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Review Article

Current insights suggest gabapentin-induced neurodegeneration

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ABSTRACT

Antiepileptic drugs (AEDs) are commonly prescribed to treat epilepsy and other neurodegenerative disorders (NDs). Gabapentin (GBP) is a newer, off-label antiepileptic/anticonvulsant for NDs that remains underexplored. Recent evidence indicates that prolonged, frequent, and high-dose use of GBP may be associated with an increased risk of various types of dementia and cognitive impairment. GBP has become 1 of the top 20 most prescribed drugs for NDs. GBP modulates voltage-gated calcium channels by binding to the alpha2delta subunit. One possible mechanism is oxidative stress, which can damage neuronal structures, impair synaptic function, and cause mitochondrial dysfunction, all of which are strongly implicated in the pathogenesis of several NDs and contribute to cognitive decline. Another factor is excitotoxicity, where abnormal glutamatergic activity causes excessive calcium influx and neuronal injury, thereby exacerbating mood problems and memory deficits. Long-term use of GBP interferes with SIRT1 (neuroprotective), CaMKII (calcium regulator), and tau phosphorylation regulation, damaging downstream signalling, disrupting central pain pathways in the spinal cord and brain (central sensitisation), damaging neuronal survival pathways, and promoting neurodegeneration. This literature review aims to synthesise current insights on GBP neurotoxic effects, including changes at the gene and protein levels, neuronal structure, function, and network connectivity, as well as strategies for managing GBP-associated NDs. Further research is needed to clarify the exact mechanisms and to develop protective strategies to reduce neurodegenerative risks, optimise seizure control, and evaluate the risks of GBP in clinical settings.

Keywords: Antiepileptic drugs, Neurodegenerative disorders, Gabapentin drug, epilepsy, Cognitive impairment, Neurological effects

INTRODUCTION

This review incorporates several references published between 1983 and 2025. A comprehensive literature search was conducted using PubMed for the same period. The search included animal studies, clinical trials, case reports, and review articles addressing the effects, misuse, drug interactions, toxicology, and pharmacological characteristics of GBP. GBP has attracted growing attention due to its increasing clinical use and possible link to neurodegenerative disease. GBP, a synthetic derivative of the neurotransmitter GABA, was initially developed for treating epilepsy and neurodegenerative diseases. Over time, extensive research has expanded its applications beyond its original purpose.[1] Today, GBP is widely used for various conditions, including chronic pain syndromes and certain psychiatric illnesses. Movement disorders such as myoclonus and dyskinesias have been recognised when GBP was added or increased, often resolving after discontinuation.[2] Narrative reviews highlight adverse

outcomes like weight gain, depression, suicidal thoughts, and increased respiratory depression, especially when combined with other CNS depressants like opioids. As time passes, GBP's safety profile has shifted from initial perceptions of CNS effects toward awareness of a broader spectrum of neurologic and psychiatric adverse effects.[3] Recent research suggests associations with an increased risk of dementia and cognitive impairment, particularly with long-term administration. Although it remains important in neurology and pain management, clinicians and patients are advised to carefully weigh benefits against potential prolonged-use cognitive risks, especially in chronic use.[4] It is also frequently used off- label due to its broad therapeutic profile. While GBP is often valued for its stabilising and calming effects on the nervous system, emerging evidence suggests that, in some individuals, it may inconsistently exacerbate anxiety/depressive symptoms. This opposing effect highlights the complex and not yet fully understood hallucinogenic characteristics of drug.[5] Antagonistic effects of GBP on brain function, including confusion, disorientation ("vague brain"), and recall deficits, have been recognised in clinical studies.[6,7]

Research investigates effects of GBP on genes and proteins implicated in neurodegeneration, such as Tau, Amyloid beta, Sirtuin-1, and calmodulin-dependent protein kinase-2.[8] Phosphorylation of Tau is controlled by various protein kinases, including serine/threonine protein kinase CaMKII alpha, which specifically phosphorylates Tau at S262 and S416.[9,10] A recent study identified an Sirt1, CaMKIIalpha, Tau signalling pathway involved in GBP-induced cognitive impairment in aged mice.[1] Neurodegenerative diseases often involve mitochondrial dysfunction and oxidative stress, but there is limited research on whether GBP affects mitochondrial bioenergetics, ROS production/ mitochondrial DNA stability.[11] GBP decreases expression of genes related to inflammation, including those encoding pro-inflammatory cytokines, chemokines, and their receptors. Studies have examined cellular signalling that reduces the production of inflammatory cytokines such as TNF-alpha, IL-1 beta, and IL-6. Activation of PPAR-γ has been shown to stimulate peroxisome proliferator-activated receptor gamma, thereby exerting anti-inflammatory effects.[4] Detailed mechanism of GBP's action remains unclear. Although it is an organisational analogue of GABA, GBP does not directly affect GABA metabolism, transport, or receptor binding. One idea is that sustained use of GBP inhibits voltage-dependent calcium channels containing α2δ subunit of GABA, which are involved in neurotransmitter release at synapse. This interference may disrupt calcium channel function and impair synapse formation.[12] Another proposed mechanism for GBP is that it promotes surface expression of extrasynaptic δ subunit-containing GABA receptors in neurons. These receptors are the most widely expressed extrasynaptic GABA receptor subtype in mammalian brain and are usually found at low levels in cultured hippocampal neurons.[13,14] Surface localisation of GABA receptors is tightly regulated through complex pathways that can be influenced by pharmacological agents. Though these adverse psychiatric reactions are not common, GBP-induced anxiety and depression are noteworthy concerns that require greater awareness and further study.[15]

The risks directly preceding instigation and following termination of GBP therapy have not been sufficiently investigated in prior studies. This is mainly important given that numerous clinical indications for GBP use are individually associated with an increased risk of suicidal ideation and NDs. In light of the considerable rise in GBP utilisation in recent years, a wide-ranging evaluation of their safety profile is warranted. This review, therefore, aims to synthesise findings from animal investigations, case reports, and clinical studies on the risk of self-harm, as well as emerging data on adverse effects, potential for misuse, and its role in complex neurological pathways.

