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REPORTS OF ORIGINAL INVESTIGATIONS

Analgesic, sedative, antipsychotic, and neuromuscular blocker use in Canadian intensive care units: a prospective, multicentre, observational study

Utilisation des analgésiques, sédatifs, antipsychotiques et bloqueurs neuromusculaires dans les unités de soins intensifs canadiennes: étude observationnelle prospective, multicentrique

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Abstract

Purpose *Our aim was to describe analgo-sedation and antipsychotic and neuromuscular blocking drug (NMBD) use in critically ill patients, management strategies, and variables associated with these practice patterns.*

Methods *This prospective observational study in 51 intensive care units (ICUs) included all patients who underwent invasive mechanical ventilation (MV) over a two-week period during 2008-2009.*

Results *We included 712 patients representing 3,620 patient-days. Median MV duration was 3.0 days (interquartile range 2-6). During MV, 92% of patients received analgo-sedation, 32% an adjunct agent (e.g., acetaminophen), 18% NMBDs, and 10% antipsychotics. Opioids were used more frequently than benzodiazepines or propofol (84.8% vs 62.2% vs 10.1% patients, respectively, $P < 0.0001$). Independent predictors of opioid and benzodiazepine use were a longer MV duration, assessment scales, physical restraints, and university-affiliated hospital. Although more than 50% of ICUs reported that assessment tools, protocols, and daily sedation interruption (DSI) were available for use, application was modest: sedation scale 53.0%, pain scale 19.1%, delirium scale 5.2%, protocol 25.0%, DSI 42.1%. Accidental device removal occurred in 4.6% of patients, with 75.8% of events during DSI. Daily sedation interruption was associated with protocol use, physical restraints, university-affiliated hospital, and short-duration MV. Variables associated with protocol use included*

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assessment scales, longer MV duration, lack of physical restraints, and admission to a community hospital.

Conclusion *Nearly all MV patients received analgo-sedation. Opioids were used more often than sedatives despite infrequent use of pain scales. Few patients received antipsychotic therapy, but physical restraint was common. Protocol use was poor compared to DSI. Duration of MV predicted the use of either.*

Résumé

Objectif *Notre objectif était de décrire l'utilisation des médicaments antalgiques-sédatifs et bloqueurs neuromusculaires (NMBD) chez des patients dans un état critique, les stratégies de prise en charge et les variables associées aux pratiques habituelles.*

Méthodes *Cette étude observationnelle prospective menée dans 51 unités de soins intensifs (USI) a inclus tous les patients ayant bénéficié d'une ventilation mécanique (VM) invasive sur une période de deux semaines au cours des années 2008-2009.*

Résultats *Nous avons inclus 712 patients représentant 3 620 jours-patients. La durée médiane de VM a été de 3,0 jours (intervalle interquartile: 2-6). Au cours de la VM, 92 % des patients ont reçu une analgésie-sédation, 32 % ont reçu un médicament d'appoint (par exemple: acétaminophène), 18 % des NMBD, et 10 % des antipsychotiques. Les morphiniques ont été utilisés plus souvent que les benzodiazépines ou le propofol (respectivement, 84,8 % contre 62,2 % et 10,1 % des patients, $P < 0,0001$). Les facteurs prédictifs indépendants de l'utilisation des morphiniques et des benzodiazépines étaient une plus longue durée de VM, les échelles d'évaluation, la contention physique et l'affiliation universitaire de l'hôpital. Bien que plus de 50 % des USI aient indiqué la disponibilité d'outils d'évaluation, de protocoles et d'interruptions quotidiennes de la sédation (DSI), leur utilisation pratique a été modeste: échelle de sédation 53,0 %, échelle de douleur 19,1 %, échelle d'évaluation du délire 5,2%, protocole 25,0 %, DSI 42,1 %. Un retrait accidentel du dispositif est survenu chez 4,6 % des patients, 75,8 % de ces événements survenant au cours d'une DSI. L'interruption quotidienne de la sédation était associée à l'utilisation d'un protocole, une contention physique, l'affiliation universitaire de l'hôpital et la courte durée de la VM. Les variables associées à l'utilisation d'un protocole incluaient les échelles d'évaluation, une plus longue durée de VM, l'absence de contrainte physique et l'hospitalisation dans un hôpital général.*

Conclusion *Presque tous les patients sous VM ont reçu une analgésie-sédation. Les morphiniques ont été utilisés plus souvent que les sédatifs en dépit de l'utilisation rare des échelles de douleur. Peu de patients ont reçu un traitement antipsychotique, mais les dispositifs de contention étaient courants. L'utilisation d'un protocole a été faible par rapport à la DSI. La durée de la VM a prédit l'utilisation des deux.*

Opioids, sedatives, antipsychotics, and neuromuscular blocking drugs (NMBDs) are used in the intensive care unit (ICU) to minimize patient discomfort, manage agitation, and facilitate tolerance of invasive monitoring and life-support technology.[1-3] Many of these medications have pharmacokinetic or pharmacodynamic limitations that pose unique challenges for critically ill patients. Important patient outcomes, including duration of mechanical ventilation (MV), length of stay, and delirium, may be influenced by drug choice, dosage, and sedation minimization strategies such as protocols and daily sedation interruption (DSI).[4-10]

International practice guidelines recommend prioritizing analgesia, use of light sedation, assessment of pain, sedation, and delirium with validated scales. They also recommend limiting NMBDs to patients refractory to deep sedation.[1,11,12] Surveys of perceived clinician practices report variable adoption of these strategies, with international variation.[3,13-17] Studies documenting utilization of these strategies also suggest a gap between recommendations and practice.[15-19] Previous studies have provided few details regarding dose, route, or method of drug administration, use of adjuncts such as non-opioid analgesics and antipsychotics, or use of sedation minimization strategies. Such details are essential for guiding future research and planning knowledge translation and educational interventions.

