**Non-prescribed use of gabapentinoids: mechanisms, predisposing factors, associated hazards and clinical management**

David S. Baldwin 1,2,3 and Vasilios Masdrakis 1, 4

1. Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
2. Southern Health NHS Foundation Trust, Southampton, United Kingdom
3. Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa
4. First Department of Psychiatry, Eginition Hospital, National and Kapodistrian University of Athens Medical School, Greece

Gabapentinoids are medications used in a range of neurological or psychiatric conditions: some (gabapentin, pregabalin) have widespread clinical use, but others (gabapentin enacarbil [a pro-drug], phenibut) are available in only few countries. Gabapentin and pregabalin have analgesic, anticonvulsant and anxiolytic effects, and are two of the most prescribed medicines, though often outside their market authorisations: for example, in the United Kingdom at least half of all gabapentinoid prescriptions may be ‘off-label’ [Montastruc et al., 2018], and concerns regarding widespread non-prescribed use led to reclassification of gabapentin and pregabalin as Class C controlled substances with accompanying regulations regarding prescriptions, in April 2019.

Gabapentinoids are substituted derivatives of gamma-aminobutyric acid (GABA) and block α2δ-subunit-containing voltage-gated calcium channels within the central nervous system, most prominently after prolonged administration [Dolphin, 2016]. Molecular pharmacological mechanisms are complex [Calandre et al., 2016]. Although gabapentin is a structural analogue of GABA, it does not bind to GABA receptors, or convert into GABA or another GABA receptor agonist, or modulate GABA transport or metabolism: furthermore, it is not a direct calcium channel blocker, but disrupts regulatory functions of α2δ subunits and their interactions with other proteins. It induces glutamate release from astrocytes in the locus coeruleus by an α2δ-independent mechanism and inhibits GABA release; these potentially anxiogenic effects are countermanded by increased expression of GABAA receptor expression within the hippocampus with increased tonic inhibitory conductance, occurring alongside α2δ-dependent anxiolytic mechanisms. Pregabalin shows high affinity binding to Type 1 and Type 2 proteins of the α2δ subunit of P/Q type voltage-gated calcium channels: it does not bind directly to GABAA or GABAB receptors or to sites allosterically linked to GABA but increases density of GABA transporter proteins and extracellular GABA through a dose-dependent increase in L-glutamic acid decarboxylase activity. Through effects on calcium channels, pregabalin reduces glutamate release and may reduce synthesis of excitatory synapses and block ‘trafficking’ of new voltage-gated calcium channels to the cell surface.

Gabapentin and pregabalin have addictive potential and the risk of misuse [Evoy et al., 2021]. There were few pre-clinical studies of abuse potential with gabapentin before it became available for clinical use, but a systematic review indicates it can be taken for recreation, ‘self-medication’ or intentional self-harm: patients with a history of substance abuse, especially current or previous opioid misuse, are at particular risk [Smith et al., 2016]. For pregabalin, the findings of 17 pre-clinical investigations are inconsistent: it may have direct and indirect effects on the reward system, and so possess potential for abuse, but also attenuates opiate withdrawal symptoms and reduces alcohol consumption in animal models of opiate and alcohol dependence, and been found helpful in facilitating withdrawal from alcohol, benzodiazepines, nicotine and zolpidem. ‘Euphoria’, described in ~5% of participants in early clinical trials with pregabalin for epilepsy [Zaccara et al., 2011], appears dose-dependent, is seen across indications, and has an uncertain course. Supra-therapeutic doses of pregabalin can result in a sense of contentment, enhanced empathy, increased sociability, dissociation and disinhibited behaviour, and non-prescribed use is reported, particularly in patients with a history of substance use disorders, or after high dosage [Hägg et al., 2020].

Early epidemiological investigations of non-prescribed gabapentinoid use were mainly small studies without broad generalisability and potential for ‘confounding by indication’. Findings from more representative samples and systematic reviews indicate that although the precise prevalence of non-prescribed use is not established, it is not insubstantial: pharmacoepidemiological studies indicate a prevalence of possible non-prescribed use of between 2-8% (gabapentin) in the United States, and 6.6% (gabapentin) and 12.8% (pregabalin) in France. In populations without a history of substance misuse the prevalence of non-prescribed use of pregabalin may lie between 0.5-8.5% [Schjerning et al., 2016].

