REVIEW

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

Use of gabapentin for neuropathic pain therapy: A view from perspective of evidence-based medicine

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Received 15 Feb 2024 After peer review 17 April 2024 Accepted 20 Apr 2024

The aim of the study was to analyze the literature sources for pharmacodynamic and pharmacokinetic features of gabapentin, providing its use in patients with neuropathic pain, as well as a comparative evaluation of its efficacy and safety when used in different doses.

Materials and methods. PubMed, Google Scholar, EMBASE, ResearchGate scientific information network and elibrary.ru databases were used as search resources. The keywords used for the search were "gabapentin", "mechanism of action", "gabapentin targets", "gabapentin pharmacodynamics", "pharmacokinetics", "pharmacokinetic parameters", "neuropathic pain", and "randomized clinical trials". The depth of the search was 26 years (from 1998 to 2024). This review resulted in 87 literature sources.

Results. Neuropathic pain (NeP) is one of the most common types of chronic pain, characterized by a high prevalence among people of the working age. Effective pharmacotherapy aimed at eliminating the pain syndrome is a key tool for improving the quality of life and preserving the work capacity of patients. Heterogeneity of etiologic factors involved in the genesis of NeP indicates the need to use drugs the analgesic effect of which is based on weakening the transmission of pain impulses in the CNS. In clinical trials, gabapentin has demonstrated efficacy in reducing the severity of pain in patients with postherpetic NeP, painful diabetic neuropathy and many other conditions accompanied by NeP. The dose of gabapentin 300 mg/day is the initial dose in the therapy of NeP and requires a further slow titration depending on the patient's response to therapy and tolerability of the drug, especially in elderly and senile patients, as well as in patients with an impaired renal function. According to the published data, the most pronounced analgesic effect is achieved in the patients against the background of the gabapentin administration at a dose of 3600 mg/day.

Conclusion. Gabapentin is the drug of choice in the management of patients with NeP of different etiology and intensity. A satisfactory safety profile and pharmacodynamic effects make gabapentin possible, despite the long history of its use, to remain a relevant drug used by a wide range of physicians, specialties, for pharmacotherapy of NeP patients.

Keywords: gabapentin; gabapentinoids; neuropathic pain; diabetic polyneuropathy; postherpetic neuralgia; chronic pain

Abbreviations: VAS – visual analogue scale; CI – confidence interval; GABA – gamma-aminobutyric acid; NeP – neuropathic pain; RR – relative risk; OR – odds ratio; RCTs – randomized clinical trials; eGFR – estimated glomerular filtration rate; SNRIs – selective norepinephrine reuptake inhibitors; ADP – average daily pain; TCAs – tricyclic antidepressants; CNS – central nervous system; α2δ-1 – alpha2-delta type 1 subunit; AMPA receptors – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; IMMPACT – Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; KCNQ2/3 – heteromeric potential-dependent potassium channels; NNT – Number Needed to Treat; LAT-1 – L-type amino acid transporter 1; MD – median deviation; NMDA receptors – N-methyl-d-aspartate receptors; NRS – Numeric Rating Scale.

For citation: O.I. Butranova, S.K. Zyryanov. Use of gabapentin for neuropathic pain therapy: A view from perspective of evidence-based medicine. *Pharmacy & Pharmacology.* 2024;12(1):74-88. **DOI:** 10.19163/2307-9266-2024-12-1-74-88

Для цитирования: О.И. Бутранова, С.К. Зырянов. Применение габапентина для терапии нейропатической боли: взгляд с позиций доказательной медицины. *Фармация и фармакология.* 2024;12(1):74-88. **DOI:** 10.19163/2307-9266-2024-12-1-74-88

Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ
(PHARMACY & PHARMACOLOGY)

ОБЗОР
DOI: 10.19163/2307-9266-2024-12-1-74-88

Применение габапентина для терапии нейропатической боли: взгляд с позиций доказательной медицины

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Получена 15.02.2024 После рецензирования 17.04.2024 Принята к печати 20.04.2024

Цель. Провести анализ литературных источников на предмет фармакодинамических и фармакокинетических особенностей габапентина, позволяющих использовать его у пациентов с нейропатической болью, а также сравнительную оценку его эффективности и безопасности при применении в различных дозах.

Материалы и методы. В качестве поисковых ресурсов были использованы базы данных PubMed, Google Scholar, EMBASE, научно-информационная сеть ResearchGate и elibrary.ru. В качестве ключевых слов для поиска использовали «габапентин»», «механизм действия», «мишени габапентина», «фармакодинамика габапентина», «фармакокинетика», «фармакокинетические параметры», «нейропатическая боль», «рандомизированные клинические исследования». Глубина поиска составила 26 лет (с 1998 по 2024 гг.). В результате настоящий обзор составили 87 источников литературы.

Результаты. Нейропатическая боль (НБ) является одним из наиболее распространенных видов хронической боли, характеризующимся высокой распространенностью среди лиц трудоспособного возраста. Эффективная фармакотерапия, направленная на устранение болевого синдрома, является ключевым инструментом повышения качества жизни и сохранения работоспособности пациентов. Гетерогенность этиологических факторов, вовлечённых в генез НБ, указывает на необходимость использования препаратов, анальгетический эффект которых основан на ослаблении передачи болевых импульсов в ЦНС. В клинических исследованиях габапентин продемонстрировал эффективность в отношении снижения выраженности боли у пациентов с постгерпетической НБ, болевой диабетической нейропатией и многими другими состояниями, сопровождающимися НБ. Доза габапентина 300 мг/сут является начальной в терапии НБ и требует дальнейшей медленной титрации в зависимости от ответа пациента на терапию и переносимости препарата, в особенности у пациентов пожилого и старческого возраста, а также пациентов с нарушенной функцией почек. Согласно опубликованным данным, наиболее выраженный анальгетический эффект достигается у пациентов на фоне применения габапентина в дозе 3600 мг/сут.

Заключение. Габапентин является препаратом выбора при ведении пациентов с НБ различной этиологии и интенсивности. Удовлетворительный профиль безопасности и фармакодинамические эффекты позволяют габапентину, несмотря на длительную историю его использования, оставаться актуальным препаратом, применяемым врачами широкого круга специальностей для фармакотерапии пациентов с НБ.