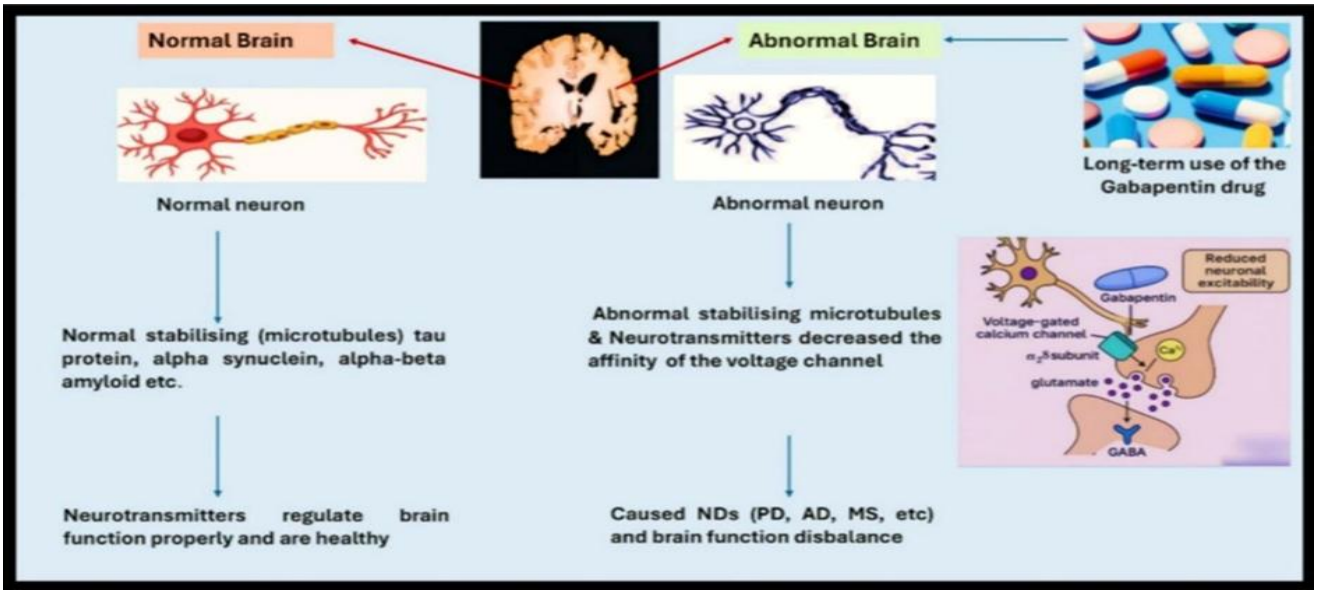

Figure 1: Graphical abstract.

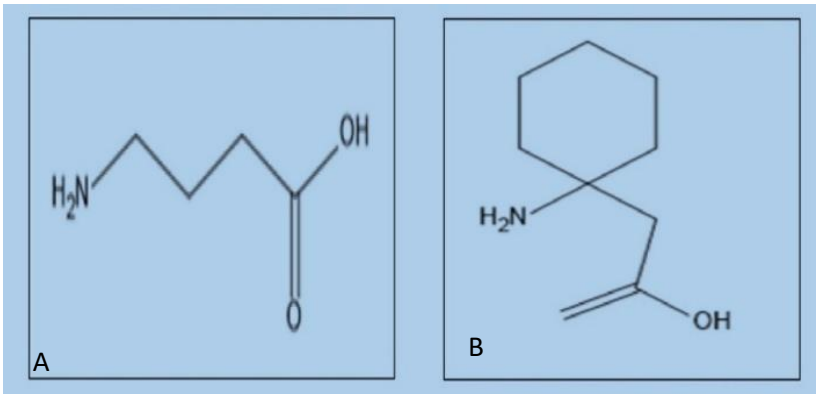

Figure 2: Chemical structure of neurotransmitter (A) Gamma-aminobutyric acid (GABA) and (B) drug gabapentin.

*Ref: ChemBioDraw tool.

LITERATURE REVIEW

Search strategies and data sources

The search data source comprises accessible literature on GBP, with an emphasis on its pharmacological profile, therapeutic applications, and safety concerns. An organised literature search was conducted using automated databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant studies published up to December 2025.

Literature review of the same case report /case studies

A survey in regional anaesthesia and pain medicine assessed health histories from over 26,000 adults with chronic low back pain, establishing a correlation between GBP use and an increased risk of dementia and cognitive impairment.[16] The report indicated that individuals taking six or more GBP medications had a 28.99% higher risk of developing dementia and an 84.99% higher risk of cognitive impairment. This risk grew with the frequency of medication use and was especially evident among adults aged 18-65 years, who had more than twice risk compared to non-users in the same age group.[17] However, numerous other studies have noted GBP's adverse effects on cognitive function. Current research also supports idea of cognitive decline-measured through neuropsychological testing-in individuals with spinal cord injury who started GBP therapy.[18] Emerging clinical evidence increasingly highlights GBP's side effects on cognitive function in older adults, such as drowsiness and disorientation. Revisions indicate that initiating GBP in cognitively normal older adults is linked to cognitive impairment, and perioperative use has been associated with a higher risk of postoperative delirium after major surgery.[19]

In most cases, GBP has also been linked to an amplified risk of suicidal thoughts and behaviour.[12] The patients should be vigilant and watch for unusual variations in mood or behaviour, including agitation, aggression, depression, or self-harm thoughts. Supplementary side effects may comprise visual disturbances, impaired coordination, dizziness, drowsiness, cognitive difficulties, irritability, emotional instability, anxiety, restlessness, hostility, and worsening depressive symptoms.[20] GBP is known to produce anxiolytic effects and a feeling of euphoria similar to that seen with opioid abuse. The drug can cause breathing depression, especially when combined with other CNS depressants. Constant use may lead to physical dependence, and unexpected stopping causes withdrawal symptoms such as sweating, anxiety, confusion, and, rarely, seizures. Comparable risks are reported with other GBPoids, including pregabalin.[21]