Risk factors for non-prescribed use have been identified. Individuals with a history of substance use disorders are at greater risk, particularly those with a history of opiate or poly-substance use: the six-month prevalence of gabapentinoid dependence and non-prescribed use in opioid-using individuals may be as high as 26% [Bonnet and Scherbaum, 2017]. This could be because gabapentinoids might reduce opioid withdrawal syndromes or are being used as alternatives as availabilities of opioids and benzodiazepines decline, or to potentiate effects of methadone or buprenorphine. Opioid-using individuals may favour pregabalin over gabapentin as it reportedly confers a more rapid, stronger ‘high’ [Bonnet and Scherbaum, 2017], presumably resulting from its more rapid and non-saturatable absorption, greater bioavailability, and stronger inhibitory action on α2δ subunits [Calandre et al., 2016]. Other risk factors for non-prescribed use include younger age, male sex, a diagnosis of anxiety, access to multiple prescribers, and physical illness.

Non-prescribed ‘overuse’ of gabapentin is associated with increased risks of all-cause and drug-related hospitalisation, particularly if combined with opioids, and pregabalin prescriptions in patients undergoing opioid maintenance therapy increase all-cause mortality: increased risk of death may result from greater respiratory depression, prolonged gastrointestinal transit increasing gabapentin concentration, and delayed onset of effect of gabapentinoids compared to injected opioids [Evoy et al., 2021]. Gabapentinoid users have increased risks of suicidal behaviour, unintentional overdoses, traffic accidents, injuries and legal offences [Molero et al., 2019]. Non-prescribed use may also be associated with withdrawal syndromes, symptoms including anxiety, depression, headache, joint and muscle pains, lethargy, shivering, and sweating: reports also describe agitation, disorientation, irritability and seizures [Evoy et al., 2021]. Possible neonatal withdrawal syndromes have been described.

Principles of clinical management of non-prescribed use of gabapentinoids are simple: remembering the potential for non-prescribed use; remaining aware of clinical risk factors associated with potential hazards; avoiding prescription of gabapentinoids to patients with current or previous alcohol or substance use disorders; warning patients about potential hazards before and during gabapentinoid treatment; following local regulations about limiting treatment periods and stipulating the dosage of renewed prescriptions; reviewing patients regularly to determine whether there is a need for continued treatment; monitoring patients carefully but sensitively for signs of dependence and indicators of non-prescribed use; supporting patients who develop problems associated with gabapentinoids whilst reducing and withdrawing treatment; and referring to colleagues with greater expertise in management of non-prescribed use if initial approaches prove unhelpful.

*(1000 words)*

**Funding:** no funding was sought or received for this article

**Declaration of interest:** DSB and VMdeclare no potential conflicts of interest

**References**

Bonnet, U., Scherbaum, N., 2017. How addictive are gabapentin and pregabalin? A systematic review. Eur Neuropsychopharmacol, 27, 1185-1215.

Calandre, E.P., Rico-Villademoros, F., Slim, M., 2016. Alpha2delta ligands, gabapentin, pregabalin and mirogabalin: a review of their clinical pharmacology and therapeutic use. Exp Rev Neurotherapeut, 16, 1263-1277.

Dolphin, A.C., 2016. Voltage‐gated calcium channels and their auxiliary subunits: physiology and pathophysiology and pharmacology. J Physiol 594, 5369-5390.

Evoy, K.E., Sadrameli, S., Contreras, J., Covvey, J.R., Peckham, A.,M., Morrison, Ml., 2021. Abuse and misuse of pregabalin and gabapentin: a systematic review update. Drugs, 81, 125-156.

Hägg, S., Jönsson, A.K., Ahlner, J., 2020. Current evidence on abuse and misuse of gabapentinoids. Drug Safety, 43, 1235-1254.

Molero, Y., Larsson, H., D’Onofrio, B.M., Sharp, D.J., Fazel, S., 2019. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden. BMJ, 365.

Montastruc, F., Loo, S.Y., Renoux, C., 2018. Trends in first gabapentin and pregabalin prescriptions in primary care in the United Kingdom, 1993-2017. JAMA 320, 2149-2151.

Schjerning, O., Rosenzweig, M., Pottegård, A., Damkier, P., Nielsen, J., 2016. Abuse potential of pregabalin. CNS Drugs, 30, 9-25.

Smith, R.V., Havens, J.R., Walsh, S.L., 2016. Gabapentin misuse, abuse and diversion: a systematic review. Addiction, 111, 1160-1174.

Zaccara, G., Gangemi, P., Perucca, P., Specchio, L., 2011. The adverse event profile of pregabalin: A systematic review and meta‐analysis of randomized controlled trials. Epilepsia, 52, 826-836.

*(10 references)*