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Alleviation of pain in painful diabetic neuropathy

Journal:	<i>Expert Opinion On Drug Metabolism and Toxicology</i>
Manuscript ID	EOMT-2016-0021.R1
Manuscript Type:	Review
Keywords:	antidepressants, antiepileptics, diabetes, metabolism, painful neuropathy, pharmacodynamics, pharmacokinetics, treatment

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Alleviation of pain in painful diabetic neuropathy

For Peer Review Only

Abstract

Introduction: Painful diabetic neuropathy (PDN) is a disabling pain condition. Its pathomechanism remains unknown, but a sensitization and neuronal hyperexcitability have been suggested. Only symptomatic pharmacological pain-alleviation treatment is currently available.

Areas covered: The origin of PDN is enigmatic, and the evidence-based therapeutic guidelines therefore consist only of antidepressants and antiepileptics as first-line recommended drugs. This article relates to a MEDLINE/PubMed systematic search (2005-2015).

Expert opinion: The results of the meta-analysis from the aspect of the efficacy of amitriptyline, duloxetine, venlafaxine, gabapentin and pregabalin are favorable, but the placebo response rate is relatively high in patients with neuropathic pain. For personalization of the medication of PDN patients, the optimum dosing, the genotyping of the metabolizing enzymes and optimum biomarkers are needed. As concerns the future perspectives, specific sodium channel subtype inhibitors acting on peripheral nociceptive neurons or modified T-type voltage-gated calcium channel blockers may be promising targets for pharmaceutical innovations. Another attractive strategy for the treatment is based on the effects of monoclonal antibodies against nerve growth factor, sodium channel, specific receptor and cytokines. Botulinum toxin A, capsaicin patch and spinal cord stimulation therapies are the nearest future therapeutic options for the treatment of PDN patients.

Keywords: antidepressants, antiepileptics, diabetes, metabolism, painful neuropathy, pharmacodynamics, pharmacokinetics, treatment

Article highlights

- The pathomechanism of painful diabetic neuropathy is unknown, and therefore only symptomatic non-specific treatment is available.
- As a tricyclic antidepressant, amitriptyline has multimodal action, and is effective with a favorable number needed to treat, but it exerts many unfavorable adverse events related to its pharmacological profile.
- The selective serotonin-norepinephrine reuptake inhibitor duloxetine has been subjected to pharmacogenomic studies.
- Venlafaxine has a strong dose-dependent effect and due to its extended release formulation, the treatment-related adverse events are low.
- Gabapentin as an antiepileptic has no metabolism and no drug-drug interactions with a high adherence level.
- Pregabalin as a gabapentinoid with linear kinetics has been strongly recommended for the treatment of painful diabetic neuropathy.

1. Introduction

Neuropathic pain (NP), one of the most devastating pain conditions by definition caused by a lesion or disease of the somatosensory system [1]. It has distinct clinical features with a heterogeneity of different causes [2, 3]. Neuropathic sensory symptoms characterized by spontaneous or evoked pain is described as electric shock-like or burning, and other sensory disturbances such as paraesthesia, dysaesthesia, allodynia, hyperpathia or hyperalgesia. The symptoms of painful diabetic neuropathy (PDN) occur symmetrically in the distal parts of the extremities in an ascending manner [4, 5]. The aetiology of NP involves a wide range of peripheral or central nervous system (CNS) disorders, including diabetic and other metabolic neuropathies, dysimmune neuropathies, postherpetic neuralgia, trigeminal neuralgia, human immunodeficiency virus (HIV)-associated neuropathy or pain after spinal cord injury, post-stroke pain, multiple sclerosis-associated pain or cancer-related pain [5].

Diabetes mellitus is a modern global medical challenge with an estimated prevalence of 366 million patients in 2030 [6]. Recent epidemiological data showed that the estimated presence of NP was around 7% of the general population in Europe [7]. Diabetic neuropathy occurs in 59-66% of insulin-dependent (type 1) and non-insulin-dependent (type 2) diabetic patients [8]. The adjusted incidence of diabetic polyneuropathy is 54 per 100,000 persons per year [9]. Several studies have reported a prevalence of PDN of 10.9-20.0% [10]. Diabetic neuropathy and pain occur more frequently in type 2 diabetes mellitus, in women and in non-Caucasians [6].

The personal and socio-economic impact of PDN is high, influencing the quality of life, the work productivity and the functional disability of the patients [11]. The total annual direct medical costs for PDN were recently estimated as 27,931 USD and for severe PDN as 30,755 USD [11]. PDN has a significant impact on the health-related quality of life [12].

The pathomechanism of NP has not yet been completely clarified, but the sensitization process is widely accepted as playing an important role. Hyperexcitability and sensitization in NP similar to migraine as a primary headache disorder involve changes in the peripheral nervous system and CNS [5, 13-16]. One of the key elements of the peripheral sensitization is the increased expression of voltage-gated sodium channels $Na_v1.8$ and $Na_v1.9$ on lesioned peripheral nerves, which are the sources of ectopic pain impulse generation. The upregulation of sodium ion channels is a consequence of nerve growth factor (NGF) release from the damaged peripheral sensory nerve fibres [17]. **NGF is the first discovered member of the neurotrophin family. Other members of this family include brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5) [18]. The receptors**