We conducted a multicenter prospective observational study to describe utilization of analgo-sedation, antipsychotics, and NMBDs for critically ill, mechanically ventilated adults in Canadian ICUs. Our

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specific objectives were to describe the following: 1) drugs used, including dose and route of administration; and 2) strategies to manage these medications. These data were to be used to 3) compare sedation practices based on the type of hospital site (i.e., community *vs* university-affiliated) and duration of mechanical ventilation (i.e., $\leq$ 48 hr, $>$ 48 hr to $<$ seven days, $\geq$ seven days); and 4) examine patient- and site-level variables associated with the use of opioids, benzodiazepines, sedation protocols, and DSI.

Methods

We conducted this prospective observational study in 51 Canadian hospitals between February 2008 and April 2009. Sites were identified from provincial registries, hospital pharmacy organizations, and our previous survey contact list.[13] We targeted a diverse sample of ICUs to acquire data reflective of university-affiliated and community hospitals across Canada. Pharmacists providing clinical services collected data using a standardized form for consecutive patients $\geq$ 16 yr of age who underwent invasive MV over a two-week study period. Based on internal auditing from three ICUs, we estimated that ten or more admissions per site would meet inclusion criteria during a two-week period and provide our target sample size of $>$ 500 patients. Data were collected from the initiation of MV until 1) extubation, 2) 24 hr after tracheostomy, 3) death, or 4) a maximum of 30 days. Research Ethics Board approval was obtained at each participating institution. The need for informed consent was waived.

Measurements

We collected the following institutional data: hospital type (university-affiliated or community); ICU type (e.g., medical/surgical); physician model (open or closed, with the closed model defined as patient care directed by the ICU team); number of hospital, ICU, and ventilation beds; availability of protocols, guidelines, or standard order sets; and assessment scales for management of sedation, pain, agitation, and delirium. We collected data on ICU pharmacist services including the staffing ratio (a dedicated pharmacist was defined as $\geq$ 0.5 full-time equivalent) and hours of clinical services.

For each patient, we collected the following data prospectively: age, sex, Acute Physiology and Chronic Health Evaluation (APACHE II) score, admitting diagnosis, admission source (e.g., emergency room), past medical and medication history, organ dysfunction while in the ICU, and MV duration. Tobacco consumption was defined as daily use. Alcohol consumption was defined as two or more drinks daily or $\geq$ 26 ounces weekly of 40% alcohol. Daily, we collected data on analgesic, sedative, antipsychotic, and NMBD use (including dose, administration route, frequency, total daily dose) and clinical utilization of protocols, guidelines, or standard order sets for drug titration; DSI (including drug interrupted, reason for interruption, re-initiation dose); and assessment scales (e.g., SAS).[20] We collected data on adjunctive agents (e.g., zopiclone), physical restraint (PR) usage, nurse-to-patient ratio, and accidental device removal.

Statistical analysis

To obtain reliable estimates of regression coefficients for multivariable logistic regression, the number of parameters in the model should not exceed the number of observations in the smaller of the two outcome categories divided by 10.[21] Across 51 ICUs, we anticipated that enrolment of $>$ 500 patients would be adequate for examining a reasonable number of independent variable associations.

We report means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on the data distribution for continuous data, and proportions for categorical data. We categorized ICUs as to whether they were located in university-affiliated or community hospitals and patients by MV duration ($\leq$ 48 hr/$>$ 48 hr to $<$ seven days/$\geq$ seven days). We compared continuous data using analysis of variance or the Kruskal-Wallis test in the case of non-normally distributed data followed by pair-wise group comparisons using *t*-tests or Mann-Whitney U-tests, respectively. Categorical variables were compared using the χ^2 test or Fisher's exact test for cases in which expected cell sizes were less than five. We expressed benzodiazepines in midazolam equivalents, opioids in morphine equivalents, and antipsychotics in haloperidol equivalents.[A]

We used univariable and multivariable logistic regressions, adjusting for correlation of observations from the same site, to evaluate factors associated with a patient ever receiving 1) benzodiazepines, 2) opioids, 3) a sedation protocol, and/or 4) DSI. Independent variables were selected based on literature[13-19,22,23] and author consensus. All models included age, APACHE II, admission type, duration of MV, use of PR, hospital type, and availability of a pharmacist on rounds. Models for opioids and benzodiazepines also included a history of sedative or opioid use prior to hospital admission, a history of smoking or alcohol use, and use of a sedation scale. For the sedation protocol and DSI models, we also included daily benzodiazepine and opioid dose and the ICU nurse-to-patient ratio. The DSI model also included use of a sedation protocol, and the sedation protocol model included use of an

[A] A. *Lexi-comp, Inc. (Lexi-Drugs)*. Lexi-Comp, Inc.; December 1, 2012.

