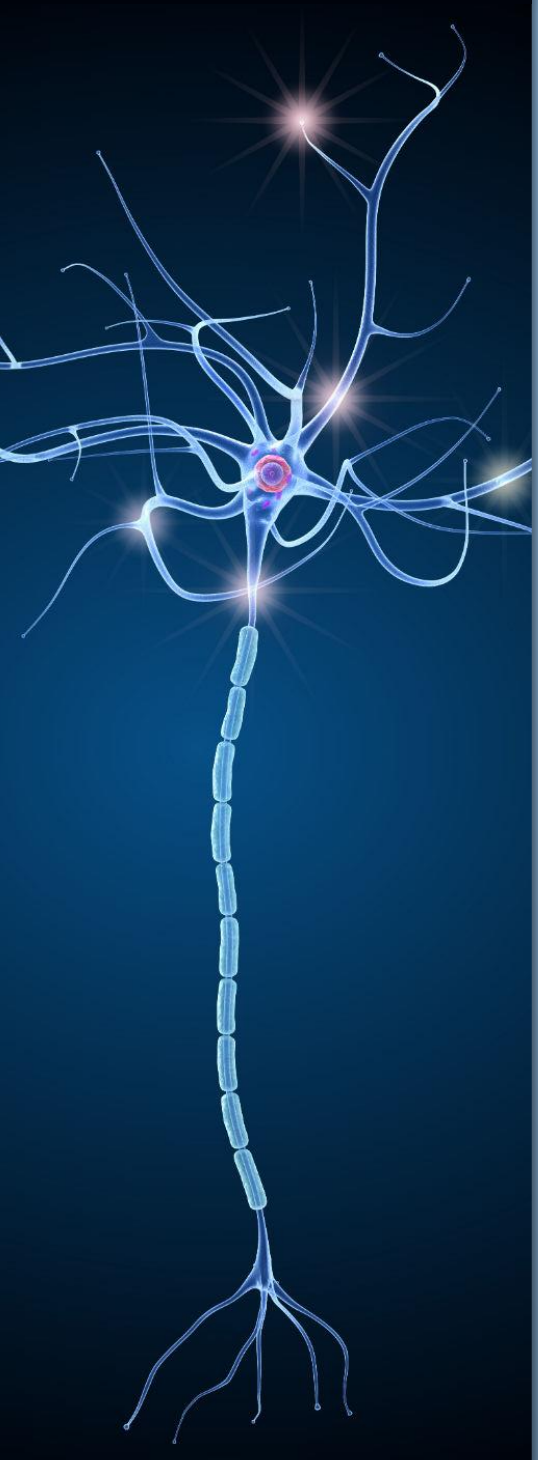


Combination of Pregabalin and Duloxetine Treatment vs. Pregabalin Monotherapy

Table of Content

Background and Objective of the Survey

The combination of pregabalin and duloxetine for the treatment of certain neuropathic pain conditions has been explored in clinical studies and compared to pregabalin monotherapy. Neuropathic pain, characterized by abnormal nerve function and signaling, can be challenging to manage and often requires multimodal treatment approaches.

Pregabalin, a calcium channel α2-δ ligand, and duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), each target different pathways involved in neuropathic pain. Pregabalin primarily acts by modulating calcium channels and reducing the release of excitatory neurotransmitters, while duloxetine enhances the availability of serotonin and norepinephrine in the central nervous system, thereby exerting analgesic effects.

Clinical studies comparing the combination therapy of pregabalin and duloxetine with pregabalin monotherapy have shown mixed results. Some trials suggest that the combination therapy provides superior pain relief and improvement in functional outcomes compared to pregabalin alone, particularly in patients with refractory neuropathic pain conditions. However, other studies have not found significant differences between the combination therapy and pregabalin monotherapy in terms of pain reduction and quality of life. Additionally, concerns regarding increased side effects, such as dizziness, somnolence, and nausea, with combination therapy highlight the need for careful patient selection and monitoring.

The objective of the survey is:

To evaluate the combination of pregabalin and duloxetine treatment vs pregabalin monotherapy

Methodology of the Survey

A survey was conducted to evaluate the combination of pregabalin and duloxetine treatment vs pregabalin monotherapy. A total of 150 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Pregabalin
- Duloxetine

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Peripheral neuropathies are among the most common neurological diseases with an incidence of 77/100,000 inhabitants per year and a prevalence of 1–12% in all age groups and up to 30% in older people. In the USA, it is estimated that patients with idiopathic neuropathies outnumber patients with Alzheimer's disease up to threefold.

The diagnosis of peripheral neuropathy necessitates a thorough workup of possible etiologies in order to identify treatable causes of this disease spectrum as early as possible. For instance, almost every 10th patient suffers from a polyneuropathy of autoimmune origin, which is amenable to causal (immunosuppressive or immunomodulatory) therapies and, therefore, must not be overlooked. Recently, even hereditary neuropathies have entered the "era of treatment in neurology", with the approval for transthyretin stabilizing agents (tafamidis), RNA interference molecules (patisiran) and antisense oligonucleotids (inotersen) in hereditary transthyretin amyloidosis ($ATTR_v$).

Pregabalin[2]

Pregabalin (PGB) is a newer generation gabapentinoid which followed the use of gabapentin (GBP). Originally synthesized over four decades ago. GBP was initially developed for use as an adjuvant antiepileptic drug (AED). However, after its release nearly two decades ago, off-label prescriptions for conditions other than epilepsy make up about 90% of GBP's use. This was secondary to limited efficacy in epilepsy as an adjuvant AED, but also because of a series of case reports describing the benefits of GBP in the treatment of neuropathic pain (NeP). After publication of randomized controlled trials in NeP conditions, GBP became a widely used pharmacotherapy for NeP, despite being off label.

PGB is a newer gabapentinoid, or AED, with great structural similarity to GBP. Just as with GBP, the use of PGB in epilepsy is limited. Instead, nearly all of PGB's use is for treatment of NeP, for which PGB was more directly targeted than with GBP. In addition, PGB is used frequently in the treatment of anxiety. Although the mechanism of action has not been

completely revealed, one known mechanism of action likely contributes to PGB's efficacy, even though other potential mechanisms may also occur.

Table 1. Pregabalin pharmacological summary.

Indications	**For primary treatment of neuropathic pain conditions including diabetic peripheral neuropathy, postherpetic neuralgia, low back pain with radiculopathy, fibromyalgia and central pain due to spinal cord injury. Also has indication for generalized anxiety disorder**
Pharmacomechanisms	Modulation of the $\alpha_2\delta$ subunit of the voltage gated calcium channel (VGCC)
	Blocking of trafficking of the $\alpha_2\delta$ subunit of the VGCC from dorsal root ganglia to the spinal dorsal horn
Chemical structure	(S)-(+)-3-(aminomethyl)-5-methylhexanoic acid; C8H17NO2

PGB was approved for NeP management in 2004 within the USA and Europe, and PGB has received further indications for various NeP conditions. Of the many treatments available for NeP management, gabapentinoids including GBP and PGB are considered as first-line treatment for most clinical guidelines. Currently, PGB is indicated for the management of NeP associated with diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN) and the management of fibromyalgia in North America. In the USA as well as in Europe, PGB is also indicated as adjunctive therapy for adult patients with partial onset seizures. PGB is the only medication in Europe approved for the treatment of central NeP. In Europe, it is also indicated for the treatment of peripheral NeP and generalized anxiety disorder, but not for fibromyalgia treatment.

Defined as pain arising from a lesion or disease affecting the somatosensory pathways within the peripheral or central nervous system, NeP is a common disorder, impacting on between 4% and 16% of the population. Fortunately, PGB is one of several pharmacotherapies used in NeP management which can modulate pain relief and also assist with management of comorbidities.

Mechanism of action, metabolism and pharmacokinetics

The mechanism of action for PGB is not completely understood. As the S-enantiomer of 3-(aminomethyl)-5-methylhexanoic acid, PGB binds with high affinity to the $\alpha_2\delta1$ site (a subunit of voltage-gated calcium channels (VGCCs) in the central nervous system. These high-affinity GBP- and PGB-binding sites are present throughout the dorsal spinal cord and brain. This is a presynaptic channel which modulates release of excitatory neurotransmitters vital for both nociception and epileptogenesis. It is known that gabapentinoids prevent trafficking of the $\alpha_2\delta1$ subunit from the dorsal root ganglia neurons to the dorsal spinal cord within animal models of NeP. This $\alpha_2\delta1$ subunit binding is thought to be responsible for both antinociceptive and probably its antiseizure effects as well. Once ligation occurs at the $\alpha_2\delta1$ subunit, a reduction in the excessive release of multiple excitatory neurotransmitters occurs; these neurotransmitters include noradrenaline, serotonin, dopamine, glutamate and substance P. Finally, PGB may elicit the internalization of VGCC at a cellular. PGB's effect is dependent upon the existence of hyperexcitation of the presynaptic neuron with minimal effects shown to occur during normal neuronal activity.

PGB is structurally related to the inhibitory neurotransmitter γ-aminobutyric acid (GABA), just as with GBP. In addition to its impact on the $\alpha_2\delta1$ subunit, there are suggestions that PGB may also modulate GABA concentrations and the glutamate synthesizing enzyme, branched-chain amino acid transaminase (cytosolic form). GBP may also modulate glutamate synthesis indirectly and increase nonsynaptic GABA responses at the GABA-A or GABA-B receptors. In addition, PGB may enhance activity of the neuronal glutamate transporter type 3, increasing glutamatergic responses. The AED mechanism for gabapentinoids is uncertain, but in animal models, gabapentinoids prevented seizures in rodent models for both maximal electroshock and pentylenetetrazole seizure models. Finally, another potential mechanism may be gabapentinoid-mediated synaptogenesis with potential blockade of new synaptic formation. When studied in animal analgesic models, gabapentinoids modulate both hyperalgesia (exaggerated response to a painful stimulus) and allodynia (pain-related behavior in response to a normally innocuous stimulus).

Although differences do not appear to be present between PGB and GBP for mechanisms of action, PGB's affinity and potency for the $\alpha_2\delta1$ subunit of the VGCC is speculated to be higher than that of GBP, although published evidence does not exist. If PGB does have increased

VGCC affinity, then this may be the reason why PGB has clinically greater efficacy at lower doses compared with GBP.

After oral administration, PGB is subject to rapid absorption. Oral bioavailability is over 90% and independent of the dose received. This is compared with 30–60% bioavailability for GBP. Following either single (25–300 mg) or multiple dose (75–600 mg/day) administrations, there is a linear association for maximum plasma concentrations (C_{max}) and area under the plasma concentration–time curve (AUC) values. There is a difference between PGB and GBP for gastrointestinal absorption, although both gabapentinoids are absorbed across the gastrointestinal tract using a system-L transporter system, GBP absorption is solely mediated by this system L transporter, leading to limitation through this saturable, active and dose-dependent transporter, producing nonlinear pharmacokinetics. PGB, however, has nonsaturable absorption, providing linear pharmacokinetics. Both gabapentinoids are also absorbed across the intestinal apical membrane via Na+-independent amino acid transporters. However, gabapentinoid transport across the intestinal basolateral membrane is likely mediated by the system L transporter. These factors may also contribute to saturable absorption of GBP across the gastrointestinal tract, as high affinity and lower capacity of GBP saturable transport and its dose-dependent decrease in oral absorption. As such, the rate of PGB absorption is threefold higher than that of GBP. These factors explain how PGB achieves a faster peak blood concentration (1 h post dose) compared with GBP (3 h).

Table 2. Pregabalin: pharmacokinetics and metabolism with comparison to gabapentin.

Structure	**Gabapentin**	**Pregabalin**
T_{max} (h)	2–3	1
$t_{1/2}$ (h)	5–7	5.5–6.7
Bioavailability	27–60%	>90%
Pharmacokinetics	Nonlinear (zero order)	Linear
Plasma protein binding	<3%	Assumed to be zero
Potency at the $\alpha_2\delta1$ subunit	+	++
Metabolism	Nil	Very limited if any metabolism occurs. Some patients may have scant *N*-methylation occur

Renal excretion	100% unchanged	92–99% unchanged
Suggested dosing schedule	three or four times daily/	two or three times daily
Effective dose	1800–3600 mg/day	150–600 mg/day
Time to effective dose using recommended titrations	14 days	5–7 days
Dosing in renal impairment (creatinine clearance, ml/min)		
≥60	1200–3600 mg/day	150–600 mg/day
30–60	600–1600 mg/day	75–300 mg/day (two or three times daily
15–30	300–900 mg/day	25–150 mg/day
<15	100–300 mg/day	25–75 mg/day (once daily)

PGB has an elimination half life of 5.5–6.7 h, independent of dose and repeated dose administration. Elimination of PGB is nearly exclusive to renal excretion, with minimal metabolism at the liver (see below). Renal excretion is supported by data demonstrating that dosing with radiolabeled PGB leads to 90% of the administered dose being recovered unchanged in the urine. There is an N-methylated derivative of PGB, which is a metabolite of PGB found in urine, that accounts for less than 1% of the dose; thus, very little metabolism of PGB occurs in human subjects. Renal elimination occurs at a rate proportional to that of the estimated creatinine clearance (CLCr). Both total and renal PGB clearances are proportionate with CLCr. Patients with CLCr of 30–60 ml/min are at greater risk of discontinuation due to adverse effects (AEs) than patients having normal CLCr; for this reason, the daily dosing of PGB should be fine tuned for patients with CLCr up to 60 ml/min and for those patients receiving hemodialysis. As mentioned earlier, for patients receiving hemodialysis, a supplemental small dose of PGB could be provided immediately after hemodialysis in order

to uphold steady-state plasma PGB concentrations. If required, hemodialysis could be used to clear large proportions of PGB.