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3 of these molecules belong to the tropomyosin receptor kinase (Trk) family. NGF binds to
4 TrkA with high affinity, whereas BDNF and NT-4 bind to TrkB, and NT-3 binds to
5 TrkC [19]. These molecules have a common Trk downstream pathway involved in the
6 induction of neuropathic pain [19]. Recent clinical findings have shown that anti-NGF
7 antibody and small molecule TrkA inhibitors alleviate neuropathic pain [18, 19].
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11 Ectopic primary afferent firing clinically explains the devastating spontaneous burning pain
12 and unpleasant electric shock-like sensations [20]. Another important mechanism of the
13 peripheral sensitization is the presence of the proinflammatory cytokines, **bradykinin,**
14 **prostaglandins, 5-hydroxytryptamine and histamine** ('inflammatory soup') along the
15 damaged peripheral nerve elements from the dorsal root ganglion (DRG) to the nociceptors in
16 the target tissue [17, 20-23]. **Human genetic studies revealed the important role of Nav1.7 in**
17 **pain sensation [24]. Nav1.7 is expressed in small-sized nociceptive DRG neurons [25] and**
18 **takes part in spinal cord nociceptive synaptic transmission involved in neuropathic pain**
19 **processing [26, 27]. The importance of Nav1.7 is also highlighted by the findings that its**
20 **expression level was found increased in DRG neurons in diabetic rats [28, 29].**
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28 Recent findings demonstrate the importance of the microglia function in the central
29 sensitization process. The central terminals of the damaged primary sensory neurons in the
30 spinal cord release adenosine triphosphate (ATP), which is able to activate the microglia via
31 purinergic (P2X4) receptors. The activated microglia releases the BDNF, which activates the
32 TrkB receptors, resulting in the down-regulation of the K⁺ - Cl⁻ cotransporter 2 of the
33 nociceptive second-order neurons in spinal lamina I. These nerve cells convey the information
34 to the thalamus (the third-order neurons) and project to the somatosensory cortex [21, 30].
35 Excitatory amino acids, mainly glutamate and its receptors (N-methyl-D-aspartate (NMDA)
36 receptors), have also been implicated in the pathomechanism of the NP [31]. The membrane
37 depolarization caused by nociceptive stimuli permits NMDA receptor-mediated synaptic
38 transmission. Calcium influx into the cells activates the non-receptor tyrosine kinase, which
39 leads to phosphorylation of the NMDA receptors [31]. This process leads to the glutamate-
40 related hypersensitivity of the neuronal cells [31] (**Figure 1**).
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50 PDN is an underdiagnosed and an undertreated condition in the daily clinical practice [4]. The
51 aim of this article is to give an overview of the current evidence-based symptomatic treatment
52 of PDN, focusing on the metabolism and toxicological properties of the strongly
53 recommended first-line drugs (antidepressants and antiepileptics) in order to promote good
54 clinical practice [3, 6, 32]. **We also provide data on future therapeutic options (i.e.**
55 **neutrophins, NO-donors, sodium channel blockers, monoclonal antibodies (mAb)**
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3 against Nav1.7, integrins and NGF, botulinum toxin type A, topical capsaicin patch,
4 TRPV1 and TRPA1 antagonists, and neuromodulation approaches), and give an outlook
5 toward personalized medicine. The realization of drug-drug and drug-gene interactions
6 (i.e. observed or inferred interactions between gene products and drug compounds) are
7 fundamental elements of novel pharmaceutical innovation and modern therapeutic
8 approaches for PDN patients [33].
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13 14 15 **2. Symptomatic pain treatment of PDN**

16 The exact pathomechanism of the origin of the pain, associated with diabetic neuropathy is
17 still lacking, and specific pharmacons for NP do not exist. The currently used drugs for NP
18 were originally developed for depression, epilepsy and cancer-related pain, but they are
19 effective at different levels in the alleviation of NP. This type of therapy is considered to be
20 successful in achieving at least a 50% pain intensity reduction [34]. In this field, it is an
21 important fact that the placebo effect for NP is higher than those for other disorders [4].
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26 Over recent decades, several therapeutic recommendations and guidelines for NP and PDN
27 have been put forward [6, 35, 36]. The recent evidence-based recommendations for the oral and
28 topical pharmacotherapy of NP were published by the Neuropathic Pain Special Interest
29 Group (NeuPSIG) of the International Association for the Study of Pain [3, 7]. The guideline of
30 NeuPSIG used the Grading of Recommendation Assessment, Development and Evaluation
31 (GRADE) system, which is based on the consensus on the rating of the quality of evidence
32 and strength of recommendations ranging from weak to strong for or against the treatment [3, 7,
33 37].
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39 This current survey analyses the pharmacological (pharmacokinetic and pharmacodynamic)
40 and toxicological properties (absorption, distribution, metabolism and excretion) of the first-
41 line (strong recommendation) drugs for PDN suggested by the NeuPSIG recommendations.
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46 47 **2.1. Antidepressants**

48 From the aspect of the efficacious treatment of PDN, among the antidepressive drugs tricyclic
49 antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are
50 beneficial. Their analgesic effect is independent of their antidepressant properties [7].
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55 56 57 **2.1.1. Tricyclic antidepressants (TCAs)**

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3 The group of TCAs involves amitriptyline (AMI), clomipramine, desipramine, imipramine
4 and nortriptyline. TCAs generally have similar efficacy as concerns PDN [3]. Particularly AMI
5 has been investigated in most clinical trials for PDN [6].
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9 10 **2.1.1.1. Amitriptyline (AMI)**

11 AMI is a more than 50-year-old drug, which was approved for the indication of depression by
12 the US Food and Drug Administration (FDA) in 1961, and is still in use for the treatment of
13 PDN world-wide [38].
14

15 The chemical structure of AMI is 3-(10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-ylidene)-
16 *N,N*-dimethylpropan-1-amine (**Figure 2**).
17

18 The mode of action of AMI is the inhibition of the re-uptake of norepinephrine and serotonin
19 at the adrenergic nerve endings in the synaptic cleft [39]. It has multimodal actions such as an
20 anticholinergic effect, histaminergic down-regulation, gamma-aminobutyric acid (GABA)-B
21 receptor up-regulation, α -adrenergic receptor antagonism and sodium, L-type calcium and
22 Kv1.1, Kv7.2, and Kv7.3 voltage-gated potassium ion channel blockade [34, 40, 41]. Importantly,
23 AMI is an agonist of the TrkA and TRkB receptors, so it influences the activation of the NGF
24 and BDNF [42]. It enhances the neuronal sensitivity to substance P, but does not inhibit the re-
25 uptake of dopamine or monoamine oxidase [39]. AMI increases the activation of the adenosine
26 A1 receptor, which leads to antinociception [40].
27

28 The pharmacokinetic parameters of 75 mg of an orally administered osmotic controlled
29 release tablet of AMI revealed that the maximum plasma concentration (C_{max}) was 15.3 (± 7.0
30 standard deviation, S.D.) ng/L, the area under the concentration vs. time curve (AUC) was
31 593 (± 229 S.D.) ng/mL x h, the time to C_{max} (T_{max}) was 25.7 (± 5.8 S.D.) h and the plasma
32 elimination half-life ($T_{1/2}$) was 20.4 (± 4.3 S.D.) h [39]. The bioavailability of AMI is 30-60%,
33 the protein binding is 96%. Its active metabolite is nortriptyline [43]. It is metabolized on the
34 first pass through the liver by cytochrome P450 (CYP450) isoenzymes (CYP2C19 and
35 CYP2D6) and is excreted renally (around 30-50%) (**Table 1**) [39].
36

