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CLINICAL FOCUS: PAIN MANAGEMENT
REVIEW

Pregabalin for neuropathic pain in primary care settings: recommendations for dosing and titration

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ABSTRACT

Pregabalin is one of the first-line treatments approved for the management of neuropathic pain (NeP). While many patients benefit from treatment with pregabalin, they are often treated with suboptimal doses, possibly due to unfamiliarity around prescribing the drug and/or side effects that can occur with up-titration. This narrative review discusses key aspects of initiating, titrating, and managing patients prescribed pregabalin therapy, and addresses concerns around driving and the potential for abuse, as well as when to seek specialist opinion. To ensure that patients derive maximum therapeutic benefit from the drug, we suggest a 'low and slow' dosing approach to limit common side effects and optimize tolerability alongside patients' expectations. When requiring titration to higher doses, we recommend initiating 'asymmetric dosing,' with the larger dose in the evening. Fully engaging patients in order for them to understand the expected timeline for efficacy and side effects (including their resolution), can also help determine the optimal titration tempo for each individual patient. The 'low and slow' approach also recognizes that patients with NeP are heterogeneous in terms of their optimal therapeutic dose of pregabalin. Hence, it is recommended that general practitioners closely monitor patients and up-titrate according to pain relief and side effects to limit suboptimal dosing or premature discontinuation.

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Abuse; adverse events; asymmetric dosing; general practice; 'low and slow' approach; neuropathic pain; pregabalin; side effects

1. Introduction

Neuropathic pain (NeP) arises as a direct consequence of a lesion or disease of the somatosensory nervous system [1], and can result in a substantial healthcare burden, and frequent comorbidities, such as poor sleep, increased anxiety, and depression [2–4]. Epidemiologic research suggests that 7–10% of the general population suffers from NeP, although the prevalence may be underestimated [5–7]. Despite multiple treatment options, many patients with NeP remain undiagnosed, untreated, or inadequately managed [8]. Indeed, one recent study in Qatar suggested ~80% of patients with painful diabetic peripheral neuropathy (pDPN), a common cause of NeP [6,9], had not previously been diagnosed or treated [10]. Similar observations of underdiagnosis and/or inadequate treatment have been noted in other countries [11–13]. A survey from Southeast Asia suggested that physicians considered the diagnosis and treatment of DPN a low priority, perhaps leading to patients reporting a lack of awareness of DPN [11]. To improve outcomes, it is important to diagnose patients early using validated screening tools, alongside a thorough physical examination [14–16]. However, it is equally important not to use crude screening tools such as the 10 g monofilament, which detects advanced large fiber neuropathy but will miss C-fiber–mediated painful neuropathy [17]. (Table 1)

Evidence-based guidelines, such as the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) [1,18], recommend pregabalin as a first-line treatment for NeP, alongside other therapeutics including tricyclic antidepressants, serotonin–noradrenaline reuptake inhibitors, and gabapentin [18]. However, nonspecialist prescribers, i.e., general practitioners (GPs) or primary care physicians (PCPs), can be uncertain with initiating and/or titrating therapeutics used for

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chronic NeP [19–21]. There is a lack of clinical studies to help guide these physicians in the optimal sequence of therapy for a specific patient [6]. As a result, patients are often maintained on lower-than-recommended doses [22–25]. For example, an observational study from the United Kingdom reported that, although pregabalin was largely prescribed according to the prescribing label, the average prescribed daily dose of pregabalin was 158 mg/day for NeP [22], which is on the lower end of the recommended dose range (i.e., 150–300 or 600 mg/day, depending on the indication [26,27]). Pregabalin is also often initiated and maintained at a lower-than-recommended dose in other countries, including the United States [23], India [24], and Japan [25].

On 7 April 2017, an international expert panel of chronic pain specialists convened to discuss dosing and adherence challenges with pregabalin in general practice. The expert opinions of this group are presented in this narrative review to help nonspecialist health-care prescribers tailor their treatment and dosing decisions effectively when prescribing pregabalin for patients with NeP.

