The atypical opioids

Buprenorphine, tramadol and tapentadol

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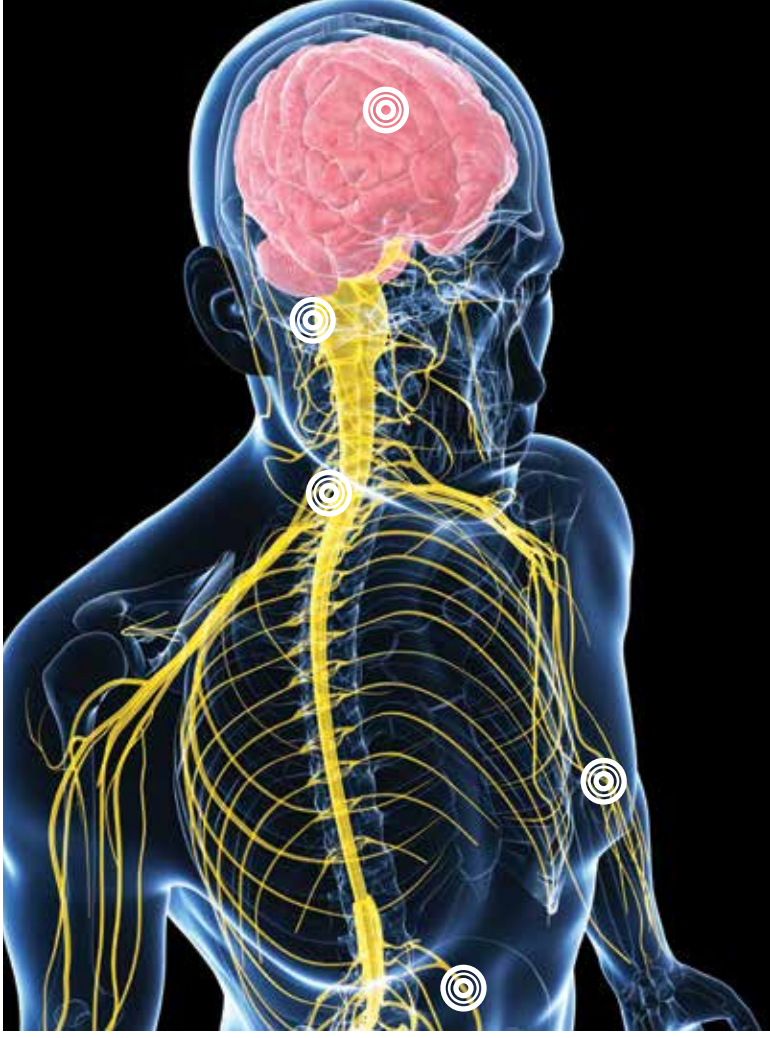
There are many differences between conventional and atypical opioids, including different efficacies, adverse effects and toxicities, as well as risk of abuse. These factors should be considered when prescribing opioids for chronic pain conditions.



When the mechanism of action of tramadol was unravelled in the late 1990s, it became obvious that, contrary to preceding beliefs that it is a partial mu-receptor agonist, it relies on multiple mechanisms of action including weak mu-receptor agonism.[1] This recognition resulted in the early suggestion to describe tramadol as an 'atypical opioid' in contrast to the conventional (or classical) opioids. Subsequently, it became obvious that tramadol, and also buprenorphine and tapentadol, have mechanisms of action that do not exclusively rely on mu-receptor agonism.[2]

It has, therefore, been suggested that the atypical opioids buprenorphine, tramadol and tapentadol (as well as cebranopadol, which is currently under investigation[3]), be classified separately from the conventional opioids such as morphine, oxycodone, hydromorphone and fentanyl. This separation is not only scientifically useful on the basis of the different mechanisms of action, but also clinically relevant as this translates into different efficacies, adverse effects and toxicity. It is the intention of this review to summarise the current knowledge about these atypical opioids.

KEY POINTS

- Atypical opioids differ from conventional opioids as they do not rely exclusively on mu-receptor agonism for their analgesic effect.
- The atypical opioids, buprenorphine, tramadol and tapentadol, have different effects and different adverse effects including toxicity and abuse potential compared with conventional opioids.
- These differences result in improved outcomes and reduced risks with the use of atypical opioids for individual patients and society as a whole.
- Atypical opioids are the preferred strong analgesics for chronic pain that requires pharmacological treatment.
- Tapentadol in particular seems to offer the best risk-benefit ratio in the pharmacological management of chronic pain with proven efficacy in nociceptive, neuropathic and mixed pain conditions, best tolerability and good safety data.