Medically, GBP has been associated with breathing issues in people using opioid analgesics, those with COPD (chronic obstructive pulmonary disease), and older adults, who are more likely to experience respiratory difficulties. Because GBP can improve the psychotropic effects of opioids, it has exploitation potential and has been linked to drug-related overdose losses.[22] GBP leads to weight gain, affecting up to about 25% of patients. This side effect is thought to happen indirectly. Rather than causing weight gain on its own, GBP may trigger gastrointestinal issues such as bloating, constipation, nausea, and changes in appetite. These effects can disrupt normal metabolism and eating patterns, contributing to gradual weight gain over time.[23]

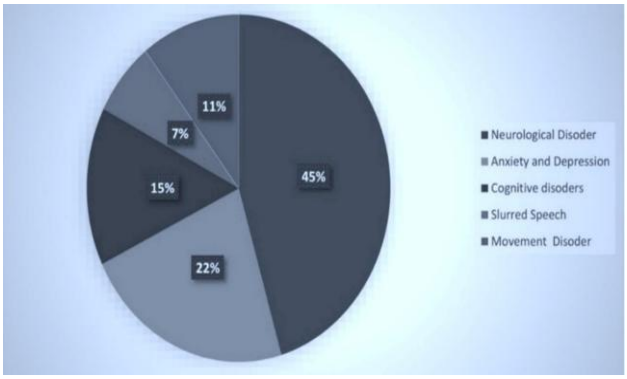

Figure 3: Relative frequency of reported gabapentin-induced neurological and adverse effects.

GBP ADVERSE CONSEQUENCES

Anxiety and depression

GBP is often used inadequately to manage anxiety disorders, especially GAD (Generalised Anxiety Disorder) and social anxiety disorder.[19] While it is recognised for reducing core anxiety symptoms such as excessive worry, fear, and physical tension, both medical evidence and patient reports indicate that GBP can occasionally trigger or worsen anxiety.[24] There have been reports of individuals developing generalised anxiety, panic attacks, irritability, and emotional instability shortly after starting the medication or after continued use.[25] GABA receptor genes such as GABRA2 and GABRA3 may contribute to anxiety or depression; DLGAP4 and VAMP2, genes involved in synaptic plasticity, also affect expressive and cognitive functions.[26] DNF and SLC6A4 regulate neuronal survival and serotonin signalling, and modifications in these pathways can lead to depression and neurodegeneration.[27] Additional research also suggests an association of GBP with the onset or worsening of depressive symptoms. Some users have reported emotional numbness, loss of motivation, disconnection from daily life, and a persistent sense of hopelessness or despair that was not present before treatment.[28]

*Movement disor*der

GBP use has been linked to numerous movement disorders.[4] GBP-induced myoclonus, characterised by sudden, brief, involuntary muscle jerks, is often observed in patients with renal impairment or after dosage escalation. The neurophysiological substrate is cortical and subcortical. Interestingly, Scheyer et al reported reflex myoclonus only with high doses of GBP. Therefore, myoclonus can be directly associated with GBP absorption.[29] The alpha2delta-1 subunit, encoded by the CACNA2D1 gene, and mitochondrial regulators such as SIRT1 may impair motor control pathways.[26,27] GBP has infrequently been associated with the development of Parkinsonism-a syndrome introducing bradykinesia, rigidity, postural instability, and resting tremor. This also mimics idiopathic PD; drug-induced Parkinsonism typically resolves after discontinuation. Such movement-related side effects are more likely to occur at doses exceeding 2500 mg per day.[30] An event report described a 73-year-old man who experienced generalised myoclonus after starting GBP therapy, with complete symptom resolution within 48 hours of discontinuation.[31]

Slurred speech

Slurred speech has been reported in some individuals taking GBP, especially at high quantities or when combined with other CNS depressants. GBP may cause ataxia-a loss of coordination in intended muscles, together with those involved in speech, leading to slurring or impaired articulation. Muscle weakness and reduced motor control may further contribute to these issues.[32] Blur, another speech-related problem, is thought to result from amplified right-hemispheric brain activity, disrupted coordination between speech development and execution areas, and dopamine irregularities 33. GBP may cause slurred speech by disrupting synaptic proteins, for example, SNAP25; mitochondrial controllers like SIRT1 can impair neurotransmitter release involved in speech motor coordination and also affect neuronal stress and dysfunction.[33]

Neurological and cognitive disorders

Learning and memory are contingent deeply on synaptic plasticity, predominantly LTP (Long-term potentiation), a process vital for memory formation. GBP's action on calcium channels might disrupt this process, leading to intellectual side effects. Several studies have linked GBP to cognitive instabilities.[32] BDNF support neuronal survival and memory formation; dysregulation may contribute to cognitive impairment. SNAP25 protein dysfunction can impair synaptic plasticity. Decreased SIRT1 protein activity may encourage oxidative stress and neurodegenerative changes that induce AD, PD, and ALS.[34]

GBP induced Parkinsonism

PDs can be ranked as idiopathic Parkinson's disease or drug-induced Parkinson (DIP), the latter being another common form and usually reversible after suspension of the causal drug. While DIP is typically connected with dopamine-blocking agents such as neuroleptics and antiemetics, recent findings suggest that drugs like GBP-though not primarily dopaminergic-may also contribute to Parkinsonian symptoms.[35] An experimental study showed that GBP exposure can impact regulatory proteins such as PINK1 (parkin), PINK2, SIRT1, SNCA (alpha-synuclein protein), TH (tyrosine hydroxylase), and DAT (dopamine transporter); NF-κB signalling pathways may induce Parkinson like motor symptoms or exacerbate neurodegenerative mechanisms in susceptible individuals. Proposed mechanisms include disturbance of dopamine signalling, imbalanced glutamatergic activity, excessive GABAergic inhibition, and neuroinflammatory processes.[36]

GBP delivers Alzheimer's disease

AD is an advanced neurodegenerative disorder marked by memory loss, cognitive impairment, and behavioural changes. It is characterised by amyloid-beta plaque deposition, neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic degeneration, and neuronal dropout-mainly within the hippocampus and cerebral cortex.[1] GBP may contribute to the development of ADs through numerous biological mechanisms. GBP disrupts key genes such as amyloid precursor protein (APP), Apolipoprotein E (APOE), Presenilin-1 (PSEN1), Presenilin-2 (PSEN2), and microtubule-associated protein tau (MAPT), the strongest genetic risk factor for late-onset

