Medicines Adverse Reactions Committee

Meeting date	**7 December 2017**	Agenda item	3.2.4
Title	**Gabapentin and the risk of respiratory depression without concomitant opioids**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active constituent	**Medicine**	**Sponsor**
Gabapentin	Arrow - Gabapentin	Teva Pharma (New Zealand) Limited
Gabapentin	Neurontin	Pfizer New Zealand Limited
Gabapentin	Nupentin	Mylan New Zealand
Gabapentin	Ranbaxy-Gabapentin	Douglas Pharmaceuticals Ltd

Funding	Nupentin, Arrow-Gabapentin and Neurontin (100 mg, 300 mg, 400 mg capsules) are funded on the Pharmaceutical Schedule.
Previous MARC meetings	Gabapentin and the risk of respiratory depression has not been discussed previously.
International action	Health Canada – September 2016 – Assessing the Potential Risk of Serious Breathing Problems with Gabapentin (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-gabapentin-assessing-potential-risk-serious-breathing.html). European Medicines Agency – June 2017 - Pharmacovigilance Risk Assessment Committee (PRAC) meeting Signal of gabapentin and respiratory depression without concomitant opioid use (www.ema.europa.eu/docs/en_GB/document_library/Minutes/2017/07/WC500232398.pdf) See section 3.3 for further information by international regulators.
Prescriber Update	Gabapentin and the risk of respiratory depression has not been discussed previously in *Prescriber Update*.
Schedule	Prescription medicine
Advice sought	**The Committee is asked to advise whether:** – data sheet updates are required to highlight the possibility of respiratory depression from the use of gabapentin alone. – this topic requires further communication other than MARC's Remarks in *Prescriber Update*.

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1.0 PURPOSE

The purpose of this paper is to review the risk of respiratory depression with gabapentin without the use of concomitant opioids.

Health Canada published a Summary Safety Review in September 2016 concerning the risk of respiratory depression with gabapentin without the use of opioids. This review concluded that there is evidence to support a risk of serious breathing problems with the use of gabapentin alone and recommended updates to gabapentin product information.

[redacted]

Also in 2017, the Pharmacovigilance Risk Assessment Committee (PRAC) in the United Kingdom (UK) reviewed this topic and recommended that the product information of gabapentin-containing products be updated to state that gabapentin has been associated with severe respiratory depression.

Medicines containing gabapentin are available and funded in New Zealand. Medsafe considers the available information on the use of gabapentin without the concomitant use of opioids should be reviewed.

2.0 BACKGROUND

2.1 Gabapentin

In New Zealand, gabapentin is an anti-epileptic medication used for the treatment of partial seizures with or without secondary generalised tonic-clonic seizures in those who have not achieved adequate control with standard anti-epileptic drugs [1]. Neurontin is indicated for use in adults and children aged 3 years and above for epilepsy [1].

Gabapentin is also used for the treatment of neuropathic pain [1].

Gabapentin is available in New Zealand as tablets or capsules ranging from 100 mg to 800 mg [2].

Oral administration of gabapentin is not dose proportional (non-linear); as dose increases, bioavailability decreases [1, 3].

2.1.1 Mechanism of action

The mechanism of action of gabapentin's analgesic and anticonvulsant effects is unknown [1, 4].

Gabapentin does not block gamma-aminobutyric acid (GABA) uptake or metabolism and has no direct GABAergic action [5].

Proposed mechanisms for the anti-allodynic effects of gabapentin are thought to be central nervous system (CNS) effects due to [5]:

- enhanced inhibitory input of GABA-mediated pathways (therefore reducing excitatory input levels)
- antagonism of NMDA receptors, and
- antagonism of calcium channels in the CNS and inhibition of peripheral nerves.

Gabapentin is structurally related to the neurotransmitter GABA however gabapentin does not bind to the $GABA_A$ or $GABA_B$ receptors or influence the degradation or uptake of GABA [4, 5].

GABA is the main inhibitory neurotransmitter in the brain and GABA transaminase is the main enzyme that degrades GABA in the brain [6]. Gabapentin is a reversible inhibitor of GABA transaminase and by modulating GABA in this way, gabapentin has an inhibitory effect on the respiratory centre in the medulla [6].

However, a 2002 review stated that potentiation of inhibitory GABA-ergic pathways seems unlikely to be responsible for its anti-allodynic effect because GABA receptor antagonists do not reduce this effect [5].

Comments:

There is a biologically plausible mechanism that gabapentin can affect the respiratory system and possibly cause respiratory depression.

2.2 Respiratory depression

Respiratory depression, or hypoventilation, refers to a difference between the elimination and production of carbon dioxide [7].

Respiratory failure is when the respiratory system fails in one or both of its gas exchange functions (oxygenation and carbon dioxide elimination) [8].

Respiratory failure can occur when lung or heart diseases cause the body to have reduced oxygen levels or higher blood carbon dioxide levels [9]. Hypoxemia occurs when the body doesn't have enough oxygen [10] and hypercapnia occurs when there is an elevation of carbon dioxide [8, 11].

Hypoxemia can affect every tissue in the body and is a state where there is insufficient oxygen to meet the metabolic demands of a given tissue [12].

