ARTICLE

Gabapentinoids: a therapeutic review

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SUMMARY

The Australian Therapeutic Goods Administration's approved indications for prescription of gabapentinoids are refractory focal epilepsy and neuropathic pain.

Use of gabapentinoids outside of the approved indications is common, but evidence for this is limited, especially for chronic nonspecific back pain and nonradicular leg pain.

Some effects of gabapentinoids encourage their nonmedical use (e.g. euphoria, sedation, disinhibition). Widespread nonmedical use has increased the incidence of accidental and deliberate poisonings.

Dependence may develop with chronic use of gabapentinoids and abrupt cessation may induce withdrawal symptoms. If the indication for continued use is unclear, gradual dose tapering as a means of deprescribing is recommended.

Clinicians should consider the indication, patient characteristics and harm–benefit profile when prescribing gabapentinoids. Some people, such as those with kidney disease, have an increased risk of harm when using these drugs.

Introduction

The use of gabapentinoids, gabapentin and pregabalin, has increased since their approval over 20 years ago.[1,2] They are approved by the Australian Therapeutic Goods Administration (TGA) for refractory focal (partial) epilepsy, and neuropathic pain. Off-label prescription of gabapentinoids is common. From 2020 to 2021, there were over 4 million prescriptions for gabapentin and pregabalin for various approved and off-label indications subsidised on the Pharmaceutical Benefits Scheme (PBS).[3]

Euphoria is a dose-dependent effect of gabapentinoids, experienced by about 10% of people. This effect may account for increased nonmedical use, especially of pregabalin.[4,5] Widespread use has increased the frequency of adverse effects, including acute toxicity, multidrug poisonings, and dependence.[2,6]

Pharmacology of gabapentinoids

Gabapentinoids are related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), but do not interact significantly with GABA receptors. Gabapentinoids have multiple molecular actions that indirectly reduce neuronal excitability and firing.[1,7,8]

Gabapentinoids are given orally. Gabapentin has saturable absorption and maximal effects occur within 2 to 3 hours. Pregabalin is rapidly absorbed and maximal effects occur within one hour. Both drugs are mostly eliminated unchanged in the urine. Their half-lives are 5 to 7 hours, and increase with declining kidney function.[1,8-10]

Approved indications for gabapentinoids

Gabapentinoids are approved by the TGA for adjunctive therapy in patients with refractory focal epilepsy, and for treatment of neuropathic pain. Pregabalin is only approved for use in adults.

Refractory focal epilepsy

Gabapentinoids are effective adjunctive treatments for refractory focal epilepsy;[11,12] however, only gabapentin is subsidised by the PBS for this indication. Both gabapentin and pregabalin reduce seizure frequency by 50% compared with placebo in short-term trials. Available data cannot be extrapolated to support drug monotherapy.[11,12]

Effective antiepileptic doses are pregabalin 150 to 600 mg daily[11] and gabapentin 600 to 1800 mg daily.[12]

Neuropathic pain

In Australia, gabapentinoids are approved for neuropathic pain, but only PBS subsidised for refractory neuropathic pain. In other countries, gabapentinoids are used first line for neuropathic pain.[1]

A 2017 trial of pregabalin for neuropathic leg pain (presumed sciatic radicular pain) found no difference in pain for those taking pregabalin (150 to 600 mg daily) compared with placebo, and more adverse events in the pregabalin group over 8 weeks.[13]

A 2017 systematic review of gabapentin for postherpetic neuralgia or diabetic neuropathy found gabapentin (1800 to 3600 mg daily) was more

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effective than placebo.[10] Evidence for gabapentin's analgesic effect in other neuropathic pain conditions was very limited.[10]

A similar 2019 systematic review of pregabalin for postherpetic neuralgia, diabetic neuropathy, and mixed or post-traumatic neuropathy, found pregabalin (300 to 600 mg daily) was more effective than placebo.[14] Evidence for pregabalin's analgesic effect in other neuropathic pain conditions was very limited.[14]

Off-label uses of gabapentinoids

Gabapentinoids are prescribed for many conditions outside of the approved indications and this is referred to as 'off-label' use (Box 1). Evidence supporting off-label use of gabapentinoids is limited.

Opioid sparing

Gabapentinoids are increasingly prescribed off label for many pain syndromes, most likely in response to escalating opioid-related harms; however, evidence to support their use is limited.

