ANTIEPILEPTIC DRUGS FOR CHRONIC NEUROPATHIC PAIN

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Resymé

Neuropathic pain is caused by damage or disease that affects the somatosensory nervous system, where the nerves react abnormal to small or no stimuli at all and produces pain. It is less understood than nociceptive pain arising from a healthy nervous system and hence is a notoriously hard condition to treat. Neuropathic pain tends to be chronic with an average duration of 7 years [1]. The cost to society and the implications for the patient in regard to comorbidity tends to be severe [2].

I decided to write a topical review to look closer at what evidence there is for the most commonly used antiepileptic drugs in the treatment of neuropathic pain (gabapentin, pregabalin, clonazepam, lacosamide, oxcarbazepine, phenytoin, valproic acid and zonisamide), what efficacy and what adverse effects one can expect.

Conclusion**:**

Pregabalin has shown the most promising results regarding its potential to relieve pain weighted against adverse effects and amount of research done of all the drugs included in this review. Forty-one per cent of patients with post herpetic neuropathy can expect at least 50% pain relief and forty-five per cent of patients with painful diabetic neuropathy can expect the same results.

Gabapentin produced similar results as pregabalin, but produced a little poorer pain relieving effect with 34% of participants with post herpetic neuropathy and 38% of participants with painful diabetic neuropathy reporting more than 50% pain relief.
Lacosamide did not produce as good pain relief and the participants reported more side effects than with gabapentin or pregabalin.
Oxcarbazepine did show some effects but did also produce the highest percentage of severe side effects.
Valproic acid and Sodium valproate has shown some efficacy at relieving pain, but there are insufficient data to draw any conclusion.
Regarding zonisamide, phenytoin and clonazepam there was too little data to draw any conclusion on the analgesic effect on chronic neuropathic pain.

The process

Starting my fourth year, I knew that I wanted to write a topical review about treatment of chronic pain. I thought that no matter what specialty I would choose later on I would come across patients with chronic pain problem. Moreover, since I knew how sparse the knowledge about the subject generally was among practitioners, I thought it would be a good subject to learn more about. I started to study the subject and read articles on the matter on and off during my fourth and into the start of my fifth year. It was however hard to define what aspect I wanted to immerse into. Finally, about February 2015, me and Lena Danielsson decided that the treatment of neuropathic pain with antiepileptic drugs was a fitting and well defined subject. Other possible treatment for neuropathic pain will not be discussed in this paper.

I decided to start my method from the most commonly used antiepileptic drugs used in the treatment of neuropathic pain and base my data from meta-analysis gathered from a search on the Cochrane database (which in turn had based their meta-analysis on searches in MEDLINE, EMBASE end Cochrane CENTRAL).

I studied their method and found them to use rigorous search and inclusion/exclusion criteria for the underlying trials.

From the beginning of Mars, I started compiling the data from the analysis to make them compatible with each other so that I could draw conclusions. I found that even though I set out to investigate the efficacy of antiepileptic drugs on neuropathic pain, it turned out to be harder to sum up the knowledge available than I had anticipated because of the sub division of neuropathic pain. I decided that it would be too short of a project to simply write about the efficacy of antiepileptic drugs on post herpetic neuropathy for example. Therefore, I kept the original title and thought that it would be a good input to show that one specific antiepileptic drug could have different efficacy on different subgroups of neuropathic pain, instead of just studying a subgroup of neuropathic pain. Though I had to confine myself to post-herpetic neuralgia, painful diabetic neuropathy and fibromyalgia since these were the most commonly conditions the drugs in question had been tested on, and hence the easiest conditions to study and to make comparisons between drugs. Central neuropathic pain was also included for pregabalin. None of the other drugs had been tested on central neuropathic pain in the included meta-analysis, it was however included in the results to highlight the variation in efficacy in different conditions. Fibromyalgia cannot be fully explained as a neuropathic pain, but it was also included for the same reason.

When I finally had a clear image of what the project would be about, it was pretty straight going, but time consuming, from mid Mars with working on the data so that comparisons could be made.

Introduction

Neuropathic pain is a notoriously difficult condition to treat due to its severity, chronicity and resistance to simple analgesics. In this review, I will aim at looking closer at the most commonly used antiepileptic drugs. What evidence there is for their use, what benefits one can expect, and what adverse effects can be expected.

Antiepileptic drugs have been used since the 1960's to treat different types of neuropathic pain. There are several different types of antiepileptic drugs used for this purpose with different ways of action. The antiepileptic drugs that will be review here are gabapentin, lacosamide, oxcarbazepine, pregabalin, valproic acid and sodium valproate. The reason for choosing these drugs is that they are the most commonly used drugs in practice to treat neuropathic pain.

Types of neuropathic pain that will be included in this review: Painful diabetic neuropathy, post herpetic neuralgia, central neuropathic pain and fibromyalgia. The reason for confining to these three conditions is that most research on neuropathic pain has been done on these conditions.

Neuropathic pain:

A commonly used definition of pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" set by IASP [3] that also define chronic pain as pain lasting for more than 3 months [4]. Neuropathic pain is caused by damage or disease that affects the somatosensory nervous system, where the nerves react abnormally to stimuli that otherwise would give none or only small amounts of pain. The nervous tissue can even react without any stimulus and might show signs of sensory loss with or without muscle weakness [4]. And hence, neuropathic pain has its own definition set by IASP, "Pain initiated or caused by a primary lesion or dysfunction in the nervous system" [5]. Up to 7% to 8% of the European population is affected, and in 5% it may be severe [6, 7], and in Norway it's estimated that up to 9% to 15% is affected [8] , with an overall female to male ratio of 6:1 [9]. Neuropathic pain tends to be chronic with a mean duration of 7.0 years [1].

Neuropathic pain can affect the central (brain and spinal cord) and/or the peripheral nervous system. The mechanisms behind neuropathic pain is not fully understood, but neuroglia (glial cells) may play a role in central sensitization. Peripheral nerve injury induces glia to release proinflamatory cytokines and glutamate, which in turn influence neurons [10]. However, other changes at the cellular and molecular level are at play, altered expression of ion channels, changes in neurotransmitters and their receptors as well as altered gene expression in response to neural input [11]. That is why morphine or paracetamol have little effect on this particular type of pain, but brings just as much adverse effects. This is also why neuropathic pain is notoriously difficult to treat, with only 40%–60% receiving partial pain relief [12], since conventional analgesic does not have the expected effect compared to nociceptive pain, and since we have poor understanding of neuropathic pain.

The cost to society is hard to estimate, but one American study estimated the health care cost to be $17,355 on a yearly basis. This was partially due to the fact that patients with neuropathic pain often had other chronic comorbidities, such as coronary heart disease and depression [2].

Neuropathic pain may be associated with an array of different sensations. Among these are dysesthesia and allodynia. The pain may be constant and/or episodic. Common qualities designated to neuropathic pain are "pins and needles", itching, tingling, burning and/or numbness.

There are many different causes for neuropathic pain, and the most common causes can be divided into the two main groups.