The oral clearance of PGB is likely to decrease with increasing age; therefore, dose reductions should be considered for older patients. It is best to divide the total daily dose as determined by the dose; for example, if 300 mg/day is targeted, then 150 mg orally twice a day could be provided. If 225 mg/day is suggested, then 75 mg orally three times a day could be prescribed.

PGB does not inhibit or induce the major cytochrome P450 system isoenzymes; therefore, PGB is rarely, if ever, associated with hepatic dysfunction. There is only minimal metabolism of PGB at the liver; an N-methylated derivative accounts for an estimated 1% of the dose provided. An absence of hepatic metabolism does not prevent drug-induced hepatotoxicity, however, as hepatotoxicity due to PGB has been described in isolated case reports.

The effects upon anesthesia and the perioperative period are unclear. PGB may possibly be associated with significant respiratory depression postoperatively. With PGB now being used more frequently perioperatively for prevention of postoperative pain, this AE may become better defined with experience. Perioperative use of PGB 300 mg provided both 1 h presurgery and 12 h later may contribute to greater AEs, including blurred vision, dizziness and headache compared with patients receiving diazepam 10 mg with a similar dosing schedule.

Dosing and initiation of pregabalin

Dosing of PGB can be suited for the individual patient, based on use of other medications, CLCr and their history of prior tolerability to medications. Patients who have a history of developing AEs due to small doses of other medications may have similar reactions to PGB. Starting doses should be 75 mg orally every night at bedtime or 75 mg orally twice a day, with this dose increased gradually as tolerated to a dose of 150 mg orally twice a day over 1–2 weeks based on efficacy. For most patients, PGB is most effective when dosing is optimized at 300 or 600 mg/day, although some patients may do well with lower doses. In general, higher doses of PGB are more likely to be intolerable. If sufficient pain relief is not achieved after 2–4 weeks of treatment using 300–600 mg/day, or if intolerability develops with doses between 75 and 600 mg/day, then these patients should discontinue PGB.

Clinical implications and clinical study outcomes

For patients with painful DPN and PHN, several studies have investigated the potential of PGB for pain relief efficacy and tolerability. For DPN, PGB has been studied through seven randomized, double-blind clinical trials. A total of three meta-analyses or pooled analyses have been performed to study the use of PGB for the treatment of DPN. Doses higher than 150 mg/day are generally suggested for PGB efficacy. This is supported by single studies demonstrating that doses of PGB of up to 150 mg/day are consistently inefficacious; however, a pooled analysis has shown that PGB at doses of 150, 300 or 600 mg/day is significantly better than placebo for patients with DPN. A number needed to treat (NNT) for responders was calculated to be six and four for PGB 300 and 600 mg/day respectively. For this pooled analysis, the onset of sustained improvement in pain had a median time of 4–5 days.

Table 3. Important randomized clinical studies of pregabalin for the treatment of NeP conditions.

Study design	PGB/comparator dosing and (patient number)	Primary outcome measure(s)	Results (95% CI) (*p* value)	50% responders (%)	Dropouts due to AEs (%)
Double blind, 8 weeks	PGB 300 (76)	Difference in mean pain score from placebo	−1.47 (−2.19 to −0.75) (0.0001)	40 (0.001)	10.5
	PBO (70)			14.5	2.9
Double blind, 5 weeks	PGB 75 (77)	Difference in mean pain score from placebo	−0.15 (−0.76 to 0.46) (0.63)	18	2.6
	PGB 300 (81)		−1.26 (−1.86 to −0.65) (0.0001)	46 (S)	3.7
	PGB 600 (82)		−1.45 (−2.06 to	48 (S)	12.2

			−0.85) (0.0001)		
	Placebo (97)			18	3.1
Double blind, 6 weeks	PGB 150 (79)	Difference in mean pain score from placebo	−0.440 (−1.080 to 0.199) (0.18)	19	2.5
	PGB 600 (82)		−1.264 (−1.890 to −0.639) (0.0002)	39 (S)	8.5
	Placebo (85)			15	4.7
Double blind, 12 weeks	PGB 150 (99)	Difference in mean pain score from placebo	−0.27 (−0.87 to 0.34) (0.75)	34.4	5.1
	PGB 300 (99)		−0.10 (−0.70 to 0.50) (0.75)	33.3	11.1
	PGB 300/600 (101)		−0.91 (−1.51 to −0.31) (0.01)	45.9 (S)	12.9
	Placebo (96)			30.1	3.1
Double blind, 13 weeks	PGB 150–600 (82)	Difference in mean pain score from placebo	−1.28 (−1.96 to −0.60) (0.0003)	49 (S)	17.1
	Placebo (85)			23	11.8
Double blind,	PGB 150–600 (48)	Difference in median pain score	40 (30–60)	48	12.5

crossover, 14 weeks					
	AMT 10–50 (47)		42.5 (30–57) (0.87)	34	36.2
Double blind, 14 weeks	PGB 300 (136)	Difference in mean pain score from placebo	−0.63 (−1.09 to −0.17) (0.0075)	29.1 (S)	7.5
	PGB 600 (45)		−0.74 −1.39 to −0.09) (0.0254)	35.6 (S)	26.7
	Placebo (136)			21.5	4.4
Double blind, 8 weeks	PGB 300/600 (89)	Difference in mean pain score from placebo	−1.69 (−2.33 to −1.05) (0.0001)	50 (S)	31.5
	Placebo (84)			20	4.8
Double blind, 8 weeks	PGB 150 (81)	Difference in mean pain score from placebo	−1.20 (−1.81 to −0.58) (0.0002)	26 (S)	11.1
	PGB 300 (76)		−1.57 (−2.20 to −0.95) (0.0001)	28 (S)	15.8
	Placebo (81)			10	9.9
Double blind, 13 weeks	PGB 150 (87)	Difference in mean pain score from placebo	−0.88 −1.53 to −0.23) (0.0077)	26.4 (S)	8.0
	PGB 300 (98)		−1.07 (−1.70 to	26.5 (S)	15.3

			−0.45) (0.0016)		
	PGB 300/600 (90)		−1.79 (−2.43 to −1.15) (0.0003)	37.5 (S)	21.1
	Placebo (93)			7.5	5.4
Double blind, 4 weeks	PGB 150–600 (91)	Median time to onset of pain relief	3.5 days (<0.0001)	46.7 (S)	4.4
	PGB 300 (88)		1.5 days (<0.0001)	39.8 (S)	18.2
	Placebo (90)		Not achieved	18.4	4.4
Open comparative study, 8 weeks	AMT 25 (15)	% satisfactory	13.4		
	PGB 150 (15)	improvement of pain	53.3		
	AMT 25 + PBG 150 (15)	(>75%)	73.3 (<0.05)		
Open label, 4 weeks	(1) PGB 300 + TENS (8)	Difference in mean pain score between groups	(1–2): −13.88 (−15.22 to −12.55)	0	
	(2) PGB 300 + TENS placebo (8)		(<0.0001)	0	
	(3) PGB 600 + TENS (7)		(1–3): 1.53 (0.15–2.92) (0.02)	0	

	(4) PGB 600 + TENS placebo (6)		(1–4): −7.55 (−8.99 to −6.11) (<0.0001)	0	
			(2–3): 15.42 (14.0–16.84) (<0.0001)		
			(2–4): 6.33 (4.85–7.81) (<0.0001)		
			(3–4): −9.09 (−10.61 to −7.57) (<0.0001)		
Open label, 4 weeks	5% LIDO (50)	Percentage of response	63.3	35.6	6
	PGB 150–600 (48)	(change from baseline ≥ 2 points or score ≤ 4 points in NRS)	46.8	20.9	6.25
Open label, 8 weeks	5% LIDO (25)	Difference in pain level compared with combination	−11.8		4

		phase at baseline			
	5% LIDO + PGB 150–600 (18)		−27.8		16.67
	PGB 150–600 (14)		−5.4		7.14
	PGB 150–600 + 5% LIDO (17)		−33.7		11.76
Double blind, 12 weeks	PGB	Difference in mean pain score from placebo	1.53 (0.92–2.15) (<0.001)	22 (S)	21
	150–600 (70)			8	13
	Placebo (67)				
Double blind, 4 weeks	PGB	Difference in mean pain score from placebo	2.18 (0.57–3.80) (0.01)	35 (S)	15
	150–600 (20)			5	15
	Placebo (20)				
Double blind, 13 weeks	PGB	Difference in mean pain score from placebo	−0.2 (−0.7 to 0.4) (0.578)		8.2
	150–600 (110)				3.7
	Placebo (109)				
Double blind, 17 weeks	PGB 150–600 (110)	Duration-adjusted difference in mean pain score from placebo	−0.69 (−0.98 to −0.2) (0.003)		19.1
	Placebo (109)				8.7

Double blind, 12 weeks	PGB 150–600 (141)	Difference in mean pain score from placebo	−1.17 (1.90 to −0.45) (0.002)–1.38 (−2.11 to −0.65) (<0.001)	48.2 (S)	17.0
DPN, PHN subjects	PGB 600 (132)			52.3 (S)	25.0
	PBO (65)			24.2	7.7
Open label, 12 weeks	5% LIDO (79)	Mean change in pain score during the combination phase	−0.7±1.2		1.3
	5% LIDO + PGB 150–600 (60)		−2.5±1.6		11.7
	PGB 150–600 (63)		−0.6±1.3		1.6
	PGB 150–600 + 5% LIDO (48)		−1.7±1.8		10.4
Double blind, 4 weeks	PGB 75-600 + OXY 10 (24)	Percentage of response	69	58	4.2
	PGB 75–600 + placebo (29)		76 (0.581)	66	3.4
Double blind, 6 weeks	PGB 150–600 (218)	Percentage of response	47.2		
	Placebo (106)		35.8 (0.07)		
Double blind, 8 weeks	PGB 150–600 (127)	Difference in mean pain	−0.62 −1.09 to	39.7 (S)	20

		score from placebo	−0.15) (0.01)		
	Placebo (127)			25.4	7
Double blind, crossover, 2 weeks	PGB 300 (25)	Difference in mean pain score from placebo	−0.81 (−1.45 to −0.17) (0.02)		4
	Placebo (25)				4
Double blind, 14 weeks	PGB 150–600 (151)	Difference in mean pain score from placebo	−0.25 (0.39)	38.9	6
	Placebo (151)			42.8	2.6
Double blind, 10 weeks	PGB 150–600 (162)	Difference in mean pain score from placebo	−0.50 (−1.00 to 0.00) (0.049)	26.1 (S)	5
	Placebo (78)			14.3	7.7
Double blind, 4 weeks	PGB 150–600 (46)	Mean change in sharp and hot pain on the NPS	'Sharp pain' p = 0.04; 'hot pain' p = 0.01		6.52
	Placebo (44)				6.82

AMT, amitriptyline; LIDO, lidocaine; NPS, neuropathic pain scale; NRS, numerical rating scale; OXY, oxycodone; PGB, pregabalin; (S), indicates statistical significance was achieved with respect to this dose of medication in this particular study; TENS, transcutaneous electric nerve stimulation.

Comparisons of PGB with other NeP agents have been performed. Flexible dosing of PGB at 150–600 mg/day provided greater responders (48% *versus* 34%), better tolerability and fewer

dropouts due to AEs than with amitriptyline, a tricyclic antidepressant (at 10–50 mg/day), but overall efficacy was similar. Comparisons between amitriptyline, duloxetine and PGB have shown similar efficacies in pain relief, with better sleep efficacy but more AEs occurring with PGB compared with the other two agents. As a final point, a recent meta-analysis indirectly compared PGB with duloxetine, a selective serotonergic noradrenergic uptake inhibitor, from three studies of duloxetine and six studies evaluating PGB, and found no difference between these two pharmacotherapies for improvement of 24 h pain severity. While PGB was superior to duloxetine for improving the patient's global impression of change, it led to more dizziness. A recently presented study examined the use of PGB, duloxetine or both in treatment of DPN. There did not appear to be any beneficial additive effect of combining these two separately acting pharmacotherapies, while indirect comparisons suggested that duloxetine treatment provided greater average pain relief upon the Brief Pain Inventory average pain outcome measure than PGB. Further comparison studies will be important in future to determine the role of PGB and other potential first-line therapies for the treatment of NeP.

In addition to the large number of studies of patients with DPN, there have been several randomized, controlled trials examining the efficacy of PGB in patients with PHN. A total of four trials have compared PGB at fixed doses of 150, 300 and 600 mg/day with placebo. A large retrospective analysis of nine placebo-controlled trials of PGB in patients with DPN or PHN identified patients responding to PGB to achieve this response by the end of only 2 days of treatment. PGB has also been compared with active comparators, including lidocaine 5% topical solution, amitriptyline, transcutaneous electric nerve stimulation and 5% topical lidocaine (for each of which PGB was found inferior). For the placebo-controlled trials, all doses of PGB were effective, with responder rates escalating based upon dose: 26% with 150 mg/day of PGB, 26–39% with 300 mg/day and 47–50% with 300–600 mg/day]. Overall, these results are supported by a meta-analysis of randomized, controlled trials of PGB for acute and chronic pain supports efficacy of PGB for PHN management.