37 As regards the pharmacogenetic aspects of AMI, the risk of the lack of efficacy or the
38 occurrence of side-effects depends on the types of metabolizer (poor, intermediate, extensive
39 or ultrarapid), and the genetic variations of CYP2C19 or CYP2D6 enzymes. The Clinical
40 Pharmacogenetics Implementation Consortium recommends therapeutic drug monitoring for
41 the guided dose adjustment [44].
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3 The results of clinical trials for managing PDN revealed a superior effect of AMI to placebo
4 [45]. The number needed to treat (NNT) of AMI is 1.3, which means an extremely good rank
5 (Table 2) [34]. The recommended daily dose of AMI for PDN is 25-100 mg [4].
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8 Due to its multimodal actions, AMI resulted in several unfavorable adverse events (AEs)
9 regarding anticholinergic, histaminergic, adrenergic, dopaminergic and serotonergic effects
10 [43]. The common (>1% frequency) AEs of AMI are dry mouth, fatigue, somnolence, weight
11 gain and dizziness [7, 46]. Contraindications for AMI use are a history of myocardial infarction,
12 arrhythmias, heart block, congestive heart failure, coronary artery insufficiency and severe
13 liver disease [47]. An increased risk of sudden cardiac death mainly occurs at a dosage of more
14 than 100 mg per day [3]. Caution is needed for AMI users with comorbidity, e.g. narrow angle
15 glaucoma, urinary retention, prostatic hypertrophy, a history of epilepsy or hyperthyroidism [7,
16 47].
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23 The Cochrane Database revealed that AMI was effective for the treatment of PDN, but its
24 wide-range use was limited by its unfavorable safety and tolerability profile [48]. The NeuSPIG
25 consensus declares that TCAs reached the strong recommendations for use in the treatment of
26 PDN [3].
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31 **2.1.2. Serotonin-norepinephrine reuptake inhibitors (SNRIs)**

32 SNRIs have dual effects: they are strong blockers of the reuptake of serotonin and
33 norepinephrine. The pharmacological group of SNRIs includes duloxetine (DUL), venlafaxine
34 (VEN), desvenlafaxine, milnacipran, levomilnacipran and sibutramine. For the treatment of
35 PDN, DUL and VEN have shown good efficacy [34].
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41 **2.1.2.1. Duloxetine (DUL)**

42 DUL was developed in 1988, and FDA approval for depression and PDN was dated in 2004
43 [34, 49]. The chemical structure of DUL is (+)-(S)-N-methyl-3-(naphthalen-1-yloxy)-3-
44 (thiophen-2-yl) propan-1-amine. It is a potent and selective dual neuronal SNRI
45 (serotonin:norepinephrine effects 10:1) [50]. It is a weak inhibitor of dopamine transporters and
46 does not have a strong effect on cholinergic, histaminergic, opioid, glutamate and GABA
47 reuptake transporters [51-53]. It does not block the monoamine oxidase types A or B [53]. DUL
48 has the capability to block the production and/or release of pro-inflammatory cytokines and/or
49 can also provoke the production of anti-inflammatory cytokines [54]. DUL has properties for
50 the modulation of nitroxidative stress by influencing the balance between pro-oxidant and
51 anti-oxidant processes [55]. One of the basic modes of action of DUL in the alleviation of pain
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3 in PDN is based on the blockade of the neuronal sodium ion channel ^[56]. DUL blocks
4 persistent late Nav1.7 Na⁺ currents preferentially, which may account in part for its analgesic
5 action ^[56]. In a preclinical study it was shown that the impaired norepinephrine homeostasis is
6 one of the major factors of the PDN model in rats, and the analgesic effect of DUL might be
7 due to the enhancement of noradrenergic signals ^[57].

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10 The pharmacokinetic parameters of **single oral dose of 60 mg of DUL tablet revealed that**
11 **C_{max} was 39-40.1 ng/L, AUC was 584-591 ng x h/mL, T_{max} was 6 h and T_{1/2} was 10.2 h** ^{[53,}
12 ^{58]}. The bioavailability of DUL is 50%, and the protein binding (mainly to albumin) is high
13 (>90%), and widely distributed throughout the tissues (the volume of distribution is
14 approximately 1640 L) ^[43, 53, 58]. The steady state of DUL is usually achieved by day 3 of
15 administration ^[53]. Its circulating metabolites are pharmacologically inactive. It is metabolized
16 by the liver (CYP1A2 and CYP2D6) and is excreted 70% in the urine and 20% in the faeces
17 ^[43].

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20 The pharmacokinetics of DUL is influenced by the demographic features of the patients, such
21 as sex, smoking, age, ethnicity, hepatic and renal function ^[58]. The genotype of the CYP2D6
22 enzyme also influences the pharmacokinetics of DUL ^[58]. A recent pharmacogenomic study
23 concluded that interleukin-6 variants (rs2066992 and rs10242595) may take part in DUL
24 response in patients with major depression ^[59]. In DUL-treated patients with major depressive
25 disorder, tests of the single-nucleotide polymorphisms demonstrated that variants in
26 corticotropin-releasing hormone receptor 1 were associated with the DUL response ^[60].

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29 As concerns the drug-drug interactions of DUL, it should be underlined that activated
30 charcoal diminishes DUL exposure and CYP1A2 blockade increases DUL exposure. In the
31 presence of fluvoxamine, the AUC of DUL is increased more than 400% and C_{max} is
32 increased more than 100% ^[58]. Smoking decreases the DUL plasma concentration (by 30%) ^[58].
33 In the presence of DUL with CYP2D6 inhibitors or in CYP2D6 poor metabolizers, the
34 exposure of DUL is less increased as compared with CYP1A2 inhibition ^[58]. DUL has the
35 capability to enhance the exposure of pharmaceuticals that are metabolized by CYP2D6, but not
36 CYP1A2 ^[58]. Pharmacodynamic trials suggested that DUL may enhance the effects of
37 benzodiazepines, but not alcohol or warfarin ^[58].

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40 The investigation of the AmpliChip CYP450 Genotyping Test for genes CYP2D6 and
41 CYP2C19 concluded that poor metabolizers accounted for around 7% of Caucasians for
42 CYP2D6 and around 25% of East Asians for CYP2C19, and ultra-rapid metabolizers for
43 CYP2D6 of around 29% in North Africa and the Middle-East ^[61, 62].

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3 The recent Cochrane Collaboration meta-analysis pointed out that 60 mg and 120 daily doses
4 of DUL were efficacious in the treatment of PDN [63]. The related NNT of benefit of DUL at
5 60 mg is 5 (95% confidential interval, CI 4 to 7) in the alleviation of pain in diabetic
6 neuropathy [63].
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9 The recommended daily dose of DUL for PDN is 60-120 mg once a day [3, 4].