2. Tailoring pregabalin dosing and titration

2.1 Challenges to dosing and adherence

Suboptimal adherence results from both patient- and physician-related factors [28]. Health-care prescribers and patients are poorly compliant and/or discontinue therapy for chronic NeP for a variety of reasons, including a lack of analgesic effectiveness, inconvenient dosing frequency, fear that potential side effects do not warrant the expected benefit of analgesia [21,23,24,29–31], and/or fear of addiction [32,33]. Adherence to therapies is a primary determinant of treatment success [28,31]. In order to improve medication adherence, prescribers need to explain key information regarding the drug and any possible side effects (what, why, when, how, and how long) at the point of prescribing to their patients [28,31]. For pregabalin, the pharmacokinetic profile can be used as an aid to improve medication adherence, as it has linear and predictable pharmacokinetics [34], with >90% bioavailability, negligible hepatic metabolism, and no binding to plasma proteins. As such, pregabalin has a low potential for drug–drug interactions. Health-care prescribers should inform patients, in plain language, about the linear dose–response relationship (i.e., higher doses are associated with greater efficacy) and the low risk of organ toxicity, although dose adjustments are recommended for patients with renal insufficiency. (*See Section 2.2 Initiating pregabalin and making dose adjustments*.)

Patients' perceptions and fears around pain-control drugs can lead them to avoid higher dosages, or even stop them taking the drug completely [29,31]. Moreover, concern around possible side effects may also result in underdosing by physicians, or nonadherence by patients [22–25,29]. To avoid the potential influence of a lack of information or misinformation about persistence of side effects, health-care prescribers should inform their patients at treatment initiation about the timeline for onset of pain relief, and that many common side effects resolve over time [35,36]. Pooled analyses (14 clinical trials) have demonstrated that the most common side effects associated with pregabalin are dizziness and somnolence, often starting during Week 1 of treatment, decreasing thereafter, and in most cases, resolving within 1 month of treatment initiation [37]. By spending a few minutes to follow up with their patients after drug prescription (e.g., through telephone or checkup visits), health-care providers, including nurses and pharmacists, can help ensure treatment adherence and take this opportunity to discuss any concerns around side effects [31]. This also allows time for discussing concerns and monitoring for the emergence or worsening of symptoms of depression, any changes in mood or behavior, and in particular, the emergence of suicidal thoughts or behavior, or thoughts about self-harm. In 2008, the US Food & Drug Administration (FDA) issued an alert regarding an increased risk of suicidal ideation and behavior in people treated with antiepileptic drugs (AEDs) [38]. The guidance was supported by pooled analyses of AED trials that demonstrated an increased risk of suicidal thinking or behavior compared with patients treated with placebo [38,39]. Health-care providers should counsel patients and their families on initiation of AED therapy, including pregabalin, that there is a risk of suicidal thoughts [27,39]. When a situation arises, health-care prescribers must balance the risk of suicidal thoughts or behavior with the risk of untreated illness on a patient-by-patient basis. As recommended in the prescribing information [27], if suicidal thoughts emerge during treatment with pregabalin, health-care prescribers must consider whether the emergence of symptoms might be related to the underlying illness.

A potential barrier to adherence and achieving recommended therapeutic doses of pain medications is concerns regarding the risk of abuse and dependency [29,32,40]. Physicians need to understand and respond to their patients' concerns, and also recognize potential indicators of abuse in their patients. Recreational abuse of pregabalin and gabapentin is increasingly reported [41,42], and is a concern internationally [43–47] both in the scientific literature and in the lay press. While physicians need to be alert to the potential for drug misuse or misappropriation, current evidence suggests that, in patients without a current or past history of substance abuse, the risk of developing dependence on pregabalin is low [33,48]. The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System provides a broad picture of abuse patterns across different countries [49,50], and can help to educate health-care prescribers around the risks of abuse and misuse in different patient populations, and the need to monitor patients for signs of abuse [48]. Recent real-world data utilizing the RADARS® System indicates that lifetime rates of abuse for pregabalin are low in relation to other drugs, including opioids and benzodiazepines [51,52]. Furthermore, subjects who reported abuse or misuse of pregabalin also frequently reported abuse of one or more other drugs [51,52]. It should be noted that overdose with pregabalin alone does not usually result in severe toxicity [32] but rather sedation and, uncommonly, seizures, unless an overdose is taken in combination with opioids or other sedatives, such as benzodiazepines [41,48,53,54]. Health-care prescribers should be aware of these data to aid treatment decisions, particularly in susceptible patients. Based upon these data, we recommend that in patients with current or past substance use disorders, gabapentinoids should be avoided or, if indispensable, administered with caution using strict therapeutic and prescription monitoring.