A 2020 systematic review of 281 randomised controlled trials (RCTs), evaluating perioperative gabapentinoid use (versus no gabapentinoids) for acute postoperative pain, found no clinically significant analgesic effect of gabapentinoids. The opioid-sparing effect was small and not significant, and more adverse effects occurred, including visual disturbance and dizziness.[16]

Similar results were found in a 2017 systematic review of 8 RCTs, evaluating gabapentinoid use in chronic low back pain, where little evidence of analgesic or opioid-sparing effect was seen.[17] A 2018 systematic review of 9 RCTs, comparing anticonvulsants (including gabapentinoids) with placebo, reported gabapentinoids were ineffective for low back pain and lumbar radicular pain, and increased the risk of adverse events when combined with opioids.[18]

Restless legs syndrome

Gabapentin and pregabalin can improve symptoms of restless legs syndrome. A 2017 meta-analysis of 35 studies of various drugs used for restless legs syndrome suggested pregabalin and gabapentin enacarbil* were equally effective. Trial data suggest treatment may continue for up to 52 weeks.[19]

Effective doses for restless legs syndrome vary; for pregabalin, it is usually 150 to 450 mg daily in divided doses.[19] For gabapentin, the effective dose may be 1200 to 3600 mg daily in divided doses.[20]

Pruritus

Gabapentinoids are effective for treating chronic pruritus of various aetiologies, including uraemic and neuropathic or neurogenic pruritus.[15,21]

Significant dose reduction is required in people with chronic kidney disease (CKD), particularly kidney failure. For people with end-stage kidney disease on peritoneal dialysis, gabapentin 100 mg at night, or pregabalin 25 mg at night, can be an effective starting dose. For people on haemodialysis, the dose frequency can be reduced to 3 times per week after haemodialysis, at which time the drug can provide almost immediate effect.[15]

Alcohol use disorder

A 2014 systematic review of anticonvulsants for alcohol dependence found gabapentin was not effective, though very few people were taking gabapentinoids, so conclusions were not possible.[22] In a 2020 small double-blind, placebo-controlled RCT over 16 weeks, gabapentin 1200 mg daily effectively promoted abstinence and prevented return to heavy alcohol use, particularly for people with severe withdrawal symptoms.[23]

Fibromyalgia

Gabapentinoids are not approved for treatment of fibromyalgia in Australia, but are commonly used.[24] A 2017 systematic review of gabapentin for fibromyalgia pain found only one trial that compared gabapentin with placebo for self-reported pain, and there was no good evidence to support its use.[24] A 2022 meta-analysis of 44 RCTs reported that pregabalin 450 mg daily improved scores on a fibromyalgia impact questionnaire, but was associated with a dose-dependent increase in adverse events. There were insufficient data on gabapentin to draw any conclusions on its utility in fibromyalgia.[25]

Box 1 Off-label uses of gabapentinoids[1,15]

- acute postoperative pain
- alcohol use disorder
- alcohol withdrawal
- anxiety disorders
- attention deficit hyperactivity disorder
- bipolar disorder
- chronic nonspecific back pain
- fibromyalgia
- headaches
- opioid sparing
- sleep disorders (e.g. restless legs syndrome, periodic limb movements of sleep/wakefulness)
- pruritus

* Gabapentin enacarbil is a prodrug of gabapentin that is not available for use in Australia.

Anxiety disorders

Some UK guidelines recommend pregabalin for treating anxiety, but the supporting data are limited to short trials (mean duration 7.3 weeks).[26] These data do not support use of pregabalin for anxiety because it is a chronic condition and pregabalin's anxiolytic effects diminish over time, similar to benzodiazepines.[26] Pregabalin may be effective for short-term treatment of anxiety but studies of longer-term efficacy and harms are required.

Nonmedical use of gabapentinoids

Gabapentinoids have become readily available via the black market or online.[4] Their dose-dependent euphoric effects may be responsible for their increased nonmedical use.[4,5] Other potentially desirable effects include sedation, disinhibition, relaxation and hallucinations.[27] People may use gabapentinoids to mitigate withdrawal symptoms from other drugs (e.g. alcohol, opioids).[28]

Gabapentinoids are often used in combination with other sedative or hypnotic drugs, including alcohol, benzodiazepines, cannabis, opioids, zolpidem and zopiclone. Pregabalin is more popular than gabapentin because of its rapid onset.[4,29] Nonmedical use of gabapentinoids is most commonly seen in people with opioid use disorder, which increases their risks of morbidity and mortality.[30]

Evidence suggests gabapentin has a lower risk of dependent use than pregabalin.[29] People with a substance use disorder (or previous history of one), particularly opioid use disorder, are at higher risk of developing tolerance to, and dependent use of, gabapentinoids.[5,29]

Gabapentinoid use in high-risk populations

Some people have a higher risk of adverse effects from gabapentinoid use, including pregnant people, people with CKD and older people.

