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REVIEW ARTICLE

Appropriate use of tapentadol: focus on the optimal tapering strategy

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ABSTRACT

Objective: Due to its opioid and non-opioid mechanism of action, tapentadol is considered an atypical opioid with improved gastrointestinal tolerability versus traditional opioids. As for all opioid analgesics it is important to understand how to discontinue a treatment when it is not needed anymore. The aim of this article was to provide an overview of opioid therapy in non-cancer pain, with a specific focus on tapering of tapentadol in patients with chronic non-cancer pain, and suggestions on how to achieve tapering.

Methods: Studies for this narrative review were identified *via* PubMed using a structured search strategy, focusing on management of chronic non-cancer pain with opioids, and the efficacy, tolerability, and pharmacology of tapentadol prolonged release. Publications were limited to English-language articles published within the last ~10 years.

Results: The review discusses the use and discontinuation of opioids in general, as well clinical data on discontinuation of tapentadol specifically. We provide a flow chart, which can be used by clinicians in the context of their own clinical experience to appropriately taper tapentadol in patients with chronic non-cancer pain. The flow chart can be easily tailored to individual patient characteristics, duration of tapentadol treatment, response to progressive dosage reduction, and likelihood of withdrawal symptom occurrence.

Conclusions: While tapentadol is associated with a low frequency of opioid withdrawal symptoms after abrupt discontinuation, use of a tapering strategy is prudent. Tapering strategies developed for opioids in general can potentially be safely individualized in tapentadol-treated patients, although research on tapering strategies for tapentadol is required.

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Introduction

Chronic non-cancer pain, defined as any non-malignant painful condition persisting beyond the expected normal time for healing (i.e. >3 months)[1–3], is prevalent and burdensome[1,4], with severe chronic pain defined as pain lasting for ≥3 months that results in high disability and severe limitation[5]. Chronic non-cancer pain is associated with a range of pathologies (e.g. low back pain, osteoarthritis, fibromyalgia, cervicobrachialgia, radiculopathy, slipped disk, spinal stenosis)[6,7] and, importantly, a variety of mechanisms (i.e. nociceptive, neuropathic, and/or nociplastic pain)[1,3,4]. Goals of chronic pain management, using pharmacologic and non-pharmacologic treatments, include provision of effective pain relief with a balance between benefits and risks for each treatment option[4].

Since its introduction several decades ago, the World Health Organization's (WHO) 3-step pain ladder has provided useful guidance for the prescribing of pain medication based on the level of pain[4]. Originally developed for cancer pain, the WHO pain ladder has been widely used in non-cancer pain[4]; however, while opioids are considered cornerstone treatment for the management of moderate-to-severe chronic cancer pain[8,9], their role in chronic non-cancer pain is controversial[4]. Recent advances in the understanding of pain anatomy and physiology, and the improved diversity of available therapeutic options have resulted in modification of the WHO pain ladder, particularly with respect to treating chronic non-cancer pain[4]. An individualized, patient-centered approach for the diagnosis and treatment of pain is essential in order to establish a therapeutic alliance between patient and clinician that will help to ensure successful outcomes[10]. This includes consideration of an opioid in selected patients when chronic non-cancer pain cannot be controlled with non-opioid options[4].

Poor tolerability of opioids often leads to treatment discontinuation[11]. Due to the risk of side effects, use of opioids requires dose titration to optimize pain control while minimizing adverse effects[9,12], regular monitoring and follow-up to ensure treatment goals are met[13], and gradual tapering in the event of dose reduction or discontinuation in order to avoid withdrawal symptoms[9].

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Tapentadol is an atypical opioid that has demonstrated analgesic efficacy across multiple chronic pain indications including osteoarthritis, low back pain, and diabetic polyneuropathy[14–20]. It has an improved gastrointestinal tolerability profile compared with classical opioids[14,18,19,21]. Tapentadol may play an important role in pain management, especially in the management of severe chronic pain. Indeed, tapentadol prolonged release (PR) is indicated in adults for the management of severe chronic pain, which can be adequately managed only with opioid analgesics[22,23].

This narrative review provides an overview of opioid therapy in non-cancer pain, with a specific focus on the evidence relating to the pharmacology and tapering of tapentadol, and concludes with guidance regarding the tapering of tapentadol based on the authors' clinical experience. Its purpose is to address the gap of translating pharmacologic and clinical data on tapering of tapentadol into real-world clinical practice.