1. Central neuropathic pain: Spinal cord injury, Stroke and multiple sclerosis.
2. Peripheral neuropathic pain: Diabetes and other metabolic conditions, Herpes zoster infection, HIV neuropathies, Toxins, physical trauma to the nervous system and

malignancies to mention a few. [13]

Even though fibromyalgia is not fully understood and cannot fully be explained as neuropathic pain, it has been shown to partially overlap pathophysiological with neuropathic pain [14].

Objectives:

To review the efficacy and adverse effects when treating chronic neuropathic pain, in the form of post-herpetic neuralgia, painful diabetic neuropathy and fibromyalgia in adults with antiepileptic drugs.

Method

The data for this topical review was gathered from meta-analysis in the Cochrane database [15]. The search keywords were “neuropathic pain” and “antiepileptic”. The meta-analysis that contained any of the names of the following drugs: gabapentin, pregabalin, clonazepam, lacosamide, oxcarbazepine, phenytoin, valproic acid and zonisamide were studied. There were only one meta-analysis for each drug made by Cochrane. Reasons for excluding the meta-analysis on three of these drugs (clonazepam, phenytoin and zonisamide) were that there had not been done enough research to come to any conclusion or that there were no studies that met the inclusion criteria set by the authors of the meta-analysis. The meta-analysis for the other drugs were included since they had enough data to come to a conclusion.

All drugs were administered orally and the dosage varied as described under the specific drugs. The number of trials and participants in the trials will be disclosed for each drug individually

All data to construct the tables in this review is gathered from the meta-analysis referred to in the beginning of each drug investigated. It will also be referred to in the top of each table.

To gather supplementary information about the drugs, I conducted internet searches. Articles and webpages found in this way is referred to separately.

The included studies were the following:

[16-20]

The excluded studies were the following:

[21-23]

RESULTS

Gabapentin:

Background:

Gabapentin was developed as an antiepileptic drug. But after its analgesic effects for patients whom suffer from various conditions of neuropathic pain was discovered, gabapentin has become one of the first hand choice in treatment of many of the underlying conditions. [24] There is some evidence that gabapentin has some effect on anxiety disorders [25], bipolar disorder [25] and restless legs [26].

Gabapentin encarbil is a prodrug for gabapentin.

Mechanism of action:

The mechanism is not fully understood but it has been shown to modulate glutamate decarboxylase and branched chain aminotransferase, two enzymes involved in GABA biosynthesis, which in turn increase GABA synthesis [27]. Gabapentin separate itself from other conventional antiepileptic in that it appears not to interact with sodium or L-type calcium ion channels, nor does it appear to interact with glutamate, glycine or NMDA receptors. [28]

Thirty-seven studies with 5633 participants studied oral daily intake of gabapentin or gabapentin encarbil. The studies had the selection criteria of being: Randomized, double-blinded studies that reported the analgesic and adverse effects in chronic post herpetic neuralgia and painful diabetic neuropathy with assessment of pain intensity, pain relief, or both, using validated scales. Participants were adults. [16]

Results:

Gabapentin helped 34 percent of the participants suffering from post-herpetic neuralgia, and 38% of the participants suffering from painful diabetic neuropathy in these studies to reduce their pain by at least half. While the participants who received placebo only 21 percent had the same results. However 46% of those treated with gabapentin did not have pain reduced by more than 30%. As shown by table 1.3 there are no significant higher risk of severe adverse effects between gabapentin/gabapentin encarbil and placebo.

Table 1.1: Efficacy of gabapentin/gabapentin encarbil vs placebo on post-herpetic neuralgia. Dosage varied with gabapentin between 1800 mg daily and 3600 mg daily and for gabapentin encarbil 1200 mg daily to 3600 mg daily. Duration varied between 4 to 12 weeks. [16]

	Number of		Percent with outcome			
Outcome	Studies	Participants	Gabapentin/encarbil	Placebo	RR (95% CI)	NNT (95% CI)
Substantial benefit						
At least 50% pain intensity reduction	6	1816	34	21	1,6 (1,3-1,9)	8.0 (6.0-12)
PGIC very much improved	2	563	15	6	2,7 (1,5-4,8)	11(7,0-22)
Any definition of substantial benefit (At least 50% pain intensity reduction or PGIC very much improved)	7	2045	34	20	1,7 (1,4-2.0)	6,8 (5,4-9,3)
Moderate benefit						
At least 30% pain intensity reduction	2	529	54	38	1,4 (1,1-1,7)	6,5 (4.0-16)
PGIC much or very much improved	7	2013	39	29	1,3 (1,2-1,5)	9,7 (6,9-16)
Any definition of substantial benefit (At least 30% pain intensity reduction or PGIC much or very much improved)	7	2045	44	27	1,6 (1,4-1,8)	5,7 (4,6-7,5)

PGIC (Patient Global Impression of Change)
NNT (number needed to treat)
RR (risk ratio/relative benefit). A RR < 1 means the outcome is less likely to occur in the experimental group than in the control group (placebo group), a RR > 1 mean the outcome is more likely in the experimental group than in the control group.

As shown in table 1.1 gabapentin gave at least 50% pain intensity reduction in 34% of the participants who got gabapentin and 21% of the participants who got placebo while 54% of the participants who got gabapentin and 38% of the participants who got placebo reported at least 30% pain intensity reduction post herpetic neuralgia.

Table 1.2 Efficacy of gabapentin in painful diabetic neuropathy. Daily dose of gabapentin of 1200 mg or more. [16]

	Number of		Percent with outcome			
Outcome	Studies	Participants	Gabapentin	Placebo	RR (95% CI)	NNT (95% CI)
Substantial benefit						
At least 50% pain intensity reduction.	6	1277	38	21	1,9 (1,5-2,3)	5,9 (4,6-8,3)
PGIC very much improved	2	744	54	43	1,2 (1,1-1,5)	9,4 (5,6-29)
Any definition of substantial benefit (At least 50% pain intensity reduction or PGIC very much improved)	6	1277	38	21	1,9 (1,5-2,3)	5,9 (4,6-8,3)
Moderate benefit						
At least 30% pain intensity reduction	2	529	54	38	1,4 (1,1-1,7)	6,5 (4.0-16)
PGIC much or very much improved	5	695	50	30	1,7 (1,4-2.0)	4,9 (3,6-7,6)
Any definition of substantial benefit (At least 30% pain intensity reduction or PGIC much or very much improved)	7	1439	52	37	1,4 (1,3-1,6)	6,6 (4,9-9,9)

As shown in table 1.2 gabapentin gave at least 50% pain intensity reduction in 38% of the participants who got gabapentin and 21% of the participants who got placebo while 54% of the participants who got gabapentin and 38% of the participants who got placebo reported at least 30% pain intensity reduction regarding painful diabetic neuropathy.