Alzheimer's.[37] These include impaired synaptic plasticity, disturbances in glutamate homeostasis, promotion of neuroinflammation, increased brain atrophy, and mitochondrial dysfunction. Taken together, these processes could damage neuronal health and cognitive resilience, underscoring the need for further investigation into GBP's potential long-term neurodegenerative effects.[38]

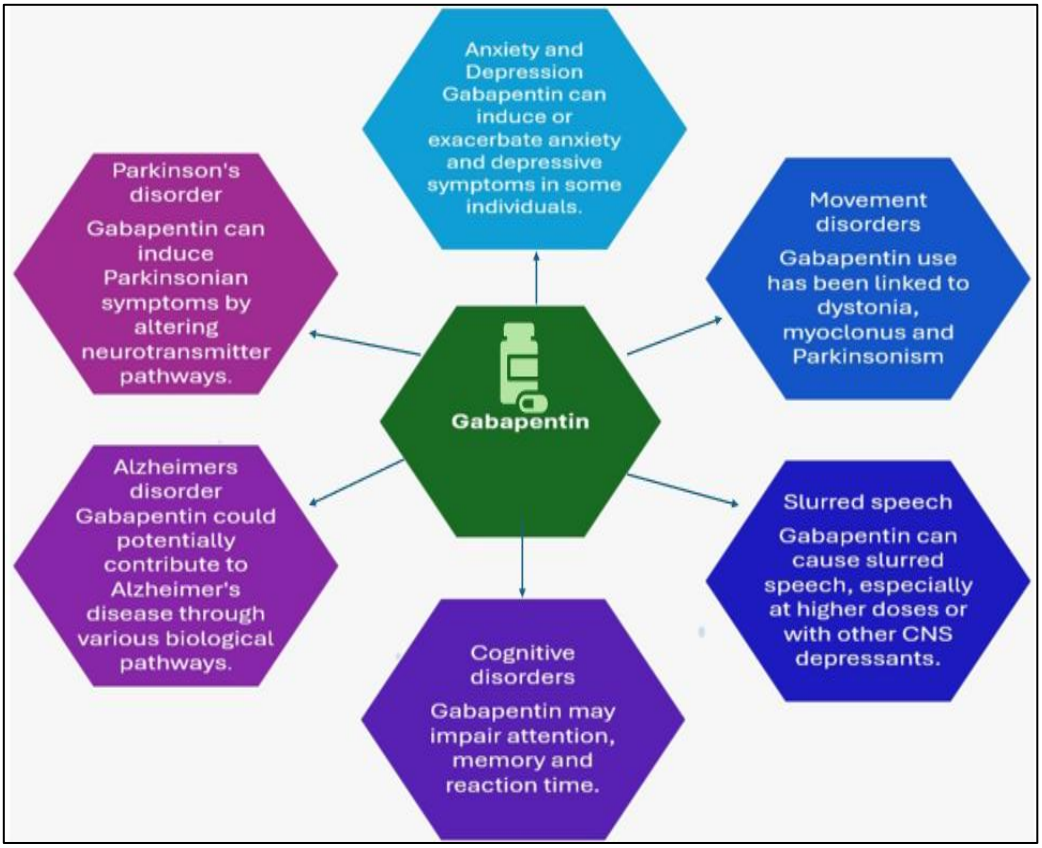

Figure 4: Schematic representation of reported neurological, cognitive and psychiatric side effects of gabapentin.
*Reference: image sources BioRender.

MECHANISTIC PATHWAYS AFFECTED BY GBP

GBP is a real-world equivalent and chemically similar to GABA, the brain's primary inhibitory neurotransmitter. Despite this similarity, GBP does not interact unswervingly with GABA receptors.[339] GBP can cross the blood–brain barrier, allowing it to act directly within the brain and nervous system. It helps calm overexcited nerve cells by modulating voltage-gated calcium channels and reducing the release of certain neurotransmitters. As a result, it declines unnecessary excitatory signalling between neurons. This sedative effect helps relieve symptoms associated with nerve overactivity, such as pain and seizures.[23] Alternatively, it targets the α2δ-1 subunit of voltage-gated calcium channels encoded by the CACNA2D1 gene within the central nervous system. By modulating these calcium channels, GBP overpowers the release of excitatory neurotransmitters-an achievement believed to underlie its antiepileptic and analgesic properties. The α2δ1 subunit is abundantly expressed in the brain, especially in the hippocampus.[14,37] GBP disrupts the α2δ-1-NMDA receptor interaction, influencing mitochondrial dysfunction, synaptic remodelling, and causing neuronal apoptosis. Experimental studies show that GBP reduces or downregulates the expression of Glial fibrillary acidic protein (GFAP), thereby inducing neurodegeneration.[37] When ubiquitin pathway carboxyl-terminal hydrolase L1(UCHL1) is impaired, protein degradation is impaired, contributing to Parkinson -like disease.[39] SIRT1 suppresses several kinase pathways. Once kinase activity increases, oxidative stress increases, so neuronal survival signalling decreases. When SIRT1 decreases, CaMKIIa become overactivated. These phosphorylation events cause microtubule destabilisation and impaired axonal transport.[1,11,40] GSK-3beta is normally inhibited by phosphorylation at Ser9, but this inhibition is lost during oxidative stress. The CDK5/p25 complex is hyperactive and mislocalized, leading to sustained phosphorylation of tau and neurofilaments due to GBP.[41] Microtubule-associated protein tau (MAPT) H1 homozygosity is associated with a roughly 1.3- to 1.5-fold increased risk compared to other genotypes; it is strongly associated with PD risk.[42] MAPT gene imbalances due to long-term use of GBP, specifically an excess of 4R-tau or 3R-tau, impair axonal transport and neurodegeneration.[1,30]