10
11 Mild AEs of DUL were frequent at a high dose, such as nausea, dry mouth, headache,
12 dizziness and fatigue [7, 53, 63]. The common AEs of DUL (60 mg per day) are somnolence
13 (20%) and constipation (14%) [34, 64]. Severe AEs of DUL were rare [63]. Precautions for the
14 use of DUL are needed in cases of hepatic disorder, hypertension and concomitant medication
15 with tramadol [7].
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18 The NeuSPIG consensus declared that DUL reached the strong recommendations for use in
19 the treatment of PDN [3].
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23 24 25 **2.1.2.2. Venlafaxine (VEN)**

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27 VEN was launched on the pharmaceutical market after FDA approval in 1993, and VEN
28 extended release (XR) in 1997 [50]. Its chemical structure is (*RS*)-1-[2-dimethylamino-1-(4-
29 methoxyphenyl)ethyl]cyclohexanol.
30

31
32 VEN, as parent drug, and its active and structurally-similar major metabolite desvenlafaxine
33 (*O*-desmethylvenlafaxine) are potent and selective dual neuronal SNRIs (VEN:
34 serotonin:norepinephrine effects 30:1; desvenlafaxine: 10:1) [50, 65]. VEN has a strong dose-
35 dependent action: in low doses it inhibits serotonin reuptake, while in higher doses it blocks
36 both serotonin and norepinephrine reuptake [66]. VEN and desvenlafaxine modulate the
37 dopaminergic neurotransmission at low affinity level [50]. They may not influence the
38 adrenergic, muscarinic, cholinergic, histaminergic, benzodiazepine or opioids receptors, or
39 monoamine oxidase [65]. There are later data regarding the antinociceptive effect of VEN,
40 which revealed that this analgetic effect may be influenced by opioid receptors and the
41 alpha2-adrenergic receptor [67]. There are findings which proved that VEN XR can modify
42 pituitary adenylate cyclase-activating peptide (PACAP) and its PAC1 receptor genes in
43 generalized anxiety disorder [68].
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47 The pharmacokinetic parameters of orally administered VEN XR tablets of 150 mg revealed
48 that C_{max} was 150 ug/L, the AUC was 1877 ug/L x h, T_{max} was 5.5 h and $T_{1/2}$ was 5 h [65]. The
49 plasma protein binding of VEN XR at 150 mg is 27% and its major metabolic pathway
50 proceeds primarily through the liver by enzymes CYP2D6 and CYP3A3/4 [50]. It is mainly
51 excreted in the urine (87%) [65].
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3 A recent Cochrane meta-analysis based on six randomized clinical trials showed a positive
4 benefit for a daily dose of VEN above 150 mg for the treatment of neuropathic pain (mostly
5 PDN) [69]. In the largest multicentre study for PDN, the VEN treatment group (150-225 mg
6 daily dose) reached a significantly greater improvement than that for the placebo group at
7 week 6 (50% versus 27%) [70]. The NNT of benefit of VEN in the treatment of PDN is 3.1 [34].

8
9 The recommended daily dose of VEN XR for PDN is 150-225 mg once a day [3].

10
11 The most common treatment-emergent AEs of VEN XR were nausea, somnolence and
12 hypertension at high dosage [7, 70]. Nausea showed a dose-proportional manner (at 75 mg 22%
13 and at 150-225 mg 10%) [71]. Precautions for the use of VEN include cardiac disease,
14 hypertension and the administration of tramadol [7].

15
16 The NeuSPIG consensus declared that VEN reached the strong recommendations for use in
17 the treatment of PDN [3].

18
19 Overall, the above-mentioned antidepressants are all effective in the treatment of PDN. As
20 concerns the safety profile of SNRIs, it is a very important fact that the SNRIs have low
21 affinity for different neuronal receptors, which results in low AEs. In spite of this, TCAs are
22 held to be „dirty drugs” as regards their multireceptorial effects, resulting in high amounts of
23 side-effects. In the daily clinical practice, besides the effectiveness and the safety profile of
24 the first-line drugs for PDN, the economic aspects are also very important factors. In most
25 countries, TCAs are readily available with low charge. DUL is a cost-effective pharmacoon for
26 the treatment of PDN in the UK [34]. The results of randomized clinical trials and real-world
27 studies showed DUL to be more cost-effective than antiepileptics like pregabalin (PREG) in
28 PDN therapy [72].

2.2. Antiepileptics

29
30 Among antiepileptics, only the GABA analogues, gabapentin (GBP), GBP XR and its
31 prodrug GBP enacarbil and pregabalin (PREG) have reached the strong recommendation level
32 in the treatment of PDN [3, 73]. Each has a similar mechanism of action to inhibit the release of
33 presynaptic excitatory neurotransmitters [74]. A wide variety of other antiepileptic drugs were
34 inconclusive for recommendation, e.g. carbamazepine, lacosamide, lamotrigine, levetiracetam,
35 oxcarbazepine, topiramate, valproate and zonisamide [3, 73].

2.2.1. Gabapentin (GBP)

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3 GBP was developed in 1993 and was first marketed in the US in 1994. The FDA later
4 approved it for PDN and postherpetic neuralgia [75]. Its chemical structure is 1-
5 (aminomethyl)cyclohexaneacetic acid.
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8 The mechanism of analgesic action of GBP in humans has not been clarified, but in animal
9 models has been proved that GBP binds to the $\alpha_2\delta$ subunit of L-type voltage-dependent
10 calcium channels [34, 76]. The consequences of this effect are the reduction of the calcium
11 currents and inhibition of the presynaptic release of neurotransmitters, such as glutamate and
12 substance P [76]. Interestingly, it is structurally related to GABA, but does not bind to GABA-
13 A or GABA-B receptors, and does not block the uptake or degradation of GABA [76]. The
14 main signs of the central sensitization are allodynia and hyperalgesia, which could be
15 diminished by GBP [76].
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18 The pharmacokinetic parameters of orally administered GBP tablets of 600 mg three times
19 daily revealed that C_{max} was 8.46 mg/L, the AUC was 53.1 mg/L x h, T_{max} was 2 h and $T_{1/2}$
20 was 6 h [76]. The plasma protein binding of GBP is less than 3% , it is not significantly
21 metabolized, and it is renally excreted in unchanged form [76]. The bioavailability of GBP is
22 inversely proportional to the dose: 60% at 900 mg/day and 27% at 4800 mg/day (administered
23 in three divided doses) [76]. **In contrast, its prodrug, enacarbil, showed essentially linear**
24 **dose-proportional pharmacokinetic properties** [77, 78]. GBP has a volume of distribution of
25 58 L after 150 mg intravenous administration [76].
26

