Neuropathic pain is a growing public health issue that affects approximately twelve percent of adults (Sicras-Mainar, Rejas-Gutiérrez, Pérez-Páramo, & Navarro-Artieda, 2016). Individual responses to treatment vary, with only forty to sixty percent of people experiencing therapeutic effects from medication and most requiring a combination of drugs (Bannister et al., 2017). This condition is predicted to increase in the future (Cruccu & Truini, 2017). To uphold the quality of life of people with neuropathic pain, it is essential that the most effective therapy is prescribed. Pregabalin and gabapentin are two drugs within the same family that can be used to treat neuropathic pain. This essay will compare their pharmacological parameters to ascertain which drug is more appropriate for people with this condition.

Pregabalin and gabapentin are both gabapentinoids and therefore have similar mechanisms of action. Bannister et al. (2017) explain that they were developed to be GABA analogues. However, neither binds to GABA receptors. It is not fully understood how they produce an analgesic effect, but it has been established that both drugs bind to the α₂δ subunit of neuronal voltage-gated calcium channels. This subunit is up-regulated after nerve injury. When gabapentinoids bind to the subunit, the release of certain excitatory neurotransmitters such as glutamate, calcitonin gene-related peptide, and substance P is reduced (Calandre, Rico-Villademoros, & Mahmoud, 2016). Because nerve injury causes neuronal hyperexcitability which leads to neuropathic pain, the reduction of these neurotransmitters produces an analgesic effect.

Although they are in the same mechanistic class, pregabalin and gabapentin can produce different therapeutic responses (Markman et al., 2017). The effects of pregabalin in neuropathic pain has been studied more in depth than gabapentin’s. Perhaps this is because gabapentin was used as an anticonvulsant until its analgesic effects were discovered. Neither of these drugs can relieve pain from mechanical and heat sources (Bannister et al., 2017). Kremer et al. (2017) suggests that this is perhaps because they do not act on the body’s opioid system. However, these authors do point out that gabapentin may produce an anti-inflammatory effect by reducing pro-inflammatory cytokines’ expression. It has not been established whether pregabalin is capable of this.

Gabapentin and pregabalin also possess unique pharmacokinetic profiles with some similarities (Sicras-Mainar et al., 2016). While both are absorbed in the small intestine and colon by active transport (Calandre et al., 2016), the absorption of pregabalin is faster and more predictable than gabapentin’s (Markman et al., 2017). This is because it has linear absorption with any dose (Calandre et al., 2016). In other words, pregabalin is dose-independent so it will produce a higher bioavailability (ninety percent) than gabapentin, rendering it more potent and reliable. On the other hand, gabapentin has zero-order saturable absorption (Raouf et al., 2017). This means that as the dose increases, the bioavailability will decrease because its absorption is dose-dependent.

Regarding distribution, once again there are similarities between the two gabapentinoids. According to Calandre et al. (2016), neither pregabalin nor gabapentin bind to plasma proteins. Their volume of distribution is similar to total body water. It has not been established what percentage of pregabalin crosses the blood-brain barrier, but between nine and fourteen percent of a dose of gabapentin can be found in the cerebrospinal fluid.

Another pharmacokinetic similarity of gabapentin and pregabalin is that both cannot be metabolised by humans and are excreted by the kidneys unchanged (Kaul, Amin, Rosenberg, Rosenberg, & Meyer, 2018). In people with normal kidney function, gabapentin’s total clearance is 100ml/min and pregabalin’s is 67-81ml/min (Raouf, Atkinson, Crumb, & Fudin, 2017). This means that tubular reabsorption does occur with pregabalin. According to Calandre et al. (2016), the literature is divided on whether tubular reabsorption occurs with gabapentin.

Turning to pregabalin and gabapentin’s pharmacodynamic features, once again pregabalin appears to be the more reliable drug. It has greater receptor affinity, binding to calcium channels six times more than gabapentin (Kaul et al., 2018). Due to its potency, people with neuropathic pain only require 150-600 milligrams of pregabalin per day in two to three divided doses (Raouf et al., 2017; Calandre et al., 2016). People require a greater dose of gabapentin to experience relief of neuropathic pain. It is usually prescribed at 1800-3600 milligrams per day, in three divided doses. Pregabalin can be given less frequently because its half-life is 16.7 hours, as opposed to gabapentin’s five to seven-hour half-life (Raouf et al., 2017).

