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REVIEW ARTICLE

Tapentadol, a novel analgesic: Review of recent trends in synthesis, related substances, analytical methods, pharmacodynamics and pharmacokinetics

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Abstract This write-up describes the comprehensive facts of tapentadol, on recent trends in synthesis, related substances, analytical methods, pharmacodynamics, pharmacokinetics, adverse effect and drug interaction. Chemically, tapentadol is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl] phenol hydrochloride. Tapentadol is a centrally-acting synthetic novel analgesic which acts as μ-opioid receptor agonist as well as norepinephrine re-uptake inhibitor. Nausea and vomiting are common side effects and tapentadol glucuronide conjugate is a major metabolite excreted in urine. It is synthesized by three different schemes while nine related substances were reported. Tapentadol and its metabolites were determined in plasma matrix by chromatographic methods using spectrofluorometric detection.

Contents

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1. Introduction

Pain is an unpleasant feeling often caused by intense or damaging stimuli, which is not simply a biological response, but a complex interaction that involves sensory, emotional and behavioral factors.[1] Pain may be chronic or acute. Nociceptive pain is caused by stimulation of peripheral nerve fibers which respond only to stimuli approaching or exceeding harmful intensity (nociceptors), and may be classified according to mode of noxious stimulation; the most common categories are as follows: thermal (heat or cold), mechanical (crushing, tearing) and chemical (iodine in a cut, chili powder in the eyes). Neuropathic pain is caused by damage or disease affecting any part of the nervous system involved (somatosensory system)[2] Peripheral neuropathic pain is due to burning, tingling, electrical, stabbing, pins and needles.[3]

Current treatment options for pain consist of several therapeutic categories such as anticonvulsants, antidepressants, local anesthetics, opioids and non-steroidal anti-inflammatory drugs. Combinations of various mechanisms of action targeting pain transmission at different levels of pain communication pathways may yield better efficacy. Most commonly used clinical agents for analgesia through μ-opioid receptor are 4,5β-epoxymorphinans (morphine), morphinans (levorphanol), phenylpiperidines (meperidine), 4-anilidopiperidines (fentanyl), and acyclic analgesics (methadone).[4] These drugs are associated with serious side effects, however, most notably addiction liability and respiratory depression, which limit their clinical usefulness. Therefore, there has been an intensive effort to find new analgesics that retain the effectiveness of morphine without or less potential side effects. The evaluation of a combined mechanism of action, μ-opioid receptor activation with norepinephrine reuptake inhibition, has been undertaken to improve the therapeutic usefulness of opioid analgesics.

Few years ago, tramadol (Fig. 1) was approved for treatment of pain which is a synthetic 4-phenyl piperidine analogue of codeine that produces analgesia in short- and long-term pain states by synergistically combining weak μ-opioid and mono-aminergically (noradrenaline and serotonin) mediated mechanisms.[5] In this sequence, tapentadol comes in picture with improved dual mechanism for treatment of severe nociceptive and neuropathic pain. Tapentadol combines μ-opioid receptor agonism and noradrenaline reuptake inhibition in one molecule.[6]

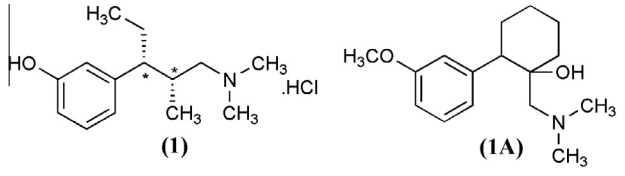

Figure 1 Structure of tapentadol hydrochloride (1) and tramadol (1A).

As tapentadol hydrochloride (TAP) is a promising novel analgesic drug with dual mechanism and hitherto, as per author literature preview there is no comprehensive report on TAP. The aim of this write-up is to provide an ample review on recent updates of TAP including recent trends in chemistry (different synthetic schemes and related substances), analytical methods, pharmacodynamics, pharmacokinetics, adverse effect and drug interactions.