Low back pain may be the most common cause of chronic pain, affecting 15–45% of the general population. Although often mechanical and nociceptive in nature, neuropathic components are present in 20–35% of this population. Two randomized, controlled studies evaluated efficacy and tolerability of PGB in patients with low back pain, demonstrating both efficacy and tolerability of PGB, the cyclooxygenase inhibitor celecoxib or their combination over 12 weeks of treatment using a double-blind design. A double-blind, placebo-substitution study evaluated the time to loss of pain relief response in patients with lumbosacral

radiculopathy causing low back pain whose condition had previously responded to PGB using a single-blind, 4-week exposure to PG. However, in the double-blind study phase, PGB and placebo were similar in time to lost response.

Some conditions causing central NeP, pain arising from lesions of the central nervous system, have also been examined for PGB efficacy. These conditions included spinal cord injury, multiple sclerosis or stroke. Studies to date have shown that flexible dosing permitted a significantly greater reduction in pain for patients treated with PGB compared with placebo for two of three studies performed. Another randomized, placebo-controlled study examining flexible dose PGB for patients with poststroke pain demonstrated no benefits upon pain relief, but PGB improved secondary outcomes, including anxiety, sleep and the clinician's global impression of change measurement. Two studies have appraised pain relief with PGB for pain associated with spinal cord injury, also demonstrating positive efficacy.

Post-traumatic NeP is possibly more refractory than other causes of NeP. Studies to date have identified PGB to have pain relief efficacy with good tolerance. More general studies examining the use of PGB in the management of a variety of NeP conditions including peripheral neuropathy, radiculopathy and trigeminal neuralgia.

As alluded to above, there are some subtle differences between PGB and GBP that may prompt clinical questions about superiority. This question occurs in an absence of any high-quality head-to-head randomized clinical trials examining PGB and GBP. There are some observational studies that have suggested that PGB may have some superior features to GBP. A *post hoc* analysis of two multicenter, prospective, 12-week studies comparing PGB and GBP for patients with DPN, PHN, trigeminal neuralgia and radiculopathy showed a greater reduction in the last-week mean pain score and a higher number of responders when PGB was provided. In addition, there were reduced healthcare costs when PGB was used, and more patients treated with PGB achieved therapeutic dose levels than patients treated with GBP. This may relate to many physicians feeling uncomfortable with GBP dosing, and a lack of understanding about appropriate dosing levels with GBP. For patients with partial epilepsy, a meta-analysis of randomized controlled trials of PGB and GBP found that PGB had improved response rates at doses of 300–600 mg compared with GBP at 1200–1800 mg. Furthermore, in generalized anxiety disorder patients, benzodiazepine use was reduced more readily in patients receiving PGB as compared to patients receiving GBP. PGB's use in generalized anxiety

disorder is also useful to reference when PGB is to be used in patients with NeP and generalized anxiety disorder.

Safety evaluation: adverse effects profile

In most published studies, PGB has been generally well tolerated, both in premarketing clinical studies and with postrelease studies. The majority of AEs experienced are noted to be mild or moderate in severity only. Often, these AEs are transient and present early on at initiation of therapies before later resolution, suggesting that they are self limited. When present after initiation, AEs may dissipate over the first 2–4 weeks of use. Overall, AEs due to PGB are usually tolerated and associated with PGB dose received. AE profiles with PGB appear to be comparable among all patient populations for incidence; this holds true for sex and for ag.

Table 4. Most common adverse events by treatment group, age, and type of neuropathic pain.

		Placebo, *n* (%)		**Pregabalin 150 mg/day, *n* (%)**		**Pregabalin 300 mg/day, *n* (%)**		**Pregabalin 600 mg/day, *n* (%)**	
Adverse effect	**Age range (years)**	**DPN**	**PHN**	**DPN**	**PHN**	**DPN**	**PHN**	**DPN**	**PHN**
		(*n* = 558)	**(*n* = 363)**	**(*n* = 176)**	**(*n* = 251)**	**(*n* = 266)**	**(*n* = 230)**	**(*n* = 513)**	**(*n* = 159)**
Dizziness	18–64	16 (4.4)	9 (13.2)	7 (5.5)	4 (7.0)	40 (22.0)	11 (24.0)	85 (24.7)	23 (48.9)
	65–74	8 (5.1)	10 (7.0)	3 (7.7)	13 (14.1)	16 (25.8)	25 (39.1)	46 (33.1)	25 (36.2)
	≥75	2 (5.9)	17 (11.2)	2 (20.0)	22 (21.6)	6 (27.3)	37 (30.6)	11 (36.7)	13 (30.2)
Somnolence / sedation	18–64	14 (3.8)	5 (7.4)	5 (3.9)	7 (12.3)	24 (13.2)	3 (6.7)	45 (13.1)	13 (27.7)

	65–74	2 (1.3)	5 (3.5)	2 (5.1)	9 (9.8)	11 (17.7)	14 (21.9)	16 (11.5)	20 (29.0)
	≥75	0	10 (6.6)	2 (20.0)	12 (11.8)	3 (13.6)	25 (20.7)	7 (23.3)	11 (25.6)
Peripheral edema	18–64	27 (7.4)	2 (2.9)	6 (4.7)	3 (5.3)	15 (8.2)	3 (6.7)	53 (15.4)	6 (12.8)
	65–74	10 (6.3)	6 (4.2)	3 (7.7)	9 (9.8)	9 (14.5)	8 (12.5)	24 (17.3)	12 (17.4)
	≥75	3 (8.8)	6 (3.9)	1 (10.0)	7 (6.9)	2 (9.1)	24 (19.8)	5 (16.7)	4 (9.3)
Infection	18–64	25 (6.8)	2 (2.9)	10 (7.9)	9 (15.8)	17 (9.3)	4 (8.9)	10 (2.9)	1 (2.1)
	65–74	8 (5.1)	7 (4.9)	4 (10.3)	7 (7.6)	5 (8.1)	3 (4.7)	6 (4.3)	1 (1.4)
	≥75	2 (5.9)	3 (2.0)	0	6 (5.9)	1 (4.5)	11 (9.1)	1 (3.3)	2 (4.7)
Dry mouth	18–64	6 (1.6)	2 (2.9)	1 (0.8)	5 (8.8)	6 (3.3)	0	18 (5.2)	8 (17.0)
	65–74	1 (0.6)	6 (4.2)	0	9 (9.8)	4 (6.5)	6 (9.4)	10 (7.2)	9 (13.0)
	≥75	0	5 (3.3)	2 (20.0)	5 (4.9)	3 (13.6)	8 (6.6)	2 (6.7)	6 (14.0)
Weight gain	18–64	3 (0.8)	1 (1.5)	6 (4.7)	3 (5.3)	9 (4.9)	4 (8.9)	34 (9.9)	5 (10.6)
	65–74	1 (0.6)	2 (1.4)	1 (2.6)	1 (1.1)	1 (1.6)	2 (3.1)	10 (7.2)	9 (13.0)
	≥75	1 (2.9)	0	1 (10.0)	1 (1.0)	0	8 (6.6)	1 (3.3)	5 (11.6)

It is unknown whether AEs with PGB differ from those with GBP, as there are no head-to-head comparisons of the two agents. While most of the studies examining GBP featured variable dosing, most PGB trials have used fixed dosing without titration. These differences in study designs could impact upon incidences of AEs found in published studies. Despite these

differences in trial design, reviewing the available studies demonstrates that AE profiles look quite similar. It is possible that GBP may more frequently lead to nausea and diarrhea, but this is uncertain.

Duloxetine[1]

Duloxetine hydrochloride, (+)-(S)-N-methyl-gamma-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride, is a selective serotonin and norepinephrine reuptake inhibitor, with molecular weight of 333.88. It is slightly soluble in water and exists as a white to slightly brownish-white solid.

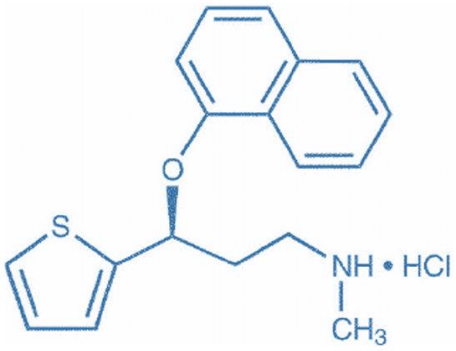


Figure 1. Chemical structure of duloxetine.

Pharmacodynamic profile

Duloxetine is a selective inhibitor of both serotonin (5-HT) and norepinephrine (NE) reuptake, and is classified as a selective serotonin norepinephrine reuptake inhibitor (SNRI). It possesses central pain inhibitory actions, probably related to its potentiation of serotonergic and noradrenergic activity in the CNS. Both 5-HT and NE have important neurotransmission activities in the descending pain inhibition pathways of the brainstem and spinal cord. Furthermore, these neurotransmitters are felt to act in a synergistic manner to reduce the transmission of pain signals from the periphery to the CNS. Duloxetine has been shown to be effective in animal models of persistent pain, including neuropathic pain. Presumably the analgesic effect of duloxetine is related to augmentation of 5-HT and NE mediated inhibitory pain pathways resulting in the decreased perception of pain.

Importantly, duloxetine has been demonstrated to have no significant activity at muscarinic, histamine-1, α1-adrenergic, dopaminergic, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, and opioid receptors. Furthermore, duloxetine has been demonstrated to have no activity on ion channels including Na^+ channels. It has, however, been shown to have balanced activity as an inhibitor of 5-HT and NE reuptake with very low activity on dopamine reuptake. Based on what is known about the activity of endogenous inhibitory pathways, a compound with these actions could possibly have good efficacy in treatment of neuropathic pain processes and possess an acceptable side-effect profile.

Duloxetine has been studied extensively in pre-clinical animal models of both persistent neuropathic pain and acute nociceptive pain. Its activity was compared in these experiments to that of a selective serotonin reuptake inhibitor (paroxetine); norepinephrine reuptake inhibitors (thionisoxetine and desipramine), and other SNRIs (venlafaxine, milnacipran, amitriptyline). In the neuropathic pain study paradigms (the formalin model and the L5/L6 nerve ligation model, both in rats), the performance of duloxetine was numerically greater (although not statistically superior) to the comparator drugs at doses which did not lead to neurologic side effects. However, duloxetine did not demonstrate efficacy in the tail-flick model of nociceptive pain, indicating a lack of a primary analgesic or anesthetic effect of the drug. These data demonstrate that duloxetine has potential for the treatment of persistent neuropathic pain owing to its ability to inhibit both 5-HT and NE reuptake.

Duloxetine has several putative phase I metabolites, including 4-hydroxy-, 5-hydroxy-, 6-hydroxy-, 5-hydroxy-6-methoxy-, 6-methoxy-5-hydroxy-, 5,6-dihydroxy-, and 4,6-dihydroxyduloxetine, as well as phase II glucuronide and sulfate conjugates. In vitro binding studies have shown that none of these circulating metabolites contributes significantly to the pharmacologic activity of duloxetine.

Pharmaceutics

Duloxetine is available in capsules which contain enteric-coated pellets of duloxetine hydrochloride. The drug is degradable in the acidic milieu of the stomach, which necessitates the enteric coated pellets to allow the compound to be principally absorbed in the small intestine. It is extremely important that capsules of duloxetine not be chewed or crushed thereby compromising the integrity of the enteric coating. The capsules are marketed containing 22.4, 33.7, and 67.3 mg of duloxetine hydrochloride to provide equivalent doses of 20, 30, and 60

mg of duloxetine respectively. There are a few inactive ingredients in the capsules, including: FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 and 60 mg capsules contain iron oxide yellow as well.

Pharmacokinetics

Absorption

Following administration of duloxetine hydrochloride there is a 2 hour delay in absorption, owing to the enteric coated pellets previously discussed. It is then well-absorbed, achieving maximal plasma concentrations (C_{max}) about 6 hours post dosing (time to maximal concentration, or T_{max}). Steady state plasma concentrations are usually accomplished about 3 days after initiation of therapy. The C_{max} for duloxetine is not affected by food, but the T_{max} is prolonged from 6 hours to 10 hours when given with the food present in the gastrointestinal tract. Furthermore, the overall extent of absorption (area under the curve, or AUC) is reduced by about 10% when administered with food. Studies demonstrate a 3 hour delay in absorption of drug in the evening dose as compared to that of the morning dose.

Distribution

The apparent volume of distribution (VD) of duloxetine is known to be 1640 L. It is highly bound to plasma proteins (>90%), but the interactions between this drug and other highly plasma protein-bound compounds have not been adequately studied. The principal proteins involved in the binding of duloxetine include albumin and α1-acid glycoprotein. The plasma protein binding of duloxetine is not significantly affected by hepatic or renal insufficiency.

Metabolism

The elimination half-life ($t_{1/2}$) of duloxetine is about 12 hours (range: 8–17 hours). It undergoes extensive hepatic metabolism to inactive compounds. This is mostly carried out by the cytochrome P-450 isoenzymes, 2D6 and 1A2, which catalyze the oxidation of the naphthyl ring. These metabolites are subsequently conjugated and then either eliminated or oxidized further prior to elimination. There are many apparent metabolites as previously discussed, but the two major ones are 4-hydroxy-duloxetine glucuronide and 5-hydroxy-6-methoxy-duloxetine sulfate. All others represent only minor routes of transformation.

