Available online on 15.11.2021 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Review Article

Tapentadol: Use and Abuse

Juvin Thomas CV [1], Sambath Kumar R [2]*, Venkateswaramurthy N[1],

[1] *Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Kumarapalayam-638183, Tamil Nadu, India*

[2] *Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam-638183, Tamil Nadu, India*

Article Info:

Article History:

Received 17 September 2021
Reviewed 20 October 2021
Accepted 26 October 2021
Published 15 November 2021

Cite this article as:

Juvin Thomas CV, Sambath Kumar R , Venkateswaramurthy N, Tapentadol: Use and Abuse, Journal of Drug Delivery and Therapeutics. 2021; 11(6):238-243

DOI: http://dx.doi.org/10.22270/jddt.v11i6.5139

Abstract

Tapentadol is a synthetic opioid analgesic that has been on the market in India since 2011. According to international studies, there is a low danger of abuse and diversion. Prescription opioid pain reliever abuse remains a major public health concern. Tapentadol, a prescription painkiller, differs from opioids such as oxycodone and morphine in that it has two modes of action: opioid receptor agonism and norepinephrine reuptake inhibition. Tapentadol has been on the market in India for eight and a half years. Our center was the topic of a single peer-reviewed research in 2017 that detailed two instances of abuse. Tapentadol is less likely to be diverted, abused, addicted, overdosed, or sold on the street than other prescribed opioids. This article reviews uses, pharmacological properties and abuse of tapentadol as it is the most serious issues like addiction, seeking behavior, withdrawal, and physical dependency .The main challenge with tapentadol use is controlling the ratio of MOR agonist to NRI. Finally, tapentadol provides both nociceptive and neuropathic pain relief, but there are concerns about abuse and reliance.

Keywords: Tapentadol, Abuse, Opioid, Addiction.

*Address for Correspondence:

Dr. R. Sambath Kumar, Professor and Head, Department of pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam-638183, Tamil Nadu, India.

ORCID ID: *https://orcid.org/0000-0003-1454-9582*

INTRODUCTION

Tapentadol is a centrally acting, multime-chanistic analgesic with a combination of l-opioid agonist activity and norepinephrine reuptake inhibition(NRI) that is used to treat moderate to severe acute andchronic pain.[1-5] The FDA approved the immediate-release formulation (Nucynta ER) of tapentadol in December 2008, and the FDA approved the extended-release (ER) formulation (Nucynta ER) in August 2011.[6] Tapentadol is a new analgesic that acts as both an agonist of the -opioid receptor (MOR) and a norepinephrine reuptake inhibitor in a single molecule (NRI). Its analgesic benefits start right away, at roughly 30 m for both acute and chronic nociceptive and neuropathic pain.[7] Surprisingly, NRI blockers can suppress this last component of tapentadol activity.[8] Furthermore, an opioid antagonist like naloxone does not reduce the efficacy of tapentadol, indicating that this molecule has a dual mode of action.[9,10] Tapentadol is not a prodrug, and its therapeutic benefits are not dependent on metabolism. It's a powerful opioid with no known active metabolites, and none of them contribute to its analgesic properties.[11, 12] Tapentadol is metabolised via glucuronidation to tapentadol-O-glucuronide, which then conjugates with glucuronic acid to create glucuronides. It is poorly processed by cytochrome P3A4 (CYP3A4) and cytochrome P2D6, which are found throughout the human body.[11, 12] Tapentadol is a prescription pain reliever that is taken by mouth, and its metabolites are eliminated in the urine. Between 1.25 and 1.5 hours after intake, the maximal serum concentration is recorded, and the half-life is four hours.[11,12] Because tapentadol is not considerably metabolised by the CYP450 system and does not activate or inhibit CYP enzymes, medication interactions are unlikely.[11,12]

Uses:

Tapentadol is a drug that is used to treat musculoskeletal pain as well as neuropathic pain caused by diabetic peripheral neuropathy.[13] In cases of opioid-related gastrointestinal (GI) intolerance, nausea, vomiting, or itching, tapentadol may be used instead of other opioid pain medications. Tapentadol, like tramadol, another dual-acting analgesic, delivers multimodal opioid and non-opioid analgesic effects.[13]