2. Chemistry

Chemically, TAP is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl] phenol hydrochloride (Fig. 1). As TAP has two chiral centers (1), it has four stereoisomers viz. RR, SS, RS and SR forms and RR form of TAP is approved as analgesic. The n-octanol: water partition coefficient log *P* value of TAP is 2.87 and two pKa values are 9.34 and 10.45.[7–11]

2.1. Synthesis

A ketone (2), 1-(3-(benzyloxy)phenyl)propan-1-one was treated (scheme 1, Fig. 2) with chloro-N,N-dimethyl-methanamine (3) in acetonitrile and acetyl chloride at room temperature (RT) and resulting amine (4) was collected by adding ether and crystallizing the product. The amine (4) was crystallized with L-(−)-dibenzoyl tartaric acid monohydrate (DBTA) in ethanol at 6–8 °C to give the desired enantiomer as a salt (5). The free base of salt 5 was generated by reaction with aqueous sodium hydroxide and then treated with ethyl magnesium bromide (Grignard reagent) in tetrahydrofuran (THF) at 10 °C followed by stirring at RT overnight to give tertiary alcohol (6). Tertiary alcohol was treated with trifluoroacetic anhydride in 2-methyl THF at 40–45 °C to give the corresponding trifluoromethyl ester which was then treated with 10% Pd/C (palladium/carbon) and hydrogenated at 3 bar (pressure) with ambient temperature. These hydrogenolytic conditions effected reductive cleavage of the trifluoromethyl ester and removal of the benzyl protecting group with retention of stereochemistry. Filtration of the catalyst followed by the addition of water and trimethyl-chlorosilane (TMSCl) to generate