Ключевые слова: габапентин; габапентиноиды; нейропатическая боль; диабетическая полинейропатия; постгерпетическая невралгия; хроническая боль

Список сокращений: ВАШ – визуальная аналоговая шкала; ДИ – доверительный интервал; ГАМК – гамма-аминомасляная кислота; НБ – нейропатическая боль; ОР – относительный риск; ОШ – отношение шансов; РКИ – рандомизированные клинические исследования; рСКФ – расчетная скорость клубочковой фильтрации; СИОЗН – селективные ингибиторы обратного захвата норадреналина; ССБ – среднесуточная боль; ТЦА – трициклические антидепрессанты; ЦНС – центральная нервная система; α2δ-1 – альфа-2 дельта субъединица типа 1; AMPA-рецепторы – рецепторы альфа-амино-3-гидрокси-5-метил-4-изоксазол-пропионовой кислоты; IMMPACT – инициатива по методам, измерению и оценке боли в клинических исследованиях; KCNQ2/3 – гетеромерные потенциалзависимые калиевые каналы; NNT – число пациентов, которых необходимо лечить; LAT-1 – система переносчиков L-аминокислот 1 типа; MD – медианное отклонение; NMDA-рецепторы – N-метил-d-аспартатные рецепторы; NRS – числовая рейтинговая шкала боли.

INTRODUCTION

A large number of chronic diseases, in particular metabolic and neurodegenerative ones, are accompanied not only by a decrease in the function of organs and systems, but also by the development of neuropathic pain (NeP), characterized by an increased pain sensitivity and the occurrence of spontaneous pain sensations. The basis of NeP is somatosensory disorders. NeP is usually chronic: persistent or recurrent pain usually lasts longer than 3 months [1].

According to the International Association for the

Study of Pain (IASP, 2019) classification, NeP is divided into peripheral and central [1]. ICD-10 diagnoses related to NeP include trigeminal neuralgia (G50.0), neuralgia after shingles (G53.0, B02.2), and a phantom limb pain syndrome (G54.6). Nevertheless, the spectrum of pathological conditions accompanied by NeP is not limited to the above-mentioned ones. Due to that, NeP is a widespread problem that has a negative impact on the quality of life and work capacity of a significant proportion of the population. The prevalence of NeP in the general population varies from 3 to 17% [2]; in general, the published data indicate that approximately one in twenty people in the Western world suffers from NeP [3].

According to a large-scale epidemiologic study that included the analysis of the UK Biobank (United Kingdom) patient database, the overall prevalence of NeP was 9.2% [4]. The scale of the NeP prevalence in the Russian Federation can be indirectly judged by the results of a 10-year analysis of visits to the Pain Research and Treatment Clinic (the period from 2011 to 2020), which revealed chronic pain in 32% of patients [5]. Among elderly and senile patients, a chronic pain syndrome is found in the absolute majority: according to the survey including 11 regions of the Russian Federation, its overall prevalence in the population ≥65 years of age was found to be 87.2% [6].

As a type of chronic pain, NeP can significantly reduce the quality of life of patients, limit their physical activity and the ability to self-care. This is due to both the pain itself and a number of conditions that it can provoke. It is important to note that NeP is more associated with the development of depression and anxiety disorders than other types of chronic pain. According to a cross-sectional study of NeP patients, 65.6% had depression and 73.7% had anxiety disorders [7]. The relevance of the NeP problem with depression and anxiety disorders in modern healthcare is well illustrated by the analysis results of the Thomson Reuters Web of Science (WoS) publication database: in 2000, the number of published articles on the relevant topic was 8, in 2020 - 106 (the total number of publications for 20 years is 915) [8]. NeP and the associated depression are causes of a sleep quality impairment: the studies have shown that more than 83% of people with NeP may suffer from some forms of insomnia [9].

NeP most often develops in patients of the working age, with significant socioeconomic consequences. According to a multicenter study of NeP outpatients (Turkey, 2021), their mean age was 55.5+14.4 years [10]. According to the US data, NeP most often affects men aged 35 to 44 years (regardless of ethnicity); in the case of women, the following differences were found: in whites, the peak incidence of NeP coincided with that of men, while in Hispanic and African-American women it was observed in the group of 45–54 years [11]. A high prevalence of NeP and associated depressive disorders in the population of people in their early 40s puts them at a significant risk for cardiovascular damage: according to the study conducted in Canada (2011–2012, 1493 patients with a spinal cord injury), NeP increased a cardiovascular risk (the adjusted odds ratio, OR) 2.27-fold (95% confidence interval, CI: 1.21 to 4.60), depression 4.07-fold (95% CI: 2.10 to 7.87) [12]. The economic consequences of NeP are illustrated by the data from a study of real clinical practice in European countries. The minimum amount of total annual direct costs of the health care system per patient with NeP was noted in Italy – 1 939 euros, the maximum – in Spain, 3 131 euros. The cost of the disease (including both direct and indirect costs) had a minimum value also in Italy, 9 305 euros; the maximum value was noted in Germany, 14 446 euros.

A basis for the management of NeP patients is the medications aimed at eliminating a pain syndrome, taking into account the heterogeneity of factors contributing to the development of the main forms of both peripheral and central NeP [14, 15], as well as providing optimal clinical outcomes, taking into account a high frequency of concomitant depression and anxiety disorders. The goals of NeP pharmacotherapy include the following ones [16]: reduction of pain by 30–50%; improvement of a sleep quality; improvement of the quality of life; preservation of the social activity and relationships; preservation of the working capacity; the improvement of organs and systems functioning, as well as the whole organism.

Domestic and international clinical guidelines for the management of NeP patients indicate gabapentinoids (gabapentin and pregabalin) as first-line drugs [17–19]. The efficacy and safety of pharmacotherapy depends on the drug dose and the administration duration.

THE AIM of the study was to analyze the pharmacodynamic and pharmacokinetic features of gabapentin, providing its use in NeP patients, as well as a comparative assessment of its efficacy and safety when used in different doses on the basis of the published data.