Elimination

Less than 1% of the given dose of duloxetine appears in the urine as unchanged parent drug. About 70% of the dose appears in the urine as inactive metabolites. Only about 20% is eliminated in the feces.

Interactions with other drugs

Since the principal metabolism pathways of duloxetine are through the cytochrome P450 isoenzymes 1A2 and 2D6 (CYP1A2 and CYP2D6), it would be anticipated that drugs that interfere with or alter the activity of these hepatic enzymes would potentially alter the blood levels of duloxetine in the patient to which the drugs were co-administered. Since duloxetine is not a substrate, inhibitor, or inducer of the important CYP3A4, there are no concerns regarding co-administration with drugs known to affect that metabolic enzyme, such as macrolide antibiotics or antifungal agents. Duloxetine has no important or measurable effects on and is not a substrate for monoamine oxidase. However, because serious problems have resulted from the co-administration of SSRI with a monoamine oxidase inhibitor (MAOI), duloxetine should not be given in combination with any MAOI or within 2 weeks of discontinuing an MAOI. Further, an MAOI should not be started within 5 days of discontinuing duloxetine. Clinically speaking, there are only a few other concerns of note that involve drugs handled by the CYP1A2 and CYP2D6 systems that require attention by the prescriber.

Inhibitors of CYP1A2

Pharmacokinetic studies looked at the interaction between duloxetine and fluvoxamine, a known potent inhibitor of CYP1A2. The results demonstrated a 5-fold increase in the AUC for duloxetine and a 2.5-fold in the C_{max}. The $t_{1/2}$ of duloxetine was increased approximately 3-fold. Other drugs known to inhibit CYP1A2 include cimetidine and quinolone antibiotics such as ciprofloxacin.

Inhibitors of CYP2D6

Paroxetine is a moderate inhibitor of CYP2D6. A pharmacokinetic study was done looking at the serum concentration curves of duloxetine when concomitantly administered with low to moderate doses of paroxetine (20 mg), showing increases in both the AUC and C_{max} of 60%

for duloxetine. Other medications with similar actions on CYP2D6, such as fluoxetine and quinidine, would be expected to have similar effects on the concentration of duloxetine and should be used with caution together with this drug.

Drugs metabolized by CYP1A2

Duloxetine has no ability to induce CYP1A2, but is known to have mild inhibitory effects on the enzyme in vitro. In clinical pharmacokinetic studies, there were no significant effects seen in the concentration of CYP1A2 substrates such as theophylline when co administered with duloxetine given 60 mg bid. Therefore, duloxetine is not felt to have significant effects on drugs metabolized by the CYP1A2 system.

Drugs metabolized by CYP2D6

Duloxetine is a moderate inhibitor of the actions of CYP2D6 and requires caution when co-administering agents metabolized by that system. Duloxetine has been shown to increase the AUC of desipramine 2.9-fold and its C_{max} by 70% when coadministered. Because of this effect, certain other drugs including other TCAs (nortriptyline, amitriptyline, and imipramine), phenothiazines, and type 1C anti-arrhythmics (flecainide, propafenone) should be administered at a lower dose than usual and monitored carefully. Because of the risk of fatal arrhythmia, duloxetine should not be co-administered with thioridazine under any circumstance.

Other drug–drug interaction concerns

There are theoretical concerns that the co-administration of duloxetine with medications that raise the gastrointestinal pH could result in a hastened dissolution of the enteric coating of the pellets of duloxetine. The concern would be that the drug might be more readily and rapidly absorbed under these conditions. However, co-administration studies done with aluminum and magnesium hydroxide suspension and with famotidine showed no change in the pharmacokinetics of a 40 mg dose of duloxetine. Studies have not been conducted with proton pump inhibitors.

Any CNS-acting medication should be used with caution when administered to patients already on other CNS-acting medications. Sedation or other impairment of CNS functioning could occur sporadically and without warning in individual patients. Therefore cautious use is warranted. Specific pharmacokinetic interactions with benzodiazepines have not been

demonstrated in studies. There appears to be no significant interaction with alcohol on initial evaluation.

Clinical efficacy

The clinical efficacy of duloxetine for pain associated with diabetic peripheral neuropathy has been demonstrated in three double-blind, placebo-controlled, randomized studies. These studies (n = 1139) were 12-week fixed-dose trials ( ) that enrolled Type I or Type II diabetics with painful diabetic neuropathy for greater than 6 months duration with at least moderate 24-hour pain severity. All three trials randomized participants to a duloxetine 60 mg qd, duloxetine 60 mg bid, or placebo treatment arm. The primary efficacy end point for all studies was mean change on average daily pain severity (measured using an 11-point Likert-type pain scale from baseline to the end of the 12-week dosing period. Secondary endpoints included other pain diary outcomes (24-hour worst pain, night pain), clinician/patient global impressions (CGI, PGI), scales from the Brief Pain Inventory (BPI), a QOL measure (Short Form-McGill Pain Questionniare; SF-MPQ), dynamic allodynia, and the Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$).

Participant profile and weekly outcomes

Table 5 shows the baseline characteristics of patients for all studies. A total of 77.8% of subjects completed the trials. In all 3 trials, subjects in the duloxetine 60 mg qd or 60 mg bid treatment arm reported a greater decrease in 24-hour average pain severity relative to placebo after the first week and this effect was maintained throughout the 12-week dosing period. In the Goldstein et al (2005) trial, subjects in the 20 mg arm did not show significant pain reduction relative to placebo. In all 3 studies, the reduction in 24-hour average pain severity was consistent with a dose dependent response.

Table 5. Baseline characteristics of patients

		Mean or percentage	SD
Age		59.88	10.57
Female		43%	
Race			
	Caucasian	84%	
	African-American	4%	
	Hispanic	9%	
	Other	3%	
Weight (kg)		94.38	21.12
Diabetes Type			
	Type I	12%	
	Type II	88%	
Years with diabetes		11.74	9.45
Years with diabetic neuropathy		3.91	4.10
Michigan Neuropathy		5.26	1.54
Screening Instrument			
Average 24 hour Pain Severity		5.87	1.45
CGI- Severity		4.49	0.87
HAM-D_{17} Total Score		3.66	3.20

Abbreviations: CGI, Clinical Global Impression; SD, standard deviation; HAM-D_{17}, 17-item Hamilton Depression Rating Scale.

Table 6. Mean change and 95% CI for mean difference between treatment arm and placebo from baseline on secondary outcome measures

	placebo mean change	**Duloxetine 60 mg qd Mean change (95% CI of difference from placebo)**	**Duloxetine 60 mg bid Mean change (95% CI of difference from placebo)**
CGI severity	−0.91	−1.40*	−1.52*
Diff. from placebo (95% CI)		−0.49 (−0.66, −0.32)	−0.61 (−0.79, −0.43)
PGI improvement	3.04	2.44	2.39
Diff. from placebo (95% CI)		−0.60 (−1.46, 0.27)	−0.65 (−1.45, 0.17)
SF-MPQ total	−4.86	−7.64*	−8.32*
Diff. from placebo (95% CI)		−2.79 (−3.83, −1.74)	−3.46 (−4.51, −2.41)
Dynamic allodynia	−0.10	−0.16*	−0.14
Diff. from placebo (95% CI)		−0.06 (−0.12, −0.03)	−0.04 (−0.09, 0.02)
HAM-D_{17} Total Score	−0.59	−0.92	−0.23
Diff. from placebo (95% CI)		−0.33 (−0.71, 0.06)	0.36 (−0.03, 0.76)

*$p < 0.05$. **Abbreviations:** BPI, Brief Pain Inventory; CGI, Clinical Global Impression; PGI, Patient's Global Impression; SF-MPQ, Short Form McGill Pain Questionnaire; HAM-D_{17}, 17-item Hamilton Depression Rating Scale.

Looking at ES allows the reader to better ascertain the magnitude of group differences as well as provide a hint of whether this difference is considered "clinically relevant" (where higher

ES is reflective of a greater clinical relevance). By convention, Cohen's d <0.2 = negligible difference; 0.2–0.49 = small; 0.5–0.79 = medium; ≥0.8 = large. The table shows that there was a medium effect for improvement in average 24-hour pain for both treatment arms relative to placebo. There also was a medium ES seen when comparing change in the duloxetine 60 mg bid and placebo arms for the following: 24-hour worst pain, BPI severity, CGI, and SF-MPQ. There was a small ES seen when comparing change in the duloxetine 60 mg bid and placebo arms for the following: night pain, BPI general activity and BPI interference. There was a small ES seen when comparing change in the duloxetine 60 mg qd arms and placebo for the following: 24-hour worst pain, night pain, BPI severity, BPI general activity, BPI interference, CGI, and SF-MPQ. There was also a statistically significant difference between change in dynamic allodynia between the duloxetine 60 mg qd and placebo arms; however, the ES was considered negligible and is thus of little or no clinical relevance.

Table 7. Effect sizes for mean differences comparing duloxetine 60 mg qd and 60 mg bid with placebo

	60 mg qd vs placebo(99% CI)	**60 mg bid vs Placebo (99% CI)**
24-hour average pain score	0.51** (0.28, 0.75)	0.56** (0.32, 0.80)
24-hour worst pain score	0.47* (0.21, 0.73)	0.53** (0.27, 0.79)
Night pain score	0.40* (0.15, 0.65)	0.48* (0.22, 0.73)
BPI severity	0.42* (0.18, 0.66)	0.51** (0.26, 0.75)
BPI general activity	0.32* (0.07, 0.57)	0.39* (0.14, 0.64)
BPI interference	0.37* (0.17, 0.57)	0.46* (0.25, 0.66)
CGI severity	0.44* (0.32, 0.56)	0.53** (0.40, 0.65)
PGI improvement	N/A	N/A
SF-MPQ total	0.43* (0.03, 1.18)	0.53** (0.05, 1.28)
Dynamic Allodynia	0.17	NA
HAM-D$_{17}$ Total Score	(0.13, 0.21) N/A	N/A

*small effect

medium effect, * large effect; N/A = no significant difference on that measure between that treatment arm and placebo.

Effect sizes were calculated using Cohen's d. By convention, Cohen's d < 0.2 = negligible difference; 0.2−0.49 = small; 0.5−0.79 = medium; ≥0.8 = large.

Abbreviations: BPI, Brief Pain Inventory; CGI, Clinical Global Impression; PGI, Patient's Global Impression; SF-MPQ, Short Form McGill Pain Questionnaire; HAM-D_{17}, 17-item Hamilton Depression Rating Scale.

The investigators in all three studies concluded that duloxetine 60 mg qd and 60 mg bid were effective for treating pain associated with diabetic neuropathy. All three studies argued that the data confirmed the proposed role of 5-HT and NE as key mediators of descending pain pathways. They also suggested that 5-HT and NE reuptake inhibition by duloxetine may offer an effective and safe alternative for the treatment of persistent pain states. Moreover, since differences in pain did not correlate with changes in mood (as measured by change in the HAM-D_{17}) and patients with MDD were excluded, it was apparent that the pain relief was not due to improvement in depression.

Safety and tolerability

Safety and tolerability of controlled trials

Safety and tolerability was evaluated for all three controlled trials as well as three long term (52 week) open label studies. We will first report the safety and tolerability findings of the blinded trials. Overall, 67/339 (19.7%) discontinued during the study period. In regards to serious adverse events (SAEs), a total of 41/1139 (3.6%) patients reported at least one SAE; however, SAEs did not differ among groups. The only group difference was for high density lipoprotein (HDL) between the duloxetine 60 mg bid and placebo treatment arms; however, the difference (0.027) is not clinically significant.

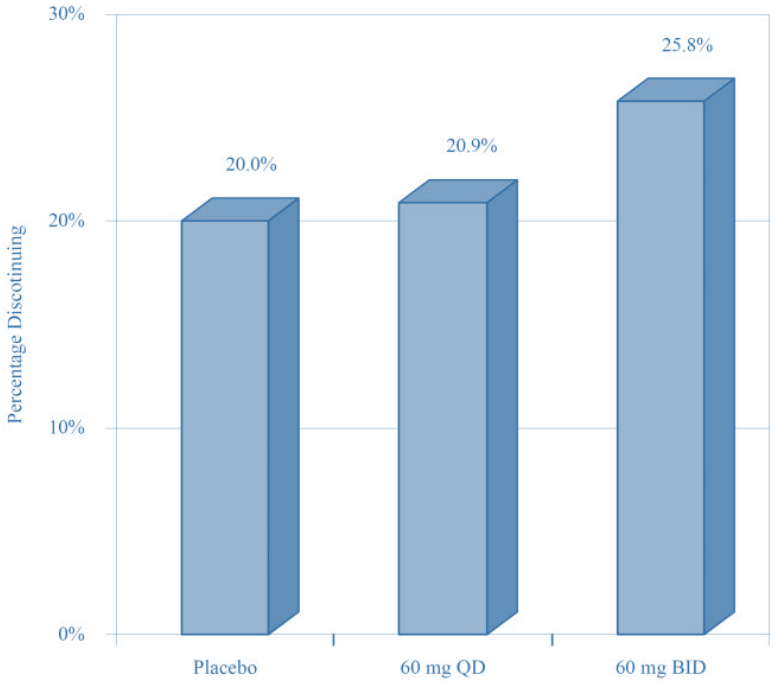


Figure 2. Percentage of patients discontinuing treatment per arm.

