Peer Review File

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Reviewer A

Comment 1: Given the low level of evidence for tapentadol in treatment of neuropathic pain and concerns for dependency and medication overuse headache with long-term use, I am not sure this case report is a helpful addition to the literature.

Reply 1: The evidence on the effectiveness of tapentadol in neuropathic pain is limited and concerns low-back pain, cancer-related pain, and diabetic neuropathy. It is worth noting, however, that tapentadol has been compared to oxycodone. Baron et al. observed in a randomized, controlled study that in severe neuropathic chronic low back pain, tapentadol was associated with more significant improvements and a better global health status than oxycodone/naloxone (Phase 3b/4 Study). There is also some evidence of lower quality, and tapentadol's safety profile is superior to oxycodone, especially regarding its gastrointestinal tolerability (e.g., Imanaka et al., 2013). In palliative medicine/pain clinics, tapentadol is commonly used in neuropathic pain, and this case may be the premise for clinical trials. Until they are carried out, and conclusions are drawn, I think it may serve as a clue for other physicians looking for an alternative if the proven methods fail in a specific group of patients who, for various reasons, cannot benefit from standard treatments, and with all applicable restrictions. I have added a comment on the limited evidence in neuropathic pain and additional references.

Changes in the text:

The evidence on the effectiveness of tapentadol in neuropathic pain is limited and concerns low-back pain, cancer-related pains, and diabetic neuropathy. It is worth noting, however, that tapentadol efficacy was compared to oxycodone by Baron et al. [8]. In a randomized, controlled study, they found that in severe neuropathic chronic low back pain, tapentadol was associated with more significant improvements and a better global health status than oxycodone/naloxone. Also, according to Imanaka et al., tapentadol’s gastrointestinal tolerability profile is superior to that of oxycodone/naloxone [9].

New references:

Baron R, Jansen JP, Binder A, et al. Tolerability, safety, and quality of life with tapentadol prolonged release (PR) compared with oxycodone/naloxone PR in patients with severe chronic low back pain with a neuropathic component: a randomized, controlled, open-label, phase 3b/4 trial. Pain Pract 2016;16:600-19.

Imanaka K, Tominaga Y, Etropolski M, et al. Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain. Curr Med Res Opin 2013;29:1399-409.

Comment 2: The patient described has a fairly unusual pattern of trigeminal neuralgia pain (only lasting 2-3 weeks at a time), and I am unsure that short-term use of tapentadol would help most patients with trigeminal neuralgia who have much longer periods of time suffering from trigeminal neuralgia.

Reply 2. This is true, but persistent pain is not decisive for trigeminal neuralgia. The diagnosis of TN was made by an experienced neurologist and confirmed by the neurologist who referred the patient and the consulting neurosurgeon. It also did not raise my doubts due to the characteristic features not matching other types of headaches according to the ICOP criteria. I have added a comment concerning my patient's TN course to take into consideration the above remarks. I have added another comment concerning tapentadol's long-term safety and an additional reference.

Changes in the text:

Although the patient had a less typical TN course with complete remissions, the pain features did not match other headaches according to the ICOP criteria.

Data concerning tapentadol's long-term effectiveness and safety remain scarce. However, they were recently confirmed by Mateos et al. in an observational study of up to 72 weeks of observation time. In line with their findings, tapentadol could also prove valuable in TN patients with a more typical disease course requiring longer therapy.

Additional reference was added:

Mateos RG, Bernal DS, Morera LMT, Ferri CM, Escobar AE. Long-term effectiveness and tolerability of pain treatment with tapentadol prolonged release. Pain Physician 2021;24:E75-E85.

Comment 3: If the patient did not want to pursue invasive surgery, other treatments such as nerve blocks or Botox could have been pursued. As someone who treats a lot of patients with trigeminal neuralgia, I would be very hesitant to treat someone with tapentadol, and I do not feel that this case report contributes substantially enough to the literature on treatment of TN to warrant acceptance.s

Reply 3. I agree, and that was my first suggestion. However:
- the waiting time for admission to public health care facilities is long in my country, and access to the procedures mentioned above is limited,

- he was asking for urgent help, being at the beginning of another relapse, and having experienced previous ineffective treatments,
- this particular patient was against ANY invasive treatments, and all options were discussed with him by me, two neurologists, and a consulting neurosurgeon,
On a side note, we encounter patients ineligible for invasive treatments in palliative medicine due to their general performance or comorbidities. Frequently they are not candidates for even minimally invasive therapies. It was not the case here. However, it is another reason why this case brings something new. I have added a comment to explain it unequivocally.

Changes in the text:
(…) including minimally invasive, e.g., nerve blocks. Despite discussing all options, he accepted only pharmacological treatment, and after another relapse started, he asked for urgent help.