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28 In the available literature, there are no *in vitro* data on GBP and CYP450 interactions in
29 humans, so GBP is neither an inducer nor an inhibitor of the hepatic metabolism of different
30 drugs [79]. However, there are data that hydrocodone and morphine can increase GBP
31 absorption and the plasma concentration of GBP [80]. Naproxen as a frequently used non-
32 steroidal antiinflammatory drug (NSAID) can increase C_{max} and the AUC of GBP [80].
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35 The recent Cochrane Database meta-analysis revealed that the efficacy of GBP for the therapy
36 of PDN was superior to placebo (38% versus 21%, NNT 5.9, 95% CI 4.6 to 8.3) [81]. A similar
37 effect was seen for standard GBP and a GBP XR formulation [81].
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40 The recommended daily dose of GBP for PDN is 1200-3600 mg in three divided doses, while
41 that of GBP XR or enacarbil is 1200-3600 mg in two divided doses [3].
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44 A recent large retrospective clinical study in the United States revealed that among newly
45 diagnosed PDN patients the most commonly prescribed drug was GBP (45%) [82]. From the
46 aspect of the adherence to treatment during the first year, GBP showed a high adherence level
47 versus PREG and DUL [82].
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3 The most common AEs of GBP were dizziness (19%), somnolence (14%), peripheral oedema
4 (7%), gait disturbance (9%), and also sedation and weight gain ^[7, 81]. Serious AEs were no
5 more frequent as compared with placebo ^[81]. A precaution concerning the application of GBP
6 in a case of renal insufficiency is that a reduced dosage is recommended ^[7].
7
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10 In a safety issue based on patient withdrawals due to AEs, a meta-analysis revealed that there
11 was less withdrawal among patients who take GBP, and the most patient withdrawals due to
12 AEs were in the case of AMI ^[83]. That study concluded in the focus of the benefit-risk
13 analysis between six antidepressants and antiepileptics that the best benefit-risk ratio was
14 shown by GBP, and the worst one by AMI ^[83].
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17 The NeuSPIG consensus declares that GBP, GBP XR and enacarbil reached the strong
18 recommendations for use in the treatment of PDN ^[3].
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23 **2.2.2. Pregabalin (PREG)**

24 The GABA analogue PREG received the US FDA approval for the treatment of PDN and
25 postherpetic neuralgia in 2004 ^[84]. Its chemical structure is (*S*)-3-(aminomethyl)-5-
26 methylhexanoic acid.
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29 The mode of anti-nociceptive action of PREG is based on the molecular binding to the $\alpha_2\delta$
30 subunit of the P/Q type of the voltage-gated calcium channel in the CNS, resulting in a
31 decreased influx of calcium ion into the neuronal cell ^[85]. The lack of the required quantity of
32 calcium ion in the nerve cells results in the blockade of the propagation of neurotransmission
33 due to inadequate synaptic vesicle fusion to the presynaptic membrane of the synapses ^[85].
34 PREG has a high affinity for $\alpha_2\delta$ type 1 and 2 proteins versus TCAs (e.g. AMI), SNRIs (e.g.
35 VEN) or other antiepileptics (e.g. carbamazepine) ^[85]. PREG shows strong binding to the pain
36 matrix-like cortex or dorsal horn of the spinal cord ^[85]. The PREG-induced blockade of
37 neurotransmitters such as glutamate, glycine, norepinephrine, substance P, calcitonin gene-
38 related peptide or acetylcholine resulted in inhibition of neuronal excitability and diminished
39 the process of the central sensitization in NP ^[85].
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48 As a gabapentinoid, PREG does not bind directly to GABA or benzodiazepine or opioid
49 receptors. PREG as a glutamic acid decarboxylase (GAD) activator can increase neural
50 GABA levels ^[86].
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53 The pharmacokinetic parameters of an orally administered single dose of a PREG capsule of
54 150 mg revealed that C_{max} was 3.99 ng/L, AUC was 28.31 ng/mL x h, T_{max} was 1.00 h and
55 $T_{1/2}$ was 5.66 h ^[87]. The kinetics of PREG showed linear features (proportional to the dosage
56 up to 900 mg per day) ^[88]. The plasma protein binding of PREG is absent and its metabolism
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3 is negligible, with no effect on the CYP450 system [79, 83, 88]. The bioavailability of PREG is
4 more than 90% and the volume of distribution 0.5 L/kg [83]. 90% is excreted in the urine as the
5 unchanged drug with minor metabolites (e.g. N-methyl-PREG) [83]. It has no interactions
6 metabolically with other antiepileptic drugs [79, 80].
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10 The results of randomized clinical trials for the use of PREG (300-600 mg per day) in PDN
11 revealed significantly better efficacy as compared with placebo [84]. The evidence-based
12 guidelines of the American Academy of Neurology announced that PREG is the only drug
13 which reached the Level A (top-tier) of evidence in the treatment of PDN [36]. The NNT of
14 PREG in the treatment of PDN is 5.0 [34].
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17 The recommended daily dose of PREG for PDN is 300-60 mg in two divided doses [3].

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19 The common major AEs of PREG are sedation, somnolence (less than or around 50%),
20 dizziness (less than or around 49%), headache (less than or around 29%), peripheral oedema
21 and weight gain [7, 84].
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24 There are data for predictive factors for AEs associated with the use of PREG in PDN patients,
25 e.g. long duration of therapy – somnolence; advanced age – unsteadiness; elevated serum
26 creatinine level – weight gain and oedema [89].
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29 Precautions for PREG therapy include a reduced dosage in the case of renal failure patients [7].

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31 The NeuSPIG consensus declares, that PREG reached the strong recommendations for use in
32 the treatment of PDN [3].
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36 Taken together, the effectiveness and safety profile of antiepileptics involved in the treatment
37 of PDN are based on their pharmacokinetic and pharmacodynamic properties. From their
38 licence permission for clinical use their prescription has been increasing, but many PDN
39 patients do not receive them or take antiepileptics below the recommended dosage [82, 90].
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45 3. Conclusions

46 PDN is a debilitating consequence of diabetes, which greatly affects the quality of life of the
47 patient. The exact pathomechanism of PDN is unknown, and causative treatment is therefore
48 unavailable. For the symptomatic treatment of PDN, there are first-line strongly
49 recommended drugs, such as antidepressants (TCAs: AMI; and SNRIs: DUL and VEN) and
50 antiepileptics (only gabapentinoids: GBP and PREG). Among antidepressants, TCAs and
51 SNRIs show similar efficacy as concerns PDN, but from the aspect of their AEs, based on
52 their pharmacokinetic and pharmacodynamic properties, huge discrepancies may be seen.
53 Gabapentinoids have a similar mode of action and effectiveness in the treatment of PDN, but
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3 some of their pharmacological properties, such as their bioavailability, absorption and kinetics
4 vary, which leads to different features of their therapeutic and safety profiles.
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8 **4. Expert opinion**

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10 The treatment of PDN patients is a great challenge for primary care physicians, diabetologists,
11 neurologists and even pain specialists. Epidemiological surveys have established that a huge
12 number of patients with NP do not receive appropriate treatment [3]. The difficulties in the
13 treatment of PDN include the unclear pathomechanism and pathogenesis, and there are no
14 specific efficacious pain relief drugs for PDN. It is interesting that the placebo response rate is
15 relatively high in NP patients, and especially PDN patients. Focusing on the efficacy of a drug
16 used for the alleviation of pain in PDN, we underline the fact, that the placebo effects are
17 usually notably strong. This shows the narrow gap between the achieved effectiveness and the
18 result of the placebo treatment, which gives a challenge for a novel pharmacological
19 innovation for the preparation of new and effective drugs for the successful treatment PDN.
20