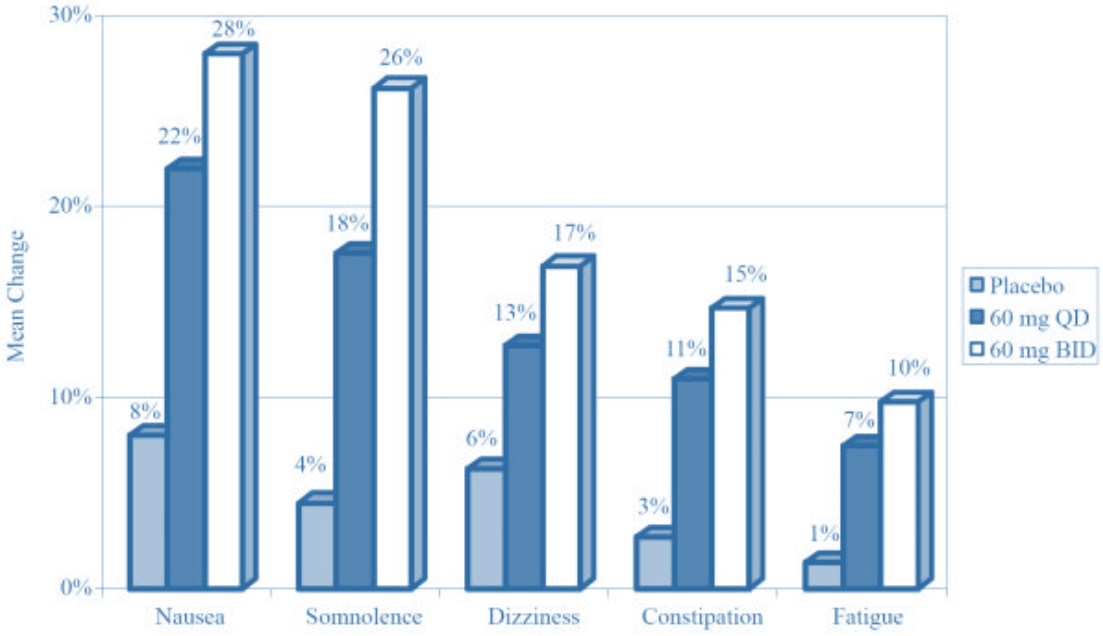


Figure 3. Treatment-emergent adverse events in controlled trials

Table 8. Mean change in HbA_{1c} and lipid profile from baseline to end point for controlled trials

	Placebo	Duloxetine 60 mg qd	Duloxetine 60 mg bid
HbA_{1c} (%)	−0.001	−0.001	<0.0004
HDL cholesterol (mmol/L)	0.012	0.014	0.039*
LDL cholesterol (mmol/L)	0.012	0.007	0.052
Triglycerides (mmol/L)	0.12	0.24	−0.25

*$p < 0.05$ indicating difference between 60 mg bid and placebo. **Abbreviations**: HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lypoprotein.

Safety and tolerability of long-term open label trials

Discontinuation and adverse events

Within the long-term open label trials participants were assigned to either a duloxetine 60 mg bid or routine care arm (at a 2:1 ratio, respectively). The completion rate was 77.6% (450/580) for the duloxetine 60 mg bid arm and 83.6% (240/287) for the routine care arm. A total of 150/867 (17.3%) patients reported at least one SAE; however, SAEs did not differ between arms. A total of 6.3% (18/287) in the routine care arm discontinued due to a SAE compared with 10.2% (77/689) in the duloxetine 60 mg bid arm (this difference was not significant). Raskin et al. and Wernicke et al (2007) reported no significant group differences for TEAEs. Wernicke et al (2006) reported 8 TEAEs that occurred more frequently in the routine care group. The only TEAE that was reported by >5% in the duloxetine 60 mg BID arm for all three studies was nausea. No TEAE was reported by >5% in the routine care arm for all three studies.

Analysis of chemistry/urinalysis

Significant differences were seen between groups on six laboratory values. Albumin g/L, alanine transaminase/serum glutamate pyruvate transaminase (ALT/SGPT) U/L, aspartate transaminase/serum glutamate oxaloacetic transaminase (AST/SGOT) U/L, total cholesterol mmol/L, gamma-glutamyl transferase (GGT) U/L, and fasting glucose all showed a greater increase among those in the duloxetine 60 mg bid arm relative to the increase among those in

the routine care arm. Further examination of the ES indicated that all of the differences were negligible except for glucose and cholesterol (where the ES was small).

Table 9. Mean change in chemistry/urinalysis profiles from baseline to end point for long-term open-label studies

	Routine care change	Duloxetine 60 mg bid mean change	Difference (95% CI of difference)
Albumin, g/L	−0.13	43.61	43.74* (12.31, 75.20)
Alkaline phosphate, U/L	2.32	4.78	2.46 (−0.09, 5.02)
ALT/SGPT, U/L	−1.85	0.47	2.32* (0.58, 4.06)
AST/SOGT, U/L	−1.70	0.23	1.93* (0.49, 3.37)
Bicarbonate, HCO_3, mmol/L	0.45	0.50	0.05 (−0.34, 0.44)
Bilirubin, total, µmol/L	−0.74	−0.80	−0.06 (−0.53, 0.40)
Calcium, mmol/L	0.01	0.01	<0.01 (−0.01, 0.02)
Chloride, mmol/L	0.60	−0.69	−1.29 (−1.85, 0.73)
Cholesterol, total, mmol/L	−0.18	0.07	0.25* (0.09, 0.40)
Creatine phosphokinase, U/L	−2.87	−4.28	−1.41 (−21.45, 18.62)
Creatinine, µmol/L	3.55	1.10	−2.45 (−4.78 0.11)
GGT, U/L	−3.69	0.56	4.27* (0.15, 8.37)
Glucose, fasting, mmol/L	−0.65	0.66	1.31* (0.63, 1.99)
Inorganic phosphorus, mmol/L	0.01	0.02	0.01 (−0.02, 0.04)
Potassium, mmol/L	0.02	0.02	<0.01 (−0.06, 0.07)
Protein, total, g/L	0.o57	0.49	−0.08 (−0.67, 0.50)
Sodium, mmol/L	0.16	−0.60	−0.76 (−1.27, 0.25)

Urea nitrogen, mmol/L	0.42	0.22	−0.20 (−0.50, 0.10)
Uric acid, µmol/L	17.53	−3.23	−20.30 (−30.22, 11.31)

*p < 0.05 **Abbreviations**: ALT/SPGT, alanine transaminase/serum glutamate pyruvate transaminase; AST/SOGT, aspartate transaminase/serum glutamate oxaloacetic transaminase; GGT, gamma-glutamyl transferase.

QOL measures

. A decrease on the SF-36 indicates a poorer QOL. Those in the routine care group showed greater decreases on all SF-36 subscales relative to change in the duloxetine 60 mg bid arm. These differences were significant for the bodily pain, physical component, and physical role subscales. In addition, those in the routine care arm had a significantly greater decrease from baseline to endpoint as measured by the European QOL (indicating a poorer QOL) scale relative to change among those in the duloxetine 60 mg bid arm. A decrease on the SF-36 scales and European QOL indicate a poorer QOL.

References:

1. Lehmann HC, Wunderlich G, Fink GR, Sommer C. Diagnosis of peripheral neuropathy. *Neurol Res Pract*. 2020;2:20.
2. Toth C. Pregabalin: latest safety evidence and clinical implications for the management of neuropathic pain. *Ther Adv Drug Saf*. 2014;5(1):38-56.
3. Smith T, Nicholson RA. Review of duloxetine in the management of diabetic peripheral neuropathic pain. *Vasc Health Risk Manag*. 2007;3(6):833-844.

Survey Form

1) In your clinical practice, what is the average age at which patients usually report to the hospital with symptoms of peripheral neuropathy?

a. 30-39 years
b. 40-49 years
c. 50-59 years
d. >60 years

2) What is the prevalence of peripheral neuropathy in your clinical practice?

a. <10%
b. 10-20%
c. 20-50%
d. >50%

3) In your clinical practice, what prevalence of diabetic peripheral neuropathy in patients of peripheral neuropathy?

a. <10%
b. 10-20%
c. 20-50%
d. >50%

4) In your clinical practice, which treatment option is most preferably used as pharmacotherapy for treatment of neuropathic pain?

a. Pregabalin & Duloxetine
b. Gabapentin & Nortriptyline
c. Pregabalin monotherapy
d. Duloxetine monotherapy
e. Gabapentin monotherapy
f. Amitriptyline monotherapy

5) In your clinical practice, what percentage of patients of neuropathic pain patients on treatment, are on [any drug] combination therapy (Not Monotherapy)?

a. <10%
b. 10-25%
c. 25-50%
d. >50%

6) In your clinical practice, amongst the patients on combination treatment what percentage of patients of neuropathic pain are on combination of Pregabalin and Duloxetine?

a. <10%
b. 10-20%
c. 20-50%
d. >50%

7) In your clinical practice, what percentage of patients of neuropathic pain on combination of Pregabalin and Duloxetine achieve pain relief?

a. <10%
b. 10-30%
c. 31-50%
d. 51-70%
e. >70%

8) In your clinical practice, what percentage of patients of neuropathic pain patients are on Monotherapy?

a. <10%
b. 10-20%
c. 20-50%
d. >50%

9) In your clinical practice, amongst the patients on monotherapy what percentage of patients of neuropathic pain are on Pregabalin monotherapy alone?

a. <10%
b. 10-20%
c. 20-50%
d. >50%

10) In your clinical practice, what percentage of patients of neuropathic pain on Pregabalin achieve pain relief?

a. <10%
b. 10-20%
c. 20-50%
d. 50-70%
e. >70%

11) Referring to the combination Pregabalin and Duloxetine, which side effect is more common with this combination in your clinical practice?

a. Somnolence
b. Dizziness
c. Nausea
d. Dryness of mouth

12) In your clinical practice, what percentage of patients have experienced side effects with Pregabalin and Duloxetine combination?

a. <10%
b. 10-20%
c. 20-50%
d. >50%

13) In your clinical practice, what percentage of patients have experienced side effects with Pregabalin monotherapy?

a. <10%
b. 10-20%
c. 20-50%
d. >50%

14) In your clinical practice, the side effects with combination of Pregabalin and Duloxetine therapy vs Pregabalin monotherapy are?

a. Less
b. More
c. Comparable

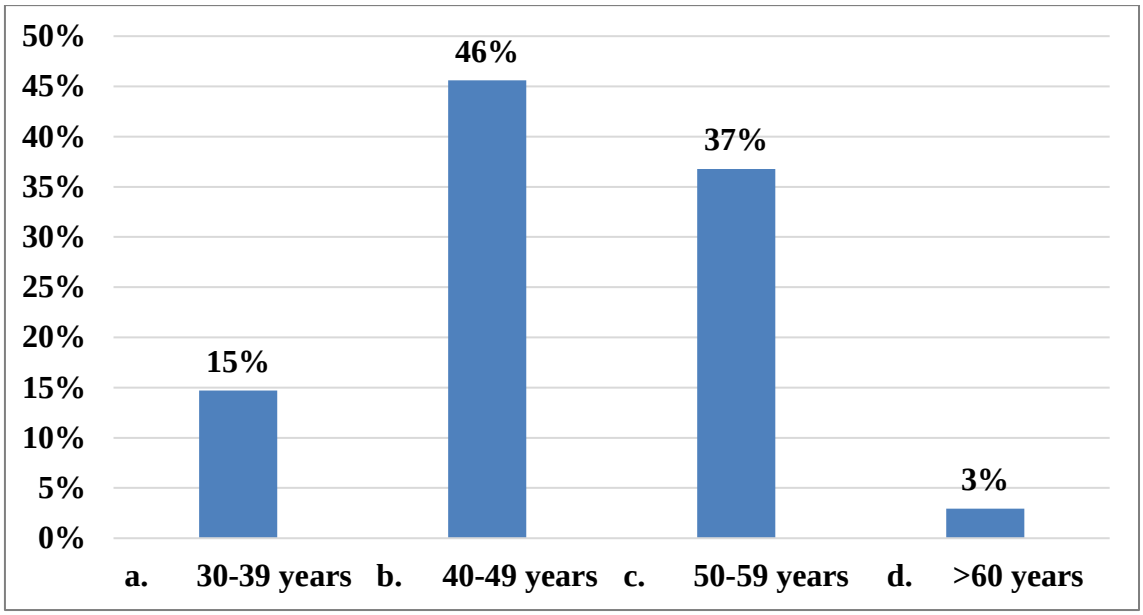
15) In which patient profile would you give combination of Pregabalin and Duloxetine treatment over monotherapy?

a. Not responding to highest dose of monotherapy
b. Intolerant to highest dose of monotherapy
c. Upfront to most patients as a first choice
d. In patients with co-existing anxiety/depression

Survey Findings

1) In your clinical practice, what is the average age at which patients usually report to the hospital with symptoms of peripheral neuropathy?

a. 30-39 years
b. 40-49 years
c. 50-59 years
d. >60 years



In the clinical practice of 46% of doctors, the average age at which patients usually report to the hospital with symptoms of peripheral neuropathy is 40-49 years**.**

