

A Report on Efficacy of Epalrestat in the Treatment of Diabetic Peripheral Neuropathy (DPN)

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Introduction

Diabetic neuropathy is nerve damage from high blood glucose (sugar) levels in people with diabetes. Nerves throughout the body can suffer damage. People with poor glucose control and who have had diabetes for a long time are at highest risk for nerve damage¹. Peripheral neuropathy affects up to 50% of diabetic patients. DPN is responsible for significant morbidity, increased mortality, and impaired quality of life².

Types and Symptoms of Diabetic Neuropathy¹

The first type (called distal polyneuropathy or DPN) affects the sensitivity of your feet, legs, hands, and arms. It also can affect the movement of your limbs. Symptoms of DPN include

- Pain, tingling, and burning
- Numbness and loss of feeling
- Muscle weakness
- Skin ulcers (open sores)

About half of people who have DPN might not have symptoms, except for losing feeling in their feet. Because of this feeling loss, they could injure their feet and not know it. Untreated foot injuries can lead to ulcers and infection and, sometimes, amputation.

The second type (called autonomic neuropathy) affects your urinary tract, digestive system, sex organs, sweat glands, eyes, and heart. Symptoms of autonomic neuropathy include

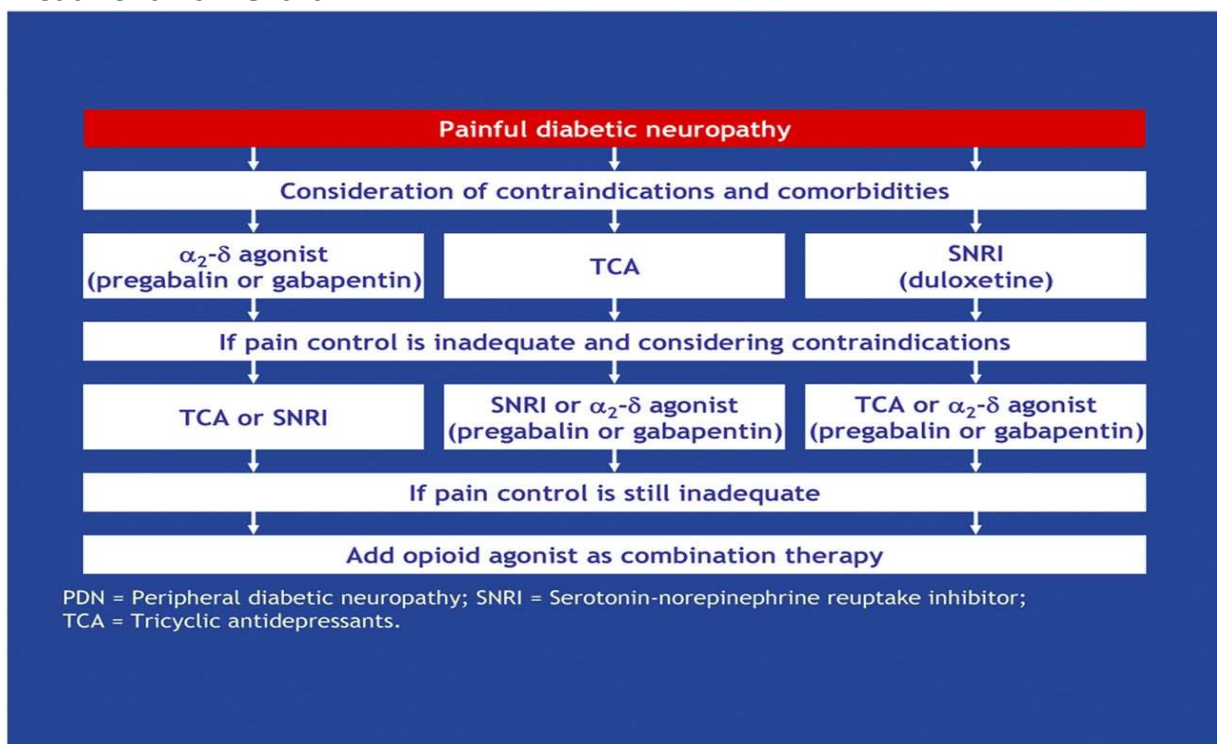
- Bladder problems (loss of bladder control, not being able to fully empty the bladder, frequent urinary tract infections)

- Digestive system problems (bloating, nausea, vomiting, diarrhea, constipation)
- Erectile dysfunction in men and sexual problems in women
- Too much or too little sweating
- Dizziness when you stand up¹

Reliability of the neurological scores for evaluation of neuropathy in Type 2 Diabetic Mellitus (T2DM) patients revealed that Modified Neuropathy Disability Score (MNDS) had 92 % sensitivity and 77% diagnostic efficacy³.

