Sedation of Acute Behavioural Disturbance

A thesis submitted to the

Faculty of Health, School of Medicine and Public Health

University of Newcastle

For the degree of Doctor of Philosophy

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Declaration

Statement of Originality

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968. Unless an embargo has been approved for a determined period.

Signed_____Dated_____

Leonie Anne Calver

Statement of Authorship

I hereby certify that this thesis is in the form of a series of six published papers of which I am the first author and one unpublished publication. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean, attesting to my contribution to the joint publications.

Signed_____ Dated_____

Leonie Anne Calver

Signed_____ Dated_____

Faculty Assistant Dean (Research Training)

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Steve, Thank you. For always insisting that I finish this PhD by giving me the option to give up anytime.

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Sedation of Acute Behavioural Disturbance

The pharmacological treatment of patients with acute behavioural disturbance (ABD) is difficult and there is little consensus of best clinical practise, which is often based on anecdote and historical practice. Multiple doses of medication and combination therapy are common and often leads to higher total doses being administered or rapid development of tolerance making sedation difficult. The choice of agent remains controversial, but recent studies indicate that droperidol is as effective as benzodiazepines. However, the cardiac safety of droperidol has been questioned. The goal of this thesis was to investigate the benefit of using a standardised sedation protocol with a simple assessment tool for reporting agitation and sedation and used a single agent droperidol for sedation. This included studying ABD in a large cohort of emergency department patients, including a subgroup of elderly patients, and acute mental health patients. The principle findings of the thesis were;

1. The sedation-agitation tool is a simple, rapid and useful measure of level of agitation/sedation in patients with ABD.
2. In a pilot study intravenous dexmedetomidine for difficult to sedate patients with ABD was not safe in the emergency department.
3. In a cohort of 46 patients who had continuous holtor monitoring following droperidol for ABD, QT prolongation was detected in four patients and there was little evidence to support droperidol being the cause.
4. Droperidol was effective for sedation in most elderly patients with ABD and adverse effects were uncommon. An initial 5mg dose appears prudent with the expectation that many will require another.
5. In a cohort of over 1000 emergency department patients with ABD, droperidol effectively sedated over 90% with one or two doses, there were no arrhythmias and only 1% had an abnormal QT, supporting the safety of high dose droperidol.
6. In acute mental health patients large initial doses of sedation were used for ABD in over 50%, and additional sedation was rare. Higher dose sedation didn't result in more rapid or effective sedation but was associated with adverse effects.
7. A controlled trial of droperidol versus haloperidol in a psychiatric intensive care unit found both equally effective for sedation of patients with ABD.

LIST OF PUBLICATIONS

- Calver L, Stokes BJ, Isbister GK. Sedation assessment tool to score acute behavioural disturbance in the emergency department. EMERGENCY MEDICINE AUSTRALASIA 23(6):732-740 2011
- Calver L, Isbister GK. Dexmedetomidine in the emergency department: Assessing safety and effectiveness in difficult-to-sedate acute behavioural disturbance. EMERGENCY MEDICINE JOURNAL 29:915-918 2012
- Calver L, Isbister GK. High dose droperidol and QT prolongation: analysis of continuous 12-lead recordings. BRITISH JOURNAL OF CLINICAL PHARMACOLOGY 77(5):880-886 01 May 2014
- Calver L, Isbister GK. Parenteral sedation of elderly patients with acute behavioral disturbance in the ED. AMERICAN JOURNAL OF EMERGENCY MEDICINE 31(6):970-973 01 Jun 2013
- Calver L, Drinkwater V, Isbister GK. A prospective study of high dose sedation for rapid tranquilisation of acute behavioural disturbance in an acute mental health unit. BMC PSYCHIATRY 13:225 Sep 2013
- Calver L, Drinkwater V, Page C, Gupta R, Isbister GK, Droperidol v. haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial. BRITISH JOURNAL OF PSYCHIATRY Nov 2014
- Calver L, Page C, Downes M, Chan B, Kinnear F, Wheatley L, Spain D, Isbister GK. The safety and effectiveness of droperidol for sedation of acute behavioral disturbance in the emergency department. ANNALS of EMERGENCY MEDICINE 2015

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OVERVIEW

Aims

The aim of this thesis is to investigate the management of Acute Behaviour Disturbance (ABD) in different health care settings focussing on the safety of a standardised sedation protocol utilising intramuscular droperidol as a single agent. This requires investigation and monitoring of the effectiveness and the safety of a newly developed protocol in a large and diverse patient population.

