Research Paper

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Pain phenotype as a predictor for drug response in painful polyneuropathy—a retrospective analysis of data from controlled clinical trials

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Abstract

The drugs available for treatment of neuropathic pain have somewhat disappointing efficacy with many patients left with limited or no effect. Individualized treatment based on phenotype according to presumed underlying pain mechanism(s) has been proposed to improve outcomes. We report a retrospective analysis of phenotype-specific effects of several neuropathic pain drugs, which were studied in a series of crossover, placebo-controlled, clinical trials. The data originate from 7 trials with similar design and outcome recordings, which all had a thorough baseline registration of symptoms, signs, and quantitative sensory testing. The latter was used to phenotype patients into subgroups reflecting presumed pain mechanisms. There were a total of 361 patient records distributed over treatments with 4 antidepressants and 4 anticonvulsants. Five of the drugs reduced total pain significantly compared with placebo. Only a few phenotype-specific differences in total pain reduction were found within the investigated drugs. Thus, imipramine reduced total pain 1.84 (CI: 0.02-3.67) and pregabalin 0.81 (CI: −0.67 to 2.29) in patients with than without gain of sensory function. Pregabalin showed a better effect in patients with preserved large fiber function with a mean difference in total pain reduction 1.31 (CI: 0.15-2.47). No phenotype-specific effects were found for venlafaxine, escitalopram, oxcarbazepine, valproic acid, levetiracetam, or St. John's wort. Thus, this post hoc analysis of 8 drugs with mainly nonselective actions on neuropathic pain mechanisms found limited usefulness of sensory phenotyping in pain as the basis for individualized treatment.

Keywords: Neuropathic pain, Sensory phenotype, Treatment, Anticonvulsants, Antidepressants, Pain mechanisms

1. Introduction

Treatment of peripheral neuropathic pain is challenging because less than 50% of the patients obtain sufficient pain relief with the first-line treatments.[10] Furthermore, several controlled drug trials failed to find an effect, although preclinical and early proof-of-concept trials with the drugs had been promising.[4,14,26,31,32] It has been suggested that this may be caused by heterogeneity of the patient populations that were studied[2,11,28] and that the drugs may actually work particularly well in subgroups of patients. Response to specific drug treatments could be related to the underlying pain mechanisms. Several mechanisms of neuropathic pain have been suggested from experimental trials, and in clinical peripheral neuropathic pain, the pattern of mechanisms at play probably differs amongst patients.[16,33] Theoretically, an optimal response to drug treatment in an individual would be obtained if the particular pain mechanism(s) at play in that exact patient matches the mechanism(s) of action of the drug. A major obstacle towards pursuing mechanism-based treatment of peripheral neuropathic pain is that the mechanism or pattern of mechanisms at play in each patient cannot easily be determined.

A crude way to assess mechanism(s) is to perform a sensory phenotyping of patients based on their pain symptoms, sensory signs, and quantitative sensory testing (QST). Using this approach, subgroups of patients can be delineated, which possibly reflect underlying pain mechanisms.[2] For example, in patients with preserved thermal sensation and any sign of gain of sensation, ectopic activity in nociceptors due to upregulation of sodium channels could be an important mechanism. Recently, it has been reported that patients with this "irritable nociceptor" phenotype achieve a better pain relief on the sodium channel blocker oxcarbazepine than patients without this phenotype.[8] Another phenotype has severe deafferentation of the painful area as its main characteristic. Typical symptoms and signs here are numbness or sensory loss on QST, and no symptoms or signs of sensory gain. Such patients are supposed to have pain-generating mechanisms located in the more proximal part of the nerve or in the central nervous system (CNS) and are therefore expected to respond to centrally acting drugs.

Trials on the effect of drugs used for peripheral neuropathic pain in relation to subgroups according to pain phenotype or pain mechanisms are sparse and inconclusive (for review, see Ref. 2). A recent retrospective analysis of data from a duloxetine and pregabalin combination treatment trial in painful diabetic neuropathy used phenotypes based on cluster analysis of specific pain symptom severity instead of symptom constellations reflecting pain mechanism and did not reveal any clinically important results.[5] We report a retrospective analysis of phenotype-specific effects of several neuropathic pain drugs which were studied in a series of

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Table 1

Overview of studies and drugs.

	Total	Combination trial	Venlafaxine	St. John's wort	Escitalopram	Valproic acid	Levetiracetam	Oxcarbazepine
Trial number		1	2	3	4	5	6	7
Drug number, dosage × times a day		Imipramine: 75 mg × 1; pregabalin: 150 mg × 2	Imipramine: 75 mg × 2; venlafaxine: 112.5 mg × 2	St. John's wort: 2700 μg × 1	Escitalopram: 20 mg × 1	Valproic acid: 1500 mg × 1	Levetiracetam: 1500 mg × 2	Oxcarbazepine: 1200 mg × 2 or 900 mg × 2*
Trial duration, wk (per period)		5	4	5	6	4	6	6
Observations, n	361	111	63	47	41	36	34	29
Age, y, median (range)	59 (21-82)	59 (29-82)	55 (31-69)	59 (30-82)	62 (37-74)	60 (34-81)	57 (21-74)	61 (44-75)
Sex, male/female	237/124	69/42	45/18	31/16	29/12	22/14	21/13	20/9
Etiology of polyneuropathy, n (%)								
Idiopathic	138 (38)	41 (37)	22 (35)	20 (42)	14 (34)	12 (33)	16 (47)	13 (45)
Diabetic	115 (32)	22 (20)	25 (40)	18 (38)	19 (46)	15 (42)	9 (27)	7 (24)
Alcohol	39 (11)	20 (18)	10 (16)	1 (2)	4 (10)	1 (3)	1 (3)	2 (7)
Drug induced	18 (5)	7 (6)	0 (0)	4 (9)	0 (0)	2 (5)	1 (3)	4 (14)
Other	51 (14)	21 (19)	6 (9)	4 (9)	4 (10)	6 (17)	7 (20)	3 (10)
Pain baseline, NRS,† median (range)	5.5 (1.5-10)	6.5 (4-10)	5.0 (1.5-9.5)‡	4.0 (1.0-7.0)‡	6.0 (3.0-9.0)	6.5 (3.0-9.0)	6.0 (4.0-9.0)	6.5 (4.0-9.0)§
Pain duration, mo, median (range)	54 (6-300)	62 (9-240)	52 (6-300)	49 (8-124)	51 (8-180)	39 (9-120)	47 (6-120)	64 (6-216)