Table 1.3: Adverse effects of gabapentin vs placebo. [16]

Daily intake of ≥ 1200 mg of gabapentin						
Number of			Percent with outcome			
Outcome	Studies	Participants	Gabapentin	Placebo	RR (95%CI)	NNH (95% CI)
Withdrawal -all causes	23	4709	20	18	1.04 (0.90-1.2)	Not calculated
Withdrawal due to adverse events	22	4448	11	7,9	1.4 (1.1-1.7)	31 (20-66)
At least one adverse event	17	4002	62	50	1.25 (1.2-1.3)	8.6 (6.8-12)
Serious adverse events	19	3952	3,2	2,8	1,2 (0,8-1,7)	Not calculated
Somnolence/drowsiness	20	4125	14	5	2,9 (2,3-3,6)	11 (9,4-14)
Dizziness	22	4576	19	6,1	3.1 (2.6-3.8)	7.6 (6.6-8.8)
Peripheral edema	12	3220	7	2,2	3,3 (2,2-4,9)	21 (16-30)
Ataxia/gait disturbance	5	544	8,8	1,2	4,5 (1,9-11)	13 (9-24)
Outcome	Studies	Participants	Gabapentin	Placebo	RR (95%CI)	NNT_P (95% CI)
Withdrawal – lack of efficacy	16	3693	1,6	3,1	0,5 (0,3-0,8)	67 (40-205)

NNH (number needed to harm)
NNT_P (number needed to prevent one participant from discontinuing due to lack of efficacy)

As shown in table 1.3 percentage with serious adverse events is not significantly higher for the group who received gabapentin than the group who received placebo. Somnolence/drowsiness, dizziness, peripheral edema, ataxia/gait disturbance was over represented by the group who received gabapentin. Fewer participants who received gabapentin withdrew from the study due to lack of efficacy.

Pregabalin:

Background:
Pregabalin was discovered by chemist Richard Bruce Silverman and is an anticonvulsant drug used for neuropathic pain therapy and as an adjuvant therapy for partial seizures in adults [29]. It has also been found effective against generalized anxiety disorder.[30] Pregabalin was designed as a more potent successor to gabapentin.

Mechanism of action:
Like gabapentin, pregabalin binds to the alpha-2-delta subunit of the voltage dependent calcium channel in the central nervous system. Pregabalin decreases the release of neurotransmitters including glutamate, norepinephrine, substance P and calcitonin gene related peptide. [31]
However, unlike anxiolytic compounds (benzodiazepines) which exert their therapeutic effects through binding $GABA_A$, pregabalin neither binds directly to these receptors nor augments $GABA_A$ currents or affect $GABA_A$ metabolism. [32]

Nineteen studies (7003 participants) that studied the effects of pregabalin in chronic post herpetic neuralgia, painful diabetic neuropathy, central neuropathic pain and fibromyalgia, were included. They were all randomized controlled trials, double blinded and investigated the analgesic effects of pregabalin using subjective pain assessment (VAS score). [17]

Results:
Regarding post herpetic neuralgia, painful diabetic neuropathy, central neuropathic pain and fibromyalgia, pregabalin showed to be effective in the treatment of pain. The efficacy generally increased with an increased daily dosage of pregabalin as well, alongside lower rates of discontinuation due to lack of efficacy with increasing dose. Forty-one per cent of patients with post herpetic neuropathy can expect at least 50% pain relief and forty-five per cent of patients with painful diabetic neuropathy can expect the same results.
With a daily dose of 600 mg pregabalin somnolence typically occurred in 15% to 25% and dizziness occurred in 27% to 46%. Discontinued treatment due to adverse event happened to 10% to 28%. The percentage of participants reporting adverse events or serious adverse events were not affected by dosage, and was not more than with placebo.
For post-herpetic neuralgia and painful diabetic neuropathy, pregabalin showed higher rates of substantial benefit than in fibromyalgia and central neuropathic pain.

Pregabalin has showed efficacy in neuropathic pain conditions and fibromyalgia. A minority of patients had substantial benefits from pregabalin while most had moderate benefits. Many had no or trivial benefits or will discontinue due to adverse events.
With pregabalin daily dose of 300 mg to 600 mg, the PGIC rating of much or very much improved was about 35% in post herpetic neuralgia, 50% in painful diabetic neuropathy and 40 % in fibromyalgia.

Table 2.1 Effects of pregabalin on post-herpetic neuralgia. [17]

	Number of		Percent with outcome			
Outcome -daily dose	Studies	Participants	Pregabalin	Placebo	RR (95% CI)	NNT (95% CI)
At least 30% pain relief						
150 mg	1	180	39	17	2,3 (1,4-3,8)	4,6 (2,9-11)
300 mg	2	369	49	24	2,1 (1,5-2,7)	4,0 (2,9-6,5)
300 mg > 8 weeks	1	191	41	17	2,4 (1,4-3,9)	4,2 (2,8-8,9)
600 mg	3	537	62	24	2,5 (2,0-3,2)	2,7 (2,2-3,4)
600 mg > 8 weeks	2	356	58	21	2,8 (2,0-3,8)	2,7 (2,2-3,7)
At least 50% pain relief						
150 mg	3	527	25	11	2,3 (1,6-3,4)	6,9 (4,8-13)
300 mg	4	713	32	13	2,5 (1,9-3,4)	5,1 (3,9-7,4)
300 mg > 8 weeks	3	535	30	11	2,7 (1,9-4,0)	5,3 (3,9-8,1)
600mg	4	732	41	15	2,7 (2,1-3,5)	3,9 (3,1-5,1)
600 mg > 8 weeks	3	551	39	14	2,8 (2,0-3,9)	4,0 (3,1-5,5)
PGIC much or very much improved						
150mg	2	342	27	15	1,8 (1,2-2,8)	8,4 (4,9-30)
300 mg	2	348	32	15	2,2 (1,4-3,3)	5,8 (3,9-12)
600 mg	1	183	37	16	2,3 (1,3-3,9)	4,9 (3,0-12)
Lack of efficacy discontinuation						NNT_P (95% CI)
150 mg	3	527	8	13	0,6 (0,3-1,0)	Not calculated
300 mg	4	713	4	11	0,4 (0,2-0,7)	15 (9-34)
300 mg > 8 weeks	3	535	6	13	0,4 (0,2-0,7)	13 (7,9-35)
600 mg	4	732	3	11	0,3 (0,1-0,5)	13 (9-24)
600 mg > 8 weeks	3	551	3	13	0,3 (0,1-0,6)	11 (7,4-22)

NNT_P (number needed to prevent one participant from discontinuing due to lack of efficacy)

As shown in table 2.1 in all cases there was a greater response with a greater dose, and at the same time lower NNT values. For discontinuation due to lack of efficacy there were fewer discontinuations with higher doses. At least 30% pain relief (moderate benefit) produced higher response rates than did at least 50% pain relief (substantial benefit) or PGIC – much or very much improved. Taking pregabalin for 8 weeks or more made no difference to the outcome.

Table 2.2

Adverse effects of pregabalin in treatment for post-herpetic neuralgia. [17]

	Number of		Percent with outcome			
Outcome – daily dose	Studies	Participants	Pregabalin	Placebo	RR (95% CI)	NNH (95% CI)
Somnolence						
150 mg	3	527	15	7	2,2 (1,3-3,7)	12 (7,3-34)
300mg	4	713	19	6	3,0 (2,1-5,3)	7,4 (5,5-11)
600 mg	4	732	25	6	4,4 (2,8-6,8)	5,2 (4,1-7,0)
Dizziness						
150 mg	3	527	13	10	1,3 (0,8-2,1)	Not calculated
300 mg	4	713	30	9	3,2 (2,3-4,6)	4,7 (3,7-6,5)
600 mg	4	732	35	9	4,0 (2,8-5,7)	3,8 (3,2-4,9)
Adverse event discontinuation						
150 mg	3	527	9	7	1,3 (0,7-2,3)	Not calculated
300 mg	4	713	17	6	2,7 (1,7-4,3)	9,3 (6,5-16)
600 mg	4	732	19	5	3,7 (2,3-6,0)	7,1 (5,3-11)

As shown in table 2.2 higher doses produced higher adverse event rates, all categories, with pregabalin, and lower NNH values.

