Medicines Adverse Reactions Committee

Meeting date	3 December 2020	Agenda item	3.2.1
Title	**Gabapentin and pregabalin safety review**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**		**Sponsor**
Gabapentin	Apo-Gabapentin 100 mg, 300 mg, 400 mg		Apotex
	Arrow - Gabapentin 100 mg, 300 mg, 400 mg		Teva Pharma
	Neurontin 100 mg, 300 mg, 400 mg, 600 mg		Upjohn
	Nupentin 400 mg		Mylan
Pregabalin	Pregabalin Pfizer 25 mg, 75mg, 150 mg, 300 mg,		Upjohn
PHARMAC funding	Apo-Gabapentin and Pregabalin Pfizer are fully funded		
Previous MARC meetings	172nd meeting held 7 December 2017: Gabapentin and the risk of respiratory depression without concomitant opioids		
International action	TGA: Gabapentinoids and risk of harmful and hazardous use (Feb 2019) Health Canada: Caution when taking gabapentin or pregabalin with opioids (Sep 2019) FDA: Serious breathing problems when used with CNS depressants or in patients with lung problems (Dec 2019)		
Classification	Prescription medicine		
Usage data	Number of people who received a dispensing of a PHARMAC funded medicine from a community pharmacy at least once during 2019: • gabapentin: 66,040 • pregabalin: 34,790		
Advice sought	**The Committee is asked to advise on the following:** • Do the gabapentin or pregabalin data sheets require updating with information regarding misuse, abuse and dependence; opioid-related death and respiratory depression; or use in elderly patients? • Is any other communication required on any of these three potential safety concerns? This could include a general article in *Prescriber Update* or a safety communication the Medsafe website.		

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1 PURPOSE

Gabapentin and pregabalin are antiepileptics that are also indicated for the treatment of neuropathic pain. Guidelines generally recommend tricyclic antidepressants, gabapentin and pregabalin as first-line medicines for neuropathic pain.

PHARMAC funding for gabapentin and pregabalin was widened in mid-2018. This led to some concerns that the use of gabapentin and pregabalin would increase leading to a higher likelihood of misuse, abuse and/or dependence. There was also some concern about the use of gabapentin and pregabalin in the elderly and whether reduced doses are needed.

During 2019, actions were taken in other countries on the use of gabapentin and pregabalin. For example, the United Kingdom classified both gabapentin and pregabalin as controlled drugs due to the rising number of deaths linked to the medicines. Gabapentinoids and risk of harmful and hazardous use was reviewed in Australia. The United States and Canada also published safety communications on the risk of respiratory depression when used with other CNS depressants, including opioids.

The purpose of this paper is to review three potential safety concerns with gabapentin and pregabalin: misuse, abuse and dependence; opioid-related death and respiratory depression; and use in elderly patients.

2 BACKGROUND

2.1 Gabapentin and pregabalin

2.1.1 Approval and funding

Gabapentin and pregabalin are often referred to collectively as gabapentinoids. Gabapentin (Neurontin) was first approved in New Zealand in 1994, and pregabalin (Lyrica, now Pregabalin Pfizer) in 2005.

PHARMAC funding for gabapentin and pregabalin was widened in 2018:

- Since 1 May 2018 pregabalin is fully funded without restriction (previously not funded).
- Since 1 June 2018 special authority requirements for gabapentin were removed and it is now fully funded without restriction.

2.1.2 Indications

Gabapentin is indicated for:

- the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures in adults and children aged 3 years and above who have not achieved adequate control with standard antiepileptic medicines.
- the treatment of neuropathic pain in adults over 18 years of age.

Pregabalin is indicated for:

- adjunctive therapy in adults with partial seizures with or without secondary generalisation.
- the treatment of neuropathic pain in adults.

Off-label (unapproved) uses for gabapentinoids may include treatment of non-neuropathic pain (eg, restless legs syndrome, migraine), generalised anxiety disorder, spasticity associated with multiple sclerosis, pruritus associated with end-stage renal disease, intractable hiccup in palliative care, alcohol use disorder, and menopausal conditions.

Comments:
The extent of unapproved uses (off-label) of gabapentin and pregabalin is unknown, as with any unapproved use of medicines.

2.1.3 Dose

The gabapentin (Neurontin) data sheet includes the following information in Section 4.2 Dose and method of administration:

- Epilepsy (adults & children >12 years old):
  - The effective dose range in clinical trials was 900 mg/day to 1800 mg/day given in divided doses (three times a day). May initiate at 300 mg three times a day on day-1 or by titrating the dose: Day-1: 300 mg; day-2: 300 mg twice a day; day-3: 300 mg three times a day.
  - Titration may be preferable for patients with renal impairment, patients with encephalopathy, patients on more than 2 other antiepileptics and those with multiple other medical problems.
  - To minimise potential side effects especially somnolence, dizziness, fatigue and ataxia, the first dose on day-1 may be administered at bedtime.
- Neuropathic pain (adults >18 years old):
  - The starting dose is 900 mg/day given in three equally divided doses and titrated if necessary based on response up to a maximum of 3600 mg/day.
- Impaired renal function in patients with neuropathic pain or epilepsy:
  - Dose adjustment is recommended in patients with compromised renal function as described in the table below and/or in those undergoing haemodialysis.

Creatinine Clearance (mL/min)	Total Daily Dose[a] (mg/day)
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150[b]-600
< 15	150[b]-300

[a] Total daily dose should be administered as a divided three times a day regimen. Doses used to treat patients with normal renal function (creatinine clearance ≥80 mL/min) range from 900 mg/day to 3600 mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance <79 mL/min).
[b] To be administered as 300 mg every other day.

The pregabalin (Pfizer) data sheet includes the following information in Section 4.2 Dose and method of administration:

- Neuropathic pain:
  - Can be started at 150 mg/day given as two divided doses. Based on individual patient response and tolerability the dose may be increased after an interval of 3 to 7 days to 300 mg/day given as two divided doses. If needed the dose can be increased to a maximum of 600 mg/day after an additional 7-day interval.
  - Since diabetes is frequently complicated by renal disease, patients with diabetic neuropathy should be assessed for renal impairment before starting and the dose adjusted appropriately.
  - The effectiveness of pregabalin in the treatment of neuropathic pain has not been assessed in controlled clinical trials for treatment periods longer than 12 weeks. The risks and benefits of treatment to an individual patient should be assessed before extending therapy for longer than 12 weeks.
- Epilepsy:
  - Can be started at 150 mg/day given as two divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg/day given as two divided doses after 1 week. The maximum dose of 600 mg/day given as two divided doses may be achieved after an additional week.
- Renal impairment:
  - As pregabalin clearance is directly proportional to creatinine clearance, dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr) as shown in the table below using the following formula:

$$CL_{cr}(ml/min) = \frac{[140 - age\ (years)]\ x\ weight\ (kg)}{72\ x\ serum\ creatinine\ (mg/dL)}\ (x\ 0.85\ for\ female\ patients)$$

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥60	150	600	BID
30 – 60	75	300	QD or BID
15 – 30	25 – 50	150	QD or BID
<15	25	75	QD
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

BID = Two divided doses
QD = Single daily dose
* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose
+ Supplementary dose is a single additional dose

- Elderly (>65 years):
    - No dose adjustment is necessary for elderly patients unless their renal function is compromised (see table above).

Comments:

In general, gabapentin and pregabalin are started at lower doses and titrated up as needed. Both require dose adjustments for renal impairment. The pregabalin data sheet is more explicit in stating doses in the elderly don't require adjustment unless their renal function is compromised.

Interestingly the pregabalin data sheet states the effectiveness of pregabalin for neuropathic pain hasn't been studied beyond 12 weeks in clinical trials and patients should be reviewed before extending treatment.

2.1.4 Mode of action and pharmacokinetics

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA), and pregabalin is an analogue of GABA.

Gabapentin and pregabalin share a similar mechanism of action: inhibiting calcium influx and subsequent release of excitatory neurotransmitters [1]. However, their pharmacokinetic and pharmacodynamic properties differ (Table 1). It is thought pregabalin may have a higher dependence potential than gabapentin due to its rapid absorption and faster onset of action.

Table 1: Summary of pharmacokinetic properties of gabapentin and pregabalin [1]

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Bockbrader et al 2010 [1]

2.1.5 Classification

In New Zealand, both gabapentin and pregabalin are prescription medicines. The Ministry's Expert Advisory Committee on Drugs (EACD) considered scheduling pregabalin as a controlled drug at their meeting on 15 October 2019. The EACD decided not to schedule pregabalin as a controlled drug, and recommended prescriber education to improve its use.

Australia also classifies gabapentin and pregabalin as prescription medicines.

In the United Kingdom, both gabapentin and pregabalin are class C controlled drugs as of 1 April 2019. The government accepted the Advisory Council on the Misuse of Drugs (ACMD) concerns and recommendations from 2016. Gabapentin and pregabalin were classified as controlled drugs due to the rising number of deaths linked to the medicines.

In the United States, pregabalin is classified as a schedule V controlled substance, while gabapentin is not a controlled substance at a federal level.

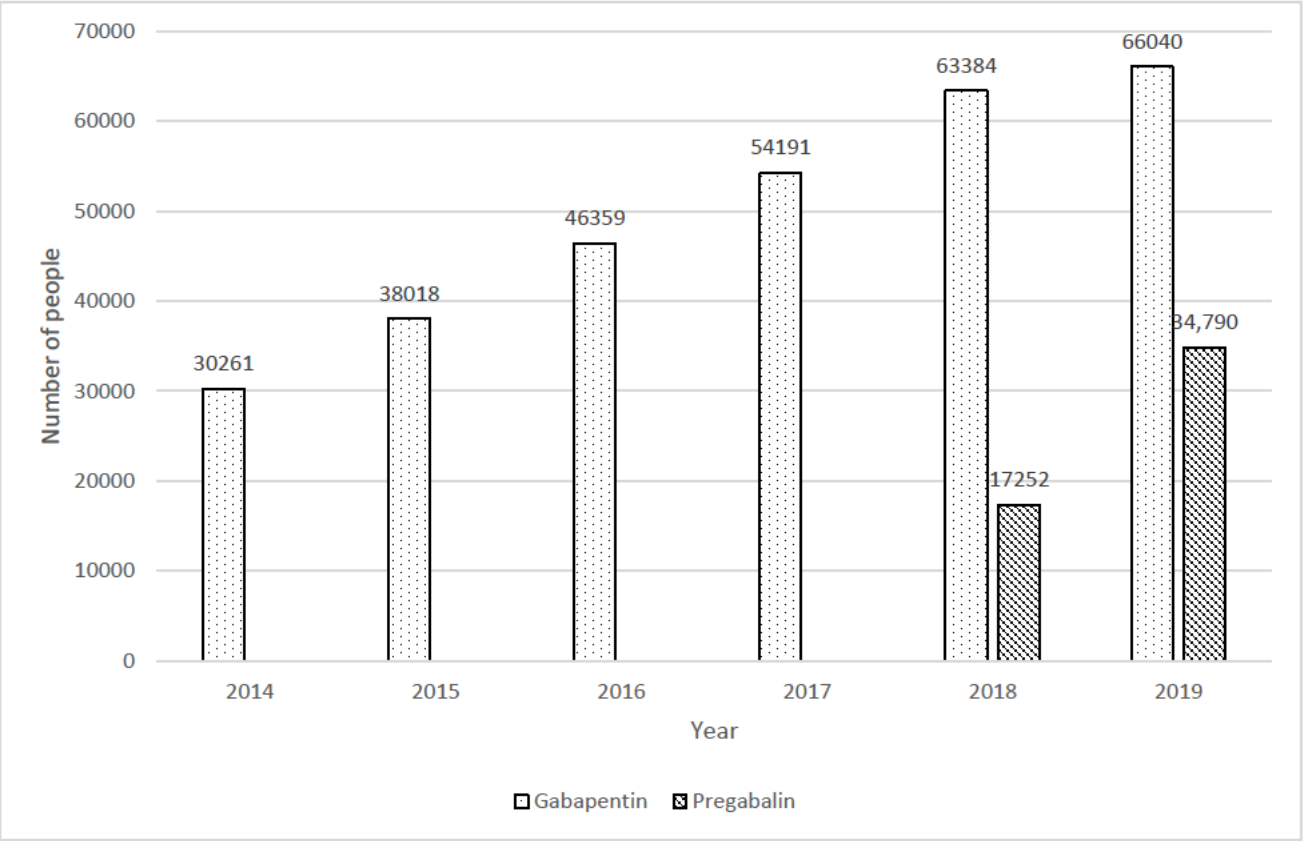
Comments:
The Ministry's EACD classifies controlled drugs based on the risk of harm to individuals or society. The criteria assessed include the likelihood or evidence of abuse, the risks to public health, therapeutic value, and ability of the drug to create physical or psychological dependence. The EACD's decision not to schedule pregabalin as a controlled drug could be due to insufficient evidence in meeting the required criteria.

2.1.6 Usage data

New Zealand's overall usage of gabapentin and pregabalin is shown in Figure 1. There is a steady increase in the number of people receiving gabapentin each year. It is unknown what indication gabapentin is being used for (epilepsy vs. neuropathic pain). The prevalence of neuropathic pain is predicted to increase due to an aging population, increased cancer survival and chemotherapy-induced neuropathy, and an increased prevalence of diabetic neuropathy [2]. Therefore, the increasing use of gabapentin over time could reflect the increasing prevalence of neuropathic pain.

The use of pregabalin appears to have doubled from 17,252 people in 2018 to 34,790 people in 2019. However, PHARMAC funding of pregabalin started on 1 May 2018 so the total number of people for 2018 is not for the full year. The use could therefore be potentially steady over time if this is accounted for.

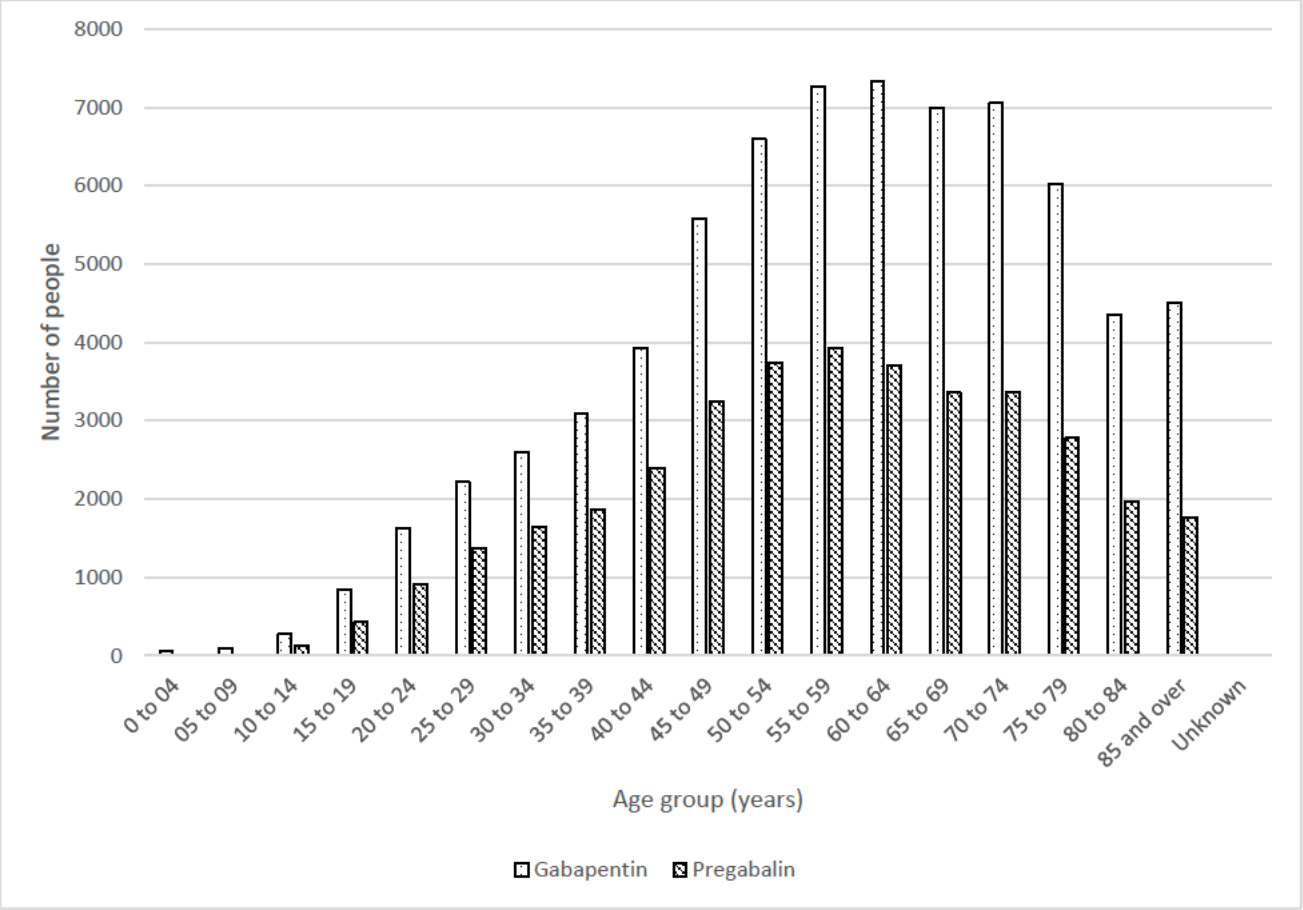
Figure 1: Usage of gabapentin and pregabalin in New Zealand 2014 to 2019, by year *



* The number of people reflects those who received a dispensing of the PHARMAC funded medicine as a named person from a community pharmacy at least once during the year (includes people who only received a repeat dispensing during the year). Data for 2014 to 2018 was extracted from the Pharmaceutical Data Web Tool on 17 September 2019 and data for 2019 was extracted using the Qlik Pharmaceutical Dispensings app on 17 July 2020. The data is not a validated statistic and therefore considered unofficial.