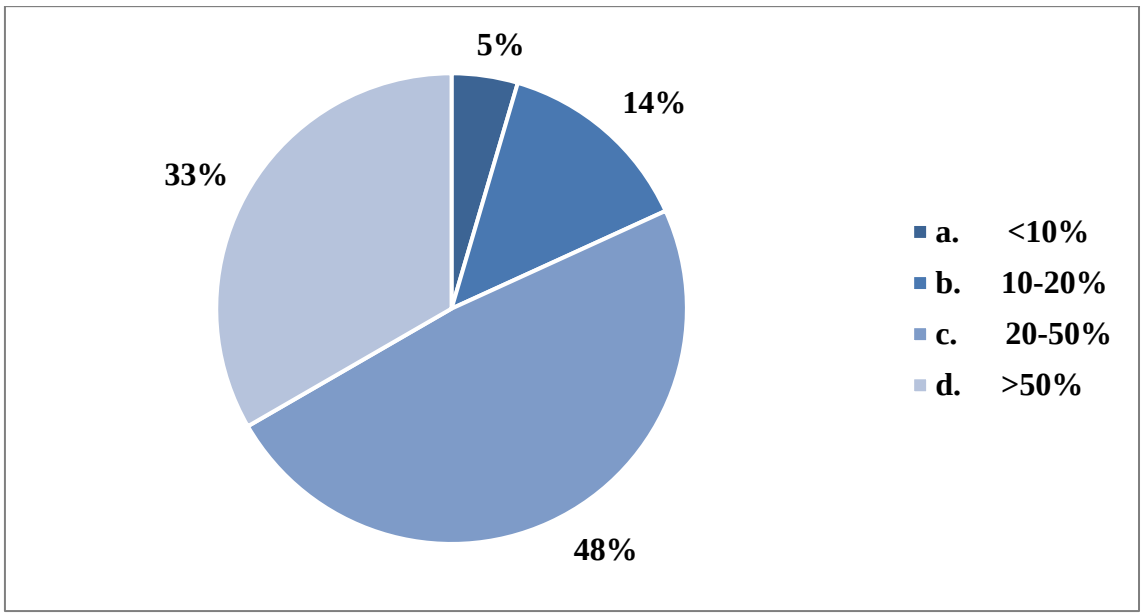
2) What is the prevalence of peripheral neuropathy in your clinical practice?

a. <10%

b. 10-20%

c. 20-50%

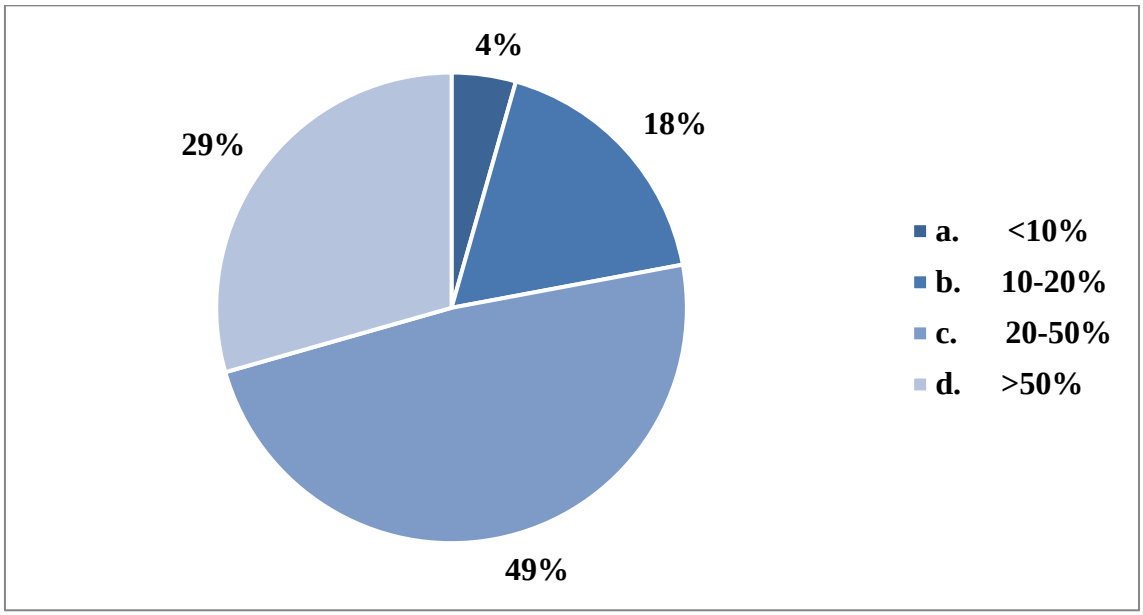
d. >50%



As per 48% of doctors, the prevalence of peripheral neuropathy in your clinical practice is 20-50%.

3) In your clinical practice, what prevalence of diabetic peripheral neuropathy in patients of peripheral neuropathy?

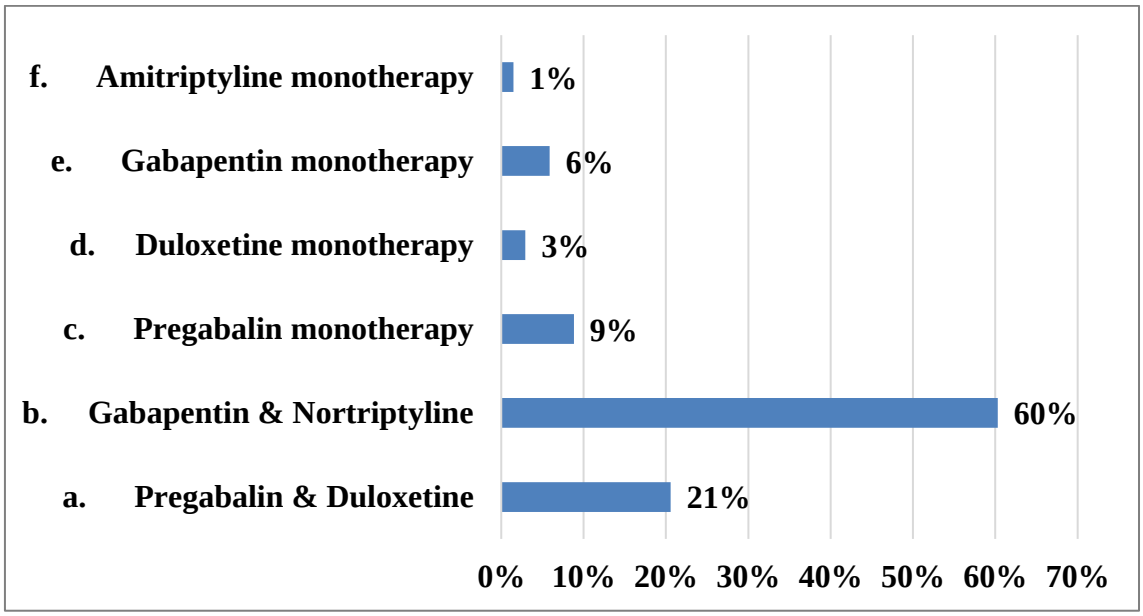
a. <10%
b. 10-20%
c. 20-50%
d. >50%



In the clinical practice of 49% of doctors, the prevalence of diabetic peripheral neuropathy in patients of peripheral neuropathy is 20-50%.

4) In your clinical practice, which treatment option is most preferably used as pharmacotherapy for treatment of neuropathic pain?

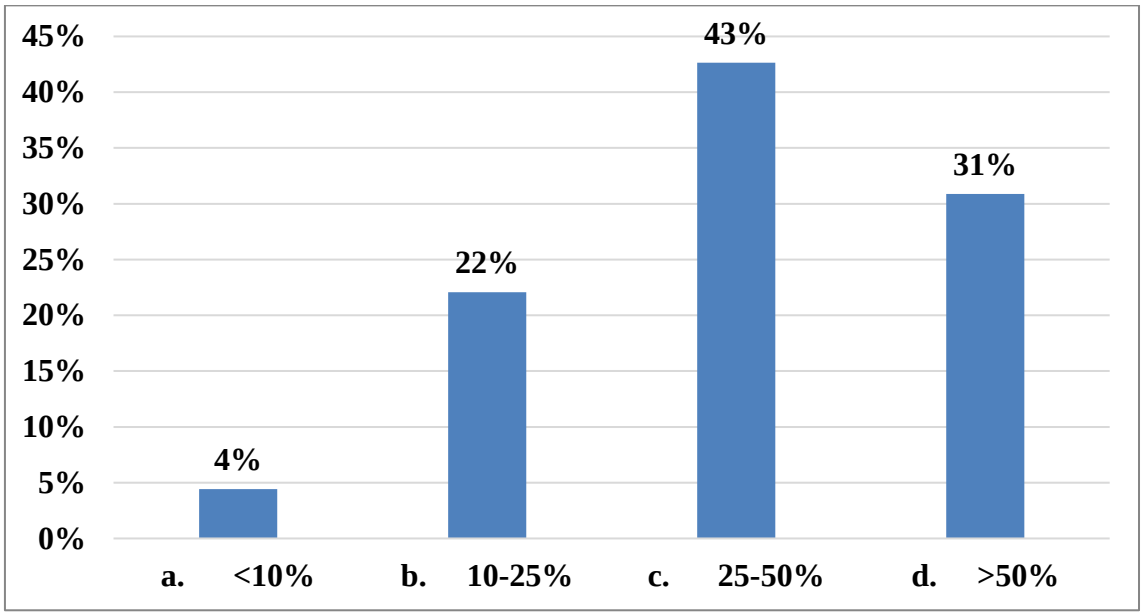
a. Pregabalin & Duloxetine
b. Gabapentin & Nortriptyline
c. Pregabalin monotherapy
d. Duloxetine monotherapy
e. Gabapentin monotherapy
f. Amitriptyline monotherapy



According to majority of doctors, 60%, Gabapentin & Nortriptyline treatment option is most preferably used as pharmacotherapy for treatment of neuropathic pain.

5) In your clinical practice, what percentage of patients of neuropathic pain patients on treatment, are on [any drug] combination therapy (Not Monotherapy)?

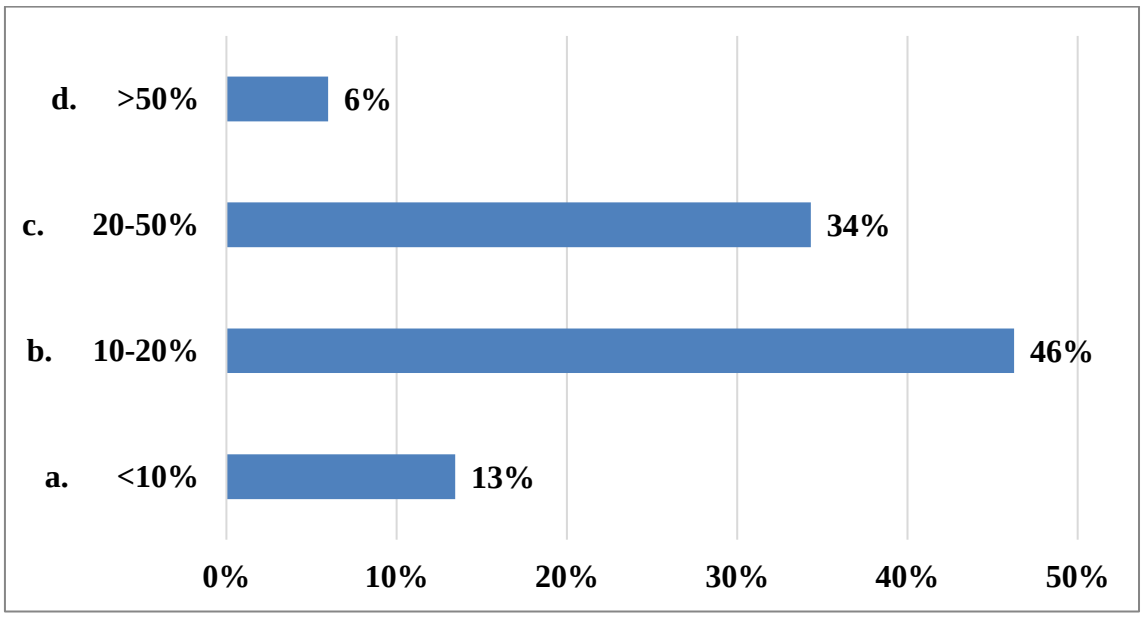
a. <10%
b. 10-25%
c. 25-50%
d. >50%



As per 43% of doctors, 43% of patients of neuropathic pain patients on treatment, are on [any drug] combination therapy (Not Monotherapy).

6) In your clinical practice, amongst the patients on combination treatment what percentage of patients of neuropathic pain are on combination of Pregabalin and Duloxetine?