Symptoms of respiratory depression can vary and include [13]:

- Tiredness
- Daytime sleepiness
- Shortness of breath
- Slow and shallow breathing
- Depression
- Bluish-coloured lips, fingers or toes
- Seizures
- Confusion
- Headaches

Respiratory depression can be treated and, if it is caused by a medicine, stopping the medicine may reverse the respiratory depressive effects [13]. Other treatment options are [13]:

- Oxygen therapy to support breathing
- Weight loss
- The use of machines to keep your airway open while sleeping
- Surgery to correct a chest deformity
- Inhaled medicines to open airways and treat lung disease.

It is known and stated in the New Zealand gabapentin data sheet that patients requiring concomitant use of gabapentin and opioids may experience increases in gabapentin levels [1]. Careful monitoring for central nervous depression, including respiratory depression, should be done and a dose reduction of either medicine may be needed [1].

This is important as there is a high likelihood of opioid and gabapentin co-prescription because they are often use together for pain [14].

2.3 Data sheets

Relevant wording regarding the risk of respiratory depression in the New Zealand data sheet, Australian product information, Health Canada's product monograph and the UK Summary of Product Characteristics (SPC) is outlined in sections 2.3.1 to 2.3.4 below.

2.3.1 New Zealand [1]

The Neurontin data sheet can be found on the Medsafe website (www.medsafe.govt.nz/profs/Datasheet/n/Neurontincaptab.pdf).

Section 4.4 – Special Warnings and Precautions for Use

Patients who require concomitant treatment with opioids may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression and the dose of Neurontin or opioid should be reduced appropriately (see section 4.5).

Section 4.5 – Interactions

There are spontaneous and literature case reports of respiratory depression and/or sedation associated with gabapentin and opioid use. These effects would be of particular concern in elderly patients.

Comments:

The New Zealand data sheet for Neurontin (dated 14 June 2017) currently only refers to the risk of respiratory depression with concomitant gabapentin and opioid use.

Although pregabalin and gabapentin are both GABA analogues, pregabalin has a different mechanism of action to gabapentin.

The interactions section of the New Zealand data sheet for Lyrica (pregabalin) currently refers to respiratory failure with concomitant use of gabapentin and other CNS depressant medicines. The data sheet (dated 6 September 2016) states:

'In post-marketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medications.'

2.3.2 Australia [15]

The Australian Product Information for Neurontin (dated 11 August 2017) currently contains the same wording as the New Zealand data sheet (see section 2.3.1). [redacted]

2.3.3 Health Canada [16]

Warnings and Precautions

Respiratory Depression

Gabapentin has been associated with central nervous system (CNS) depression including sedation, somnolence, loss of consciousness as well as serious cases of respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment and the

elderly are at higher risk of experiencing these severe adverse effects. Concomitant use of CNS depressants with gabapentin is also a contributing factor.

Concomitant Use With Opioids

Concomitant use of opioids with Neurontin potentiates the risk of respiratory depression, profound sedation, syncope, and death. Gabapentin concentrations may also increase in patients receiving concomitant opioid (See Drug Interactions).

Patients who require concurrent treatment with opioids or other CNS depressants should be observed carefully for signs and symptoms of CNS depression, and the dose of gabapentin or opioid should be reduced accordingly. See also Dosage and Administration, Dosing Considerations.

Drug Interactions

Morphine

A literature article reported that when a 60 mg controlled release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule in healthy volunteers (N= 12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine in this study. Because this was a single dose study, the magnitude of the interaction at steady state and at higher doses of gabapentin are not known.

Adverse Reactions

Respiratory System: Hypoventilation.

Comments:

The Health Canada product monograph for Neurontin was revised in September 2017 in response to a Summary Safety review carried out by Health Canada (see section 3.3.1) [17]. Updates to product information for gabapentin were recommended to warn about this risk without concomitant opioid use (see section 3.3.1).

In contrast to the current New Zealand data sheet and Australian product information, information regarding the risk of respiratory depression with gabapentin in the absence of concomitant opioid use is present in the Warnings and Precautions section of the Canadian product monograph. Hypoventilation is also listed as an adverse reaction. [redacted]

These updates were highlighted in the January 2017 Health Canada InfoWatch publication [18].

2.3.4 United Kingdom [19]

Section 4.4 Special warnings and precautions for use

Concomitant use with opioids

Patients who require concomitant treatment with opioids should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression. Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin or opioids should be reduced appropriately (see section 4.5).

Respiratory depression

Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

Section 4.8 Undesirable effects

Respiratory, thoracic and mediastinal disorders: respiratory depression.

Comments:

The Health Canada product monograph and the UK Summary of Product Characteristics (SPC) both include information on the risk of respiratory depression from the use of gabapentin without concomitant opioids.

The New Zealand data sheet and the Australian product information only include information on the risk of respiratory depression with the concomitant use of gabapentin and opioids.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Cavalcante et al, 2017 [20]

This study retrospectively reviewed electronic health records of 8567 patients who underwent major laparoscopic procedures (≥90 minutes) from 1 January 2010 to 31 July 2014 with the aim of determining whether gabapentin was associated with respiratory depression during phase-1 post-anaesthesia recovery.

The authors noted that when taken in isolation, gabapentinoids do not have respiratory depressive properties but when taken in combination with remifentanil (ultrashort-acting opioid), pregabalin potentiated respiratory depression.

Multivariable and propensity score-matched analyses were performed to assess potential associations between pre-operative use and post-operative respiratory depression. The primary endpoint was defined as the occurrence of nurse-diagnosed respiratory-specific events, administration of naloxone to treat respiratory depression, the need for unplanned use of non-invasive positive-pressure ventilator (NIPPV) devices (for patients not using these devices preoperatively) or cases notable for a failure to extubate trachea or that required reintubation during phase-I recovery.