When compared to equal analgesic doses of conventional opioids, tapentadol has less side effects, which could be due to the fact that the analgesic pathways for this molecule are only partially mediated by opioid agonist mechanisms.[14]

Tapentadol's use could broaden the pharmaceutical toolkit against NP, which is notoriously difficult to treat with other analgesics or co-analgesics such antidepressants or anticonvulsants.[15-20]

It is used to treat moderate to severe chronic pain as well as neuropathic pain in adults with diabetic peripheral neuropathy (DPN). It is not, however, intended for use as an analgesic for acute pain or minor pain that is not expected to last for a long time. It's also not indicated for postoperative pain unless the patient is already on long-term opioid medication before surgery.[21]

Pharmacological properties:

In vitro, the drug's MOR binding affinity was significantly lower than that of morphine, despite its analgesic effectiveness in animal models being just two to three times that of morphine.[22] emphasizing the role of NRI activity in the analgesic effect In certain animal analgesia models, tapentadol's opioid and noradrenergic processes were synergistic.[23] Depending on the type of pain, the relative influence of each may vary.[24] Tapentadol showed analgesic effects in a variety of preclinical pain types, confirming its dual mechanism. The main metabolite of tapentadol (tapentadol-O-glucuronide) has no effect on opioid receptors, synaptosomal reuptake systems, or other binding sites.[22]

Tapentadol serum concentrations peak 3–6 hours after PR pill delivery.[25,26] When the tablets are taken twice daily, steady-state levels are reached on the second day, with an accumulation ratio of 1.5.[25] Tapentadol PR pills can be taken with or without food, and following intravenous administration, they have a volume of distribution of 540 L, and is just 20% bound to serum proteins. The medication is extensively metabolized, primarily through glucuronidation, with the primary enzymes implicated being UGT1A6, UGT1A9, and UGT2B7, 2C9, CYP2C19, and CYP2D6 are additional enzymes that break down the medication. Tapentadol and its metabolites are mostly (99%) excreted through the kidneys.[25] According to population pharmacokinetic modeling, the drug's apparent oral clearance after PR pill dose is 257 L/h.[27] andIt has a terminal half-life of 5–6 hours on average.[25]

Tapentadol PR should be used with caution in mild hepatic impairment (beginning at the lowest dose of 50 mg once daily) and is not suggested in individuals with severe renal or hepatic impairment (because to a lack of data).[25] Tapentadol PR dosage does not normally need to be adjusted in elderly people, while the dosage should be carefully chosen.[25]

Pharmacodynamics:

Mu-receptors can be found in the periaqueductal gray region, the spinal cord's superficial dorsal horn, and numerous layers of the cerebral cortex. The descending modulation of pain is mediated by norepinephrine (noradrenaline).[28] Tapentadol is a synthetic analgesic that operates as a mu-opioid receptor agonist and a norepinephrine re-uptake inhibitor in the central nervous system (NRI)[29] Through mu-opioid agonistic action, it changes sensory and emotional elements of pain, slows pain transmission at the spinal cord, and affects pain perception activity. It causes analgesia by increasing the amount of norepinephrine in the brain by preventing its re-absorption into nerve cells at central nervous system sites.[28, 30, 31]

Drugs that impede the reuptake of norepinephrine and/or serotonin are effective in the treatment of chronic pain and can boost the analgesic effects of morphine. As a result, TAP and morphine may have a synergistic impact. It has a lower analgesic potency due to its inability to connect to the mu-opioid receptor. TAP was approved for the treatment of moderate to severe pain in adults because it works for a wide range of pain types, from acute to chronic. [32]

Pharmacokinetics:

TAP is absorbed 32 % when taken orally.[30] Gastric pH or gastrointestinal motility had no effect on its pharmacokinetics, and it could be taken with or without food.[33] It is broadly dispersed throughout the body and does not require metabolic activation to function. TAP enantiomer (RR-form) penetrates the blood–brain barrier quickly and has a rapid onset of action.[30] TapentadolCmax and AUC values increased with a dosage of 50–150 mg, and plasma protein binding was roughly 20%.[34] After oral dosing, the plasma half-life is approximately 4 hours.[32] After 1 hour, the maximal effect is reached, and the activity lasts 4–6 hours.[30]