Search criteria

Relevant guidelines, recommendations, and studies, regarding opioid-induced abstinence, and its management with specific reference to opioid tapering were identified *via* searches of PubMed. Keywords associated with the efficacy, tolerability, and pharmacology of tapentadol PR were used, as well as those relating to management of chronic non-cancer pain with opioids. Publications were limited to English-language articles published within the last ~10 years. The following structured keyword searches were conducted: tapering AND opioid (98 papers identified); tapering AND addiction (4); tapering AND guideline AND opioid (1); tapering opioids (599); and tapentadol tapering (4). The results were filtered and papers were selected for inclusion in the review after careful review by Dr. Renato Vellucci.

Treatment of chronic severe non-cancer pain with opioids: an overview

Initiation of opioids

The therapeutic pain-relieving effects of classical opioids are primarily mediated *via* activation of mu-opioid receptors, a component of a major afferent nociceptive pathway[3,12,24,25]. Unfortunately, mu-opioid receptor agonism is also the mechanism which produces the major adverse effects of classical opioids (e.g. constipation and respiratory depression)[3,12,24,25]. Atypical opioids, such as tapentadol, combine multiple mechanisms of analgesic action, including mu-opioid receptor agonism along with other mechanisms targeting alternative pain (patho) physiologies[3,24]. The pharmacologic effect is only partially due to conventional opioid mechanisms, and sparing mu receptors may limit the appearance of certain adverse effects such as gastrointestinal toxicities. Clinicians should be aware of the specific advantages and disadvantages of different opioids when selecting between them based on the patient's profile. For example, tapentadol could be selected over other opioids because of its fewer gastrointestinal adverse effects and lower risk of drug–drug interactions[6].

Given the serious health risks associated with opioids, their prescription requires careful consideration[11]. While there is no international consensus regarding the use of opioids in chronic non-cancer pain, opioids are generally administered in patients with persistent problematic pain despite optimized non-opioid therapy[2,7,26]. Generally, guidelines make no specific recommendations for one opioid over another[2,7,9,12,26], but focus on patient variables that may influence choice of opioid, formulation and dose for each patient, which should be considered prior to their use. Multifactorial patient differences, including genetic variability in mu-opioid and other opioid receptors, and individual differences in receptor expression regulation, opioid receptor binding affinities, and drug metabolizing enzymes and transporters, contribute toward the need to individualize pain treatment[12,27]. Pain sensation and perception vary between patients[6]. Additionally, response to a drug can vary between patients[6,27]. The type of pain is also important, as certain pain conditions (e.g. fibromyalgia) may not adequately respond to opioids[6].

Patient profiling prior to prescription can help to mitigate the risks associated with opioid use. Administration of an opioid should only be undertaken with a thorough knowledge of both the individual (e.g. age, sex, genetics, organ function) and the opioid in order to avoid unsafe and inappropriate use[6]. Patient factors such as a history of drug abuse, excess alcohol consumption, smoking, etc. should be considered. Opioid treatment agreements (also referred to as opioid treatment contracts) are bilateral agreements between the patient and prescriber defining the responsibilities of these two parties, and may be considered for use as part of a risk mitigation strategy[28]. However, good quality evidence supporting their effectiveness in reducing the risk of opioid misuse and abuse is currently lacking[29].

Pain treatment should be highly individualized and dynamic[6]. There is no universal agreement on starting doses of individual opioids, but the aim is to use titration to identify the minimum opioid dose required to treat pain with tolerable side effects[9,12]. Guidelines regarding appropriate titration schedules are also lacking[6]. Titration schedules may vary depending on the individual pharmacokinetics and tolerability profile of the specific opioid.

In co-operation with the patient, physicians should establish clear therapeutic goals when initiating treatment[7]. Alongside pain reduction, other goals of treatment may include improvement of functional recovery[30]. Non-pharmacologic therapy (e.g. exercise therapy, cognitive behavioral therapy) may be an appropriate addition, in this respect, for some types of chronic non-cancer pain[7]. Setting well-defined therapeutic goals then requires regular follow-up (monitoring) to ensure goals are being met, where the time points for follow-up are planned and agreed to by the patient. Regular follow-up should take place at a minimum of once every three months[7]. If individual therapeutic goals are not being met during opioid treatment, appropriate action

should be taken (e.g. discontinuing opioid treatment, see below)[7].

Discontinuation of opioids

Despite the frequent perception that initiation of an opioid leads to long-term treatment, in clinical practice often shorter term opioid treatment allows for adequate pain control and regaining of function[30], with subsequent dose reduction or discontinuation.