Methodology:

Most of the thesis was accomplished by collecting data prospectively from a cohort of patients with ABD in the emergency department (ED) of six hospitals. Within this cohort a number of smaller nested trials to answer specific research questions was conducted. Patients with ABD in the ED given droperidol had clinical details recorded. Data sheets and protocols developed by our study group previously were altered and introduced as part of the hospital's medical records. This ensured accurate data collection for analysis.

Step 1: The effectiveness and safety study: Following the completion of the initial randomised controlled trial of droperidol verses midazolam (DORM) the findings were incorporated into a protocol for the management of ABD . This protocol was introduced into six metropolitan and regional emergency departments and the data collected. The effectiveness of droperidol for the management of ABD was assessed by the time to sedation using a tool to map the level of agitation and the safety of droperidol was assessed by the proportion of adverse events . This included using both standard 12-lead recordings and digital 12-lead holter recordings and regular vital signs monitoring.

Step 2: Sub-sets from the effectiveness and safety study were extracted to investigate difficult to sedate patients and the effects of droperidol on the elderly.

Step 3: To provide findings of investigations of droperidol when used in the mental health care setting.

The broad aim of this project is to have evidence to support the hypothesis that a structured pharmacological protocol using droperidol as the first line sedative medication is a safe and effective approach for ABD and is generalisable to a number of patient populations.

To fulfil these aims, the proposed PhD study program consists of the following 7 main study areas:

1. Evaluation of a scoring system for assessing level of agitation/sedation.
2. A prospective study of difficult to sedate patients using dexmedetomidine.
3. A retrospective analysis of the elderly patients given droperidol for ABD.
4. A retrospective audit of sedation of ABD in the psychiatric intensive care unit.
5. Randomised controlled trial of haloperidol (previous standard care) versus droperidol in the sedation of ABD in Pyschiatric Intensive Care Unit.
6. Investigation of the effects of droperidol on the QT interval using holter recordings.
7. A multi-site prospective observational study of the structured protocol of droperidol use for ABD emergency departments (DORM II).

Outcomes:

Establishing the most effective and safest drug for the sedation of violent and acutely disturbed patients has huge implications for the care of these patients in multiple healthcare settings. This thesis provides findings that intramuscular droperidol is effective for initial sedation, and suggests re-dosing strategies for patients not sedated with an initial dose. The thesis provides comprehensive electrocardiogram data on the cardiac effects of droperidol and the development of an evidence based clinical guideline. The study results enabled a clinical guideline which is evidence-based to be implemented which may be implemented in a varietyof healthcare settings.

Link to Publications

1. **Sedation Assessment Tool to score acute behavioural disturbance in the emergency**
   Calver L, Stokes BJ, Isbister GK. EMERGENCY MEDICINE AUSTRALASIA. 23(6):732-740 2011