Pregnant people

Gabapentinoids should be avoided during pregnancy because safety data in pregnancy are limited. Rates of congenital malformation in pregabalin-exposed pregnancies are higher (3.3 to 7.7%) than unexposed pregnancies (3.3%).[31] A 2023 observational study of over 2700 pregabalin-exposed pregnancies reported congenital malformations in 5.9% of pregabalin-exposed pregnancies compared with 4.1% of nonexposed pregnancies.[32,33] Other studies have not confirmed these findings and suggest no increased risk; however, all were either underpowered or observational studies.[31,34]

For gabapentin use, a 2020 large population-based cohort study of several thousand pregnancies found no significant association between exposure in the first trimester and major malformation, apart from a slightly increased risk of cardiac malformation. Exposure at any time during pregnancy increased the risk of babies being born small for gestational age. Exposure in the first or third trimesters increased the risk of preterm birth and neonatal intensive care admission.[35]

People with kidney disease

As gabapentinoids are predominantly excreted by the kidney, cautious starting doses and careful dose adjustments are required for people with acute or chronic kidney disease. When creatinine clearance is below 30 mL/minute, the half-lives of both gabapentin and pregabalin are prolonged.[8]

For people with CKD, starting gabapentin at 300 mg or more daily, or pregabalin at 75 mg or more daily, is associated with a higher rate of hospitalisation due to serious adverse events.[36] For people with kidney failure, higher doses of gabapentinoids are associated with higher risks of altered mental status, falls and fractures.[37]

Older people

The incidence of adverse effects of gabapentinoids may be increased in older people,[1] but this is not necessarily only age related.[38] A 2010 analysis of 11 studies on the effectiveness and safety of pregabalin in older people with neuropathic pain found a dose-dependent risk of adverse events.[39] Clinicians should only use pregabalin at the lowest effective dose for analgesia in older people, aiming for minimal adverse effects.

Older people with reduced kidney function may be at risk of drug accumulation and toxicity.[39,40] Polypharmacy also increases their risk of adverse effects.[41]

Adverse effects of gabapentinoids

Although perceived as relatively safe drugs, gabapentinoids are associated with significant harms.[14] Combining gabapentinoids with other sedative drugs increases the risk of adverse effects.

Gabapentinoids are centrally acting drugs and the most common adverse effects (in up to 30% of adults) are sedation and dizziness.[10,14] Other common adverse effects include:

- for pregabalin—nausea, vomiting, headache, bowel disturbance, diplopia, dysarthria, vertigo
- for gabapentin—vertigo.[42]

A 2019 large population-based cohort study demonstrated that gabapentinoid use is associated with increased risk of suicidal behaviour and suicide, unintentional overdose and serious injuries.[43]

Gabapentinoid toxicity

Toxicity from gabapentinoids presents as central nervous system depression (ranging from drowsiness to coma) because of their inhibitory effects, and is worsened by concomitant use of other sedative drugs.

In the last 20 years in Australia, the incidence of accidental and deliberate gabapentinoid poisoning increased significantly.[2,6] From 2012 to 2017 there was a tenfold increase in ambulance attendances to people with pregabalin toxicity, which coincided with increased prescribing and nonmedical use of pregabalin.[6]

A retrospective study reported there were 887 fatalities involving a gabapentinoid between 2000 and 2020. Pregabalin was identified in 93% of cases and gabapentin in 73%. The vast majority (81%) of the deaths were accidental. Other drugs were detected in almost all people, most commonly opioids (90%), sedatives or hypnotics (77%) and antidepressants (60%).[44]

Withdrawal from gabapentinoids

Gabapentinoid withdrawal symptoms can occur from 12 hours to 7 days after drug cessation. The most common signs and symptoms are listed in Box 2.[45,46]

Box 2 Signs and symptoms of gabapentinoid withdrawal[45,46]

Signs of gabapentinoid withdrawal

- agitation, confusion and disorientation
- sweating, salivation
- tachycardia, hypertension
- dysarthria, tremor, myoclonus, asterixis, akathisia, seizure, status epilepticus
- behavioural disturbance, catatonia, psychosis