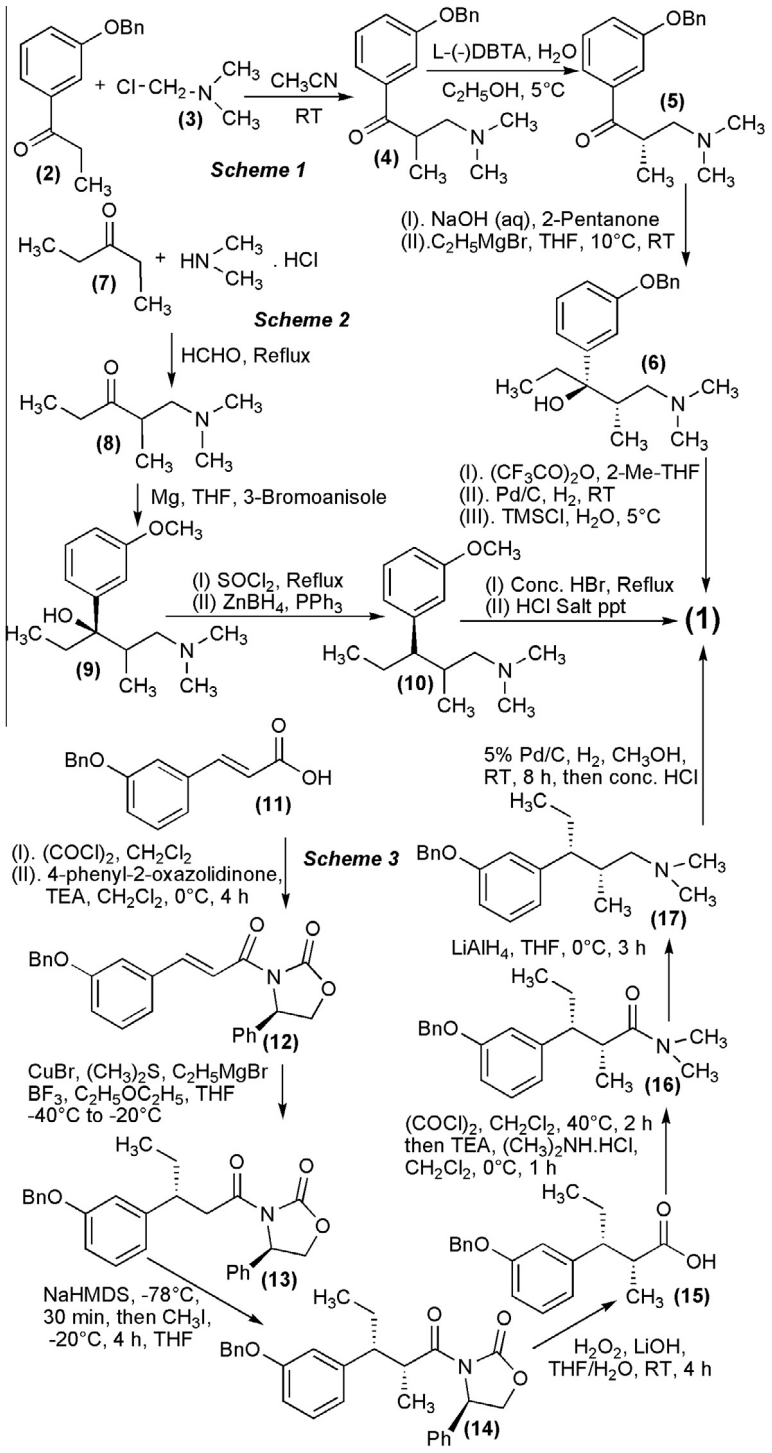

Figure 2 Different synthetic schemes for tapentadol hydrochloride.

HCl in situ and allowing the product to crystallize out at 5–8% gave the desired tapentadol hydrochloride (1).[12]

Mannich reaction was applied to prepare side chain as 1-(dimethylamino)-2-methylpentan-3-one (8) from pentan-3-one (7), formaldehyde and dimethyl amine which were refluxed (scheme 2, Fig. 2). It (8) was treated with 3-bromoanisole in the presence of THF and magnesium to form alcohol derivative (9) which was refluxed with sulfuryl dichloride, followed by treatment of zinc borohydride ($ZnBH_4$) and triphenylphosphine (PPh_3). The resulting intermediate (10) was refluxed with hydrogen bromide and hydrochloride salt of tapentadol was precipitated by methylene chloride in aqueous sodium bicarbonate and addition of water and trimethyl-cholorosilane (TMSCl) with 2-butanone.[13]

Tapentadol was synthesized enantioselectively by scheme 3 (Fig. 2). Benzoyl derivative of cinnamic acid (11) was activated by oxalyl dichloride in the presence of methylene chloride and protected by (R)-4-phenyl-2-oxazolidinone in the presence of

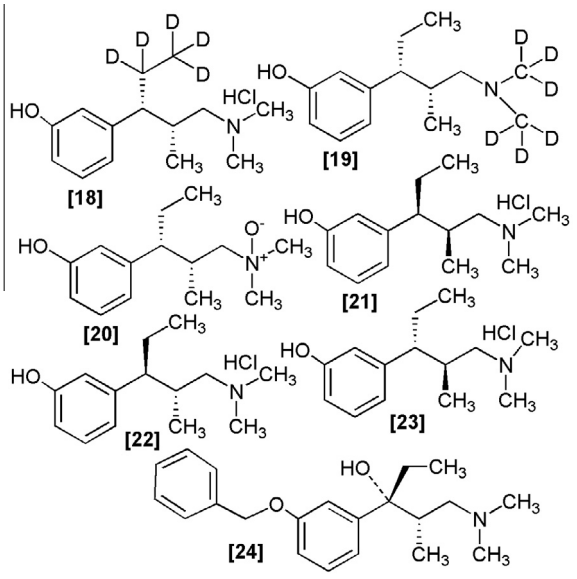

Figure 3 Tapentadol related substances – (18) tapentadol-d5-hydrochloride, (19) tapentadol-d6 hydrochloride, (20) tapentadol-N-oxide, (21) [S,S] tapentadol hydrochloride, (22) [R,S] tapentadol hydrochloride, (23) [S,R] tapentadol hydrochloride, and (24) 3′-*O*-benzyl-(1R)-hydroxy tapentadol.