* Oxcarbazepine doses at 2400 mg/d as standard, 1800 mg/d for patients >70 years of age. Adjustable dosage (because of side effect profile): mean daily dosage was 1684 to 1846 mg.
† NRS: numeric rating scale 0 to 10 points (0 = no pain, 10 = worst pain ever).
‡ Baseline scores as summation of 4 specific pain symptoms (constant pain, pain paroxysms, touch-evoked pain, and pain on pressure) on the NRS (nonmodified).
§ Oxcarbazepine study had 2 baseline periods, one before each treatment period. The value given is an average of the 2 baseline periods.

almost uniform, placebo-controlled clinical trials. The trials had similar design, used nearly the same outcomes, and all had at trial entrance a thorough registration of symptoms, signs, and QST. The analysis was preformed to explore whether there was any signs of phenotype-specific effects on pain of the different drugs.

2. Methods

2.1. Study design

This was a retrospective analysis of data from 7 randomized, double-blind, placebo-controlled, crossover trials[8,14,15,21,22,27,29] of almost similar design. The trials were performed at Odense University Hospital, Aarhus University Hospital and Aalborg University Hospital from 1999 to 2014. All the included trials met the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized, controlled trials and have been reported in detail previously.

2.2. Patients

Patients with painful polyneuropathy of various etiologies were included in the analysis. Patients were male and female, age >18 years, and had symptoms compatible with polyneuropathy for more than 6 months with distal symmetric pain localisation and sensory disturbance in the area of pain. Polyneuropathy diagnosis had to be confirmed by clinical signs and electrophysiological tests or skin biopsy. In most of the trials,[8,14,15,21,22] the patients had to have a median total pain rating of at least 4 on a 0- to 10-point numeric rating scale (NRS) (0 = no pain, 10 = worst possible pain) during 1 week of pain medication. In 2 trials,[27,29] it was sufficient with at least 4 on the NRS for 1 of 4 specific pain phenomena, ie, constant pain (burning, pressing, or deep aching), pain paroxysms, touch-evoked pain, or pain on pressure. To be included in the analysis, the patients needed to have data from at least 2 treatment periods (one being a placebo period). Therefore, in the 3- and 4-armed studies,[14,27] a number of patients were included based on observations from only 2 periods. The trials were designed to investigate the independent effect of the drugs on peripheral neuropathic pain. Hence, all concomitant treatments for neuropathic pain used before inclusion were either discontinued or patients on such treatments excluded. Other causes of pain were exclusion criteria in all 7 trials. Please confer articles on individual trials[8,14,15,21,22,27,29] for the exact inclusion and exclusion criteria.

2.3. Randomization and treatment

For patients with ongoing medication for their neuropathic pain, treatments were slowly discontinued during a prestudy period of 1 week. After 1 further week for baseline observations, the patients entered the computer-generated, randomized treatment sequence with treatment periods of 4 to 6 weeks duration. Treatment periods were separated by 1 or 2 week(s) for washout. Drug doses and duration of treatment periods are detailed in **Table 1**. All trials were double blind with some of them using trial drugs of identical appearance and some using double-dummy technique.[14,27] Paracetamol in doses up to 3000 mg were used as escape medication. In 2 trials,[8,15] additional tramadol 50 mg daily was allowed as escape medication.

2.4. Assessments

2.4.1. Symptoms

The data used in the analysis originated from ratings in diaries. All ratings were entered in diaries in the morning covering the symptoms experienced during the preceding 24 hours. Total pain intensity (5 trials) and specific pain symptoms (all trials) were rated using the 0 to 10-point NRS throughout all baseline and treatment periods. For the 2 trials[27,29] in which total pain intensity was not scored, the mean score of the 4 registered specific pain symptoms (constant pain, paroxysms, touch-evoked, and pain on pressure) was used. Because this would lead to an unrealistically low total score for some patients (eg, a patient with 4 on constant pain and 0 on the 3 other pain symptoms would have a total pain intensity of 1), we used a correction factor, making the patients' baseline score = 10 (similar to the method used in Ref. 27).

2.4.2. Bedside examination

A full clinical examination was performed by a neurologist at the time of inclusion. The examination included assessment of muscular function, deep tendon reflexes, vibration sensation, touch sensation (hypoesthesia), pinprick sensation (hyperalgesia), temperature sensation, and dynamic mechanical allodynia.

2.4.3. Quantitative sensory testing

The most painful site on each individual patient was located, and QST was performed at this site at baseline. The following was assessed: pressure pain thresholds with pressure algometer (Somedic AB, Stockholm, Sweden) (all trials); mechanical allodynia by stroking skin with a sponge rubber brush,[14,15,21] or stroking skin with cotton wool[22] or stimulation with an electronic toothbrush[27,29]; cold allodynia with Thermoroller at 20°C (Somedic AB, Stockholm, Sweden)[14,15,21] or application of a drop of acetone[22]; pain by repetitive pinprick stimulation using von Frey hair, 2 Hz during 30 seconds (all trials); cold and warm detection

Table 2

Definition of phenotypes by symptoms and signs/QST.