There are several situations that may require dose reduction or opioid discontinuation. The first of these is if pain improves[31,32]. A "drug holiday" can be used to evaluate if an opioid is still needed in the event that the painful condition may have resolved or healed, or be adequately controlled with concomitant non-pharmacologic treatments[7,31]. Secondly, analgesic effects of opioids can attenuate over time due to physiologic tolerance, physical dependence or opioid-induced hyperalgesia[30,33]. This can manifest as no meaningful improvement in pain or function[7,31,32], which can be assessed using a range of instruments.

One common instrument is the 3-item Pain, Enjoyment of Life and General Activity (PEG) scale, for which a clinically meaningful improvement in pain and function is considered to be $a \geq 30\%$ improvement[7,13]. The Brief Pain Inventory (BPI) and EuroQol-5D (EQ-5D) questionnaires can also be useful in clinical practice. These scales have distinctly different functions and there is no defined threshold for a clinically meaningful improvement in pain with these tools, since each patient differs (i.e. with respect to functioning, pain, quality of life). Thus, physicians should, instead, check whether the patient is not improving. The BPI can be used as a "fishing net" to capture the variability of pain over time (part of pain severity) and to identify when to increase or decrease the opioid dose in the light of goals agreed with the patient. The BPI–Pain interference Scale is useful for observing performance over time, as well as effects on singular domains (e.g. sleep, etc.) that require intervention, often with a multimodal perspective. In the opinion of the authors, the 5 L version of the EQ-5D summary index and visual analogue scale is preferable to the 3 L version, both in general and for low back pain, as it is generally compatible with the average abilities of patients. Thus, tapering of opioids should be considered if the multiple goals of treatment are not met at any time during the therapeutic process, without use of specific cut-off values for the BPI or EQ-5D.

Tolerance should also be considered if the patient is receiving higher opioid doses without evidence of benefit from the higher dose[31,32]. The European Pain Federation recommends that dose reduction be considered after six months of opioid therapy, in consultation with the patient, in order to determine whether continued opioid therapy is appropriate[12]. Non-pharmacologic therapies should be explored[12].

Finally, opioids should be discontinued in the case of development of adverse effects (i.e. sedation, reduced concentration and memory, drowsiness, mood changes, constipation, dry mouth, abdominal pain, nausea, hormonal changes leading to sexual dysfunction and osteopenia), or signs and symptoms of dependence and abuse, outweighing the benefits of long-term opioid treatment[7,31]. The risk of harm from opioids increases with escalating doses, and a large proportion of patients experience adverse effects with long-term opioid use[11]. Long-term opioid treatment can be associated with the risk of incurring a substance use disorder[25], with development of addiction. Use of opioids for pain control in drug-dependent patients requires prompt referral to a specialist service due to the complexity of these cases[12].

Regular follow-up of patients is recommended to determine whether opioids are meeting treatment goals and whether they can be reduced to a lower dosage or should be discontinued[13,32]. It is critical that a patient is in voluntary agreement with the decision to discontinue treatment, particularly if treatment is going to be tapered, as patient agreement is key to the success of tapering. Ideally, the criteria for discontinuing/tapering opioid treatment (such as specific targets/goals not being met) would have been agreed upon at the initiation of treatment as part of the opioid treatment contract. Prior to making any changes, it is important to discuss the perceptions of risks, benefits, and adverse effects of continued opioid therapy with the patient[32]. The primary goal of opioid prescribing is to improve pain management[34].

Since activation of mu-opioid receptors can result in the development of tolerance, and physical and psychologic addiction[25], dose reduction or discontinuation of opioids should involve gradual tapering. Abrupt discontinuation can result in opioid-withdrawal symptoms such as agitation, anxiety, muscle aches, insomnia, sweating, abdominal cramping, diarrhea, nausea, and vomiting[9]. There is good guidance on tapering strategies for opioids in general[13]. Tapering plans should be individualized and should minimize symptoms of opioid withdrawal while maximizing pain treatment with non-pharmacologic therapies and non-opioid medications[13]. Recent evidence from a large retrospective administrative claims database study in the United States (US) suggests that patients should be carefully monitored during opioid tapering since there may be an increased risk of mental health adverse events (e.g. emergency department or inpatient hospital admissions for depression/anxiety/suicide attempt)[35,36], although the nature of the data analyzed precluded determining whether individuals identified as undergoing tapering did so with or without medical supervision. Nevertheless, their findings support US recommendations for careful monitoring of patients during tapering, including for psychological distress[32].

