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A Review on Pregabalin - As an Anticonvulsant Drug

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ABSTRACT

The main objective of the article is to formulate Pregabalin 20 mg/mL oral solution. Pregabalin (PGB) is notable drug substance for analgesic and anticonvulsant drug. The study examined PGB's pharmacokinetics, adverse drug reactions, risks, and modes of action. PGB is a calcium channel inhibitor that has analgesic and antiepileptic properties by binding to the α2-δ subunit. It limits hepatic metabolism and exhibits diminished protein binding capacity. Drug-drug interactions with pharmacokinetic properties are rare to occur. It does not require serum drug monitoring and has an immense safety tolerance. Due to PGB's advantageous pharmacological properties, it can be used as a primary or supplementation treatment for a number of illnesses, including post-herpetic neuralgia, diabetic peripheral neuropathy, partial seizures, and generalized anxiety disorders.

Keywords: Pregabalin, Anticonvulsant Drug

INTRODUCTION:

Pregabalin is a medication that is used in conjunction with other anticonvulsants to treat limited onset seizures, fibromyalgia, and neuropathic pain issues. The pregabalin and inhibitory neurotransmitter gamma-amino butyric acid (GABA) have similar structure. [1] Among other problems, it can be used to treat fibromyalgia, post-herpetic neuralgia, and neuropathic pain. There is evidence that pregabalin works by binding to the α2δ subunit of voltage-dependent calcium channels, while the exact mechanism of action is yet unknown. If taken improperly, it could lead to dependency, although people with prior or present drug use problems seem to be more at risk. [2]

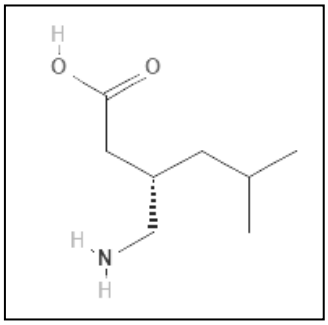

Figure 1: Chemical Structure Pregabalin

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Drug Profile:

Table 1: Physical Properties of Pregabalin [3]

Appearance	White or almost white powder
Solubility	Sparingly soluble in water, freely soluble in basic aqueous solutions, freely soluble in acidic aqueous solutions
Molecular Formula	$C_8H_{17}NO_2$
Molecular Weight	159.23
Chirality	Pregabalin is a chiral molecule. It has one chiral centre, it exhibits optical isomerism and its pharmaceutically active isomer is the S isomer
Melting range	190°C to 198°C
Isomerism	It does not exhibit geometrical isomerism
pKa	Carboxylic acid (pKa:4.2) and an amine (pKa:10.6)
Partition Coefficient	Log P -1.35(Minus 1.35)
Specific optical rotation	+10.0° to 12.0°

Mechanism of Action:

Pregabalin share structural similarities of Gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. Pregabalin lipophilic analog has been altered to improve diffusion through the blood-brain barrier. However, Pregabalin does not bind to GABA-A or GABA-B receptors directly. It also doesn't metabolize into an agonist of the GABA receptor. Pregabalin binds to alpha-2-delta subunit-containing pre-synaptic voltage-gated calcium channels in central nervous system tissues in human. The release of excitatory neurotransmitters and the influx of calcium into neurons caused by depolarization are both reduced by the binding of the alpha-2-delta subunit. Pregabalin analgesic and anticonvulsant properties could be explained by this mechanism. Pregabalin does not alter cyclooxygenase activity and is not known to have any effect on sodium channels, dopamine receptors, serotonin receptors, or opiate receptors [4]. The diagrammatic representation of mechanism of action of pregabalin is illustrated in below figure.

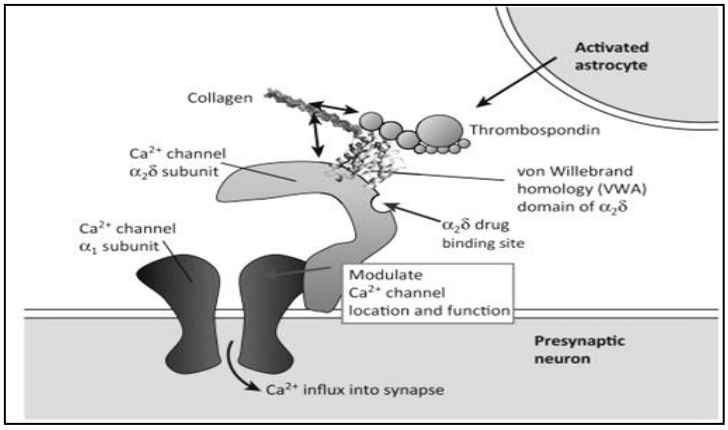

Figure 2: Mechanism of Action of Pregbalin

Indications:

Pregabalin is meant for the treatment neuropathic pain related to,

- Diabetic peripheral neuropathy and
- Post-herpetic neuralgia

Also, Pregabalin is related to the treatment of neuropathic pain with spinal cord injury.

