ORIGINAL RESEARCH **Open Access**

Characterization of hospitalized patients who received naloxone while receiving opioids with or without gabapentinoids

Payal H. Desai, PharmD, BCCCP[1]; Olesya Taylor, PharmD, BCPS[2]; Kunal J. Shah, PharmD[3]; Kirk E. Evoy, PharmD, BCACP, BC-ADM, CTTS[4]; Alyssa M. Peckham, PharmD, BCPP[5]

Abstract

Introduction: Gabapentin and pregabalin (gabapentinoids) can be given with opioids for opioid-sparing and adjuvant analgesic effects. In the context of certain comorbidities and high dosages, coadministration of these agents can lead to respiratory depression or oversedation, necessitating naloxone administration.

Methods: A retrospective chart review from January 2015 to December 2017 was conducted to include patients who received naloxone and opioids with or without gabapentinoids. Exclusion criteria included pregnancy or having received naloxone in the emergency department, intensive care, or pediatrics units. The primary outcome was to characterize differences between groups regarding comorbidities, history of renal or hepatic dysfunction, history of SUD, opioid tolerance, initiation and dose appropriateness of gabapentinoids, and dose intensity of gabapentinoids and opioids. Secondary outcomes were concomitant CNS depressant use and naloxone episodes for documented respiratory depression.

Results: Of 126 patients who met inclusion criteria, 36 received opioids and gabapentinoids (gabapentinoid group) and 90 received opioids alone (nongabapentinoid group). There were 136 naloxone episodes between the 2 groups. More than 50% of the naloxone episodes in the gabapentinoid group involved opioids of at least 90 oral morphine mg equivalents. Respiratory depression accounted for 39% and 15.8% of the naloxone episodes in the gabapentinoid and nongabapentinoid groups, respectively.

Discussion: There may be increased naloxone episodes among patients receiving opioids and gabapentinoids. Future studies are needed to evaluate the incremental risk of respiratory depression and oversedation as it pertains to concomitant medication administration and patient-specific factors.

Keywords: naloxone, opioids, gabapentinoids, gabapentin, pregabalin, respiratory depression, oversedation

[1] (Corresponding author) Clinical Pharmacist, Cardiac Surgery, Morristown Medical Center, Atlantic Health System, Morristown, New Jersey, pdesai811@gmail.com, ORCID: https://orcid.org/0000-0001-8525-7865; [2] Staff Pharmacist, Department of Pharmacy, Morristown Medical Center, Atlantic Health System, Morristown, New Jersey; Medical Science Liaison, Immuno-Inflammation, GSK, Research Triangle Park, North Carolina, ORCID: https://orcid.org/0000-0001-5808-5535; [3] Assistant Manager, Clinical Pharmacy, Morristown Medical Center, Atlantic Health System, Morristown, New Jersey, ORCID: https://orcid.org/0000-0003-4364-4992; [4] Clinical Assistant Professor, The University of Texas at Austin College of Pharmacy, Austin, Texas; Ambulatory Care Clinical Pharmacist, University Health System, San Antonio, Texas, ORCID: https://orcid.org/0000-0003-0913-7145; [5] Assistant Clinical Professor, Bouvé College of Health Sciences, School of Pharmacy, Northeastern University, Boston, Massachusetts; Advanced Practice Clinical Pharma-

cist, Massachusetts General Hospital, Boston, Massachusetts, ORCID: https://orcid.org/0000-0002-9638-7005

Introduction

Gabapentinoids, gabapentin and pregabalin, are γ-aminobutyric acid (GABA) analogues that bind to the α-2-δ subunit of voltage-gated calcium channels.[1,2] These agents are widely prescribed and are considered first-line for

neuropathic pain.[2,3] However, clinicians use gabapentinoids for various pain conditions to reduce opioid requirements.[4] Although traditionally thought to have favorable safety profiles, recent data have associated gabapentinoids with potential misuse, particularly among those with opioid use disorder.[5] It has been hypothesized that gabapentinoids may be misused to potentiate opioid effects.[5,6]

In excess, opioids may cause oversedation and respiratory depression, which may be compounded by concomitant gabapentinoids.[5,7] Gabapentin exposure in those using opioids was associated with a 60% increase in opioid-related death, especially when gabapentin was used at higher doses.[7] Pregabalin similarly increased this risk.[8] Although gabapentinoids do not act on opioid receptors and the exact mechanism for this increased risk is unknown, additive CNS depression or pharmacokinetic/pharmacodynamic drug interactions may be responsible.

