mg	Minor head injury	BPs<90 (80/46)	Spontaneously resolved, no IVF
79 Female	5 mg	Mental illness	BPs<90 (83/48) O_2 sats<90% (80%)	Resolved with oxygen and 500 ml IVF
82 Male	5 mg	Drug withdrawal	RR<12 (RR 10)	Spontaneously resolved, O_2 sats remained 97% on air
86 Male	5 mg	Postictal	O_2 sats<90% (88%)	Resolved with oxygen

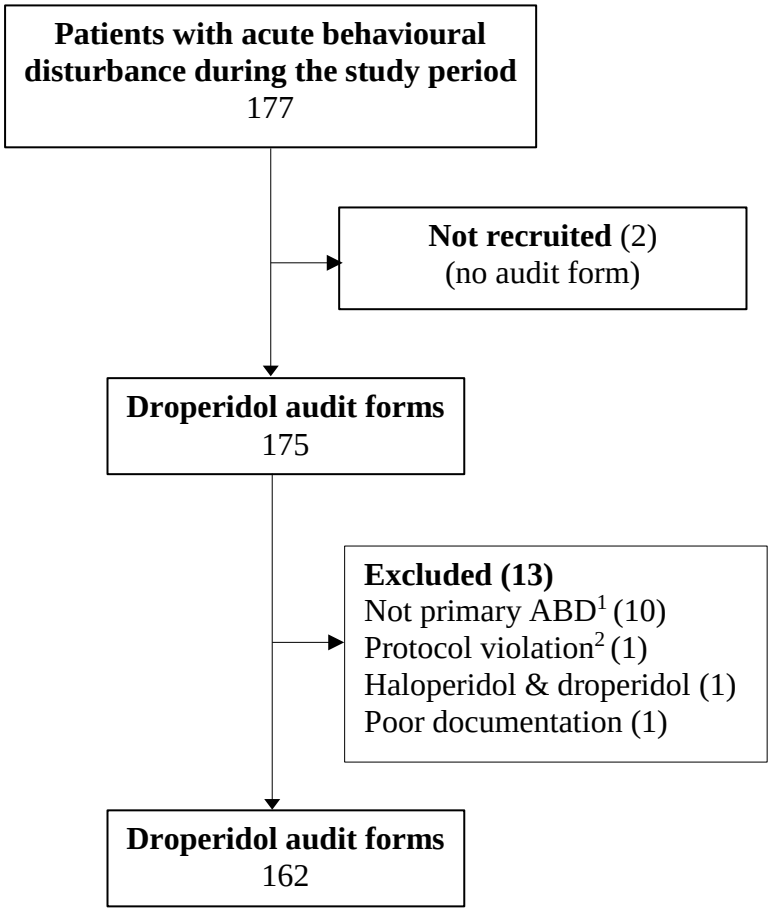
ABD – Acute behavioural disturbance; RR – Respiratory rate; O_2 sats – Oxygen saturation; BPs – Systolic blood pressure; IVF – Intravenous fluid

[a]All single doses of 5mg droperidol except for 10mg (given as two 5mg doses 15 minutes apart)

Figure 1. Sedation Assessment Tool (SAT)[21]