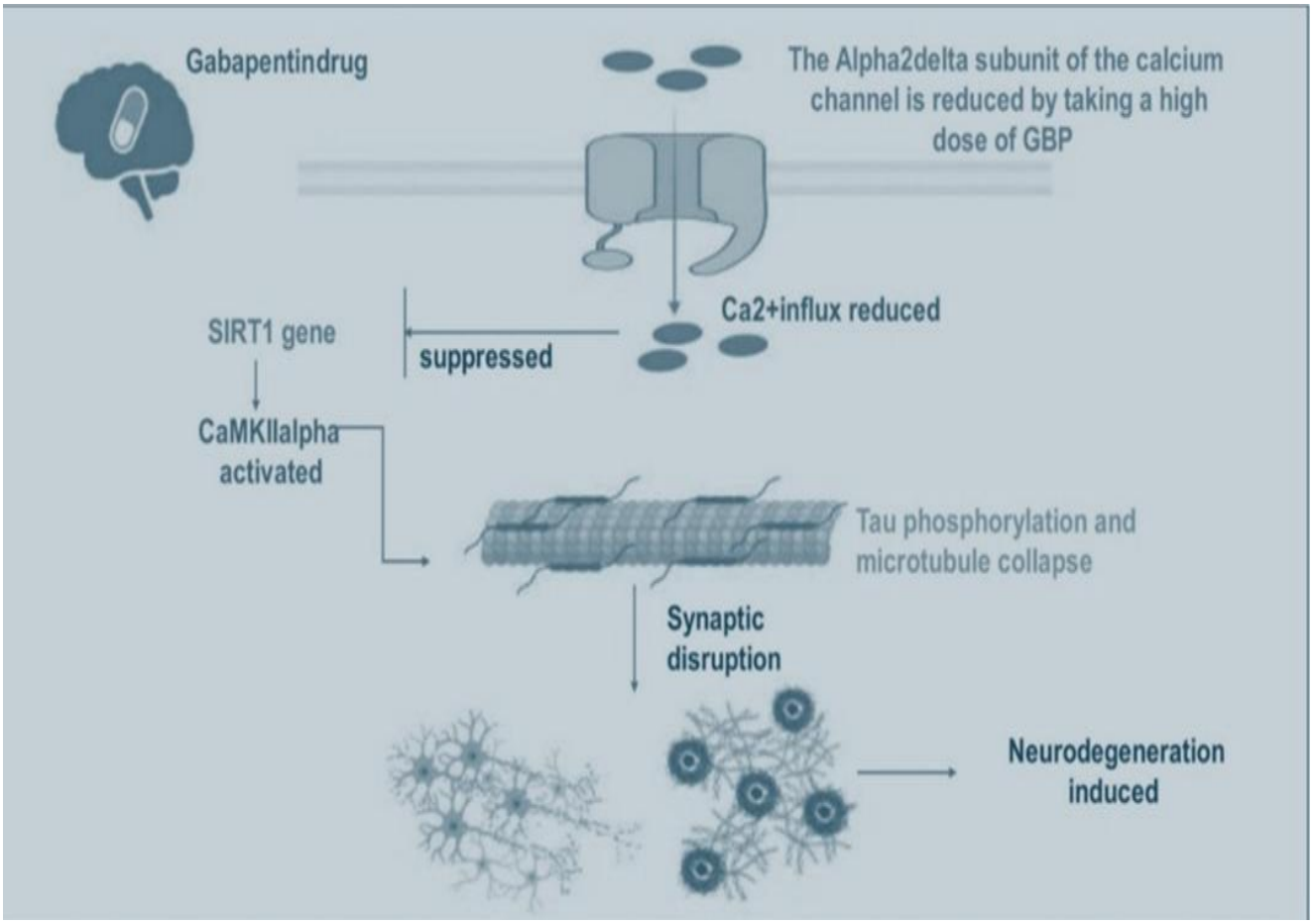

Figure 5: Mechanistic pathways of gabapentin impact on calcium pathways, tau phosphorylation, and neuronal loss.

INTERACTION OF GBP WITH OTHER GENERAL DRUGS

Globally, studies suggest that GBP may interact with other medications, either substantially or minimally.[42] Specifically, reviews indicate that GBP does not significantly affect hepatic enzymes, plasma protein binding, or the metabolism of other drugs, making it especially suitable for elderly patients and those with hepatic impairment.[43] The concomitant use of GBP with losartan has been linked to an increased risk of dizziness and somnolence. Similarly, high doses of caffeine may worsen GBP-related adverse effects such as drowsiness and dizziness. Co-administration with opioids significantly raises the risk of CNS depression, respiratory distress, excessive sedation, and potential misuse. Pregabalin and verapamil interact with GBP by targeting the same CACNA2D1 gene and α2δ -1VCCP, resulting in reduced glutamate release.[14,37] GBP combined with Diazepam or valproic acid affects the GAD gene and enzyme, increasing the inhibitory neurotransmitter GABA, which may contribute to cognitive impairment.[44] Interactions with anaesthetics such as tramadol and morphine can modulate the OPRM1 (opioid receptor Mu1) gene, SIRT1, CAMK2A, and MAPT, thereby affecting SIRT1, CaMKIIalpha, and tau protein, which regulate neuronal signalling and neurotransmitter levels. Once this signalling imbalance occurs, it can lead to neuronal disruption.[11] GBP interacts with antidepressants such as fluoxetine or sertraline, which affect the SLC6A4 gene (solute carrier family 6 member 4, encoding SERT or 5-HTT). Abnormal serotonergic signalling has been linked to neurodegenerative conditions such as PD and AD. Additionally, combining GBP with antipsychotics may further impair alertness, concentration, and motor coordination.[30,44] Conversely, GBP may reduce the efficacy of ethacrynic acid, a loop diuretic. The use of mefloquine with GBP has been linked to an increased risk of seizures. Additionally, NSAIDs, including naproxen, may heighten adverse effects when used with GBP. Concurrent use of GBP and certain antidepressants may also raise the risk of serotonin syndrome, a rare but potentially life-threatening condition.[19,45] However, there is no evidence that GBP directly acts on serotonin receptors.[37] Compared with medications like pregabalin and duloxetine, GBP offers similar levels of pain relief, although it may take longer to become effective.[46] This manuscript, therefore, examines the impact of GBP on NDs and other health issues, its potential to worsen drug-related complications, and the broader implications for clinical use.