Naloxone, an opioid antagonist that displaces opioids at receptor sites, can reverse opioid-induced respiratory depression.[9] Opioid use with concomitant CNS depressants is a risk factor associated with requiring naloxone rescue therapy. Additional risk factors include tobacco use and comorbid renal, cardiac, or respiratory disease.[10] In a study[11] of hospitalized patients who received naloxone, gabapentin was the most commonly coadministered CNS depressant with opioids. Another study[12] evaluated patients who received gabapentinoids, opioids, and naloxone versus patients who received opioids and naloxone and found no significant difference in respiratory depression between groups. However, the small sample size limited the generalizability of these findings. Given these limited, conflicting data, this study assessed differences in patient and medication characteristics among those receiving concomitant opioid and gabapentinoid therapy versus opioid therapy alone in a hospital setting.

Methods

This was a single-center, retrospective chart review at a large academic medical center. Patients admitted to a general medical floor who were ages ≥18 years, had received opioids with or without gabapentinoids, and were administered naloxone from January 1, 2015 to December 31, 2017 were included. Exclusion criteria included pregnancy or having received naloxone in the emergency department, intensive care, or pediatric units. Emergency department and intensive care units were excluded given the higher likelihood of fluctuations in hemodynamics and renal function in critical illness. Two groups were evaluated: patients who received gabapentinoids, opioids, and naloxone (ie, gabapentinoid group), and patients who received opioids and naloxone without gabapentinoids (ie, nongabapentinoid group). This study was deemed exempt by the IRB.

Study Outcomes and Definitions

The primary outcome was to characterize patients in each group. Specific characteristics evaluated included demographics and comorbidities that increase opioid-related respiratory depression risk, such as age ≥65 years, COPD, obstructive sleep apnea, and heart failure with reduced or preserved ejection fraction, in addition to obesity (eg, BMI ≥30 kg/m²), history of renal dysfunction (eg, chronic kidney disease stage 3-5 or receiving hemodialysis or peritoneal dialysis), history of hepatic dysfunction (eg, hepatitis or cirrhosis [Child-Pugh class C or worse]), history of SUD, and surgery the day prior to naloxone administration. Other characteristics reviewed included temporal initiation of the gabapentinoid (ie, continued from home or started during hospitalization), opioid tolerance (eg, ≥60 oral morphine milligram equivalents [MME] per day for ≥7 days), appropriate gabapentinoid dose (ie, not exceeding recommended dose based on creatinine clearance), cumulative gabapentinoid dose (ie, total dose during 48 hours preceding naloxone episode), and cumulative opioid dose (ie, total dose during 24 hours preceding naloxone episode).[13] Characteristics were classified as patient specific or naloxone episode specific. Patient-specific characteristics were those that did not change if a patient had multiple naloxone episodes, including high-risk comorbid conditions, history of renal or hepatic dysfunction, history of SUD, opioid tolerance, and initiation of gabapentinoids. The remaining characteristics were categorized as naloxone episode–specific characteristics, given that a single patient could have multiple naloxone episodes.

Secondary outcomes included concomitant CNS depressant use and naloxone episodes for documented respiratory depression. Respiratory depression was defined as either ≤8 breaths/min, an oxygen saturation <92%, or a decrease of >5% from baseline in patients with a baseline oxygen saturation of <90%.[11,12] Naloxone administration for respiratory depression or oversedation was considered to be 2 separate indications. However, naloxone episodes for documented oversedation could not be evaluated given the lack of use of a validated scale to assess sedation in nonintubated patients at our institution. The specific CNS depressants reviewed included benzodiazepines, muscle relaxants, first-generation antihistamines, z-hypnotics, antipsychotics, and sedating antidepressants (defined in this study as those with histamine 1-receptor antagonist effects; Table 1).