Symptoms of gabapentinoid withdrawal

- headache
- anxiety, cravings
- gastrointestinal disturbance, nausea, vomiting, diarrhoea
- chills
- insomnia, fatigue

Neonatal withdrawal has also been reported after maternal gabapentinoid use during pregnancy.[47]

There are limited case reports and case series published about gabapentinoid withdrawal, which may overestimate its severity. NSW Health's clinical guidance on the management of withdrawal from alcohol and other drugs strongly recommends dose tapering in all people taking a gabapentinoid to limit withdrawal.[45] Depending on the amount and duration of use, gradual dose tapering may be the most effective strategy and can be undertaken in either an inpatient setting over 5 to 7 days, or as an outpatient with a staged supply over 4 to 6 weeks (e.g. reduce the dose by 20% at weekly intervals until cessation).[45]

Simple symptomatic management is usually required for withdrawal symptoms.

Harm minimisation

There is limited evidence for harm-minimisation strategies specifically for gabapentinoids. When the indication for gabapentinoid treatment is unclear, particularly when there is a risk of adverse events, deprescribing is recommended. Deprescribing tools can help decision making.[48] It is important to consider the risk of withdrawal, especially when high doses and long durations (more than 4 weeks) are involved (see above).

Real-time prescription monitoring programs aim to track and manage use of drugs of addiction. Areas where prescription monitoring programs are vigorous have been associated with fewer deaths from drug toxicity compared to areas with weaker programs.[49] Such programs may be useful to identify 'at-risk' prescriptions and reduce harms. Health professionals should familiarise themselves with local monitoring programs and the drugs they target.

Conclusion

Use of gabapentinoids (including nonmedical use) has increased over the last 20 years. Clinicians should be aware of the limited approved indications for gabapentinoids. Caution is required when prescribing these drugs off label because there are significant risks of serious adverse events (including death), development of dependence and withdrawal symptoms on abrupt cessation. All people who are taking a gabapentinoid should be managed with dose tapering over days to weeks to prevent withdrawal. <