Pregabalin also indicated for the pain related with fibromyalgia.

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Pregabalin is recommended as additional therapy for the treatment of seizures with partial onset in patients 1 month of age and older, as well as for the control of neuropathic pain related to spinal cord injury, post-herpetic neuralgia, fibromyalgia, and diabetic peripheral neuropathy. [5] The Maximum dose for the adult patient should be adjusted with decreased renal function. The recommended maximum doses for the indication are given in the following table.

Table 2: Dosage and Recommendation of Pregabalin

INDICATION	DOSING REGIMEN	MAXIMUM DOSE
Neuropathic pain associated with diabetic peripheral neuropathy (DPN)	3 divided doses per day	300 mg per day within one week
Posttherpetic neuralgia (PHN)	2 or 3 divided doses per day	300 mg per day within one week Maximum dose of 600 mg per day
Adjunctive therapy for the treatment of partial-onset seizures inpatients 1 month of age and older	2 or 3 divided doses per day	Maximum dose of 600 mg per day
Fibromyalgia	2 divided doses per day	300 mg per day within one week Maximum dose of 450 mg per day
Neuropathic pain associated with spinal cord injury	2 divided doses per day	300 mg per day within one week Maximum dose of 600 mg per day

Pharmacokinetics:

However sharing the same structure to gamma-aminobutyric acid (GABA), pregabalin is not able to bind to GABA receptors.[6] Instead of that, it connects the central nervous system's pre-synaptic voltage-gated calcium channels' alpha2-delta subunit. Pregabalin doesn't affect the function of sodium channels, cyclooxygenase, opiate receptors, serotonin receptors, or dopamine receptors.[7]

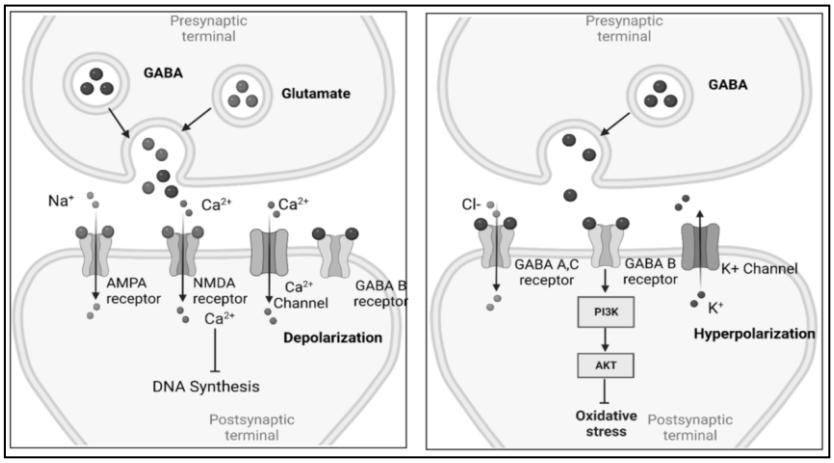

Figure 3: Role of gamma-aminobutyric acid (GABA) and Glutamate as neurotransmitters

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Bioavailability:

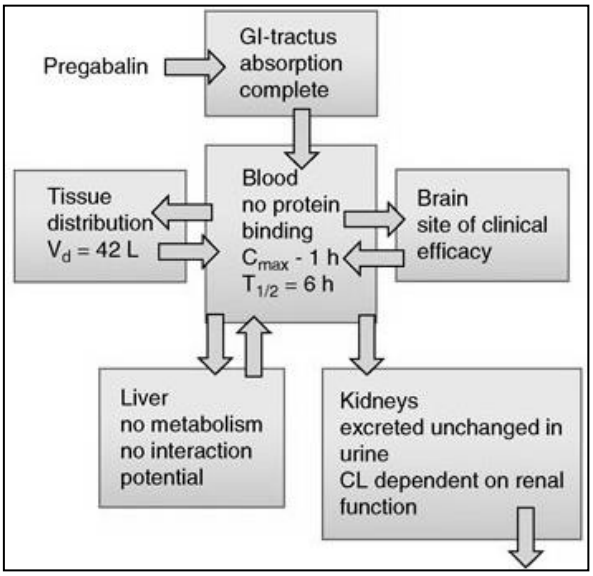

Figure 4: Bioavailability of Pregabalin

After oral treatment, pregabalin absorbs quickly, reaching peak plasma concentrations in 0.7–1.3 hours. Oral pregabalin has a 90% bioavailability that does not change by dosage or duration of administration.[8]