In summary, adherence is a multifaceted issue and ongoing patient education, motivation, and support are key to improving compliance [28,31]. It is essential to communicate regularly with your patients in order to maintain an optimal dose of

pregabalin, especially in patients with multiple comorbidities and more complex drug regimens for which they are already experiencing difficulties with adherence. More information on ways to improve adherence is given under *Section 2.3 Managing treatment expectations can improve drug adherence*.

2.2 Initiating pregabalin and making dose adjustments

The prescribing information for pregabalin recommends that the dose for treatment of NeP starts at 150 mg divided into two (BID) or three (TID) equal doses per day, increasing to 300 mg/day divided into two doses after 3–7 days, and, if necessary (and depending on therapeutic indication), increasing again to a maximum dose of 600 mg/day the following week [26,27]. In our clinical experience, even patients who start on a pregabalin dose of 150 mg/day can develop early side effects, potentially leading to discontinuing therapy. Thus, we recommend that the health-care prescriber starts pregabalin at a low dose, and go slowly when titrating to a therapeutic dose (hereafter termed the 'low and slow' approach) [30]. Treatment can be initiated with a dose as low as 25 mg/day (in elderly or frail patients) or 50 mg/day in the evening, with regular monitoring of tolerability. Subsequently, as long as the patient tolerates the therapy, doses can be incrementally up-titrated weekly, to achieve a maximal clinical response.

We recommend that patients are advised to initiate pregabalin therapy in the evening. Although the prescribing information states that pregabalin can be taken with or without food [26,27], we recommend an initial single daily dose with the evening meal. For some patients, a single evening dose of 150 mg/day will be sufficient to manage pain and/or improve sleep with minimal side effects [37]. Those requiring titration to higher doses can add a daytime dose to the evening dose. In such cases, we recommend initiating an 'asymmetric dosing' approach, with the larger dose in the evening. Part of the rationale for this is that if pain relief and improved sleep quality are achieved at night, then patients may not require an equal pregabalin dose in the morning, thus limiting side effects during the day. There is a reciprocal relationship between sleep quality and pain [55], and pregabalin has been associated with improved sleep quality [37], including more time spent in restful rapid eye movement sleep, which is the most restorative sleep phase [56]. Consistent with this, a pooled study of 16 pregabalin trials in patients with NeP showed that improvements in sleep were associated with a significant indirect effect on reduction in pain scores [57]. Another advantage to evening dosing is that it enables weaning from previous regimens that may have negatively affected sleep, or have addictive potential [58]. To manage expectations as they titrate their dose, patients should be informed in advance that an improvement in sleep occurs before they achieve a clinically meaningful reduction in pain relief [56,57,59].

When initiating centrally acting medications, including pregabalin, euphoria, an exaggerated feeling of physical and emotional well-being and optimism that is inconsistent with apparent stimuli or events, is a commonly reported side effect, and should be monitored after treatment initiation. The relationship between pregabalin treatment and early treatment response in patients who report euphoria has recently been explored [60]. In a pooled analysis of >13,000 patients treated with pregabalin or placebo, 'euphoria events' were more commonly reported in subjects who also reported early improvements in pain or sleep scores [60]. It is possible that some of these patients reported 'euphoria events' because they were experiencing rapid pain relief and/or sleep improvement after long-standing pain and/or sleep disturbance rather than due to 'euphoria' *per se* [60]. Given that reports of euphoria occur early in treatment [60], physicians should remain vigilant, in order to manage the need to discontinue or potentially down-titrate pregabalin in patients who are treatment responders.

By informing patients of expected efficacy (as well as side effects) while encouraging a 'low and slow' approach, the patients themselves can help determine the optimal titration tempo for their individual therapeutic needs. In a pooled study (six clinical trials) of flexibly dosed pregabalin for NeP, a larger percentage of subjects who shifted to higher doses achieved 30% or 50% pain responder status (as measured by percentage pain score reduction from baseline) compared with patients who remained on the lower dose [61]. Thus, health-care prescribers should monitor patients receiving a subtherapeutic dose of pregabalin as suboptimal efficacy can lead to potential premature drug discontinuation (e.g., from a patient assuming that the drug does not work). The goal is for dose titration to reach a tolerable and effective dose, up to 150, 300, or even 600 mg/day (depending on therapeutic indication) [26,27], and then to maintain the effective dose.