Gabapentinoid daily dose cutoffs were extrapolated from previous studies and categorized as low (gabapentin <900 mg; pregabalin <150 mg), moderate (gabapentin

TABLE 1: Specific agents assessed in secondary outcome regarding concomitant medications

Drug Class	Medications Included
Benzodiazepines	Lorazepam, clonazepam, alprazolam, diazepam, midazolam, chlordiazepoxide
Muscle relaxants	Carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, tizanidine, baclofen
First-generation antihistamines	Diphenhydramine, chlorpheniramine, hydroxyzine, promethazine
Z-hypnotics	Zolpidem, zaleplon, zopiclone
Antipsychotics	Chlorpromazine, clozapine, olanzapine, quetiapine, thoridazine
Sedating antidepressants	Amitriptyline, doxepin, maprotiline, trimipramine, nefazodone, trazodone, mirtazapine

900-1799 mg; pregabalin 150-299 mg), or high (gabapentin $\geq$1800 mg; pregabalin $\geq$300 mg).[7,12] Opioid daily dose was categorized as low (<50 MME), moderate (50-89 MME), or high ($\geq$90 MME). These cutoffs follow Centers for Disease Control and Prevention guidelines for prescribing opioids for chronic pain, which state that doses above 90 MME/d should be avoided if possible because of overdose risk.[14] The cumulative opioid amount given in the 24 hours preceding a naloxone episode was calculated by converting each opioid to oral MME using the Practical Pain Management opioid conversion calculator and adding them together.[15]

Opioid tolerance and gabapentinoid initiation were determined from preadmission medication lists. Renal function was quantified by creatinine clearance (mL/min) using the Cockcroft-Gault equation and calculated with the patient's highest serum creatinine in 48 hours prior to a naloxone episode. Vital signs, including oxygen saturation and respiratory rate, 1 hour before and after a naloxone episode as well as doses and timing of naloxone administrations were collected. A naloxone episode was defined as administration of naloxone with <2 hours between naloxone doses.[12] If $\geq$2 hours had elapsed between doses, these administrations were considered separate episodes.

Statistical Analysis

Baseline characteristics were analyzed using χ^2 test or Fisher exact test for categoric data, as appropriate, and Student t test or Mann-Whitney U test for continuous data, as appropriate. The primary and secondary outcomes were analyzed using descriptive statistics.

Results

In total, 126 patients met inclusion criteria, with 36 patients in the gabapentinoid group and 90 patients in the

TABLE 2: Baseline characteristics of the study

Variable	Gabapentinoid n = 36	Nongabapentinoid n = 90	P Value
Sex, No. (%)			.329
Male	17 (47.2)	34 (37.8)	
Female	19 (52.8)	56 (62.2)	
Age, median (IQR), y	65.5 (57.5-76.25)	73.5 (57.25-81)	.159
Race, No. (%)			
White	31 (86.1)	73 (81.1)	.609
Other	3 (8.3)	6 (6.7)	.714
Black	1 (2.8)	10 (11.1)	.176
Asian	0 (0)	1 (1.1)	>.999
Unknown	1 (2.8)	0 (0)	.286
Weight, median (IQR), kg	75.6 (57.5-91.16)	74.8 (61.9-88)	.928
BMI, median (IQR), kg/m²	26.5 (20.7-30.9)	26.1 (22.4-32)	.473
Naloxone episodes, No.	41	95	

nongabapentinoid group. Baseline characteristics were similar between groups (Table 2). There were 136 total naloxone episodes identified: 41 and 95 in the gabapentinoid and nongabapentinoid groups, respectively. The most common high-risk demographics/comorbidities seen in the gabapentinoid and nongabapentinoid groups, respectively, were age $\geq$65 years (52.8% and 67.8%), obesity (27.8% and 30.0%), history of renal dysfunction (25.0% and 17.8%), and COPD (19.4% and 13.3%; Table 3). Hepatic dysfunction was less prevalent among the gabapentinoid and nongabapentinoid groups (2.8% and 0%, respectively). A higher percentage of patients in the gabapentinoid group had an SUD history compared with patients in the nongabapentinoid group (11.1% and 4.4%, respectively). Opioid-naive patients accounted for most patients who received naloxone in both groups. For 11 patients, opioid tolerance was unknown because of an incomplete preadmission medication list.

A total of 67% of gabapentinoid group patients continued gabapentinoid therapy from home upon admission, and 90.2% were receiving an appropriate gabapentinoid dose (Table 4). The cumulative opioid dose in the 24 hours preceding a naloxone episode was high ($\geq$90 MME) for more than half of the episodes in the gabapentinoid group and for about one third of episodes in the nongabapentinoid group (n = 21, 51.2% and n = 34, 35.8%, respectively). For 1 patient in the nongabapentinoid group, the cumulative dose was indeterminate because of additional opioid exposure during the intraoperative period.