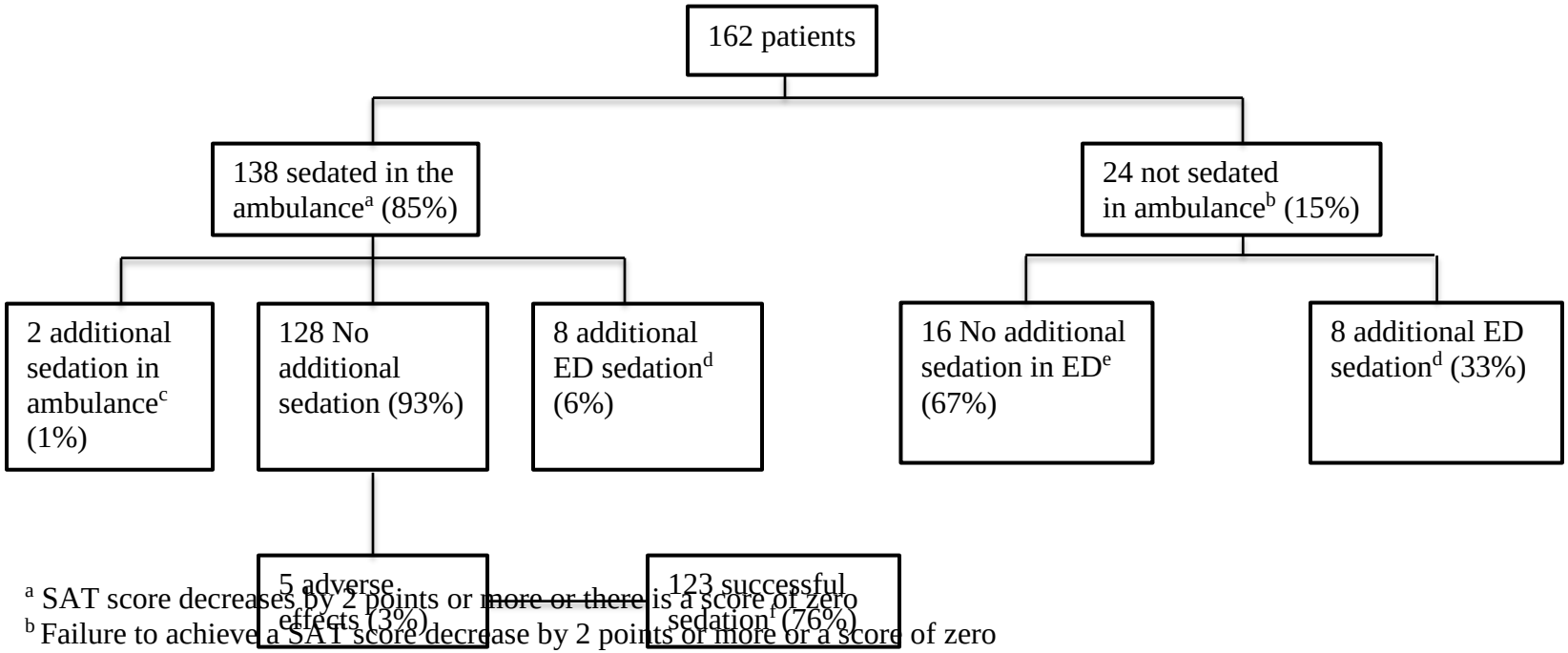
Score	Responsiveness	Speech
+3	Combative, violent, out of control	Continual loud outbursts
+2	Very anxious and agitated	Loud outbursts
+1	Anxious/restless	Normal/Talkative
0	Awake and calm/cooperative	Speaks normally
-1	Asleep but rouses if name is called	Slurring or prominent slowing
-2	Responds to physical stimulation	Few recognizable words
-3	No response to stimulation	Nil

Figure 2. Flow chart of all patients with acute behavioural disturbance during the study period.



[1] Droperidol used in the setting where acute behavioural disturbance (ABD) was not the primary condition e.g. trauma or fractures in combination with other drugs e.g. opiates and/or benzodiazepines.
[2] Intravenous dosing (non protocol doses) of droperidol by medical officer in prehospital setting

Figure 3. Flow chart of all 162 patients based on sedation outcome, additional sedation and adverse events



[a] SAT score decreases by 2 points or more or there is a score of zero
[b] Failure to achieve a SAT score decrease by 2 points or more or a score of zero
[c] Number of patients who received additional sedation during the ambulance journey to hospital
[d] Number of patients who received additional sedation within one hour of arrival to the ED
[e] Settled in ED and did not required any sedation within first one hour of arrival to the ED
[f] Defined as sedated, no adverse effects or requirement for any additional sedation
ED – Emergency Department