triethyl amine (TEA) and methylene chloride at 0 °C to form cyclic amide (12). It was treated with an organocuprate prepared from a CuBr-$(CH_3)_2S$ (copper bromide – dimethyl sulfide) complex and ethylmagnesium bromide in THF at −20 °C to form stereoselectively conjugate addition product (13). The methylation reaction proceeded efficiently to get intermediate (14) with excellent stereoslectivity. Conjugate product was exposed to sodium hexamethyldisilazide (NaHMDS) at −78 °C for 30 min followed by methyl iodide in THF at −20 °C for 4 h. Removal of the chiral auxiliary under base hydrolysis conditions ($LiOH/H_2O_2$ in H_2O/THF) yielded α, β-disubstituted acid (15). Treating 15 with oxalyl chloride followed by dimethylamine hydrochloride in the presence of TEA in CH_2Cl_2 afforded the corresponding dimethylamide (15). Subsequent reduction of amide 16 with $LiAlH_4$ in dry THF gave *o*-benzyl-tapentadol (17). Finally, RR form of tapentadol hydrochloride (1) was yielded by debenzylation of 17 under a hydrogen atmosphere followed by treatment of hydrochloric acid.[14]

2.2. Related substances

As structure-wise TAP is closely related to tramadol which is a synthetic 4-phenylpiperidine analogue of codeine and centrally acting analgesic with efficacy and potency ranging between weak opioids and morphine.[15,16] In similar way, TAP has two chiral centers and RR form is approved as analgesic. Thus, stereoisomers of TAP, as related substances (Fig. 3) come into picture viz. SS form (21), RS form (22) and SR form (23).[20] Michal et al. have reported the enantioselective HPLC determination of tapentadol above enantiomers using cellulose-based chiral stationary phase in normal phase mode.[11]

Deuterated TAP, tapentadol-d_5 (18) and tapentadol-d_6 (19) were also used as internal standards for the determination of