About 97 percent of the medication undergoes substantial first-pass hepatic metabolism.[30] Phase I pathways metabolize a tiny amount of TPA, but phase II pathways metabolize the majority of it.[35]

TAP has a lesser risk of drug–drug interactions due to the limited participation of phase I metabolic pathways. TAP is deactivated after biotransformation by metabolic enzymes, meaning it has no active metabolites. The most common metabolite is glucuronide conjugate (27%), which is followed by [30] After oral treatment, the sulfate conjugate (15%) of the dose is eliminated in urine in a conjugated state. CYP2C9 and CYP2C19 metabolize it to N-desmethyltapentadol (13 percent) and hydroxytapentadol (2 percent) respectively, which are then conjugated. As a result, the cytochrome P450 system plays a smaller role in TAP drug metabolism than it does in the conjugation phase. In urine, just 3% of the medication is excreted in its unmodified form. TAP and its metabolites are primarily eliminated (99%) through the kidney.[35, 36,37]

Drug Interactions:

In combination with mixed MOR agonists/antagonists or partial MOR agonists, tapentadol PR must be used with caution.[25] If buprenorphine patients require tapentadol PR, temporary withdrawal of buprenorphine is a possibility; if used with buprenorphine, greater tapentadol PR dosages may be required, necessitating AE monitoring for respiratory depression.[25] When using tapentadol PR with respiratory depressants, the risk of respiratory depression is increased, and its sedative effects are increased by CNS depressants; if taking tapentadol PR with such medicines, consider reducing the dosage. Patients who are acutely drunk with alcohol, hypnotics, centrally acting analgesics, or psychiatric drugs should not take tapentadol PR.[25]

Tapentadol PR is unlikely to cause clinically significant glucuronidation-mediated medication interactions.[25] If tapentadol PR is used with medicines that strongly block the UGT isoenzymes involved in its metabolism, exposure to tapentadol may rise. If you're stopping or starting strong enzyme inducers at the same time, proceed with caution.[25]

Tapentadol PR and monoamine oxidase inhibitors (MAOIs) may have additive effects on noradrenaline at synapses; as a result, tapentadol PR should be avoided when on MAOI therapy or within 14 days of finishing it. Tapentadol has caused serotonin syndrome in serotoninergic drug users, though symptoms normally improve if the serotoninergic substance is stopped.CYP-mediated medication interactions are unlikely to be clinically significant with tapentadol PR because tapentadol does neither stimulate or inhibit CYP enzymes in vitro.Drug interactions via protein binding-site displacement are also rare due to low serum protein binding.[25]

Dosage and Administration:

In a number of European countries, notably the United Kingdom,[25] Tapenadol PR 50–250 mg tablets are used to treat severe chronic pain in people that cannot be treated effectively with opioid analgesics. The tablets should be taken without chewing or dividing twice day (every 12 hours). The dosage should be tailored to the severity of the pain, the patient's ability to be monitored, and their prior treatment history, including the nature, mode of administration, and average daily dose of previous therapy.[25] Patients who are already using opioids may need a greater starting dose of tapentadol PR than those who aren't. The dosage of tapentadol PR should be titrated to achieve appropriate analgesia while minimizing adverse effects; the total daily dosage should not exceed 500 mg.[25] Tapentadol PR abuse/addiction should be considered for patients at higher risk of abuse, misuse, addiction, or diversion; all recipients should be closely monitored for indicators of abuse/addiction.[25]

Dosing Issues:

Individualize the tapentadol SR dose based on the degree of the pain and the patient's reaction. Tapentadol SR tablets should be taken twice a day, with or without food, about 12 hours apart. [38]

Overdose Management:

There is little clinical experience with tapentadol overdose. Symptoms such as vomiting, circulatory collapse, and respiratory depression/arrest are predicted to be comparable to those seen with other opioid analgesics. In the event of an overdose, the most important thing to remember is to keep breathing. Although opioid antagonists like naloxone can be administered as a specific antidote to respiratory depression, respiratory depression after an overdose may last longer than the opioid antagonist's duration of action.[38]

Use in pregnancy, older people and children:

Tapentadol is a category C drug that has not been tested in pregnancy. While nursing, tapentadol should be avoided. Due to a lack of safety and efficacy data, do not use in children under the age of 18. When prescribing tapentadol to older people, use caution, as with any opioids.[38]

Interactions with medicines:

Other central nervous system depressants, such as phenothiazines, sedatives, hypnotics, or other CNS depressants (including alcohol), may cause an additive CNS depression, resulting in respiratory depression, hypotension, deep drowsiness, or coma in those who take tapentadol SR simultaneously. Avoid taking tapentadol SR with any of these medications if at all feasible. If it's inevitable, keep a close eye on things and try lowering one or both of your medications' doses. Combining MAOIs with tapentadol (or using tapentadol in individuals who have recently taken MAOIs) may induce cumulative effects on noradrenaline levels, which could lead to serious cardiovascular events. [38]

Serotonin toxicity:

Tapentadol only has a minor impact on serotonin reuptake.[39] However, there is a theoretical risk of serotonin syndrome if tapentadol is taken with other serotonergic medications such as SSRIs, SNRIs, TCAs, MAOIs, St John's wort, and triptans.[38]

There have been a few reports of serotonin syndrome in patients who were also taking tapentadol SR.[38]

Internet Discussion and Surveys:

Internet forums about prescription drug abuse by recreational drug users record uncensored data on the patterns and preferences of nonmedical opioid usage in real time among prescription drug abusers, providing a unique data source for assessing opioid abuse liability. The proportion of posts discussing tapentadol (0.0003) was the lowest of the nine compounds tested in a survey gathering slightly under 2,000,000 messages written by recreational drug abusers in online forums between January 1, 2011 and September 30, 2012. It was much lower than the proportions for the other comparators (oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, buprenolone, and buprenolone).[40]

Adverse Events:

These side effects may be the result of the mu-opioid receptor agonism. Convulsions, hypersensitivity,nausea, dizziness, vomiting, somnolence and delayed stomach emptying have all been described infrequently.[30]

Symptoms of mu opioid agonisms are exacerbated by TAP overdose. As a result, treatment should be focused on reversing the onset of symptoms. Supportive therapies (such as oxygen and vasopressors) should be employed to manage circulatory shock and pulmonary edema, as well as controlled ventilation for the patient.[30]

Drug Abuse:

Tapentadol has been in the Indian market for eight and a half years. In 2017, our centre was the subject of a single peer-reviewed study detailing two incidences of abuse.[41] The Indian Pharmacovigilance Program has issued no drug safety alerts or advisories, and Tapentadol's current drug label does not indicate that it is a class H or H1 substance.[42] Tapentadol is more likely than Tramadol to be abused. Despite these findings, real-world evidence reveals that Tapentadol has a lower rate of diversion, abuse, addiction, overdose, and street demand than other prescription opioids in the United States. [43]

Prescription opioid abuse is a well-known public health problem in the United States, with significant morbidity and death, as well as the social and legal ramifications of substance abuse and addiction.[44,45] Prescription opioids are an important therapy option for the management of acute and chronic pain in some patients, but they are not for everyone.[46,47] The most prevalent reason for prescription opioid usage is pain alleviation.[48,49] The need for proper access to opioid medication must be balanced against the possible dangers, including opioid misuse and addiction, according to a recent recommendation from the US Department of Health and Human Services on opioid analgesic dosage decrease or termination.[50] Current efforts to combat the opioid crisis and manage chronic pain are centered on developing novel medications that treat pain effectively while posing a lower risk of abuse and addiction.[51] Although conventional opioids generally interact with the mu-opioid receptor, the pharmaceutical opioid classes have significant variances in potencies, pharmacokinetic properties, and propensity for abuse and addiction.[51,52]

Tapentadol affects both ascending and descending brain pathways, modulating pain signals.[53] Since 2008 and 2011, the medicine has been offered in immediate-release (IR) and extended-release (ER) versions in the United States.[54,55] However, it is used less frequently than other opioid formulations. The IR formulation is for the treatment of acute pain that necessitates the use of an opioid analgesic and for

which other therapies are ineffective.[54] ER indications include neuropathic pain associated with diabetic peripheral neuropathy, which requires daily, around-the-clock, long-term opioid medication and for which alternate treatment alternatives are insufficient.[55] Despite the fact that continuous opioid therapy has been found to increase the risk of drug addiction,[56] In pre-marketing investigations of tapentadol IR15, dependency was not recorded, and it occurred in less than 1% of patients treated with tapentadol ER in 10 Phase 2 and 3 clinical studies.[54]