Table 2.3 Effect of pregabalin on painful diabetic neuropathy. [17]

	Number of		Percent with outcome			
Outcome – daily dose	Studies	Participants	Pregabalin	Placebo	RR (95% CI)	NNT (95% CI)
At least 30% pain relief						
150 mg	No data					
300 mg	2	482	59	45	1,3 (1,1-1,6)	6,8 (4,3-17)
300 mg > 8 weeks	1	304	58	52	1,1 (0,9-1,4)	Not calculated
600 mg	3	819	63	43	1,5 (1,3-1,7)	5,1 (3,8-7,8)
600 mg > 8 weeks	2	641	62	48	1,3 (1,1-1,5)	6,8 (4,4-15)
At least 50% pain relief						
150 mg	2	359	27	23	1,1 (0,8-1,6)	Not calculated
150 mg > 8 weeks	1	195	34	30	1,1 (0,8-1,7)	Not calculated
300 mg	4	823	40	26	1,5 (1,2-1,8)	7,5 (5,1-14)
300 mg > 8 weeks	3	645	38	29	1,3 (1,1-1,6)	11 (6,1-54)
600 mg	6	1360	45	25	1,7 (1,5-2,0)	5,0 (4,0-6,6)
600 mg > 8 weeks	4	1005	46	30	1,5 (1,3-1,8)	6,3 (4,6-10)
PGIC much or very much improved						
150 mg	1	195	45	34	1,4 (0,96-2,0)	Not calculated
300 mg	2	359	48	30	1,6 (1,2-2,1)	5,6 (3,6-13)
300 mg > 8 weeks	1	195	42	33	1,3 (0,9-1,8)	Not calculated
600 mg	4	875	56	33	1,8 (1,5-2,1)	4,2 (3,3-5,8)
600 mg > 8 weeks	3	702	54	36	1,5 (1,3-1,8)	5,4 (3,9-9,2)
Lack of efficacy discontinuation						NNT_P (95% CI)
150 mg	2	359	4	7	0,7 (0,7-1,5)	Not calculated
150 mg > 8 weeks	1	195	8	11	0,7 (0,3-1,7)	Not calculated
300 mg	2	341	3	8	0,4 (0,2-1,0)	Not calculated
600 mg	4	869	4	11	0,3 (0,2-0,5)	14 (9-31)
600 mg > 8 weeks	3	702	4	14	0,3 (0,2-0,5)	10 (6,9-20)

As shown in table 2.3 in all categories there was a greater response with a higher dose, and same or lower NNT numbers with higher dose. Discontinuation due to lack of efficacy were no fewer for higher doses, and had a measurable NNT_P number due to higher discontinuation rate with placebo. At least 30% pain relief (moderate benefit) tended to produce higher response rates and lower NNT values than did at least 50% pain relief (substantial benefit) and the much or very much PGIC. Taking pregabalin for 8 weeks or more showed no difference in the outcome.

Table 2.4 Adverse effects of pregabalin in treatment for painful diabetic neuropathy. [17]

	Number of		Percent with outcome			
Outcome – daily dose	Studies	Participants	Pregabalin	Placebo	RR (95% CI)	NNH (95% CI)
Somnolence						
150 mg	2	359	5	2	2,3 (0,7-7,5)	Not calculated
300 mg	4	823	16	4	4,6 (2,7-7,9)	7,8 (6,0-11)
600 mg	6	1351	15	2	4,6 (2,9-7,3)	8,8 (7,0-12)
Dizziness						
150 mg	2	359	6	2	2,8 (0,9-8,7)	Not calculated
300 mg	4	823	23	5	4,7 (3,0-7,5)	5,5 (4,4-7,4)
600 mg	3	1122	46	10	4,4 (3,4-5,8)	2,8 (2,5-3,2)
Adverse event discontinuation						
150 mg	2	359	4	4	1,0 (0,4-2,9)	Not calculated
300 mg	4	823	11	5	2,3 (1,4-3,8)	16 (9,9-37)
600 mg	6	1351	18	6	2,6 (1,8-3,7)	8,8 (6,8-12)

As shown in table 2.4 higher doses of pregabalin produced higher adverse event rates regarding Dizziness and discontinuation. Regarding somnolence, there were no difference between 300 mg and 600 mg.

Table 2.5 Effect of pregabalin on central neuropathic pain. [17]

	Number of		Percent with outcome			
Outcome – daily dose	Studies	Participants	Pregabalin	Placebo	RR (95% CI)	NNT (95% CI)
At least 30% pain relief						
600 mg	1	136	42	13	3,1(1,6-6,1)	3,5 (2,3-7,0)
At least 50% pain relief						
600 mg	2	176	25	7	3,6 (1,5-8,4)	5,6 (3,5-14)
Lack of efficacy discontinuation						NNT_P (95% CI)
600 mg	2	177	6	24	0,3 (0,1-0,6)	5,4 (3,5-12)

As shown in table 2.5 there were fewer discontinuation due to lack of efficacy with 600 mg than placebo. In comparison, 50% pain relief rate showed lower efficacy and a higher NNT than 30% pain relief rate.

Table 2.6 Adverse effects of Pregabalin in treatment of central neuropathic pain. [17]

	Number of		Percent with outcome			
Outcome – daily dose	Studies	Participants	Pregabalin	Placebo	RR (95% CI)	NNH (95% CI)
Somnolence						
600 mg	2	177	42	17	2,5 (1,5-4,1)	4,0 (2,6-8,3)
Dizziness						
600 mg	2	177	27	14	2,0 (1,1-3,6)	7,8 (4,1-82)
Adverse effects discontinuation						
600 mg	2	177	20	14	1,5 (0,7-2,8)	Not calculated

As shown in table 2.6 pregabalin 600 mg produced significantly more somnolence and dizziness, but not a significantly higher rate of discontinuation due to adverse events than Placebo.