Table 1 Site demographics

Characteristics	All sites $n = 51$	University-affiliated $n = 23$	Community $n = 28$	P value*
Institution size				
> 400 beds	20 (39.2)	14 (60.9)	6 (21.4)	0.004
> 1 ICU	21 (41.2)	15 (65.2)	6 (21.4)	0.002
Study ICU				
Closed ICU	41 (80.4)	20 (87.0)	21 (75.0)	0.48
ICU beds	14.9	18.5 (8.2)	10.1 (5.8)	<0.001
Proportion of ventilated ICU patients				0.005
< 25%	6 (11.8)	1 (4.3)	5 (17.9)	
25-50%	16 (31.3)	5 (21.7)	11 (39.3)	
51-75%	13 (25.5)	4 (17.4)	9 (32.1)	
≥ 76%	16 (31.3)	13 (56.5)	3 (10.7)	
ICU type				0.56
Mixed medical/surgical	43 (84.3)	20 (87.0)	23 (82.1)	
Medical	4 (7.8)	1 (4.4)	3 (10.7)	
Surgical/trauma	1 (2.0)	0 (0)	1 (3.6)	
Cardiovascular	3 (5.9)	2 (8.7)	1 (3.6)	
Pharmacist support[a]				
Dedicated ICU pharmacist[b]	44 (86.3)	20 (87.0)	24 (85.7)	1.00
Attends daily rounds	38 (74.5)	21 (91.3)	17 (60.7)	0.02
Available after rounds	36 (70.6)	20 (87.0)	16 (57.1)	0.03
Standardized strategies[c]				
Sedation assessment tool	33 (64.7)	14 (60.9)	19 (67.9)	0.60
Pain assessment tool	24 (47.1)	11 (47.8)	13 (46.4)	0.93
Delirium assessment tool	7 (13.7)	5 (21.7)	2 (7.1)	0.22
Daily sedation interruption	23 (45.1)	9 (39.1)	14 (50.0)	0.44
Sedative-analgesic protocol	28 (54.9)	12 (52.2)	16 (57.1)	0.72
NMBD protocol	8 (15.7)	2 (8.7)	6 (21.4)	0.27

Data presented as: n (%) or mean (standard deviation) unless indicated. n = number of patients; ICU = intensive care unit; NMBD = neuromuscular blocking drug

* Comparison of university affiliated and community hospital using χ^2 or Fisher's exact test if any expected count was < 5

[a] Categories are not mutually exclusive

[b] ≥ 0.5 Full-time equivalent

[c] Standardized strategies were guidelines, prescriptive order sets, protocols, and assessment tools that were available for use for all patients in the ICU

assessment scale. Prior to multivariable modeling, the set of predictors was assessed for multi-collinearity using tolerance statistics. A tolerance value < 0.4 was used to indicate the presence of multi-collinearity. In such cases, only one member of a correlated set (the more clinically meaningful variable) would be retained for the model. The goodness-of-fit of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). All tests were two-tailed, with $P < 0.05$ considered significant.

Results

Institutional characteristics

Most ICUs cared for mixed populations (43, 84.3%), had a closed intensivist staffing model (41, 80.4%), and had dedicated pharmacist coverage (44, 86.3%) (Table 1). Compared with community ICUs, university-affiliated ICUs had more beds and more MV capability. They were also more likely to have a pharmacist attend rounds and provide clinical services after rounds (Table 1). Of 33 (64.7%) ICUs using sedation scales, 11 (33.3%) used the Sedation-Agitation Scale,[20] ten (30.3%) the Ramsay scale,[24] nine (27.3%) the Richmond Agitation Sedation Scale,[25] and three (9.1%) other scales. In the 24 ICUs (47.1%) using pain assessment tools, 14 (70.0%) used the visual analogue scale (VAS), five (25.0%) used the numeric rating scale (NRS),[26] and one (5.0%) assessed verbal or facial expression. No ICU reported use of a validated behavioural pain assessment scale. Seven ICUs assessed for delirium: four (57.1%) used the CAM-ICU,[27] two (28.5%) the Intensive Care Delirium Screening Checklist,[28] and one (14.2%) the NEECHAM Confusion Scale.[29]