Table 1: Drug-drug interactions of gabapentin and their underlying mechanisms with associated AEs.

Drug interaction	Mechanism	Consequences
Opioids (morphine, tramadol)	Additive CNS and respiratory depression	Sedation, dizziness, respiratory depression, increased overdose risk[11]
Benzodiazepines (diazepam, lorazepam)	Synergistic CNS depressant effect	Drowsiness, confusion, impaired coordination, and falls[37]
Alcohol	Potentiates CNS depression	Severe sedation, cognitive impairment, respiratory suppression[45]
Antidepressants (TCAs, SSRIs)	Additive sedative and cognitive effects	Increased fatigue, dizziness, impaired concentration[44]
Antipsychotics	Enhanced CNS depressant	Extrapyramidal symptoms, sedation and confusion[30,44]
Antiepileptic (gabapentin, valproate, carbamazepine)	CNS Effects	Somnolence, dizziness, slurred speech, cognitive slowing [14,37]
CNS depressants (fluoxetine and sertraline)	Pharmacodynamic	Risk of coma, respiratory failure[46]

EVIDENCE AND DISCUSSION OF GBP: INITIATES NEURODEGENERATIVE CHANGES

Recent research indicates that high doses of GBP can induce various neurodegenerative changes.[11,12,26,31,41] In adult rats, chronic GBP treatment at therapeutic doses was examined, revealing a significant increase in neurons showing degenerative features in the hippocampus and decreased Nissl substance activity in both the hippocampus and striatum-indications of neurodegeneration with sustained GBP exposure.[47] GBP is prescribed more frequently to women than men, partly because neuropathic pain is more common among women.[48,49] A 2025 study demonstrated that long-term GBP use reduces SIRT1 gene expression and increases CAMK2A activity, which correlates with hyperphosphorylation of tau protein in the hippocampus, associated with memory deficits and neurodegeneration-like changes.[1] Additionally, women face a complex risk of developing dementia and Alzheimer's disease. In an alternate animal model using albino rats, high-dose GBP caused noticeable neurobehavioral deficits and hippocampal tissue damage. Still, treatment with vitamin E (alpha-tocopherol) significantly mitigated these effects, suggesting oxidative damage as a possible mechanism of GBP neurotoxicity.[50] Long-term administration in rats has been associated with hippocampal neuron degeneration; however, conflicting studies in nerve injury models indicate potential protective effects, demonstrating the complexity and context-dependence of these findings.[50,51] Furthermore, a review of 102 reports involving 204 cases identified GBP-associated movement disorders such as myoclonus, dyskinesias, dystonia, akathisia, and Parkinsonian symptoms. Most patients fully recovered after stopping the medication, indicating these adverse effects may be reversible.[30] Finally, research shows that individuals on high-dose GBP have a 29% increased risk of dementia and an 85% higher likelihood of developing cognitive impairment.[52]

Table 2: Gabapentin induces neurodegenerative changes in neuronal tissue.

Category	Mechanistic effects	Observed neurodegenerative changes	Experimental insights
Oxidative stress	Mitochondrial dysfunction and impaired redox balance	Increased ROS, lipid peroxidation and reduced antioxidant enzymes.	Rodent and avian brain tissue studies[36]
Neuroinflammation	Disruption of calcium signalling and immune modulation	Elevated TNF-alpha, IL-beta, Microglial and astrocyte activation	Immunohisto-chemistry ELISA assays[48]
Mitochondrial dysregulation	Inhibition of voltage-gated Ca2+ channels	Decreased ATP production, altered mitochondrial membrane potential	Electron microscopy, biochemical assays[49]
Neurotransmitter imbalance	Reduced excitatory neurotransmission and synaptic vesicle release	Altered GABA, glutamate, dopamine and serotonin levels	Neurochemical assays, behavioural studies[26]
Synaptic plasticity	Calcium-dependent synaptic dysfunction	Reduced synaptophysin, PSD-95, impaired LTP	Western blot, electrophysiology[30]
Neuronal apoptosis	Oxidative stress-mediated intrinsic apoptotic pathway	Increased Bax Bcl-2 ratio, caspase-3 activation, DNA fragmentation	Western blot[7]

Continued.

Category	Mechanistic effects	Observed neurodegenerative changes	Experimental insights
Cognitive and behavioural decline	Hippocampal neuronal damage and synaptic loss	Memory impairment, reduced learning ability, anxiety-like behaviour	Morris water maze, avian cognition tests[52]
Neurogenesis suppression	Disruption of BDNF And CREB Signalling Pathways	Reduced hippocampal progenitor cell proliferation	Immunohistochemistry[50]
Myelin integrity disruption	Altered calcium homeostasis and oligodendrocyte stress	Decreased MBP expression, axonal degeneration	Histopathology, immunostaining[51]
Regional brain vulnerability	Region-specific metabolic and synaptic demands	Hippocampus, cortex, and cerebellum are particularly affected	Histological brain region analysis[7]

GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

Emerging research on GBP-induced neurodegeneration points to possible gene-level changes, but there is a lack of strong mechanistic, in silico, and clinical evidence. Therefore, this remains an important area for future studies in neuropsychiatry, psychopharmacology, and neurodegeneration. GBP has not been definitively linked to diseases like Alzheimer's or Parkinson's; most findings only show associations or shared pathways. Molecular mechanisms such as mitochondrial dysregulation, neuroinflammation, and neurofibrillary tangles appear similar across cases. The connection between GBP -related gene variations and clinical symptoms, cognitive decline, or movement disorders is still unclear. Well-designed studies with ageing and disease-specific models are crucial to assess potential risks. MRI can track hippocampal and cortical atrophy, while DTI can evaluate white matter changes. PET scans with tau or amyloid tracers are necessary to determine if GBP speeds up key pathologies of Alzheimer's, Parkinson's, and ALS. Recognising these knowledge gaps will help clinicians optimise GBP's benefits and reduce long-term neural or neurodegenerative risks.