Conflicts of interest: none declared

REFERENCES

1. Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. Br J Pain 2020;14:104-14. https://doi.org/10.1177/2049463720912496
2. Cairns R, Schaffer AL, Ryan N, Pearson SA, Buckley NA. Rising pregabalin use and misuse in Australia: trends in utilization and intentional poisonings. Addiction 2019;114:1026-34. https://doi.org/10.1111/add.14412
3. Australian Institute of Health and Welfare. Alcohol, tobacco & other drugs in Australia. Canberra: AIHW; 2023. https://www.aihw.gov.au/reports/alcohol/alcohol-tobacco-other-drugs-australia/contents/drug-types/non-medical-use-of-pharmaceutical-drugs [cited 2023 Aug 10]
4. Lancia M, Gambelunghe A, Gili A, Bacci M, Aroni K, Gambelunghe C. Pregabalin Abuse in Combination With Other Drugs: Monitoring Among Methadone Patients. Front Psychiatry 2019;10:1022. https://doi.org/10.3389/fpsyt.2019.01022
5. Schjerning O, Rosenzweig M, Pottegård A, Damkier P, Nielsen J. Abuse Potential of Pregabalin: A Systematic Review. CNS Drugs 2016;30:9-25. https://doi.org/10.1007/s40263-015-0303-6
6. Crossin R, Scott D, Arunogiri S, Smith K, Dietze PM, Lubman DI. Pregabalin misuse-related ambulance attendances in Victoria, 2012-2017: characteristics of patients and attendances. Med J Aust 2019;210:75-9. https://doi.org/10.5694/mja2.12036
7. Verma V, Singh N, Singh Jaggi A. Pregabalin in neuropathic pain: evidences and possible mechanisms. Curr Neuropharmacol 2014;12:44-56. https://doi.org/10.2174/1570159X1201140117162802
8. Raouf M, Atkinson TJ, Crumb MW, Fudin J. Rational dosing of gabapentin and pregabalin in chronic kidney disease. J Pain Res 2017;10:275-8. https://doi.org/10.2147/JPR.S130942
9. Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol 2003;43:277-83. https://doi.org/10.1177/0091270003251119
10. Wiffen PJ, Derry S, Bell RF, Rice AS, Tolle TR, Phillips T, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2017;6:CD007938. https://doi.org/10.1002/14651858.CD007938.pub4
11. Panebianco M, Bresnahan R, Marson AG. Pregabalin add-on for drug-resistant focal epilepsy. Cochrane Database Syst Rev 2022;3:CD005612. https://doi.org/10.1002/14651858.CD005612.pub5
12. Panebianco M, Al-Bachari S, Hutton JL, Marson AG. Gabapentin add-on treatment for drug-resistant focal epilepsy. Cochrane Database Syst Rev 2021;1:CD001415. https://doi.org/10.1002/14651858.CD001415.pub4
13. Mathieson S, Maher CG, McLachlan AJ, Latimer J, Koes BW, Hancock MJ, et al. Trial of Pregabalin for Acute and Chronic Sciatica. N Engl J Med 2017;376:1111-20. https://doi.org/10.1056/NEJMoa1614292
14. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. Cochrane Database Syst Rev 2019;1:CD007076. https://doi.org/10.1002/14651858.CD007076.pub3
15. Rayner H, Baharani J, Smith S, Suresh V, Dasgupta I. Uraemic pruritus: relief of itching by gabapentin and pregabalin. Nephron Clin Pract 2012;122:75-9. https://doi.org/10.1159/000349943
16. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, et al. Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain: A Systematic Review and Meta-analysis. Anesthesiology 2020;133:265-79. https://doi.org/10.1097/ALN.0000000000003428
17. Shanthanna H, Gilron I, Rajarathinam M, AlAmri R, Kamath S, Thabane L, et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med 2017;14:e1002369. https://doi.org/10.1371/journal.pmed.1002369
18. Enke O, New HA, New CH, Mathieson S, McLachlan AJ, Latimer J, et al. Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis. CMAJ 2018;190:E786-E93. https://doi.org/10.1503/cmaj.171333
19. Winkelman JW. Treating Severe Refractory and Augmented Restless Legs Syndrome. Chest 2022;162:693-700. https://doi.org/10.1016/j.chest.2022.05.014
20. Silber MH, Buchfuhrer MJ, Earley CJ, Koo BB, Manconi M, Winkelman JW, et al. The Management of Restless Legs Syndrome: An Updated Algorithm. Mayo Clin Proc 2021;96:1921-37. https://doi.org/10.1016/j.mayocp.2020.12.026
21. Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. J Am Acad Dermatol 2016;75:619-25 e6. https://doi.org/10.1016/j.jaad.2016.02.1237
22. Pani PP, Trogu E, Pacini M, Maremmani I. Anticonvulsants for alcohol dependence. Cochrane Database Syst Rev 2014:CD008544. https://doi.org/10.1002/14651858.CD008544.pub2
23. Anton RF, Latham P, Voronin K, Book S, Hoffman M, Prisciandaro J, et al. Efficacy of Gabapentin for the Treatment of Alcohol Use Disorder in Patients With Alcohol Withdrawal Symptoms: A Randomized Clinical Trial. JAMA Intern Med 2020;180:728-36. https://doi.org/10.1001/jamainternmed.2020.0249
24. Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. Cochrane Database Syst Rev 2017;1:CD012188. https://doi.org/10.1002/14651858.CD012188.pub2
25. Migliorini F, Maffulli N, Eschweiler J, Knobe M, Tingart M, Colarossi G. Pharmacological management of fibromyalgia: a Bayesian network meta-analysis. Expert Rev Clin Pharmacol 2022;15:205-14. https://doi.org/10.1080/17512433.2022.2044792
26. Horowitz MA, Kelleher M, Taylor D. Should gabapentinoids be prescribed long-term for anxiety and other mental health conditions? Addict Behav 2021;119:106943. https://doi.org/10.1016/j.addbeh.2021.106943
27. Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. Drugs 2017;77:403-26. https://doi.org/10.1007/s40265-017-0700-x
28. Hofmann M, Besson M. Gabapentinoids: The rise of a new misuse epidemics? Psychiatry Res 2021;305:114193. https://doi.org/10.1016/j.psychres.2021.114193
29. Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. Eur Neuropsychopharmacol 2017;27:1185-215. https://doi.org/10.1016/j.euroneuro.2017.08.430
30. Evoy KE, Sadrameli S, Contreras J, Covvey JR, Peckham AM, Morrison MD. Abuse and Misuse of Pregabalin and Gabapentin: A Systematic Review Update. Drugs 2021;81:125-56. https://doi.org/10.1007/s40265-020-01432-7
31. Andrade C. Safety of Pregabalin in Pregnancy. J Clin Psychiatry 2018;79. https://doi.org/10.4088/JCP.18f12568
32. Dudukina E, Szépligeti SK, Karlsson P, Asomaning K, Daltveit AK, Hakkarainen K, et al. Prenatal exposure to pregabalin, birth outcomes and neurodevelopment - a population-based cohort study in four Nordic countries. Drug Saf 2023;46:661-75. https://doi.org/10.1007/s40264-023-01307-2
33. Medicines and Healthcare products Regulatory Agency. Pregabalin (Lyrica): findings of safety study on risks during pregnancy. Drug Safety Update 2022;14:2-6. https://www.gov.uk/drug-safety-update/pregabalin-lyrica-findings-of-safety-study-on-risks-during-pregnancy [cited 2023 Aug 10]
34. Patorno E, Bateman BT, Huybrechts KF, MacDonald SC, Cohen JM, Desai RJ, et al. Pregabalin use early in pregnancy and the risk of major congenital malformations. Neurology 2017;88:2020-5. https://doi.org/10.1212/WNL.0000000000003959
35. Patorno E, Hernandez-Diaz S, Huybrechts KF, Desai RJ, Cohen JM, Mogun H, et al. Gabapentin in pregnancy and the risk of adverse neonatal and maternal outcomes: A population-based cohort study nested in the US Medicaid Analytic eXtract dataset. PLoS Med 2020;17:e1003322. https://doi.org/10.1371/journal.pmed.1003322
36. Muanda FT, Weir MA, Ahmadi F, Sontrop JM, Cowan A, Fleet JL, et al. Higher-Dose Gabapentinoids and the Risk of Adverse Events in Older Adults With CKD: A Population-Based Cohort Study. Am J Kidney Dis 2022;80:98-107.e1. https://doi.org/10.1053/j.ajkd.2021.11.007