After an extensive literature review we found there was not an applicable tool to measure the level of aggression and depth of sedation designed specifically for the emergency department. We needed a tool which is easy to understand, quick to score from a distance and did not involve the participation from the patient. A summary of current tools used are summarized in Table 1 (page 46) of the SAT publication and a description of their features and applicability is stated. To address the short comings of current tools the Sedation Assessment Tool (SAT) was developed to meet our primary and secondary outcomes of the studies to follow. The evaluations of the SAT showed the usefulness and benefits of using a tool to assess the level of aggression and sedation. The original DORM randomized controlled trial (RCT) of Droperidol verses Midazolam for acute behaviour disturbance illustrated the need for a data collection form to meet the needs of the emergency department and the trial's outcome measures. One of the secondary outcomes was effectiveness of sedation, which was measured as the time to sedation. The data sheet used included a scale called Altered Mental Status Score (AMSS) designed by Martel et al and was very effective in gaining the information required for the RCT. The results from the score were used to extend the study into the next phase. However the tool used to score the patient had some features which were not practical and sections of the tool were not being used or recorded. The tool required alteration to make it simpler whilst providing a sound assessment of the level of aggression and depth of sedation. In the paper we provided a plot to compare the changes with the original AMSS over time to ensure the alterations of the tool did not affect prediction of the need to give additional sedation. The necessity for the newly developed tool to be evaluated and published was to ensure a credible tool to score the level of aggression/sedation could be used as outcomes in further studies.. These outcomes required a score to establish the initial level of agitation to identify the need for sedation as well as a score to provide evidence of the effectiveness and time to sedation.. It also provided a sound means to prompt the need for additional sedation which is an important secondary outcome. To ensure the tool was practical for use in the emergency department the time it took for staff to score a patient and the inter-rater reliability were tested and reported favourably. .

2. **Dexmedetomidine in the emergency department: assessing safety and effectiveness in difficult to sedate acute behavioural disturbance**
   Calver L, Isbister GK. EMERGENCY MEDICINE JOURNAL. 29:915-918 2012

   In difficult to sedate patients the need to explore other drugs for the sedation of acute behaviour disturbance was highlighted due to the lack of options which were safe and economical. Difficult to sedate patients were defined as those who failed multiple attempts to sedate them and required alternative strategies to manage them. A small number of patients were identified as difficult to sedate after the administration of droperidol 10mg followed by an additional dose of 10 mg but these patients remained problematic. As a last resort using aneasthetic agents such as propofol were sometimes the only alternative which is associated with considerable risk and cost. The use of dexmedetomidine for sedation has been extensively studied in the settings of intensive care unit and the operating theatre but not explored in the emergency department for the management of acute behavioural disturbance. In an attempt to resolve this dilemma of how to safely sedate these patients in the emergency department a pilot study was extended from the DORM II safety and effectiveness study already established. Dexmedetomidine proved to be initially effective in sedating most of the thirteen patients in the study however the sedation was not sustained and higher doses were required. Dexmedetomidine provides light sedation therefore the noise in the emergency department was problematic and impacted on the effectiveness. The larger doses needed to sustain sedation resulted in an increased rate of complications. Monitoring the effects and titration of the dexmedetomidine was resource burning and required intervention for maintenance of cardio-vascular stability. The study was discontinued on the grounds of an unbalanced risk /benefit ratio. The study provided valuable information on the safety and effectiveness of a drug being specific to particular settings only. This pilot study was important to this thesis because it explored an area of management which is yet to be resolved. Dexmedetomide had the potential to be of benefit in this very high risk cohort and it had previously not been trialled in the emergency department setting for ABD.

3. **High dose droperidol and QT prolongation: analysis of continuous 12-lead recordings**

   Calver L, Isbister GK. BRITISH JOURNAL OF CLINICAL PHARMACOLOGY. 77(5):880-886 01 May 2014

The cardiac risk of droperidol in doses for sedation of acute behavioural disturbance has not been investigated before. After decades of safe use Droperidol was issued a black box warning due to concerns regarding its cardiac safety. This was primarily due to non-peer reviewed spontaneous reports which included flawed evidence and has resulted in a restriction and often withdrawal of its use for the treatment of ABD. The reports that droperidol causes QT prolongation were based on

varied and outdated methods of measurement and did not consider other contributing factors and comorbidities. The controversy over the best QT interval measurement technique, the most accurate rate correction formula, and the likely-hood of developing an arrhythmia after drug administration adds to the confusion of how to assess the risk of some drugs. This study employed expensive and not readily available monitoring equipment which required special training research time to analyse the recordings. It involved using a continuous 12-lead recording to detect any change of the QT interval. Cardiac monitoring was commenced following the minimum dose of droperidol10mg and up to a maximum of 40 mg which is reflects the doses given in current clinical practice. This paper included key information on the co-morbidities and contributing factors that possibly could cause QT prolongation and describes the method of measurement to help determine the associated risk. The findings give insight into the importance of including influences that can change length of the QT interval, and explains the importance of not using the QT measurement as an isolated sign of a drug related effect.