	% of patients*	Symptoms/signs/QST
By symptoms		
IRN	14	No numbness and (tingling/prickling and burning pain and paroxysms)
Ecto	63	Paroxysms of lancinating pain
Deaff	49	Numbness and (no mechanical allodynia or no cold allodynia)
By signs/QST		
GAIN	79	Mechanical allodynia or cold allodynia or pain on pressure or hyperalgesia
LOSS	37	(Abnormal cold or warm detection threshold) and (mechanical hypoesthesia or abnormal vibration)
IRN	62	(Normal cold and warm detection threshold) and GAIN
Wind-up	47	Pain on repetitive mechanical pinprick
Deaff LF	22	(Mechanical hypoesthesia and abnormal vibration) and (normal cold or warm detection threshold)
Deaff SF	9	(Abnormal cold and warm detection threshold) and (no mechanical hypoesthesia or normal vibration)
Normal LF	15	No mechanical hypoesthesia and normal vibration
Normal SF	54	Normal cold and warm detection threshold

* Percentage of patients with that specific phenotype. Patients may be included in several phenotypes.
Deaff LF, deafferentation large fibers; Deaff SF, deafferentation small fibers; Deaff, deafferentation; Ecto, Ectopic activity; GAIN, gain of sensation; IRN, irritable nociceptor; LOSS, loss of sensation; Normal LF, normal large fibers; Normal SF, normal small fibers; QST, quantitative sensory testing.

thresholds with a Thermotest (Somedic AB) (all trials). The oxcarbazepine trial differed by having used the standardized QST protocol of the German Research Network on Neuropathic Pain.[25]

2.4.4. Phenotypes

The pain phenotype subgrouping was performed in an attempt to reflect underlying mechanism(s) as suggested in previous publications.[2,25,30] Subgrouping was based on pain symptoms, sensory signs, QST, or a combination of such. The dichotomous data used in the analysis came from baseline registration of symptoms (numbness, tingling, burning, paroxysms, mechanical and cold allodynia), signs at clinical examination (hypoesthesia, hyperalgesia, vibration), and findings on QST (mechanical and cold allodynia, pain on pressure, pain on repetitive stimuli, cold and warm detection thresholds). For pain on pressure and cold and warm detection thresholds, the reference values from the German Research Network on Neuropathic Pain[25] were used. Pain on repetitive stimulation was set to be abnormal if the pain registered by the patient during stimulation increased. The phenotype definitions are described in **Table 2**.

2.4.5. Drugs

The analysis contains 8 drugs with possible mode(s) of action that could affect mechanism(s) in the pain pathway. Four antidepressants including the first-line treatments tricyclic antidepressant (TCA) (imipramine) and serotonin-norepinephrine reuptake inhibitor (SNRI) (venlafaxine) and 4 anticonvulsants also including first-line treatment pregabalin are presented in the analysis. An overview of the presumed mode(s) of action of each of the 8 drugs is provided in **Figure 1**.

2.5. Data analysis and statistics

The median value of total pain intensity ratings was determined for baseline and the last week of each treatment period. If the patient stopped the treatment prematurely, the last week with observations was carried forward (LOCF). In all 7 trials, LOCF was only performed for patients having sufficient data on a steady-state dose of that particular drug. We calculated mean differences with 95% CIs in drug vs placebo responses for the 2 drug groups (antidepressants and anticonvulsants) and each individual drug. For each drug, we determined the change in total pain intensity from baseline to end of treatment and present the mean