Figure 2 shows the use of these medicines during the year 2019 by age group. The trend for use in various age groups is similar for gabapentin and pregabalin (highest in 50 to 74 year-olds).

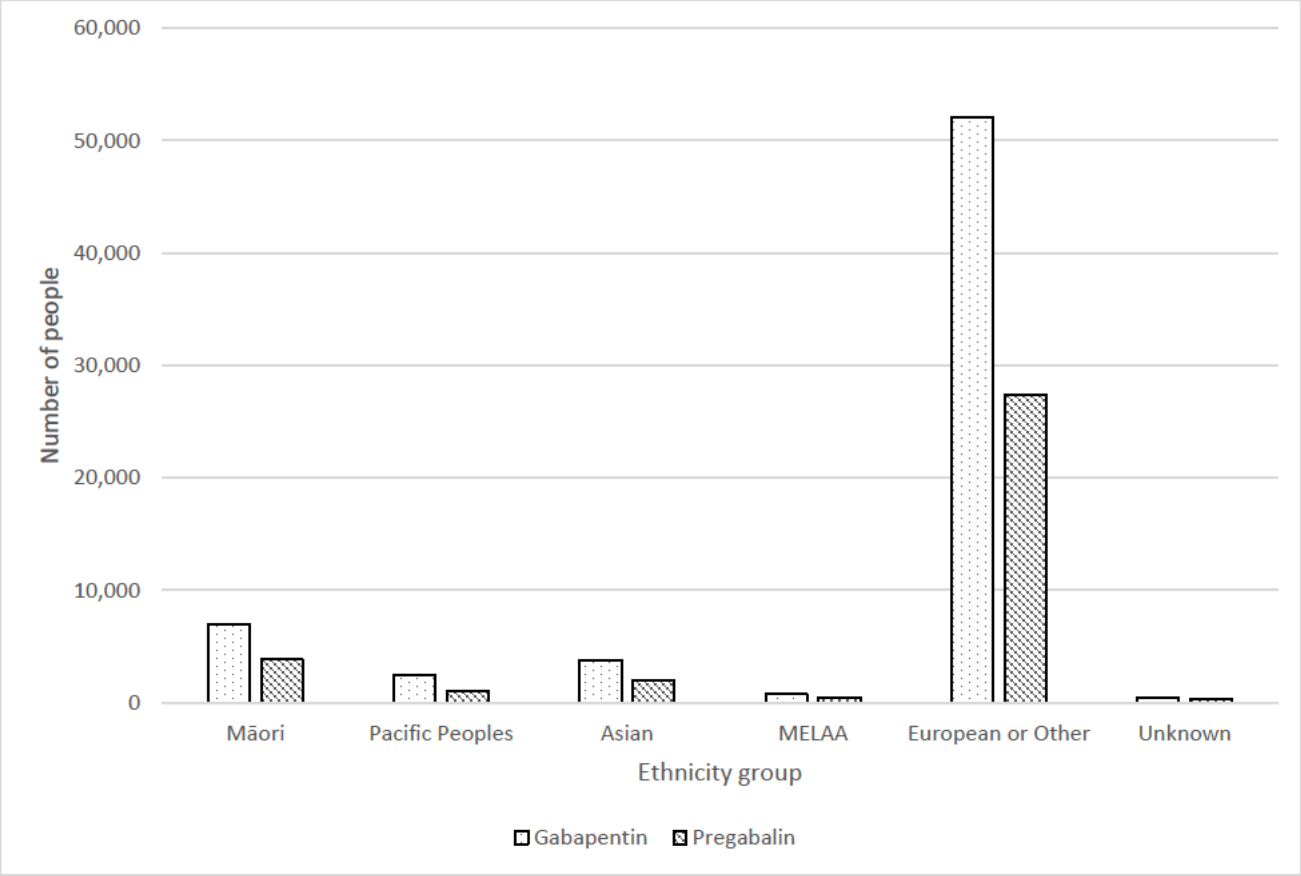
Figure 2: Usage of gabapentin and pregabalin in New Zealand 2019, by age group *



* The number of people reflects those who received a dispensing of the PHARMAC funded medicine as a named person from a community pharmacy at least once during the year (includes people who only received a repeat dispensing during the year). Data was extracted using the Qlik Pharmaceutical Dispensings app on 17 July 2020. The data is not a validated statistic and therefore considered unofficial.

Figure 3 shows the use of gabapentin and pregabalin in 2019 by ethnicity. The number of people receiving a dispensing for gabapentin or pregabalin is highest in the European or other group followed by Māori.

Figure 3: Usage of gabapentin and pregabalin in New Zealand 2019, by ethnicity *



* The number of people reflects those who received a dispensing of the PHARMAC funded medicine as a named person from a community pharmacy at least once during the year (includes people who only received a repeat dispensing during the year). Data was extracted using the Qlik Pharmaceutical Dispensings app on 21 September 2020. The data is not a validated statistic and therefore considered unofficial.

2.1.7 Spontaneous adverse reaction reports to CARM (Annex 1)

Spontaneous reports of adverse reactions where gabapentin or pregabalin are coded by CARM as suspect medicines are shown in this section. Cases where both gabapentin and pregabalin are involved may appear in both the gabapentin subsection (2.1.6.1) and pregabalin subsection (2.1.6.2). The usual limitations of data from spontaneous adverse reaction reports apply when interpreting data in this section.

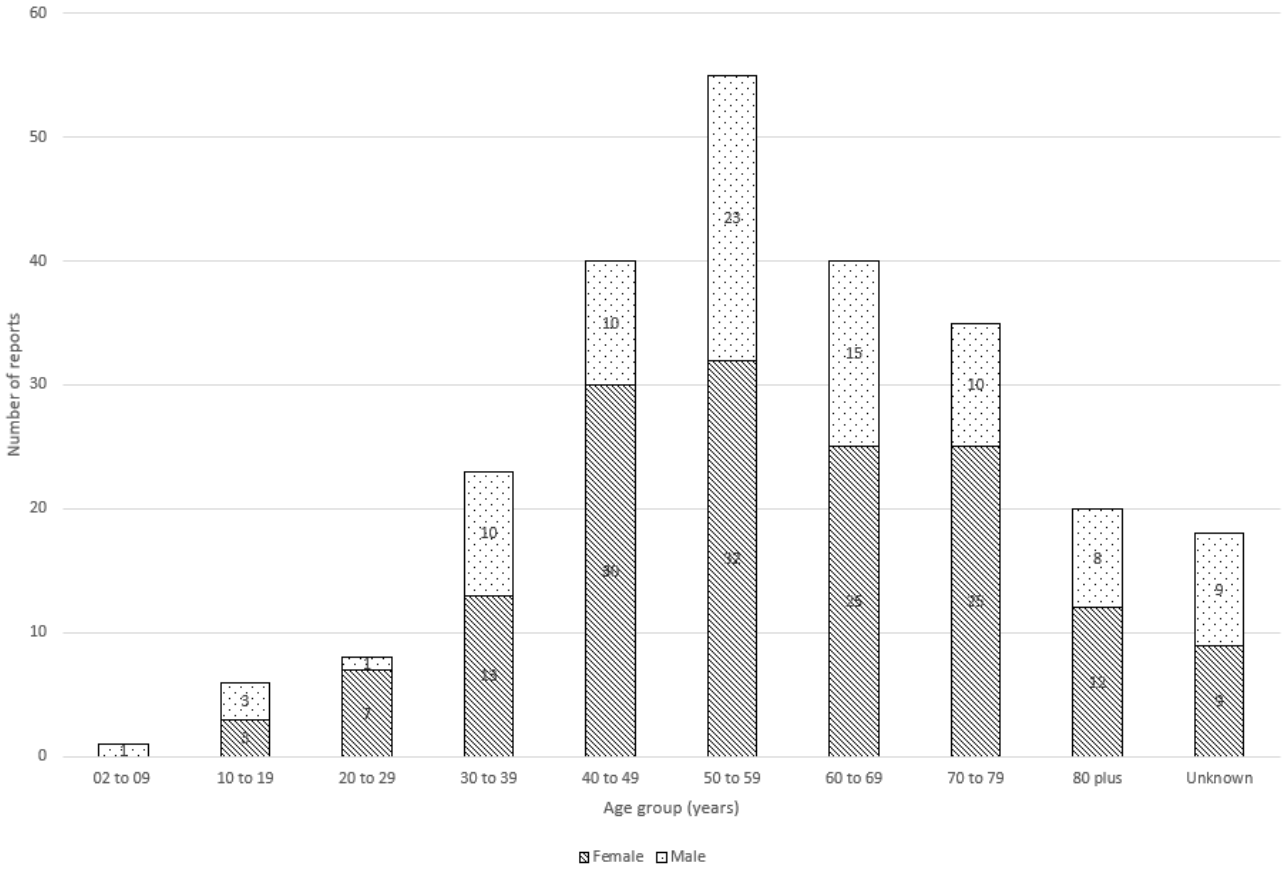
2.1.7.1 Gabapentin

Up to 30 June 2020, CARM received 248 adverse reaction reports where gabapentin was coded as the suspect medicine. Of these 248 reports:

- [redacted]
- 7 cases indicated abuse, misuse or dependence [redacted]
- The relevant reaction terms reported in the 7 cases indicating abuse, misuse or dependence were withdrawal syndrome (n=4), drug withdrawal syndrome (n=3), and drug-alcohol interaction (n=1).

Figure 4 shows the 248 reports by age and gender. The majority of cases were female (n=156; 63%) and there were 95 reports (38%) in patients aged 60 years and older.

Figure 4: Reports to CARM where gabapentin was reported as the suspect medicine, by age and gender, up to 30 June 2020*



* 2 reports where age and gender were unknown

[redacted]

Table 2: Line listing of the 14 serious reports reported since 2015 where gabapentin was coded as the suspect medicine

ID	Date	M/F	Age	Medicine(s)	Reaction(s)	Other info
117123	Jul 2015	F	71	gabapentin*, zoledronate*, prednisone, nortriptyline, colecalciferol, aspirin, simvastatin, cilazapril, omeprazole, spironolactone, oestradiol, furosemide, carvedilol, paracetamol + codeine	interstitial nephritis, renal failure aggravated, hypocalcaemia, myocardial infarction	[redacted]
119219	Jan 2016	M	73	gabapentin*	papular rash, erythema, pruritus	[redacted]
119540	Feb 2016	M	14	gabapentin*	dispensing dose error	[redacted]
120098	Mar 2016	M	37	gabapentin*	hemiparesis, paraesthesia, palpitation, memory impairment, dyspepsia	[redacted]
122156	Sep 2016	F	68	paracetamol*, ibuprofen*, gabapentin*, nortriptyline*, fluoxetine*	fatty liver, cholestatic hepatitis	[redacted]
122281	Sep 2016	F	72	gabapentin*	dizziness, stroke	[redacted]
127167	Jan 2018	F	50	gabapentin*	depersonalisation, slurred speech, amnesia, confusion	[redacted]

129614	Aug 2018	F	71	morphine*, pembrolizumab*, gabapentin*, methadone*, dexamethasone*, omeprazole, metoclopramide, folic acid, laxsol, fluconazole, paracetamol, carboplatin, pemetrexed	confusion, speech disorder	[redacted]
130055	Sep 2018	M	35	gabapentin*	myoclonic jerks	[redacted]
130777	Nov 2018	F	59	tramadol, gabapentin*, ibuprofen, oxycodone*, codeine	dry mouth, tooth caries	[redacted]
133747	Jul 2019	M	57	gabapentin*, baclofen*	confusion, decreased consciousness, medication error (no dose adjustment)	[redacted]
135633	Jan 2020	F	42	liposomal amphotericin*, gabapentin*, methadone*, piperacillin + tazobactam, multivitamins	hyperkalaemia, cardiac arrest	[redacted]
135955	Jan 2020	F	79	ceftriaxone*, gabapentin*	neutropenia	[redacted]
136057	Feb 2020	F	64	omeprazole*, naproxen*, doxycycline*, gabapentin*, ascorbic acid*	acute renal failure, renal calculus (crystalluria), interstitial nephritis, renal tubular necrosis, acute ischaemic renal failure	[redacted]

* = suspect medicine as coded by CARM

The seven cases indicating misuse, abuse or dependence are summarised in Table 3. Five of these cases were reported prior to 2011 and the remaining two were reported in 2019.

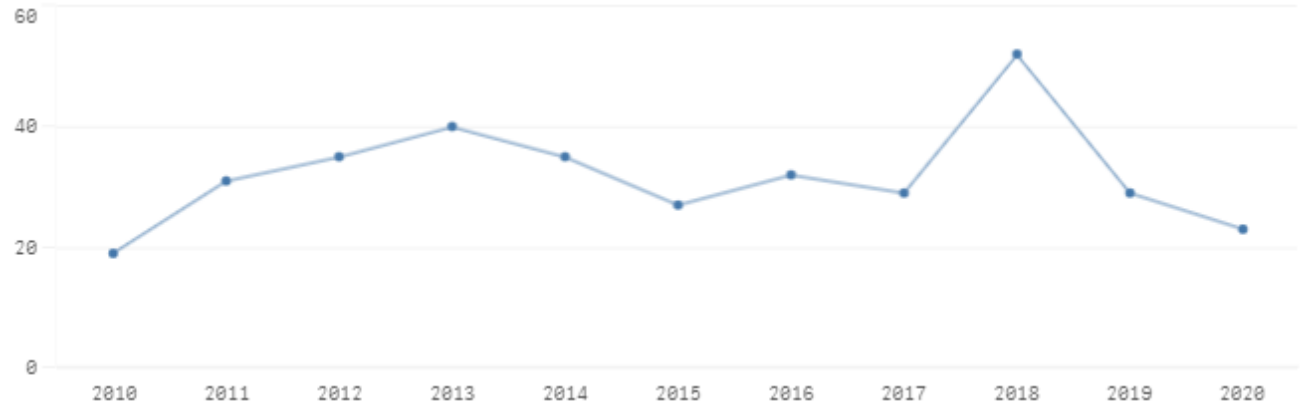
Table 3: Line listing of the seven cases coded with terms that can be synonymous with misuse, abuse or dependence of gabapentin [redacted]

ID	Date	M/F	Age	Medicine(s)	Reaction(s)
036058	Oct 1997	F	49	gabapentin*, carbamazepine, valproate	drug withdrawal syndrome, tremor, agitation, paranoid reaction, anxiety
051356	May 2002	M	57	mexiletine*, gabapentin*, tenoxicam	anger, mood swings, withdrawal syndrome, drug-alcohol interaction
062548	Oct 2004	F	49	gabapentin*, carbamazepine, nadolol, tenoxicam, bendrofluazide	chest pain, palpitation, drug withdrawal syndrome, tremor
064084	Feb 2005	F	54	gabapentin*	impaired concentration, memory impairment, withdrawal syndrome, depersonalisation, anxiety
093296	Dec 2010	F	76	gabapentin*, nortriptyline, omeprazole	parosmia, withdrawal syndrome
135012	Nov 2019	F		gabapentin*, pregabalin*	mood swings, tearful, nausea, hyperacusis, withdrawal syndrome
135138	Nov 2019	F	50	gabapentin*	cognitive function abnormal, dyspnoea, fatigue, drug withdrawal syndrome, tinnitus

* = suspect medicine as coded by CARM

Analysis of the number of reports over time using Qlik (data extracted 2 November 2020) showed from 2010 to 2020, there was a peak of reports in 2018 when PHARMAC funding was widened (n=52), but the number of reports has since reduced to previous levels of about 25 reports per year in 2019 and 2020 (Figure 5).