4.Parenteral sedation of elderly patients with acute behavioural disturbance in the emergency department

Calver L, Isbister GK. AMERICAN JOURNAL OF EMERGENCY MEDICINE. 31(6):970-973 01 Jun 2013

Determining the most appropriate drug to manage acute behavioural disturbance in the elderly remains a challenge today. Elderly frequently present to the emergency department in a confused state and can become increasingly distressed in the noisy and unfamiliar environment. If sedation is required treatment is complicated by multiple co-morbidities, poly-pharmacy and impaired organ function that makes it difficult to predict their pharmaco-dynamic response. The damaged reputation of droperidol from the black box warning prompted much uncertainty as to the appropriateness of its use in this vulnerable group. All sedation used for acute behavioural disturbance carries inherent risk and this risk/benefit need to be weighed specifically in the patients over the age of 65 years. New generation antipsychotics have recently been used for this purpose yet have a limited effect. Alternatively midazolam is unpredictable and associated with adverse effects. Therefore a prospective observational study was needed to report the safety and effectiveness of droperidol which provides information of the effect, doses required and frequency of adverse effects. All patients over the age of 65years administered with droperidol for ABD were included in the paper . The proportion of patients requiring re-sedation highlighted the need for rapid sedation only to be used as an initial emergency measure to avoid harm, or enable an examination while a management plan can be implemented. The conclusion of recommending half doses initially with an expectation that another half dose may be required for effective sedation was an important finding of the paper.

5. **A prospective study of high dose sedation for rapid tranquilisation of acute behavioural disturbance in an acute mental health unit.**
Calver L, Drinkwater V, Isbister GK. BMC PSYCHIATRY. 13:6 pages 18 Sep 2013

This paper was designed primarily to test the generalisability of droperidol for ABD. In the mental healthcare setting little consensus exists as to what is the safest and most effective drug and dose to use regardless of numerous clinical practice guidelines. Mental health units have exposure to acute behavioural disturbance on a regular basis. In the past droperidol was a mainstay for the management of ABD but was replaced by haloperidol following the black box warning. The local mental health care institution had an increased interest in droperidol since the regular use in the emergency department and offered an opportunity to investigate a potential role in the treatment of acute behavioural disturbance in the psychiatric acute care setting. The goal to determine the baseline of current practice within the institution prior to commencing a randomized control trial produced interesting findings. The treatment of ABD proved difficult to ascertain as the details and outcomes of the sedation were not well documented. Therefore a form was introduced into the psychiatric intensive care unit to track each episode of acute behaviour disturbance when parenteral sedation was given. The form was not prescriptive and the treatment for ABD remained clinicians choice. The purpose of the form was to familiarize the staff in using a tool to monitor the time to sedation and track any adverse drug related effects and use of additional sedation. This brought about a change in clinical practice which included recording vital signs and documenting the effects of the drugs used. This study found large doses of antipsychotics and benzodiazepines were used both as monotherapy and in combination with no significant gain in the reducing the time to sedation. The doses given require close observation and monitoring of vital signs, which was incorporated into the form which for the purposes of the study, but since have remained standard clinical practice. The results of the study highlighted the need for a structured protocol and questioned the necessity of administering double doses based on no substantial evidence.

6. A randomized controlled trial of haloperidol verses droperidol for sedation of aggressive behaviour in mental health Calver L , Drinkwater V, Page C, Gupta R, Isbister GK, BRITISH JOURNAL OF PSYCHIATRY. 2014