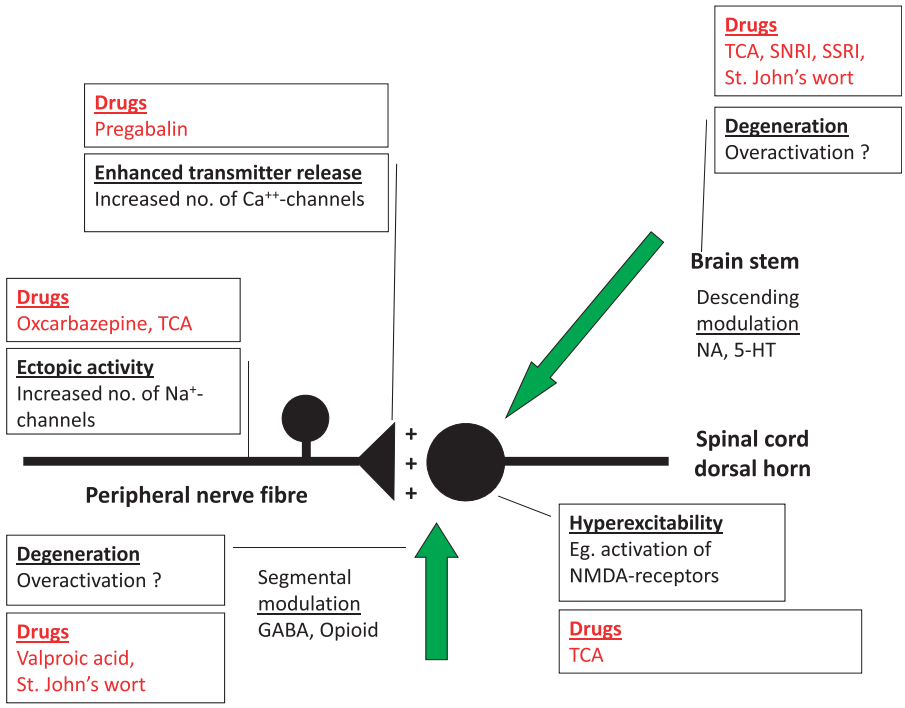

Figure 1. Presumed pain mechanisms and mode of action of drugs. Many pain mechanisms are presumably at play in peripheral neuropathic pain. Ectopic activity is probably driven by upregulation of sodium channels in the peripheral nerves. In the dorsal horn degeneration of inhibitory GABAergic interneurons, upregulation of calcium channels and activation of NMDA-receptors are presumed to be main mechanisms of pain enhancement. Further "up-steam" changes in the ascending and descending monoaminergic modulatory projections and probably also within the brain itself are of interest for modulating pain signals. Drugs within the antidepressant and anticonvulsant categories have main mode of action corresponding to some of these presumed mechanisms. Antidepressants: venlafaxine (SNRI) and escitalopram (SSRI) are mainly modulating signaling in the descending pain pathways from the brainstem to the dorsal horn but also interact with circuits in the brain. Imipramine (TCA) is also supposed to cause a weak blockade of the NMDA-receptors and have sodium channel effects. St. John's wort contains many biological active compounds and could affect pain signals at many levels. The main mechanism of action is presumed to be a weak inhibition of MAO-A and MAO-B and an inhibition of synaptosomal uptake of the monoamine neurotransmitters, thereby increasing the synaptic levels of all 3 monoamine neurotransmitters: serotonin, norepinephrine, and dopamine. However, St. John's wort has also been shown to have affinity for the adenosine, GABA, and glutamate receptors. Anticonvulsants: pregabalin interfere with the voltage-gated calcium channels in the dorsal horn by inhibiting the upregulation of channels and by direct calcium influx reducing effects. Levetiracetam binds to the transmembrane vesicle protein SV2A and thereby interacts with the calcium-dependent exocytosis of neurotransmitter into the synaptic gap probably at many levels in the CNS. Oxcarbazepine works mainly by blocking the voltage-sensitive sodium channels on the peripheral nerves but may also have an effect on calcium and potassium channels. Valproate has multiple actions but the potentiating effect on GABA inhibition in the dorsal horn is probably the main target in relation to pain. 5-HT, serotonin; CNS, central nervous system; MAO, monoamine oxidase; NA, norepinephrine; NMDA, N-methyl-D-aspartate; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; GABA, gamma-aminobutyric acid. References can be found in the original studies. For St. John's wort also see review by Butterweck V 2003.[6]

difference with 95% CIs for patients having each particular phenotype vs patients not having that phenotype (phenotype-specific difference). It was anticipated that some of the specific phenotype groups would be rather small and placebo adjustments would have a tendency to minimize minor difference that might be present. Therefore, we presented all values as pure responses to the drugs. The phenotype-specific differences for the placebo response were calculated separately to insure no major bias was introduced.

3. Results

3.1. Observations

The total data set consisted of 361 patient records—86 for imipramine, 56 for pregabalin, 47 for St. John's wort, and between 29 and 41 for the remaining 5 drugs. In 106 (29%) of observations, LOCF was used. An overview of the origin of the data together with basic information from the 7 studies and their patients are provided in **Table 1**. In the imipramine and pregabalin combination study,[14] 52 patients had data from both drugs to be compared with placebo data. In addition, 4 patients had data from pregabalin only (leading to 56 patient records for pregabalin), and 3 patients had data from imipramine only (leading to 55 patient records for imipramine). In the venlafaxine vs imipramine study,[27] 31 patients had full data and further 1 patient had data from venlafaxine only (leading to 32 patient records for venlafaxine). The median baseline pain score was 5.5 on the NRS, and the median duration of pain was 54 months.

3.2. Drug(s) vs placebo

The mean differences in total pain score between baseline score and end of treatment score for the various drugs and placebos are shown in **Figure 2**. In the 2 overall groups, the active drug reduced pain significantly more than placebo, antidepressants with the largest effect. Imipramine, venlafaxine, escitalopram, pregabalin, and oxcarbazepine reduced pain more than placebo, whereas levetiracetam and valproic acid and St. John's wort did not have a significant effect over placebo.

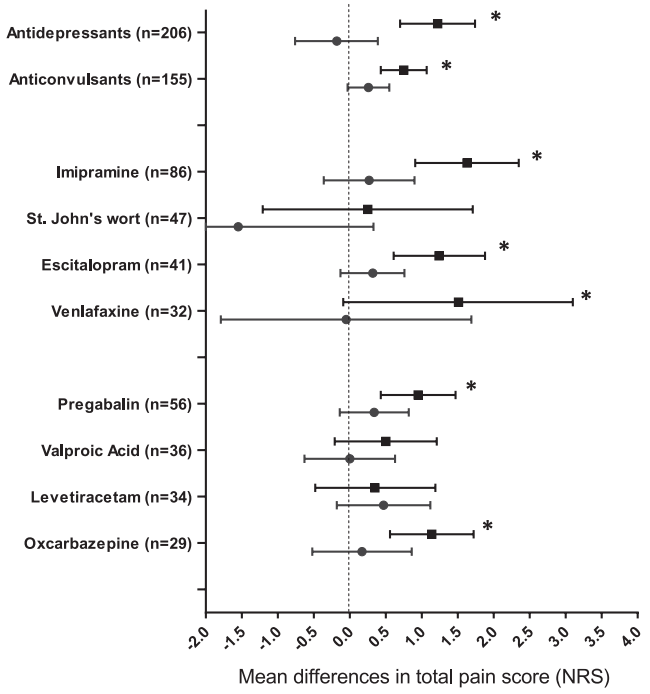

Figure 2. Mean differences (CI) in total pain intensity reduction from baseline to last week of treatment for drug/drug group (■) and placebo (•). A positive score represents a reduction in pain. *Significantly different from placebo. NRS, numeric rating scale 0 to 10 point (0 = no pain, 10 = worst pain ever).

3.3. Drug(s) by phenotype

The mean difference amongst patients with or without the described phenotype, ie, the phenotype-specific difference in total pain intensity on the NRS caused by the drug(s), is shown in **Figures 3 and 4**.

3.4. Antidepressants (n = 206)

Significant differences and strong trends for each of the individual antidepressants are shown in **Figure 3**. For imipramine, the phenotype with gain of sensation had a difference = 1.84 (CI: 0.02-3.67). For escitalopram, the phenotype with general loss had a difference = 0.98 (CI: 0.31-2.28). For St. John's wort, a difference = 2.98 (CI: −0.06 to 6.02) for the phenotype ectopic activity (paroxysms) and also a strong trend for normal small fiber function with a difference = 2.70 (CI: −0.15 to 5.54) was found. For venlafaxine, only trends were found.