Figure 5: Number of reports where gabapentin was reported as the suspect medicine, by year since 2010 *



* x-axis = year, y-axis = number of reports; data extracted from Qlik on 2 November 2020 and is not considered an official statistic

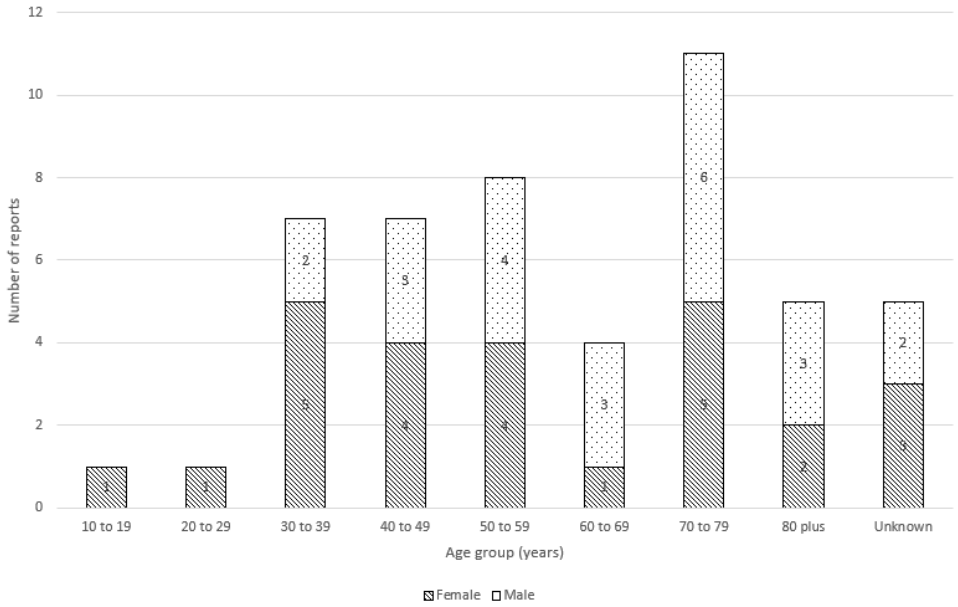
2.1.7.2 Pregabalin

Up to 30 June 2020, CARM received 50 adverse reaction reports where pregabalin was coded as the suspect medicine. Of these 50 reports:

- [redacted]
- 7 cases indicated abuse, misuse or dependence [redacted]
- Withdrawal syndrome was the relevant reaction term reported in all 7 cases indicating abuse, misuse or dependence.

Figure 6 shows the 50 reports by age and gender. There were 20 reports (40%) in patients aged 60 years and older.

Figure 6: Reports to CARM where pregabalin was reported as the suspect medicine, by age and gender, up to 30 June 2020 *



* 1 report of unknown gender

[redacted]

Table 4: Line listing of the 12 serious reports where pregabalin was coded as the suspect medicine

ID	Date	M/F	Age	Medicine(s)	Reaction(s)	Other info
091455	Aug 2010	M	55	pregabalin*, venlafaxine*, baclofen	suicide	[redacted]
100857	Apr 2012	F	40	pregabalin*	anaphylaxis, angioedema	[redacted]
109841	Jan 2014	F	58	pregabalin*, venlafaxine*	suicide attempt	[redacted]
119601	Feb 2016	M	71	pregabalin*, methadone*	accident, bladder carcinoma, withdrawal syndrome	[redacted]
130125	Sep 2018	F	72	levothyroxine, pregabalin*, morphine	chest pain, confusion, somnolence, dizziness, progression of disease	[redacted]
130646	Oct 2018	F	75	pregabalin*	throat swelling, tongue swelling, muscle weakness, speech disorder, malaise	[redacted]
131279	Dec 2018	M	83	pregabalin*, gabapentin, diasip	excessive sedation, delirium, diarrhoea	[redacted]
131980	Mar 2019	F	89	pregabalin*	asthenia	[redacted]
132557	Apr 2019	F	37	pregabalin*, levothyroxine	ataxia, coordination abnormal, hypoaesthesia, vision blurred	[redacted]
132962	May 2019	M	52	morphine*, pregabalin*	suicidal ideation, suicide attempt	[redacted]

135419	Dec 2019	M	79	pregabalin*, morphine	confusion aggravated, disorientation, dyskinesia, miosis, dyspnoea	[redacted]
136065	Feb 2020	F	87	pregabalin*, aspirin, cilazapril, atorvastatin, triazolam, ropinirole, codeine, amitriptyline, morphine, Crystaderm	bullous eruption	[redacted]

* = suspect medicine as coded by CARM

The seven cases indicating misuse, abuse or dependence are summarised in Table 5. There are three cases reported since 2018 when PHARMAC funding started.

Table 5: Line listing of the seven cases coded with terms that can be synonymous with misuse, abuse or dependence of pregabalin [redacted]

ID	Date	M/F	Age	Medicine(s)	Reaction(s)
094871	Apr 2011	M	44	pregabalin*	amnesia, impaired concentration, withdrawal syndrome
096116	Jul 2011	M	34	pregabalin*	abdominal pain, headache, withdrawal syndrome
096253	Jul 2011	M	58	pregabalin*	dizziness, ulcerative stomatitis, bullous eruption, withdrawal syndrome
119601	See Table 4				
131036	Nov 2018	F	34	pregabalin*, dothiepin, quetiapine, clonazepam	panic reaction, suicidal ideation, agitation, therapeutic response decreased, withdrawal syndrome
133627	Jul 2019	F	40	pregabalin*	withdrawal syndrome
135012	Nov 2019	F		gabapentin*, pregabalin*	mood swings, tearful, nausea, hyperacusis, withdrawal syndrome

* = suspect medicine as coded by CARM

Analysis of the number of reports over time using Qlik (data extracted 2 November 2020) showed there was an increase in reports in 2018 when PHARMAC funding started (n=18) (Figure 7).

Figure 7: Number of reports where pregabalin was reported as the suspect medicine, by year since 2010*

* x-axis = year, y-axis = number of reports; data extracted from Qlik on 2 November 2020 and is not considered an official statistic

2.1.8 National Poisons Centre data

The numbers of patients with an exposure to a gabapentinoid based on calls to the National Poisons Centre (NPC) from 1 January 2014 to 30 September 2020 are summarised in Table 6. Overall most calls relate to gabapentin rather than pregabalin. There is an increasing trend over time, except for 2018 (the year PHARMAC funding started) where there was a slight dip in the number of calls.

Table 6: Summary of calls to the National Poisons Centre regarding gabapentin or pregabalin, 1 January 2014 to 30 September 2020

	2014	2015	2016	2017		2018		2019		2020**		Total
Reason for exposure	G	G	G	G	P	G	P	G	P	G	P	Row totals
Abuse				1		2		2	1	1		8
Child Exploratory	5	8	10	22		11	1	12	1	14	4	90
Intentional***	7	9	23	18	1	12	2	16	5	10	12	120
Other										1		1
Therapeutic error	13	18	15	35		27	3	31	13	23	8	182
Unintentional	5		4	3		1		2	6	7	2	32
Unknown	2			2		2		3	1	2	1	14
Substance totals	32	35	52	81	1	55	6	66	27	58	27	
Total gabapentinoid	32	35	52	82		61		93		85		451
Total exposure patients	22,391	22,525	21,695	21,053		21,311		22,926		17,604**		

G=gabapentin; P=pregabalin; *26 calls were 'linked contacts'. These are multiple contacts about the same exposure event, and may lead to the exposure being double-counted here. **Up to 30 September 2020. ***Generally intentional self-harm.

There are some limitations with NPC data. The distinction between abuse and intentional (self-harm) is not always clear in contacts to the NPC, and some unintentional exposures may also be due to drug abuse/misuse-type behaviour. This may be difficult to determine due to the NPC staff interacting via phone (not face-to-face), and often interacting with third-party callers (eg, healthcare professionals) calling on behalf of the patient. In such calls (as with other calls) there may be limited time to discuss motives behind the exposure as the main focus is on risk assessment and acute medical management advice.

There are some duplicates in the 128 abuse and intentional calls (highlighted in green in Table 6), leaving 119 unique records once these duplicates are accounted for. The age distribution of abuse and intentional gabapentinoid exposure patients are shown in Figure 8. Ethnicity was only reported for 16 patients (Māori=2, European=13, other ethnicity=1).

Figure 8: Age distribution of abuse and intentional gabapentinoid exposure patients

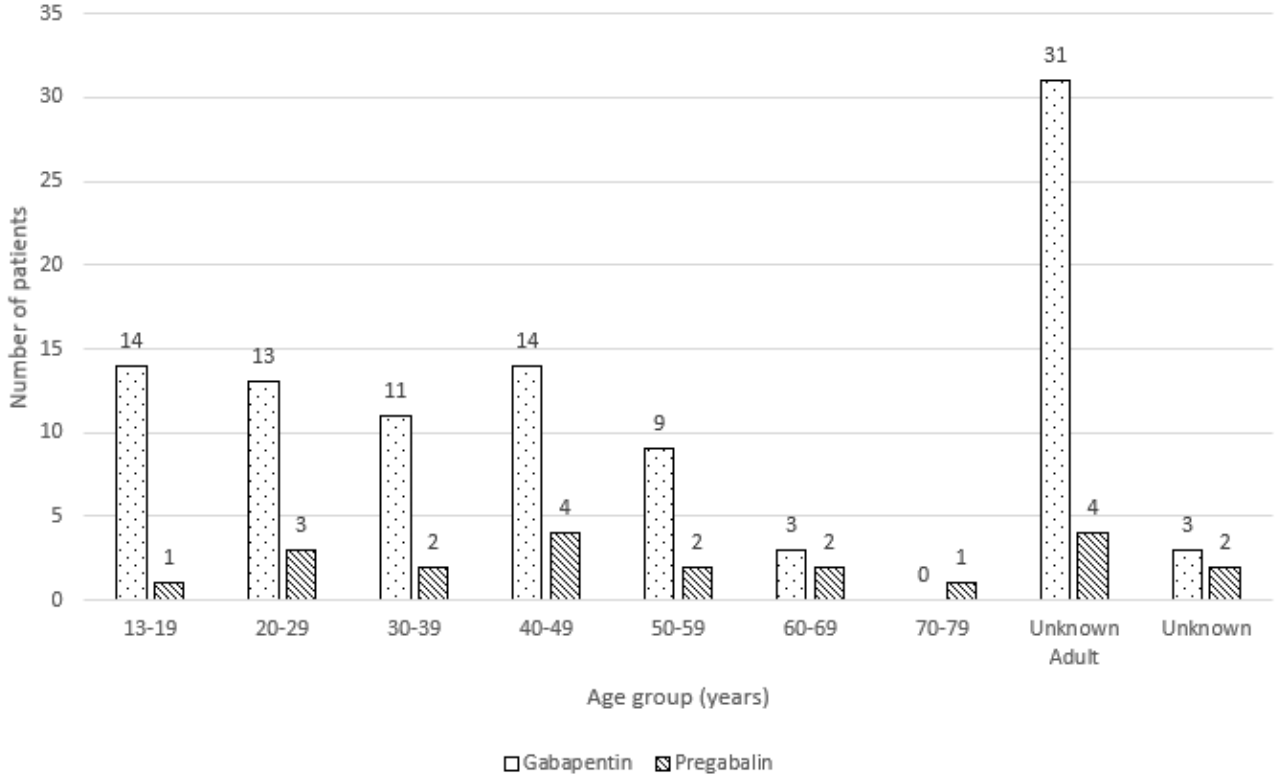


Table 7 summarises the abuse and intentional gabapentinoid exposures by reason for exposure, caller relationship to the patient and number of substances involved. Of note is the high proportion of calls from healthcare professionals (overall rate for all calls is about 15–17%). The number of substances involved for abuse and intentional gabapentinoid exposures indicates gabapentinoids are commonly involved in poly-substance exposures (73/119; 61% involved more than one substance).

Table 7: Summary of abuse and intentional gabapentinoid exposures, 1 January 2014 to 30 September 2020, by reason for exposure, caller relationship to patient, and number of substances involved

	gabapentin	pregabalin	total
Reason for exposure			
Abuse	6	1	7
Intentional	92	20	112
Caller relationship to patient			
Healthcare professionals:			
Ambulance	17	6	23
Caregiver	1		1
Doctor	29	6	35
Govt. dept. (police)	2		2
Nurse	11	1	12
Other health	4	3	7
General public:			
Friend/parent/relative/spouse/partner	21	5	26
Self	10		10
Workplace associate	1		1
Unknown	2		2
Number of substances involved			
1	41	5	46
2	18	8	26
3	14	5	19
4	11	2	13
5	5		5
6	3		3
7	2		2
9	4	1	5

2.1.9 NDIB seizure data

[redacted]

[redacted]

2.1.10 Public interest

In March 2019, Tony Wall (reporter for stuff.co.nz) made enquiries into the use of gabapentin in New Zealand. His article was subsequently published on 7 April 2019 under the headline 'Prescription drug gabapentin, linked to opioid overdoses, has taken off in NZ'. This article noted actions taken in the US and UK based on the misuse of gabapentin, and actions taken in Canada when gabapentinoids are used with opioids. A nurse and medical chair of the NZ National Association of Opioid Treatment Providers were interviewed and they had concerns about its misuse. The article also noted the increasing use of gabapentin over time (2013 to 2017).

In May 2019, a clinical pharmacist emailed Medsafe and David Reith suggesting the issues relating to the safety and addictive/misuse potential of gabapentin and pregabalin are raised, reiterated and strengthened as soon as possible. Medsafe forwarded this request to the Health Quality and Safety Commission (HQSC) as some of the concerns raised fall into their area of safe use of medicines and prescribing. This was tabled at HQSC's medication safety expert advisory group's (EAG) meeting on 4 September 2019. The EAG discussed:

- re-classification as controlled drugs
- processes and costs of putting them into DHB's monitored medicines category
- difficulties in oversight, particularly in the private sector
- variations in guidelines and prescribing practices
- effectiveness as pain relief
- management by, and access to, acute and chronic pain services
- other education and resources for consumers
- an 'analgesic' stewardship programme, which could encompass gabapentinoids as well as opioids.

The EAG noted further consideration is needed following investigation of the response or actions by Medsafe and MARC. The resulting action was for HQSC to contact Medsafe and MARC and investigate their response. At their next meeting on 27 November 2019, it was reported to the group that reclassification of these medicines as controlled drugs by the EACD requires evidence of harm, and Medsafe had not received any official reports of harm, therefore no changes were being planned. Considering the high risk of harm, the National Medication Safety Advisory Group (NMSAG; new name for the same group) considered it important to pursue at least a cautionary approach to minimising that risk. The group discussed various options for risk minimisation and agreed to keep this as an agenda item for upcoming meetings and discuss further once the Atlas data is available, as this will inform how best to approach minimising the risk. This group meets every three months, but there have been no meeting minutes published since November 2019, therefore progress is uncertain.

2.2 Guidelines for neuropathic pain

2.2.1 NICE guidance

The National Institute for Health and Care Excellence (NICE) guidance for neuropathic pain in adults (last updated 19 July 2019) includes the following information. The definition of neuropathic pain according to the International Association for the Study of Pain (IASP, 2011) is 'pain caused by a lesion or disease of the somatosensory nervous system'. The nature and exact location of a lesion or health condition associated with neuropathic pain is not always clear especially in non-specialist settings. Common conditions that have peripheral neuropathic pain as a symptom include painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-surgical chronic neuropathic pain, and neuropathic cancer pain. Conditions that can cause central neuropathic pain include stroke, spinal cord injury and multiple sclerosis.