The incidence of respiratory depression was 153 (95% confidence interval [CI], 146– 161) episodes per 1000 cases. Multivariable analysis showed that gabapentin was associated with respiratory depression (odds ratio [OR], 1.47 [95% CI, 1.22–1.76]; P < .001). These results were confirmed by propensity score–matched analysis among a subset of patients who did not have analgesia supplemented by intrathecal opioids (OR, 1.26 [95% CI, 1.02–1.58]; P = .04). Older patients and those who received more intraoperative opioids had increased risk of respiratory depression. Those who had an episode of respiratory depression had a longer phase-I recovery (P < .001) and an increased rate of admission to a higher level of care (P = .03).

The authors concluded the main finding of this study is that the use of the gabapentin is associated with increased rates of respiratory depression during phase-1 recovery among patients undergoing laparoscopic surgery. Patients who had episodes of respiratory depression were older, received midazolam and had a slightly higher intraoperative dose of opioids. Intraoperative management must consider the patient's age and the opioid-sparing and sedating effects of gabapentin to reduce the rate of respiratory depression. Intraoperative use of opioids (and sedatives) should be reduced when gabapentin is used, especially in patients who may be prone to respiratory depression (eg elderly, morbidly obese or deconditioned patients).

Table 1 Comparison of Patients With and Without Respiratory Events

	Univariate			Multivariable Model	
Variable	Respiratory Event (n = 1311)	Event Free (n = 7256)	*P* value	OR (95% CI)	*P* value
Patient and surgical factors					
Age (y)	59.8 ± 12.8	57.4 ± 14.2	<.001		<.001
<50	259 (19.8)	1977 (27.2)		1.00	
50–59	361 (27.5)	1922 (26.5)		1.41 (1.16, 1.71)	
60–69	404 (30.8)	2109 (29.1)		1.43 (1.15, 1.77)	
≥70	287 (21.9)	1248 (17.2)		1.86 (1.43, 2.42)	
Male sex	769 (58.7)	3823 (52.7)	<.001	1.11 (0.97, 1.27)	.13
Outpatient gabapentinoid use	26 (2.0)	193 (2.7)	.15	0.83 (0.54, 1.26)	.38
Charlson comorbidity index	4 [3, 5]	4 [2, 5]	<.001	0.99 (0.95, 1.02)	.50
Body mass index (kg/m^2)	29.8 ± 7.3	31 ± 8.1	<.001	0.99 (0.98, 0.99)	.001
Obstructive sleep apnea	293 (22.3)	1723 (23.7)	.29	1.09 (0.93, 1.28)	.31
Upper abdominal procedure[b]	518 (39.5)	3369 (46.4)	<.001	0.70 (0.61, 0.80)	<.001
Surgery duration, minutes	199 ± 71	203 ± 73	.06	0.99 (0.99, 0.99)	<.001
Preoperative medication					
Gabapentin[c]	230 (17.5)	1145 (15.8)	.11	1.47 (1.22, 1.76)	<.001
Sustained-release opioids[d]	56 (4.3)	483 (6.7)	.001	0.54 (0.40, 0.72)	<.001
Intraoperative medication					
Neuraxial opioids[e]	104 (7.9)	515 (7.1)	.30	1.07 (0.82, 1.38)	.64
Local anesthetic	745 (56.8)	3609 (49.7)	<.001	1.27 (1.12, 1.44)	<.001
Midazolam[f]	905 (69.0)	4432 (61.1)	<.001	1.34 (1.16, 1.54)	<.001
Droperidol	564 (43.0)	4116 (56.7)	<.001	0.69 (0.60, 0.79)	<.001
Ketamine[g]	309 (23.6)	2127 (29.3)	<.001	0.82 (0.71, 0.96)	.011
Isoflurane	672 (51.3)	3049 (42.0)	<.001	1.22 (1.08, 1.39)	.002
Intraoperative opioids (mg IV ME)[h]	35.7 [30, 41.7]	35 [28.3, 40.0]	<.001	1.02 (1.01, 1.02)	<.001

Abbreviations: CI, confidence interval; IV ME, intravenous morphine equivalents; OR, odds ratio.

[a]Data are presented as number (%), mean ± SD, median [25th percentile, 75th percentile], or OR (95% CI).

[b]Upper abdominal procedures included colectomy or hemicolectomy (n = 869), nephrectomy (n = 596), bariatric surgery (n = 569), cholecystectomy (n = 459), abdominal exploration or small bowel resection (n = 417), Nissen fundoplication (n = 346), major hepatobiliary surgery (n = 331), splenectomy (n = 140), adrenalectomy (n = 129), and gastrectomy (n = 31). Lower abdominal procedures included prostatectomy (n = 2494), hysterectomy (n = 1385), hernia repair (n = 142), sigmoidectomy or abdominoperineal resection or ileal pouch anal anastomosis (n = 137), sacrocolpopexy (n = 136), salpingo-oophorectomy (n = 125), pyeloplasty (n = 57), ileocecal resection (n = 46), uterine myomectomy (n = 43), proctectomy (n = 41), partial cystectomy (n = 32), appendectomy (n = 30), and ileostomy (n = 12).

[c]Patients in the gabapentin group received doses of 300 mg (n = 349 [25.4%]) or 600 mg (n = 1017 [74%]), with few outliers receiving doses below (n = 1; 200 mg), within (n = 4; 400 mg), or above (n = 4; 900–1500 mg) this interval.