ОБЗОР
DOI: 10.19163/2307-9266-2024-12-1-74-88

MATERIALS AND METHODS

Abstract databases such as PubMed, Google Scholar, EMBASE, ResearchGate scientific information network and elibrary.ru were used as a source of materials for writing the review article. Each author independently searched the publications to exclude errors. The publications in three areas – pharmacodynamics, pharmacokinetics, and clinical efficacy and safety – were analyzed. In the area of "pharmacodynamics", the following key words and word combinations were used: "gabapentin", "mechanism of action", "gabapentin targets", "gabapentin pharmacodynamics"; in the area of "pharmacokinetics" they were: "gabapentin", "pharmacokinetics", "pharmacokinetic parameters". The analyzed period for these arears was 26 years (from 1998 to 2024), a total of 13 792 publications were found, after excluding duplicates, literature reviews, invalid papers (pharmacokinetics of gabapentin in animals), publications presented only in abstracts, the total number of papers included in the review for these two areas, was 27. In the area "efficacy and safety of gabapentin", the keywords for the search included "gabapentin", "neuropathic pain", "randomized clinical trials". The search was performed on publications from 2014 to 2024. 8 762 publications were found. After excluding duplicates, literature reviews, invalid publications, and publications with unavailable full text, 56 papers were included in this review.

RESULTS AND DISCUSSION

NeP mechanisms and gabapentin targets

Despite the progress in the study of cellular and molecular pathways, there is no unified consensus in understanding the mechanisms of NeP development to date. The complexity lies in the fact that in a single patient, several mechanisms are most often involved in the development of NeP, the most well-known of which [20] are as follows: mechanisms of central sensitization, mechanisms of peripheral sensitization, processes associated with neuroinflammation, dysfunction of descending nociceptive modulatory systems, response to an oxidative stress, and glial cell activation.

The involvement of each of these mechanisms is determined by the type of NeP (peripheral or central), as well as the etiologic factors underlying its development. The main types of peripheral and central NeP, as well as the main etiological factors inducing them, are shown in Fig. 1.

The leading role in the genesis of central NeP is played by damage to the sensory pathways of various parts of the central nervous system (CNS) due to blood flow disorders, strokes, infectious diseases, traumas, and multiple sclerosis [21]. The result of central sensitization is the formation of an increased level of the spontaneous activation of nociceptive sensory neurons, a decrease in the threshold of peripheral stimulation of neurons, and an increase in their response to the suprathreshold stimulation. Two types of neurons with opposite effects on the nociceptive transmission are located in the dorsal horns of the spinal cord: excitatory neurons expressing the vesicular transporter glutamate-2 and inhibitory neurons expressing the vesicular transporter gamma-aminobutyric acid (GABA). The main process underlying the central sensitization is the activation of a type of a glutamate receptor such as N-methyl-d-aspartate receptors (NMDA). They contain 4 subunits (two GluN1 and two GluN2) that form a channel for Na^+, K^+, and Ca^{2+} ions. Normally, this channel is closed due to the blocking action of extracellular Mg^{2+}. The receptor activation accompanied by a channel opening requires the binding of glycine and glutamate to the receptor subunits GluN1 and GluN29 in conjunction with a membrane depolarization to relieve a magnesium blockade. Through the open channel, Ca^{2+} ions rush inside the cell, which increases the cell membrane depolarization promoting an additional calcium influx. Presynaptic NMDA receptors can be activated by endogenous glutamate without removing the Mg^{2+}-block. The activation of most postsynaptic NMDA receptors requires a pronounced depolarization of neurons simultaneously with glutamate binding [22]. The outcome of the NMDA receptor activation is an increase in intracellular calcium, leading to the vesicle exocytosis and neurotransmitter release [22]. The NMDA receptor hyperactivity is a major component of the development and maintenance of chronic NeP [23]. This is due to their contribution to the enhancement of the spinal nociceptive transmission induced by a peripheral nerve damage. The intrinsic activation of presynaptic NMDA receptors in the dorsal horns of the spinal cord characteristic of NeP is accompanied by an enhanced release of glutamate from nociceptive primary afferent terminals [24].

The enzymes that cause their phosphorylation (casein kinase 2, protein kinases A and C, Ca^{2+} / calmodulin-dependent protein kinase II, and tyrosine kinases Src and Fyn) and interaction with such a protein component as the alpha2-delta subunit of potential-dependent

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
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(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

Ca^{2+} channels type 1 (α2δ-1) play an important role in the hyperactivation of NMDA receptors of dorsal horn neurons [24]. The α2δ-1 subunit forms a complex with NMDA receptors and can also interact with neurexin-1α, thrombospondins (adhesion molecules) and other presynaptic proteins [25]; α2δ-1 can also interact with alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPA receptors) [26]. The maximum expression of α2δ-1 is observed in dorsal radicular ganglia and dorsal horns of the spinal cord [27].

An overexpression of α2δ-1 is observed in conditions that provoke NeP: a trauma to nerve tissues, chemotherapeutic drugs in oncology, calcineurin inhibitors, opioid-induced hyperalgesia and an acquired tolerance to analgesics, and cerebral blood flow disorders. As a result, an increased formation of α2δ-1-NMDA-receptor complexes (primarily involving presynaptic receptors), leading to the enhanced release of neurotransmitters, was found in NeP [23, 25, 28].

Gabapentin is a structural analog of GABA, but has no significant effect on GABA receptors. It has been shown to act at the level of neurons of the peripheral gray substance, increasing the pain threshold and reducing the intensity of a regional cerebral blood flow in this area [29]. A key element of gabapentin's mechanism of action in NeP involves α2δ-1 binding (Fig. 2). This has important consequences determining the analgesic activity of gabapentin. First, it prevents the formation of α2δ-1-NMDA-receptor complex and allows to stop the process of NMDA receptor activation, which is important for the elimination of NeP [25, 26, 30]. Second, it leads to the modification of neurexin-α-1 effects in synapses, which reduces the rapidly released pool of presynaptic vesicles. Third, α2δ-1 binding by gabapentin promotes the inhibition of astrocyte thrombospondins, which reduces the number of newly formed excitatory synapses and the intensity of their operation (the processes initiated by an injury / inflammation) [25, 27]. The normalization processes of presynaptic and postsynaptic activation of NMDA-receptors of the posterior horns neurons of the spinal cord, accompanied by a reduction / elimination of pain sensations, is a central component of the gabapentin action mechanism.

Gabapentin has also a mechanism (absent in its structural relative, pregabalin) that is independent of α2δ-1 and is associated with a pronounced activating effect on heteromeric potential-dependent potassium channels (KCNQ2/3) responsible for M-currents [31]. Additionally, gabapentin is known to increase the expression of the GABA-A receptor subunit δ (δGABA-A) subspecies responsible for the tonic inhibitory conduction predominantly in the cerebellum and hippocampus [32]. At the early stages of the NeP onset, the analgesic effect of gabapentin is realized in the area of locus coeruleus neurons: it inhibits a presynaptic release of GABA and induces a glutamate release from astrocytes, which increases the neurons activity of this localization and leads to an increase in descending a noradrenergic inhibition [33].