Commonly used pharmacological treatments include antidepressants (tricyclics, SSRIs, SNRIs), antiepileptics, topical treatments and opioids. For all neuropathic pain (except trigeminal neuralgia), the choice is between amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment. If the initial treatment is not effective or not tolerated, offer one of the remaining 3 medicines and consider switching again if the 2nd and 3rd medicines tried are also not effective or not tolerated. Consider tramadol only if acute rescue therapy is needed. Consider capsaicin cream for people with localised neuropathic pain who wish to avoid or who cannot tolerate oral treatments. Treatments for neuropathic pain in non-specialist settings that should not be started unless advised by a specialist to do so include cannabis sativa extract, lamotrigine, levetiracetam, morphine, topiramate, venlafaxine and sodium valproate.

2.2.2 Best Practice Advocacy Centre (bpac^{nz}) guidance

An article on upcoming subsidy changes for gabapentin and pregabalin was published in the *Best Practice Journal* on 9 March 2018 prior to the PHARMAC funding changes. This article discussed the treatment options for neuropathic pain. Tricyclic antidepressants (TCAs), gabapentin and pregabalin are recommended first-line pharmacological treatments for patients with neuropathic pain. Gabapentin and pregabalin are not superior to TCAs for neuropathic pain. Patients who are more susceptible to adverse effects, such as frail elderly people, may be started on lower doses and titrated more gradually.

This article also covered the potential for misuse of gabapentinoids, including diversion. It states gabapentinoids are misused in order to produce euphoria, a state of relaxation and sociability or amplify the effects of other recreational drugs. Reports suggest pregabalin may have a greater potential for misuse than gabapentin as it is more likely to produce euphoria and has greater bioavailability at high doses. Clinicians and pharmacists should be alert for early requests for repeat prescriptions or consider whether patients may be obtaining prescriptions from multiple doctors. Establishing an appropriate analgesic plan with the patient prior to prescribing, including the expected duration of use, may help reduce the potential for misuse.

The article also notes adding opioids with caution. In some cases, first-line medicines will not be sufficient in patients with severe neuropathic pain and they will also require an opioid (eg, tramadol or morphine). Gabapentin or pregabalin can be continued in patients prescribed opioids, however, caution is required as the combination of these medicines can increase the risk of potentially fatal adverse effects, such as respiratory and CNS depression. The risk of accidental overdose is also increased and the ability to perform tasks such as driving or operating machinery may be affected.

Likewise, the article on managing patients with neuropathic pain published in the *Best Practice Journal* in 2016 recommends the following medicines for initial treatment of neuropathic pain:

- tricyclic antidepressants, such as amitriptyline and nortriptyline
- gabapentin (note this article was published when gabapentin was still funded by PHARMAC under special authority and pregabalin wasn't funded at all)
- carbamazepine for patients with trigeminal neuralgia or diabetic polyneuropathy.

2.2.3 New Zealand Formulary (NZF) guidance

Chapter 4.7.4 Pain management of common specific conditions in the New Zealand Formulary (NZF) contains information on neuropathic pain. Tricyclic antidepressants, gabapentin, or pregabalin are the first-line medicines used for neuropathic pain. Treatment choice should be based on adverse effect profile, interactions with existing treatment, and comorbidities. Amitriptyline (unapproved indication) can be an effective treatment for neuropathic pain, and its sedative side effect may be useful if sleep is problematic for the patient. Nortriptyline (unapproved indication) may be better tolerated than amitriptyline. It is less likely to cause postural hypotension and has fewer antimuscarinic effects. At least 4 to 8 weeks of treatment with a first-line medicine is needed to allow for dose titration and sufficient duration of treatment at a therapeutic dose to assess efficacy. For patients who experience a partial response but feel that response is inadequate, increasing the dose or switching to another first-line medicine may be considered. Amitriptyline (or other tricyclic antidepressants) and either gabapentin or pregabalin can be used in combination if the patient has an inadequate response to either medicine at the maximum tolerated dose.

A number of other second-line agents have been used, including tramadol, SSRIs, venlafaxine, other antiepileptics, quetiapine, clonidine and ketamine. However, there is no derived pathway to determine the choice of second-line agents. Choice is dependent on patient factors such as the specific type of neuropathic pain and other comorbidities. Consultation with a pain specialist is recommended.

Comments:

All three guidance documents (NICE, bpac^{nz}, NZF) include gabapentin or pregabalin as first-line pharmacological treatment options for neuropathic pain.

Of the tricyclic antidepressants currently available in NZ, clomipramine appears to be the only one indicated for “chronic painful conditions”.

3 SAFETY CONCERNS

3.1 Misuse, abuse and dependence

Definitions of misuse, abuse and dependence include the following [3, 4]:

- Misuse – any intentional therapeutic use of a medicine in an inappropriate way. This includes using a medicine in a manner or for a purpose other than indicated, including but not limited to, taking another person's medicine, unprescribed or non-recommended route of administration, or a higher dose than prescribed.
- Abuse – any intentional non-therapeutic use of a medicine for the purpose of achieving a desirable psychological or physiological effect.
- Dependence – behavioural, cognitive, and physiological phenomena that may develop after exposure to a substance, typically on a repeated basis. The physical and psychological elements associated with abuse, which include compulsion, withdrawal, and tolerance.

There are reports that some patients abuse gabapentinoids as an adjunct to opioids to potentiate the "opioid high" [5]. Pregabalin is known as "Bud" or "Budweisers" by recreational users because it is said to make them feel the same high as if they were drunk [6].

The misuse, abuse and dependence of any medicine is a challenging area. This includes the difficulties in quantifying the size of the problem as regulatory mechanisms to capture this information are limited, resulting in information or evidence that is often anecdotal. There is also a risk in inadvertently publicising that a medicine can be misused or abused for a particular effect (eg, euphoric effects, relaxation, sedation etc.).

There are many literature articles on the misuse, abuse or dependence of gabapentin or pregabalin. Some of the most relevant and recent articles are summarised below.

3.1.1 NZMJ article – Ponton 2018 [7]

Title: Pregabalin misuse: preventing potential problems in New Zealand

Methods: A review of the literature of papers documenting the misuse of gabapentin and pregabalin with a specific focus on pregabalin.

Results: There is a growing body of evidence on the potential of misuse of pregabalin. It produces a range of sensations, including euphoria, sedation and dissociation. It is commonly used in conjunction with other medicines, most notably sedatives and opioids, leading to an additive effect. Although generally safe when taken alone, pregabalin is a growing feature of drug-related deaths.

Conclusion: Prescribers need to be alert to the potential for pregabalin misuse. This should be achieved through prescribing with great care (eg, not prescribing to new or unknown patients, not in response to direct patient requests for it by name, supplying in limited quantities), regular review of patients and stopping treatment by slow withdrawal when lack of efficacy is seen.

Comments:
This article published in July 2018 highlighted the potential for pregabalin misuse following PHARMAC's proposal to fully fund pregabalin from 1 May 2018. The author is based at the School of Pharmacy, University of Auckland. Using data from other countries, this article comments on the history of pregabalin, its misuse, deaths and approaches to prescribing.

3.1.2 Swedish study – Molero et al 2019 [8]

Title: Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population-based cohort study in Sweden

Study setting and methods: 191,973 participants included from the Swedish Prescribed Drug Register who collected prescriptions for gabapentinoids (pregabalin or gabapentin) during 2006 to 2013. Primary outcomes

were suicidal behaviour, unintentional overdoses, head/body injuries, road traffic incidents and offences, and arrests for violent crime. Outcomes were collected from the Swedish Patient Register which includes all admissions to hospitals in Sweden.

Stratified Cox proportional hazards regression was conducted comparing treatment periods with non-treatment periods within an individual. Participants served as their own control, thus accounting for time invariant factors (eg, genetic and historical factors), and reducing confounding by indication. Additional adjustments were made by age, sex, comorbidities, substance use, and use of other antiepileptics.

Results: Of the 191,973 participants 120,664 were dispensed pregabalin, 85,360 gabapentin and 14,051 were dispensed both medicines. Pregabalin users were younger and associated with a higher prevalence of all outcomes compared with gabapentin users (Table 9).

During the study period 10,026 (5.2%) participants were treated for suicidal behaviour or died from suicide, 17,144 (8.9%) experienced an unintentional overdose, 12,070 (6.3%) had a road traffic incident or offence, 70,522 (36.7%) presented with head/body injuries and 7984 (4.1%) were arrested for a violent crime.

In within-individual analyses (Figure 9), gabapentinoid treatment was associated with increased hazards of suicidal behaviour and deaths from suicide (age adjusted hazard ratio 1.26, 95% CI 1.20 to 1.32), unintentional overdoses (1.24, 95% CI 1.19 to 1.28), head/body injuries (1.22, 95% CI 1.19 to 1.25), and road traffic incidents and offences (1.13, 95% CI 1.06 to 1.20). Associations with arrests for violent crime were less clear (1.04, 95% CI 0.98 to 1.11).

When the medicines were examined separately, pregabalin was associated with increased hazards of all outcomes, whereas gabapentin was associated with decreased or no statistically significant hazards.

Table 9: Sociodemographic and medical characteristics of participants prescribed and dispensed gabapentinoids. Values are numbers (percentages)

Figure 9: Within-individual associations between gabapentinoid treatment and adverse outcomes

When stratifying on age, results for gabapentinoids showed increased hazards of suicidal behaviour in people <55 years old and reduced or no associations in those aged ≥55 years old. The highest hazards were in the age group 15-24 years (1.67, 95% CI 1.52 to 1.84). Patterns were similar for other outcomes; younger participants (15-34 years) showed increased hazards whereas older participants (≥55 years) showed reduced or no associations (Figure 10).

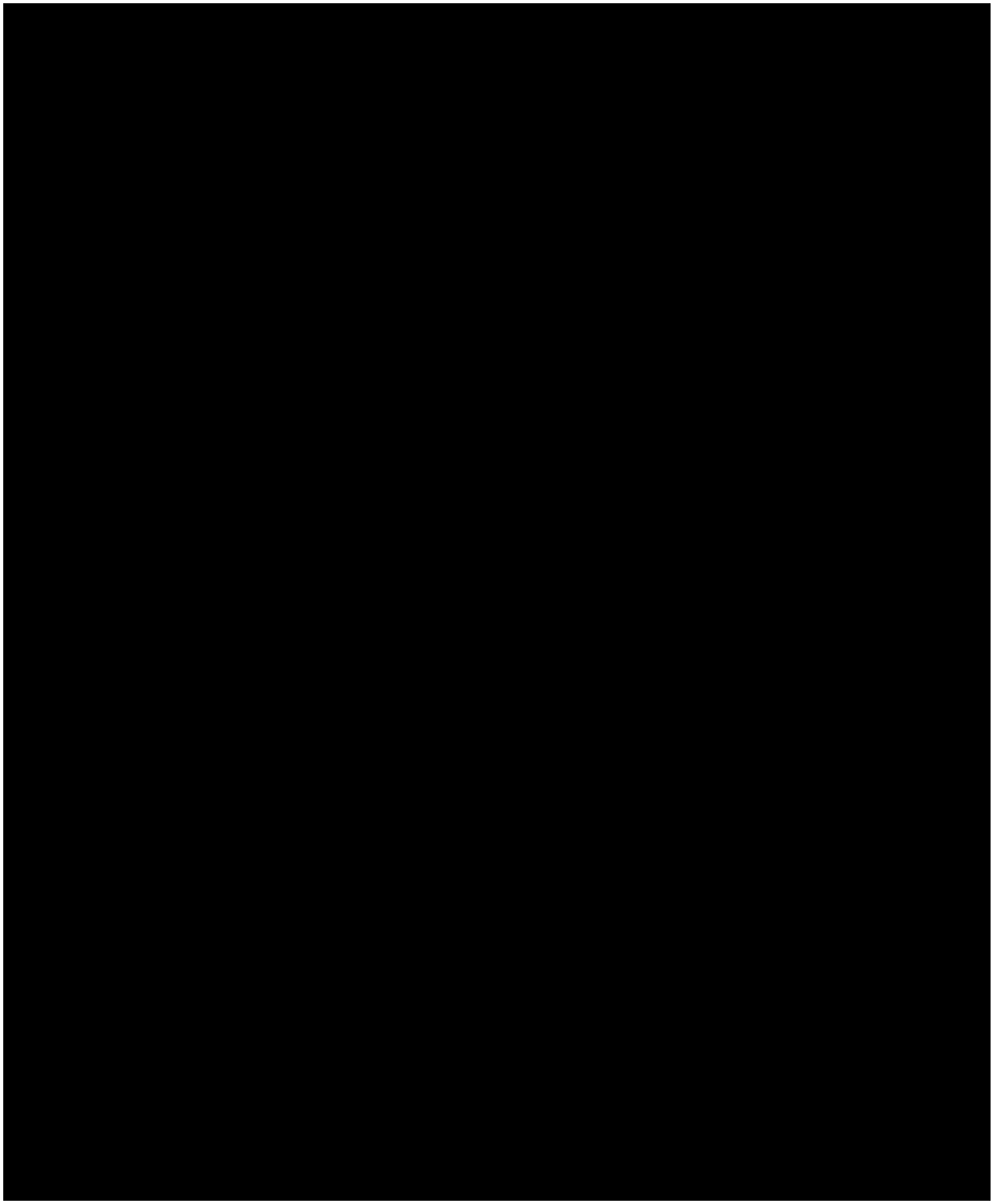
Within-individual associations were further investigated by excluding participants who used other antiepileptics or with substance use disorders during follow-up (Table 10).

The authors analysed participants who had a diagnosis of comorbid epilepsy, psychiatric disorders, or musculoskeletal disorders before the start of gabapentinoid treatment. In comorbid psychiatric disorders, gabapentinoids were associated with lower risk for all outcomes.

Conclusion: The authors conclude this study suggests that gabapentinoids are associated with an increased risk of suicidal behaviour, unintentional overdoses, head/body injuries and road traffic incidents and offences. Pregabalin was associated with higher hazards of these outcomes than gabapentin.

Table 10: Within-individual associations between gabapentinoid treatment and adverse outcomes, excluding participants who used other antiepileptics or with substance use disorders during follow-up

Figure 10: Within-individual associations between gabapentinoid treatment and adverse outcomes by age



Comments:

This study found gabapentinoid treatment in those aged 55 and older was associated with decreased hazards or no clear associations with suicidal behaviour, unintentional overdoses, head/body injuries, road traffic incidents or offences, and arrests for violent crime. However, associations were increased for all outcomes in the younger age group of 15-24 years. This could reflect the general increase in these risks in this age group:

- In 2016 the rates of suicide in New Zealand were highest among youth aged 15 to 24 years (16.8 per 100,000) and those aged 25 to 44 years (16.3 per 100,000).
- Road deaths, serious injuries and minor injuries in 2018 were highest in the 20 to 24 year age group followed by the 15 to 19 year age group.
- Data collected by New Zealand Police on recorded crime offenders statistics show offender proceedings were highest for the15 to 20 and 20 to 25 year age groups during the period July 2014 to September 2020.

The study had a higher proportion of participants in the younger age groups taking pregabalin vs. gabapentin (4.8% vs. 1.8% in those aged <25; 10.4% vs. 4.6% in those aged 25-34 years).

There was no information on indications for gabapentinoids as this information was not available. However in Sweden, gabapentin is indicated for epilepsy and neuropathic pain, whereas pregabalin is also indicated for generalised anxiety disorder. Therefore, the finding of higher hazards with pregabalin compared to gabapentin could be due to confounding by indication.

3.1.3 Australian study – Cairns et al 2019 [9]

Title: Rising pregabalin use and misuse in Australia: trends in utilisation and intentional poisonings

Design: Population-based retrospective cohort study from four sources.

The first source was dispensings in the 10% sample of Australian Pharmaceutical Benefits Scheme (PBS). The PBS 10% sample data set is provided by the Department of Human Services (DHS) and is a random 10% sample of PBS-eligible Australians. Dispensing data was obtained from the PBS 10% sample for pregabalin, gabapentin and carbamazepine from July 2012 to February 2017. This allowed for analysis of time trends and drug utilisation. Pregabalin has been listed on the PBS for neuropathic pain since March 2013 so data from March 2013 to February 2017 were used for in-depth latent class analysis (LCA). A year was defined as 1 March to 28 February.