3.5. Anticonvulsants (n = 155)

Significant differences and strong trends for each of the individual anticonvulsants are shown in **Figure 4**. For pregabalin, the phenotype with normal large fiber function had a difference = 1.31 (CI: 0.15 to 2.47) and the phenotype with deafferentation of large fibers had a difference = −1.74 (CI: −0.51 to −2.97). Also, a trend was found for the phenotype gain of sensation with a difference = 0.81 (CI: −0.67 to 2.29). For oxcarbazepine, the phenotype with deafferentation of large fibers (n = 7) had a difference = −1.31 (CI: −0.03 to −2.60). For valproic acid, a strong trend was found for the phenotype gain of sensation with a difference = 1.26 (CI: −0.17 to 2.69). For levetiracetam, the phenotype irritable nociceptor (IRN) (signs/QST) had a difference = −1.71 (CI: −0.11 to −3.30), and strong trends were found for the phenotype deafferentation of large fibers with a difference = 1.48 (CI: −0.31 to 3.27) and normal large fiber function with a difference = −2.06 (CI: −4.34 to 0.23).

3.6. Placebo by phenotype

There were no significant phenotype-specific differences in the total pain reduction with placebo treatments (P = 0.17-0.97), except for the phenotype with normal large fibers, P = 0.03.

4. Discussion

This post hoc analysis of 7 randomized controlled trials comprising 8 drugs for the treatment of peripheral neuropathic pain focused on phenotype-specific effect of the drugs. In the nonselected total patient groups, the effect of 5 of the drugs separated nicely from placebo, whereas 3 drugs had no or only marginal effect on pain. The 5 drugs that separated from placebo comprised the first-line treatments imipramine, venlafaxine, and pregabalin as well as the lower ranking drugs, escitalopram and oxcarbazepine.

Many of the drugs showed no phenotype-specific effect, ie, there was no specific phenotype that achieved a better response on that particular drug. Only few significant phenotype-specific

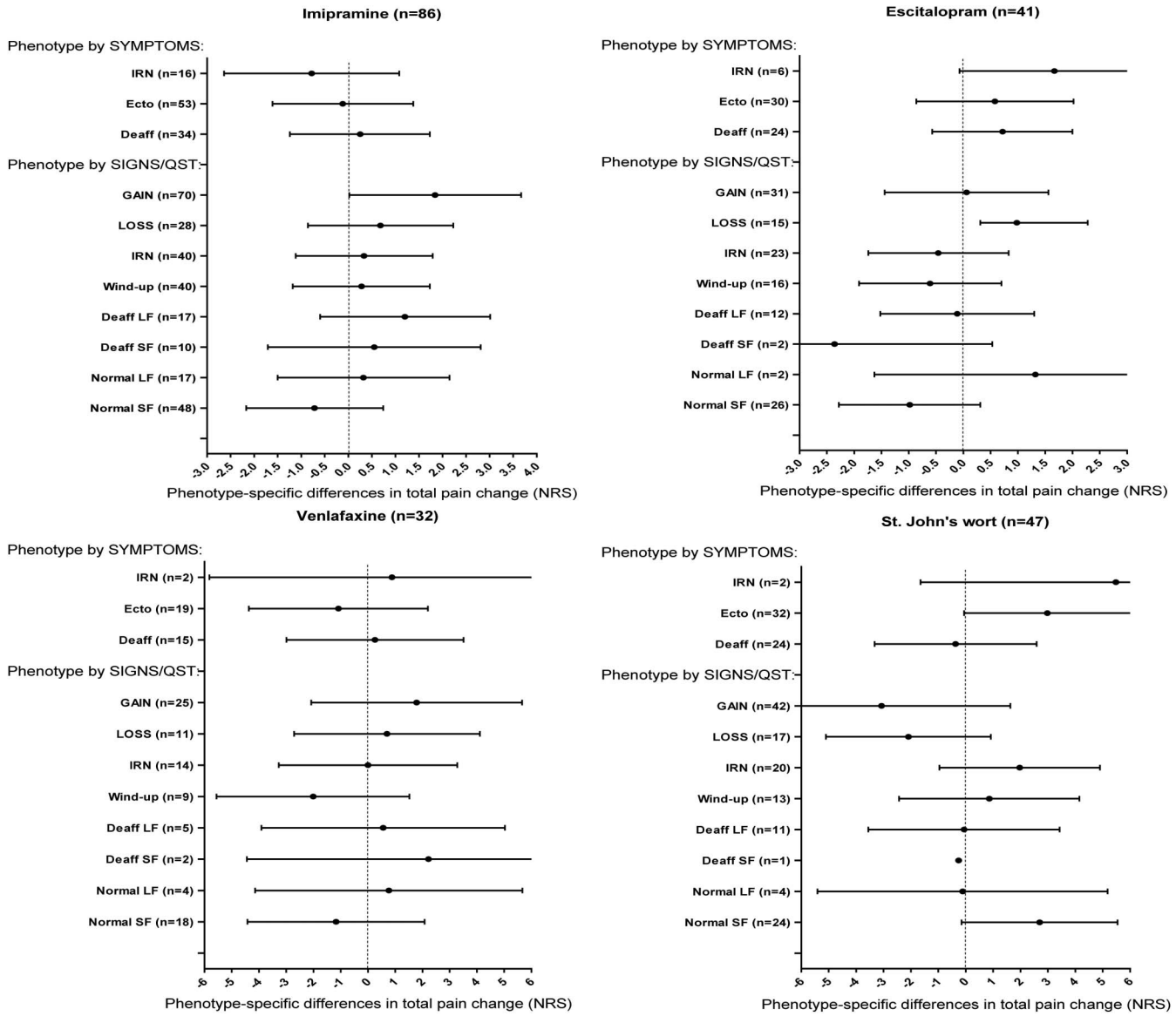

Figure 3. Phenotype-specific differences in change in total pain for specific antidepressant drugs presented as mean difference with 95% CIs between patients with and without the actual phenotype. Number of patients (n) indicated. For phenotype abbreviations, see Table 1. Deaff LF, deafferentation of large fibers; Deaff SF, deafferentation of small fibers; Deaff, deafferentation; Ecto, ectopic activity; GAIN, gain of sensation; IRN, irritable nociceptor; LOSS, loss of sensation; Normal LF, normal large fibers; Normal SF, normal small fibers; NRS, numeric rating scale 0 to 10 point (0 = no pain, 10 = worst pain ever).

differences and strong trends were found. The lack of clear-cut phenotype-specific effect is not surprising and emphasizes the fact that these drugs are heterogeneous with either unspecific or multiple molecular mechanisms of action.