Postmarketing Evaluation of Tapenadol:

Abuse of tapentadol was reported substantially less frequently (P 0.001) than abuse of the other drugs. Except for fentanyl IR, which had the lowest unadjusted abuse prevalence, tapentadol IR had a significantly lower abuse prevalence than all other comparators. With the exception of hydromorphone ER, tapentadol ER misuse was less common. Tapentadol as a chemical, as well as its IR and ER forms, had low prescription-adjusted estimates, which were among the lowest recorded and among the lowest of the Schedule II comparators. Except for hydromorphone ER (P = 0.06), tapentadol ER had a lower prescription-adjusted risk than the other drugs.[40]

The limited potential for abuse and misuse of tapentadol found in post-marketing investigations could be explained by its pharmacologic characteristics and finite upper dose constraints, but the specific explanation is unknown.[54,55] Because tapentadol is almost entirely metabolized in phase II, it has no clinically significant cytochrome P450 drug interactions.[54] Tapentadol is also unaffected by cytochrome P450 phenotypic outliers, such as poor or extensive isoenzyme metabolizers, making for a simpler transition when switching from other opioids that avoid the phase I metabolism pathway (e.g., morphine, oxymorphone, and hydromorphone) and potentially avoiding mathematical errors when switching from other opioids that avoid the phase I metabolism pathway (e.g., morphine, oxymorph)[57, 58]

Furthermore, tapentadol has little or no effect on serotonin reuptake blockage, reducing the risk of medication interactions and side effects associated with serotonin agonist activity and serotonin withdrawal.[39] Tapentadol has been demonstrated to be efficacious and well-tolerated in patients with chronic pain when used as indicated, with a lower rate of gastrointestinal side effects than other powerful opioids.[59]

CONCLUSION:

Tapentadol is a one-of-a-kind synthetic opioid molecule with NRI properties. It causes acute nociceptive as well as persistent neuropathic analgesia. However, after glucuronidation, it is largely present in the form of conjugated metabolites and is excreted fast and completely via the kidneys. Precautions are urged against using central nervous system depressants concurrently, or using tapentadol within 14 days of stopping monoamine oxidase inhibitors.

Tapentadol abuse, addiction seeking behavior, withdrawal, and physical dependency are the most serious issues. The main challenge with tapentadol use is controlling the ratio of MOR agonist to NRI. Finally, tapentadol provides both nociceptive and neuropathic pain relief, but there are concerns about abuse and reliance.

Conflicts of Interest: Nil

Funding statement: Nil

Acknowledgement: we would like to express our thanks to the head, Department of pharmacy practice and our

Department staffs to their valuable suggestions and recommendations.

REFERENCES:

1. Tzschentke TM, Christoph T, Kogel BY. The muopioid receptor agonist/noradrenaline reuptake inhibition (MOR-NRI) concept in analgesia: The case of tapentadol. CNS Drugs 2014; 28(4):319-29. https://doi.org/10.1007/s40263-014-0151-9

2. Tzschentke TM, Jahnel U, Kogel B, Christoph T, Englberger W, De Vry J. Tapentadol hydrochloride: A next-generation, centrally acting analgesic with two mechanisms of action in a single molecule. Drugs Today 2009; 45(7):483-96. https://doi.org/10.1358/dot.2009.45.7.1395291

3. Raffa RB, Elling C, Tzschentke TM. Does 'strong analgesic' equal 'strong opioid'? Tapentadol and the concept of 'micro-load'. AdvTher 2018; 35 (10):1471-84. https://doi.org/10.1007/s12325-018-0778-x

4. Stollenwerk A, Sohns M, Heisig F, Elling C, von Zabern D. Review of post-marketing safety data on tapentadol, a centrally acting analgesic. AdvTher 2018; 35(1):12-30 https://doi.org/10.1007/s12325-017-0654-0