The second source was intentional poisoning calls to New South Wales Poisons Information Centre (NSWPIC) (2004 to 2016), which captures 50% of Australian poisoning calls and allowed for estimating time-trends in pregabalin misuse/overdose and report on demographics and co-ingested drugs. The NSWPIC was searched for intentional exposure calls where pregabalin, gabapentin or carbamazepine was a coded substance.

The third source was intentional poisonings in two Australian toxicology service databases (Hunter Area Toxicology Service (HATS), Princess Alexandra Hospital Toxicology Service (PAH)), which was used to complement NSWPIC data. A search for intentional pregabalin exposures from January 2012 to December 2015 was conducted.

Lastly, poisoning fatalities in NSW coronial records (2005 to 2016) was used to examine fatal outcomes of pregabalin misuse/overdose.

Measurements: Trends in dispensing, poisoning, death; demographics and patient characteristics, proportion of users at high risk of misuse (latent class analysis, LCA) and characteristics of high-risk users. Where possible, pregabalin was compared with gabapentin and carbamazepine (other antiepileptics used for neuropathic pain).

Results: Monthly dispensing of pregabalin, gabapentin and carbamazepine as well as intentional poisonings for these three medicines reported to the NSWPIC are shown in Figure 11. Pregabalin dispensing increased from 132,012 in 2013 to 352,945 in 2016 (an average of 73,424 per year; 95% CI 61,726 to 85,121). This suggests a rapid and continuing rise since PBS listing in 2013. Gabapentin exposures remained stable, while carbamazepine poisonings decreased during the study period. Overall, exposures to all other anticonvulsants remained stable.

NSWPIC received 1158 reports of intentional pregabalin poisonings, with a 53.8% increase per year, 2005 to 2016 (95% CI 44 to 64.2%). There were 88 pregabalin-associated deaths in NSW with a 57.8% increase per year (95% CI 30.0 to 91.6) with deaths increasing substantially since PBS listing in 2013. Patients overdosing on pregabalin commonly co-ingested opioids, benzodiazepines and illicit drugs, and had high rates of psychiatric and substance use comorbidities.

LCA analysis to classify people based on volume of dispensing and other prescribing behaviours likely to put them at risk of misuse revealed four classes of pregabalin users. Class 1 individuals, labelled as 'high risk' of misuse accounted for 14.7% of people prescribed pregabalin, and were more likely to be younger, male, co-prescribed benzodiazepines or opioids, have more individual prescribers and higher pregabalin strengths dispensed. The proportion of 'high risk' users remained relatively stable from 2013 to 2016 but due to increasing volumes of dispensing, the absolute number of 'high risk' users is increasing.

Conclusions: There has been a dramatic increase in pregabalin use, poisonings and deaths in Australia since it became subsidised publicly in 2013. One in seven Australians dispensed pregabalin appears to be at high risk of misuse.

Figure 11: Monthly dispensing and intentional poisonings reported to the NSWPIC for pregabalin, gabapentin and carbamazepine *

Comments:

This study found pregabalin overdoses commonly involved co-ingestion of other medicines such as opioids and benzodiazepines as well as illicit drugs. There has been an increase in the use of pregabalin, poisonings and deaths in Australia since becoming subsidised in 2013. As with New Zealand, gabapentin and pregabalin are both prescription medicines in Australia (not controlled drugs).

3.1.4 Systematic review – Evoy et al 2017 [10]

Title: Abuse and misuse of pregabalin and gabapentin

Methods: Clinical or epidemiological studies, meta-analyses, and case reports/series regarding abuse, misuse, or overdose of pregabalin or gabapentin were included, as were clinical studies conducted to identify their abuse liability. Studies reporting gabapentin or pregabalin toxicity, withdrawal, or dependence without misuse/abuse were excluded, though select data from such studies were included in the discussion.

Results: 59 studies were included in this systematic review (24 epidemiological, three clinical abuse liability, 16 abuse/misuse/dependence case reports/series, 17 acute overdose case reports/series – one included both an epidemiological study and case series and was included in both counts).

Analysis of these studies indicates increasing numbers of patients are self-administering higher than recommended doses to achieve euphoric highs. In the general population, a 1.6% prevalence of gabapentinoid abuse was observed, whereas prevalence ranged from 3% to 68% among opioid abusers. An international adverse event database identified 11,940 reports of gabapentinoid abuse from 2004 to 2015, with >75% reported since 2012.

Gabapentinoid abuse typically involves supratherapeutic doses, often in clear excess of the recommended maximum dose in order to achieve euphoric effects.

Despite the concerning reports presented, gabapentinoid abuse currently appears less common than that of drugs such as opioids and predominantly occurs in high-risk populations. As gabapentinoids have an important role in treating many chronic conditions, current evidence does not suggest that their use be restricted, but instead that greater emphasis be placed on identifying signs and risk factors of abuse as well as safe prescribing.

Conclusion: Evidence suggests gabapentinoids possess potential for abuse, particularly in individuals with a history of opioid abuse, and reports of such abuse are increasingly being documented. Prescribers should be aware of high-risk populations and monitor for signs of abuse.

Comments:

This systematic review suggests gabapentinoid abuse is less common than opioids. Monitoring for signs of abuse and prescribers being aware of high-risk populations are recommended as ways of managing the risks of abuse. See section 2.1.4 where the Ministry's EACD recommended prescriber education to improve the use of pregabalin rather than scheduling as a controlled drug.

3.1.5 Review of gabapentin misuse – Quintero 2017 [11]

Title: Review about gabapentin misuse, interactions, contraindications and side effects

Methods: This review consists of 99 biographical references (from 1983 to 2016) obtained from a PubMed search. It includes animal studies, clinical studies, case studies and reviews related to gabapentin misuse, potential interactions, side effects and contraindications.

Results: Individual clinical studies and large sample studies reported that gabapentin can be misused or abused and generate general health problems. In general, it seems gabapentin has risks of being misused based on increased levels of prescriptions, related fatalities, recreational misuse and higher doses of self-administration. The main reasons for gabapentin misuse are: getting high, alleviating opioid withdrawal symptoms and potentiating methadone effects.

The prevalence of problems related to gabapentin use described in different studies are in the range of 1.1 to 19%. An online UK survey from 2014 [12] reported a prevalence of 1.1% for lifetime misuse, data from EudraVigilance reported by Chiappini et al [13] showed a prevalence of 4.8% for misuse/abuse/dependence, a study in Kentucky [14] reported a prevalence of 15% for misuse, a study in former inmates [15] reported a prevalence of 16% for misuse, and a Scottish study [16] reported a prevalence of 19% for use without a prescription.

Conclusions: The main reasons for gabapentin misuse are getting "high", alleviating opioid withdrawal and potentiating methadone.

Comments:

The author is based at Florida State University, Panama. From the studies included in this review, the prevalence of problems related to gabapentin use ranged from 1.1% in an online UK survey to 19% in a Scottish study.

3.1.6 Gabapentin systematic review – Smith et al 2016 [3]

Title: Gabapentin misuse, abuse, and diversion: A systematic review

Methods: Peer-reviewed articles demonstrating gabapentin misuse characterised by taking larger doses than prescribed or taking it without a prescription, abuse, dependence and diversion.

Results: 33 articles were included: 23 case studies, 11 epidemiological reports (1 article described both types). This review focused on epidemiological and toxicological studies using case studies as secondary data. While all the articles included in this review described gabapentin misuse/abuse, 12 were documented reports of overdose involving gabapentin.

The 11 epidemiological studies (all cross-sectional) selected for this analysis obtained data from unique sources. Of these 11 studies, four involved substance misuse/abuse populations, two examined toxicology records, one used a population-based sample, two involved reports to a poison centre, and two analysed websites with qualitative information regarding gabapentin abuse.

Over half of the case report articles (n=14) were from patients presenting to a hospital or general clinic with overdose or withdrawal-like symptoms, two came from substance abuse clinics, three from psychiatric facilities, two from the penal system, one from post-mortem toxicology findings, and one from poison centre reports.

Prevalence of gabapentin misuse in the general population was reported to be 1%, 40-65% among individuals with prescriptions, and between 15-22% within populations of people who abuse opioids. Gabapentin was primarily misused for recreational purposes, self-medication or intentional self-harm and was misused alone or in combination with other substances, especially opioids, benzodiazepines, and/or alcohol. Individuals with histories of drug abuse were most often involved in its misuse.

Evidence from the US indicates gabapentin misuse among individuals with prescriptions for gabapentin involved a higher amount than prescribed. Potential explanations are tolerance and addiction. Over half of the articles (n=7) mentioned or referred to diversion of gabapentin. There appeared to be a street market demand for gabapentin. An American study stated that gabapentin tablets were sometimes sold or traded for illicit drugs. In Scotland, the Drug and Crime Enforcement Agency identified the growing use of gabapentin as a cutting agent in Heroin. In the UK and US, epidemiological studies reported the illicit market value for gabapentin ranged from <1–7 USD per pill depending on strength.

Motivations for misusing gabapentin could be classified largely into three basic categories: recreational (eg, get high or substitute for more expensive drugs), self-harm, and self-medication (eg, for pain or withdrawal symptoms from other substances). Descriptive reports on gabapentin reveal an array of subjective experiences similar to opioids (eg, euphoria, talkativeness, increased energy, sedation), benzodiazepines (eg, sedation), and psychedelics (eg, disassociation).

Conclusion: The authors conclude epidemiological and case report evidence suggests that gabapentin is being misused internationally at a rate of about 1%, with substance abuse populations at special risk for misuse/abuse.

Comments:
From the studies included in this systematic review, the prevalence of gabapentin misuse in the general international population was 1%, among individuals with prescriptions the prevalence of misuse was 40 to 65%, and within populations of people who abuse opioids was 15 to 22%. Interestingly, the prevalence of misuse was higher among individuals with prescriptions compared to those who abuse opioids.

3.1.7 Systematic review of pregabalin abuse – Schjerning et al 2016 [17]

Title: Abuse potential of pregabalin: A systematic review

Methods: A systematic literature search with review of preclinical, clinical and epidemiological data on the abuse potential of pregabalin.

Results: The authors included preclinical (n=17), clinical (n=19) and epidemiological (n=13) studies addressing the abuse potential of pregabalin. They also reviewed case reports (n=9) reporting abuse of pregabalin.

Preclinical studies indicated pregabalin has modulatory effects on the GABA and glutamate systems and therefore has abuse potential.

The clinical studies involved patients treated with pregabalin for the following indications: fibromyalgia, neuropathy, anxiety disorders, restless legs syndrome, pancreatitis, and healthy volunteers. Euphoria was described in 14 of the 19 clinical studies. Withdrawal symptoms were not described in any of the clinical studies reviewed. One study reported overdosing as an adverse effect.

The nine case reports/series described 10 different patient cases. All cases were categorised as abuse-related events according to ACTTION definitions. Pregabalin overdosing was described in all 10 cases. Diversion was described in three cases, tampering in one case and withdrawal symptoms in two cases. Seven patients had a history of or ongoing substance abuse and four patients had no abuse history beside use of nicotine. The median age was 34 years (range 19 –47). Median value of highest single dose reported was 2400 mg (range 800–7500 mg). Four patients were women and six were men.

There were 13 epidemiological studies on the misuse and abuse of pregabalin. Three were drug utilisation studies, three were reviews of ADR reports, five explored abuse and misuse in substance abuse populations, and two were post-mortem studies.

Conclusions: Overall, the available literature suggests an important clinical abuse potential of pregabalin and prescribers should pay attention to signs of abuse, especially in patients with a history of substance abuse.

Comments:
Clinical studies included in this systematic review involved patients using pregabalin for off-label (unapproved) indications such as restless leg syndrome and anxiety disorders. The conclusion of this systematic review is similar to that of Evoy et al (2017).

3.1.8 Study using FAERS data – Evoy et al 2019 [18]

Title: Reports of gabapentin and pregabalin abuse, misuse, dependence, or overdose: An analysis of the Food and Drug Administration Adverse Events Reporting System (FAERS)

Methods: A query was designed using SafeRx, an indexed, searchable database of FAERS data from October 2012 to December 2016. All-cause and abuse-related (including abuse, misuse, dependence, overdose events) ADR reports for gabapentin and pregabalin were isolated as well as limited demographic data. The proportional reporting ratio (PRR) was calculated to compare signal detection.

Results: A total of 10,038 all-cause ADRs were reported to FAERS for gabapentin, including 576 (5.7%) abuse-related events. For pregabalin, 571 all-cause ADRs were identified, including 58 (10.2%) related to abuse. Compared to all-cause ADRs, those involved in abuse-related events were younger and more likely to be male. The PRR of pregabalin versus gabapentin abuse-related events was 1.77, indicating that the number of abuse-related events in relation to the total number of reported ADRs for that medicine was greater for pregabalin compared to gabapentin.

Table 11 shows information on the number of gabapentin and pregabalin events and associated deaths reported annually.

Conclusion: Though not traditionally thought of as drugs of abuse, over 600 cases of gabapentinoid abuse were reported in the timeframe analysed prompting the need for further study and regulatory investigation.

Table 11: Gabapentin and pregabalin events and associated deaths, by year

Comments:

The PRR (a disproportionality calculation used for signal detection) from spontaneous adverse reactions reported to the US FDA for abuse-related events for pregabalin vs. gabapentin was 1.77. This suggests abuse-related events in relation to the total number of reported adverse reactions for that medicine was greater for pregabalin compared to gabapentin.

3.1.9 Study using EMA EudraVigilance data – Chiappini et al 2015 [13]

Title: A decade of gabapentinoid misuse: an analysis of the European Medicines Agency's 'suspected adverse drug reactions' database

Aim: Identify and access cases of gabapentinoid misuse or dependence as reported to the European Medicines Agency's (EMA) EudraVigilance database, in order to identify the size of this problem and characteristics of these reactions.

Methods: All spontaneous reports of misuse/abuse/dependence were retrieved for both gabapentin (2004-2015) and pregabalin (2006-2015). A descriptive analysis by source, sex, age and type of report was performed.

Results: A total of 7,639 (6.6% of a total of 115,616) ADR reports of abuse/misuse/dependence were retrieved for pregabalin during Mar 2006 to 15 Jul 2015. The number of reports increased over time with a peak in 2013. Of these, 32.2% were classified as intentional product misuse, 31.9% as drug dependence and 22.3% as drug abuse.

For gabapentin, 4,301 (4.8% of 90,166) ADR reports of abuse/misuse/dependence were retrieved during Mar 2004 to 15 Jul 2015. The number of reports increased over time. Of these, 28.3% were classified as intentional product misuse, 31.8% as drug dependence and 24.8% as drug abuse.

Adult females were most often involved in ADR reports of abuse/misuse/dependence for both medicines. Analysis of proportional reporting ratios (PRR) for abuse/dependence/intentional product misuse values seem to indicate these ADRs were more frequently reported for pregabalin (1.25; 1.39; 1.58, respectively) compared to gabapentin.

A total of 27 and 86 fatalities, respectively, associated with pregabalin and gabapentin. Opioids were most commonly taken concomitantly, followed by antidepressants and benzodiazepines. A range of recreational substances (eg, alcohol, amphetamines, cannabis, ketamine) were also reported concomitantly.

Conclusion: Despite data collection/methodological limitations, the data seem to suggest gabapentinoid misuse may be a cause for concern, especially in patients with a history of substance misuse. Healthcare professionals should be vigilant when prescribing these medicines.

Comments:

The PRR for abuse/dependence/intentional product misuse seem to indicate these were more frequently reported for pregabalin (1.25, 1.39, 1.58, respectively) compared to gabapentin. This finding is in-line with the PRR calculated from FAERS data in the Evoy et al 2019 study. Healthcare professionals are again reminded to be vigilant when prescribing these medicines.

3.1.10 US study on gabapentin reclassification – Peckham et al 2018 [5]

Title: Gabapentin use, abuse, and the US opioid epidemic: the case for reclassification as a controlled substance and the need for pharmacovigilance

Overview: At the time of writing, the authors state gabapentin remains a non-controlled substance at the federal level. This has forced certain states to design their own legislative initiatives. The authors describe state-by-state efforts to enhance pharmacovigilance and call for a re-evaluation of the schedule status of gabapentin at the federal level, and design and implementation of a national pharmacovigilance program.