The above pharmacodynamic effects of gabapentin are possible provided that a sufficient level of concentrations in plasma and CNS tissues is formed.

Pharmacokinetics of gabapentin

Gabapentin realizes its action mechanism by penetrating the CNS and neuronal membranes. It was created as a lipophilic analog of GABA, which ensures its entry into various CNS structures. Despite its lipophilicity, gabapentin is transported across cell membranes primarily by facilitated transport via the L-amino acid type 1 (LAT-1) carrier system and only to a minor extent by a passive diffusion; the absorption occurs in the proximal small intestine and is dose-dependent due to the saturation of the carrier system; the absorption profile is described by a hyperbolic function [34]. Its bioavailability reaches 60% for a dose of 900 mg/day and decreases to 27% in patients taking 4800 mg/day[1]. Thus, increasing the dose results in a slight decrease in absorption, which may limit the risk of intoxication when taking ultra-high doses. The absorption and bioavailability of the delayed-release form, gabapentin enacarbil, are somewhat different: it is transported by the monocarboxylate transporter type 1 and sodium-dependent multivitamin transporters (process is unsaturated and, therefore, nondependent); after the absorption, hydrolysis under the action of nonspecific carboxylesterases leads to the formation of active gabapentin. The range of gabapentin bioavailability values varies from 64.8 to 82.9% [35]. Food intake has no effect on the bioavailability of conventional gabapentin, but contributes to its increase for gabapentin enacarbil[2]. The volume of the gabapentin distribution is 0.8 l/kg, it practically does not bind to plasma proteins, its transport across the blood-brain barrier is carried out by LAT-1 [36]. The concentration

[1] DrugBank Online: Gabapentin: Uses, Interactions, Mechanism of Action. Available from: https://go.drugbank.com/drugs/DB00996

[2] Gabapentin | C9H17NO2 | CID 3446 – PubChem. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Gabapentin#section=Absorption-Distribution-and-Excretion)

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DOI: 10.19163/2307-9266-2024-12-1-74-88

of gabapentin in cerebrospinal fluid is 9 to 20% of that in plasma, the concentration in breast milk is almost equal to that in plasma[3]. Gabapentin is not a substrate for cytochromes P450 and has no effect on them; it is not metabolized and excreted with urine unchanged with the participation of the processes of tubule secretion [37]. The clearance of gabapentin varies from 6 to 9 l/h. A renal function is the main factor determining the rate of gabapentin excretion: in norm, the elimination half-life ranges from 5 to 7 h; when creatinine clearance drops below 30 ml/min, it increases to 52 h[4].

Pharmacokinetic parameters of gabapentin in elderly and senile patients were studied in Ahmed G.F. et al. (2017), which included 75 patients (median age, 79 years) [38]. The difference compared to younger patients was a significant decrease in clearance, up to 2.93 l/hour, associated with a decreased renal function in this patient population.

The effect of diseases on the pharmacokinetics of gabapentin was demonstrated in a study including patients with different levels of DM control. In patients with hyperglycemia the apparent volume of distribution was increased by 68% compared to subjects without diabetes. There was also a 36% decrease in the maximum concentration of gabapentin in patients with high glycemia compared to study participants without diabetes (1.6 *vs* 2.5 mcg/mL). Nevertheless, the reliability of the obtained changes was not established by the authors, which suggests an insignificant effect of hyperglycemia on the pharmacokinetic parameters of gabapentin [39].

Changes in gabapentin plasma concentrations are the result of abnormalities in the excretion phase of the drug from the body; factors such as hepatic insufficiency, plasma protein abnormalities, and drug interactions have not shown significant effects. Gabapentin has a wide therapeutic index; its effective plasma concentrations range from 2 to 20 mg/l [40]. At the same time, the risk of toxic effects against the background of high doses is relatively low, which is associated with an absorption limitation, especially pronounced when using doses of more than 4800 mg/day, which was noted in patients who had received the drug for epilepsy therapy [41]. Accordingly, the maximum dose of gabapentin used in the treatment of NeP (3600 mg) is not accompanied by such a significant decrease in absorption.

The pharmacokinetics of gabapentin suggests a minimal risk of drug interactions. The occurrence of some motor disorders when combining gabapentin with losartan and etacrynic acid, a decrease in the anticonvulsant activity of gabapentin when used together with caffeine, were obtained in laboratory experiments involving mice; a clinical significance of these phenomena in humans has not been confirmed [42]. Synergism with regard to an analgesic effect was demonstrated in patients when taken together with tramadol, metamizole [42], celecoxib. When interacting with antacids (magnesium oxide) there was observed a decrease in the maximum concentration of gabapentin by 33%, against the background of proton pump inhibitors (omeprazole) – by 29%, and a significant decrease in its bioavailability was noted exactly for the combination with magnesium oxide, but not with omeprazole [43]. The most clinically significant interactions are observed when gabapentin is used together with opioids [44, 45]. The patients who have to receive gabapentin and opioid analgesics simultaneously require a careful medical monitoring aimed at a timely detection of such side effects as somnolence, sedation and respiratory depression. In combination therapy, the dose of both gabapentin and opioid analgesics should be reduced.

Efficacy and safety of gabapentin in clinical practice

Gabapentin has a long history of use: having been used in the 1970s primarily as an anticonvulsant, now, according to the most current clinical guidelines, it is the first-line drug for the management of patients with NeP [17–19].

The efficacy of gabapentin in NeP has been the subject of a large number of randomized clinical trials (RCTs) as well as systematic reviews and meta-analyses of RCTs. Since 2000, the Cochrane community has published systematic reviews addressing this issue. The latest one is dated 2017 (37 studies, 59 143 patients with NeP receiving gabapentin or gabapentin enacarbil at a dose of 1200 mg/day or more). Based on the definitions laid out in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), the authors determined that the number of patients with postherpetic NeP to be treated with gabapentin for moderate benefit (pain reduction of ≥30%, NNT30) was 5.7 and for significant benefit (pain reduction of ≥50%, NNT50) was 6.8. Similar parameters for patients with diabetic polyneuropathy were 6.6 and 5.9, respectively [46]. The authors noted that gabapentin was most

[3] DrugBank Online: Gabapentin: Uses, Interactions, Mechanism of Action.
[4] Ibid.

effective in postherpetic NeP, diabetic polyneuropathy and mixed NeP. The proportion of patients who discontinued the drug for any reason (analysis of 22 studies, *n*=4 617) was 20% for gabapentin (a dose of 1200 mg or more) and 19% for placebo, indicating a satisfactory tolerability profile of therapy.