5. Hartrick CT, Rozek RJ. Tapentadol in pain management: A mu-opioid receptor agonist and noradrenaline reuptake inhibitor. CNS Drugs 2011; 25(5):359-70. https://doi.org/10.2165/11589080-000000000-00000

6. Murphy DL, Lebin JA, Severtson SG, Olsen HA, Dasgupta N, Dart RC. Comparative rates of mortality and serious adverse effects among commonly prescribed opioid analgesics. Drug Saf 2018; 41 (8):787-95. https://doi.org/10.1007/s40264-018-0660-4

7. Kress HG. Tapentadol and its two mechanisms of action: is there a new pharmacological class of centrally-acting analgesics on the horizon? Eur J Pain 2010; 14:781 https://doi.org/10.1016/j.ejpain.2010.06.017

8. Torres-Sanchez S, Borges GDS, Mico JA, Berrocoso E. Opioid and noradrenergic contributions of tapentadol to the inhibition of locus coeruleus neurons in the streptozotocin rat model of polyneuropathic pain. Neuropharmacology. 2018; 135:202-210. https://doi.org/10.1016/j.neuropharm.2018.03.014

9. Walczyk H, Liu CH, Alafris A, Cohen H. Probable tapentadol-associated serotonin syndrome after overdose. Hosp Pharm. 2016; 51(4):320-327. https://doi.org/10.1310/hpj5104-320

10. Barkin RL, Barkin SJ. Treating postoperative pain in the patient who is in recovery or remission from opioid abuse: focus on tapentadol. J Opioid Manag. 2017;13(3):133-134. https://doi.org/10.5055/jom.2017.0378

11. Terlinden R, Ossig J, Fliegert F C et al. Absorption, metabolism, and excretion of 14C-labeled tapentadolHCl in healthy male subjects. Eur J Drug MetabPharmacokinet, 2007; 32(3):163-69. https://doi.org/10.1007/BF03190478

12. Terlinden R, Kogel BY, Englberger W, Tzschentke TM: In vitro and in vivo characterization of tapentadol metabolites. Methods Find ExpClinPharmacol, 2010; 32(1):31-38 https://doi.org/10.1358/mf.2010.32.1.1434165

13. Vadivelu N, Huang Y, Mirante B et al: Patient considerations in the use of tapentadol for moderate to severe pain. Drug, Healthc Patient Saf, 2013; 5:151-59. https://doi.org/10.2147/DHPS.S28829

14. Langford RM, Knaggs R, Farquhar-Smith P, Dickenson AH: Is tapentadol different from classical opioids? A review of the evidence. Br J Pain, 2016; 10(4):217-21 https://doi.org/10.1177/2049463716657363

15. Kress HG, Ahlbeck K, Aldington D, et al. Managing chronic pain in elderly patients requires a CHANGE of approach. Curr Med Res

Opin. 2014; 30:1153-1164. https://doi.org/10.1185/03007995.2014.887005

16. Kress HG, Koch ED, Kosturski H, et al. Tapentadol prolongedrelease for managing moderate to severe, chronic malignanttumor-related pain. Pain Physician. 2014; 17:329- https://doi.org/10.36076/ppj.2014/17/329

17. Pergolizzi J, Alon E, Baron R, et al. Tapentadol in the managementof chronic low back pain: a novel approach to a complexcondition? J Pain Res. 2011; 4:203-210. https://doi.org/10.2147/JPR.S19625

18. Steigerwald I, Müller M, Davies A, et al. Effectiveness and safetyof tapentadol prolonged release for severe, chronic low back painwith or without a neuropathic pain component: results of anopen-label, phase 3b study. Curr Med Res Opin.2012; 28:911-936. https://doi.org/10.1185/03007995.2012.679254

19. Baron R, Eberhart L, Kern KU, et al. Tapentadol prolonged releasefor chronic pain: a review of clinical trials and 5 years of routineclinical practice data. Pain Pract. 2017; 17:678-700. https://doi.org/10.1111/papr.12515

20. Horgas AL. Pain management in older adults. NursClin North Am.2017; 52:e1-e7. https://doi.org/10.1016/j.cnur.2017.08.001