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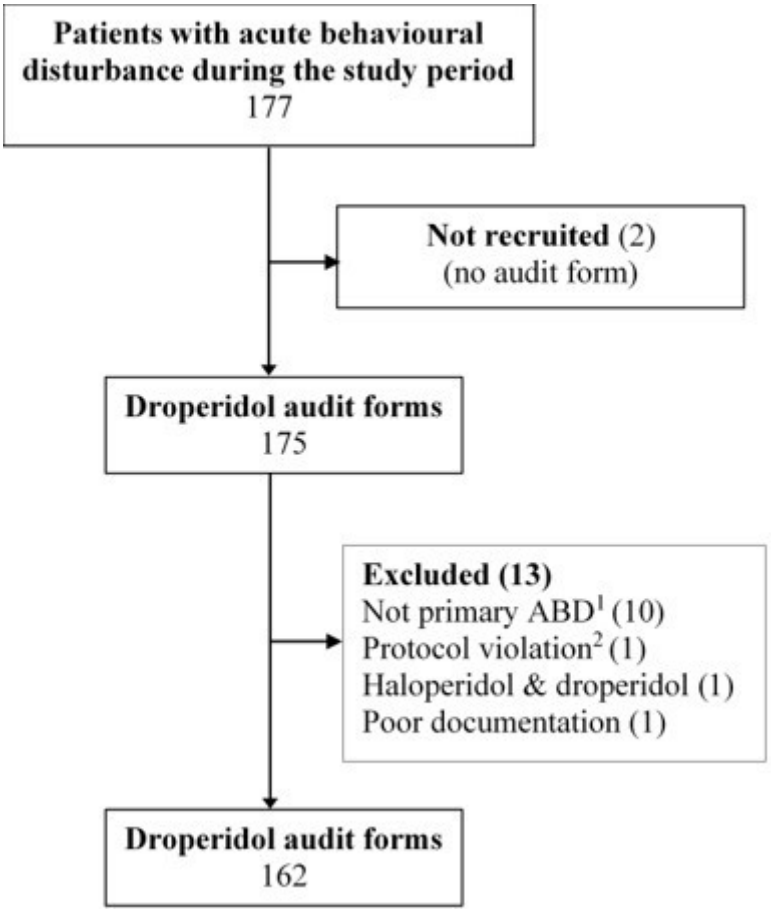

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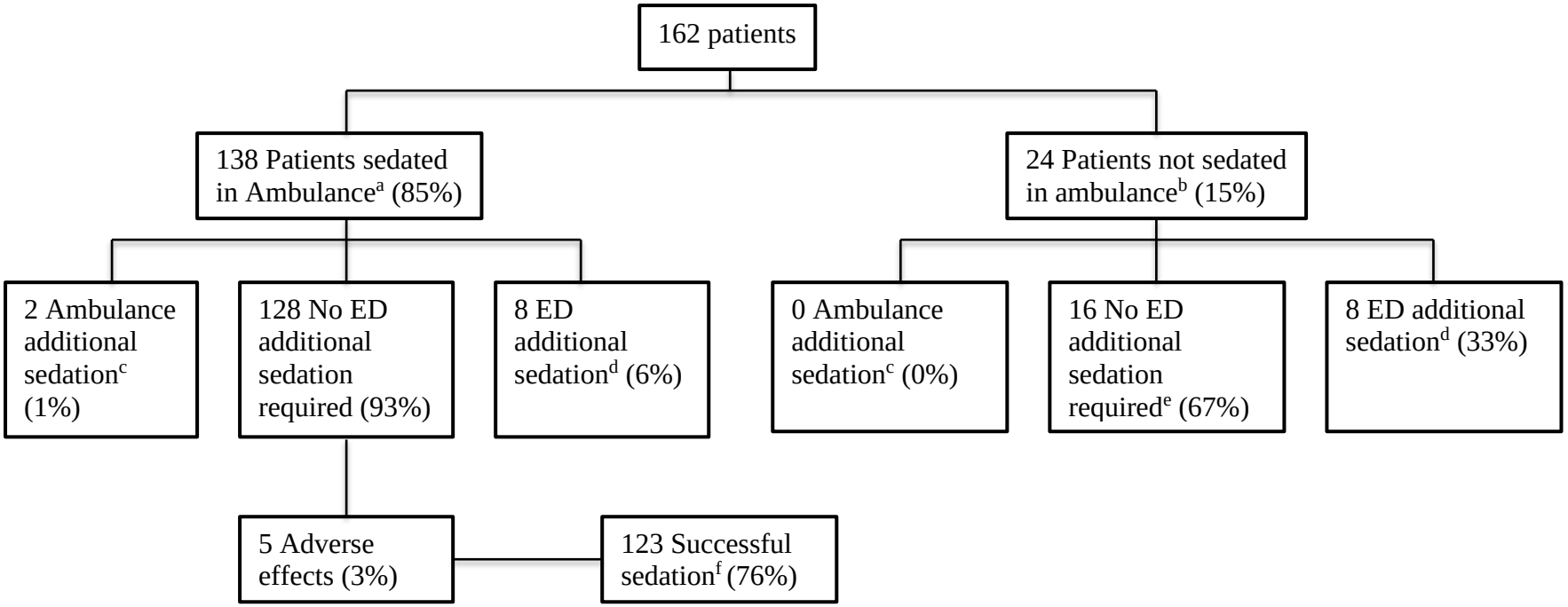
Figure 3. Flow chart of all 162 patients based on sedation outcome, additional sedation and adverse events



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