Currently, plethora of drugs developed which prevents nerves damage⁴. Duloxetine and Pregabalin have been approved in US for painful DPN⁵, whereas Epalrestat is marketed in Japan⁶. The most effective drugs would be inhibitors of nerve damage process like Aldose Reductase Inhibitor (ARI)⁴. These drugs could offer the advantage of being effective even with persistent hyperglycaemia⁴. Epalrestat is a non - competitive inhibitor of aldose reductase, the rate-limiting enzyme in the polyol pathway⁷. Epalrestat was assessed in clinical trials at doses of 50 mg TDS⁸.

Treatment Flow Chart



Comparison of Clinical Parameters

Parameter	Epalrestat^{9,10}	Pregabalin^{11,12}	Duloxetine^{12,13}
Innovator	Ono Pharmaceutical Co. Ltd.	Pfizer	Eli Lilly and Company
Regulatory Approvals	PMDA - 1992, CDSCO - 2011	USFDA - 2004, CDSCO - 2005	USFDA - 2004, CDSCO - 2005
DEA Class	Not a controlled substance	Schedule - V	Not a controlled substance
Black Box Warning	No	No	Yes (for suicidal thought induction)
Strengths	Tablets: 50mg(IR), 150mg (SR)	Capsules: 25mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg. Oral Solution: 20 mg/ml.	Capsules: 20mg, 30mg, 60mg
Dosage Regimen	50mg (IR) - TID or 150mg (SR) - OD	In DPN: 100mg - TID	In DPN: 60mg - OD
Approved Indications	Diabetic Neuropathy	Neuropathic pain associated with diabetic peripheral neuropathy (DPN), Post herpetic neuralgia (PHN), Adjunctive therapy for the treatment of partial onset seizures in patients 4 years of age and older,	Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Diabetic Peripheral Neuropathic Pain (DPNP), Fibromyalgia (FM), Chronic

		Fibromyalgia, Neuropathic pain associated with spinal cord injury	Musculoskeletal Pain
Indications in Clinical Trials	-	Phase - III : Tonic - Clonic Epileptic Seizures	Phase - II/III: Chronic Fatigue Syndrome
Adverse Effects	Elevated Liver Enzymes - 1% - 3%, Headache - 3% - 5%, Vomiting - 1% -3%, Diarrhea - 1% - 2%	Somnolence - 13%, Dizziness - 23%, Peripheral edema - 9%, Weight gain - 4%, Confusion - 2%, Asthenia - 4%	Palpitations - 2%, Dizziness - 10%, Abnormal dreams - 2%, Somnolence - 10%, Tremors - 3%, Insomnia - 10%, Erectile dysfunction - 5%, Agitation - 5%, Anxiety - 3%, Decreased Libido - 4%, Nausea - 25%, Diarrhea - 10%, Constipation - 10%, Dry mouth - 15%, Blurred vision - 3%

The Pharmacokinetic Parameters of Epalrestat are not available

Comparison of Efficacy between Epalrestat and Methylcobalamin⁹

Outcome	Epalrestat			Methylcobalamin		
	4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks
% decrease in sensory loss from Baseline	13.8%	30%	63.8%	12.2%	18.8%	34.8%
% decrease in spontaneous pain from baseline	15.2%	30.4%	77.7%	11.9%	19.4%	30.9%
% decrease in numbness from baseline	15%	28.8%	65.3%	12%	18%	31.9%
% decrease in burning from baseline	14.9%	44.2%	88.4%	13.6%	20.1%	39.6%
% decrease in muscle cramps from baseline	14.1%	27.5%	67.6%	12.1%	17.6%	29%

Comparison of Efficacy between Epalrestat, Pregabalin and Duloxetine

Outcome	Epalrestat ⁹	Pregabalin ¹¹	Duloxetine ¹³
% Improvement in pain from baseline	77.7% (at 12 weeks)	60% patients had \geq 30% decline in pain and 50% patients had \geq 50% decline in pain (at 8 weeks)	60% patients had \geq 30% decline in pain and 50% patients had \geq 50% decline in pain (at 12 weeks)