Results: Figure 12 is a visual summary of requirements in US states.

Figure 12: Gabapentin regulation, legislation, and monitoring requirements within each US state, as at 1 March 2018

The state of Kentucky is the only state to have reclassified gabapentin as a schedule-V controlled substance. At the time of publication, the most common state-level legislative and/or regulatory approach to monitor the dispensing of gabapentin is to require reporting of the event to a prescription drug monitoring program (PDMP). Eight states (Minnesota, Ohio, Virginia, Wyoming, West Virginia, Massachusetts, North Dakota, Nebraska) have implemented this policy. Monitoring of dispensing will facilitate uniform collection and subsequent analysis of data with the potential to detect and mitigate outliers in the prescribing of gabapentin.

Discussion: While state-level efforts to combat the diversion and abuse of gabapentin, and thus the opioid epidemic, are to be commended, such efforts are not a substitute for a strategic national approach.

Comments:

Pregabalin is a schedule-V controlled substance in the US. The authors in this study make the case that gabapentin should be reclassified as a schedule-V controlled substance at the national level (currently state-level and Kentucky is the only state where gabapentin is a controlled substance).

3.1.11 Gabapentin US study – Mersfelder et al 2016 [19]

Title: Gabapentin: Abuse, dependence, and withdrawal

Data sources: A PubMed literature search (1993 to October 2015) was performed and additional references were identified from a review of literature citations.

Data synthesis: A total of 18 case reports or case series were identified regarding addiction to or withdrawal from gabapentin. All the cases of addiction were in patients who had a previous history of alcohol, cocaine, or opioid abuse. On average, the patients were taking more than 3000 mg/day (600 to 8000 mg/day). Two surveys reported that the misuse of gabapentin was 1.1% in the general population and 22% in drug abuse treatment centres. Withdrawal, when reported, occurred within 12 hours to 7 days of discontinuation of the medicine.

Conclusion: There have been numerous documented cases of gabapentin abuse, dependence and withdrawal. A history of alcohol or substance abuse appears to be an important part of a patient's medical history when evaluating their risk for addiction and dependence behaviours.

Comments:

The conclusion of this US gabapentin is similar to that of Evoy et al (2017) whereby evaluating a patient's risk for addiction and dependence behaviours is important when prescribing.

3.1.12 Finnish postmortem toxicology study – Häkkinen et al 2014 [20]

Title: Profiles of pregabalin and gabapentin abuse by postmortem toxicology

Objective: To estimate the proportion of all pregabalin- and gabapentin-related fatalities attributable to abuse.

Methods: The authors investigated all medico-legal death cases in Finland in which pregabalin or gabapentin was found in postmortem toxicology during 2010-2011. Postmortem toxicology analysis was performed at the Hjelt Institute, Department of Forensic Medicine, Finland – all postmortem toxicology samples taken at autopsy in Finland are analysed in this laboratory. During 2010-2011 there were 101,472 deaths in Finland, and a medico-legal autopsy was performed in 22,421 cases (22.1% of all deaths). Toxicological analyses were performed in 13,766 cases.

A case was considered as a pregabalin or gabapentin abuser case if the deceased was a known drug abuser; or if there were new injection marks or injection equipment near the body; or if amphetamines, cannabis, GHB or other illicit drugs were found in the toxicological investigation; and pregabalin or gabapentin was found in the toxicological investigation but had not been prescribed for medical use.

Results: Pregabalin was found in 316 cases and gabapentin in 43 cases. Drug abuse was associated with 48.1% of the pregabalin and 18.6% of the gabapentin findings. Pregabalin poisoning accounted for 10.1% of all pregabalin cases and gabapentin poisoning for 4.7% of all gabapentin cases. In the pregabalin abuser group, 91.4% of cases showed concomitant opioid use, while in the rest of these cases neither alcohol nor opioids were detected, but other central nervous system acting drugs were found in each case. In the gabapentin abuser group, 87.5% of cases showed concomitant opioid use.

Conclusions: Nearly half of the deceased with a positive pregabalin finding were drug abusers, whereas less than a fifth of gabapentin use was attributed to abuse. Pregabalin, and to a lesser extent gabapentin, should be considered and classified as a benzodiazepine-like drug with considerable abuse potential.

Comments:
As with other studies, this Finnish study found a high rate of concomitant opioid use in gabapentin and pregabalin abusers (87.5% and 91.4%, respectively).

3.1.13 TGA advisory committee on medicines review (Australia)

The TGA's Advisory Committee on Medicines (ACM) discussed gabapentinoids and risk of harmful and hazardous use at their 1 February 2019 meeting. The ACM noted off-label use is occurring in Australia for non-neuropathic pain and generalised anxiety disorder.

A safety signal for the harmful and hazardous use of gabapentinoids, in particular pregabalin, was detected following analysis of the TGA's ADR database. These include reports with a fatal outcome.

The ACM noted the following:

- Premarket studies for pregabalin suggested a low potential for abuse; such studies commonly exclude people with a history of substance abuse.
- Some people are at higher risk of harmful and hazardous use of pregabalin: people with depression, people who concomitantly use opioids and/or benzodiazepines, and young men.
- Pregabalin appeared to have a higher addictive potential than gabapentin.

The ACM considered there to be sufficient and compelling evidence of a strong signal for the harmful and hazardous use of pregabalin. Evidence included multiple sources from Australia and internationally, including data regarding fatalities, drug utilisation, prescribing patterns, adverse event reporting, and trends in intentional poisonings. The ACM accepted the conclusion of Cairns et al [9] (see section 3.1.3) stating "One in seven Australians dispensed pregabalin appears to be at high risk of misuse".

The ACM noted pregabalin may have a higher potential for dependence and abuse than gabapentin because it is more rapidly absorbed, has a higher affinity for the α2-δ subunit of presynaptic voltage-gated calcium channels, and has a longer half-life. Strengthened risk minimisation strategies put in place for pregabalin should also apply to gabapentin to prevent a shift to gabapentin.

Regulatory mechanisms for minimising the risk of hazardous and harmful use associated with gabapentinoids were discussed. A multifaceted approach to harm reduction could include the following:

- Changes to the Australian data sheet for pregabalin and gabapentin to prominently address the risk of hazardous and harmful use including risk factors and discontinuation advice.
- A targeted and coordinated professional education strategy to ensure prescribers are aware of the current concerns around harmful and hazardous use and understand the full extent of this problem. This could include a TGA web statement, liaison with NPS MedicineWise, and/or collaboration with the relevant clinical colleges.

The ACM also discussed other mechanisms for minimising the risk of hazardous and harmful use, including potential changes to the Poisons Standard (there is no equivalent of this in NZ) and/or the Pharmaceutical Benefits Scheme (similar to PHARMAC) entries for pregabalin and gabapentin.

3.1.14 New Zealand data sheets

The following information is included in the gabapentin (Neurontin) NZ data sheet (same information as the Australian data sheet):

> *Post-marketing cases of abuse and dependence have been reported with gabapentin. As with other CNS drugs, patients should be carefully evaluated for a history of drug abuse and observed for possible signs of gabapentin abuse.*

The following information is included in the pregabalin (Pfizer) NZ data sheet (same information as the Australian Lyrica data sheet):

> *There have been post-marketing reports of substance misuse and abuse with pregabalin. As with any CNS drug, patients should be carefully evaluated for a history of substance abuse and observed for signs of pregabalin misuse or abuse (eg, development of tolerance, increase in dose, drug-seeking behaviour.*

3.2 Opioid-related death and respiratory depression

Opioids and gabapentinoids can be used for neuropathic pain. Therefore, the likelihood for concomitant use is high.

The mechanism by which gabapentin may increase the risk of death in opioid users could be explained pharmacodynamically (ie, additive respiratory depression) and pharmacokinetically (ie, increased gabapentin concentrations) [1]. A pharmacokinetic interaction most likely reflects increased gabapentin absorption, which primarily occurs in the upper small intestine [1]. Therefore, opioid-induced slowing of gastrointestinal transit could lead to increased gabapentin bioavailability [1].

3.2.1 Canadian gabapentin study – Gomes et al 2017 [21]

Title: Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study

Methods: A population-based nested case-control study among opioid users who were residents of Ontario, Canada between 1 August 1997 and 31 December 2013 using administrative databases.

Cases, defined as opioid users who died of an opioid-related cause, were matched with up to 4 controls who also used opioids on age, sex, year of index date, history of chronic kidney disease, and a disease risk index. After matching, 1256 cases and 4619 controls were included.

The index date was defined as the date of death. The index date for potential controls was randomly assigned according to the distribution of index dates for included cases. Individuals with invalid identifiers and those with a prior diagnosis of cancer or evidence of palliative care in the 6 months preceding the index date were excluded. Consequently, analyses were limited to patients receiving opioids for non-cancer pain. All study patients were required to have at least 1 opioid prescription overlapping with their index date and at least 6 months of continuous eligibility for public drug benefits prior to their index date.

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 1799 mg daily) or high ≥1800 mg daily). A sensitivity analysis to test the specificity of the findings, the authors examined the effect of concomitant NSAID use in the preceding 120 days. Two post hoc sensitivity analyses were also conducted. In the first, high-dose gabapentin was further stratified into high dose (1900 to 2499 mg daily) and very high dose (≥2500 mg daily) to investigate the association between opioid-related death and higher gabapentin doses. In the second, gabapentin exposure was defined on the basis of a gabapentin prescription where the days' supply overlapped the index date.

Results: 2,914,971 database-eligible individuals who received a prescription opioid over the study period were identified. Of these, 1391 potential cases met the inclusion criteria and 1256 (90.3% of these were matched to at least 1 control, leading to a total of 4619 controls included in the study. The majority of cases (94.5%) and controls (94.2%) were aged <65 years, and over 40% (42.1% of cases and 43.8% of controls) were in the lowest income quintile. Cases tended to receive higher opioid doses, were more likely to have received a long-acting opioid during the exposure window, and were more likely to have recent exposure to antidepressants, benzodiazepines, and other CNS depressants.

Overall, 12.3% of cases (155 of 1256) and 6.8% of controls (313 of 4619) were prescribed gabapentin in the prior 120 days. Unadjusted odds ratios (OR) and adjusted odds ratios (aOR) are shown in Figure 13. After multivariable adjustment, co-prescription of opioids and gabapentin was associated with a significantly increased odds of opioid-related death (adjusted odds ratio (aOR) 1.49, 95% CI 1.18 to 1.88) compared to opioid prescription alone. In the dose-response analysis, moderate-dose (aOR 1.56, 95% CI 1.06 to 2.28) and high-dose (aOR 1.58, 95% CI 1.09 to 2.27) gabapentin use was associated with a nearly 60% increase in the odds of opioid-related death relative to no concomitant gabapentin use.

No significant association was found between co-prescription of opioids and NSAIDs and opioid-related death (aOR 1.14, 95% CI 0.98 to 1.32). In an exploratory analysis of patients at risk of combined opioid and

gabapentin use, 46% (45,173 of 98,288) of gabapentin users in calendar year 2013 were found to receive at least 1 concomitant prescription for an opioid.

Conclusions: Among patients receiving prescription opioids, concomitant treatment with gabapentin was associated with a substantial increase in the risk of opioid-related death.

Figure 13: Association between co-prescription with gabapentin and opioids and opioid overdose

Comments:

The aOR of 1.49 (95% CI 1.18 to 1.88) seen in this study suggests co-prescription of opioids and gabapentin is associated with increased odds of opioid-related death compared to opioid prescription alone.

The authors performed a sensitivity analysis to test the specificity of the findings by examining the effect of concomitant NSAID use in the preceding 120 days. The aOR of 1.14 (95% CI 0.98 to 1.32) suggests there is no significant association between co-prescription of opioids and NSAIDs and opioid-related death.

3.2.2 Canadian pregabalin study – Gomes et al 2018 [22]

This Canadian study was performed by the same authors as the gabapentin study. It was published as a brief research report in *Annals of Internal Medicine*.

Title: Pregabalin and the risk for opioid-related death: A nested case-control study

Methods: The authors conducted a nested case-control study investigating the association between exposure to concomitant pregabalin and opioid-related death in residents of Ontario, Canada who were aged ≥15 years, had public drug coverage, and were prescribed opioid analgesics between August 1997 and December 2016.

Case patients were defined as those who died of an opioid-related cause, excluding deaths determined to be suicide or homicide; the index date was the date of death. Each case patient was matched to up to 4 control participants (age, sex, index year, history of chronic kidney disease, Charlson comorbidity index score). Sensitivity analysis conducted where case patients were matched with controls on the basis of whether they were recently prescribed a benzodiazepine, antidepressant, or other CNS depressant.

Recent exposure in the primary analysis defined as receipt of a pregabalin prescription in the 120 days preceding the index date. In a secondary analysis, the authors explored the dose-response relationship by stratifying pregabalin exposure into low or moderate (≤300 mg/day) or high (>300 mg/day) doses. Sensitivity analysis conducted and concomitant pregabalin exposure was defined as receipt of a pregabalin prescription overlapping the index date. To test the specificity of their findings, the authors used concomitant use of NSAIDs as a predefined control exposure.

Results: A total of 1417 cases who experienced opioid-related death were matched to 5097 control patients. Case patients were more likely to have recently been prescribed other CNS depressants, receive more medicines annually and have more comorbidities than control participants.

Results are shown in Figure 14. After multivariable adjustment, exposure to concomitant pregabalin within the previous 120 days significantly increased the odds of opioid-related death vs. exposure to opioid analgesics only (aOR 1.68, 95% CI 1.19 to 2.36). Consistent results were seen in sensitivity analyses evaluating pregabalin use overlapping the index date (aOR 1.81, 95% CI 1.26 to 2.00) and after matching on prior use of CNS depressants (aOR 2.00, 95% CI 1.39 to 2.88).

In the dose response analysis, a high dose of pregabalin was associated with markedly increased odds of opioid-related death relative to no pregabalin exposure (aOR 2.51, 95% CI 1.24 to 5.06) whereas a low or moderate dose of pregabalin was associated with lower but still significant odds of opioid-related death (aOR 1.52, 95% CI 1.04 to 2.22). As expected, there was no association between co-prescription of NSAIDs with opioids and risk for opioid-related mortality (aOR 1.04, 95% CI 0.90 to 1.19).

Figure 14: Association between concomitant use of opioids and pregabalin and risk for opioid-related death

Discussion and conclusion: This study found evidence of an interaction between pregabalin and opioids similar to that previously observed with gabapentin and opioids. The authors recommend caution when co-prescribing gabapentinoids with opioids particularly when the dose of either medicine is high.

US FDA comment: The US FDA stated in an accompanying editorial that from a regulatory perspective, they appreciate the type of careful exploration presented by Gomes and colleagues and further investigation of the consequences of combined use of all CNS-active medicines are critically needed. The US FDA is implementing processes to support such work and engaging in initiatives to determine what changes, if any, are needed to address the labelling concerns raised by the authors.

Comments:
The adjusted odds ratios in this pregabalin study are higher than that seen in the gabapentin study, and the confidence intervals are also wider.

3.2.3 Post mortem UK study – Nahar et al 2019 [23]

Title: Misuse and mortality related to gabapentin and pregabalin are being under-estimated: A two-year post-mortem population study

Methods: Between 1 January 2016 and 31 December 2017, 3750 deceased from Coroners' cases in London and South East England underwent a routine drugs screen and a specific screen for gabapentin and pregabalin. The prevalence of both medicines was determined in the cohort and subcategories of heroin users and non-heroin users. The prevalence was then compared to tramadol (Class C drug in the UK).

Results: Of 3750 samples analysed, 118 (3.1%) were positive for gabapentin, 229 (6.1%) for pregabalin and 120 (3.2%) were positive for tramadol. The most common medicine class observed with gabapentin and pregabalin was non-heroin-related opioids at 60.2% and 64.6%, respectively. Non-heroin-related opioids were subcategorised into individual medicines and their use with gabapentin and pregabalin are shown in Figure 15.

Conclusion: The authors conclude gabapentin and pregabalin are extensively used with opioids.