TABLE 3: Patient-specific characteristics of the study, No. (%)

Characteristic	Gabapentinoid n = 36	Nongabapentinoid n = 90
High-risk comorbid condition		
Age ≥65 y	19 (52.8)	61 (67.8)
Obesity	10 (27.8)	27 (30)
COPD	7 (19.4)	12 (13.3)
HFrEF or HFpEF	6 (16.7)	11 (12.2)
OSA	1 (2.8)	8 (8.9)
History of renal dysfunction	9 (25)	16 (17.8)
History of hepatic dysfunction	1 (2.8)	0 (0)
History of SUD	4 (11.1)	4 (4.4)
Opioid tolerance		
Naive	21 (58.3)	73 (81.1)
Tolerant	10 (27.8)	11 (12.2)
Unknown[a]	5 (13.9)	6 (6.7)
Initiation of gabapentinoid		
Continued from home	24 (66.7)	
Initiated inpatient	12 (33.3)	

HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; OSA = obstructive sleep apnea.

[a]A total of 11 patients did not have complete documentation of dose and frequency of opioids taken at home.

Patients met criteria for respiratory depression in 39% and 15.8% of naloxone episodes in the gabapentinoid and nongabapentinoid groups, respectively (Figure). In about one quarter of these episodes for each group, criteria for respiratory depression were indeterminate because of

TABLE 4: Naloxone episode–specific characteristics, No. (%)

Characteristic	Gabapentinoid n = 41	Nongabapentinoid n = 95
Appropriate gabapentinoid dose	37 (90.2)	
Opioid dose intensity		
<50 MME[a]	13 (31.7)	45 (47.4)
50-89 MME	7 (17.1)	15 (15.7)
≥90 MME	21 (51.2)	34 (35.8)
Unknown[b]	0 (0)	1 (1.1)
Gabapentinoid dose intensity		
Low	14 (34.1)	
Moderate	16 (39)	
High	11 (26.8)	

MME = morphine milligram equivalents.

[a]For 5 patients in the nongabapentinoid group, cumulative opioid amount at 48 hours was used to determine opioid intensity.

[b]For 1 patient in the nongabapentinoid group, dose intensity was unknown because the patient received opioids in surgery only.

incomplete documentation of vital signs before and after naloxone administration. The most common concomitant CNS depressants administered in both groups were benzodiazepines (gabapentinoids, 43.9%; nongabapentinoids, 45.3%). In the gabapentinoid group this was followed by sedating antidepressants (24.4%), first-generation antihistamines (17.0%), antipsychotics (9.8%), muscle relaxants (9.8%), and hypnotics (5.3%). In the nongabapentinoid group, benzodiazepines were followed by muscle relaxants (9.5%), first-generation antihistamines (9.5%), sedating antidepressants (8.4%), antipsychotics (4.2%), and hypnotics (3.2%).
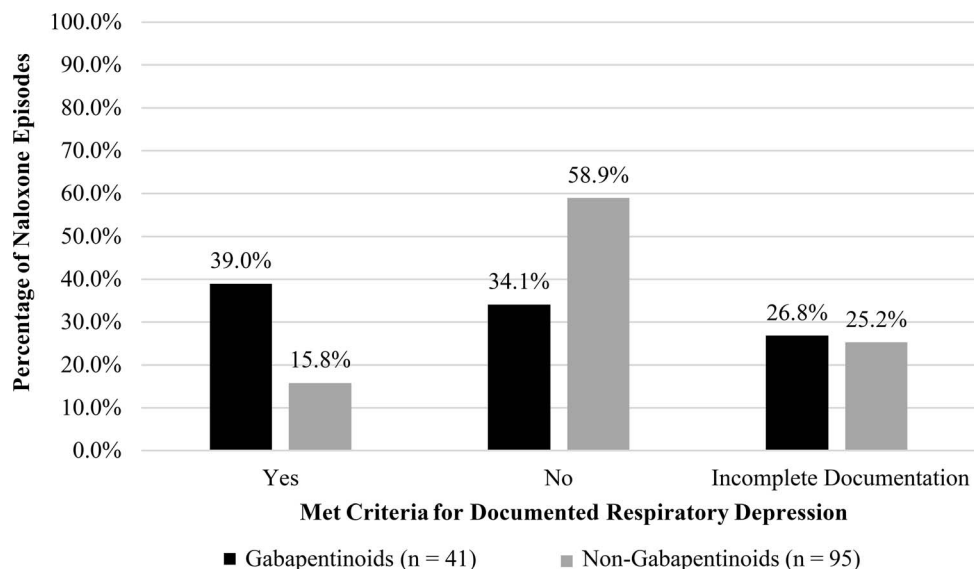

FIGURE: Naloxone episodes for documented respiratory depression

Discussion

Among those receiving naloxone in the gabapentinoid group, the most common patient characteristic was age ≥65 years, which opposes the Beers Criteria recommendation to avoid concomitant opioids and gabapentinoids in this population.[16] Similar precautions should be extended to patients with obesity, history of renal dysfunction, and COPD, because these were common characteristics seen in this group.