Within the antidepressant group, the TCA imipramine and the SNRI venlafaxine are most important because they are both first-line treatments.[10] There was a larger response on imipramine in patients with gain of sensation. There were no phenotype-specific effects of venlafaxine. With respect to suggested mechanism of action, these 2 antidepressants share a mono-aminergic action with presynaptic reuptake inhibition of serotonin and norepinephrine and differ by imipramine having an additional sodium channel blocking effect.[28] This difference would explain whether the effect on, eg, IRNs had been better on imipramine and not on venlafaxine, but there was no such difference. There was a trend towards better effect of venlafaxine with the sensory gain phenotype, and maybe the lack of phenotype separation is caused by small sample size. It does make sense that TCA may work well in patients with sensory gain which can be due to both peripheral as well as central pain mechanisms. These mechanisms could be targeted by the descending inhibitory control systems, which are supposed to be activated by the mono-aminergic effect of the drugs. Better response to escitalopram in patients with general sensory loss or IRN based on symptoms, and of St. John's wort in patients with paroxysmal pain or patients with preserved small fiber function is not easily explained and may be spurious findings. Escitalopram, which works on serotonin receptors only,[21] did not seem to provide any special benefit to the patients with gain of sensory function. Hence, the norepinephrine effects of imipramine and venlafaxine may be another explanation why these 2 drugs affect the phenotype with gain of sensory function. Further support to the notion on norepinephrine as major transmitter in the descending inhibitory control systems are found in studies on conditioned pain modulation (CPM), in which it was shown that the efficacy of duloxetine (a balanced SNRI drug) and tapentadol (a combined

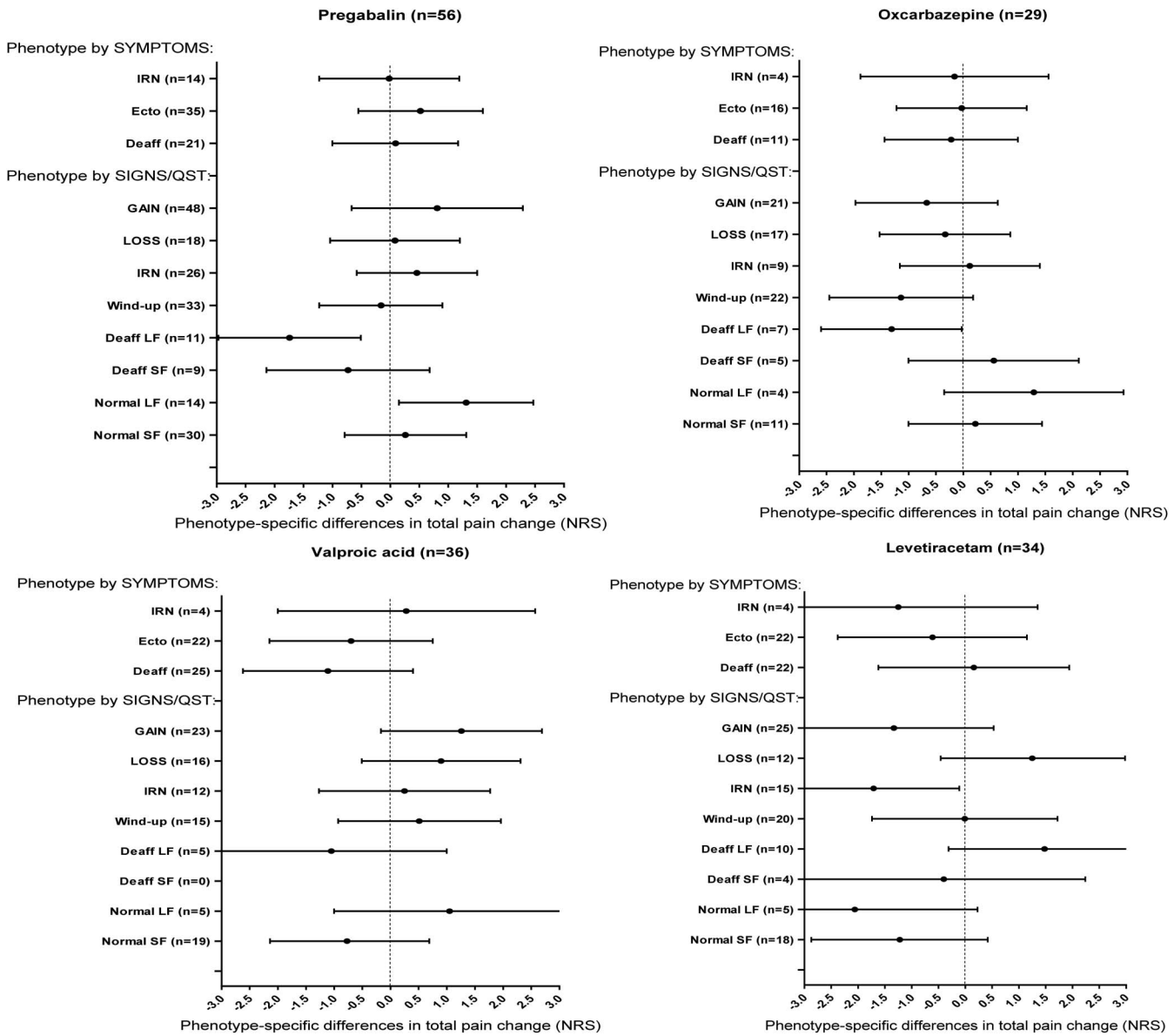

Figure 4. Phenotype-specific differences in change in total pain for specific anticonvulsant drugs presented as mean difference with 95% CIs between patients with and without the actual phenotype. Number of patients (n) indicated. For phenotype abbreviations, see Table 1. Deaff LF, deafferentation of large fibers; Deaff SF, deafferentation of small fibers; Deaff, deafferentation; Ecto, ectopic activity; GAIN, gain of sensation; IRN, irritable nociceptor; LOSS, loss of sensation; Normal LF, normal large fibers; Normal SF, normal small fibers; NRS, numeric rating scale 0 to 10 point (0 = no pain, 10 = worst pain ever).