21 Unfortunately, the recent evidence-based guidelines consist of only a few first-line strongly
22 recommended drugs for the treatment of PDN, such as amitriptyline, duloxetine, venlafaxine,
23 gabapentin and pregabalin. All of these have unfavourable AEs and contraindications. The
24 correct choice of drugs is a real art of medicine. It is a perpetually recurring question for the
25 medical staff to decide which PDN patient should receive which effective, well-tolerated and
26 safe drug. Unfortunately, the demographic data or disease characteristics are not predictors for
27 the pain alleviation treatment, and they do not help in the choice of the proper medication for
28 PDN patients. Another problem is that there are no optimum biomarkers of this field at the
29 present. There are some promising data which showed a positive correlation between plasma
30 tumor necrosis factor (TNF)alpha levels and macrophages, inducible nitric oxide synthase
31 (iNOS) and TNFalpha expression and the severity of the pain in PDN patients [91]. **Nitric
32 oxide (NO) is an indigenous gas, and its elevated level has been implicated in the
33 pathomechanism of PDN [92, 93]. Other potential biomarkers may include certain
34 angiogenic and anti-angiogenic factors such as vascular endothelial growth factor,
35 soluble endoglin, endothelin-1, and NO, molecules with plasma levels found elevated in
36 diabetic patients compared to controls [94]. The furoxan NO donor, PRG150, was
37 investigated in the streptozotocin-induced diabetic rat model of PDN and demonstrated
38 a dose-dependent analgesic effect, which may represent a novel promising approach in
39 PDN [93]. Furthermore, a NO-donating pregabalin, NCX1404, exerted strong**
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3 **antiallodynic response in the streptozocin-induced murine model of PDN. Repeated**
4 **dosing with NCX1404 re-established normal nociceptive response in this model** [95].
5 **Oxidative stress has a role in the development of microvascular complications in**
6 **patients with diabetic neuropathy. A clinical study revealed a decreased serum prolidase**
7 **enzyme activity, which may be associated with increased NO levels and oxidative stress**
8 **in diabetic patients with neuropathy** [96]. **In a randomized placebo-controlled study, a**
9 **NO-releasing patch (NitroSense Derma Protect) showed a significant reduction in pain**
10 **of PDN patients** [97].

11 We highlight the importance of finding the optimum dose of drugs for PDN, especially in the
12 elderly due to the genotyping of the CYP450 enzymes, which play a crucial role in the
13 metabolism of these drugs. It is similarly important for better personalizing treatment of PDN
14 patients to integrate the CYP genotyping with therapeutic drug monitoring for the safe use of
15 medications.

16 In the near future it is recommended to guide pharmacogenetic studies based on the genetic
17 polymorphisms in different genes (e.g. novel techniques such as AmpliChip CYP450
18 Genotyping Test), which can reflect the treatment response to drugs used in PDN.

19 At the bedside, one of the major challenges is the interindividual variability to the response to
20 the drug used for PDN. As concerns the comorbidities of PDN, the polymedication and the
21 genetic polymorphism are other important issues from the aspect of the drug metabolization
22 and the drug-drug interactions. For the patients who are ultrarapid metabolizers, the
23 pharmacological medications are usually ineffective, while those who are poor metabolizers
24 are at high risk of life-threatening toxicity. There is therefore a need for a new aspect of the
25 treatment of PDN patients such as determining the genotyping of CYP variant alleles.

26 In the coming years, it will be strongly recommended to use the genotyping analysis of
27 CYP450 drug-drug and drug-gene interactions in the daily clinical practice in order to
28 estimate the effectiveness and safety of the prescribed drugs for PDN. This advanced
29 diagnostic method might serve as the basis of the request for personalized medicine.

30 The analysis of drug-drug interactions is a crucial part for pharmacokinetic and
31 pharmacodynamic studies of the drugs used for PDN. There is a need for methods to evaluate
32 pharmacons of this type, e.g. micellar electrokinetic chromatography electrospray ionization-
33 tandem mass spectrometry, which is a cost-effective technique for measuring VEN and
34 desvenlafaxine enantiomers [98].

35 One of the potential fields for the causal therapy of PDN is the sodium channel isoforms
36 (Nav1.3, Nav1.7, Nav1.8 and Nav1.9) on the peripheral nociceptive neurons. Preclinical and
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3 clinical trials have revealed that the blockers of these subtypes of the sodium channels give us
4 new fashionable effective drugs against PDN [27].

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6 The sodium channel voltage sensor monoclonal antibody which targets the peripheral and
7 central Nav1.7 channel diminishes itch and neuropathic pain in an animal model [26]. This
8 channel-specific antibody may therefore be a potential therapeutic option in human PDN [26,
9 99].

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12 Another potential research area may be the modification of the glycosylation of the subclass
13 of T-type voltage-gated calcium channels (Cav3.2), which are related to the hyperexcitable
14 state of nociceptors in diabetic animal models [100]. In the preclinical state of this research field,
15 the classical streptozotocin-induced diabetic rodent model as a reliable way to induce strong
16 mechanical allodynia and thermal hyperalgesia is not sufficient to mimic all the aspects of the
17 clinical picture of PDN. For future perspectives there is a need for new animal models which
18 serve the innovation of the targeted treatment of PDN.

19
20 One of the most promising therapeutic options arises from the technique of fully humanized
21 monoclonal antibodies (mAb). **There are preclinical data pinpointing the role of integrins,
22 receptors for extracellular matrix proteins, in the processes of inflammatory and
23 neuropathic hyperalgesia and the chronification of pain [101-103]. The mAbs against the
24 beta1 integrin subunit demonstrated an inhibitory effect on prostaglandin E2- and
25 epinephrine-induced hyperalgesia in rats [101, 102]. These findings may provide new
26 therapeutic options for the treatment of PDN. Antibodies against NGF (e.g. tanezumab,
27 fulranumab and fusinumab) in the treatment of osteoarthritis of the hip or knee showed
28 superiority in efficacy in pain relief (Western Ontario and McMaster – WOMAC pain)
29 and Patient's Global Assessment compared to placebo [104]. Unfortunately, unexpected
30 AEs with tanezumab were reported, such as rapid osteonecrosis with an unknown cause
31 at present, a complication necessitating joint replacement surgery [105]. Based on this
32 finding, the US Food and Drug Administration placed the studies of all anti-NGF
33 monoclonal antibodies on clinical hold [105]. In an early truncated Phase II double-blind
34 placebo-controlled trial with fulranumab for the treatment of PDN resulted in a dose-
35 dependent efficacy, and there was no case necessitating joint replacement therapy [106].
36 Another randomized controlled study with tanezumab for PDN demonstrated pain
37 reduction versus placebo; however, there was no significant difference in Patient's
38 Global Assessment scale [107].**