Table 2 Patient demographics

Characteristics	All patients $n = 712$	MV $\leq$ 48 hr $n = 164$	MV $>$ 48 hr to $<$ 7 days $n = 372$	MV $\geq$ 7 days $n = 176$	P value*
Age (yr)	60.8 (16.7)	61.7 (15.6)	60.0 (17.5)	61.8 (15.9)	0.39
Male	443 (62.2)	104 (63.4)	235 (63.2)	104 (59.1)	0.61
APACHE II	19.6 (7.9)	19.7 (8.0)	19.7 (8.0)	19.2 (7.5)	0.78
Admission source					
Emergency department	205 (28.8)	40 (24.4)	117 (31.5)	48 (27.3)	0.22
Hospital ward	128 (18.0)	31 (18.9)	70 (18.8)	27 (15.3)	0.58
Operating room	293 (41.2)	77 (47.0)	141 (37.9)	75 (42.6)	0.13
ICU in another hospital	32 (4.5)	3 (1.8)	17 (4.6)	12 (6.8)	0.08
Admission type					
Medical	280 (39.3)	60 (36.6)	149 (40.1)	71 (40.3)	0.71
Surgical	248 (34.8)	50 (30.5)	134 (36.0)	64 (36.4)	0.41
Cardiac	85 (11.9)	35 (21.3)	36 (9.7)	14 (8.0)	0.0001
Trauma	35 (4.9)	14 (8.5)	13 (3.5)	8 (4.6)	0.04
Other[a]	64 (9.0)	5 (3.1)	40 (10.8)	19 (10.8)	0.01
Past medical history					
Renal disease[b]	62 (8.7)	12 (7.3)	36 (9.7)	14 (8.0)	0.61
Liver disease[c]	32 (4.5)	3 (1.8)	19 (5.1)	10 (5.7)	0.16
NYHA class III-IV	39 (5.5)	8 (4.9)	22 (5.9)	9 (5.1)	0.86
Neurological disease[d]	92 (12.9)	24 (14.6)	41 (11.0)	27 (15.3)	0.28
Psychiatric disease[e]	98 (13.8)	25 (15.2)	43 (11.6)	30 (17.0)	0.18
Medication and substance history					
Sedatives[f]	227 (31.9)	60 (36.6)	119 (32.0)	48 (27.3)	0.18
Opioids	140 (19.7)	47 (28.7)	62 (16.7)	31 (17.6)	0.004
Antidepressants	93 (13.1)	19 (11.6)	45 (12.1)	29 (16.5)	0.30
Antipsychotics	56 (7.9)	14 (8.5)	26 (7.0)	16 (9.1)	0.65
Tobacco[g]	125 (17.6)	34 (20.7)	66 (17.7)	25 (14.2)	0.28
Alcohol[h]	181 (25.4)	40 (24.4)	91 (24.5)	50 (28.4)	0.58
Recreational drug use	33 (4.6)	8 (4.9)	19 (5.1)	6 (3.4)	0.67

Data presented as n (%) or mean (standard deviation) unless indicated. MV = mechanical ventilation; APACHE = Acute Physiology and Chronic Health Evaluation, ICU = intensive care unit; NYHA = New York Heart Association. *P-value applies to comparison across groups categorized by duration of MV using analysis of variance for continuous variables and χ^2 analyses for proportions

[a] Other = burn, neurological, neurosurgical, obstetrical, transplant

[b] Renal disease = serum creatinine $>$ 180 $\mu mol \cdot L^{-1}$, end-stage renal disease, or dialysis

[c] Liver disease = Child Pugh Grade C or higher, or known esophageal varices

[d] Stroke, seizure, dementia, Parkinsons disease

[e] Bipolar, schizophrenia, depression

[f] Includes benzodiazepine and non-benzodiazepine sedatives (e.g., chloral hydrate, trazodone, zopiclone)

[g] Daily use

[h] $\geq$ Two drinks daily or $\geq$ 26 oz weekly of 40% alcohol

Patients

We included 712 patients in the study, representing 3,620 patient-days (Table 2). Altogether, 497 (69.8%) were from university-affiliated hospitals. The median MV duration was 3.0 days (IQR 2-6), although 53 (7.4%) patients were still being ventilated at day 30. Physical restraints were applied to 374 patients (52.5%) on 1,569 (43.3%) patient-days. The mean (SD) duration of use was 4.1 (4.0) days. Accidental device removal occurred in 33 (4.6%) patients, including endotracheal tubes (21 events, 18 patients), feeding tubes (12 events, ten patients), and intravenous catheters (seven events, five patients). Among the accidental removals, 25 of 33 patients (75.8%)

Table 3 Opioid, sedative, antipsychotic, and neuromuscular blocking drug administration

	All patients	MV ≤ 48 hr $n = 164$	MV > 48 hr/ < 7 days $n = 372$	MV ≥ 7 days $n = 176$	*P* value*
Analgo-sedation route of administration, *n* (%)					
Intravenous infusion ± intravenous bolus	595 (83.6)	125 (76.2)	305 (82.0)	165 (93.8)	<.0001
% Patient days		84 (55)	68 (40)	64 (35)	<.0001
Intravenous bolus only	61 (8.6)	21 (3.0)	37 (9.9)	3 (1.7)	<.0001
% Patient days		2 (15)	12 (21)	21 (25)	<.0001
Enteral therapy[a]	152 (21.3)	3 (1.8)	74 (19.9)	75 (42.6)	<.0001
% Patient days		15 (37)	9 (20)	21 (31)	<.0001
Topical therapy[a]	5 (0.7)	1 (0.6)	2 (0.5)	1 (0.6)	0.9946
% Patient days		5 (22)	0 (3)	0 (1)	<.0001
Morphine[a,b], *n* (%)	604 (84.8)	133 (81.1)	308 (82.8)	163 (92.6)	0.0036
% Patient days		82 (40)	66 (38)	69 (33)	<.0001
Daily dose (mg)		23.2 (37.1)	62.9 (77.1)	106.0 (113.4)	<.0001
Monotherapy	188 (26.4)	93 (56.7)	86 (23.1)	9 (5.1)	<.0001
Midazolam[a,c], *n* (%)	443 (62.2)	47 (28.7)	234 (62.9)	162 (92.1)	<.0001
% Patient days		29 (45)	44 (40)	61 (32)	<.0001
Daily dose (mg)		13.2 (25.1)	36.0 (67.3)	62.6 (119.9)	0.0006
Monotherapy	43 (6.0)	10 (6.1)	24 (6.5)	9 (5.1)	0.83
Propofol, *n* (%)	72 (10.1)	9 (5.5)	37 (10.0)	26 (14.8)	0.01
% Patient days		5 (23)	7 (22)	5 (16)	0.71
Daily dose (mg)		668 (638)	1532 (1709)	1476 (1529)	0.32
Monotherapy	7 (1.0)	3 (1.8)	3 (0.8)	1 (0.6)	0.44
Any antipsychotic[d], *n* (%)	68 (9.6)	1 (0.6)	22 (5.9)	45 (25.6)	<.0001
% Patient days		1 (8)	3 (14)	11 (23)	<.0001
Daily dose (mg)		9.8 (11.8)	8.2 (7.0)	7.5 (8.0)	
Any NMBD[e], *n* (%)	130 (18.3)	11 (6.7)	58 (15.6)	61 (34.7)	<.0001
% Patient days		7 (25)	7 (18)	5 (11)	0.66