μ-opioid receptor agonist and norepinephrine reuptake inhibitor) is dependent on activation of descending inhibitory pain pathways.[20,36]

The effect of the first-line anticonvulsant pregabalin is apparently linked to large fibers, with better effect with preserved large fibers and less effect with loss of fibers. The same pattern was seen for valproic acid, and pregabalin and valproic acid also share a tendency towards better effect in patients with gain of sensation. For oxcarbazepine and levetiracetam, the phenotype groups with indication of some specific effects were too small to allow for a valid conclusion. As for antidepressants, patients with gain of sensation may benefit most from the centrally acting anticonvulsants pregabalin and valproic acid. Pregabalin interacts with the $\alpha_2\delta$ subunit of the voltage-dependent calcium channels,[3,9] and this diminishes neurotransmitter release and thus impulse transmission maybe several places in the pain pathway in CNS. The main mechanism of valproic acid is to increase gamma-aminobutyric acid (GABA) levels in the CNS and potentiate GABA responses,[18] and with GABA being an inhibitory transmitter, this may reduce neural activity.

Thus, this analysis points at gain of sensation as a phenotype which should be attacked by centrally acting drugs of both antidepressant and anticonvulsant types. Taking the multiple mechanisms of action and the site of action "up-stream" in the pain pathway of the antidepressant imipramine and the anticonvulsant pregabalin into account, it is not surprising that we do not see major differences between the drugs. Furthermore, this may explain that none of these drugs have pronounced phenotype-specific effects. It is doubtful whether sensory phenotyping will be able to distinguish between different CNS mechanisms of neuropathic pain. Moreover, these types of drugs are not ideal for search of phenotype-specific effects. In line with this, the current evidence for phenotype-specific effects is on drugs with selective mechanism of action and in patients with a phenotype

suggesting a distinct peripheral mechanism of action.[7,8,23] For example, the IRN phenotype in peripheral neuropathic pain with a presumed mechanism involving upregulated sodium channels on nociceptors predicts the response of the rather selective sodium channel blocker oxcarbazepine.[8]

Clinical phenotypes based on symptoms, signs, and QST do not directly reflect the underlying molecular mechanism of pain.[1,2,16] This is actually what is needed to be able to match the molecular mechanisms of the drugs we used. Sensory phenotyping is at best suggestive of molecular mechanisms and location of pain generation. These methods are used because it has been difficult to translate the pathophysiological mechanisms identified in animal experiments[1] into the clinic as suggested decades ago.[19,34,35] It has been difficult to convincingly predict an effect of antidepressant and anticonvulsant drugs on neuropathic pain in clinical practice.[24] In addition to unclear relationships between molecular pain mechanisms and clinical symptoms and signs, the complexity of both the biology of pain modification and pharmacology of the compounds used for neuropathic pain may explain this fact.

The present analysis has certain limitations. First, although the 7 studies were performed uniformly and with a detailed patient characterization, this is a retrospective analysis of data that were not collected with the purpose of studying phenotype-specific effects. Second, the phenotyping did not follow the QST protocol of, eg, the German Network on Neuropathic Pain[25] or the standardized multidimensional symptom registration of the Neuropathic Pain Symptom Inventory.[12] However, our data contained similar information with respect to a thorough rating of specific pain symptoms test, test of signs, and affection of different nerve fiber type and function by QST or clinical examination. Third, the definition of the various phenotypes is a topic of discussion. Although inspired by the large cluster analysis,[2,25,30] there are no certain definitions of any phenotype, and other definitions of the phenotypes could possibly have led to other results and perhaps a different conclusion. Fourth, the inclusion of 3 overall negative studies might serve as a diluting factor and bias results. However, one or all of these drugs could have an effect on a specific phenotypic subgroup, which is exactly the reason for doing subgroup exploratory analysis. Fifth, the treatment periods are rather short (4-6 weeks). However, this is common for crossover designs, and treatment periods in each study were settled based on drug pharmacokinetics and the time for response usually seen in studies in this type of pain. Another problem is that the number of patients within some phenotype categories was too low to provide useful information. This was probably the case for oxcarbazepine, escitalopram, venlafaxine, and valproic acid. Finally, most of the drugs included in the analysis had pharmacological actions which are nonspecific[13,17] and not ideal with respect to studying phenotype-specific action, ie, multiple mechanisms of action and/or less well-defined site(s) of action (see above).

It may be a problem that this exploratory analysis includes patients with polyneuropathy only. Patients with other types of damage to the peripheral nervous system, such as traumatic nerve injuries or postherpetic neuralgia, might have shown a different pattern in the sensory phenotype profiles and also given different results. For future trials, we would recommend to include patients with various causes of peripheral neuropathic pain in a prospective design with random treatment allocation. The patients should be stratified in sensory phenotypic subgroups or in CPM subgroups at baseline. The specific approach, ie, sensory phenotyping or CPM would depend on the drug(s) which had to be tested, and drugs with a single mechanism of action would be preferable. If the drug mechanism was believed to be one primarily working on central or descending pain pathways, CPM should be included as the most appropriate method of phenotyping.

In conclusion, many of the drugs do not show any marked phenotype-specific effects. The TCA imipramine and the calcium channel $\alpha_2\delta$ ligand pregabalin may have advantages in patients with a phenotype characterized by gain of sensory function. The effect of pregabalin seems to be better in patients with preserved large fiber function. Thus, phenotyping may be useful to improve treatment outcome, but it will probably only become more meaningful, as more selective compounds targeting specific molecular mechanism are being developed. Prospective phenotype stratification may possibly improve the outcomes of future clinical trials of neuropathic pain. But so far we need more convincing evidence for this concept.