Gabapentin and pregabalin have demonstrated a comparable efficacy and safety in patients with NeP due to the spinal cord injury. According to a systematic review and meta-analysis of 8 studies, there was no significant difference between the two drugs in reducing pain scores (mean difference, MD=-0.37; 95% CI: -1.67, 0.93; *p* >0.05) [47]. A meta-analysis published one year later (2021) showed a greater efficacy of pregabalin and gabapentin in eliminating NeP against the background of the spinal cord injury compared to carbamazepine, amitriptyline and placebo [48].

According to a meta-analysis by Ko Y.C. et al (2021), gabapentin in patients with diabetic painful neuropathy reduced pain (as measured by a visual analog scale, VAS) equally effectively compared to duloxetine (MD=-1.23; 95% CI: -6.09 to 3.62; *p*=0.62), it was also found to be accompanied by an improvement in patients' functional status [49].

The updated data on the efficacy of gabapentin were obtained in a systematic review and meta-analysis of 50 RCTs devoted to the treatment of NeP (2023): the authors found that NNT30 was 7, NNT50 - 8. The same paper evaluated the similar parameters for pregabalin; they were 8 and 10, respectively, indicating a slightly greater effect of gabapentin [50]. Another meta-analysis in 2023 evaluated the efficacy of gabapentinoids in postherpetic NeP (14 RCTs, *n*=3 545): the standard MD of the Numerical Rating Scale (NRS) score for gabapentin was -2.16 (95% CI: -3.40 to -0.92; *p* <0.05), for pregabalin -0.78 (95% CI: -0.98 to -0.58; *p* <0.05) [51]. In a large meta-analysis of 119 studies on patients with various types of chronic pain, including NeP, 8 studies evaluated gabapentin, analyzing those where a comparison had been made with placebo, the authors noted a significant reduction in pain, MD was -1.49 (95% CI: -2.76 to -0.23; *p* <0.05) [52]. Of interest are the results of a meta-analysis of 30 comparative double-blind RCTs with parallel groups or crossover studies that examined the analgesic effect of at least two first-, second-, and third-line drugs in NeP (*n*=4 087) published in 2024 [53]. 10 RCTs (*n*=920) compared the effect of tricyclic antidepressants (TCAs) with pregabalin or gabapentin; the pooled effect showed no difference in the analgesic effect between TCAs and pregabalin / gabapentin (MD=0.10; 95% CI: -0.13 to 0.32; *p*=0.39), there was no significant difference in the depression severity and drug tolerability either. In 8 RCTs, pregabalin/gabapentin was compared with selective norepinephrine reuptake inhibitors (SNRIs), the pooled effect showed a greater effect of the SNRIs efficacy, but a further group analysis showed no differences. The tolerability of the drugs was also comparable [53].

Since the 2000s, most of the researchers have determined that effective doses of gabapentin for the treatment of NeP are larger than 900 mg/day. One of the first large-scale reviews of RCTs on the efficacy and safety of gabapentin in patients with NeP indicated the following dosing guidelines: start, on average, at a dose of 900 mg/day (300 mg/day on the first day, 600 mg/day on the second day, 900 mg/day on the third day) with a further dose titration up to 1800 and up to 3600 mg/day in patients with severe NeP [54]. Many studies demonstrating the efficacy and favorable tolerability profile of gabapentin in high doses (up to 3600 mg/day) have been published [46, 55, 56].

The analysis of the efficacy and safety of different gabapentin enacarbil doses, performed as part of a randomized, double-blind, placebo-controlled trial including patients with postherpetic NeP, showed the most pronounced reduction in mean daily pain (MDP) compared to placebo when using a dose of 3600 mg/day (MD=-1.07; 95% CI: -1.68 to -0.45; *p*=0.002). A significant reduction in pain was achieved in 76% of patients using the drug at this dose versus 70% in the 2400 mg/day group and 67% in the 1200 mg/day group [55]. Of interest are the comparative evaluation results of efficacy and safety of different gabapentin doses and forms obtained in a systematic review and metaanalysis of 7 RCTs, including 2014 patients in the efficacy evaluation group and 2050 patients in the safety evaluation group (authors searched for all publications of the relevant topics from 1966 to 2017). The results showed the largest reduction in MDP with gabapentin (conventional form) at a dose of 3600 mg/day, with a standardized mean difference in MDP values of -0.86 (95% CI: -1.13 to -0.58; *p* <0.00001), with the smallest reduction in MDP demonstrated for the delayed-release forms (Table 1). The authors have also demonstrated that at doses of 1800 to 3600 mg/day, gabapentin significantly improved the sleep quality and reduced the pain intensity by at least 50% in the majority of patients taking it. The safety analysis of high gabapentin doses revealed such side effects as dizziness, drowsiness and peripheral edema [57]. The MDP reduction against the background of using different doses of gabapentin and gabapentin enacarbil is demonstrated in Table 1.

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DOI: 10.19163/2307-9266-2024-12-1-74-88