Table 2.7 Effect of pregabalin on fibromyalgia. [17]

	Number of		Percent with outcome			
Outcome – daily dose	Studies	Participants	Pregabalin	Placebo	RR (95% CI)	NNT (95% CI)
At least 30% pain relief						
150 mg	1	263	31	27	1,1 (0,8-1,7)	Not calculated
300 mg	4	1374	39	28	1,4 (1,2-1,6)	9,2 (6,3-17)
450 mg	4	1376	43	28	1,5 (1,3-1,8)	6,6 (5,0-9,8)
600 mg	3	1122	39	28	1,4 (1,2-1,6)	9,1 (6,1-18)
At least 50% pain relief						
150 mg	1	263	12	12	1,0 (0,5-1,9)	Not calculated
300 mg	4	1374	21	14	1,5 (1,2-1,9)	14 (9,0-33)
450 mg	4	1376	25	14	1,7 (1,4-2,1)	9,8 (7,0-16)
600 mg	3	1122	24	15	1,6 (1,3-2,1)	11 (7,1-21)
PGIC much or very much improved						
150 mg	1	263	32	27	1,2 (0,8-1,8)	Not calculated
300 mg	4	1374	36	28	1,5 (1,2-1,9)	11 (7,3-26)
450 mg	4	1376	42	28	1,5 (1,3-1,8)	6,8 (5,1-10)
600 mg	3	1122	41	28	1,5 (1,2-1,7)	7,7 (5,4-13)
PGIC very much improved						
150 mg	No data					
300 mg	4	1352	17	11	1,7 (1,2-2,9)	16 (9,9-37)
450 mg	4	1354	19	11	1,8 (1,4-2,4)	11 (7,9-20)
600 mg	3	1095	12	7	1,7 (1,1-2,4)	21 (12-83)
Lack of efficacy discontinuation						NNT_P (95% CI)
150 mg	1	263	9	14	0,7 (0,3-1,3)	Not calculated
300 mg	4	1374	4	10	0,4 (0,3-0,7)	18 (12-34)
450 mg	4	1376	3	10	0,3 (0,2-0,5)	15 (11-25)
600 mg	3	1122	2	9	0,3 (0,2-0,5)	15 (11-26)

As shown in table 2.7 600 mg pregabalin seemed to produce no better results than 450 mg for any outcome. Discontinuation due to lack of efficacy were lower with higher doses. A daily dose of 150 mg was not different from placebo on any measure. A daily dose of 450 mg gave the best reported response with a daily dose of 600 mg fairing almost as good results.

Table 2.8 Adverse effects of pregabalin in treatment of fibromyalgia. [17]

	Number of		Percent with			
Outcome – daily dose	Studies	Participants	Pregabalin	Placebo	RR (95% CI)	NNH (95% CI)
Somnolence						
150 mg	1	263	16	5	3,5 (1,5-8,3)	8,8 (5,4-24)
300 mg	4	1374	20	5	4,0 (2,8-5,8)	6,7 (5,5-8,7)
450 mg	4	1376	21	5	4,2 (2,9-6,0)	6,4 (5,2-8,1)
600 mg	3	1122	23	5	4,5 (3,1-6,7)	5,7 (4,6-7,3)
Dizziness						
150 mg	3	527	13	10	1,3 (0,8-8,3)	Not calculated
300 mg	4	1374	32	10	3,1 (2,4-3,9)	4,6 (3,9-5,7)
450 mg	4	1376	43	10	4,1 (3,2-5,2)	2,8 (2,5-3,2)
600 mg	3	1122	46	10	4,4 (3,4-5,8)	2,8 (2,5-3,2)
Adverse event discontinuation						
150 mg	1	263	8	8	1,1 (0,5-2,5)	Not calculated
300 mg	4	1374	16	10	1,6 (1,2-2,1)	17 (11-43)
450mg	4	1377	20	10	1,9 (1,5-2,5)	11 (7,6-18)
600 mg	3	1122	28	11	2,5 (1,9-3,3)	5,9 (4,6-8,0)

As shown in table 2.8, higher doses produced higher rates of adverse events, in all categories, with pregabalin, and lower NNH values.

Table 2.9 Participant experiencing at least one adverse event or serious adverse event. [17]

	Number of		Percent with outcome			
Outcome – daily dose	Studies	Participants	Pregabalin	Placebo	RR (95% CI)	NNH (95% CI)
At least one adverse event						
150 mg	2	449	77	71	1,2 (0,97-1,4)	Not calculated
300 mg	8	2190	82	67	1,2 (1,17-1,29)	6,6 (5,4-8,7)
450 mg	4	1379	82	67	1,2 (1,15-1,27)	6,3 (5,1-8,5)
600 mg	9	2540	83	67	1,3 (1,25-1,37)	6,1 (5,1-7,7)
At least one serious adverse event						
150 mg	3	542	4,1	4	1,0 (0,5-2,5)	Not calculated
300 mg	8	1566	3,6	2,9	1,2 (0,7-2,1)	Not calculated
450 mg	2	740	2,7	1,6	1,7 (0,6-4,5)	Not calculated
600 mg	9	2101	3,7	3,2	1,2 (0,7-1,8)	Not calculated

As shown in table 2.9, most participants reported at least one adverse event, regardless if they were given pregabalin or placebo. However, there was no indication of a dose-response relationship.

Lacosamide:

Background:
Lacosamide is an anti convulsant medication developed for adjuvant treatment of partial-onset seizures. [33] It has shown to significantly reduce seizure frequency when given in addition to other antiepileptic drugs. [34] lacosamide has been used as an off label drug in the management of psychiatric conditions including bipolar disorder, depression, mania, dementia, OCD, and panic disorder.

Mechanism of action:
Lacosamide is believed to act through voltage-gated sodium channels [35] by enhancing the slow inactivation of voltage-gated channels without affecting the fast inactivation of voltage-gated channels. This inactivation prevents the channel from opening, helping to end the action potential. [35] lacosamide also modulates collapsin response mediator protein 2, preventing the formation of abnormal neuronal connections in the brain.[36]
Lacosamide does not affect dopaminergic, serotonergic, adrenergic, muscarinergic or cannabinoid receptors and does not block potassium or calcium currents. [37] And it does not affect GABA directly or its transaminase. [37]

Five studies (1863 participants) with chronic painful diabetic neuropathy and one study (159 participants) with fibromyalgia were included. All were parallel group designed with placebo controlled, randomized, double blinded of 8 weeks or longer.
Peripheral diabetic neuropathy studies:
All studies had a study duration of 10 – 18 weeks, with stable maintenance phases of 4 (one study) or 12 weeks.
Fibromyalgia study:
The only study had a duration of 12 weeks.
The doses used were 400 mg and 600 mg daily intake of lacosamide, given as a divided dose. Too little data with a daily intake of 200 mg were available to make an analysis on the benefits, however the adverse effects will be evaluated. [18]

Results:
Lacosamide had limited efficacy in the treatment of peripheral diabetic neuropathy. Higher doses did not give consistently better analgesic effects, but had a significantly increased rate of withdrawals due to adverse event. Regarding fibromyalgia, only one study, with 159 participant, were included with a daily intake of 400 mg. It showed analgesic effect on the same line as when lacosamide were used for treating peripheral diabetic neuropathy. However, since only one study with a low number of participants were included, one cannot draw certain conclusions regarding lacosamid's analgesic effects on fibromyalgia. It is therefore likely that lacosamide is without any useful benefit in treating neuropathic pain due to the insufficient benefits and the increasing rate of withdrawals due to adverse events as the dosage increases.