[d]Median [25th percentile, 75th percentile] dose of sustained-release opioids was 5 [5, 5] mg IV ME for both the respiratory event and event-free groups (*P* = .47).

[e]Median [25th percentile, 75th percentile] dose of neuraxial opioids was 16 [14, 20] vs 20 [14, 20] mg IV ME for the respiratory event and event-free groups, respectively (*P* = .51).

[f]Median [25th percentile, 75th percentile] dose of midazolam was 2 [2, 2] mg for both the respiratory event and event-free groups (*P* = .39).

[g]Median [25th percentile, 75th percentile] dose of ketamine was 20 [10, 20] vs 20 [20, 20] mg for the respiratory event and event-free groups, respectively (*P* = .16).

[h]In total, 1299 patients with respiratory depression (99.1%) and 7204 patients without respiratory depression (99.3%) were administered fentanyl (*P* = .48), with both groups having the same median [25th percentile, 75th percentile] dose of 250 [250, 250] mcg (*P* = .27). Long-acting opioids were used in 1130 patients with respiratory depression (86.2%) and in 6159 without respiratory depression (84.9%; *P* = .24), with a median [25th percentile, 75th percentile] dose of 12 [7.5, 15] vs 10.5 [6, 15] IV ME (*P* < .001). Of the long-acting opioids, hydromorphone was used in 865 (66.0%) and 4822 (66.5%), morphine in 2 (0.2%) and 16 (0.2%), and oxymorphone in 265 (20.2%) and 1350 (18.6%) patients with and without respiratory depression, respectively. Remifentanil was not included in morphine equivalent calculations; it was administered in 2 (0.2%) and 7 (0.1%) patients with or without respiratory depression, respectively.

Table 2 Patient Characteristics, Stratified by Preoperative Gabapentin Use

	All Patients Not Receiving Neuraxial Opioids			Propensity Score–Matched Sample		
Variable	Gabapentin (n = 965)	No Gabapentin (n = 6983)	Standardized Difference	Gabapentin (n = 965)	No Gabapentin (n = 1930)	Standardized Difference
Patient and surgical factors						
Age (y)	52.4 ± 13.3	58.7 ± 13.6	0.47	52.4 ± 13.3	52.4 ± 14.8	0.01
Male sex	281 (29.1)	3981 (57.0)	0.59	281 (29.1)	581 (30.1)	0.02
Outpatient gabapentinoid use	25 (2.6)	174 (2.5)	0.01	25 (2.6)	59 (3.1)	0.03
Charlson comorbidity index	3 [1, 5]	4 [2, 5]	0.39	3 [1, 5]	3 [1, 5]	0.01
Body mass index (kg/m^2)	30.5 ± 8.7	31.2 ± 8.0	0.08	30.5 ± 8.7	30.6 ± 8.1	0.01
Obstructive sleep apnea	157 (16.3)	1751 (25.1)	0.22	157 (16.3)	310 (16.1)	0.01
Upper-abdominal procedure	425 (44.0)	2999 (43.0)	0.02	425 (44.0)	892 (46.2)	0.04
Preoperative medication						
Sustained-release opioids	34 (3.5)	499 (7.2)	0.16	34 (3.5)	76 (3.9)	0.02
Intraoperative medication						
Local anesthetic	558 (57.8)	3695 (52.9)	0.10	558 (57.8)	1051 (54.5)	0.07
Midazolam	636 (65.9)	4115 (58.9)	0.14	636 (65.9)	1250 (64.8)	0.02
Droperidol	660 (68.4)	3682 (52.7)	0.32	660 (68.4)	1281 (66.4)	0.04
Ketamine	472 (48.9)	1809 (25.9)	0.49	472 (48.9)	897 (46.5)	0.05
Isoflurane	470 (48.7)	2840 (40.7)	0.16	470 (48.7)	900 (46.6)	0.04
Intraoperative opioids (mg IV ME)	32.3 ± 12.6	36.0 ± 11.2	0.31	32.3 ± 12.6	32.9 ± 10.6	0.05

Abbreviation: IV ME, intravenous morphine equivalents.

[a]Data are presented as number (%), mean ± SD, or median (25th percentile, 75th percentile).

Table 3 Outcomes of Patients With and Without Respiratory Depression

Outcomes	Respiratory Depression (n = 1311)	Event Free (n = 7256)	*P* Value
Duration of phase-I recovery (min)	195 ± 80	117 ± 55	<.001
Intensive care unit admission	101 (7.7)	407 (5.6)	.004
First 48 h after PACU discharge			
Emergency response team intervention	18 (1.4)	62 (0.9)	.09
Tracheal reintubation[b]	4 (0.3)	6 (0.1)	.05
Intensive care unit admission from ward	30 (2.3)	103 (1.4)	.03
30-day postoperative outcomes			
Myocardial infarction	4 (0.3)	10 (0.1)	.25
Deep venous thrombosis or pulmonary embolism	2 (0.2)	10 (0.1)	.71
Death	5 (0.4)	15 (0.2)	.22

Abbreviation: PACU, postanesthesia care unit.
[a]Data are presented as number (%) or mean ± SD.
[b]Reasons for reintubation among the respiratory depression cohort included pulmonary edema (n = 1), hypercarbic respiratory failure (n = 1), and shock (n = 2); among the respiratory event–free group, reasons for reintubation included hypercarbic respiratory failure (n = 2) and shock or hypotension (n = 4).