Table 3: Pharmacokinetic Parameters of Pregabalin

Pharmacokinetic Parameters	**Range**
Absorption	Pregabalin absorbed in small intestine
Metabolism	Pregabalin undergoes little or no metabolism. The main metabolite is N-methylpregabalin
Excretion	Excreted virtually unchanged (<2% metabolism) by the kidneys
C_{max} (Maximum Concentration)	0.7 – 1.3 hours
Bioavailability	90 %
T_{max} (Time to reach Maximum Concentration)	1 hour and steady state is achieved within 24-48 hours
V_d (Volume of Distribution)	42 L
Protein Binding	No Protein Binding
$T_{½}$ (Half – Life)	6 hours
% excreted uncharged in urine	98%

Absorption:

The absorption of pregabalin rate is decreased when taken with food, resulting in a decrease in concentration of pregabalin of approximately 25% to 30% and takes increased time to attain maximum concentration of time approximately 3 hours. However, intake of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin.

Pregabalin is rapidly and widely absorbed after an oral dose given while fasting. Irrespective of dosage, pregabalin oral bioavailability is claimed to be ≥ 90%. After one or more doses, C_{max} is reached in 1.5 hours, and steady state is reached in 24-48 hours when administration is repeated. It appears that AUC and C_{max} are dosage proportionate.

Food slows down the rate at which pregabalin is absorbed, which lowers the C_{max} by about 25–30% and raises the T_{max} to about 3 hours. Food's influence does not; however, seem to have a clinically significant effect on pregabalin's overall absorption. Pregabalin can therefore be taken with or without food.

Metabolism:

Pregabalin undergoes reduced or no metabolism. It was discovered through nuclear medicine research that pregabalin accounted for almost 98% of the radioactivity found in the urine. N-methylpregabalin is the primary metabolite. [9]
In humans, pregabalin undergoes very little metabolism. 90% of the radio-labeled pregabalin dose that was given was found in the urine as unaltered pregabalin after the dose was given. 0.9% of the dose was made up of the primary pregabalin metabolite detected in urine, the N-methylated derivative of pregabalin. Pregabalin (S-enantiomer) did not racemize to the R-enantiomer in mice, rats, rabbits, or monkeys used in preclinical research.

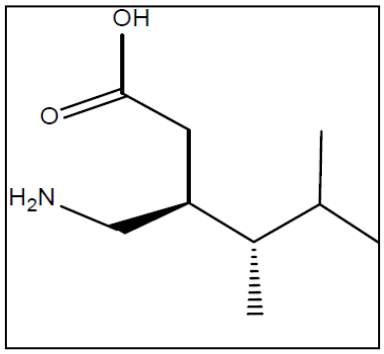

Figure 5: Active metabolite of Pregabalin (N-Methylpregabalin)

Volume of distribution:

The apparent volume of distribution following oral administrated of pregabalin treatment is approximately 0.5 L/kg. Pregabalin is able to pass through the blood brain barrier (BBB) despite not being extremely lipophilic. Large amino acids are more easily transported over the blood-brain barrier by System L transporters, and pregabalin's substrate status has been established. Based on available data, system L transporters may be in charge of pregabalin uptake within the blood-brain barrier (BBB).
Pregabalin has been demonstrated to cross the placenta in rat studies.
The system L transporter, which moves big amino acids across the blood-brain barrier, is a substrate of pregabalin. Pregabalin has been demonstrated to penetrate the blood brain barrier in mice, rats, and monkeys, despite the lack of data in humans. [10]

Route of Elimination:

Most of pregabalin is excreted in urine. Also, pregabalin does not seem to racemize to the R enantiomer in the body, according to preclinical research. [11]
Pregabalin has a mean elimination half-life of 6.3 hours in people with normal renal function. It is mainly excreted from the systemic circulation by the kidneys as an unmodified medication. In young, healthy participants, the mean renal clearance was calculated to be between 67.0 and 80.9 mL/min. Pregabalin's non-binding nature to plasma proteins suggests that renal tubular reabsorption is the mechanism underlying its clearance rate. The clearance of creatinine is almost directly correlated with pregabalin (CLcr). [12]