37. Ishida JH, McCulloch CE, Steinman MA, Grimes BA, Johansen KL. Gabapentin and Pregabalin Use and Association with Adverse Outcomes among Hemodialysis Patients. J Am Soc Nephrol 2018;29:1970-8. https://doi.org/10.1681/ASN.2018010096
38. Hilmer SN. ADME-tox issues for the elderly. Expert Opin Drug Metab Toxicol 2008;4:1321-31. https://doi.org/10.1517/17425255.4.10.1321
39. Semel D, Murphy TK, Zlateva G, Cheung R, Emir B. Evaluation of the safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies. BMC Fam Pract 2010;11:85. https://doi.org/10.1186/1471-2296-11-85
40. Denic A, Glassock RJ, Rule AD. Structural and Functional Changes With the Aging Kidney. Adv Chronic Kidney Dis 2016;23:19-28. https://doi.org/10.1053/j.ackd.2015.08.004
41. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf 2014;13:57-65. https://doi.org/10.1517/14740338.2013.827660
42. Robertson K, Marshman LAG, Plummer D, Downs E. Effect of Gabapentin vs Pregabalin on Pain Intensity in Adults With Chronic Sciatica: A Randomized Clinical Trial. JAMA Neurol 2019;76:28-34. https://doi.org/10.1001/jamaneurol.2018.3077
43. Molero Y, Larsson H, D'Onofrio BM, Sharp DJ, Fazel S. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden. BMJ 2019;365:l2147. https://doi.org/10.1136/bmj.l2147
44. Darke S, Duflou J, Peacock A, Farrell M, Lappin J. Characteristics of fatal gabapentinoid-related poisoning in Australia, 2000-2020. Clin Toxicol (Phila) 2022;60:304-10. https://doi.org/10.1080/15563650.2021.1965159
45. NSW Health. Management of withdrawal from alcohol and other drugs: clinical guidance. Sydney: NSW Ministry of Health; 2022. https://www.health.nsw.gov.au/aod/professionals/Pages/clinical-guidance.aspx [cited 2023 Aug 8]
46. Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. Ann Pharmacother 2016;50:229-33. https://doi.org/10.1177/1060028015620800
47. Carrasco M, Rao SC, Bearer CF, Sundararajan S. Neonatal Gabapentin Withdrawal Syndrome. Pediatr Neurol 2015;53:445-7. https://doi.org/10.1016/j.pediatrneurol.2015.06.023
48. Liacos M, Page AT, Etherton-Beer C. Deprescribing in older people. Aust Prescr 2020;43:114-20. https://doi.org/10.18773/austprescr.2020.033
49. Pardo B. Do more robust prescription drug monitoring programs reduce prescription opioid overdose? Addiction 2017;112:1773-83. https://doi.org/10.1111/add.13741