LIMITATIONS

In addition to providing insight into disparities in GBP medication and timing of management, molecular pathways associated with GBP-suggested genes, proteins, and enzymes, such as CaMKIIalpha, CACNA2D1, SIRT1, CAMK2A, MAPT, MT1A, PPT2, and OPRM1, are reported, but strong molecular validation is limited. There are a few large-scale human genomic or transcriptomic studies examining the effects of GBP on the brain. Co-existence of tau and alpha-synuclein-related changes. The area of neuron-specific neurodegeneration changes associated with GBP is still to be investigated.

CONCLUSION

GBP is recognised as an effective treatment for epilepsy and blood clot prevention, with added benefits for neuropathic pain and anxiety. Nonetheless, growing evidence indicates that it may activate gene and protein pathways linked to neurodegeneration, demanding cautious review. High doses of GBP have been linked to neurotoxicity, leading to cell damage and increased degenerating cells. Disrupted serotonergic signalling and reduced activity of the substantia nigra caused by GBP contribute to unstable movements, alongside factors involving tau phosphorylation, synaptic adaptability, and neuroimmune responses. Researchers should carefully evaluate GBP's effects and benefits. Much of the current evidence stems from experimental and preclinical studies, and clear causal link between GBP and neurodegeneration has yet to be established. Extensive human genomic and long-term studies are needed to clarify its neural impacts and underlying molecular pathways. Further research is essential to determine optimal dosing, treatment timing, and patient outcomes for enhanced benefits.

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REFERENCES

1. Xia SS, Zerong Y, Xinbo W, Xinbo W, Jinsheng Y, Li N, et al. Long-term gabapentin treatment impairs cognitive function in aged mice via tau hyperphosphorylation. Front Pharmacol. 2025;16:1616775.
2. Vickers Smith R, Boland EM, Young AM, Lofwall MR, Quiroz A, Staton M, et al. A qualitative analysis of gabapentin misuse and diversion among people who use drugs in Appalachian Kentucky. Psychol Addict Behav. 2018;32(1):115-21.
3. Park CM, Inouye SK, Marcantonio ER, Metzger E, Bateman BT, Lie JJ, et al. Perioperative Gabapentin Use and In-Hospital Adverse Clinical Events Among Older Adults After Major Surgery. JAMA Internal Med. 2022;182(11):1117-27.

4. Khanam PS, Kannaiah SK. Advances in Machine Learning for Alzheimer's disease Diagnosis: A Comprehensive Overview and Comparative Analysis. 2024 8th International Conference on Inventive Systems and Control. 2024.
5. Goa K, Sorkin E. Gabapentin. Drugs. 2012;46:409-27.
6. Bonnet U, Richter EL, Isbruch K, Scherbaum N. On the addictive power of gabapentinoids: a mini-review. Psychiat Danubina. 2018;30(2):142-9.
7. Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. 2016;50(3):229-33.
8. Rusciano D. Molecular Mechanisms and Therapeutic Potential of Gabapentin with a Focus on Topical Formulations to Treat Ocular Surface Diseases, Pharmaceuticals. 2024;17(5):623.
9. Yamamoto H, Hiragami Y, Murayama M, Ishizuka K, Kawahara M, Takashima A. Phosphorylation of tau at serine 416 by Ca^{2+}/calmodulin-dependent protein kinase II in neuronal soma in the brain. J Neurochem. 2005;94(5):1438-47.
10. Hector A, McAnulty C, Piché-Lemieux ME, Alves-Pires C. Tau hyperphosphorylation induced by the anaesthetic agent ketamine/xylazine involved the calmodulin-dependent protein kinase II. FASEB J. 2020;34(2):2968-77.
11. Wang Y, Mandelkow E. Tau in physiology and pathology. Nature Reviews. Neuroscience. 2016;17(1):5-21.
12. Varadi G. Mechanism of Analgesia by Gabapentinoid Drugs: Involvement of Modulation of Synaptogenesis and Trafficking of Glutamate-Gated Ion Channels. J Pharmacol Exp Ther. 2024;388(1):121-33.
13. Ghit A, Assal D, Al-Shami AS, Hussein DEE. $GABA_A$ receptors: structure, function, pharmacology, and related disorders. J Genetic Engineering Biotechnol. 2021;19(1):123.
14. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol. 2006;6(1):108-13.
15. Yeşil B, Yurtaslan A. Gabapentin withdrawal in a depressed patient: A case report. Anatolian J Psychiat. 2016;17(3):1.
16. Rajput HS. Mechanism of Action of Gabapentin. 2025. Available at: https://pharmacyfreak.com/mechanism-of-action-of-gabapentin-2/. Accessed on 17 January 2026.
17. Kim YK, Jeong-Gill L, Ji-Yeon S, Sung-Moon J, Kyoung-Woon J. The effects of gabapentin pretreatment on brain injury induced by focal cerebral ischemia/reperfusion in the rat. Korean J Anesthesiol. 2010;58(2):184-90.
18. Shem K, Barncord S, Flavin K, Mohan M. Adverse cognitive effects of gabapentin in individuals with spinal cord injury: preliminary findings. Spinal Cord Ser Cases. 2018;4:9.
19. Markota M, Morgan RJ. Treatment of Generalised Anxiety Disorder with Gabapentin. Case Rep Psychiat. 2017;6045017.
20. Yuen ASC, Chen B, Chan AYL, Hayes JF, Osborn DPJ, Besag FMC, et al. Use of gabapentinoid treatment and the risk of self-harm: population-based self-controlled case series study. BMJ. 2025;389:e081627.
21. Lennox R, Mangin D. Gabapentin misuse. CMAJ. 2019;191(2):E47.
22. Sheng-En T, Shun-Fa Y, Yu-Hsun W, Chao-Bin Y. Association between gabapentin use and risk of dementia in adults with chronic pain: A nested case-control study. J Affect Disord. 2024;358:205-10.
23. Kaye AD, Cassagne G, Abbott BM, Dubuisson AM, Fagan JJ, Indovina I, et al. Emerging Clinical Roles of Gabapentin and Adverse Effects, Including Weight Gain, Obesity, Depression, Suicidal Thoughts and Increased Risk of Opioid-Related Overdose and Respiratory Depression: A Narrative Review. Curr Pain Headache Rep. 2025;29:95.
24. Panebianco M, Al-Bachari S, Weston J, Hutton JL, Marson AG. Gabapentin add-on treatment for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2018;10(10):CD001415.
25. James SWH, Atkinson LZ, Al-Juffali N, Awad A, Geddes JR, Tunbridge EM, et al. Gabapentin and pregabalin in bipolar disorder, anxiety states, and insomnia: Systematic review, meta-analysis, and rationale. Mol Psychiatry. 2021;27(3):1339-49.
26. Yakovchik AY, Tolynyova DV, Kashtanova DA, Sutulova ER, Ivanov MV, Mamchur LA, et al. Genetics of psycho-emotional well-being: genome-wide association study and polygenic risk score analysis. 2024;14:1188427.
27. Kwon Y, Blazyte A, Jeon Y, Kim YJ, An K, Jeon S, et al. Identification of 17 novel epigenetic biomarkers associated with anxiety disorders using differential methylation analysis followed by machine learning-based validation. Clin Epigenetics. 2025;17(1):24.
28. Kuehn BM. Growing Role of Gabapentin in Opioid-Related Overdoses Highlights Misuse Potential and Off-label Prescribing Practices. JAMA. 2022;328(13):1283-5.
29. Schoch KM, DeVos SL, Miller RL, Chun SJ, Michaela N, David FW, et al. Increased 4R-Tau Induces Pathological Changes in a Human-Tau Mouse Model. Neuron. 2016;90(5):941-7.
30. Rissardo JP, Araujo de Matos UM, Caprara ALF. Gabapentin-Associated Movement Disorders: A Literature Review. Medicines. 2023;10(9):52.
31. Oh G, Moga DC, Moga DC, Fardo DW, Fardo DW, Abner EL, et al. The association of gabapentin initiation and neurocognitive changes in older adults with normal cognition. 2022;13:910719.
32. Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse, and diversion: A systematic review. Addiction. 2017;111(7):1160-74.
33. Chen RJ, Sharma S. GABA Receptor. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2026.
34. Brianna Costales BS, Goodin AJ. Outpatient Off-Label Gabapentin Use for Psychiatric Indications Among U. S. Adults. Psychiatr Serv. 2021;72(11):1246-53.