Comments

Contradictory to reviews and recommendations made by international regulators, the authors comment in the introduction to the article that when taken in isolation, gabapentinoids do not have respiratory depressive properties. The reviews that this comment was based on were done using poison centre data and the authors reported inherent limitations in the data [21, 22]. One review had a small number of cases (20) [21].

This study's conclusions are that gabapentin use is associated with increased rates of respiratory depression in patients after laparoscopic surgery. The patients' were older and taking a slightly higher opioid dose.

This study is limited to patients who had undergone laparoscopic surgery.

3.1.2 Gomes et al, 2017 [14]

This population-based nested case-control study using administrative databases among opioid users in Ontario, Canada between 1 August 1997 and 31 December 2013 aimed to investigate whether co-prescription of opioids and gabapentin is associated with an increased risk of accidental opioid-related mortality. The authors noted that prescription opioid use is highly associated with opioid-related death and whilst gabapentin is widely perceived as safe, drug-induced respiratory depression has been associated with gabapentin use alone or in combination with other medicines. Co-prescription of gabapentin and opioids is likely as they are both commonly prescribed for pain.

Potential risk factors for gabapentin-related respiratory depression include advancing age, renal insufficiency, chronic lung disease and dose.

Cases are opioid users who died of an opioid-related cause. After matching each case with up to 4 controls, 1256 cases and 4619 controls were included in the study.

Table 4 Baseline characteristics of individuals who died of an opioid overdose (cases) and matched controls

Variable	Cases (*N* = 1,256)	Controls (*N* = 4,619)	Standardized Difference
Demographic characteristics			
Age ≥ 65 years	69 (5.5%)	266 (5.8%)	0.01
Age, years (mean ± SD)	47.5 ± 10.0	47.8 ± 9.9	0.03
Age < 65 years	46.4 ± 8.2	46.1 ± 8.3	0.03
Age ≥ 65 years	70.8 ± 6.2	70.7 ± 6.2	0.01
Male	716 (57.0%)	2,619 (56.7%)	0.01
Income quintile			
1	529 (42.1%)	2,025 (43.8%)	0.04
2	285 (22.7%)	1,047 (22.7%)	0.00
3	202 (16.1%)	699 (15.1%)	0.03
4	132 (10.5%)	477 (10.3%)	0.01
5	100 (8.0%)	341 (7.4%)	0.02
Missing	8 (0.6%)	30 (0.6%)	0.00
Location of residence			
Rural	150 (11.9%)	548 (11.9%)	0.00
Urban	1,103 (87.8%)	4,062 (87.9%)	0.00
Missing	≤5 (0.2%)	9 (0.2%)	0.01
Opioid dose			
<20 MME daily	141 (11.2%)	1,162 (25.2%)	0.37
20–49 MME daily	228 (18.2%)	1,340 (29.0%)	0.26
50–99 MME daily	202 (16.1%)	680 (14.7%)	0.04
100–199 MME daily	189 (15.0%)	488 (10.6%)	0.13
≥200 MME daily	496 (39.5%)	949 (20.5%)	0.42
Prior medication use			
Number of drugs used in past 6 months (median [IQR])	11 (7–15)	9 (6–13)	0.30
Past medication use (120 days)			
Antidepressants—SSRIs	566 (45.1%)	1,690 (36.6%)	0.17
Antidepressants—other	622 (49.5%)	1,736 (37.6%)	0.24
Benzodiazepines	971 (77.3%)	2,604 (56.4%)	0.46
Other psychotropic drugs/CNS depressants	448 (35.7%)	1,190 (25.8%)	0.22
Methadone/buprenorphine	78 (6.2%)	212 (4.6%)	0.07
Pregabalin	12 (1.0%)	29 (0.6%)	0.04
Long-acting opioid during exposure window	784 (62.4%)	1,828 (39.6%)	0.47
Patient comorbidity			
Charlson Comorbidity Index			
No hospitalization	551 (43.9%)	2,529 (54.8%)	0.22
0	388 (30.9%)	1,219 (26.4%)	0.10
1	171 (13.6%)	447 (9.7%)	0.12
2 or more	146 (11.6%)	424 (9.2%)	0.08
History of alcohol use disorder	327 (26.0%)	1,074 (23.3%)	0.07
Chronic kidney disease	58 (4.6%)	173 (3.7%)	0.04
Mental health diagnoses			
Affective disorder	256 (20.4%)	902 (19.5%)	0.02
Anxiety/sleep disorders	1,027 (81.8%)	3,779 (81.8%)	0.00
Psychoses	180 (14.3%)	572 (12.4%)	0.06
Other mental health diagnoses	913 (72.7%)	3,280 (71.0%)	0.04
Chronic lung disease	294 (23.4%)	1,040 (22.5%)	0.02
Diabetes	203 (16.2%)	734 (15.9%)	0.01
Health services utilization (median [IQR])			
Visits to a physician in past year	42 (23–78)	36 (19–64)	0.19
Doctors prescribing opioids in past 6 months	1 (1–2)	1 (1–2)	0.18
Pharmacies dispensing opioids in past 6 months	1 (1–2)	1 (1–2)	0.22

Data are number (percent) unless otherwise indicated.
CNS, central nervous system; MME, morphine milligram equivalent; SSRI, selective serotonin reuptake inhibitor.