More research comparing the therapeutic effects of pregabalin and gabapentin on neuropathic pain is required (Markman et al., 2017). Pandey et al. (2015) found that both drugs had similar effects on diabetic patients with neuropathic pain, and that both were more effective than a placebo. Kremer et al. (2017) claim that both can also maintain a therapeutic effect for three days after administration. However, Markman et al. (2017) found that pregabalin can be effective for neuropathic pain when gabapentin fails to provide relief due to intolerance or for other reasons. Kaul et al. (2016) also found that pregabalin was effective for some paediatric patients with neuropathic pain from burns while gabapentin was not.

Both gabapentin and pregabalin are generally well-tolerated drugs (Evoy, Morrison, & Saklad, 2017). Their associated side-effects are short-lived and dose-dependent (Mukai et al., 2018). Overdose can cause hypotension, tachycardia, and central nervous system depression but patients rarely require intensive care (Evoy et al., 2017). Because these drugs are not metabolised by humans, they also rarely cause pharmacokinetic drug-drug interactions (Fornasari, 2017) other than potentiating the effects of other central nervous system depressants (Calandre et al., 2016). However, if these medications are stopped abruptly, they can cause withdrawal symptoms similar to benzodiazepine and ethanol withdrawal (Toth, 2014). Because of this it is important that both drugs are titrated slowly if treatment is discontinued. Both drugs are not advised during pregnancy due to the unknown effects on the foetus.

Although not all of them are thoroughly understood, the side effects caused by gabapentin are linked to its action in the central nervous system (Kaul et al., 2018). The inhibition of excitatory neurotransmitters causes dizziness and somnolence, even in small doses. These are pharmacodynamic effects. Other common side effects caused by gabapentin include ataxia, forgetfulness, tremors, anxiety, and blurred vision (Bannister et al., 2017).

Pregabalin causes similar side effects to gabapentin but Kaul et al. (2018) claim that they are less common. Somnolence and dizziness seem to decrease after the first week (Mukai et al., 2018). Like gabapentin, these are pharmacodynamic effects caused by pregabalin’s mechanism of action that reduces the release of excitatory neurotransmitters. Unlike gabapentin, pregabalin can cause euphoria temporarily (Schjerning, Rosenzweig, Pottegard, Damkier, & Nielsen, 2016). This is another pharmacodynamic side effect from the drug’s action in the brain. It can also cause blurred vision, dry mouth, constipation, and peripheral oedema (Kaul et al., 2018). It is unknown why pregabalin causes some of these adverse effects.

When considering pregabalin or gabapentin for neuropathic pain, it is important to understand their pharmacological differences to make the best choice. The literature maintains that both are similar in how well they are tolerated and how effective they are for neuropathic pain (Sicras-Mainar et al., 2016). However, pregabalin requires less frequency of administration due to its potency and therefore it is more user friendly. As previously mentioned, some people find it effective when gabapentin is not. On the other hand, its potency and rapid absorption combined with its potential to cause euphoria means that pregabalin has more abuse potential than gabapentin (Schjerning et al., 2016). It may not be appropriate for people with known substance misuse.

There are other relevant non-pharmacological factors that may influence choice of gabapentinoid in neuropathic pain. In some countries, pregabalin is approved for more neuropathic conditions than gabapentin (Markman et al., 2017). The costs of pregabalin and gabapentin differ around the world, but pregabalin is generally the cheaper drug (Sicras-Mainer et al., 2016). Paradoxically, prescribers seem to favour the more expensive drug in their country.

In summary, pregabalin and gabapentin are two very similar drugs frequently prescribed for neuropathic pain. This condition is a growing problem in society, and it is essential that the most appropriate treatment is provided for patients and that health care professionals have evidence-based knowledge of both drugs. While these drugs are from the same family and have many similarities, the literature shows that pregabalin is more potent, requires smaller doses, is frequently more effective, and often cheaper than gabapentin. Although it is not suitable for everyone, considering this evidence, pregabalin may be the most appropriate medication for the majority of people with neuropathic pain.