35. Pacheco-Paez T, Montastruc F, Rousseau V, Chebane L, Lapeyre-Mestre M, Renoux C, et al. Parkinsonism Associated with Gabapentinoid Drugs: A Pharmacoepidemiologic Study. Mov Disord. 2020;35(1):176-80.
36. Taylor CP. Mechanisms of action of gabapentin. Rev Neurol (Paris). 1997:153(1):S39-45.
37. Li S, Selkoe DJ. A mechanistic hypothesis for the impairment of synaptic plasticity by soluble Aβ oligomers from Alzheimer's brain. J Neurochem. 2020;154(6):583-97.
38. Raudino F, Valduce-Como O, Mascalzi MG, Zagami A. Gabapentin and Behavioural Disorders in Severe Alzheimer's Disease. J Clin Psychopharmacol. 2004;24(4):459-60.
39. Mi Z, Povysheva N, Rose ME, Ma J, Zeh DJ, Harikumar N, Bhuiyan, et al. Abolishing UCHL1's hydrolase activity exacerbates ischemia-induced axonal injury and functional deficits in mice. J Cerebral Blood Flow Metabolism. 2024;44(11):1349-61.
40. Iqbal K, Liu F, Gong CX, Alonso AdelC, Grundke-Iqbal I. Mechanisms of tau-induced neurodegeneration. Acta Neuropathologica. 2009;118(1):53-69.
41. Pedicone C, Weitzman SA, Renton AE, Goate AM. Unravelling the complex role of MAPT-containing H1 and H2 haplotypes in neurodegenerative diseases. Mol Neurodegener. 2024;19(1):43.
42. Amudha S, Babu A. Review about Gabapentin Misuse, Interactions, Contraindications and Side Effects. JCHR. 2025;15(1):303-9.
43. Quintero GC. Review about gabapentin misuse, interactions, contraindications and side effects. J Exp Pharmacol. 2017;9:13-21.
44. Borowicz-Reutt KK. Effects of Antiarrhythmic Drugs on Antiepileptic Drug Action-A Critical Review of Experimental Findings. Int J Molecular Sci. 2022;23(5):2891.
45. Bicket MC, Mao J. Chronic Pain in Older Adults. Anesthesiol Clin. 2015;33(3):577-90.
46. Zaccara G, Gangemi PF, Cincotta M. Central nervous system adverse effects of new antiepileptic drugs. A meta-analysis of placebo-controlled studies. Seizure. 2008;17(5):405-21.
47. Olaibi OK, Osuntokun OS, Ijomone OM. Effects of chronic administration of gabapentin and carbamazepine on the histomorphology of the hippocampus and striatum. Ann Neurosci. 2014;21(2):57-61.
48. Ghazisaeidi S, Muley MM, Salter MW. Neuropathic Pain: Mechanisms, Sex Differences, and Potential Therapies for a Global Problem. Ann Rev Pharmacol Toxicol. 2023;63:565-83.
49. Mogil JS, Parisien M, Esfahani SJ, Diatchenko L. Sex differences in mechanisms of pain hypersensitivity. Neurosc Biobehavioral Rev. 2024;163:105749.
50. El-Kattan MA, Saeed E, Khattab MA, Maksoud F, Eldein ME, Abdel-Roaf NE, et al. Gabapentin-Induced Sub-Chronic Neurotoxicity in Rats and the Protective Role of Alpha-Tocopherol. Gabapentin-Induced Sub-Chronic Neurotoxicity in Rats and the Protective Role of Alpha-Tocopherol. Turk Patoloji Dergisi. 2025;41(3):90-104.
51. Ozcagli E, Soylemez-Yesilcimen E. P31-30 Gabapentin-Induced Effects on Telomerase Activity and DNA Damage in HEK-293 Cells: An *In vitro* Study Toxicology Letters. 2025;411:S422.
52. Zhao D, Baek J, Hume AL, McPhillips EA, Lapane KL. Geographic Variation in the Use of Gabapentinoids and Opioids for Pain in a Commercially Insured Adult Population in the United States. J Pain Res. 2022;15:443-54.

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