Relevant factors to consider when choosing a tapering approach include the length of treatment. In the case of early withdrawal (i.e. when a patient has been receiving opioids for up to 1 year), a decrease of 10% per week is suggested[13]. Whereas, with late/difficult withdrawal (i.e. where the patient has been receiving opioids for >1 year or shows signs of anxiety and depression), a decrease of 10% per month is suggested as a reasonable starting point[13].

Patient profiling prior to tapering may also be useful. A history of substance abuse, alcohol, and smoking may suggest that a patient may encounter issues during tapering,

thus requiring special considerations (e.g. medication-assisted treatment for opioid use disorder)[32]. For patients receiving high opioid dosages, a switch to buprenorphine may help those finding it difficult to taper[32].

Tapentadol for chronic non-cancer pain

A brief overview of tapentadol pharmacology

Tapentadol combines two different mechanisms of action—mu-opioid receptor agonism (MOR) and noradrenaline reuptake inhibition (NRI), both of which contribute to its analgesic effects[37–39], differentiating it from other centrally acting analgesics[40]. These mechanisms are complementary and synergistic, providing effective relief from nociceptive and neuropathic pain[38,40]. Tapentadol has strong analgesic activity with an improved gastrointestinal tolerability profile compared with classical opioids[18,41–46].

Due to the synergistic mechanisms of tapentadol action[47], less opioid action is needed to achieve comparable analgesia to classical strong opioids. This is reflected in the concept of μ-load (defined as the percentage contribution of the opioid component to the degree of adverse effects relative to a pure/classical mu-opioid at equianalgesic doses). The μ-load of tapentadol was shown to be ≤40% that of morphine, oxycodone or fentanyl[24,48], which translated into lower incidences of nausea, vomiting, and constipation compared with classical opioids[18,43,46,49], and fewer treatment discontinuations due to CNS-related adverse events compared with oxycodone/naloxone PR (4.6% vs 17.2%)[41]. This relatively lower risk of adverse effects with tapentadol permits rapid up-titration, facilitating swift achievement of pain control[45]. In both opioid-naïve and opioid-experienced patients, a titration regimen in which twice-daily (BID) doses of tapentadol PR are increased by 50 mg BID every three days is appropriate for most patients to achieve adequate pain control[22].

Tapentadol tapering and withdrawal: current clinical evidence

While withdrawal symptoms may represent a significant problem for patients discontinuing opioids, resulting in the need for gradual tapering, the reduced opioid action and/or NRI activity of tapentadol[24] also seems to have implications for a reduced need of tapering. Abrupt discontinuation of tapentadol has been evaluated using the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) assessments in several studies. Phase III and long-term safety trials have provided withdrawal data after 15 weeks' treatment[14,19] as well as after up to 2 years of tapentadol treatment[50].

A randomized, double-blind, active- and placebo-controlled, parallel-arm, multicenter, phase III study in 1030 patients with moderate-to-severe chronic osteoarthritis-related knee pain demonstrated that abrupt discontinuation of tapentadol extended release (ER) after 15 weeks of treatment was associated with no (82.9% of patients) or mild (17.1%) opioid withdrawal based on COWS assessment completed up to 5 days after discontinuation[14]. SOWS total scores at 3, 4 or ≥5 days after the last dose of tapentadol ER were similar to those in placebo-treated patients[14]. Similarly, results of a prospective, randomized, double-blind, placebo- and active-controlled phase III study of tapentadol ER in patients with chronic low back pain showed that abrupt discontinuation of tapentadol after 15 weeks resulted in no (92.5%) or mild–moderate (4.8%) opioid withdrawal according to COWS assessment[19].

One-year and ≥2-year safety data showed similar results, with the majority of patients experiencing no opioid withdrawal after abrupt discontinuation of longer term tapentadol treatment, and the remainder experiencing mild–moderate opiate withdrawal symptoms according to COWS and SOWS assessment[50,51]. Furthermore, COWS results from pooled analyses of nine randomized, multiple-dose phase II or III studies in patients with chronic osteoarthritis pain, low back pain, or pain related to diabetic peripheral neuropathy of up to one year found that most patients (85% [972 of 1145]) experienced no opioid withdrawal, and that all occurrences of opioid withdrawal were of mild-to-moderate intensity after discontinuation of tapentadol ER[45,52].