Haloperidol is the most commonly used drug recommended in the current guidelines in the mental healthcare setting for acute behavioural disturbance. With an increased use of droperidol locally the decision of which drug to use in the mentally disturbed patient was controversial. The introduction of a randomised controlled trial into this setting provided the opportunity to test if droperidol was equally effective in patients who had a mental illness as it has proven to be in patients who are

intoxicated or psycho-stimulated in the emergency department setting. The sedation of the undifferentiated ABD is a key factor for the development of a protocol. Haloperidol is reputedly less sedating than droperidol therefore the potential to provide an option which had this advantage was worth exploring. There was also a question as to whether regular use of antipsychotics may have a blunting effect of the sedative qualities of droperidol. The results from the RCT proved neither of these hypothesis were true and both study drugs were equally effective. There was a large proportion of eligible patients who were excluded from the study due to clinicians preference not to include them. These patients had the same baseline demographics and agitation scores as those recruited to the randomised controlled trial and were given different doses and combinations. The outcomes of time to sedation and adverse effects for this group not recruited were equal to the study patients, indicating that alternative drugs and doses to haloperidol or droperidol 10 mg had no benefit. Notably both studies in the mental health care settings report a very small number of patients receiving additional sedation even though a proportion did not a achieve sedation within the time designated. The importance of this paper to the thesis is that it reinforces not only the effectiveness of droperidol for ABD in a different health care setting, it also adds weight to the need for a set protocol with clear guidelines can be effective regardless of the underlying etiology of the ABD.

7.The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioural Disturbance in the Emergency Department

Calver L, Page C, Downes M, Chan B, Kinnear F, Wheatley L, Spain D, Isbister GK.ANNALS of EMERGENCY MEDICINE. 2014

To challenge the criticism and address the concerns of cardiac toxicity of droperidol, a large scale multi-centre safety study was needed. The numbers needed to power this study required a dedicated group of emergency department clinicians to commit to assist in implementing and supervising and promoting the observational study within their departments. This study is the culmination of years of identifying patients to be sedated with droperidol who were then monitored as per the protocol and collecting the faxed data sheets and entering them into the data base. Much of the information entered did not fit within the study criteria due to the dangerous nature of these episodes and reluctance of staff to interact with these difficult to deal with patients by obtaining an ECG. Many data sheets provided information relevant to the effectiveness outcomes of the study only or the cardiac safety of the study only. To get the time to sedation plus an electrocardiograph within the two hour period was a challenge to the staff within a busy emergency department. The total number of patients who were sedated with droperidol during this four year period was remarkable and yet hundreds more received droperidol within the study sites and were not recruited. This is an indication of the difficulties associated with managing this complex patient group. The sample size of over 1000 with ECGs

within the two hour post droperidol time-frame for the safety study and time to sedation recorded for effectiveness was achieved over a four and a half year period. The primary outcome of the study showed a very small proportion of patients who had QT prolongation following droperidol and the small proportion of adverse effects was an important finding . The ability to track these patients and identify other probable attributable causes was gained from previous studies within this thesis. This study provides the important information to add to the already existing body of studies dedicated to management of ABD. To help resolve the uncertainty of which drug, dose, route, requirement additional sedation, expected time of sedation and likelihood of adverse effects improves the care to the patient and removes the chaos and risk associated with acute behavioural disturbance.

List of Additional publications

- Calver L, Downes MA, Isbister GK. Assessment of QT prolongation in high-dose droperidol administration using continuous 12-lead holter recording. 2011 International Congress of the European Association of Poisons Centres and Clinical Toxicologists, Dubrovnik, Croatia, 24 May 2011 - 27 May 2011. Clinical Toxicology. Informa Healthcare, New York, NY. 49: 203-204. 2011 (Conference)
- Calver L, Page BC, Downes M, Chan B, Isbister GK. Droperidol for sedation of acute behavioural disturbance. Society for Academic Emergency Medicine Annual Meeting 2012, Chicago, 09 May 2012 - 12 May 2012. Academic Emergency Medicine. Blackwell Publishing, Hoboken, NJ. 19: S365. 2012 (Conference)
- Calver L, Page BC, Downes M, Chan B, Isbister GK. Safety of droperidol for sedation and acute behavioural disturbance. Society for Academic Emergency Medicine Annual Meeting 2012, Chicago, 09 May 2012 - 12 May 2012. Academic Emergency Medicine. Blackwell Publishing, Hoboken, NJ. 19: S370. 2012 (Conference)
- Calver Leonie Anne. Sedation for Acute Behavioural Disturbance in the Emergency Department intravenous or intramuscular, droperidol or midazolam-The DORM study. ICEM 2010 International Conference on Emergency Medicine. Singapore (pp339) June 2010 (Conference)
- Calver L Intramuscular droperidol vs midazolam for violence and acute behavioural disturbance in the emergency department. Critical Care Conference Hunter New England NSW Health (pp 11)April 2010 (Conference)
- Calver L. Sedation for acute behavioural disturbance in the emergency department; intravenous or intramuscular, droperidol or midazolam-The DORM study. 2nd Improving Delivery of Emergency Care Conference. Gold Coast QL govt. August 2010 (Conference)
- Isbister GK, Calver L. Managing aggressive and violent patients. Australian Prescriber 34(6):National Prescribing Service 2011 (Journal article)