The primary exposure was concomitant gabapentin use in the 120 days preceding the index date. A secondary analysis characterised gabapentin dose as low (<900 mg daily), moderate (900 to 1,799 mg daily) or high (≥1,800 mg daily). A sensitivity analysis examined the effect of concomitant non-

steroidal anti-inflammatory drug (NSAID) use in the preceding 120 days. Overall, 12.3% of cases (155 of 1,256) and 6.8% of controls (313 of 4,619) were prescribed gabapentin in the prior 120 days.

After multivariable adjustment, co-prescription of opioids and gabapentin was associated with a significantly increased odds of opioid-related death (odds ratio [OR] 1.99, 95% CI 1.61 to 2.47, p < 0.001; adjusted OR [aOR] 1.49, 95% CI 1.18 to 1.88, p < 0.001) compared to opioid prescription alone.

In the dose-response analysis, moderate-dose (OR 2.05, 95% CI 1.46 to 2.87, p < 0.001; aOR 1.56, 95% CI 1.06 to 2.28, p = 0.024) and high-dose (OR 2.20, 95% CI 1.58 to 3.08, p < 0.001; aOR 1.58, 95% CI 1.09 to 2.27, p = 0.015) gabapentin use was associated with a nearly 60% increase in the odds of opioid-related death relative to no concomitant gabapentin use.

As expected, the authors found no significant association between co-prescription of opioids and NSAIDs and opioid-related death (OR 1.11, 95% CI 0.98 to 1.27, p = 0.113; aOR 1.14, 95% CI 0.98 to 1.32, p = 0.083). In an exploratory analysis of patients at risk of combined opioid and gabapentin use, the authors found that 46.0% (45,173 of 98,288) of gabapentin users in 2013 received at least 1 concomitant prescription for an opioid.

The authors consider the mechanisms by which gabapentin may increase the risk of death in opioid are likely pharmacodynamics and pharmacokinetic. Additive respiratory depression and increased gabapentin concentrations with concomitant opioid use as well as increased gabapentin absorption may occur. Opioid-induced slowing of gastrointestinal transit could increase gabapentin bioavailability.

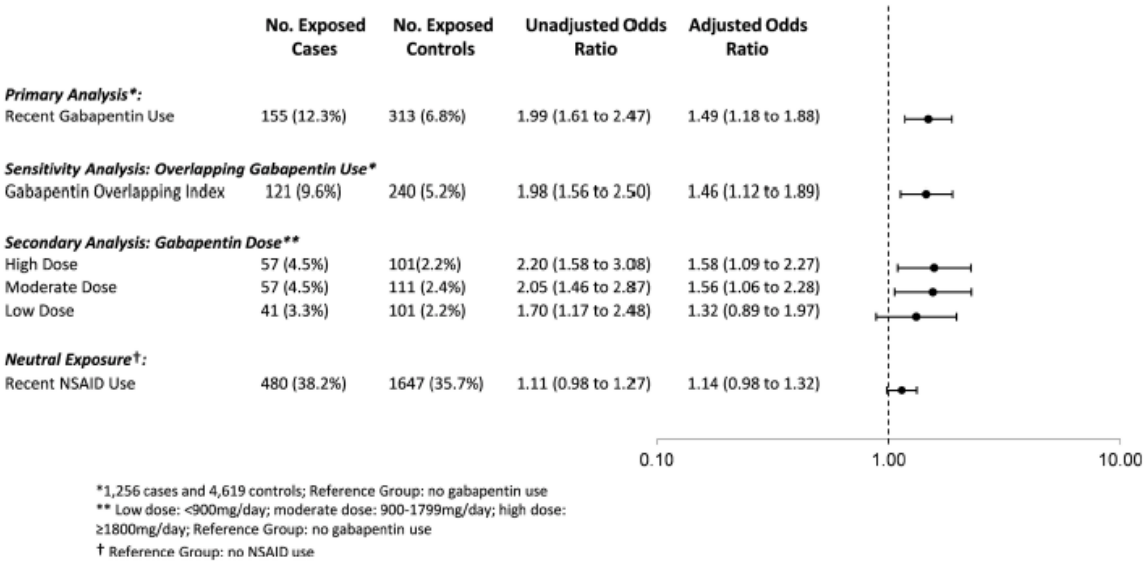


Figure 1 Association between co-prescription with gabapentin and opioids and opioid overdose

The authors note that this study was limited to individuals eligible for public drug coverage in Ontario and they were only able to identify prescriptions reimbursed by the government and dispensed from retail pharmacies. Information on indication for gabapentin use was not available. Furthermore, as with all observational studies, confounding due to unmeasured variables is a potential source of bias.

This study found that in patients prescribed opioids, co-prescription of gabapentin was associated with a considerable increase in the risk of opioid-related death. Due to the high likelihood of patients taking both gabapentin and opioids together, the authors consider there are clear clinical consequences of a drug interaction given the large number of people at risk of this fatal outcome. It is important for clinicians to carefully consider whether to continue prescribing this combination of products and when co-prescription is necessary patients should be monitored and medicine doses adjusted accordingly.

Comment

This recent study has been included for completeness however it focuses on the use of gabapentin with concomitant opioids.

A warning of the risk of central nervous system depression associated with the use of gabapentin and opioids is present in the data sheets for gabapentin-containing products. However it is noted that some data sheets refer to respiratory depression with morphine rather than opioids as a group (Arrow – Gabapentin, Ranbaxy Gabapentin). Newer data sheets (Neurontin, Nupentin) seem to refer to respiratory depression with opioids generally.