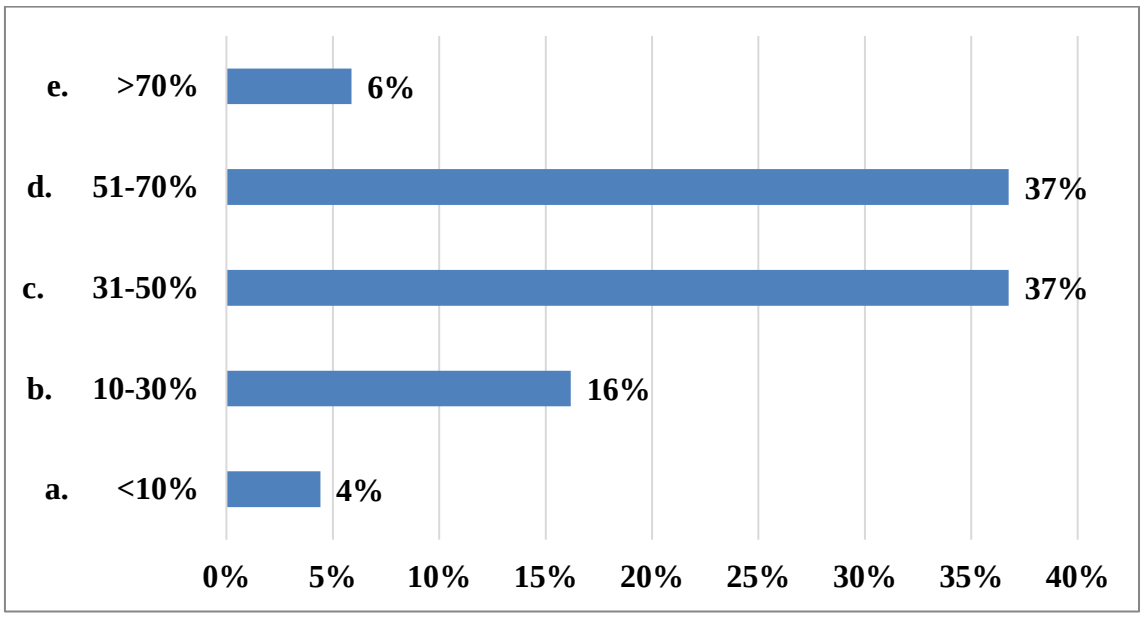
a. <10%
b. 10-20%
c. 20-50%
d. >50%



In the clinical practice of 46% of doctors, amongst the patients on combination treatment 46% of patients of neuropathic pain are on combination of Pregabalin and Duloxetine.

7) In your clinical practice, what percentage of patients of neuropathic pain on combination of Pregabalin and Duloxetine achieve pain relief?

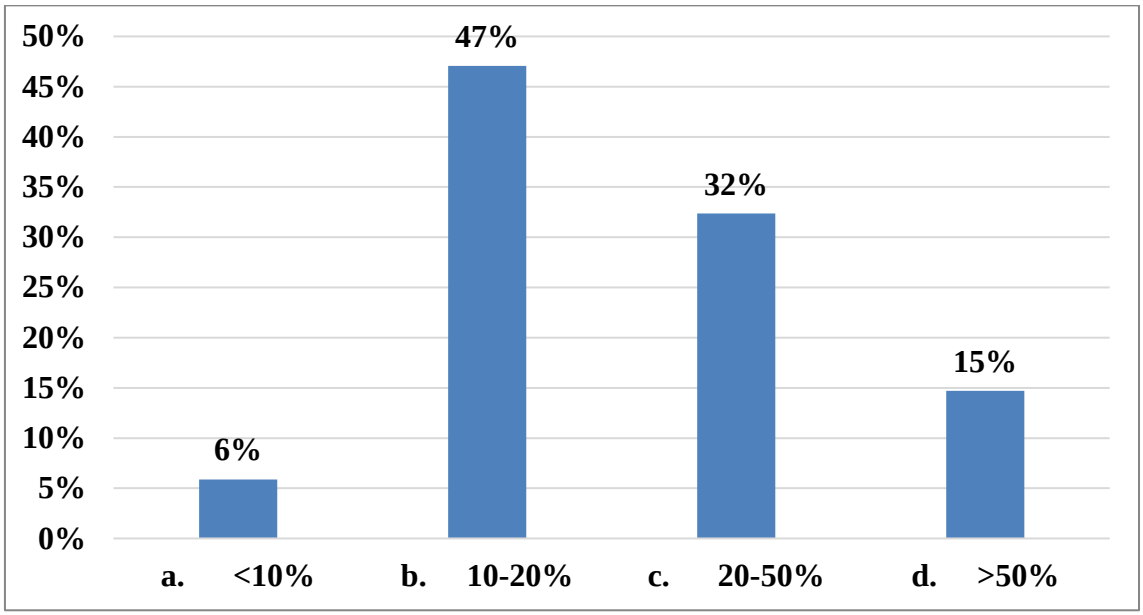
a. <10%
b. 10-30%
c. 31-50%
d. 51-70%
e. >70%



As per 37% of doctors, 31-50% of patients of neuropathic pain on combination of Pregabalin and Duloxetine achieve pain relief while as per another 37 % of doctors, the percentage is 51-70%.

8) In your clinical practice, what percentage of patients of neuropathic pain patients are on Monotherapy?

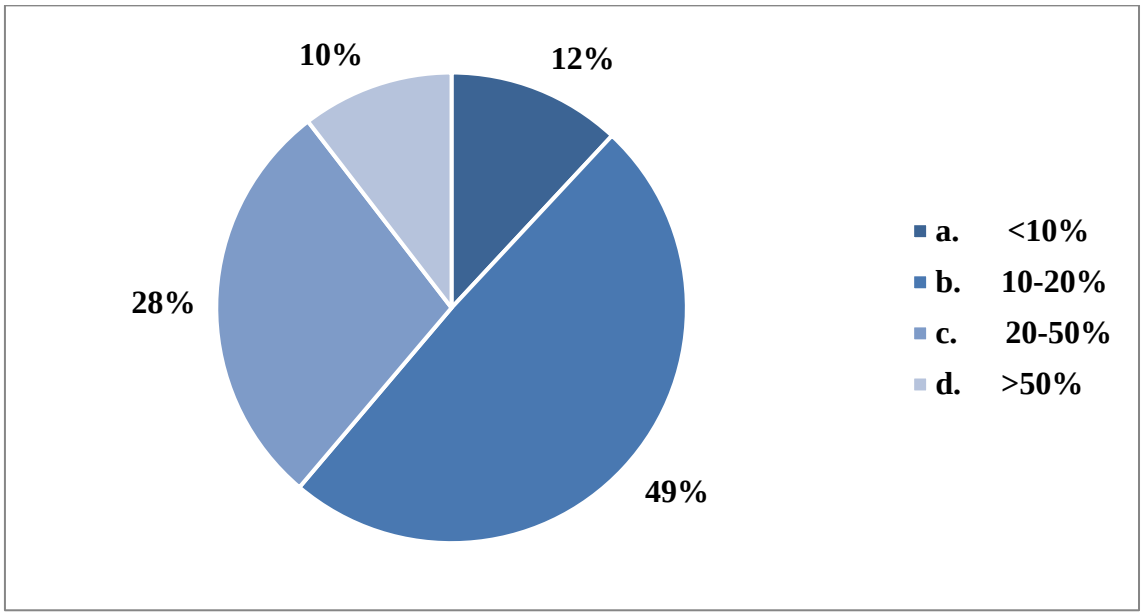
a. <10%
b. 10-20%
c. 20-50%
d. >50%



In the clinical practice of 47% of doctors, 10-20% of patients of neuropathic pain patients are on Monotherapy.

9) In your clinical practice, amongst the patients on monotherapy what percentage of patients of neuropathic pain are on Pregabalin monotherapy alone?

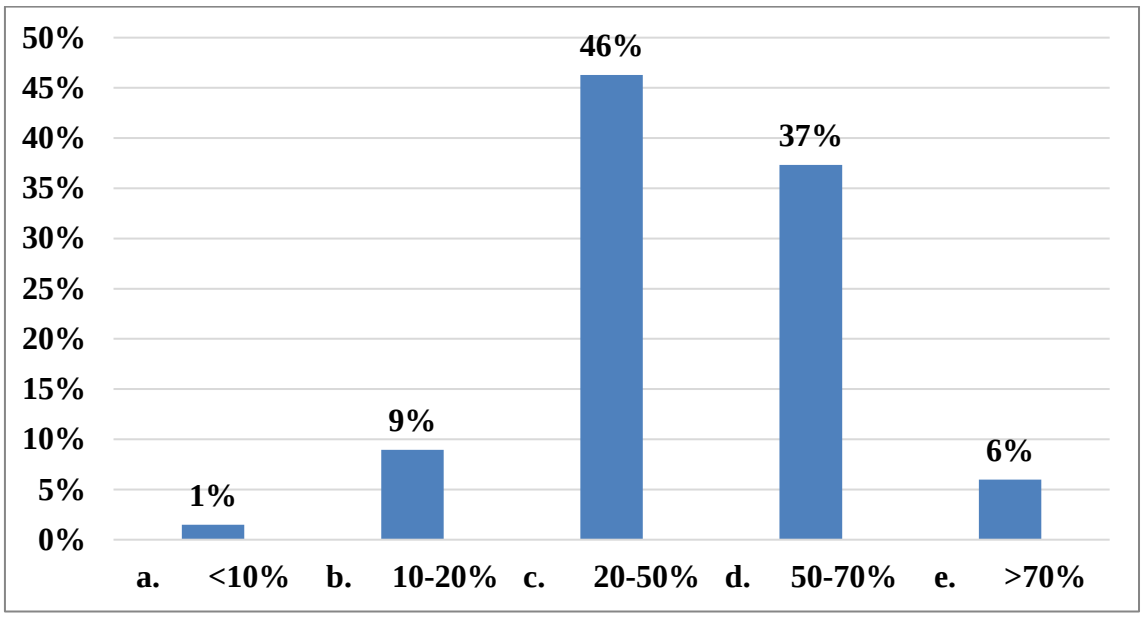
a. <10%
b. 10-20%
c. 20-50%
d. >50%



According to 49% of doctors, amongst the patients on monotherapy 10-20% of patients of neuropathic pain are on Pregabalin monotherapy alone.

10) In your clinical practice, what percentage of patients of neuropathic pain on Pregabalin achieve pain relief?

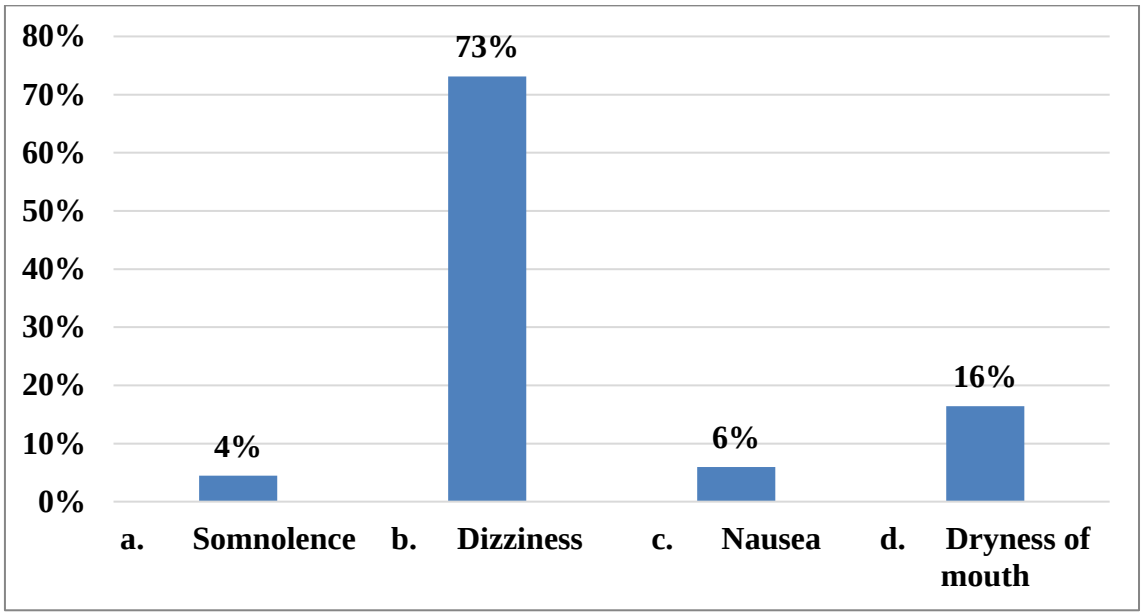
a. <10%
b. 10-20%
c. 20-50%
d. 50-70%
e. >70%



According to 46% of doctors, 20-50% of patients of neuropathic pain on Pregabalin achieve pain relief.

11) Referring to the combination Pregabalin and Duloxetine, which side effect is more common with this combination in your clinical practice?