Table 3.1: Efficacy with different doses of lacosamide in different pain conditions. [18]

Outcome – Daily dose	Number of		Percent with outcome		RR (95% CI)	NNTB (95%CI)
	Studies	Participants	Lacosamide	Placebo		
Moderate benefit (≥30% reduction of pain on a VAS scale) - Peripheral diabetic neuropathy						
400 mg	4	715	54	44	1,3 (1,1-1,5)	9,8 (5,7-36)
600 mg	2	407	54	30	1,8 (1,3-2,3)	4,3 (3,0-7,3)
Substantial benefit (≥50% reduction of pain on a VAS scale) - Peripheral diabetic neuropathy						
400 mg	2	412	35	25	1,4 (1,01-1,9)	10 (5,2-120)
600 mg	2	407	28	25	1,1 (0,79-1,6)	Not calculated
PGIC much/very much improved (the top 2 categories on the standard 7-point scale) - Peripheral diabetic neuropathy						
400 mg	4	715	33	24	1,5 (1,2-1,9)	12 (6,6-52)
600 mg	2	408	24	17	1,4 (0,92-2,1)	Not calculated
PGIC much/very much improved (the top 2 categories on the standard 7-point scale) – Fibromyalgia						
400 mg	1	159	37	27	Not calculated	Not calculated

NNTB: Number needed to treat for an additional beneficial outcome

As shown in table 3.1 there was no increase in the efficacy when the dose of lacosamide was increased and only a limited benefit of using lacosamide compared to placebo.

Table 3.2: Adverse event with different doses of lacosamide. [18]

Number of			Percent with outcome			
Outcome – daily dose	Studies	Participants	Lacosamide	Placebo	RR (95% CI)	NNTH (95% CI)
Any adverse event						
200 mg	2	392	78	81	0,95 (0,86-1,1)	Not calculated
400 mg	5	874	72	68	1,1 (0,99-1,2)	Not calculated
600 mg	3	594	79	73	1,1 (1,01-1,2)	Not calculated
Serious adverse events						
200 mg	2	392	4,3	7	0,59 (0,25-1,4)	Not calculated
400 mg	5	1304	6,6	6,3	1,02 (0,66-1,6)	Not calculated
600 mg	3	594	8	6	1,4 (0,74-2,6)	Not calculated

NNTH: Number needed to treat for an additional harmful outcome

As shown in table 3.2 there is no significant difference between lacosamide and placebo on any adverse event. In the serious adverse events category we can see an increasingly rate of report of events as the dosage increases.

Table 3.3 withdrawals with different doses of lacosamide. [18]

	Number of		Percent wit outcome			
Outcome/daily dose	Studies	Participants	Lacosamide	Placebo	RR (95% CI)	NNTH (95% CI)
All causes						
200 mg	2	392	30	29	0,99 (0,72-1,4)	Not calculated
400 mg	5	874	34	28	1,3 (1,03-1,6)	16 (7,9-345)
600 mg	3	594	55	26	2,1 (1,7-2,7)	3,4 (2,7-4,7)
Lack of efficacy						
200 mg	2	392	3,4	2,5	1,3 (0,4-4,3)	Not calculated
400 mg	5	874	3,6	5,9	0,63 (0,34-1,2)	Not calculated
600 mg	3	594	4,4	3	1,4 (0,57-3,3)	Not calculated
Adverse events						
200 mg	2	392	11	11	0,92 (0,51-1,7)	Not calculated
400 mg	5	874	18	9,1	2,01 (1,4-2,9)	11 (7,5-22)
600 mg	3	594	35	9,1	3,8 (2,5-5,8)	3,9 (3,2-5,1)

As shown in table 3.3 an increasingly number of participants withdrew from the study due to adverse events as the dosage increased. There was no significant difference in withdrawals due to lack of efficacy.

Oxcarbazepine:

Background:
Oxcarbazepine is a anti convulsant and mood stabilizing drug used for treating epilepsy, anxiety, mood disorders, benign motor tics and neuropathic pain, which have been under some argument. In September of 2010 Novartis pled guilty to marketing oxcarbazepine for the unapproved use of neuropathic pain. [38] However, it is in use as an off label drug for neuropathic pain.

Mechanism of action:
The mechanism of action is not fully understood However, oxcarbazepine and its rapidly formed metabolite 10-monohydroxy (MHD) limits the frequency of firing of sodium-dependent action potentials by cultured mouse central neurons and reduce Vmax progressivly in a use dependent manner at concentrations below therapeutic plasma concentrations in oxcarbazepine- treated patients. This suggest that blockage of voltage sensitive sodium channels could contribute to the antiepileptic effect. Additional actions e.g. an effect on potassium channels might be clinically important. [39]

Three multicenter, randomized, placebo-controlled, double-blind trials with a total of 634 participants were included that investigated oxcarbazepine in people with chronic painful diabetic neuropathy. These were from a series of studies funded by the manufacturer.
The three included trials all had a large sample of participants and standardized protocols. The methodological quality of the trials was assessed according to the Cochrane “Risk of bias” tool. All three trials were rated as at a high risk of bias mainly because of a large and imbalanced proportion of missing outcome data across groups.
These trials were of moderate quality and only included data from the single positive trial, and did not take into account negative results regarding oxcarbazepine's effect on peripheral diabetic neuropathy since they did not meet the inclusion criteria for this review. [19]

Results:
Even though the results indicate that oxcarbazepine has some effect on painful diabetic neuropathy, there is not enough data to draw any conclusions. For further disclosure, see discussion.

Table 4.1 oxcarbazepine (1800mg/day) versus placebo for painful diabetic neuropathy. Median follow-up after 16 weeks. [19]

Outcome	Percent with outcome		RR (95% CI)	No of participants (studies)	NNTB/NNTH (95% CI)
	Placebo	Oxcarbazepine			
Reduction in patient reported pain score by 50% from baseline (VAS)	18,20%	34,80%	RR 1,91 (1,08-3,39)	146 (1 study)	NNTB 6,0 (3,3-41,0)
Reduction in patient reported pain scores by 30% from baseline (VAS)	28,60%	44,90%	RR 1,57 (1,01-2,44)	146 (1 study)	NNTB 6,1 (3,1-113,6)
Patients with obvious or significant improvement after 16 weeks treatment	30,10%	43,90%	RR 1,46 (1,13-1,88)	493 (2 studies)	NNTB 6,4 (4,1-14,4)
Serious adverse effects	2,5%	9,10%	RR: 3,65 (1,45-9,2)	634 (3 studies)	NNTH 17,4 (11,0-42,0)

As shown in table 4.1 34% of the participants who received oxcarbazepine had a 50% reduction in pain from the baseline as measured in VAS compared to 18,2% in the placebo group. 9.1% of the participants in the oxcarbazepine group reported serious adverse effects while 2,5% in the placebo group reported serious adverse effects

Table 4.2 oxcarbazepine versus placebo for painful diabetic neuropathy, adverse effects. [19]

Adverse events leading to withdrawals			
Oxcarbazepine		Placebo	RR (95% CI)
No of studies	Percentage	Percentage	
Adverse events			
3 studies 634 participants	25,60%	6,80%	3,83 (2,29-6,40)
Serious adverse events			
3 studies 634 participants	8,30%	2,50%	3,65 (1,45-9,20)

As shown in table 4.2 there are significantly higher percentage of reported adverse events and serious adverse events leading to withdrawal.