The 'low and slow' approach recognizes that patients with NeP are heterogeneous in terms of their optimal therapeutic dose. Response to drugs is influenced by multiple individual differences (e.g., in pathophysiology, renal function, genetics, age, level of sensitivity to pain [62]), all of which can complicate identifying the optimal effective dose and tolerability profile. The 'low and slow' approach increases the therapeutic dose more slowly than recommended in the prescribing information [27] (up to the maximum recommended doses), because some patients need more careful titration to manage potential side effects.

2.3 Managing treatment expectations can improve drug adherence

When using the 'low and slow' dosing approach, health-care prescribers should manage patient expectations by talking through common side effects and explaining that the reason for slow titration is to optimize tolerability, to monitor side effects, and to achieve the optimal effective dose for them, as an individual patient. Because pregabalin demonstrates dose-proportional efficacy in the treatment of NeP [63], patients need to be aware that they may not achieve the optimal therapeutic effect immediately with the 'low and slow' approach, and that therapeutic sleep benefits often precede pain relief [56,57,59]. Otherwise, patients who are not currently at their optimal dose could conclude too early that pregabalin is ineffective and opt to discontinue treatment. As noted above, we recommend that health-care prescribers educate their patients on common side effects such as

dizziness, blurry vision, dry mouth, sleepiness, and trouble concentrating, and emphasize that these are often transient, occurring only during the first 2–4 weeks of treatment [35,36]. Weight gain is more likely in younger patients with lower baseline body mass index and has been shown to emerge later than other common side effects (>56 days) [59,64]. However, reassuringly, a pooled analysis of more than 40 studies showed that 82% of patients did not have any significant weight change [64]. By contrast, peripheral edema, when it occurs, is unlikely to improve. Explaining that side effects are frequently transient should encourage patients to persist with early therapy and to ensure adherence and persistence with therapy. (*See Section 2.4 When to make dose adjustments*.)

There is potential for patients to assume that a lack of side effects translates to a lack of drug effect, yet the presence or absence of side effects is not related to treatment outcomes [65]; therefore, when communicating potential side effects to a patient, the importance of remaining adherent to treatment [28,31] to achieve the best response to therapy must be emphasized. Moreover, patients should be informed that while a reduction in pain level is expected and 100% pain relief is desirable, it is rarely achieved in our experience.

2.4 When to make dose adjustments

Depending on the clinical profiles and responses of a patient, dose adjustments are often warranted. The timeline of dose adjustments should be tailored to the responses and needs of the individual. If side effects (e.g., sedation, drowsiness, balance disturbance) persist for longer than a week, the dose should be increased more slowly, or down-titrated. For individuals who have achieved a maximum tolerated dose with an acceptable and stable treatment response over a suitable period of time (e.g., 6 months or longer), pregabalin should be reduced slowly, in regular 3-month intervals, to assess whether lower doses are sufficient to control pain, or if treatment might even be discontinued.

If a patient does not show a response to treatment while receiving a sufficient dose (minimum 300 mg) within 6 weeks, or if they experience serious or concerning adverse events that they cannot tolerate, then pregabalin therapy should be discontinued and another first-line treatment should be tried. A switch to gabapentin (and vice versa) might be a potential option, as evidence shows that patients who were switched between gabapentinoids, either as monotherapy or in combination with other analgesics, showed substantial and clinically relevant improvements in relieving pain and related symptoms [66,67]. McQuoid (2019) summarized three approaches to switching between gabapentinoids [68]; 1. Stop/start: take the last dose of pregabalin at night and start the target dose of gabapentin the following day, as simulated elsewhere [69]; 2. Stop/start approach with a 4-day cross-taper: give 50% of the pregabalin dose and 50% of the target gabapentin dose for 4 days, then discontinue pregabalin and initiate target dose of gabapentin, also based on a simulation study [69]; 3. Taper down pregabalin and then gradually up-titrate gabapentin. However, it has to be kept in mind that discontinuation symptoms have been reported with abrupt cessation of both gabapentin and pregabalin [26,27]; therefore, when a down-titration or discontinuation is warranted, doses should be gradually reduced (e.g., over 3–7 days). For certain serious adverse events (e.g., angioedema, hypersensitivity reactions), the patient should be advised to discontinue pregabalin immediately and seek medical help [26,27]. (*For further information see Section 2.7 How to stop therapy*).