With these findings in mind, prescribing of high-dose opioids to those with gabapentinoids or other CNS depressants, or to those considered opioid naive, should be done cautiously because these factors were identified in most of the naloxone episodes in this study. To mitigate the risk of respiratory depression and oversedation in such patients, clinicians may consider several approaches for judicious prescribing. A conservative dosing approach for opioids should be considered, especially if the patient is opioid naive. Pain management should be optimized using a multimodal approach with both nonpharmacologic (ie, heat and cold compress, rest, or relaxation) and nonopioid pharmacologic interventions other than gabapentinoids (ie, nonsteroidal anti-inflammatories, acetaminophen, or lidocaine) for an opioid-sparing effect. Hospitals may also consider additional monitoring for high-risk patients who are prescribed concomitant opioids and CNS depressants by routine use of continuous pulse oximetry, frequent vitals, and sedation scores to help prevent adverse effects.

Although the risk of respiratory depression with opioids is well known, related concerns with gabapentinoids are becoming more recognized. In December 2019, the FDA added a warning to gabapentinoid prescribing information regarding respiratory depression risk in patients using gabapentinoids alone or concomitantly with opioids, especially those who have respiratory conditions or are elderly.[17] They also recommended clinical trials be conducted to assess these potentially synergistic effects because this would inform clinical practice regarding coprescribing of these agents.

To our knowledge, this is the first study to examine dose appropriateness and prescribing patterns of gabapentinoids in patients who received naloxone and opioids. Few patients were observed to have an inappropriate gabapentinoid regimen based on renal function, and most patients received a low to moderate gabapentinoid cumulative dose. However, more than half of the patients in the gabapentinoid group received ≥90 MME of opioids in the 24 hours preceding a naloxone episode. Similarly, Savelloni and colleagues[12] previously observed that patients in the gabapentinoid group received a higher average daily MME than those not receiving gabapentinoids. We found that all 10 patients who were considered to be opioid tolerant in the gabapentinoid group had received a high daily dose of opioids. Although the current study cannot discern whether adding a gabapentinoid led to naloxone administration, it is prudent to consider the possible compounding sedative effects of gabapentinoids alongside high-dose opioids. Pharmacokinetic and pharmacodynamic studies in humans are limited to explain the interaction between these agents. However, studies[18-20] evaluating rat models have demonstrated that concomitant gabapentin and morphine administration leads to enhanced analgesic response, as evidenced by increased morphine area under the curve compared with morphine monotherapy. Extrapolating these data to humans may explain the additive analgesic and adverse effects seen when these agents are given together. Further research is needed to determine whether these effects are dose dependent.

The major limitation of this study was its retrospective and descriptive nature, which is heavily reliant on accurate chart documentation in the electronic medical record. Furthermore, there was incomplete documentation of vital signs both before and after naloxone administration, rendering it uncertain whether naloxone was given for respiratory depression in some cases. The amount of opioids administered in the intraoperative period was difficult to ascertain because of incomplete documentation. Therefore, intraoperative opioids were not included in the calculated cumulative 24-hour amount administered prior to a naloxone episode, possibly affecting cumulative opioid dose calculated for those patients. Lastly, our institution does not use a validated sedation scale for monitoring opioid sedation, which was used in other studies.[11,12] Thus, we could not account for naloxone administration for oversedation. Finally, despite small sample size, this is the largest study to date evaluating gabapentinoid and nongabapentinoid populations who received naloxone, which represents an important addition to the current body of evidence.

Conclusion

This study of hospitalized patients receiving naloxone characterized opioid overdose risk factors among patients receiving opioids with or without gabapentinoids. As a result of the findings, we aim to conduct a follow-up study to determine if certain risk factors are associated with an increased risk of respiratory depression and oversedation when gabapentinoids and opioids are given concomitantly. Data from future studies may help guide prescribing practices and decrease potential adverse effects when these agents are used together.