Data presented as *n* (%) or mean (standard deviation) for the case of percentage of patient days

* *P*-value applies to comparison across groups using analysis of variance for continuous variables and χ^2 analyses for proportions. MV = mechanical ventilation; *n* = number; NMBD = neuromuscular blocking drug

[a] Any use; either alone or in combination with intravenous therapies

[b] Opioids presented in morphine equivalents: 10 mg morphine = 2 mg hydromorphone = 0.1 mg fentanyl

[c] Benzodiazepine presented in midazolam equivalents: 1 mg midazolam = 0.5 mg lorazepam

[d] Antipsychotic = aripiprazole, chlorpromazine, clozapine, haloperidol, loxapine, methotrimeprazine, olanzapine, prochlorperazine, quetiapine, risperidone, ziprasidone. Dose presented in haloperidol equivalents

[e] Neuromuscular blocking drug = atracurium, cisatracurium, pancuronium, rocuronium, vecuronium, succinylcholine

experienced the event during DSI (27 events: 12 endotracheal tubes, eight feeding tubes, seven intravenous catheters).

Sedative and opioid administration

The data for medication administration based on MV duration are shown in Table 3. Most patients (656, 92.1%) received an opioid or sedative at least once, which is equivalent to a mean (SD) of 90% (23%) patient-days. Opioids were used more often than sedatives ($P < 0.0001$) and for a greater percentage of patient-days ($P < 0.0001$). Fentanyl (54.3%) was the most common opioid, followed by morphine (35.0%) and hydromorphone (7.7%). Benzodiazepines comprised the most commonly used sedative: midazolam (72.3%), lorazepam (21.2%), clonazepam (3.5%), diazepam (2.4%). For patients who underwent MV with seven or more days, opioids and benzodiazepines were used equally (92.6% *vs* 92.1%, $P = 0.82$). For patients ventilated fewer than seven days, an opioid was used more frequently than a benzodiazepine: for ≤ 48 hr of MV, 81.1% opioid *vs* 28.7% benzodiazepine ($P < 0.0001$); for > 48 hr to < seven days of MV, 82.8% opioid *vs* 62.9% benzodiazepine

Table 4 Variables associated with benzodiazepine and opioid use ($n = 711$)

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Outcome: Benzodiazepine exposure		
Age (by 10 yr)	1.05 (0.96 to 1.14)	1.02 (0.91 to 1.15)
APACHE II score (continuous)	1.00 (0.98 to 1.02)	1.01 (0.99 to 1.04)
Patient type		
Surgical	1.02 (0.72 to 1.43)	0.96 (0.61 to 1.51)
Other*	0.74 (0.50 to 1.08)	0.85 (0.52 to 1.41)
Medical	1	1
History of sedative or opioid use	0.81 (0.59 to 1.12)	0.87 (0.57 to 1.33)
History of smoking	1.00 (0.68 to 1.47)	1.21 (0.72 to 2.02)
History of alcohol use	1.07 (0.76 to 1.50)	0.82 (0.52 to 1.31)
Duration of MV (by 24 hr)	1.58 (1.46 to 1.71)	1.49 (1.37 to 1.61)
University hospital	0.54 (0.39 to 0.75)	0.65 (0.42 to 0.99)
Dedicated ICU pharmacist	0.78 (0.48 to 1.29)	0.87 (0.46 to 1.65)
Sedation scale	3.69 (2.70 to 5.03)	1.81 (1.22 to 2.69))
Physical restraints	3.75 (2.75 to 5.14)	1.64 (1.11 to 2.42)
Outcome: Opioid exposure		
Age (by 10 yr)	0.96 (0.88 to 1.06)	0.94 (0.84 to 1.06)
APACHE II score (continuous)	1.00 (0.98 to 1.02)	1.02 (0.99 to 1.04)
Patient type		
Surgical	1.04 (0.73 to 1.47)	1.22 (0.74 to 2.02)
Other*	0.99 (0.67 to 1.46)	0.83 (0.52 to 1.32)
Medical	1	1
History of sedative or opioid use	0.60 (0.44 to 0.83)	0.64 (0.42 to 0.96)
History of smoking	1.04 (0.70 to 1.54)	1.26 (0.76 to 2.10)
History of alcohol use	1.15 (0.81 to1.62)	1.02 (0.64 to 1.62)
Duration of MV (by 24 hr)	1.70 (1.53 to 1.88)	1.57 (1.41 to 1.74)
University hospital	0.94 (0.68 to 1.31)	1.62 (1.04 to 2.54)
Dedicated ICU pharmacist	0.98 (0.59 to 1.63)	0.99 (0.51 to 1.93)
Pain scale	4.81 (3.44 to 6.73)	2.40(1.59 to 3.61)
Physical restraints	4.63 (3.35 to 6.39)	2.33(1.58 to 3.44)