In the case of weight gain, if the therapeutic benefits outweigh the increase in weight and the patient wishes to continue, then alternative approaches to limit weight gain should be considered. This is especially relevant in patients with diabetes, where there are an increasing number of therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists or sodium-glucose co-transporter-2 (SGLT2) inhibitors, which can aid weight loss [70,71]. Otherwise, pregabalin should be reduced stepwise to achieve a balance between pain relief and weight gain. In the case of peripheral edema, clinical experience shows that it is usually necessary to taper down and discontinue pregabalin, as it seems to be a dose-independent side effect that is unlikely to improve. For patients with comorbid conditions or the elderly, some ongoing dose adjustments may be required. For example, elderly patients, or those with a neurological disease or gait disturbance, can be vulnerable to falls when initiating treatment with pregabalin (e.g., due to dizziness), and therefore require a lower overall dose to achieve optimal benefit. In addition, the prescribing information recommends a 50% dose reduction in patients with an estimated glomerular filtration rate (eGFR) of 30 to <60 mL/min [26,27]. For medications with concentration-dependent efficacy, extending the interval while maintaining the same dose is appropriate. Hemodialysis is known to remove ~50–60% of pregabalin; hence, supplemental doses are generally recommended after hemodialysis.

2.5 When to add a concomitant therapy

Patients may be taking one or more concomitant medications by the time they seek treatment for NeP. Pregabalin is excreted relatively unchanged in urine, undergoes negligible metabolism, and has not been found to bind plasma proteins, which supports a low likelihood of drug–drug interactions [27,63,72]. In our clinical practice, and consistent with this, patients, including the elderly, do not experience clinically relevant interactions between pregabalin and other drugs [27,63], potentially making it a good candidate for combination therapy. Thus, patients who exhibit a partial response to pregabalin monotherapy (at the maximum tolerated dose) can benefit from concomitant treatment with an additional recommended first-line or second-line drug for NeP [73–76]. Validated electronic scales, such as the painDETECT questionnaire (Pfizer Inc, NY, USA) available in certain countries, including Germany [77], or simple pencil-and-paper visual analog scales or questionnaires (e.g., painDETECT, DN4, LANSS) can help to improve decision-making about initiating add-on therapies for individual patients [78].

Certain drugs are not considered first choice for concomitant therapy with pregabalin because of similar common side effects such as weight gain (e.g., tricyclic antidepressants, mirtazapine) or sedation (e.g., amitriptyline). Patients taking

concomitant thiazolidinedione antidiabetic agents should be counseled on a possible additive effect on edema and weight gain, as recommended in the prescribing information [27]. Exceptions can be made for patients who might benefit from an expected side effect (e.g., weight gain in cancer patients). Also, any drug that causes peripheral edema should be avoided. When combining pregabalin with a drug that also causes dizziness (a common side effect with pregabalin), patients should be informed of the possibility of this side effect and that they should proceed with caution, encouraging the 'low and slow' approach. In clinical practice, pregabalin will often be co-ingested with another drug, as two or more medications are required to achieve either an additive beneficial effect or a reduction in side effects associated with a single medication [18,73]. More specifically, when pregabalin is combined with an opioid, this combination (similar to other combinations of opioids with medications that cause sedation) can increase the risk of opioid-related respiratory depression, and thereby the risk of toxicity, including opioid-related death [54]. Therefore, conventional opioids, which are usually third-line treatment options for neuropathic pain, should be used with extreme caution in combination with pregabalin. Physicians should also take time to discuss the potential impact of medications that cause dizziness on driving when initiating pregabalin or adding a concomitant medication with a similar side-effect profile. (*See Section 2.6 How to discuss possible impact on driving*.)

We would not recommend adding a concomitant therapy for patients who have shown a full response to pregabalin, nor for those who have shown no response. In the latter case (i.e., treatment nonresponders), an alternative recommended therapy should be explored.