The warnings and precautions section of the Neurontin (gabapentin) UK SPC also refers to morphine and gabapentin concomitant use but additionally refers to opioids more generally in this section.

3.1.3 Quintero, 2017 [3]

This publication search of PubMed aimed to review the risks of gabapentin misuse, its potential interactions with other drugs, side effects and contraindications. 99 references from January 1983 to December 2016 were included in the review.

The different publications identified a range of side effects including teratogenic effects (rodent studies), central hypoventilation and/or respiratory failure, deficits in visual field, myopathy, self-harm or suicidal behaviour, mitochondrial toxicity, somnolence, dizziness and diarrhoea. Teratogenic effects were not seen in other studies in nonhuman species. The review noted the studies that reported central hypoventilation associated with gabapentin use were small sample sizes (n=1) and therefore the reliability of these findings is uncertain. Studies with larger sample sizes are needed to confirm these effects.

3.1.4 Ongley D et al, 2014 [23]

Two cases of severe respiratory depression in elderly patients were reported in Australia in the setting of analgesia. One was awaiting orthopaedic surgery and one experienced respiratory depression post-operatively. They both had obstructive sleep apnoea and had been administered 300 mg of gabapentin even though their opioid use had ceased because of efficacious continuous regional analgesia. The authors note this is consistent with two studies that showed no benefit of gabapentin for early postoperative pain in the presence of effective regional analgesia.

An algorithm has been developed for perioperative pregabalin administration and dose adjustment based on the acronym SNORE (sleep deprivation, neuraxial opioids, obstructive sleep apnoea, renal insufficiency, elderly patients).

The authors state, in patients where gabapentin is indicated but there is some perceived risk, it is their practice to start with 100 mg of gabapentin once daily, observe for effect and titrate to three times daily (to be ceased on discharge).

They conclude with the following points:

1. all gabanoids require dose adjustment based on patient factors and anaesthetic administered
2. opioid-sparing medications may not be required in patients with minimal pain (e.g. regional anaesthesia)
3. opioid-sparing medication is in itself capable of causing respiratory depression, particularly in combination with opioids.

3.1.5 Batoon et al, 2001 [6]

A letter to the editor of the Journal of the American Geriatrics Society discussed recurrent hypoventilation and respiratory failure during gabapentin therapy in a 69 year old patient.

This case study concerned a 69 year old man with chronic obstructive pulmonary disease (COPD), insomnia and an anxiety disorder who was admitted with worsening shortness of breath and wheezing. In the previous 3 years, he had required four hospitalisations for COPD exacerbation due to pneumonia. The patient's concomitant medicines were albuterol and ipratropium bromide inhalers, clonazepam and zolpidem. Two months before admission for worsening shortness of breath and wheezing he had been started on 300 mg gabapentin three times daily for painful peripheral neuropathy and five weeks later he was hospitalised for severe hypercapnia requiring mechanical ventilation. His respiration rate was 30/minute at admission. Four attempts at extubation were unsuccessful due to respiratory distress, expiratory wheezing and hypercapnia. Gabapentin was discontinued on day 10 and the patient continued to improve despite continuing treatment with his other medicines.

Gabapentin is eliminated from the systemic circulation by renal excretion (elimination half-life 5-9 hours) but renal clearance is reduced in older patients and in patients with impaired renal function. Dose adjustment of gabapentin may therefore be necessary in patients who have an age or disease-related decline in renal function.

Somnolence, dizziness, ataxia, nystagmus and headache were the most commonly observed adverse events in clinical studies. The authors considered that a causal relationship between the use of gabapentin and hypercapnic respiratory failure may be established due to a temporal relationship between gabapentin and hypoventilation and subsequent respiratory failure. The patient's recovery following gabapentin withdrawal supports this.

GABA transaminase is an enzyme that degrades GABA in the brain. Gabapentin is a reversible inhibitor of GABA transaminase and modulates the neurotransmitter GABA which has an inhibitory effect on the respiratory centre. The authors consider that this effect might be exaggerated in patients with COPD and that COPD may have predisposed their patient to hypoventilation and respiratory failure after gabapentin was started.

Comment
The positive dechallenge seen in this study provides support for an association between respiratory depression and gabapentin however the patient had COPD and may also be experiencing age-related decline in renal function.

3.2 Company reports

3.2.1 Pfizer (Annex 1)

[redacted]

[redacted]

3.3 Regulator reports

The following sections contain a summary of the reports written by international regulators on this topic. The full reports can be found in Annexes 2 and 3.

3.3.1 Health Canada (Annex 2)

[redacted]