Valproic acid and sodium valproate

Background:
Valproic acid was first synthesized in 1882 by B.S Burton, but it was first used as a antiepileptic drug in 1962 when its anti-seizure properties was discovered. Today it is one of the most commonly used antiepileptic drugs. [40]
Valproic acid is a liquid at room temperature, but it can be mixed with a base such as sodium hydroxide to form the salt sodium valproate, which is a solid at room temperature and may be administered as a pill. They are both anticonvulsant and mood stabilizing drugs, used primarily for the treatment of epilepsy, manic or mixed episodes associated with bipolar disorder and prevention of migraine headaches, but they have also been used in the treatment of neuropathic pain as an off label drug. [41]

Mechanism of action:
The mechanisms of action is not fully understood , but it has been shown to protect against reduction in phosphatidylinositol (3,4,5) triphosphate (PIP3) as a potential mechanism of action. [42] In addition, its anticonvulsant effects has been attributed to the blockade of sodium voltage dependent channels and increased levels of GABA in the brain. [43]

Results:
There is some evidence that valproic acid and sodium valproate may have some effect on painful diabetic neuropathy and post herpetic neuralgia. There is however a lack of studies done to come to any conclusion. For further disclosure, see discussion.

Three studies was included with a total of 130 participants, 66 who got medication and 64 who got placebo. [20]
Agrawal 2009 [44] and Kochar 2004 [45] both considered the use of sodium valproate in the treatment of chronic diabetic neuropathy using prospective, single centered, randomized, double blinded placebo controlled trials of three months duration.
Kochar 2005 [46] considered the use of divalproex sodium (valproic acid and sodium valproate in molar ratio 1:1) in the treatment of chronic post herpetic neuralgia also using prospective, single centered, randomized, double blinded placebo controlled trials, but of eight weeks duration.

Table 5.1 Treatment of painful diabetic neuropathy with sodium valproate. [20]

Study	Medication and dosage	Participants who got medication	Participants who got placebo	Mean VAS before test medicated	Mean VAS before test placebo	Mean VAS after 3 month medicated	Mean VAS after 3 month placebo	P-value
Agrawel 2009			20		7,4 ± 0,3		6,2 ± 0,3	P<0,01
Agrawel 2009	20 mg/kg/day	20		8.0 ± 0,2		6,9 ± 0,2		P<0,001
Kochar 2004	500 mg/day	21		6.0 ± 2,0		3.0 ± 2,1		P<0,001
Kochar 2004			18		5,7 ± 1,7		6,0 ± 1,8	

VAS: Visual Analogue Scale, subjective pain scale from 0 – 10 where 0 is no pain and 10 is the worst thinkable pain.

As shown in table 5.1 both studies show a decrease in the reported pain using the VAS scale. However in the Agrawel 2009 study the mean pain reported after the treatment remained above 6

which is considered moderate to severe pain. In the Kochar 2004 study did the participant receiving sodium valproate decrease their lever of reported pain to 3 on the VAS scale, which is considered to be mild.

Table 5.2 Treatment of post herpetic neuralgia with Divalproex (valproic acid and sodium valproate in molar ratio 1:1) Kochar 2005 study only. Duration 8 weeks. [20]

Dosage	Participants with treatment	Participants with placebo	Completed the study	Participants with >50% pain relief	Mean VAS before study	Mean VAS after study	P-Value
1000mg/ day	23		22	13 (57%)	7.0 ± 0,9	3,1 ± 3.0	P<0,0001
		22	18	2 (8,7%)	6,3 ± 0,9	5,5 ± 1,8	

As shown in table 5.2 in the group who got treated with Divalproex 57% of the participants had 50% or more pain relief, while 8,7% in the placebo group reported the same effect.

Table 5.3 reported adverse effects. [20]

	Number of participants reporting				
Study - group	Nausea	Sedation	Change in liver enzymes	Minor drowsiness	Severe vertigo
Agrawal 2009 – Placebo	1 (5%)	0	0	0	0
Agrawal 2009 – Medicated	2 (10%)	1 (5%)	1 (5%)	0	0
Kochar 2004 - medicated	2 (9,5%)	0	1 (4,8%)	1 (4,8%)	0
Kochar 2004 – placebo	No data	No data	No data	No data	No data
Kochar 2005 - medicated	3 (13%)	0	0	0	1 (4,3%)
Kochar 2005 – placebo	No data	No data	No data	No data	No data

As shown in table 5.3 there were higher a number, and more severe, of reported adverse effects in the groups who received the medication than placebo. However, two of the studies only reported adverse effects in the group who received the medication. It is unknown whether this is due to lack of adverse effects in the placebo group.

Main results

Table 6.0 comparison between drugs.

Drug and dosage that had the best effect	Number of studies	Number of participants	Conditions studied	Percentage with at least 50% pain relief	Percentage with at least 30% pain relief	Percentage reporting adverse effect	Percentage reporting severe adverse effect
Gabapentin (1200-3600 mg/day)	37	5633	PHN, PDN	PHN: 34% PDN: 38%	PHN: 54% PDN: 54%	62,00%	3,20%
Pregabalin (600 mg/day)	19	7003	PHN, PDN, CNP, FIM	PHN: 41% PDN: 45% CNP: 24% FIM: 25%	PHN: 62% PDN: 63% CNP: 39% FIM: 43%	83,00%	3,70%
Lacosamide (400 mg/day)	5	1863	PDN	PDN: 35%	PDN: 54%	72,00%	6,60%
Oxcarbazepine (1800 mg/day)	3	634	PDN	PDN: 44,9%	PDN: 34,8%	-	9,10%
Valproic acid & sodium valproate (20 mg/kg/day to 500 mg/day)	3	130	PDN, PHN	PDN: 1 study reduced the mean VAS from 8±0,2 to 6,9±0,2 with 20mg/kg/day 1 study reduced the mean VAS from 6,0± 2,0 to 3,0±2,1 with 500 mg/day PHN: 1 study with 45 participants achieved 50 % pain reduction in 57% with 1000 mg/day Between 5% to 10% reported minor adverse effects (nausea, sedation, minor drowsiness) while 4,3% to 5% reported severe adverse effects (Severe vertigo, change in liver enzymes)			

PHN: Post herpetic neuralgia
PDN: Painful diabetic neuropathy
CNP: Central neuropathic pain
FIM: Fibromyalgia

As shown in table 6.0, there were little difference in efficacy between PHN and PDN where they have been tested with the same drug. Participants with CNP or FIM did not report as good results as participants with PDN or PHN given the same treatment. All of the drugs had a high number of participants reporting some form of adverse effects, except for oxcarbazepine were these numbers were not available. Oxcarbazepine is however the drug were the participants reported the most severe adverse effects. Gabapentin and pregabalin fared the best when it came to reporting severe adverse effects.

Gabapentin and pregabalin clearly produced the best results when pain relieving effects are weighted against the adverse effects. The large number of studies and participants give extra weight to choosing gabapentin or pregabalin as a first hand choice in treating neuropathic pain.

The efficacy of pregabalin increased with dosage and hence the best dosage for relieving pain for pregabalin was 600 mg/day, since it was the biggest dose given in the trials. But at the same time the severe adverse events reported increased with dosage. It should be noticed that there were no significantly higher risk of adverse or severe adverse effect between gabapentin, pregabalin and placebo.

The optimal dosage for relieving pain for gabapentin is unclear since the author of the underlying review combined the results for daily dosage between 1200 mg/day to 3600 mg/day. Here it is more difficult to know if there is a clear dose/adverse event relationship since the authors of the

underlying article compiled the data for all dosages.