2.6 How to discuss possible impact on driving

The legal systems in most parts of the world have different thresholds for driving under the influence of drugs (DUID), and most countries do not differentiate between a patient taking a prescribed drug for pain at the right dose and frequency, and an abuser taking an illegal drug or abusing a prescription-only medicine. Therefore, DUID is a term used to designate the action of driving an automobile after the consumption of drugs or medications, other than alcohol, that interfere with the capacity to operate a vehicle safely. Prescription medications pose a unique challenge: to provide therapeutic benefit without compromising patient safety or the safety of the driving public. Patients (and doctors) reportedly worry about the possible effects of prescription medications on driving performance and cognitive function [79,80]. It is known that some centrally acting drugs produce negative effects on psychomotor or mental performance [81], which can be exacerbated in patients who are taking other prescription medications or even illegal substances [79,80,82]. Drug impairment diminishes with chronic stable medication usage [79,83], and with this, we have to balance the need for providing pain relief against the need for public roadway protection.

Although available evidence is limited, studies suggest that pregabalin does not impair driving performance, only mildly reducing the training effects during driving simulation experiments [82,84], even in combination with oxycodone [80]. However, as noted in the prescribing information, common side effects of pregabalin include dizziness and somnolence, and an impaired ability to drive or operate machinery [27]. Accordingly, physicians should advise patients not to drive until they have gained sufficient experience with pregabalin to gauge that their mental, visual, and/or motor performance is not adversely affected [27]. In clinical practice, 'fitness to drive' should be based on a daily individual assessment by the patient themselves, if and when they are experiencing any side effects. Physicians should also educate patients not to drive while changing their dose (up or down), or when adding any concomitant medication with a similar side-effect profile, and for at least 1 week thereafter, to allow adjustment to the new stable dosing. Although there is no universal approach or legal regulation, it remains the doctor's responsibility to advise patients of the need for any driving restrictions. This should be done with an in-person explanation of precautions, and necessary guidance given in oral and written form, on a patient-by-patient basis.

2.7 How to stop therapy

Many potent prescription medications, like opioids and benzodiazepines, require a scheduled taper when the physician and patient believe it is time to discontinue the substance or to switch to a different medication. Although no studies have been published about abruptly discontinuing pregabalin treatment, immediately stopping a centrally acting compound, especially in the case of long-term, high-dose use, has the potential to produce discontinuation symptoms. Discontinuation symptoms for pregabalin include changes in sleep patterns, such as insomnia, nausea, headache, or diarrhea, and cases of anxiety and hyperhidrosis [26,27]. As pregabalin is an AED, discontinuing therapy abruptly can change the seizure threshold in susceptible patients, and this should be monitored in patients who are predisposed to epilepsy [26,27].

Rather than stopping a drug suddenly, tapering, i.e., the process of slowly decreasing doses of the drug on a clear timeline, can help the body adjust to the loss of the chemical, decreasing the chances for discontinuation symptoms. The half-life of pregabalin is, on average, 6.3 hours [26,27], indicating that the drug stays in the body for approximately 1.5 days after the final dose. However, there is no exact timeline that can be followed for discontinuation of pregabalin; the individual timing will depend on how long the patient took the drug, how large the dose was, and physiological factors such as age, gender, and body weight. In patients who have been taking pregabalin for a short duration at a lower dose, discontinuation symptoms, in our experience, should be minimal, and 1 week should be enough for the drug to fully clear the system [34,63,72]. In case of pregnancy, however, an immediate discontinuation can be discussed with the patient.

2.8 When to refer to a specialist

A key concern for physicians in primary care surrounds when a patient should be referred to a pain specialist. We

Table 1. Summary of key recommendations for prescribing and titrating pregabalin for the ongoing management of patients with neuropathic pain (NeP).