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40 Another class of mAb against the receptor for advanced glycation and products, which is
41 expressed through the sensory nervous system, resulted in a dose-related attenuation of NP in
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3 a mouse NP model ^[108]. Neutralized mAb against interleukin-17A diminished the
4 hyperalgesia in a spinal nerve ligation model in mice ^[109]. Another type of mAb against high-
5 mobility group box-1 strongly alleviated the mechanical hypersensitivity and the expression
6 of matrix metalloproteinase-9 in the partial sciatic nerve ligation model in mice ^[110]. On the
7 basis of the preclinical and early clinical results, we emphasize that mAbs targeting the
8 different sites of the pain matrix may give a strong possibility for the causal therapy of PDN.
9
10 Further perspectives emerge from the intradermal application of the botulinum toxin type A
11 for PDN. Early clinical studies suggested some effectiveness for benefit for PDN patients ^[111].
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13 Due to these early clinical data, further larger randomized controlled studies are required for
14 the evaluation of the efficacy of botulinum toxin type A in this disease.
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19 **The Transient Receptor Potential (TRP) cation channels, including Ankyrin repeat**
20 **domain 1 (TRPA1) and Vanilloid type 1 (TRPV1), have crucial roles in the nociceptive**
21 **process** ^[112, 113]. Recent reports demonstrated that a topical 8% patch of capsaicin, **the**
22 **classical TRPV1 agonist**, may have a beneficial outcome in PDN patients ^[114]. The release of
23 the final results is waited urgently. **In healthy human volunteers, the pharmacokinetic**
24 **profile of TRPV1 antagonists (ABT-102 and JNJ-38893777) were evaluated, and they**
25 **also showed a good tolerability** ^[115, 116]. **In a phase 2a (proof-of-concept) study, one of the**
26 **potent and selective TRPA1 antagonist (GRC17536) demonstrated efficacy in patients**
27 **with PDN** ^[117]. **Phase 3 studies are warranted in the near future to provide more**
28 **accurate data. At the experimental level, a novel oxime compound, as a potent TRPA1**
29 **and TRPV1 antagonist, has been proven to have promising efficacy on primary sensory**
30 **neurons** ^[113]. **This compound might be a new candidate for drug development for the**
31 **treatment of neuropathic pain** ^[113].
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41 In the case of pharmacologically refractory PDN, one of the ultimate choices is spinal cord
42 stimulation. A multicenter randomized clinical trial concluded that spinal cord stimulation
43 significantly alleviated the pain in PDN patients ^[118]. Neuromodulation methods, such as
44 spinal cord stimulation are invasive and expensive techniques, and careful patient selection is
45 therefore needed. From the aspect of drug innovation, the targeting of good clinical efficacy,
46 tolerability, safety and comparable cost-effectiveness are very important research fields.
47 Innovative drug technology is additionally needed to achieve these goals. One example in
48 which immediate release versus an XR formulation of VEN were compared, the XR
49 formulation showed less AEs (e.g. nausea and dizziness) due to the novel pharmacological
50 technology ^[50].
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3 Currently prescribed first-line strongly recommended symptomatic treatment for PDN
4 (amitriptyline, duloxetine, venlafaxine, gabapentin, pregabalin) are efficacious, but all have
5 limitations due to their precautions and AEs. To attain the better adherence of PDN patients,
6 the ultimate goal is a large pharmacogenetic study, with the aim of the drug-drug and drug-
7 gene interactions.
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11 12 13 **Conflict of interest**

14
15 The authors declare that they have no conflict of interest and have received no payment in the
16 preparation of their manuscript.
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20 21 22 **Acknowledgements**

23
24 This work was supported by the project TÁMOP-4.2.2.A-11/1/KONV-2012-0052, by the
25 Hungarian Brain Research Programme (NAP, Grant No. KTIA_13_NAP-A-III/9. and by the
26 MTA-SZTE Neuroscience Research Group of the Hungarian Academy of Sciences and the
27 University of Szeged.
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Figures

Figure 1. Scheme of sensitization and hyperexcitability of mechanism of neuropathic pain

Modified (Ref.: [5])

Abbreviations:

ATP: adenosine triphosphate, BDNF: brain-derived neurotrophic factor, DRG: dorsal root ganglion, $Na_v1.8$ and $Na_v1.9$: voltage-gated sodium channels, NMDA-R: N-methyl-D-aspartate receptor, NGF: nerve growth factor, P2X4: purinergic receptor, TrkB: tropomyosin receptor kinase B

Figure 2. Chemical structures of the first-line drugs for painful diabetic neuropathy

(Ref.: [88, 119-122])

Table legends**Table 1. Pharmacokinetic and pharmacodynamic properties of the first-line drugs for the treatment of PDN**

Abbreviations: AUC: the area under the concentration vs. time curve, C_{max} : the maximum plasma concentration, h: hours, iv: intravenously, L: litre, NA: not available, PDN: painful diabetic neuropathy, Ref.: references, T_{max} : the time to C_{max} , $T_{1/2}$: the plasma elimination half-life, XR: extended release

Table 2. Recommended daily doses and adverse events of the first-line drugs for the treatment of PDN

Abbreviations: NNT: number needed to treat; PDN: painful diabetic neuropathy; XR: extended release

(Ref.: [3, 4, 7, 34, 46, 53, 63, 64, 81, 84])