21. Available from: http://www.nucynta.com (accessed on11.01.2013).

22. Tzschentke TM, Christoph T, Kögel B, et al. (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (TapentadolHCl): a novel μ-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. J PharmacolExpTher. 2007; 323(1):265-76. https://doi.org/10.1124/jpet.107.126052

23. Schröder W, Tzschentke TM, Terlinden R, et al. Synergistic interaction between the two mechanisms of action of tapentadol in analgesia. J PharmacolExpTher. 2011; 337(1):312-20. https://doi.org/10.1124/jpet.110.175042

24. Schröder W, Vry JD, Tzschentke TM, et al. Diferential contribution of opioid and noradrenergic mechanisms of tapentadol in rat models of nociceptive and neuropathic pain. Eur J Pain. 2010; 14(8):814-21. https://doi.org/10.1016/j.ejpain.2010.05.005

25. Grunenthal Ltd. Palexia SR prolonged release tablets: summary of product characteristics. 2017. https://www.medicines.org.uk/. Accessed 30 Oct 2018.

26. Gohler K, Brett M, Smit JW, et al. Comparative pharmacokinetics and bioavailability of tapentadol following oral administration of immediate- and prolonged-release formulations. Int J ClinPharmacolTher. 2013; 51(4):338-48. https://doi.org/10.5414/CP201722

27. Huntjens DR, Liefaard LC, Nandy P, et al. Population pharmacokinetic modeling of tapentadol extended release (ER) in healthy subjects and patients with moderate or severe chronic pain. Clin Drug Investig. 2016; 36(3):213-23. https://doi.org/10.1007/s40261-015-0371-x

28. Mick G, Serpell A, Makin AH. Acute pain physiology and pharmacological targets: the present and future. Acute pain1998; 3:31-7. https://doi.org/10.1016/S1366-0071(98)80018-1

29. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO,Griffin JW, et al. Neuropathic pain: redefinition and a gradingsystem for clinical and research purposes. Neurology2008; 70(18):1630-5. https://doi.org/10.1212/01.wnl.0000282763.29778.59

30. Paice JA. Mechanisms and management of neuropathic pain incancer. J Support Oncol 2003; 1(2):107-20. PMID: 15352654

31. Liu KKC, Sakya SM, O'Donnell CJ, Flick AC, Li J. Syntheticapproaches to the 2009 new drugs. Bioorg Med Chem2011; 19(3):1136-54. https://doi.org/10.1016/j.bmc.2010.12.038

32. Available from: <http://en.wikipedia.org/wiki/Pain> (accessed26.12.12).

33. Cagnardi P, Villa R, Zonca A, Gallo M, Beccaglia M, Luvoni GC,et al. Pharmacokinetics, intraoperative effect and postoperativeanalgesia of tramadol in cats. Res Vet Sci 2011; 90:503-9. https://doi.org/10.1016/j.rvsc.2010.07.015

34. Babette K, Jean DV, Thomas MT, Thomas C. The antinociceptiveand antihyperalgesic effect of tapentadol is partially retained inOPRM1 ((-opioid receptor) knockout mice. NeurosciLett2011; 491:104-7. https://doi.org/10.1016/j.neulet.2011.01.014

35. Schneider J, Jahnel U, Linz K. Neutral effects of the novelanalgesic tapentadol on cardiac repolarization due to mixed ionchannel inhibitory activities. Drug Dev Res 2010; 71:197-208. https://doi.org/10.1002/ddr.20360

36. Tayal G, Grewal A, Mittal R, Bhatia N. Tapentadol- a novelanalgesic. J AnaesthClinPharmacol 2009; 25(4):463-6. https://doi.org/10.1016/j.bfopcu.2013.04.003

37. Australian Public Assessment Report for Tapentadol. Therapeuticgoods administration, Department of health and ageing, Australian government, Feb 2011.

38. BioCSL. Palexia Product Information. 2012. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=pi&q=Tapentadol (accessed 15 December 2013).