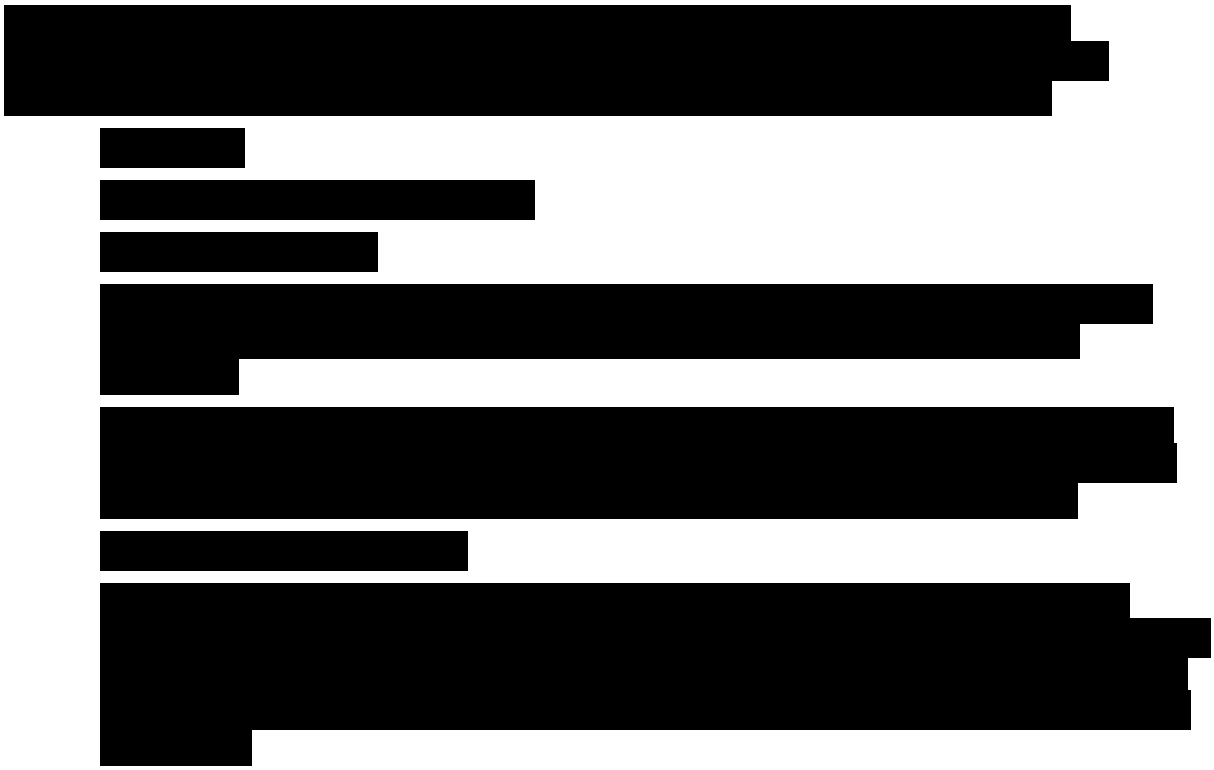
[redacted]

Comments

See section 2.3.3 for Canadian product information. The Neurontin Canadian product information has been updated to warn about the risk of respiratory depression with gabapentin without concomitant opioid use.

3.3.2 Therapeutic Goods Administration (TGA) (Annex 3)

[redacted]



Comment

Product information warning about the risk of respiratory depression without concomitant opioid use that has been updated in Canada and the UK is stated in sections 2.3.3 and 2.3.4 respectively.

3.3.3 European Pharmacovigilance Risk Assessment Committee (PRAC) (Annex 4)

In June 2017, having considered the available evidence in EudraVigilance and the literature, the PRAC recommended Marketing Authorisation Holders of gabapentin-containing products amend the product information to warn against the risk of respiratory depression from the use of gabapentin alone.

Comments:

The product information of Neurontin has been updated in the UK and information warning about the risk of respiratory depression from gabapentin use alone is stated in section 2.3.4.

3.3.3.1 Medicines and Healthcare products Regulatory Agency (MHRA) [24]

In October 2017, the MHRA published a Drug Safety Update article highlighting the rare risk of severe respiratory depression with gabapentin even without concomitant opioid medicines (www.gov.uk/drug-safety-update/gabapentin-neurontin-risk-of-severe-respiratory-depression). The article warns that patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system depressants and elderly people might be at higher risk of experiencing severe respiratory depression and dose adjustments might be necessary.

3.4 CARM data

At 30 September 2017, 208 cases associated with the use of gabapentin have been reported to the Centre for Adverse Reactions Monitoring (CARM). Of these, no cases reported respiratory depression.

3.4.1 Worldwide data

[redacted]

Comments:

No cases have been reported in New Zealand in association with respiratory depression from the use of gabapentin.

4.0 DISCUSSION AND CONCLUSIONS

Reviews have been undertaken by international regulators on the risk of respiratory depression from the use of gabapentin without concomitant opioids. Medsafe has also taken the opportunity to review the available information.

Reviews carried out by Health Canada and by the UK PRAC concluded there is an association between the use of gabapentin alone and the risk of respiratory depression and that product information updates are warranted as a result. Product information for Neurontin (gabapentin) in Canada and the UK have already been updated.

There appears to be a biologically plausible mechanism that gabapentin can affect the respiratory system and cause respiratory depression. Gabapentin is a reversible inhibitor of GABA transaminase and by modulating GABA in this way, gabapentin has an inhibitory effect on the respiratory centre in the medulla [6].

Respiratory depression is a serious adverse reaction and it is important that patients and healthcare professionals are aware of the possibility of this occurring with certain medicines.

The New Zealand data sheet for Neurontin (dated 14 June 2017) currently only refers to the risk of respiratory depression with concomitant gabapentin and opioid use.

[redacted]

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- data sheet updates are necessary to highlight the possibility of respiratory depression from the use of gabapentin alone.
- this topic requires further communication other than MARC's Remarks in *Prescriber Update*.

6.0 ANNEXES

1. Pfizer review [confidential]
2. Health Canada review [confidential]
3. TGA review [confidential]
4. PRAC Recommendations on Signals

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