Half Life:

The Elimination Half life of pregabalin is 6.3 hours. [5]

Clearance:

The estimated mean renal clearance in young, healthy participants is between 67.0 and 80.9 mL/min.
This clearance rate indicates a potential involvement of renal tubular reabsorption, given that pregabalin does not bind to plasma proteins. [5]

Toxicity:

- Twenty adverse effects were found to be substantially correlated with pregabalin in a comprehensive analysis that included 38 randomized controlled trials. The majority of these effects are related to the central nervous system and cognition. Vertigo, dizziness,

balance issues, ataxia, blurred vision, diplopia, amblyopia, somnolence, confusional state, tremor, attention disturbance, abnormal thinking, asthenia, fatigue, euphoria, edema, peripheral edema, dry mouth, and constipation are among the adverse effects that have been identified [13].

- Pregabalin toxicity is most commonly seen as somnolence, disorientation, restlessness, agitation, sadness, affective disorder, and seizures (dosage range: 800 mg/day, single dosages up to 11,500 mg).

- For pregabalin overdose, patients should get standard supportive treatment as there is no known counteragent. When necessary, emesis or stomach lavage can assist get rid of unabsorbed pregabalin (medical professionals should still take the usual measures to keep the airway open).

- The pharmacokinetic characteristics of pregabalin imply that in cases of extreme toxicity, extracorporeal elimination techniques like hemodialysate could be helpful. Nonetheless, there have been instances where patients with extremely elevated pregabalin blood levels have responded well to supportive therapy alone [14].

Treatment for Toxicity:

- If necessary, emesis or stomach lavage can be used to get rid of medications that weren't absorbed. The patient should get general supportive treatment. Keep an eye on the patient's vital signs, airway, and clinical state. For the most recent information on managing a pregabalin overdose, get in touch with a Certified Poison Control Center.

- Standard hemodialysis techniques can be used to remove pregabalin; this will remove around 50% of the drug in 4 hours.

Adverse Effect:

- The majority of pregabalin side effects that were observed was mild to moderate, dose-dependent, and happened during the first two weeks after starting therapy.

- The central nervous system (CNS) adverse events were the most frequent. The two most frequent adverse events that resulted in quitting pregabalin were somnolence and dizziness.

- Some patients had symptoms such as insomnia, headaches, nausea, anxiety, jitters, irritability, hyperhidrosis, and diarrhea when stopping pregabalin suddenly or quickly [15].

- Pregabalin-related adverse reactions were the most common across all patient populations in premarketing controlled trials, occurring in more than or equal to 5% of patients and twice as often in those receiving a placebo. These adverse reactions included sleeplessness, vertigo, blurred vision, difficulty focusing or paying attention, dry mouth, edema, and weight gain [17].

- Pregabalin-related weight gain is dose-dependent and affected up to 14% of individuals taking 600 mg daily.

- Pregabalin use for an extended period of time can lead to physical dependence and increase the risk of misuse, particularly in patients using opioid medications or those with a history of substance abuse [18].

Contraindication:

- Patients with a hypersensitivity to pregabalin should not use pregabalin. Angioedema is one of the hypersensitivity actions that have happened to pregabalin patients [18].

- Pregabalin in pregnant women has not been the subject of sufficient research. Pregabalin may be harmful to the fetus. Inform patients that there might be a danger to the developing foetus [19].

- Breastfeeding is not advised since pregabalin has been found in the milk of nursing women; instead, an alternate medication is recommended [20].

Acknowledgement:

- Pregabalin is one antiepileptic medication that may raise the risk of suicidal thoughts or actions. Keep an eye out for signs of suicidal thoughts or actions, new or worsening depression, and other behavioral or emotional abnormalities in patients receiving pregabalin medication.

- Keep an eye on any weight gain, edema, respiration rate, or other adverse effects in the patient that can affect adherence to pregabalin medication.

- Assess the effectiveness of the treatment on a regular basis by evaluating the illness and any side effects that the patient may mention [21].

Prescription of Pregabalin:

- One common drug used to treat seizures and pain issues is pregabalin. Despite the drug's relative safety, the patient has to be routinely observed by the internist, pharmacist, nurse practitioner, and primary care physician.

- Every appointment should include a mental health evaluation because the medication has been known to induce depression and suicidal ideation. Patients should be informed about the additional negative effects, advised not to drive while using the medicine, and advised not to use it in combination with alcohol or other anti-seizure drugs.