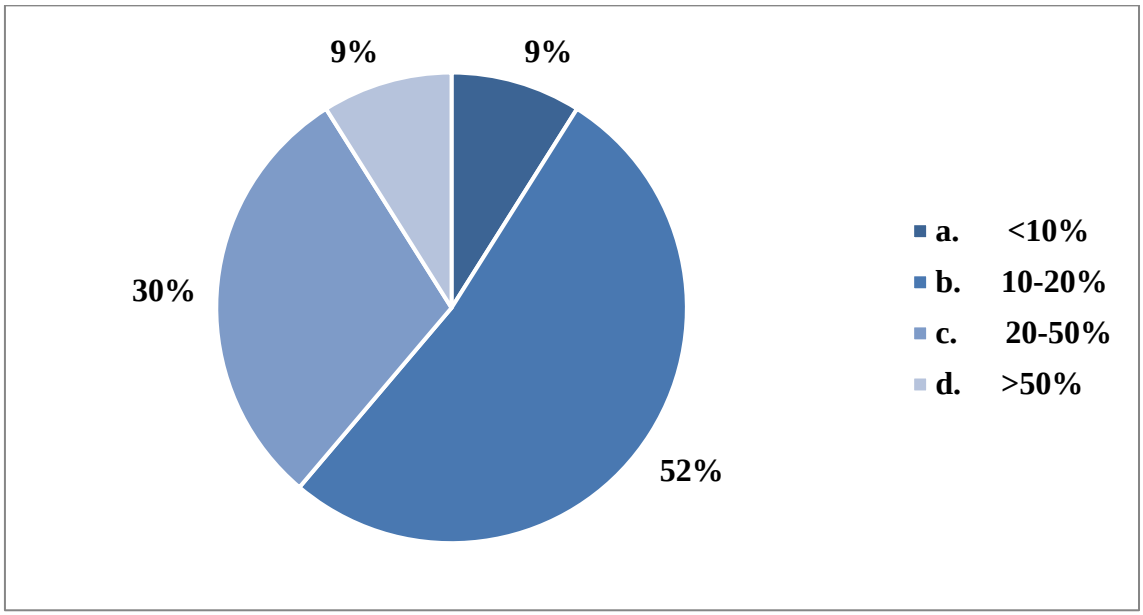
a. Somnolence
b. Dizziness
c. Nausea
d. Dryness of mouth



As per majority of doctors, 73%, referring to the combination Pregabalin and Duloxetine, side effect of dizziness is more common with this combination in their clinical practice.

12) In your clinical practice, what percentage of patients have experienced side effects with Pregabalin and Duloxetine combination?

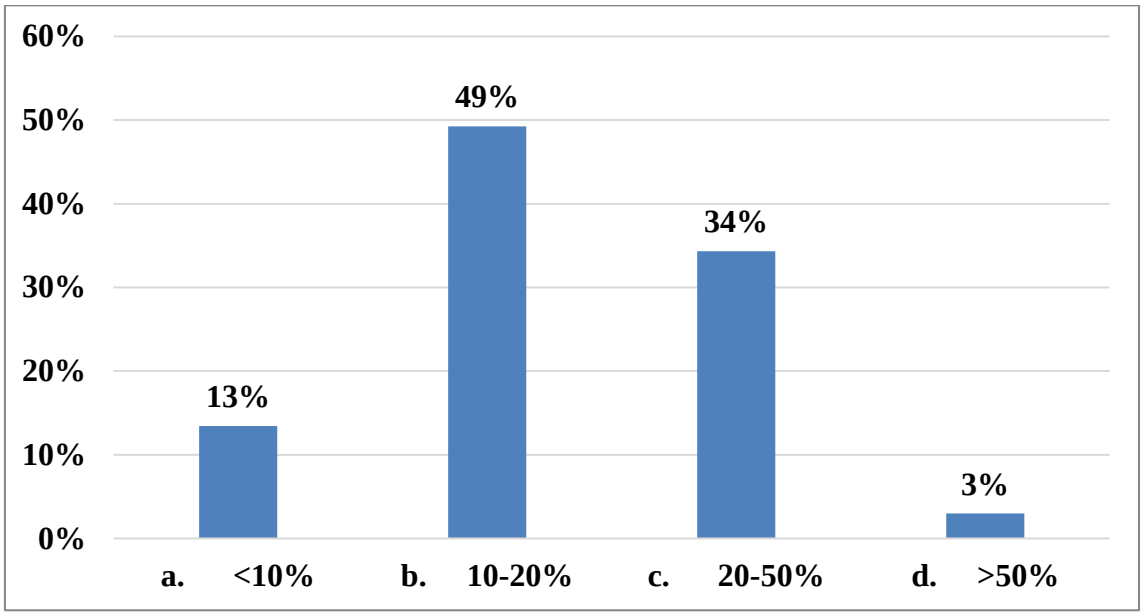
a. <10%
b. 10-20%
c. 20-50%
d. >50%



In the clinical practice of 52% of doctors, 10-20% of patients have experienced side effects with Pregabalin and Duloxetine combination.

13) In your clinical practice, what percentage of patients have experienced side effects with Pregabalin monotherapy?

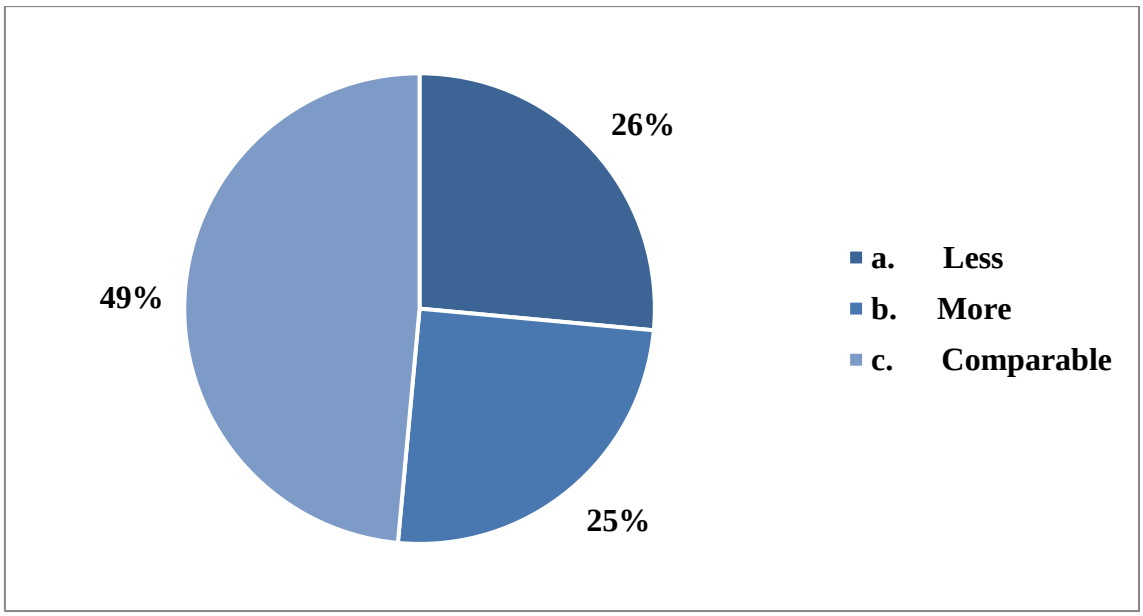
a. <10%
b. 10-20%
c. 20-50%
d. >50%



According to 49% of doctors, 10-20% of of patients have experienced side effects with Pregabalin monotherapy.

14) In your clinical practice, the side effects with combination of Pregabalin and Duloxetine therapy vs Pregabalin monotherapy are?

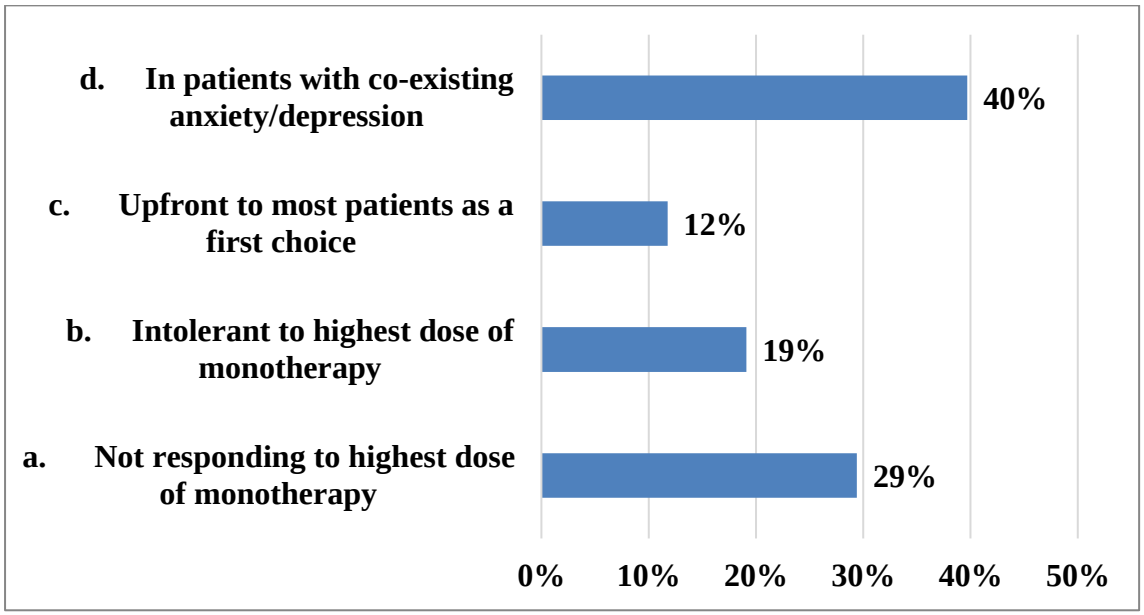
a. Less
b. More
c. Comparable



49% of doctors have observed comparable side effects with combination of Pregabalin and Duloxetine therapy vs Pregabalin monotherapy.

15) In which patient profile would you give combination of Pregabalin and Duloxetine treatment over monotherapy?

a. Not responding to highest dose of monotherapy
b. Intolerant to highest dose of monotherapy
c. Upfront to most patients as a first choice
d. In patients with co-existing anxiety/depression



40% of doctors would give combination of Pregabalin and Duloxetine treatment over monotherapy in patients with co-existing anxiety/depression.

Summary

- In the clinical practice of 46% of doctors, the average age at which patients usually report to the hospital with symptoms of peripheral neuropathy is 40-49 years**.**
- As per 48% of doctors, the prevalence of peripheral neuropathy in your clinical practice is 20-50%.
- In the clinical practice of 49% of doctors, the prevalence of diabetic peripheral neuropathy in patients of peripheral neuropathy is 20-50%.
- According to majority of doctors, 60%, Gabapentin & Nortriptyline treatment option is most preferably used as pharmacotherapy for treatment of neuropathic pain.
- As per 43% of doctors, 43% of patients of neuropathic pain patients on treatment, are on [any drug] combination therapy (Not Monotherapy).
- In the clinical practice of 46% of doctors, amongst the patients on combination treatment 46% of patients of neuropathic pain are on combination of Pregabalin and Duloxetine.
- As per 37% of doctors, 31-50% of patients of neuropathic pain on combination of Pregabalin and Duloxetine achieve pain relief while as per another 37 % of doctors, the percentage is 51-70%.
- In the clinical practice of 47% of doctors, 10-20% of patients of neuropathic pain patients are on Monotherapy.
- According to 49% of doctors, amongst the patients on monotherapy 10-20% of patients of neuropathic pain are on Pregabalin monotherapy alone.
- According to 46% of doctors, 20-50% of patients of neuropathic pain on Pregabalin achieve pain relief.
- As per majority of doctors, 73%, referring to the combination Pregabalin and Duloxetine, side effect of dizziness is more common with this combination in their clinical practice.
- In the clinical practice of 52% of doctors, 10-20% of patients have experienced side effects with Pregabalin and Duloxetine combination.
- According to 49% of doctors, 10-20% of of patients have experienced side effects with Pregabalin monotherapy.
- 49% of doctors have observed comparable side effects with combination of Pregabalin and Duloxetine therapy vs Pregabalin monotherapy.
- 40% of doctors would give combination of Pregabalin and Duloxetine treatment over monotherapy in patients with co-existing anxiety/depression.

Consultant Opinion

Market Opportunities:

Recognize the high prevalence of neuropathic pain, especially in patients aged 40-49 years, as an opportunity for pharmaceutical companies to develop innovative treatments that address the specific needs of this patient population.

Value for Healthcare Professionals:

Provide healthcare professionals with updated guidelines and educational resources on the management of neuropathic pain, highlighting the efficacy and safety profiles of different pharmacotherapy options like Gabapentin, Nortriptyline, Pregabalin, and Duloxetine.

Adverse Effect Management:

Focus on developing pharmacotherapy options with improved tolerability profiles to minimize common side effects such as dizziness associated with combinations like Pregabalin and Duloxetine, thereby enhancing patient adherence and satisfaction.

Withdrawal Management:

Develop strategies and resources to support healthcare providers in managing patients transitioning from combination therapy to monotherapy or vice versa, ensuring continuity of care and optimal treatment outcomes.

Market Positioning:

Position combinations like Pregabalin and Duloxetine as effective treatment options for neuropathic pain, particularly in patients with co-existing anxiety/depression, emphasizing their potential to address multiple symptoms and improve overall patient well-being.

Personalized Treatment Decisions:

Encourage healthcare providers to individualize treatment decisions based on patient-specific factors such as comorbidities, treatment response, and tolerability, optimizing the selection and dosing of pharmacotherapy for each patient.

Improving Patient Outcomes:

Promote patient education and counseling about the expected benefits and potential side effects of pharmacotherapy for neuropathic pain, empowering patients to actively participate in treatment decisions and adhere to prescribed regimens.

Innovation and Research:

Support ongoing research and clinical trials to evaluate the efficacy, safety, and comparative effectiveness of different pharmacotherapy options for neuropathic pain, providing healthcare providers with robust evidence to guide treatment decisions and improve patient care.

By addressing these aspects, both healthcare professionals and pharmaceutical companies can collaborate to optimize the management of neuropathic pain, enhance patient outcomes, and drive innovation in this therapeutic area.

NOTES

NOTES

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

Weston Medical Education Foundation of India

CTS-77, Shop No.11, Swapna Siddhi CHS LTD, Akurli Road Near Malad Sahakari Bank
Kandivali (E), Mumbai - 400101. M: 9322615653 I W: www.wmefi.co.in