Conclusion

- Epalrestat, an aldose reductase inhibitor has exhibited a greater efficacy over Pregabalin and Duloxetine in terms of improvement in pain.
- The efficacy of Epalrestat at 12 weeks is double than that of Methylcobalamin in all the parameters such as decrease in sensory loss, numbness, burning and muscle cramps. However, in India Epalrestat comes in combination with Methylcobalamin 500mcg, which seems even more beneficial.
- Due to lack of availability of data regarding Epalrestat, comparison of Pharmacokinetic parameters is not possible for now.
- Indications wise, Epalrestat is exclusively approved for DPN, while Pregabalin and Duloxetine have several other indications.
- As per a study, Compared to Pregabalin and Duloxetine, Epalrestat caused limited and non-worrisome adverse events except liver enzyme elevation in 1 – 3% of patients.
- In safety point of view, Duloxetine carries a black box warning for inducing suicidal thoughts, and Pregabalin being a neuroleptic drug, has a potential for abuse and is listed under DEA Schedule V.
- Looking at the above considerations, it can be said that the safety vs. efficacy profile of Epalrestat is favorable. However, it cannot be concluded due to limited availability of data.

References

1. Silvio Inzucchi, MD, Julio Rosenstock, MD, Guillermo Umpierrez, MD. Diabetic Neuropathy. *The Journal of Clinical Endocrinology & Metabolism*, Volume 97, Issue 5, 1 May 2012, Page 35A, <https://doi.org/10.1210/jcem.97.5.zeg35a>.
2. Alam U, Riley DR, Jugdey RS, Azmi S, Rajbhandari S, D'Aout K, et al. Diabetic neuropathy and gait: a review. *Diabetes Ther.* 2017;8:1253-64.
3. Ambreen A, Muhammad AH, Umar AK, Nadeem A, Mujeeb AB. Reliability of the neurological scores for assessment of sensorimotor neuropathy in type 2 diabetics. *JPMA.* 2010;160:66. Alvin P. Diabetes Mellitus. In: Longo, Fauci,

- Kasper, Hauser, Jameson, Loscalzo. Harrison's principal of internal medicine. 18th ed, New Delhi: McGraw Hills Publication; 2012. pp. 2968-3032.
4. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. *PharmacolTher.* 2008;120(1):01-34.
 5. Alvin P. Diabetes Mellitus. In: Longo, Fauci, Kasper, Hauser, Jameson, Loscalzo. Harrison's principal of internal medicine. 18th ed, New Delhi: McGraw Hills Publication; 2012. pp. 2968-3032.
 6. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant α -lipoic acid: a meta-analysis. *Diabet Med.* 2004;21:114-21.
 7. Handelsman DJ, Turtle JR. Clinical trial of an aldose reductase inhibitor in diabetic neuropathy. *Diabetes.* 1981;30:459-64.
 8. Hotta N, Sakamoto N, Shigeta Y, Kikkawa R, Goto Y. Clinical investigation of Epalrestat an aldose reductase inhibitor on diabetic neuropathy in Japan. *J Diabetes Compl.* 1996;10:168-72.
 9. Manish Maladkar et al. Evaluation of efficacy and safety of epalrestat and epalrestat in combination with methylcobalamin in patients with diabetic neuropathy in a randomized, comparative trial. *Journal of Diabetes Mellitus* 03(01). DOI: 10.4236/jdm.2013.31004.
 10. SachinDevendraraoShende, Mirza Shiraz Baig, SudhakarMadhukarDoifode. Evaluation of Efficacy and Safety of Epalrestat (150 mg) Compared to Epalrestat (50 mg) in Patients Suffering from Diabetic Peripheral Neuropathy. *Journal of Clinical and Diagnostic Research.* 2018 Apr, Vol-12(4): OC15-OC18.
 11. Label (PDF)-FDA. LYRICA (*pregabalin*). PRESCRIBING INFORMATION. Available online:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021446s026,022488s005lbl.pdf.
 12. Drug Information. Adis Insight. Available online:
<https://adisinsight.springer.com/search>.
 13. Label (PDF)-FDA. CYMBALTA (*duloxetine hydrochloride*). HIGHLIGHTS OF PRESCRIBING INFORMATION. Available online:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022516lbl.pdf.