Figure 15: Concomitant use of non-heroin-related opioids with gabapentin (GBP) and pregabalin (PGL) in post-mortem blood

3.2.4 Pregabalin post mortem UK study – Eastwood and Davison 2016 [24]

Title: Pregabalin concentrations in post-mortem blood – A two year study

Background: Post-mortem blood concentrations of pregabalin in individuals prescribed the medicine have been reported to range from 0.4 to 17 mg/L in femoral blood, and 1.5 to 11 mg/L in heart blood. Within the usual therapeutic dose range, there is a linear relationship between dose and plasma concentrations. Therapeutic plasma concentrations for a 150 mg/day dose are reported to range from 0.29 to 2.84 mg/L, and from 0.87 to 14.2 mg/L for a 600 mg/day dose.

Methods: This study reviewed the post-mortem blood concentrations of pregabalin analysed in the authors' lab (Toxicology Department, Queens Road, Teddington, Middlesex, UK) between 2012 and 2014 to try and assign the likely therapeutic and fatal ranges.

Post-mortem blood is typically taken from the femoral vein, but the site of sampling was not specified in some cases.

Results: Pregabalin was detected in 70 post-mortem blood samples of which 33% were at concentrations considered to be in excess of the reference range (above 17 mg/L). Pregabalin concentrations ranged from 0.05 mg/L to 226 mg/L (median 8 mg/L) in the group as a whole and in one case a pregabalin concentration of 76 mg/L was determined to be the likely cause of death as no other drugs of significance were involved.

The data did not present a clear therapeutic range, as a wide range of pregabalin concentrations were found within subjects prescribed different doses of the medicine, thereby making it difficult to distinguish between therapeutic use and abuse. Additionally, the presence of multiple drugs in most cases, did not allow for pregabalin levels to be directly related to toxicity.

There were 13% of subjects showing concurrent use of heroin (measured by detection of 6-MAM), and a further 28% with morphine present in the absence of 6-MAM. Methadone was detected in 19% of the cases with 20% showing the concurrent use of cocaine. Over 55% of subjects had used diazepam, again supporting other literature reports which note a prevalence of benzodiazepine use in combination with pregabalin.

Of the 23 cases with pregabalin concentrations above 17 mg/L, 19 cases (86%) showed the concurrent use of at least one of the following: morphine, heroin, methadone, cocaine and benzodiazepines. Figure 16 shows the increased concomitant use of abused drugs in cases where the measured pregabalin concentration is greater than 17 mg/L compared to all cases.

Figure 16: Concomitant drug use (%) in all cases and in cases where pregabalin concentration is greater than 17 mg/L

Conclusion: Despite the majority of subjects being prescribed pregabalin, there is the potential to over medicate or abuse this medicine making it difficult to establish an accurate therapeutic range or identify a potentially fatal range for the medicine. Identifying a fatal range is further complicated by all cases having at least one other drug present, and the causes of death in many of the cases was attributed to multiple drug toxicity.

3.2.5 Pregabalin post mortem Australian study – Thompson et al 2020 [25]

Title: Pregabalin and its involvement in coronial cases

Methods: The authors examined case characteristics and outcomes of coronial cases submitted to the laboratory and analysed for pregabalin between 2015 and 2017 (Queensland, Australia).

Results: Pregabalin was identified in about 5% (332 cases) of all coronial cases submitted during this time. A high rate of concurrent medicine use with pregabalin was evident (Figure 17), with pregabalin being the sole medicine detected in only 3 out of 332 cases. Opioids and benzodiazepines were the most commonly identified classes concomitantly used with pregabalin at 79% and 70%, respectively, followed by antidepressants (65%), antipsychotics (32%), alcohol (21%), cannabis (20%) and amphetamines (15%). Other CNS depressants (24%) included sedating antihistamines, carbamazepine, valproate and gabapentin, while other miscellaneous drugs (52%) included medicines such as paracetamol, metformin, ibuprofen, beta-blockers and metoclopramide.

Since opioids were the most commonly detected medicine class used with pregabalin, these cases were further examined (Figure 18). Oxycodone was the most common opioid and was seen in 39% of pregabalin and opioid cases. Morphine and codeine were the next most common, with heroin confirmed in only 5% of all opioid positive cases.

Figure 17: Frequency of medicine classes used in combination with pregabalin

Figure 18: Frequency of opioids used in combination with pregabalin (*other includes dextromethorphan and pholcodine)

Post mortem blood pregabalin concentrations ranged from <0.05 to 140 mg/kg (median 5.5 mg/kg). However, limited interpretation of levels could be achieved as the medicine was rarely identified in the absence of other medicines. Cause of death was found to be medicine-related in 58% of all cases with mixed drug toxicity specifically mentioned as related to cause of death in 40% of cases.

Conclusion: The increased use and polydrug trends seen with pregabalin highlight the need for clinical and forensic toxicology laboratories to continue to monitor this medicine, and potentially look to include it in routine work where possible.

3.2.6 Gabapentin post-mortem US study – Slavova et al 2018 [26]

Title: Prevalence of gabapentin in drug overdose postmortem toxicology testing results

Methods: Death certificates and post mortem toxicology result reports from five US states/jurisdictions (Kentucky, North Carolina, West Virginia, Maricopa County, Northeast Tennessee) were used to identify residents who died from drug overdoses in year 2015 and to calculate prevalence rates of gabapentin in post mortem toxicology by jurisdiction.

Results: On average, 22% of all drug overdose decedents in the study tested positive for gabapentin (Table 12). The percentage of gabapentin-positive overdose deaths varied significantly among jurisdictions: 4% in Northeast Tennessee, 7% in Maricopa County, 15% in West Virginia, 20% in North Carolina, and 41% in Kentucky. Among the drug overdose decedents who tested positive for opioids (including heroin), 26% also tested positive for gabapentin, with significant variation among states/jurisdictions. There was a significant difference in the gender distribution among drug overdose decedents who tested positive for gabapentin (46% male) vs. those who tested negative for gabapentin (65% male).

Table 12: Resident drug overdose deaths with positive toxicology for gabapentin and/or other drugs, by jurisdiction, 2015

Conclusions: Routine gabapentin post mortem testing and linking of death certificate, medical examiner, coroner, toxicology, and prescription history data will provide more reliable information on the extent of gabapentin misuse, diversion, and implications for clinical care.

3.2.7 Gabapentin post-mortem US study – Tharp et al 2019 [27]

Title: Gabapentin-related deaths: Patterns of abuse and postmortem levels

Methods: The authors review 104 cases of decedents who tested positive for gabapentin in post mortem blood samples and an additional 53 nonfatal cases of motor vehicle drivers suspected of driving under the influence (Western District, Virginia, US).

Results: In 47.1% of the fatality cases, gabapentin was directly involved in death. Most of the gabapentin-related deaths were accidental (43 as the cause and 8 as a contributing factor) with nine cases being suicidal in manner. In the cases where gabapentin was determined to be directly related in causing death, 38 out of 49 (77.6%) also had at least one opioid present compared with rates in drivers that tested positive for gabapentin where an opioid was present in only 7 out of 53 cases (13.2%). The most common opioid present in cases where gabapentin was determined to be directly involved in death were oxycodone (17/49 cases), hydrocodone (10/49 cases) and buprenorphine (7/49 cases).

In cases in which gabapentin was determined to be a cause of death, the blood concentrations ranged from 1.1 to 134.0 mg/L. Persons who died of a gabapentin-related drug death were prescribed the medicine legitimately 91.4% of the time, with 84.2% of those also having a known prior history of abuse or misuse of prescription medicines.

Summary: Findings confirm those of previous papers that the risk of gabapentin abuse is significantly higher in persons with a history of abusing other medicines and the combination of opiates with gabapentin is a clear risk factor in those persons for a gabapentin-related death.

3.2.8 Gabapentinoid deaths in Scotland – Torrance et al 2020 [28]

Title: Trends in gabapentinoid prescribing, co-prescribing of opioids and benzodiazepines, and associated deaths in Scotland

Methods: The NHS in Scotland is administered through 14 geographical NHS boards. The prescribing information system is a national individual-level dataset of prescriptions issued, dispensed, and reimbursed from community pharmacies, and all prescribing data are stored securely by the information services division.

National level data was examined from the information services division. Prescribing data for two NHS health board regions in Scotland (NHS Tayside and NHS Fife) were provided by the health informatics centre (HIC), University of Dundee. The HIC is recognised as a leader in health data linkage and maintains a clinical data repository of eHealth data, including prescribing. The authors examined:

1. Trend in number of prescription items of gabapentin and pregabalin (2006 to 2016).
2. Factors associated with receiving a gabapentinoid prescription, including sociodemographic factors, co-prescribing and mortality.
3. Drug-related deaths (DRDs) data, including those associated with gabapentin or pregabalin, obtained from National Records of Scotland (NRS) (2007 to 2016).

Results: From 2006 to 2016, the number of gabapentin prescriptions in Scotland increased 4-fold (164,630 to 694,293), and pregabalin 16-fold (27,094 to 435,490). In 2016 'recurrent users' (≥3 prescriptions) had mean age 58.1 years, were mostly females (62.5%) and were more likely to live in deprived areas.

Co-prescribing was common with almost 60% of those receiving gabapentinoids also prescribed an opioid (49.9%), benzodiazepine (26.8%), or both (17.1%) in 2016 (Table 13). The mean age of patients prescribed gabapentinoids along with opioid, benzodiazepines, or both was 57.3 years.

There was a total of 1312 deaths in 2016 identified in the dataset (4.5% of those prescribed a gabapentinoid in 2016), with 54 of these (4.1%) classified as DRDs. There has been a steady increase in the number of DRDs in Scotland and in NHS Tayside where gabapentin and pregabalin were implicated in or potentially contributed to the cause of death, although the percentages are higher in Tayside compared with the national rates for both medicines (gabapentin 23% vs. 14%; pregabalin 33% vs. 12% in 2017). In Tayside, gabapentin or pregabalin were implicated in the cause of death in 22 of 56 (39%) drug deaths in 2016. In 17 (77%) of these

fatalities, the person had not been prescribed a gabapentinoid. In 2016, gabapentinoids were the 3rd most common group of substances to be found in toxicology of drug deaths at post mortem (39 detection of pregabalin, gabapentin, or both), after opioids and benzodiazepines.

Table 13: Co-prescribing of opioids, benzodiazepines, or both with gabapentinoids in NHS Tayside and NHS Fife (2016), n (%) of all those prescribed gabapentinoid at least once

Conclusions: Gabapentinoid prescribing has increased dramatically since 2006, as have dangerous co-prescribing and death (including DRDs). Older people, women, and those living in deprived areas were particularly likely to receive prescriptions. Their contribution to DRDs may be more related to illegal use with diversion of prescribed medicine.

3.2.9 Mortality and morbidity in dialysis patients – Waddy et al 2020 [29]

Title: Concomitant use of gabapentinoids with opioids is associated with increased mortality and morbidity among dialysis patients

Methods: The authors used the United States renal data system (a national registry of ESRD patients in the US) to identify patients treated with dialysis for all of 2010. Patients were grouped into 4 categories of drugs exposure status:

1. no prescriptions of either an opioid or gabapentinoid
2. ≥1 prescription of an opioid and no prescriptions of gabapentinoids
3. no prescription of opioids and ≥1 prescription of gabapentinoids
4. ≥1 prescription of both an opioid and gabapentinoid.

Outcomes included 2-year all-cause death, dialysis discontinuation, and hospitalisations assessed in 2011 and 2012.

Results: The study population included 153,758 dialysis patients. Concomitant prescription of an opioid and gabapentin (15%) was more common than concomitant prescription of an opioid and pregabalin (4%). In adjusted analyses (Table 14), concomitant prescription of either was associated with increased risk of death (HR 1.16, 95% CI 1.12 to 1.19), dialysis discontinuation (HR 1.14, 95% CI 1.03 to 1.27), and hospitalisation (HR 1.33, 95% CI 1.31 to 1.36). Concomitant prescription of an opioid and pregabalin compared to no prescription of either was associated with increased mortality (HR 1.22, 95% CI 1.16 to 1.28) and hospitalisation (HR 1.37, 95% CI 1.33 to 1.41), but not dialysis discontinuation (HR 1.13, 95% CI 0.95 to 1.35). Prescription of opioids and gabapentinoids compared to only being prescribed opioids was associated with higher risk of hospitalisations but not mortality, or dialysis discontinuation.

Conclusions: Concomitant prescription of opioids and gabapentinoids among US dialysis patients is common, and both medicines have independent effects on outcomes. Future research should prospectively investigate the potential harms of such medicines and identify safer alternatives for treatment of pain in end-stage renal disease patients.

Table 14: Hazard ratios and 95% confidence intervals for mortality, dialysis discontinuation, and hospitalisations by medicines among the prevalent dialysis population, 2010

3.2.10 Cancer-related pain – Madden et al 2020 [30]

Title: Frequency of concomitant use of gabapentinoids and opioids among patients with cancer-related pain at an outpatient palliative care clinic.

Objective: To determine the frequency of combined use of gabapentinoids among patients receiving opioids for cancer-related pain. Also examined if concomitant use of opioids and gabapentinoids together was associated with increased scores of fatigue and drowsiness on the Edmonton Symptom Assessment Scale (ESAS) compared to patients on opioids.

Methods: Retrospective study of patients on opioids and opioids plus gabapentinoids at their third visit to the outpatient supportive care centre (University of Texas) during 1 February 2015 to 1 December 2017. Data were extracted from chart review. Eligible patients were 18 years or older with a diagnosis of local, advanced, or metastatic cancer taking either an opioid or an opioid and gabapentinoid concomitantly and had at least three visits to the outpatient supportive care clinic.

Results: A total of 1116 patient records were reviewed. There were 48% (508/1059) of patients on opioids. Of these patients, 51% (257/508) were on opioids only, and 49% (251/508) were on opioids plus gabapentinoids. ESAS scores, morphine equivalent daily doses (MEDD), and gabapentinoid equivalent doses (GEDD) for the opioid alone and the opioid plus gabapentinoid groups are shown in Table 15. There was no difference in the MEDD between those patients on opioids alone (median 75 mg) vs. those on opioids plus gabapentinoids (median 68 mg). The median gabapentinoid equivalent daily dose was 900 mg.

Table 15: Edmonton symptom assessment scale scores, morphine equivalent daily doses, and gabapentinoid equivalent daily doses for patients on opioids vs. opioids plus gabapentinoids

Conclusion: Almost 50% of advanced cancer patients receiving opioids for pain were exposed to gabapentinoids. Maximal efforts should be made to minimise potential complications from the concomitant use of opioids with gabapentinoids.

3.2.11 Misuse in a London prison – Soni & Walters 2019 [6]

Title: A study of the reasons for prescribing and misuse of gabapentinoids in prison including their co-prescription with opioids and antidepressants

Purpose and methods: Electronic medical case files of male prisoners in a category B prison in London were studied to establish a prevalence during an eight-month period (1 December 2017 to 31 July 2018) of the use of and the reasons for prescribing gabapentinoids in prison and also to establish prescribing standards in prison and compliance with these. In addition, the prevalence of co-prescription of gabapentinoids with opioids and antidepressants, particularly tricyclic antidepressants such as amitriptyline, was also assessed in light of the increased risk of respiratory depression resulting in death when these medicines are used in combination.

Results: A total of 109 cases were identified of prisoners having been prescribed gabapentinoids, pregabalin in 66 cases (61%) and gabapentin in 43 cases (39%). In 36 cases (33%) prescriptions were for unapproved indications. In 51 cases (47%) gabapentinoids were prescribed with an opioid substitute. In 14 cases (13%), prescribed gabapentinoids were diverted to other prisoners. Analgesics prescribed in combination with gabapentinoids were naproxen (3 cases), tramadol (3 cases), and dihydrocodeine, paracetamol+codeine, oxycodone and baclofen (1 each).

Practical implications: The initiation of gabapentinoids in prison should be avoided. For prisoners who are also receiving opioid substitutes or are abusing opiates, it may be unsafe to continue gabapentinoids. Issues raised by this study are likely to apply to other prisons, secure forensic psychiatric facilities and community mental health and primary care.

3.2.12 US FDA safety communication

On 19 December 2019, the FDA issued a safety communication on serious breathing problems with gabapentin and pregabalin when used with CNS depressants (eg, opioids, anti-anxiety medicines, antidepressants, antihistamines) or in patients with lung problems (eg, COPD). The elderly are also at higher risk.

The FDA are requiring new warnings about the risk of respiratory depression to be added to the data sheets for gabapentinoids. FDA is also requiring the drug manufacturers to conduct clinical trials to further evaluate their abuse potential, particularly in combination with opioids, because misuse and abuse of these products together is increasing, and co-use may increase the risk of respiratory depression. Special attention will be paid to the respiratory depressant effects during this abuse potential evaluation.