Acknowledgment

References

1. Peckham AM, Evoy KE, Ochs L, Covvey JR. Gabapentin for off-label use: evidence-based or cause for concern? Subst Abuse. 2018;12:1178221818801311. DOI: 10.1177/1178221818801311. PubMed PMID: 30262984; PubMed Central PMCID: PMC6153543.
2. Neurontin [package insert]. New York: Pfizer Inc; 2020.
3. Lyrica [package insert]. New York: Pfizer Inc; 2020.
4. Goodman CW, Brett AS. Gabapentin and pregabalin for pain–is increased prescribing a cause for concern? N Engl J Med. 2017;377(5):411-4. DOI: 10.1056/NEJMp1704633. PubMed PMID: 28767350.
5. Peckham AM, Fairman KA, Sclar DA. All-cause and drug-related medical events associated with overuse of gabapentin and/or opioid medications: a retrospective cohort analysis of a commercially insured US population. Drug Saf. 2018;41(2):213-28. DOI: 10.1007/s40264-017-0595-1. PubMed PMID: 28956286.
6. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. Drugs. 2017;77(4):403-26. DOI: 10.1007/s40265-017-0700-x. PubMed PMID: 28144823.
7. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: a population-based nested case-control study. PLoS Med. 2017;14(10):e1002396. DOI: 10.1371/journal.pmed.1002396. PubMed PMID: 28972983.
8. Gomes T, Greaves S, van den Brink W, Antoniou T, Mamdani MM, Paterson JM, et al. Pregabalin and the risk for opioid-related death: a nested case-control study. Ann Intern Med. 2018;169(10):732-4. DOI: 10.7326/M18-1136. PubMed PMID: 30140853.
9. Naloxone hydrochloride injection [package insert]. Rockford (IL): Mylan Inc; 2014.
10. Pawasauskas J, Stevens B, Youssef R, Kelley M. Predictors of naloxone use for respiratory depression and oversedation in hospitalized adults. Am J Health Syst Pharm. 2014;71(9):746-50. DOI: 10.2146/ajhp130568. PubMed PMID: 24733138.
11. Yung L, Lee KC, Hsu C, Furnish T, Atayee RS. Patterns of naloxone use in hospitalized patients. Postgrad Med. 2017; 129(1):40-5. DOI: 10.1080/00325481.2017.1263139. PubMed PMID: 27858510.
12. Savelloni J, Gunter H, Lee KC, Hsu C, Yi C, Edmonds KP, et al. Risk of respiratory depression with opioids and concomitant gabapentinoids. J Pain Res. 2017;10:2635-41. DOI: 10.2147/JPR.S144963. PubMed PMID: 29180889.
13. FDA [Internet]. Extended-release (ER) and long-acting (LA) opioid analgesics Risk Evaluation and Mitigation Strategy (REMS) [cited 2019 May 28]. Available from https://www.fda.gov/media/86875/download
14. Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain–United States, 2016. JAMA. 2016; 315(15):1624-45. DOI: 10.1001/jama.2016.1464. PubMed PMID: 26977696; PubMed Central PMCID: PMC6390846.
15. Practice Pain Management Opioid Calculator [Internet]. Remedy Health Media, LLC [cited 2019 May]. Available from https://opioidcalculator.practicalpainmanagement.com/starting.php
16. The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674-94. DOI: 10.1111/jgs.15767. PubMed PMID: 30693946.
17. Center for Drug Evaluation and Research [Internet]. Serious breathing difficulties with gabapentin and pregabalin [cited 2020 Jan 14]. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin
18. Meymandi MS, Sepehri G, Mobasher M. Gabapentin enhances the analgesic response to morphine in acute model of pain in male rats. Pharmacol Biochem Behav. 2006;85(1):185-9. DOI: 10.1016/j.pbb.2006.07.037. PubMed PMID: 16979227.
19. De la O-Arciniega M, Díaz-Reval MI, Cortés-Arroyo AR, Dominguez-Ramierz AM, Lopez-Munoz FJ. Anti-nociceptive synergism of morphine and gabapentin in neuropathic pain induced by chronic constriction injury. Pharmacol Biochem Behav. 2009;92(3):457-64. DOI: 10.1016/j.pbb.2009.01.013. PubMed PMID: 19463259.
20. Papathanasiou T, Juul RV, Heegaard AM, Kreilgaard M, Lund TM. Co-administration of morphine and gabapentin leads to dose dependent synergistic effects in a rat model of postoperative pain. Eur J Pharm Sci. 2016;82:97-105. DOI: 10.1016/j.ejps.2015.11.015. PubMed PMID: 26610393.