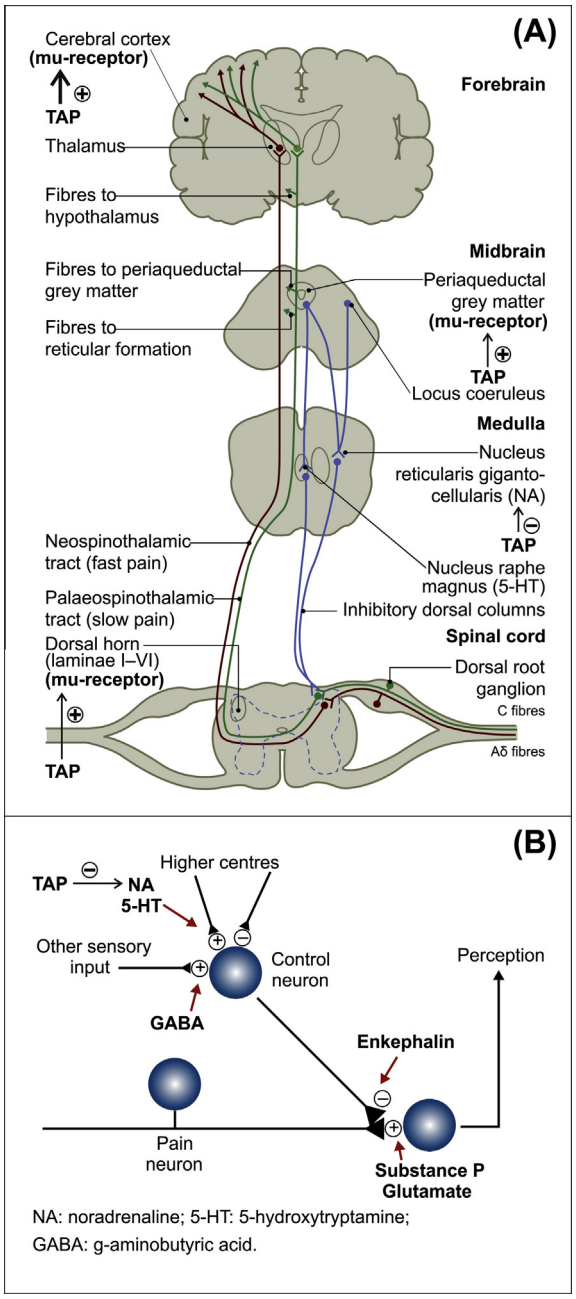

Figure 4 Possible mechanism of action for tapentadol; where (+) means agonistic action of mu-receptor and (−) means inhibition of norepinephrine re-uptake (Reuse with the permission of Elsevier Limited, The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1 GB,UK).[26]

TAP along with its metabolites and to study the pharmacokinetics of the drug[17–19] Tapentadol-N-oxide (20) and tapentadol-*O*-sulfate (27) were reported as process related impurities but Kathirvel et al. have not established the structure of these impurities by different characterization techniques.[21] Both N-desmethyltapentadol (27) and tapentadol-*O*-sulfate (28) (Fig. 4) were reported as its metabolites as well as process related impurities.[15–17] 3′-*O*-Benzyl-(1R)-hydroxy tapentadol (24) was also mentioned as a process related substance of TAP.[22]

3. Analytical methods

Very few analytical methods were reported for the determination of TAP. Dousa et al. have achieved better resolution for all enantiomers on Chiralpak AD-H by using a mixture of heptane–propan-2-ol–diethylamine (980:20:1). The detection was carried out by fluorescence detector in a short analysis time.[11] TAP was determined in canine plasma by LC method, where chromatographic separation was achieved on C18 column (150×4.6 mm, 5 μm) at 25 °C by gradient elution (acetonitrile and 33 mM acetic acid) with spectrofluorimetric detection. This validated method was applied to determine pharmacokinetic parameters in dog on oral administration of the drug, where the LOD and LOQ were 0.3 ng/mL and 1.0 ng/mL, respectively.[23] Pharmacokinetics of TAP was also reported in dogs after oral and intravenous administration. Different types of breeds (Greyhound, Staffordshire BT and mixed) for dog (male and female) were used to determine terminal phase rate constant, terminal half-life, time of peak, peak plasma concentration, area under the plasma concentration–time curve extrapolated to infinity, volume of distribution, clearance, mean resident time and oral bioavailability.[24] TAP and its metabolites (N-desmethyltapentadol-glucuronide, tapentadol-glucuronide and N-desmethyltapentadol) were determined by an ultra-performance liquid chromatographic (UPLC) hyphenated with mass spectroscopy (MS); where UPLC column BEH Shield RP18 (2.1×50 mm $\times$ 1.7 μm) was coupled with a tandem quadrupole detector operating in positive ESI mode. Authentic nonhydrolyzed and hydrolyzed urine specimen were analyzed using tapentadol-d_5 as an internal standard by multiple reaction monitoring (MRM) analysis.[17] An another gradient LC method was reported to determine tapentadol and its metabolite N-desmethyltapentadol in urine and oral fluid by using a mixture of ammonium formate (20 mM, pH 6.4) and methanol on C18 (4.6×50 mm $\times$ 1.8 mm), which was coupled to triple-quadrupole MS, operating in positive electrospray ionization (ESI) mode. Methamphetamine-d_5 was used as an internal standard for linear regression line and there was no interference shown from urine and oral fluid specimens collected from drug-free individuals in the LC–MS–MS analysis.[25]