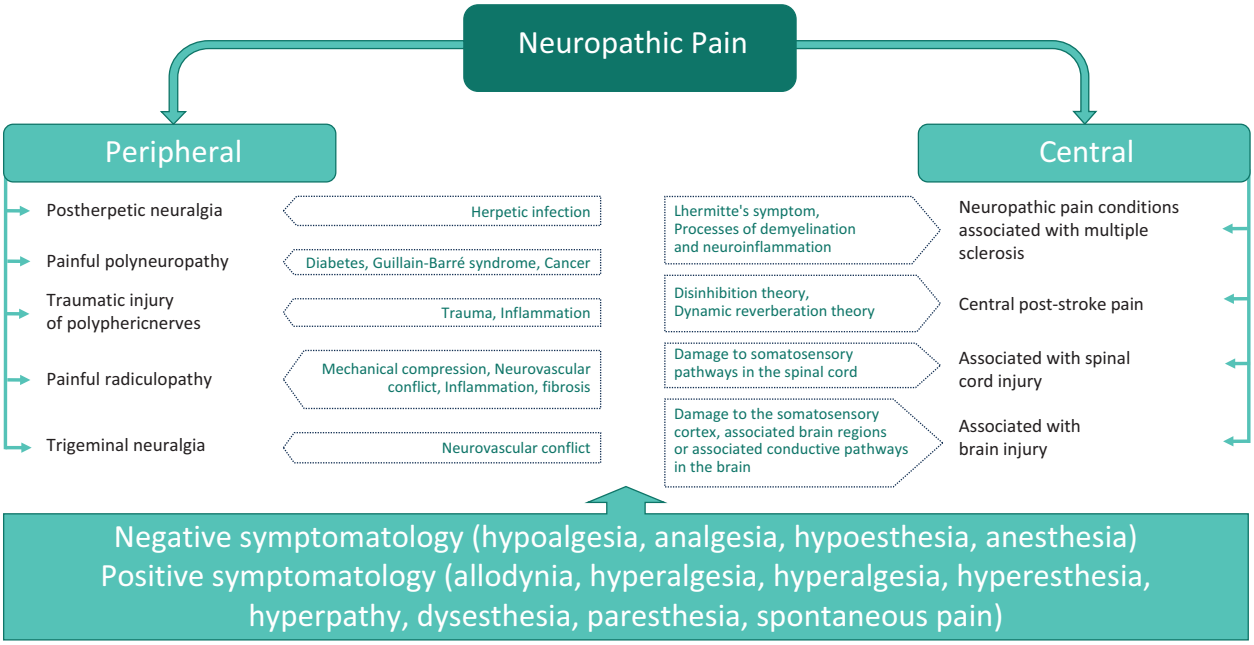

Figure 1 – Varieties of NB and their main etiologic factors

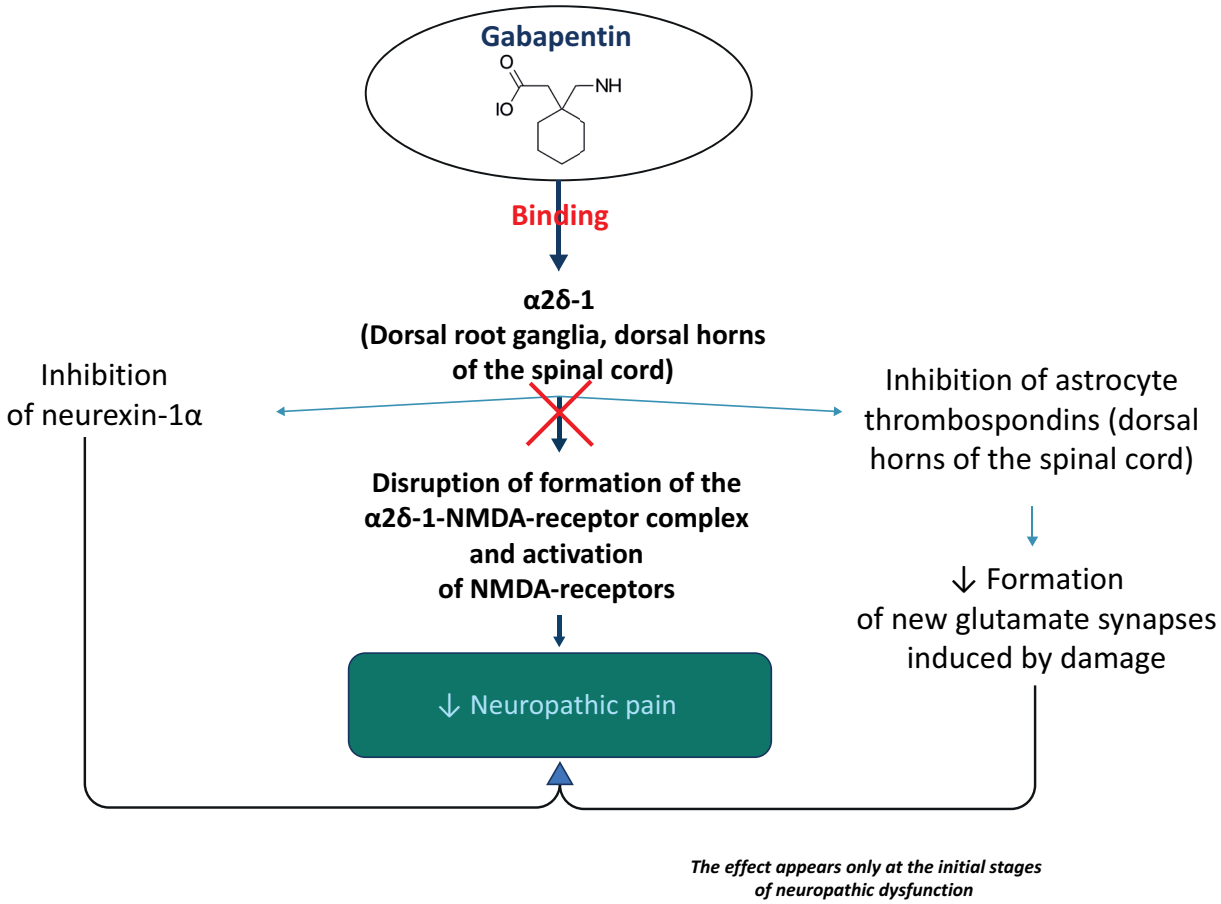

Figure 2 – Action mechanism and main targets of gabapentin underlying the NeP elimination

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
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Table 1 – ADP reduction rates depending on gabapentin dose

Drug	Dose	MD magnitude of MDP reduction
Conventional form	3600 mg/daily	–1.07; 95% CI: from –1.68 to –0.45; *p*=0.002 [55] –0.86; 95% CI: from –1.13 to –0.58; *p* <0.00001 [57]
Gabapentin enacarbil	3600 mg/daily	–0.50; 95% CI: from –0.79 to –0.20; *p*=0.0009 [57]
Gabapentin enacarbil	2400 mg/daily	–0.70; 95% CI: from –1.33 to –0.07; *p*=0.029 [55] –0.33; 95% CI: from –0.62 to –0.03; *p*=0.03 [57]
Gabapentin enacarbil	1200 mg/daily	–0.81; 95% CI: from –1.40 to –0.23; *p*=0.013 [55] –0.43; 95% CI: from –0.66 to –0.20; *p*=0.0002 [57]
Gabapentin ER	1800 mg once daily	–0.21; 95% CI: from –0.42 to –0.01; *p*=0.04 [57]
Gabapentin ER	1800 mg twice daily	–0.25; 95% CI: from –0.57 to 0.06; *p*=0.12 [57]

Note: MD – median deviation; CI – confidence interval; MDP – mean daily pain.