OR = odds ratio; CI = confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation; MV = mechanical ventilation; ICU = intensive care unit

* Defined as any patient type other than medical or surgical

($P < 0.0001$). Variables associated with a patient ever receiving a benzodiazepine or an opioid are shown in Table 4. Longer duration of MV, use of a sedation scale, and PR were associated with ever receiving a benzodiazepine. Longer duration of MV, treatment at a university hospital, use of a pain scale, and PR were associated with ever receiving an opioid.

An antipsychotic was administered to 68 patients (9.6%), for a mean (SD) duration of 4.0 (3.1) days. Nearly all (67, 98.5%) were ventilated > 48 hr. Haloperidol, intravenously or enterally, was used more frequently (33.1%) than quetiapine (21.8%), olanzapine (20.1%), risperidone (10.6%), or methotrimeprazine (7.9%). At least one dose of an adjunct agent was administered to 228 (32.0%) patients. The adjunct agents included acetaminophen (176, 24.7%), zopiclone (90, 12.6%), gabapentin or pregabalin (46, 6.4%), non-steroidal anti-inflammatory drugs (23, 6.5%), trazodone (22, 3.1%), clonidine (18, 2.5%), epidural local anesthetic (17, 2.4%), and antidepressants (nine, 1.3%). Neuromuscular blocking drugs were administered to 130 patients (18.3%) – primarily those ventilated > 48 hr (119, 91.5%) – for a mean duration of 1.9 (SD 1.8) days. Neuromuscular blocking drugs administered were rocuronium (67.7%), cisatracurium (14.2%), succinylcholine (13.0%), and pancuronium (5.1%) in a single intravenous bolus dose for the majority of patients (71, 54.6%). Of 58 patients who received more than one NMBD dose, 44 (75.9%) were given intermittent doses and 14 (24.1%) continuous infusions with or without a bolus dose. Only 17 of 58 patients (29.3%) underwent monitoring with peripheral nerve stimulation.

Drug administration strategies

Validated sedation assessment scales were used more commonly than pain scales and for more days. The proportion of patients managed with a sedation or pain scale increased with the duration of MV (Table 5). Delirium was rarely assessed, but when it was assessed it was in patients with > 48 hr of MV. Sedative infusions were stopped at least once in 300 (42.1%) patients. Fewer patients had opioid infusions stopped (172, 24.2%). The main reason for stopping the infusions was to prepare the patient for extubation or for neurological assessment – not as part of a planned daily interruption protocol. Only 22.0% of all sedative and opioid infusions were stopped and resumed as part of such a protocol.

Predictors for using a sedation protocol were non-medical or non-surgical diagnosis (e.g., cardiac, neurological), longer duration of MV, use of an assessment scale, treatment in a community hospital, and PR use (Table 6). Variables associated with DSI were treatment at a university hospital, use of an assessment protocol, higher daily opioid dose, use of PR, and short-duration MV (Table 6).

Table 5 Sedation, pain, and delirium assessment and administration strategies*

	All patients	MV ≤ 48 hr $n = 164$	MV > 48 hr/< 7 days $n = 372$	MV ≥ 7 days $n = 176$	*P* value*
Use of sedation scale	377 (53.0)	63 (38.4)	197 (52.7)	117 (66.5)	<.0001
Days	1.9 (3.7)	0.1 (0.26)	1.0 (1.3)	5.3 (5.8)	<.0001
Use of pain scale	136 (19.1)	16 (9.8)	81 (21.8)	39 (22.2)	0.002
Days	0.84 (2.9)	0.1 (0.3)	0.6 (1.4)	2.0 (5.2)	<.0001
Use of delirium scale	37 (5.2)	1 (0.6)	15 (4.0)	21 (11.9)	<.0001
Days	0.2 (1.1)	0.0 (0.1)	0.1 (0.3)	0.6 (2.2)	<.0001
Analgo-sedation titrated with protocol	178 (25.0)	64 (39.0)	69 (18.6)	45 (25.6)	<.0001
Days	0.6 (2.2)	0.1 (0.2)	0.3 (0.8)	1.9 (3.9)	<.0001
Daily sedation interruption	300 (42.1)	6 (3.7)	163 (43.8)	131 (74.4)	<.0001
Days	0.8 (1.4)	0.0 (0.2)	0.6 (0.8)	2.0 (2.2)	<.0001
Daily analgesia interruption	172 (24.2)	2 (1.2)	82 (22.0)	88 (50.0)	<.0001
Days	0.4 (0.9)	0.0 (0.1)	0.3 (0.6)	1.1 (1.5)	<.0001
Reason for daily interruption					
Protocol	35 (4.9)	0 (0)	13 (3.5)	22 (12.5)	<.0001
Days	0.1 (0.7)	0 (0)	0.1 (0.3)	0.4 (1.2)	<.0001
Neurological assessment	130 (18.3)	2 (1.2)	46 (12.4)	82 (46.6)	<.0001
Days	0.4 (1.0)	0.0 (0.1)	0.2 (0.4)	1.1 (1.6)	<.0001
Hemodynamic instability	3 (0.4)	0 (0)	0 (0)	3 (1.7)	0.010
Days	0.0 (0.1)	0 (0)	0 (0)	0 (0.1)	0.017
Extubation	154 (21.6)	3 (1.8)	102 (27.4)	49 (27.8)	<.0001
Days	0.3 (0.6)	0.0 (0.1)	0.3 (0.5)	0.4 (0.7)	<.0001