Co-author Statement

Manuscript: Dexmedetomidine in the emergency department: assessing safety and effectiveness in difficult to sedate acute behavioural disturbance. Emergency Medicine Australasia. 23(6):732-740. 2011

Co-author: Geoffrey K Isbister

I, _____, attest that the Research Higher Degree candidate Leonie Calver contributed to the design of the study, the review of the monitoring of the effectiveness, the data collection and contributed to the writing of the paper.

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Manuscript: High dose droperidol and QT prolongation: analysis of continuous 12-lead recordings. British Journal of Clinical Pharmacology. 77(5):880-886 May 2014

Co-author: Geoffrey K Isbister

I, _____, attest that the Research Higher Degree candidate Leonie Calver contributed to the design of the study, the review and analysis of the holter monitor recordings, collation of the data and writing of the paper.

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Manuscript: Sedation Assessment tool to score acute behavioural disturbance in the emergency department. Emergency Medicine Australasia. 23(6):732-740. 2011

Co-author: Barrie Stokes

I, _____, attest that the Research Higher Degree candidate Leonie Calver contributed to the design of the sedation assessment tool, the methods in which to test for effectiveness, the implementation of the tool, the data collection and writing of the paper.

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Co-author Statement

Manuscript: A randomized controlled trial of haloperidol verses droperidol for sedation of aggressive behaviour in acute mental health. British Journal of Psychiatry. Nov 2014.

Co-author: Colin Page

I, _____, attest that the Research Higher Degree candidate Leonie Calver contributed to the design of the study, implementation of the trial into the department, the distribution and supply of the study drugs, design and review of the data sheets, data input, collation, analysis and writing of the paper.

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Co-author Statement

Manuscript: Droperidol v. haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial. British Journal of Psychiatry.Nov 2014

Co-author: Geoffrey K Isbister

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Manuscript: A randomized controlled trial of haloperidol verses droperidol for sedation of aggressive behaviour in acute mental health. British Journal of Psychiatry. Nov, 2014

Co-author: Rahul Gupta

I, _____, attest that the Research Higher Degree candidate Leonie Calver contributed to the design of the study, implementation of the trial into the department, the distribution and supply of the study drugs, design and review of the data sheets, data input and writing of the paper.

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Co-author: Vincent Drinkwater

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Manuscript: Parenteral sedation of elderly patients with acute behavioural disturbance in the ED. American Journal of Emergency Medicine. 31(6):970-973. June 2013

Co-author: Geoffrey K Isbister

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Co-author Statement

Manuscript: A multi-site prospective safety study of droperidol for acute behavioural disturbance in the emergency department

Co-author: Betty Chan

I, _____, attest that the Research Higher Degree candidate Leonie Calver contributed to the design of the study, the recruitment of the sites, ethics applications, implementation of the study, data collection and input and writing of the paper.

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Co-author Statement

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Co-author: David Spain

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Co-author: Fran Kinnear

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Manuscript: The safety and effectiveness of droperidol for acute behavioural disturbance in the emergency department 2015

Co-author: Geoffrey K Isbister

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Manuscript: A prospective study of high dose sedation for rapid tranquilisation of acute behavioural disturbance in an acute mental health care unit. BMC Psychiatry 13:225 Sep 2013

Co-author: Geoffrey K Isbister

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