Conflict of interest statement

F. W. Bach reports to have been compensated as an investigator in clinical trials on neuropathic pain sponsored by Pfizer and Grünenthal. N. B. Finnerup reports personal fees from Pfizer, grants and personal fees from Grünenthal, personal fees from Astellas, personal fees from Norpharma, grants from EU/EFPIA; outside the submitted work. T. S. Jensen reports to be on Advisory Board for Pfizer, Grünenthal and Orion. The other authors have no conflicts of interest to declare.

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References

[1] Attal N, Bouhassira D. Pharmacotherapy of neuropathic pain: which drugs, which treatment algorithms? PAIN 2015;156(suppl 1):S104–14.
[2] Baron R, Förster M, Binder A. Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach. Lancet Neurol 2012;11:999–1005.
[3] Bauer CS, Nieto-Rostro M, Rahman W, Tran-Van-Minh A, Ferron L, Douglas L, Kadurin I, Sri Ranjan Y, Fernandez-Alacid L, Millar NS, Dickenson AH, Lujan R, Dolphin AC. The increased trafficking of the calcium channel subunit alpha2delta-1 to presynaptic terminals in neuropathic pain is inhibited by the alpha2delta ligand pregabalin. J Neurosci 2009;29:4076–88.
[4] Beydoun A, Shaibani A, Hopwood M, Wan Y. Oxcarbazepine in painful diabetic neuropathy: results of a dose ranging study. Acta Neurol Scand 2006;113:395–404.
[5] Bouhassira D, Wilhelm S, Schacht A, Serge P, Kosek E, Cruccu G, Freynhagen R, Tesfaye S, Lledo A, Choy E, Marchettini P, Micó JA, Spaeth M, Skljarevski V, Tölle T. Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomised, double-blind, COMBO-DN study. PAIN 2014;155:2171–79.
[6] Butterweck V. Mechanism of action of St John's wort in depression: what is known? CNS drugs 2003;17:539–62.
[7] Campbell CM, Kipnes MS, Stouch BC, Brady KL, Kelly M, Schmidt WK, Petersen KL, Rowbotham MC, Campbell JN. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. PAIN 2012;153:1815–23.
[8] Demant D, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup N, Jensen TS, Sindrup SH. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled, phenotype stratified study. PAIN 2014;155:2263–73.
[9] Fink K, Dooley DJ, Meder WP, Suman-Chauhan N, Duffy S, Clusmann H, Göthert M. Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology 2002;42:229–36.

[10] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice ASC, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73.
[11] Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. PAIN 2010;150:573–81.
[12] Freeman R, Baron R, Bouhassira D, Cabrera J, Emir B. Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs. PAIN 2014;155:367–76.
[13] Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol 2013;12:1084–95.
[14] Holbech JV, Bach FW, Finnerup NB, Brøsen K, Jensen TS, Sindrup SH. Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. PAIN 2015;156:958–66.
[15] Holbech JV, Otto M, Bach FW, Jensen TS, Sindrup SH. The anticonvulsant levetiracetam for the treatment of pain in polyneuropathy: a randomized, placebo-controlled, cross-over trial. Eur J Pain 2011;15:608–14.
[16] Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. PAIN 2003;102:1–8.
[17] Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. Lancet Neurol 2014;13: 924–35.
[18] Löscher W. Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. Prog Neurobiol 1999;58:31–59.
[19] Max MB. Towards physiologically based treatment of patients with neuropathic pain. PAIN 1990;42:131–7.
[20] Niesters M, Proto PL, Aarts L, Sarton EY, Drewes AM, Dahan A. Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. Br J Anaesth 2014;113:148–56.
[21] Otto M, Bach FW, Jensen TS, Brøsen K, Sindrup SH. Escitalopram in painful polyneuropathy: a randomized, placebo-controlled, cross-over trial. PAIN 2008;139:275–83.
[22] Otto M, Bach FW, Jensen TS, Sindrup SH. Valproic acid has no effect on pain in polyneuropathy: a randomized, controlled trial. Neurology 2004; 62:285–8.
[23] Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurol 2008;64:274–83.
[24] Rasmussen PV, Sindrup SH, Jensen TS, Bach FW. Therapeutic outcome in neuropathic pain: relationship to evidence of nervous system lesion. Eur J Neurol 2004;11:545–53.
[25] Rolke R, Baron R, Maier C, Tölle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Bötefür IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihöfner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. PAIN 2006;123:231–43.
[26] Shaibani A, Fares S, Selam JL, Arslanian A, Simpson J, Sen D, Bongardt S. Lacosamide in painful diabetic neuropathy: an 18-week double-blind placebo-controlled trial. J Pain 2009;10:818–28.
[27] Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology 2003;60:1284–9.
[28] Sindrup SH, Jensen TS. Are sodium channel blockers useless in peripheral neuropathic pain? PAIN 2007;128:6–7.
[29] Sindrup SH, Madsen C, Bach FW, Gram LF, Jensen TS. St. John's wort has no effect on pain in polyneuropathy. PAIN 2001;91:361–5.
[30] Scholz J, Mannion RJ, Hord DE, Griffin RS, Rawal B, Zheng H, Scoffings D, Phillips A, Guo J, Laing RJ, Abdi S, Decosterd I, Woolf CJ. A novel tool for the assessment of pain: validation in low back pain. PLoS Med 2009;6:e1000047.
[31] Thienel U, Neto W, Schwabe SK, Vijapurkar U. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurol Scand 2004;110:221–31.
[32] Vinik AI, Tuchman M, Safirstein B, Corder C, Kirby L, Wilks K, Quessy S, Blum D, Grainger J, White J, Silver M. Lamotrigine for treatment of pain associated with diabetic neuropathy: results of two randomized, double-blind, placebo-controlled studies. PAIN 2007;128:169–79.
[33] von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron 2012;73:638–52.
[34] Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. Life Sci 2004; 74:2605–10.
[35] Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain? PAIN 1998;77:227–9.
[36] Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. PAIN 2012;153:1193–8.