It seems however that pregabalin should be the first drug of choice, followed by gabapentin, due to the higher percentage of participants reporting at least 50% and at least 30% pain relief compared to gabapentin.

Lacosamide did not produce as much pain relief and the participants reported more side effects than with gabapentin or pregabalin.

Oxcarbazepine did show some effects but did also produce the highest percentage of severe side effects. More independent research is needed before one can draw any conclusions since all of the trials that the underlying study was based on were funded by the manufacturer and was based on data from the single positive trail since the negative trails did not provide enough data to be included in this review.

Valproic acid and sodium valproate has shown some effectiveness at relieving pain, but there are insufficient amount of data to draw any conclusion. Since the studies done on valproic acid and sodium valproate did not use the same system of reporting their results, comparison between valproic acid and sodium valproate and other drugs were difficult. It could be that when more research has been done that it will show that valproic acid and sodium valproate have a place in the treatment of neuropathic pain. However, the data included in this study could not conclude whether valproic acid and sodium valproate has any definite benefits in the treatment of neuropathic pain.

DISCUSSION

There are limited knowledge about gabapentines effect on neuropathic pain conditions except post herpetic neuralgia, diabetic neuropathy and fibromyalgia. However, in this review I have only looked at post herpetic neuralgia and diabetic neuropathy. Therefore, gabapentin might have different degree of analgesic effect on different conditions of neuropathic pain.

Gabapentin is one of the most researched antiepileptic drugs used in the treatment of neuropathic pain, and the large number of studies/participants included in this study give the results a lot of weight.

We can see that "only" 34% to 38% of the participants who received gabapentin had their pain reduced by 50% while 21% of the participants who received placebo experienced the same results. This shows that gabapentin is not a miracle drug to cure neuropathic pain, and at the same time it is notoriously difficult to predict who will benefit from the treatment. The studies that this review was based on used different methods of reporting their findings and hence the data had to be pooled in large groups to be able to find commonalities so they could be evaluated against each other. Therefore it is not possible to draw any conclusions about the optimum dosage of gabapentin or the optimum/minimum treatment period.

On the other hand it has been shown that gabapentin has an effect on treating neuropathic pain and since the studies show that there is no significant higher risk of adverse effect between gabapentin and placebo, it still one of the first line drug for treating neuropathic pain.

Daily doses of pregabalin of 300 mg to 600 mg produced useful benefits for patients with painful diabetic neuropathy, post herpetic neuralgia, central neuropathic pain and fibromyalgia. The PGIC much or very much improved ranged from 35% to 50%, and a daily dose of 150 mg did not showed conclusively any benefits. This shows that more than half of the patients being treated with pregabalin will not have any substantial benefit from it.

Pregabalin is one of the antiepileptic drugs used for treatment of neuropathic pain that have been researched the most. Therefore, combined with the large amounts of participants in this study, these findings are considered to give a good estimate of what patients in general practice can expect.

Lacosamide has shown, at best, marginal benefits for treating peripheral diabetic neuropathy, while the serious adverse event were significant with clear dose response.

This study only evaluated lacosamide's effect on peripheral diabetic neuropathy and fibromyalgia. And while the studies on peripheral diabetic neuropathy show no/little significant benefit of treatment with lacosamide, there is insufficient data to give a conclusive answer regarding fibromyalgia or any other neuropathic pain condition. However, I can see no obvious reason why lacosamide should have a significant better response regarding other forms of neuropathic pain.

The results indicate a potential effect in relieving pain in patients suffering from painful diabetic neuropathy. However, such results were mainly based on data from the single positive trail since the negative trails did not provide enough data to be included in this review. Therefore, the efficacy of oxcarbazepine for painful diabetic neuropathy is still uncertain. We can also conclude that there is a significant higher chance of adverse effects compared to placebo.

All of these trials had been founded by the manufacturer and were rated as having a high risk of bias judged by the Chochrane «risk of bias tool». Therefor more research is necessary before a conclusion can be made.

There is some evidence that valproic acid and sodium valproate may be effective in treatment of painful diabetic neuropathy and post herpetic neuralgia. However the scant evidence indicate that further analyses is required before these medications can be used in the mainstream treatment of neuropathic pain. They should only be tried when other treatment have failed or are not tolerated. Sodium valproate alone has not been evaluated in this review.

Gabapentin and pregabalin has the best results when the efficacy, adverse effects and amount of research done are being weighed against each other for the different drugs included in this review. It is however difficult to select which one of them should be the first hand choice since they gave similar results. Gabapentin seems to produce a little poorer pain relief and produces less adverse effect, while the severe adverse effect were practically the same. Pregabalin produced marginally pain relief but somewhat more adverse effects. It should be noticed that there were no significantly higher risk of adverse or severe adverse effect between gabapentin, pregabalin and placebo.

It is notable that none of the drugs included in this study could give more than 50% of the participants >50% pain relief. This shows how difficult it is to treat neuropathic pain with drugs. Both since it is not fully understood as a disease and since it has sub groups that can vary greatly in etiology. It is also difficult to predict who will benefit from the treatment, for the same reasons.

Neuropathic pain is chronic in nature with a mean duration of 7 years. All of the conditions discussed in this review are chronic and the results are not meant to be compared with the efficacy of the individual drugs to lessen acute pain. This study has not come to any conclusion of an optimal intervention period.

To be able to compare one drug against another they must be tested with the same method and evaluated according to the same scale. This turned out to be a problem in some cases when different scales and methods were used or different ways of reporting the results was implemented. As with valproic acid and sodium valproate where the results had to be discussed separately.

It is also clear that even though gabapentin and pregabalin has been researched extensively, there is still work to be done on other drugs before one can draw a final conclusion on whether they have any place in the treatment of neuropathic pain. And more research need to be done regarding other groups of neuropathic pain before one can truly call the drug to be effective against neuropathic pain.

Only mono therapy has been evaluated in this review and the limitations that this entail should be taken into account. Especially since neuropathic pain has a lot of comorbidity and is a multifaceted disease that require a multi angel approach. There are several other treatment practices that are used for the treatment of neuropathic pain, and medical poly therapy can come into play.

It is likely that the results in this review would change somewhat if a more extensive search would have been made. It is however unlikely that there will be any significant change in the results regarding gabapentin and pregabalin, given the same criteria, since the large amount of data in the underlying studies included in this study.

This review has not taken into account that some countries will not use pregabalin as a first hand drug since it might be more expensive than other alternative.

Neuropathic pain consist of many underlying diagnoses and one cannot draw the conclusion that if a drug has worked on one condition, the same results would be expected on another condition, as the results of this review show. The most common researched condition was painful diabetic neuropathy in these studies, and that made it easier to compare the efficacy between drugs. We can also see that the same drug and dosage could have very different effects on different types of pain conditions that are chronic in nature.

In the results the efficacy of the drugs to relieve pain, adverse effect and the amount of research done of the drugs were subjectively weighted by me to come to a conclusion of which drug should be the first hand choice

Even though gabapentin and pregabalin seems to be the best choices of drugs for treating neuropathic pain. There is still many patients that will not have any significant benefit from the drug but might get the adverse effects, and it is up to the practitioner and the patient to decide if it is worth trying.

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