Reports submitted to the FDA and data from the medical literature show serious breathing difficulties can occur when gabapentinoids are taken by patients with pre-existing respiratory risk factors. Among 49 case reports submitted to the FDA over the 5-year period from 2012 to 2017, 12 people died from respiratory depression with gabapentinoids, all of whom had at least one risk factor. This number includes only reports submitted to FDA so there may be additional cases.

Two randomised, double-blind, placebo-controlled clinical trials in healthy people, three observational studies, and several studies in animals were reviewed. One trial showed using pregabalin alone and using it with an opioid pain reliever can depress breathing function. The other trial showed gabapentin alone increased pauses in breathing during sleep. The three observational studies at one academic medical centre showed a relationship between gabapentinoids given before surgery and respiratory depression occurring after different kinds of surgeries. Animal studies showed pregabalin alone and pregabalin plus opioids can depress respiratory function.

Comments:

The status of the clinical trials that FDA are requiring the sponsors to conduct are unknown. There is likely to be considerable time before these studies are completed.

3.2.13 Health Canada safety communication

On 17 September 2019, Health Canada advised on the increased risk of opioid overdose and serious side effects when taking gabapentin or pregabalin with an opioid. When used with opioids, gabapentinoids increase the risk of opioid overdose. Serious side effects of using gabapentinoids and opioids at the same time include respiratory depression, increased sedation, dizziness, fainting and death.

3.2.14 New Zealand data sheets

3.2.14.1 Gabapentin

The following information is included in Section 4.4 Warnings and precautions of the gabapentin (Neurontin) NZ data sheet (contains more information than the Australian data sheet):

> ***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. This may occur without concomitant opioid use. 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 increases the risk of respiratory depression.*
>
> *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).*
>
> *Caution is advised when prescribing gabapentin concomitantly with opioids due to risk of CNS depression. In a population-based, observational, nested case-control study of opioid users, co-prescription of opioids and gabapentin was associated with an increased risk for opioid-related death compared to opioid prescription use alone (adjusted odds ratio [aOR], 1.49 [95% CI, 1.18 to 1.88, p <0.001]).*

Section 4.5 Interactions of the gabapentin (Neurontin) NZ data sheet also includes the following (contains more information than the Australian data sheet):

> *There are spontaneous and literature case reports of respiratory depression, sedation, and death associated with gabapentin when co-administered with CNS depressants, including opioids. In some of these reports, the authors considered the combination of gabapentin with opioids to be a particular concern in frail patients, in the elderly, in patients with serious underlying respiratory disease, with polypharmacy, and in those patients with substance abuse disorders.*

3.2.14.2 Pregabalin

The following information is included in Section 4.4 Warnings and precautions of the pregabalin (Pfizer) NZ data sheet (same information as the Australian Lyrica data sheet):

> ***Opioids***
> *Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression. In an observational study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk of opioid-related death compared to opioid use alone (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19 to 2.36]).*

Section 4.5 Interactions of the pregabalin NZ data sheet also includes the following (same information as the Australian Lyrica data sheet):

> *In post-marketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and other CNS depressant medications, including in patients who are substance abusers. There are post-marketing reports of events related to reduced lower gastrointestinal tract function (eg, intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics.*

Comments:
The gabapentin (Neurontin) NZ data sheet contains more information on respiratory depression and use with CNS depressants (eg, opioids) than the Australian data sheet and pregabalin NZ data sheet.

3.3 Use in elderly patients

The bpac^{nz} gabapentinoid article (see section 2.2.2) states patients who are more susceptible to adverse effects, such as frail elderly people, may be started on lower doses and titrated more gradually. This is based on the American Diabetes Association position statement on diabetic neuropathy which states adverse effects may be more severe in older patients and may be attenuated by lower starting doses and more gradual titration.

The NZF is also includes consideration to use lower initial doses and/or slower titration in those susceptible to CNS adverse effects (eg, elderly or frail patients) for both gabapentin (eg, starting 100 mg once daily at night and increase weekly to 100 mg twice daily then to 100 mg three times daily) and pregabalin (eg, 25 to 75 mg once daily at night).

3.3.1 Pooled post-hoc analysis of Pfizer pregabalin RCTs – Semel et al 2010 [31]

Title: Evaluation of the safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies

Methods: This is a post hoc analysis of Pfizer-sponsored clinical studies of pregabalin in patients with painful diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN) to evaluate the efficacy and safety of pregabalin in older patients. Data from 11 double-blind, randomised, placebo-controlled clinical studies were pooled. The studies that met the selection criteria had a similar design with a 1-week titration period in the double-blind phase; 1 study had no titration period and another had a 2-week titration period. Patients were randomised to receive pregabalin at fixed doses ranging from 75 to 600 mg/day or placebo. One study included a flexible-dose of pregabalin (150 to 600 mg/day). Efficacy outcomes included change in Daily Pain Rating Scale score; safety was based on adverse events.

Patients were excluded if they had low creatinine clearance (defined as ≤30 mL/min or ≤60 mL/min depending on the study). In two studies of patients with PHN, the dose of pregabalin was adjusted based on baseline renal function: patients with creatinine clearance >60 mL/min received pregabalin 600 mg/day and those with values of >30 to 60 mL/min were assigned to 300 mg/day.

For the pooled analysis, patients with DPN or PHN were combined and stratified into the following age groups: 18 to 64 years, 65 to 74 years, and ≥75 years. Only data for pregabalin at doses of 150 to 600 mg/day were evaluated because 75 mg/day is not an approved dose.

Results: A total of 2516 patients were included in the analysis. There were 1236 patients aged 18 to 64 years, 766 patients aged 65 to 74 years, and 514 patients ≥75 years. Baseline mean pain and sleep interference scores were comparable across treatment and age groups.

Comparable dose-related improvements in endpoint mean pain score was observed for pregabalin across age groups and similar results were observed for improvements in endpoint mean sleep interference scores. The placebo response on pain and sleep interference scores appeared higher in the younger age group compared with the older age groups. While these results suggested a trend for increasing pregabalin-mediated pain reductions with increasing age driven by an inverse relationship between placebo response and age, it was not statistically significant.

The most common adverse events (AEs) that occurred in ≥10% of any age or treatment group were dizziness, somnolence, peripheral oedema, asthenia, dry mouth, weight gain, and infection. In patients with either DPN or PHN, the percentage of patients with a given AE was not noticeably different in patients aged ≥75 years versus those aged 65 to 74 years (Table 16). Relative risks for the most common AEs increased with pregabalin dose but appeared unrelated to age regardless of dose. A trend for higher AE-related discontinuations with increasing age was observed, particularly in patients with PHN at higher pregabalin doses.

Table 16: Most common adverse events by treatment group, age, and type of neuropathic pain

Significant improvements in endpoint mean pain were observed for all pregabalin doses vs. placebo in all age groups, except for the lowest dose (150 mg/day) in the youngest age group. Clinically meaningful pain relief was observed in all age groups.

The most common AEs were dizziness, somnolence, peripheral oedema, asthenia, dry mouth, weight gain, and infections. The relative risks for these AEs increased with pregabalin dose, but did not appear to relate to older age or type of neuropathic pain.

Conclusions: Pregabalin (150–600 mg/day) significantly reduced pain in older adults (age ≥65 years) with neuropathic pain and improvements in pain were comparable to those observed in younger patients. Titration of pregabalin to the lowest effective dose should allow for effective pain relief while minimising AEs in older patients with neuropathic pain. Due to the high prevalence of polypharmacy in older patients, the absence of known drug-drug interactions makes pregabalin an important treatment option for older patients with pain of neuropathic origin.

Comments:

In some, but not all, studies in this pooled analysis, the assigned dose of pregabalin was reduced based on the patient's renal function at baseline. Because of these age-related impairments and the varying criteria for dose reductions based on creatine clearance measures, it can't be assumed that patients in a particular dose group had identical exposure to pregabalin and this could have influenced the incidence of AEs in the higher dose groups.

Dizziness and somnolence were the most common AEs among older patients and this could potentially be minimised by initiating pregabalin at low doses and slowly titrating to a dose where pain relief is obtained, while taking into account any renal function impairment.

Data were not evaluated for 75 mg/day doses because this is not an approved dose. Note the NZF has a recommendation to consider start at doses of 25 to 75 mg once daily at night for those susceptible to CNS adverse effects (eg, elderly or frail patients).

3.3.2 Catalan atrial fibrillation cohort study – Ortiz de Landaluce et al 2018

Title: Gabapentin and pregabalin and risk of atrial fibrillation in the elderly: A population-based cohort study in an electronic prescription database

Methods: The authors examined this association in the Catalan Health Service (CHS) electronic prescription claims database. Patients ≥65 years old starting treatment with either gabapentin or pregabalin between 1 January and 31 March 2015, free of cardiovascular disease and who did not receive the alternate study medicines were studied. In clinical practice, the most common uses of gabapentin and pregabalin are lower back pain and/or sciatica, and anxiety. The authors therefore aimed to compare these patients with those who initiated treatment with other medicines alternatively used in the same conditions (ie, opiate analgesics for pain, and alprazolam or diazepam for anxiety).

The two primary outcome variables were a first claim of an oral anticoagulant plus an antiarrhythmic (OAC + AA), or of an oral anticoagulant or an antiplatelet agent plus an antiarrhythmic (OAC/APA + AA) in the 3 months after treatment initiation.

Results: 5402 individuals aged ≤65 years initiated treatment with gabapentin, 6053 with pregabalin, 37,500 with opiate analgesics and 19,849 with alprazolam or diazepam. Out of the 5402 patients who initiated treatment with gabapentin, 4490 (83.1%) were already on cardiovascular medicines. The corresponding figure for pregabalin was 4979 (82.3%).

In all four cohorts, the rates of treatment initiation with antithrombotic drugs (OAC/APA) or with OAC/APA plus an antiarrhythmic (OAC/ACA + AA) in the 3 months after the dispensing of the medicines of interest increased considerably with age, and it was higher with gabapentin and pregabalin compared with opiate analgesics or alprazolam/diazepam. Compared with opiate analgesics, both gabapentin and pregabalin were associated with an increased risk of initiating OAC/APA + AA (Table 17). The incidence was 6 of 668 (9 per 1000 patients) with gabapentin vs. 12 of 3889 (3.1 per 1000) with opiates, relative risk (RR) 2.91 (95% CI 1.10 to 7.73), and for pregabalin it was 6 of 698 (8.6 per 1000) RR 2.79 (95% CI 1.05 to 7.40). The comparison with alprazolam/diazepam gave similar results. The risks did not vary by age, sex, or co-treatment with NSAIDs, and they increased with dose.

Risks for the primary variable (OAC + AA) did not reach statistical significance due to low numbers of patients, both in comparison with opiate analgesics and with alprazolam/diazepam.

There were 561 patients treated with gabapentin at doses <1200 mg per day (84%), and 107 (16%) with ≥1200 per day. For pregabalin, 579 patients received <150 mg per day (83%) and 119 (17%) received >150 mg per day. The relative risks for the variables were twice as high among patients receiving the higher doses, compared with those on lower doses.

Conclusion: In elderly patients free of cardiovascular disease, an association between new exposure to gabapentin or pregabalin and initiating treatment for AF was found. These results require confirmation in other studies.

Table 17: Risk estimates for the primary and secondary variables

Comments:

The numbers of treatment initiation for OAC+AA, OAC/APA+AA, or AA were low and are therefore reflected in the wide confidence intervals. Anxiety is not an indication for use for gabapentin or pregabalin in New Zealand.

3.3.3 New Zealand data sheets

The following information relating to the elderly is included in the gabapentin (Neurontin) NZ data sheet:

- The respiratory depression warning section states that the elderly are at higher risk of experiencing these adverse effects (see section 3.2.14 for full wording).
- The interactions section states there are literature reports where the authors considered the combination of gabapentin with opioids to be a particular concern in frail patients, in the elderly, in patients with serious underlying respiratory disease, with polypharmacy, and in those patients with substance abuse disorders (see section 3.2.14).
- The pharmacokinetics section states in elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. The elderly (≥65 years) subsection states in a study examining the effect of age on the elimination of gabapentin, apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those younger than 30 years of age to about 125 mL/min in those >70 years of age. Renal clearance also declined with age; however, the decline in the renal clearance of gabapentin can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age-related compromised renal function.

The following information relating to the elderly is included in the pregabalin (Pfizer) NZ data sheet:

- The elderly (>65 years) subsection of Section 4.1 Dose and administration states no dose adjustment is needed for elderly patients unless their renal function is compromised.
- The use in the elderly (>65 years) subsection of Section 4.4 Warnings and precautions states pregabalin treatment has been associated with dizziness and somnolence, which may increase the occurrence of accidental injury (falls) in the elderly population.
- The undesirable effects section states in a total of 998 elderly patients (>65 years), no overall differences in safety were observed compared with patients <65 years of age.
- The pharmacokinetics section states pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function.

4 DISCUSSION AND CONCLUSIONS

Usage based on dispensing data suggests there is a steady increase in the number of people receiving gabapentin each year, but the indication for use is not known. It is possible the increasing use of gabapentin is due to an increase in prevalence of neuropathic pain due to our aging population, increase in cancer survival and chemotherapy-induced neuropathy, and an increase in prevalence of diabetic neuropathy. Trends in usage data for pregabalin are not yet known because this is based on PHARMAC funding which only started in May 2018.

New Zealand data on the prevalence of misuse, abuse and dependence with gabapentin and pregabalin are lacking. The Ministry's expert advisory on drugs (EACD) considered scheduling pregabalin as a controlled drug in 2019. The EACD decided not to schedule pregabalin as a controlled drug, which could be due to the lack of data on its risks of harm to individuals or general population. The EACD recommended prescriber education to improve the use of pregabalin. The misuse, abuse and dependence of any medicine is a challenging area. This includes the difficulties in quantifying the size of the problem as regulatory mechanisms to capture this information are limited, resulting in information or evidence that is often anecdotal.

Estimates in other countries for problems related to gabapentin range from 1.1% in an online UK survey to 19% in a Scottish study as reported by Quintero 2017 [11]. A systematic review by Smith et al 2016 [3] estimated the prevalence of gabapentin misuse in the general international population at 1%, increasing to 15 to 22% within populations of people who abuse opioids. A study by Cairns et al 2019 estimated one in seven Australians dispensed pregabalin appeared to be at high risk of misuse [9].

Based on spontaneous reporting to CARM up to 30 June 2020, there are 7 cases coded with terms that can be synonymous with abuse, misuse or dependence out of a total of 248 reports where gabapentin was the suspect medicine, and 7 cases out of a total of 50 reports with pregabalin. These cases appear to be mainly ones of dependence with patients experiencing withdrawal symptoms on trying to stop treatment.

Information in the gabapentin and pregabalin New Zealand data sheets state there have been post-marketing cases of misuse, abuse and dependence and patients should be carefully evaluated for a history of drug abuse and observed for possible signs of misuse or abuse.

The risk of opioid-related death and respiratory depression with gabapentin and pregabalin has received some recent attention. Studies by Gomes et al [21, 22] found increased odds of opioid-related death with co-prescription of opioids and gabapentin or opioids and pregabalin compared to opioids alone. The five studies based on post-mortem data found opioids or multiple medicines were often involved in deaths relating to gabapentin and pregabalin.

The New Zealand data sheets for gabapentin contain extensive warnings on the risk of respiratory depression particularly when used with other CNS depressants, including opioids. However, the pregabalin data sheet contains less information than the gabapentin data sheet.

Using reduced doses of gabapentin and pregabalin in the elderly has also come to Medsafe's attention. There are recommended dose adjustments in both data sheets for patients with impaired renal function. The pregabalin data sheet is more explicit in stating that no dose adjustments are needed for elderly patients (>65 years) unless their renal function is compromised.

5 ADVICE SOUGHT

The Committee is asked to advise on the following:

- Do the gabapentin or pregabalin data sheets require updating with information regarding misuse, abuse and dependence; opioid-related death and respiratory depression; or use in elderly patients?
- Is any other communication required on any of these three potential safety concerns? This could include a general article in *Prescriber Update* or a safety communication the Medsafe website.

6 ANNEXES

1. CARM data

7 REFERENCES

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