4. Pharmacology

4.1. Pharmacodynamics

The mu-receptors are present in periaqueductal gray region, superficial dorsal horn of the spinal cord, and several layers of cerebral cortex. Norepinephrine (noradrenaline) is involved with descending modulation of pain (Fig 4).[1] Tapentadol is a centrally-acting synthetic analgesic which acts as mu-opioid receptor agonist as well as norepinephrine re-uptake inhibitor (NRI).[2] It modifies sensory and affective aspects of pain through mu-opioid agonistic action, inhibits the transmission of pain at the spinal cord and affects the activity of pain perception. It increases the level of norepinephrine in the brain by inhibiting its re-absorption into nerve cells at the central nervous system sites, which leads to analgesia (Fig. 4).[1,3,27] This combination of complementary mechanisms of action additively or synergistically results in potent analgesic activity similar to potent narcotic analgesics without their side effects.

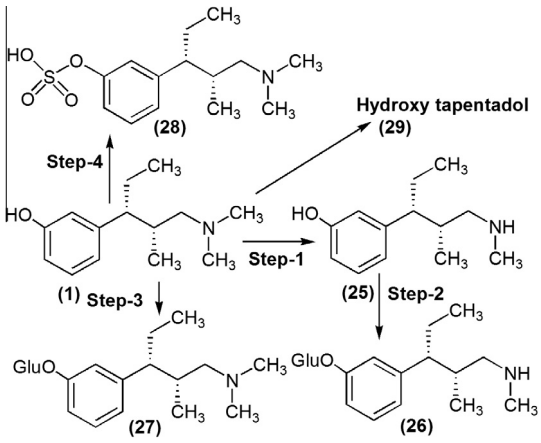

Figure 5 Metabolism of tapentadol.

The drugs which block the reuptake of norepinephrine and/or serotonin are efficacious in the treatment of chronic painful conditions and can enhance the analgesic effect of morphine. Thus, TAP may have synergistic effect with morphine. It is less potent in producing analgesia due to its poor ability in binding to mu-opioid receptor. TAP was approved for treatment of moderate to severe pain in adults, as it is effective against a large spectrum of pain conditions, ranging from acute to chronic pain.[4]

4.2. Pharmacokinetics

TAP is 32% absorbed on oral administration.[3] Its pharmacokinetics was not affected by gastric pH or gastrointestinal motility and may be given with or without food.[5] It is widely distributed throughout the body and no metabolic activation is required for its action. TAP enantiomer (RR-form) readily crosses the blood–brain barrier; a rapid onset of action after administration.[3] Cmax and AUC values of tapentadol were increased with dose of 50–150 mg and plasma protein binding is about 20%.[6] The plasma half life is approximately 4 h after oral administration[4] and peak effect is attained after 1 h while duration of action is 4–6 h.[3]

The drug undergoes extensive first pass hepatic metabolism about 97%.[3] A small amount of TPA is metabolized by phase I pathways while mainly metabolized via phase II pathways.[7] Hydroxylation and N-demethylation play a minor role in the metabolic fate of TAP, which forms hydroxyl tapentadol (29) and N-desmethyl tapentadol (25), respectively (Fig. 5).

Due to minor involvement of phase I metabolic pathways, TAP has lower possibility of drug–drug interactions. Biotransformation by metabolic enzymes results in deactivation of TAP i.e., it has no active metabolites. Glucuronide conjugate (27) as a major metabolite (55%) followed by[3] sulfate conjugate (15%) of dose is excreted in urine in a conjugated form after oral administration. It is also metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19; and to hydroxy tapentadol (2%) by CYP2D6, which are further conjugated. Thus, drug metabolism of TAP is less mediated by cytochrome P450 system than conjugation phase. Only 3% of drug is excreted as unchanged form of drug in urine. Both TAP and its metabolites are excreted mainly (99%) through the kidney.[7,28,31]

Table 1 Reported adverse effects of TAP.[8,32]