Recommendations on the tapering and withdrawal of tapentadol

Despite the above-mentioned low frequency of COWS- and SOWS-assessed mild-to-moderate opioid-withdrawal symptoms, tapering of tapentadol is recommended out of caution[22]. The availability of multiple dosages (25, 50, 100, 150, 200, 250 mg PR tablets) facilitates progressive adjustment of tapentadol dose, promoting easy weaning. However, there are currently no protocols specifically addressing tapentadol tapering. Based on our long experience with tapentadol, tapering plans should be individualized, as with classical opioids.

A 10% dose reduction every two weeks would be reasonable in patients who have been receiving tapentadol for up to two years, especially when initiating tapering from higher dosages (e.g. 500–400 mg/day). A short follow-up visit should be scheduled within the first three days for assessment of withdrawal symptoms. In the event of worsening pain or withdrawal phenomena, the tapering schedule should be modified and appropriate rescue therapy scheduled. Subsequently, monthly follow-up visits could be scheduled, with tailored adjustments based on patient response, up to eventual treatment suspension. This schedule is also valid when tapering in patients receiving lower doses of tapentadol (e.g. starting tapering from a dose of 200 mg/day) or in those who have been receiving tapentadol for shorter periods of time (i.e. weeks or months).

Figure 1 summarizes a proposed algorithm to guide clinicians in appropriately assessing patients receiving tapentadol for the treatment of chronic non-cancer pain. To provide everyday clinical context, the flow chart details clinical decisions regarding a patient with low back pain receiving treatment with tapentadol 200 mg twice daily. In addition, Figure 2 provides a practical example for tapering of tapentadol that can be further tailored to the individual patient.

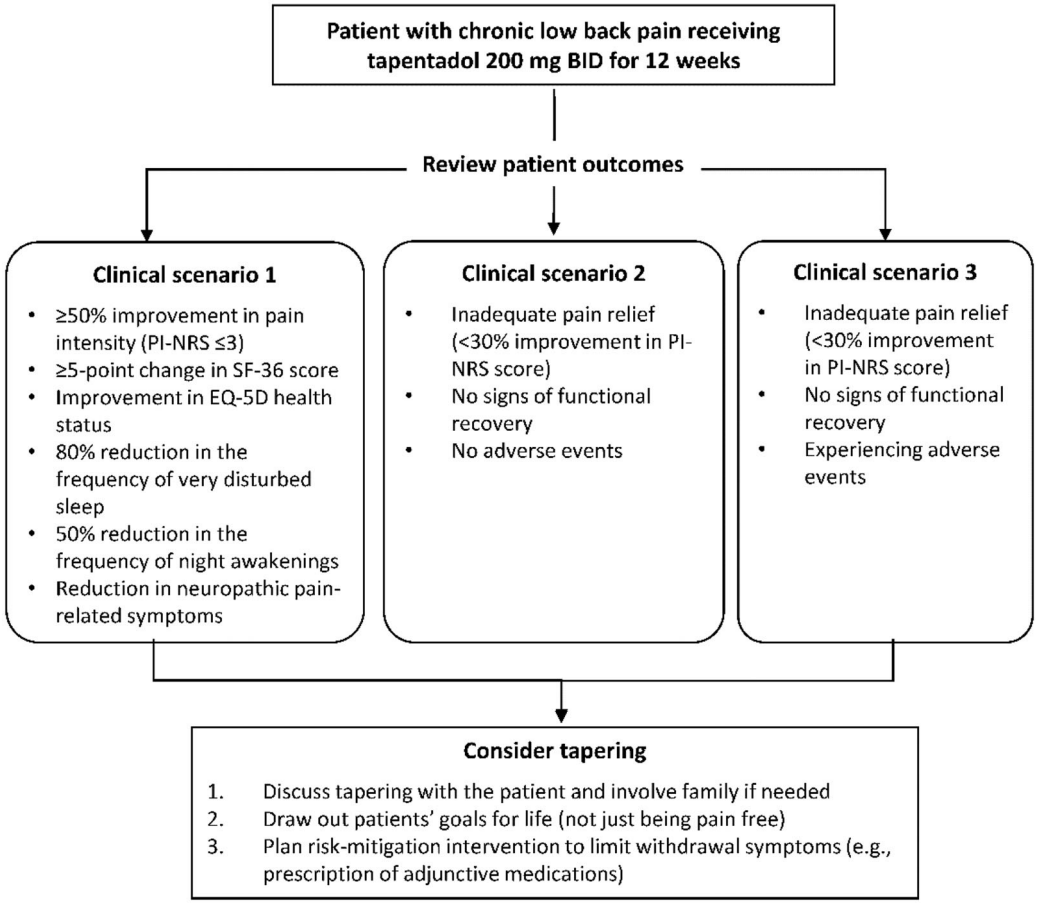

Figure 1. Proposed flow chart for the assessment of patients with chronic non-cancer pain following 12 weeks of tapentadol treatment. Abbreviations. BID, Twice daily; EQ-5D, EuroQol-5D questionnaire; PI-NRS, Pain intensity numerical rating scale; SF-36; 36-item short form survey.