39. Raffa RB, Buschmann H, Christoph T, et al. Mechanistic and functional differentiation of tapentadol and tramadol. Expert opinion on pharmacotherapy 2012; 13:1437-49. [PubMed]. https://doi.org/10.1517/14656566.2012.696097

40. McNaughton EC, Black RA, Weber SE, Butler SF. Assessing abuse potential of new analgesic medications following market release: an evaluation of Internet discussion of tapentadol abuse. Pain Med. 2015; 16(1):131-140. https://doi.org/10.1111/pme.12547

41. Basu, A., Mahadevan, J., Ithal, D., Selvaraj, S., Chand, P., Murthy, P. Is tapentadol a potential Trojan horse in the postdextropropoxyphene era in India? Indian J. Pharmacol. 2018; 50(1):44. https://doi.org/10.4103/ijp.IJP_21_17

42. Indian Pharmacopoeia Commission, 2019. Pharmacovigilance Program of India Updates. [cited 30.08.19]; Available at:. https://www.ipc.gov.in/mandates/pvpi/pvpiupdates/8-category-en/416-drug-safety-alerts.html.

43. Faria J, Barbosa J, Moreira R, Queirós O, Carvalho F, Dinis-Oliveira RJ. Comparative pharmacology and toxicology of tramadol and tapentadol. Eur J Pain. 2018; 22(5):827-844. https://doi.org/10.1002/ejp.1196

44. Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. N Engl J Med. 2016; 374(2):154-163. https://doi.org/10.1056/NEJMra1508490

45. Garland EL, Froeliger B, Zeidan F, et al. The downward spiral of chronic pain, prescription opioid misuse, and addiction: cognitive, affective, and neuropsychopharmacologic pathways. NeurosciBiobehav Rev. 2013; 37(10 Pt 2):2597-2607. https://doi.org/10.1016/j.neubiorev.2013.08.006

46. IOM Committee on Advancing Pain Research Care and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press; 2011.

47. Scholten W, Henningfield JE. Negative outcomes of unbalanced opioid policy supported by clinicians, politicians, and the media. J Pain Palliat Care Pharmacother. 2016; 30(1):4-12. https://doi.org/10.3109/15360288.2015.1136368

48. Han B, Compton WM, Blanco C, et al. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 National Survey on Drug Use and Health. Ann Intern Med. 2017; 167(5):293-301. https://doi.org/10.7326/M17-0865

49. McCabe SE, West BT, Boyd CJ. Motives for medical misuse of prescription opioids among adolescents. J Pain. 2013; 14(10):1208-1216. https://doi.org/10.1016/j.jpain.2013.05.004

50. HHS. HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics. Washington, DC: US Department of Health and Human Services; 2019.

51. Pergolizzi JV, Jr., LeQuang JA, Taylor R, Jr., et al. Designing safer analgesics: a focus on mu-opioid receptor pathways. Expert Opin Drug Discov. 2018; 13(10):965-972. https://doi.org/10.1080/17460441.2018.1511539

52. Drewes AM, Jensen RD, Nielsen LM, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. Br J ClinPharmacol. 2013; 75(1):60-78. https://doi.org/10.1111/j.1365-2125.2012.04317.x

53. Caputi FF, Nicora M, Simeone R, et al. Tapentadol: an analgesic that differs from classic opioids due to its noradrenergic mechanism of action. Minerva Med. 2019; 110(1):62-78. https://doi.org/10.23736/S0026-4806.18.05909-8

54. Nucynta (tapentadol) tablets for oral use C-II [package insert]. Stoughton, MA: Collegium Pharmaceutical, Inc.; 2018.

55. Nucynta ER (tapentadol) extended-release oral tablets C-II [package insert]. Stoughton, MA: Collegium Pharmaceutical, Inc.; 2018.

56. McAnally H. Rationale for and approach to preoperative opioid weaning: a preoperative optimization protocol. Perioper Med (Lond). 2017; 6:19.

57. Fudin J, Raouf M, Wegrzyn EL. Opioid Dosing Policy: Pharmacological Considerations Regarding Equianalgesic Dosing. Lenexa, KS: AIPM; 2017.

58. Smith HS. Opioid metabolism. Mayo Clin Proc. 2009; 84(7):613-624. https://doi.org/10.1016/S0025-6196(11)60750-7

59. Pergolizzi JV, Jr, Taylor R, Jr, et al. Tapentadol extended release in the treatment of severe chronic low back pain and osteoarthritis pain. Pain Ther. 2018; 7(1):37-57. https://doi.org/10.1007/s40122-018-0095-8