Data presented as *n* (%) or mean (standard deviation). MV = mechanical ventilation

* *P*-value applies to comparison across groups

Discussion

Analgesics, sedatives, antipsychotics, and neuromuscular blocking drugs are part of the complex management of mechanically ventilated, critically ill patients. As gaps exist between published evidence, self-reported survey results, and clinical practice,[15,18] it is important to document actual, not perceived, practices given the link between these medications and adverse consequences. This study provides data on the use of these medications and management strategies in a diverse sample of mechanically ventilated patients. It highlights gaps between recommendations and clinical practice. We found that nearly all patients received analgesics and sedatives during MV, primarily as continuous infusions. Despite professional society recommendations,[1] use of continuous infusions without targeted sedation strategies, such as a protocol, was frequent. More patients received opioids than sedatives, potentially reflecting recommendations to treat pain first – although pain scales were rarely used.

Overall, 92% of patients received opioids and sedatives at least once during MV. Previous international surveys indicate tremendous variation in the percentage of patients receiving sedatives, the medications selected, and the method of administration.[3] In an observational study of 1,381 mechanically ventilated patients in 44 French ICUs, Payen *et al.*[16] identified high utilization of opioids and sedatives (~ 80%) during the first week of MV, but other observational studies have reported much lower utilization.[2,17-19,30] Surprisingly, we found that opioids and sedatives were most commonly administered via continuous infusion with infrequent intermittent bolus doses or enteral therapy. This use of continuous infusion is similar to that reported by Payen *et al.*[16] but was used more frequently than reported in other studies.[15,17,A,30] In our 2002 physician survey of perceived practice, respondents reported equal use of continuous infusions and intermittent boluses.[13] It is unclear if physicians underestimated their use of continuous infusions, or if our findings reflect an actual change in Canadian practice over time. We also found that propofol was seldom used, in contrast to other observational studies,[15,16,22] even for patients ventilated < 48 hr, which may relate to concerns about perceived costs and adverse effects.

In terms of drug selection, opioids were administered more often than sedatives. Interestingly, nearly 50% of patients ventilated < 48 hr were managed with an opioid alone. This is greater than in other studies[2,15] and suggests use of an 'analgesia-first' based strategy, which has been recommended in guidelines.[1,11,12] Patients cared for based

Table 6 Variables associated with sedation administration strategies at a patient level ($n = 711$)

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Outcome: Sedation protocol		
Age (by 10 yr)	1.01 (0.89 to 1.13)	1.01 (0.88 to 1.16)
APACHE II (continuous)	1.00 (0.97 to 1.02)	1.02 (0.99 to 1.05)
Patient type		
Surgical	1.24 (0.78 to 1.99)	0.95 (0.55 to 1.65)
Other*	1.43 (0.86 to 2.37)	2.00 (1.11 to 3.63)
Medical	1	1
Duration of MV (by 24 hr)	1.07 (1.04 to 1.10)	1.05 (1.01 to 1.09)
Sedation–analgesia scale	5.73 (3.62 to 9.07)	5.92 (3.50 to 10.03)
Daily benzodiazepine^ dose (5 mg increments)	1.01 (0.99 to 1.02)	1.00 (0.98 to 1.02)
Daily opioid+ dose (5 mg increments)	1.01 (1.00 to 1.02)	1.00 (0.99 to 1.02)
Proportion of days with 1:1 nursing	0.99 (0.99 to 1.00)	0.99 (0.99 to 1.00)
Physical restraints	1.19 (0.80 to 1.77)	0.57 (0.35 to 0.93)
University hospital	0.33 (0.22 to 0.49)	0.30 (0.19 to 0.49)
Dedicated ICU pharmacist	0.63 (0.35 to 1.15)	0.57 (0.28 to 1.18)
Outcome: Daily sedation interruption		
Age (by 10 yr)	0.96 (0.88 to 1.05)	0.99 (0.88 to 1.10)
APACHE II (continuous)	0.99 (0.98 to 1.01)	1.00 (0.97 to 1.02)
Patient type		
Surgical	1.06 (0.75 to 1.50)	0.95 (0.62 to 1.45)
Other*	1.24 (0.85 to 1.82)	1.22 (0.76 to 1.96)
Medical	1	1
Duration of MV (by 24 hr)	1.26 (1.20 to 1.32)	0.46 (0.31 to 0.66)
Sedation-analgesia protocol	3.61 (2.64 to 4.92)	2.20 (1.51 to 3.21)
Daily benzodiazepine^ dose (5 mg increments)	1.01 (1.00 to 1.03)	0.97 (0.95 to 1.00)
Daily opioid+ dose (5 mg increments)	1.03 (1.02 to 1.04)	1.01 (1.00 to 1.03)
Proportion of days with 1:1 nursing	1.00 (0.99 to 1.00)	1.00 (1.00 to 1.01)
Physical restraints	3.24 (2.37 to 4.42)	1.84 (1.27 to 2.67)
University hospital	1.12 (0.81 to 1.55)	1.54 (1.04 to 2.28)
Dedicated ICU pharmacist	0.89 (0.54 to 1.47)	0.77 (0.43 to 1.40)