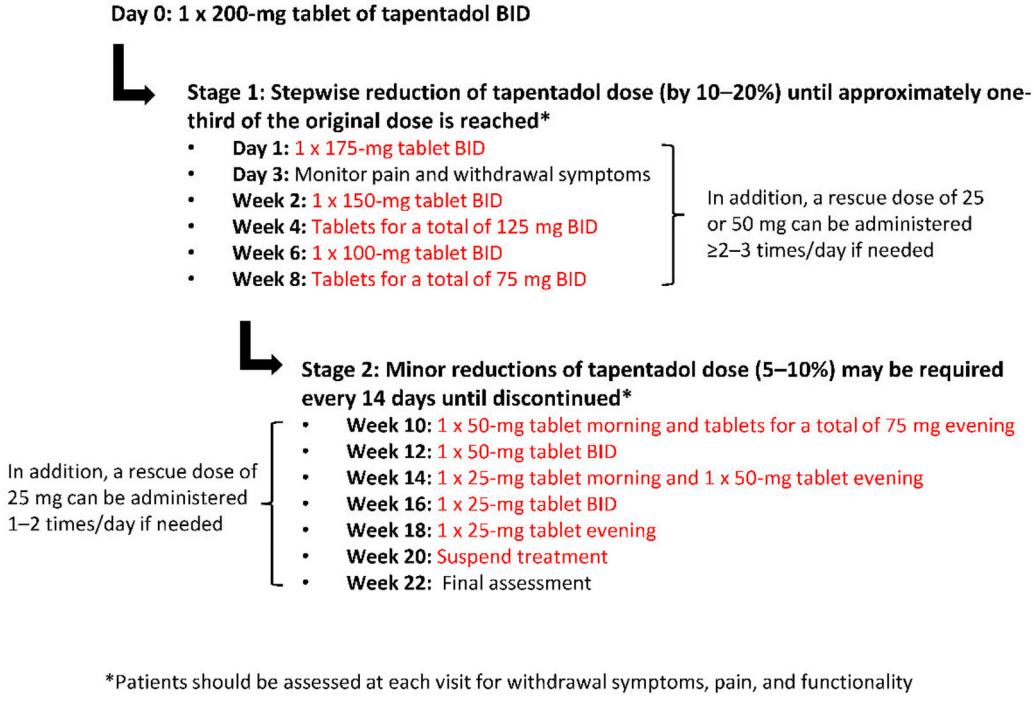

Figure 2. A conservative protocol for the tapering of tapentadol in patients with chronic non-cancer pain, especially after longer treatment. The proportional reduction of tapentadol dosages has been approximated to provide the reader with a practical example of a tapering protocol based on the authors' experience. Depending on treatment duration and patient response to tapering, greater decreases can be made (i.e. reductions in tapentadol dose can be increased by 30–40%), especially during Stage 2 of tapering. *Patients should be assessed at each visit for withdrawal symptoms, pain, and functionality. Abbreviation. BID, Twice daily.

The figure shows the most conservative approach to tapering; however, clinicians are advised to tailor the suggested tapering scheme according to individual patient characteristics, duration of tapentadol, response to progressive dosage reduction, and likelihood of withdrawal symptom occurrence.

Conclusions

Tapentadol is associated with a low frequency of opioid-withdrawal symptoms after abrupt discontinuation as shown in multiple trials. Nevertheless, for many patients, especially after long-term tapentadol treatment, use of a tapering strategy is prudent, although evidence from clinical trials for this strategy remains limited. In our experience, tapering strategies developed for opioids in general can be safely individualized in tapentadol-treated patients. More clinical studies on the tapering of tapentadol, specifically examining our proposed algorithm, would be a welcome addition to the available evidence on this topic.

Transparency

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Author contributions

All authors contributed equally to manuscript conceptualization (with emphasis on pharmacologic aspects), drafting and critical revision. All contributors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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