The array of published RCTs, systematic reviews and meta-analyses is the basis for the development of clinical guidelines for the management of patients. Finnerup N.B. et al. published the results of their own RCTs meta-analysis devoted to the treatment of NeP (the total number was 229) and simultaneously presented the recommendations of the Neuropathic Pain Special Interest Group (NeuPSIG), working as part of the International Association for the Study of Pain (IASP) [58]. The NNT50 for gabapentin was 6.3. Gabapentin at the doses ranging from 1200 to 3600 mg was listed by the authors as a first-line treatment for the management of NeP patients with a high level of evidence (including the conventional form, a slow-release form, and gabapentin enacarbil).

The expert consensus of the Chinese Association for the Study of Pain indicates that gabapentin should be used for an effective NeP control at a dose of 900–1800 mg/day, but does not limit the upper limit of the daily dose [59]. In 2024, an updated consensus on the use of the drugs affecting ion channels for the therapy of chronic pain was published in China. According to its provisions, gabapentin is recommended for the therapy of postherpetic NeP, diabetic polyneuropathy, and many other types of NeP [60]. As the drug of choice for NeP therapy, gabapentin is also noted in the Chinese Guidelines for the Treatment of Chronic Pain Disorders with Non-opioid Analgesics [61]. The consensus of Indian experts on the management of patients with NeP lists gabapentin as the first-line treatment and recommends titrating it to 1800 mg/day [62].

The updated 2022 American Academy of Neurology (AAN) clinical guidelines for the management of patients with painful diabetic polyneuropathy suggest using gabapentin at a dose of 900 to 3600 mg/day for 4–8 weeks [63]. A similar approach was recommended by the American Diabetes Association (ADA) in 2017: the starting dose should be about 300 mg followed by titration to an effective dose of 900 to 3600 mg/day[5]. The updated ADA 2022 guidelines state that a minimum dose of 1800 mg/day should be used in most patients and increased in patients with severe NeP to a maximum dose of 3600 mg/day; lower doses are recommended only for the patients with a reduced estimated glomerular filtration rate (eGFR) [64]. Clinical guidelines for the management of patients with NeP developed in France in 2020, also recommend the use of gabapentin as the first-line treatment for various types of NeP at doses of 1200–3600 mg/day, with gabapentinoid, pregabalin, classified as the second-line treatment [65].

Russian recommendations (Methodical Recommendations on the Diagnosis and Treatment of Neuropathic Pain, Russian Interregional Public Organization for the Study of Pain, Society for the Study of Pain) indicate that gabapentin is effective in doses of 1200–3600 mg/day; it should be slowly titrated in an individual regimen starting at 300 mg/day[6]. According to the clinical recommendations “Chronic pain in elderly and senile patients” developed by the All-Russian public organization “Russian Association of Gerontologists and

[5] Pop-Busui R, Ang L, Boulton AJM, Feldman EL, Marcus RL, Mizokami-Stout K, Singleton JR, and Ziegler D. Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy. Arlington (VA): American Diabetes Association; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK580224/ DOI: 10.2337/db2022-01

[6] [Guidelines on neuropathic pain diagnosis and treatment]. Yakhno N.N., editor. Moscow. RAMS; 2008. 32 p. Russian

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DOI: 10.19163/2307-9266-2024-12-1-74-88

Geriatrics", in elderly and senile patients, it is necessary to use lower doses of gabapentin, the initial dose should be 300 mg, titrated until the development of the analgesic effect[7].

Consensus clinical guidelines on diagnosis and rational therapy of patients with a painful form of diabetic polyneuropathy developed by leading Russian professional medical communities (2019), give the following dosing regimen of gabapentin as the first-line drug. On the first day 300 mg/day should be taken, on the second day – 600 mg/day, on the third day – 900 mg/day, further on – the titration during 3–8 weeks to reach 1800–3600 mg/day and the administration for at least 2 weeks at the maximum tolerated dose [66].

Many international clinical guidelines specify gabapentin as the first-line treatment in the management of patients with NeP but do not provide doses: UK, NICE guidelines, 2020[8], Germany, 2020 [16] and 2021 [67], Canada, 2021 [68], China, 2023 [69] and 2024 [61]. Similarly, without a dose indication, gabapentin is presented in the practice guideline for the management of patients with trigeminal neuralgia published by Lambru G. et al. (2021). It is listed among the first-line drugs for both idiopathic, classical and secondary forms [60].

Physicians using them are guided by the data in the instructions for the drug and the patient's response to a gradual increase in dose (in most cases, the titration period takes 2 weeks). In general, practice indicates a good tolerability of gabapentin. Risks appear, first of all, when they are used in combination with opioids, as it will be discussed below.

Gabapentin safety

The gabapentin safety is well illustrated by the data from a 2017 Cochrane review that found the occurrence of adverse events in 11% of patients taking gabapentin (1200 mg/day or more) versus 8.2% of patients taking placebo (a risk ratio of 1.4 (1.1 to 1.7)), and the number of patients to be treated for the occurrence of an adverse event was 30 (20 to 66) [46]. The most current safety data on gabapentinoids (gabapentin and pregabalin) are reported in a systematic review and meta-analysis of 50 RCTs (*n*=12 398) published in 2023. Among the side effects of gabapentin, weight gain (relative risk, OR=5.61; 95% CI: 1.04 to 30.22), dizziness (OR=3.33; 95% CI: 2.39 to 4.65), peripheral edema (OR=3.06; 95% CI: 1.25 to 7.48), and somnolence (OR=2.91; 95% CI: 2.10 to 4.03) were the most prominent. Side effects of pregabalin included an impaired coordination (OR=7.21; 95% CI: 1.36 to 38.25), gait disturbances (OR=6.71; 95% CI: 1.57 to 28.71), ataxia (OR=6.02; 95% CI: 2.31 to 31.15), euphoria (OR=6.01; 95% CI: 3.02 to 11.97), and weight gain (OR=4.97; 95% CI: 3.08 to 8.00) [50].