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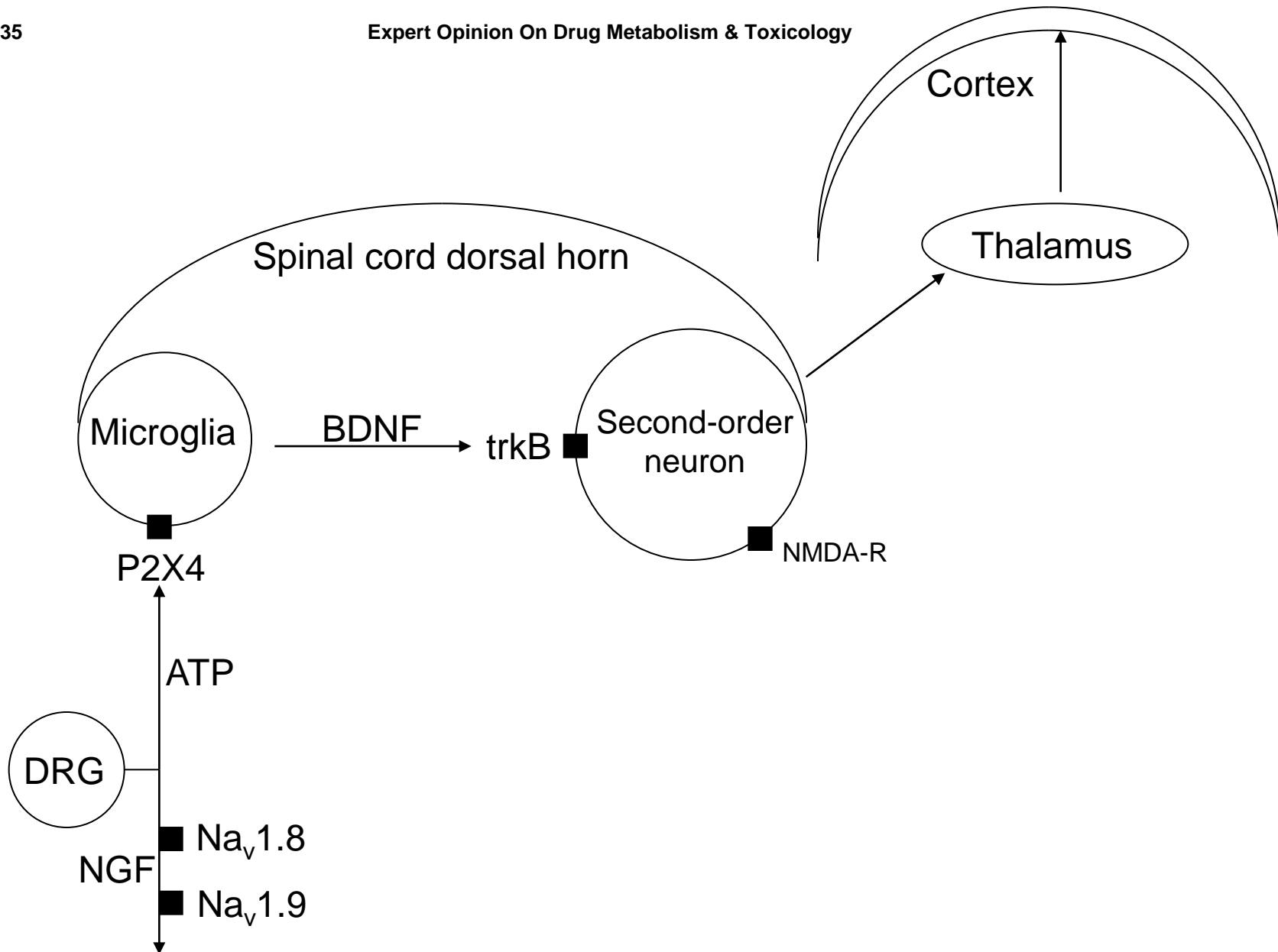
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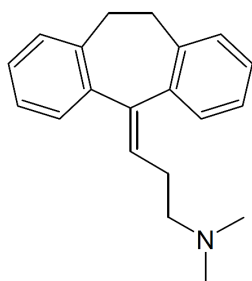
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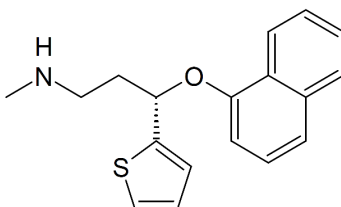


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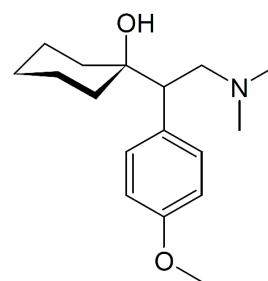
Figure 2. Chemical structures of the first-line drugs for PDN



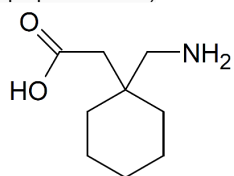
Amitriptyline
(3-(10,11-Dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-*N,N*-dimethylpropan-1-amine)



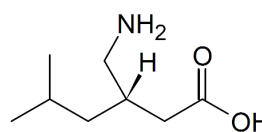
Duloxetine
(+)-(S)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine



Venlafaxine
(*RS*)-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol



Gabapentin
1-(Aminomethyl)cyclohexaneacetic acid



Pregabalin
(*S*)-3-(Aminomethyl)-5-methylhexanoic acid

Table 1. Pharmacokinetic and pharmacodynamic properties of the first-line drugs for the treatment of PDN

Drugs	C _{max}	T _{max}	AUC	T _{1/2}	Bioavailability	Protein binding	Volume of distribution	Metabolism	Excretion	References
Antidepressants										
Amitriptyline (75 mg tablet)	15.3 ng/L	25.7 h	593 ng/mL x h	20.4 h	30-60%	96%	NA	CYP2C1 9 CYP2D6	urine (30-50%) faeces (NA)	[39, 43]
Duloxetine (60 mg tablet)	39- 40.1 ng/L	6 h	584-591 ng x h/mL	10.2 h	50%	>90%	1640 L	CYP1A2 CYP2D6	urine (70%) faeces (20%)	[50, 53, 58]
Venlafaxine XR (150 mg tablet)	150.0 ug/L	5.5 h	1877 ug/L x h	5.0 h	NA	27%	NA	CYP2D6 CYP3A3 /4	urine (87%) faeces (NA)	[65]
Antiepileptics										
Gabapentin (600 mg tablet)	8.5 mg/L	2.0 h	53 mg/L x h	6.0 h	60% (900 mg/day) 27% (4800	<3%	58 L (150 mg iv.)	nil	urine (NA) faeces (NA)	[76, 79, 83]

					mg/day)					
Pregabalin (150 mg capsule)	4.0 ng/L	1 h	28 ug/mL x h	5.7 h	90%	absent	0.5 L/kg	nil	urine (90%) faeces (NA)	[87, 88]

Abbreviations: AUC: the area under the concentration vs. time curve, C_{max} : the maximum plasma concentration, h: hours, iv: intravenously, L: litre, NA: not available, PDN: painful diabetic neuropathy, Ref.: references, T_{max} : the time to C_{max} , $T_{1/2}$: the plasma elimination half-life, XR: extended release

Table 2. Recommended daily doses and adverse events of the first-line drugs for the treatment of PDN

Drugs	Recommended daily dose (mg)	NNT	Adverse events
Antidepressants			
Amitriptyline	25-100 mg	1.3	dry mouth, fatigue, somnolence, weight gain, dizziness
Duloxetine	60-120 mg	6.0	nausea, dry mouth, headache, dizziness, fatigue, somnolence, constipation
Venlafaxine Venlafaxine XR	150-225 mg	3.1	nausea, somnolence, hypertension
Antiepileptics			
Gabapentin Gabapentin XR Gabapentin enacarbil	1200-3600 mg	5.9	dizziness, somnolence, peripheral oedema, gait disturbance, sedation, weight gain
Pregabalin	300-600 mg	5.0	sedation, somnolence, dizziness, headache, peripheral oedema, weight gain

Abbreviations: NNT: number needed to treat; PDN: painful diabetic neuropathy; XR: extended release
(Ref.: [3, 4, 7, 34, 46, 53, 63, 64, 81, 84])

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