Reviewer B

Comment 1. Please list all drugs that the patient used previously. It would be helpful to know how long the patient took these medications as a sufficient trial is needed to determine efficacy.

Reply 1:
The list was added as a table (Table 1). As you rightly spotted, the actual efficacy depends on the period. All conclusions should be drawn with all applicable restrictions due to his pain pattern and the patient's independent decisions, which I also commented on in an additional sentence (see Comment 2).

Drug	Dosage	Treatment period	Why perceived unsatisfactory
carbamazepine	3 x 100 mg	12 days	somnolence, confusion, dizziness, ataxia, limited efficacy, discontinued by the patient
phenytoin	100-100-200 mg (400 mg/day)	9 days	drowsiness, confusion, limited efficacy

			during therapy, discontinued by the patient
gabapentin	3 x 300 mg up to 3 x 600 mg	2 weeks	minimal relief, discontinued by the neurologist due to somnolence and at the patient's request
clonazepam	3 x 0.5 mg	single days, unable to determine	unacceptable somnolence, minimal relief, discontinued by the patient
lamotrigine	25 mg -> 50 mg	10 days	blurred vision, discontinued by the patient

Changes in the text:
A list of previously used drugs with doses and patient tolerability is presented in Table 1.

Also, another comment concerning this issue was added (see Comment 2).

Comment 2. Any comments regarding what led to such a rapid resolution in pain without recurrence? Many patients with TN with concomitant continuous pain can see improvement or resolution of pain in 1-2 weeks but the pain usually returns after lowering or discontinuing the drug.

Reply 2. I added an extended commentary on this issue (below).

Changes in the text:
Many patients with TN with concomitant continuous pain experience improvement in 1-2 weeks. However, the pain usually returns after drug discontinuation. In this case, despite the patient's negative opinion of the previous treatments, their actual efficacy could not be assessed due to the limited therapy periods, treatment discontinuations and

less typical course of the disease with complete remissions between the episodes. Another question is, however, what led to such a rapid improvement on tapentadol. Most likely, it can be attributed to a hyperadditive synergism of an opioid and norepinephrine reuptake inhibitor activities as well as neuron plasticity.

Comment 3. How can you exclude spontaneous remission?

Reply 3. I cannot. Thank you for this insightful remark. The previous pattern, dynamics, and pain chronification argue against this possibility. I added a comment to make it clear.

Changes in the text:
Spontaneous remission, in this case, also cannot be ruled out. However, the previous pattern of pain, its dynamics, and pain chronification argue against this possibility.

Comment 4. It is important to also include potential side-effects of tapentadol as it is not devoid of its limitations and side-effects when compared to anti-epileptic drugs. After all, this is also an opioid with risk of dependence and numerous side-effects, particularly if used long-term.

Reply 4. I added a more detailed comment concerning long-term efficacy and safety, as indicated by Reviewer A. I also introduced an additional paragraph to take your note into account and a new reference (Baron et al., 2014).

Changes in the text:

Data concerning tapentadol's long-term effectiveness and safety remain scarce. However, they were recently confirmed by Mateos et al. in an observational study of up to 72 weeks, concerning people with knee and low back pain. In line with their findings, tapentadol could also prove valuable in TN patients with a more typical course of the disease, requiring longer therapy [5].

As with all opioids, tapentadol is associated with the risk of side effects, which may limit its use. The most common (≥1/10 patients) are dizziness and somnolence (usually transient), nausea, and vomiting. Anxiety, sleep disorders, abnormal dreams, constipation, diarrhea, dyspepsia, muscle cramps, excessive sweating, pruritus, and asthenia have also been reported. Many side effects are similar to those of antiepileptic drugs, but no comparative studies exist. Still, according to Baron et al., the incidence of the composite of dizziness and/or somnolence was significantly lower with

tapentadol alone (16.9%; 500 mg a day) than tapentadol 300 mg combined with pregabalin 300 mg/day (27.0%; P = 0.0302), as demonstrated in people with severe, chronic low back pain with a neuropathic component [6].

New reference:

Baron R, Martin-Mola E, Müller M, et al. Effectiveness and safety of tapentadol prolonged release (PR) versus a combination of tapentadol PR and pregabalin for the management of severe, chronic low back pain with a neuropathic component: a randomized, double-blind, phase 3b study. Pain Pract 2015;15:455-70.

Comment 5. There are several grammatical errors that need to be reviewed and corrected, as well as using different word choices. There are also several spelling errors. Some examples include:
line 68: Provision (did you mean division)
line 72: lachrymation (spelling)
line 83: cancelled (discontinued would be a better term)
line 88: efficient
Please review the entire article for errors

Reply 5: The text has been professionally proofread, and all errors have been corrected.

My remarks

1. I replaced “hyperactive synergism” with "hyperadditive synergism”.
2. Due to the transformation of the facility, one of my affiliations has changed.