(1) Diagnosis	• Screen for NeP using simple, validated screening tools and confirm by recording medical history, clinical examination, and, if required, other diagnostic measures.
(2) Treatment considerations	• Select an appropriate first-line treatment [73] for NeP considering age, comorbidities, potential risks, and contraindications. • Pregabalin may be recommended, particularly if impaired sleep, anxiety, and/or polypharmacy are prominent features in a patient.
(3) Pharmacokinetic considerations	• Understand that pregabalin has a linear and predictable pharmacokinetic profile, with high bioavailability, no known drug–drug interactions, and no recorded impact on the liver or kidneys [63].
(4) Manage patient expectations	• Inform the patient of when they can expect a therapeutic benefit, as well as what side effects might arise and how long these take to resolve (generally during the first 2–4 weeks of treatment). • This knowledge will help the patient to adhere to the dosing regimen if there is an initial delay in effectiveness during the titration period, or if side effects arise.
(5) Treatment initiation	• Take a 'low and slow' approach: begin with a pregabalin dose of 50 mg/day (or 25 mg in elderly and frail patients) taken at night, and implement regular increases to achieve an effective and tolerated dose (as required, up to the maximum dose recommended in the prescribing labels [26,27]). • Advise patients not to drive while changing their dose (up or down) or if they are experiencing dizziness or somnolence, which can impair their ability to drive or operate machinery.
(6) Evening or asymmetrical dosing options	• Prescribe an asymmetrical dosing scheme, i.e., with a higher evening than morning dose to take advantage of the potential interrelationship of sleep improvement and pain reduction.
(7) Achieve therapeutic dose and well-tolerated dose	• Titrate 'low and slow' to a dose that achieves a therapeutic benefit (up to maximum allowed dose, depending on the therapeutic indication [26,27]). • If side effects occur that might lead to early discontinuation (e.g., sedation, drowsiness, balance disturbance), then slowly taper down and monitor effect(s). Involve the patient in their drug titration decisions.
(8) Combination therapy for partial response to pregabalin	• Consider adding concomitant recommended first-line (tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, lidocaine patches) or second-line (atypical opioids tramadol or tapentadol) treatment options for NeP [1,18,74], in the event that only partial analgesia is achieved at the maximum tolerated dose of pregabalin.
(9) When to discontinue pregabalin treatment	• Discontinue pregabalin by tapering the dose if no analgesic effect is achieved after 2 weeks at maximum tolerated doses or if patient experiences side effects they cannot tolerate. Switch to another first-line treatment [1,18]. • Advise pregnant women of the potential risk to a fetus. An immediate discontinuation can be discussed.
(10) How to discontinue pregabalin treatment	• Taper pregabalin gradually over a minimum of 1 week, rather than discontinuing abruptly, to avoid discontinuation symptoms. Exceptions should be made for development of angioedema or hypersensitivity reactions, in which cases, pregabalin should be immediately discontinued and medical help sought.
(11) Longer-term treatment	• Reduce pregabalin dose at regular intervals (e.g., 3-monthly) to assess whether lower doses are sufficient to control pain or if pregabalin should be discontinued.
(12) When to refer	• Refer to a specialist if no satisfactory improvement in pain or sleep is achieved after 4–6 weeks of treatment with pregabalin, or with other first-line pain medications, in spite of titration to a maximum tolerated dose; if psychosocial problems create a major barrier to treatment; or if pain is severe in intensity (≥7 on a 10-point numeric rating scale) over longer time.

recommend referral of patients with NeP when pregabalin and other first-line treatments fail to provide sufficient analgesia [18], despite titration to maximum tolerated doses and sufficient treatment periods of 4–6 weeks. However, if a patient rates pain as severe in intensity (≥7 on a 11-point numeric rating scale [NRS]) and there is minimal relief (i.e., ≤1 point on the NRS within 4 weeks), an immediate referral should be made. Finally, if the patient experiences any psychosocial problems that present a major barrier to treatment and are not manageable in a general practice setting, then they should be referred to a multidisciplinary pain management center.

3. Conclusion

Pregabalin is a first-line analgesic for NeP with a proven track record of efficacy and tolerability. However, there is a pattern of underdiagnosis and subtherapeutic dosing of drugs in NeP. To achieve the optimal balance between response to treatment and tolerability, we recommend that physicians in primary care (GPs, PCPs) prescribe pregabalin according to a 'low and slow' titration schedule tailored to the patient's clinical response, alongside ensuring realistic expectations of treatment outcomes and an awareness of the potential side effects, with regular follow-up. Indeed, empowering patients with this knowledge while encouraging a 'low and slow' approach should help them determine the optimal titration tempo for their individual therapeutic needs.

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