According to the meta-analysis of 8 safety studies of different drugs in NeP patients, the discontinuation rate of gabapentin was similar to that of placebo [48].

The safety profile of gabapentin is quite favorable, it should be noted that side effects are more common in patients using it together with opioids [70–72]. Monotherapy with gabapentin is usually not accompanied by the development of serious adverse drug reactions (ARs); the formation of dependence is not typical either [73].

Acute poisoning associated with gabapentin overdose is not a routine phenomenon in clinical practice either. This may be partly explained by a dose-dependent decrease in absorption and, consequently, bioavailability, against the background of high doses. A clinical case describing an acute overdose with gabapentin (5200 mg administered at once) against the background of a number of other drugs in a 39-year-old man, is available from published works. The clinical picture included severe rhabdomyolysis and acute tubular necrosis, which required renal replacement therapy, after 3 months all parameters returned to normal [74].

A meta-analysis of 11 RCTs (2376 patients with postherpetic NeP, including a gabapentin group (doses of 1200, 1800, 2400 and 3600 mg/day) – 1 424 people, placebo – 952) showed that the risk ratio for ARs with gabapentin compared to placebo was slightly more than one: 1.29 (95% CI: 1.06 to 1.57) [75]. An earlier meta-analysis including 12 RCTs evaluating the efficacy and safety of gabapentin showed the following. The relative risk of discontinuation due to ARs was lower with higher doses: 1.8 (95% CI: 0.82 to 3.8) for the 1800 mg/day, 1.4 (95% CI: 0.91 to 2.0) for the 2400 mg/day, and 1.4 (95% CI: 0.85 to 2.4) for the 3600 mg/day [76].

In general, the published data indicate the following spectrum of adverse events associated with gabapentin: dizziness, confusion, general weakness, impaired coordination of movements, gastrointestinal symptoms, and weight gain. A dependence formation is not characteristic of gabapentin: according to Meaadi J. et al. (2023), among 50 analyzed studies there was not a single one in which the occurrence of euphoria – the main substrate of the dependence formation – had been noted [50].

When prescribing gabapentin for NeP therapy, its tolerability should be taken into account. In case of ARs as dizziness or drowsiness, it is necessary to

[7] Clinical guidelines "Chronic pain in elderly and senile patients", 2020. Available from: https://static-0.minzdrav.gov.ru/. Russian

[8] Neuropathic pain in adults: pharmacological management in non-specialist settings. London: National Institute for Health and Care Excellence (NICE); 2020 Sep 22. (NICE Clinical Guidelines, No. 173.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK552848/

return to the previous dose, slowing down the titration process. During the entire period of selection of an individual effective dose, the patient should be under medical supervision, which is necessary to choose an adequate dosing regimen, an optimal duration of therapy and control the occurrence of side effects. The gabapentin dose titration is one of the fundamentally important factors determining the magnitude of an analgesic effect in NeP patients. The purpose of the titration is to select an individual effective dose within the range studied in clinical trials, which minimizes the risks of occurrence and provides control over potential adverse events. When managing a patient with NeP, it is necessary to carry out a regular monitoring of pain intensity (once every 2–4 weeks) using available tools, a VAS, is most often used in this role. The goal of pharmacotherapy is to reduce the intensity of NeP by 30–50% of the initial value [17–19].

Among the ways to reduce the risk of gabapentin ARs, there are the following ones. The main way is to start with a low dose (300 mg/day) and further on a slow titration until the desired therapeutic effect is achieved. It is important to use doses and dosing regimens that are well studied in clinical trials and correspond to those given in the instructions for medical use or a general characterization of the drug. A strict control of a number of drug prescriptions received by the patient also contributes to reducing the risks of adverse reactions. The phenomenon of polypragmasy is very common among patients receiving drugs affecting the central nervous system and makes a significant contribution to the risks of pharmacotherapy [77, 78]. Clinically unjustified switching from the original drug to generics is also important. A number of studies have demonstrated that there are subpopulations of patients for whom the probability of achieving a comparable bioavailability to the originator when switching to a generic drug is reduced. There is an increased variability of pharmacokinetic parameters of gabapentin in patients with an impaired absorption and a reduced renal function, respectively, there is a high probability that the use of generics in this case will not allow to achieve the required values of the drug concentration in plasma [79]. The original preparation of gabapentin available on the Russian pharmaceutical market is Neurontin®. The use of the original drug is characterized by a greater efficacy and safety compared to generics, which follows from the results of pharmacokinetic studies [79].

Achieving therapeutic efficacy of the drug is impossible without an adequate level of patient adherence to pharmacotherapy. Taking into account the need to titrate the dose of gabapentin from lower to higher, it is worth noting the importance of such a factor as an availability of the drug in various dosages, which allows the patient to take the drug with greater comfort. The original preparation of gabapentin is presented in the form of capsules (300 mg) and film-coated tablets (600 mg). The latter are convenient to use in patients requiring high doses of gabapentin.

CONCLUSION

According to current Russian and international clinical guidelines, gabapentin is the drug of choice in the management of patients with NeP of different etiology and intensity. A satisfactory safety profile and pharmacodynamic effects demonstrated in clinical trials allow gabapentin, despite its long history of use, to remain a relevant drug used by physicians of a wide range of specialties for pharmacotherapy of NeP patients. The data set accumulated in RCTs was obtained primarily for original gabapentin, different dosage forms of which can provide a comfortable process of a dose titration for the patient and achieve an effective pain control. In most studies involving patients with NeP and a normal renal function, the target therapeutic dose of gabapentin, contributing to a maximum analgesic effect against a satisfactory safety profile, was 1800–3600 mg/day (divided into three doses), which allows us to recommend this dose as optimal for the main population of NeP patients.

FUNDING

This review work was supported by Viatris. The sponsor had no influence on the selection of material for the publication, the data analysis and interpretation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

All authors have made equivalent contributions to the preparation of the publication. All authors confirm their authorship compliance with the ICMJE international criteria (all authors made a significant contribution to the conceptualization, research and preparation of the article, read and approved the final version before publication). Olga I. Butranova – conceptualization and design of the paper, search and analysis of sources, interpretation of obtained data, writing the layout of the paper, writing the final version of the paper Sergei K. Zyryanov – search and analysis of sources, interpretation of obtained data, critical evaluation of the paper for significant intellectual content, writing the final version of the paper, final approval of the version for publication.

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