Adverse drug reactions	
Very common	Nausea, vomiting, dizziness, somnolence, headache
Common	Decreased appetite, anxiety, confessional state, hallucination, sleep disorders, abnormal dreams, tremor, flushing, constipation, dyspepsia, dry mouth, pruritis, hyperhidrosis, rash, muscle spasms, asthenia, fatigue, feeling of body temperature change
Uncommon	Depressed mood, disorientation, agitation, nervousness, restlessness, euphoric mood, disturbance in attention, memory impairment, presyncope, sedation, atexia, dysarthria, hypoaesthesia, paraesthesia, muscle contractions involuntary, visual disturbance, heart rate increased, blood pressure decreased, respiratory depression, oxygen saturation decreased, dyspnoea, abnormal discomfort, urticaria, sensation of heaviness, urinary hesitation, pollakiuria, drug withdrawal syndrome, edema, feeling abnormal, feeling drunk, irritability, feeling of relaxation
Rare	Hypersensitivity, thinking abnormal convulsion, depressed level of consciousness, coordination abnormal, heart rate decreased, impaired gastric emptying

Table 2 Drug interactions of TAP.

Drug	Interaction	Ref.
General anesthetics	CNS depression	4
Mu-opioid analgesics, phenothiazines, other tranquilizers, sedatives, hypnotics or other CNS depressants (including alcohol, opioids or illicit drugs)	CNS depression, respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with TAP	3
Serotonergic drugs such as selective serotonin re-uptake inhibitors (SSRI), serotonin–norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), monoamine oxidase inhibitors I (MAOI) and triptans	Life-threatening serotonin syndrome (agitation, hallucinations, coma); autonomic instability (tachycardia, labile blood pressure, hyperthermia); neuromuscular aberrations (hyperreflexia, incoordination); gastrointestinal symptoms (nausea, vomiting, diarrhea)	3
Disease		
In patients with paralytic ileus or in patients concurrently using or within 14 days of using monoamine oxidase inhibitors (MAOIs)	Significant respiratory depression, acute or severe bronchial asthma	4
In elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation.	Respiratory depression occurs more frequently. TAP should be employed only under careful medical supervision at the lowest effective dose in such patients.	3
Head injury and increased intracranial pressure	Used with caution	4
In patients with pancreatic or biliary tract disease and moderate hepatic impairment	Used with caution	4

4.3. Adverse effects and interactions

The most common side effects of TAP are related to gastrointestinal tract (nausea and vomiting) and the nervous system (dizziness, headache and somnolence).[4,29] Due to its mu-opioid receptor agonism, gastrointestinal and central nervous system related adverse effects may also exist (Table 1). Convulsion, hypersensitivity and impaired gastric emptying were rarely reported.[3]

Due to overdose of TAP, symptoms of mu opioid agonisms are precipitated. Therefore, treatment should be focused on rescue from precipitated symptoms. Controlled ventilation for patient should be of primary attention and supportive measures (including oxygen and vasopressors) should be used to manage circulatory shock and pulmonary edema.[3]

Probenecid may interact with the pharmacokinetics of tapentadol; its metabolic interaction may be more prominent than its secretion interaction. Table 2 shows the indicative list of drug interaction of TAP.

4.4. Therapeutic uses

It is indicated in moderate to severe chronic pain and neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults. But it is not intended for use as an analgesic for acute pain and mild pain which is not expected to persist for an extended period of time. It is also not recommended in postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery.[30]

5. Conclusion

The present work gives a quick comprehensive review on recent trends of tapentadol as novel analgesic including its different synthetic schemes, impurities and related substances, analytical methods for different matrixes, pharmacodynamics, pharmacokinetics, adverse effect and drug interactions. Thus, tapentadol (R,R – form) is a novel opioid pain reliever for moderate to severe acute pain with a dual mechanism of action

(mu-opioid receptor agonist and noradrenaline reuptake inhibitor) and it is also effective in managing pain associated with osteoarthritis and low back pain.

6. Conflict of interest

None.

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