- Medication reconciliation and monitoring for possible drug interactions are tasks that pharmacists should do. Before giving, nurses should confirm the dosage and let the physicians know if they have any concerns. A neurologist, psychiatrist, or other professional should be consulted before making any changes to the treatment plan for the patient.

REFERENCES:

1. Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg. 2007 Dec; 105(6):1805-15. doi: 10.1213/01.ane.0000287643.13410.5e.
2. Bonnet U, Scherbaum N: How addictive are gabapentin and pregabalin? A systematic review. Eur Neuropsychopharmacol. 2017 Oct 5. pii: S0924-977X(17)30897-0. doi: 10.1016/j.euroneuro.2017.08.430
3. https://pubchem.ncbi.nlm.nih.gov/compound/Pregabalin#section=InChI
4. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channelalpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res. 2007 Feb; 73(2):137-50. [PubMed: 17126531]
5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021446s036,022488s014lbl.pdf
6. Rajappa GC, Vig S, Bevanaguddaiah Y, Anadaswamy TC: Efficacy of Pregabalin as Premedication for Post-Operative Analgesia in Vaginal Hysterectomy. Anesth Pain Med. 2016 May 14;6(3):e34591. doi: 10.5812/aapm.34591. eCollection 2016 Jun.
7. Cross AL, Sherman Al: Pregabalin .
8. Bockbrader HN, Radulovic LL, Posvar EL, Strand JC, Alvey CW, Busch JA, Randinitis EJ, Corrigan BW, Haig GM, Boyd RA, Wesche DL. Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol. 2010 Aug;50(8):941-50. doi: 10.1177/0091270009352087. Epub 2010 Feb 10. PMID: 20147618.
9. Calandre, E. P., Rico-Villademoros, F., & Slim, M. (2016). Alpha2delta ligands, gabapentin, pregabalin and mirogabalin: a review of their clinical pharmacology and therapeutic use. Expert Review of Neurotherapeutics, 16(11), 1263–1277. https://doi.org/10.1080/14737175.2016.1202764
10. Takahashi Y, Nishimura T, Higuchi K, Noguchi S, Tega Y, Kurosawa T, Deguchi Y, Tomi M: Transport of Pregabalin Via L-Type Amino Acid Transporter 1 (SLC7A5) in Human Brain Capillary Endothelial Cell Line. Pharm Res. 2018 Oct 29;35(12):246. doi: 10.1007/s11095-018-2532-0.
11. Stump P: [Pregabalin--profile of efficacy and tolerability in neuropathic pain]. Drugs Today (Barc). 2009 Oct;45 Suppl C:19-27.
12. Lee DW, Lee HJ, Kim HJ, Chang SH, Park DJ: Two cases of pregabalin neurotoxicity in chronic kidney disease patients. NDT Plus. 2011 Apr;4(2):138. doi: 10.1093/ndtplus/sfq219.
13. Zaccara G, Gangemi P, Perucca P, Specchio L: The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. Epilepsia. 2011 Apr;52(4):826-36. doi: 10.1111/j.1528-1167.2010.02966.x. Epub 2011 Feb 14.
14. Wood DM, Berry DJ, Glover G, Eastwood J, Dargan PI: Significant pregabalin toxicity managed with supportive care alone. J Med Toxicol. 2010 Dec;6(4):435-7. doi: 10.1007/s13181-010-0052-3.
15. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. Cochrane Database Syst Rev. 2019 Jan 23;1(1)

16. Preuss CV, Kalava A, King KC. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Apr 29, 2023. Prescription of Controlled Substances: Benefits and Risks.
17. Chalabianloo F, Schjøtt J. [Pregabalin and its potential for abuse]. Tidsskr Nor Laegeforen. 2009 Jan 29;129(3):186-7
18. Ortega-Camarero MA, Avila R, Prados Castaño M, Piñero M, Quiralte J, Cimbollek S. Challenge-based pregabalin induced urticaria and angioedema. A case report. Allergol Immunopathol (Madr). 2012 Sep-Oct;40(5):323.
19. Andrade C. Safety of Pregabalin in Pregnancy. J Clin Psychiatry. 2018 Oct 02;79(5).
20. Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. Drugs. 2017 Mar;77(4):403-426.
21. Abrahamsson T, Berge J, Öjehagen A, Håkansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study. Drug Alcohol Depend. 2017 May 01;174:58-64.

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Conflict of Interest Statement: All authors have nothing else to disclose.