**References**

Bannister, K., Qu, C., Navratilova, E., Oyarzo, J., Yanhua Xie, J., King, T., … Porreca, F. (2017). Multiple sites and actions of gabapentin-induced relief of ongoing experimental neuropathic pain. *Pain, 158*(12), 2386-2395. doi: 10.1097/j.pain.0000000000001040

Calandre, E.P., Rico-Villademoros, F., & Mahmoud, S. (2016). Alpha₂delta ligands, gabapentin, pregabalin and mirogabalin: A review of their clinical pharmacology and therapeutic use. *Expert Review of Neurotherapeutics, 16*(11), 1263-1277. doi: [10.1080/14737175.2016.1202764](https://doi.org/10.1080/14737175.2016.1202764)

Cruccu, G., & Truini, A. (2017). A review of neuropathic pain: From guidelines to clinical practice. *Pain and Therapy, 6*(1), 35-42. doi: [10.1007/s40122-017-0087-0](https://dx.doi.org/10.1007/s40122-017-0087-0)

Evoy, K.E., Morrison, M.D., & Saklad, S.R. (2017). Abuse and misuse of pregabalin and gabapentin. *Drugs, 77*(4), 403-426. doi: 10.1007/s40265-017-0700-x

Fornasari, D. (2017). Pharmacotherapy for neuropathic pain: A review. *Pain and Therapy,* 6(1), 25-33. doi: 10.1007/s40122-017-0091-4

Kaul, I., Amin, A., Rosenberg, M., Rosenberg, L., & Meyer III, W.J. (2018). Use of gabapentin and pregabalin for pruritus and neuropathic pain associated with major burn injury: A retrospective chart review. *Burns, 44*(2), 414-422. doi: http://dx.doi.org/10.1016/j.burns.2017.07.018

Kremer, M., Yalcin, I., Nexon, L., Wurtz, X., Ceredig, R.A., Daniel, D., ... Barrot, M. (2016). The antiallodynic action of pregabalin in neuropathic pain is independent from the opioid system. *Molecular Pain, 12*, 1-12. doi: 10.1177/1744806916633477

Markman, J.D., Jensen, T.S., Semel, D., Li, C., Parsons, B., Behar, R., & Sadosky, A.B. (2017). Effects of pregabalin in patients with neuropathic pain previously treated with gabapentin: A pooled analysis of parallel-group, randomized, placebo-controlled clinical trials. *Pain Practice, 17*(6), 718-728. doi: 10.1111/papr.12516

Mukai, R., Hasegawa, S., Umetsu, R., Nakao, S., Shimada, K., Uranishi, H., … Nakamura, M. (2018). Evaluation of pregabalin-induced adverse events related to falls using the FDA adverse event reporting system and Japanese Adverse Drug Event Report databases. *Journal of Clinical Pharmacy and Therapeutics, 44*(2), 285-291.

Pandey, A., Sompura, S., Pandey, S., Chaturvedi, M., Maheshwar, P.K., & Kumar, S. (2015). Double-blind randomized placebo-controlled trial to compare the effects of gabapentin, pregabalin and tramadol + acetaminophen combination in improvement of pain in patients with painful diabetic neuropathy. *International Journal of Diabetes in Developing Countries, 35*(3), 389-392. doi: <https://doi.org/10.1007/s13410-015-0357-5>

Raouf, M., Atkinson, T.J., Crumb, M.W., & Fudin, J. (2017). Rational dosing of gabapentin and pregabalin in chronic kidney disease. *Journal of Pain Research, 10*, 275-278. doi: 10.2147/JPR.S130942

Schjerning, O., Rosenzweig, M., Pottegard, A., Damkier, P., & Nielsen, J. (2016). Abuse potential of pregabalin: A systematic review. *CNS Drugs, 30*(1), 9-25. doi: 10.1007/s40263-015-0303-6

Sicras-Mainar, A., Rejas-Gutiérrez, J., Pérez-Páramo, M., & Navarro-Artieda, R. (2016). Cost of treatment of peripheral neuropathic pain with pregabalin or gabapentin in routine clinical practice: Impact of their loss of exclusivity. *Journal of Evaluation in Clinical Practice, 23*(2), 402-412. doi: <https://doi.org/10.1111/jep.12634>

Toth, C. (2014). Pregabalin: Latest safety evidence and clinical implications for the management of neuropathic pain. *Therapeutic Advances in Drug Safety, 5*(1), 38-56. doi: 10.1177/ 2042098613505614