OR = odds ratio; CI = confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation; MV = mechanical ventilation; ICU = intensive care unit

* Defined as any patient type other than medical or surgical

^ Benzodiazepines presented in midazolam equivalents: 1 mg midazolam = 0.5 mg lorazepam

+ Opioids presented in morphine equivalents: 10 mg morphine = 2 mg hydromorphone = 0.1 mg fentanyl

on a pain scale, subjected to PR, having a longer MV duration, and admitted to a university hospital were more likely to receive opiates. We found that 32% of patients also received adjunctive therapy, primarily oral analgesics that were likely added for opioid-sparing effects. Payen *et al.* reported similar non-opioid analgesic use during a one-week study period.[16] No other studies have reported use of non-opioid analgesics.

Nearly two-thirds of patients received a benzodiazepine during MV, which is similar to or greater use than in other studies.[15,16] We also found that the percentage of patients managed with benzodiazepines varied greatly depending on MV duration, with those ventilated more than seven days more likely to receive such treatment. Benzodiazepine use was also associated with use of a sedation scale and PR. Antipsychotics were administered to only 10% of patients. Delirium scales were rarely used despite the association of delirium with adverse clinical consequences.[31] The low utilization of antipsychotics could reflect clinicians' reluctance to use antipsychotics without a delirium assessment or because of the limited safety and outcome data for narcotic usage.[1,32] Agitation may have been managed with PR. Use of antipsychotics and delirium assessment scales was similar to use reported in our 2002 survey[13] and in reports from U.S. and Australian/New Zealand investigators.[15,30]

Pain and sedation assessment tools appear to reduce analgesic and sedative drug use, MV duration, and length of ICU stay.[33,34] Professional society guidelines stress the importance of pain and sedation assessment in adults and support the use of protocols targeting light sedation or DSI.[1,11,12] Assessment scales, protocols, and DSI were available and recommended for use in approximately 50% of ICUs. However, clinical use of these strategies was low and similar to that in our 2002 self-report survey.[13] The most striking discrepancy was noted with pain scales: Nearly 50% of ICUs had pain scales available for use, but they were used to manage therapy in only 19% of patients. Because the use of pain scales was less than expected, we were unable to explore their efficacy for controlling pain. Standardized sedation–analgesia protocols were available for use in 54% of ICUs but were applied to only 25% of patients. In contrast, we did not note a difference between DSI protocol availability and actual application. In a U.S. study, 66% of 85 ICUs reported that DSI was used, but the actual use was in only 36% of patients.[15] Similarly, seven of 23 ICUs (30.4%) in Australia and New Zealand reported using DSI, yet sedation was interrupted in only 10% of patients.[30]

We identified that MV duration was a predictor of both use of a sedation–analgesia protocol and DSI. As we hypothesized, patients with longer MV duration were more likely to be managed with a sedation protocol, probably reflecting an attempt to avoid drug accumulation in patients

with an expected longer stay. In contrast, we observed that DSI use was associated with short-duration MV: DSI potentially reduced the duration of MV by enabling recognition of extubation readiness. The use of a sedation–analgesia assessment scale was associated with use of either a protocol or DSI, suggesting that sedation strategies may have been clustered for some patients. Interestingly, sedation protocol usage was associated with less PR use than when DSI was used, suggesting that these strategies are associated with different depths of sedation and agitation. In contrast, a multicenter randomized trial comparing a sedation protocol alone with combined use of a sedation protocol and DSI in 430 patients found similar high rates of restraint application in the two groups.[35]

Strengths of our study include the prospective study design, large number of community and university-affiliated ICUs, a national scope, detailed patient and center-level data, and a diverse patient mix. One study limitation was voluntary center participation, raising the possibility that study results may not reflect practice in all Canadian ICUs. Another limitation is our conversion of all drugs to a single drug within the class, which allowed inferential analyses but precluded consideration of various pharmacokinetics (e.g., half-life, metabolism, elimination) within the class that could influence outcomes, such as MV duration. Finally, this study was carried out before dexmedetomidine was available in Canada.

In conclusion, the results of our large prospective observational study provide insight into actual sedation practices for mechanically ventilated patients in Canadian ICUs. We found that nearly all patients were managed with continuous-infusion opioids and sedatives. We also found that actual practice was different from what we expected because the available clinical tools – such as protocols and assessment scales – were not necessarily applied at the bedside. We believe that greater efforts should be directed towards facilitating optimal use of these medications, including a barriers assessment, analysis of facilitators, and establishing quality improvement initiatives. National collaborative and accreditation bodies could play key roles in achieving these goals.

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Conflicts of interest None declared.

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