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Buprenorphine

Pharmacology

Buprenorphine has the most complex pharmacology of the three atypical opioids discussed here.[4] Our understanding has changed over time, but this has not yet been fully elucidated. These issues have resulted in some contradictory messages in the literature and significant confusion among clinical practitioners.[5] Briefly, buprenorphine is a potent but partial agonist at the mu-opioid receptor with high receptor affinity explaining its long duration of action.[6] It is also a potent kappa-receptor antagonist.[5] Furthermore, buprenorphine is an agonist at the nociceptin or opioid-receptor-like 1 (ORL-1) receptor; the latter effects possibly explain some of the many advantageous effects of buprenorphine.[7] In addition, buprenorphine binds to delta-opioid receptors.

Overall, buprenorphine behaves quite differently from conventional opioids with primarily mu-agonist effects. The interplay between these multiple receptor effects is complex and species specific. For example, the inverted U-shaped dose-effect curve for buprenorphine that was found in rodents led to concerns over a possible submaximal analgesic effect in humans, but this has not been confirmed in clinical practice.[5]

Efficacy

Buprenorphine has been extensively investigated as a sublingual preparation, in particular for opioid substitution in the management of opioid addiction.[8,9] In this setting, the analgesic effects of buprenorphine are sufficient to cover severe postoperative pain, therefore leading to a reversal of the previous advice to discontinue buprenorphine substitution before major surgery.[10] Contrary to the findings in animal experiments, all available data on humans show no analgesic ceiling effect with no plateau of the dose-response curve in clinically meaningful doses and no antagonistic effect of buprenorphine when combined with other mu-agonists.[11,12]

The high potency and good lipophilicity of buprenorphine made it an ideal candidate for the development of transdermal delivery systems.[13] Most value for the treatment of cancer and chronic noncancer pain lies in use of these buprenorphine patches for transdermal application;[14,15] the following text will primarily address transdermal buprenorphine, if not otherwise stated.

In comparative trials, buprenorphine has provided equivalent analgesia to morphine, hydromorphone, oxycodone, fentanyl and methadone.[7] The conversion from transdermal buprenorphine to oral morphine suggests an equianalgesic ratio in the range of 1:110.[5,16] Buprenorphine also has proven efficacy and low rates of toxicity in elderly patients and its effects are minimally affected by renal failure or haemodialysis.[7]

Safety and adverse effects

Buprenorphine has a ceiling effect for respiratory depression, and it is likely that respiratory depression linked to buprenorphine is primarily caused by its active metabolite norbuprenorphine.[17,18] The observation of this ceiling effect reduces the risk of respiratory depression, but does not mean that buprenorphine has no respiratory depressant effect;[6] there are published reports of fatalities and significant respiratory depression with sublingual buprenorphine.[19,20] In this context it is of interest that, although combinations of buprenorphine with a benzodiazepine increase the risk of fatal outcomes,[19] they seem to be safer than methadone with a benzodiazepine.[21] With transdermal buprenorphine, respiratory depression with fatal consequences has a zero incidence in a data analysis from the US National Poison Data System.[22]

With regard to long-term use, buprenorphine seems to cause less tolerance than conventional mu-receptor agonists such as fentanyl.[23] It has an antihyperalgesic effect and may attenuate opioid-induced hyperalgesia, possibly due to less glial activation via Toll-like receptor 4, an important mechanism in central sensitisation and neuropathic pain, but also in opioid-induced hyperalgesia.[24-26]

Conventional opioids have significant immunosuppressive effects, which have been recently related to dose-dependent increases in infection risk with long-term opioid use.[27,28] In the experimental setting, buprenorphine does not reduce natural killer cell activity and seems to be less immunosuppressive;[29,30] these data have not been confirmed in humans and their clinical relevance is unclear.[6] With regard to hypogonadism and testosterone suppression (opioid-induced androgen deficiency), the effects of buprenorphine seem to be minimal compared with conventional opioids.[31]

It has been shown in several studies that buprenorphine causes less cognitive dysfunction than conventional opioids with regard to parameters such as visual pursuit test and driving-related psychomotor battery, as well as complex psychomotor and cognitive performance.[7] These experimental data may even translate into improved clinical outcomes; in an epidemiological study buprenorphine was the only strong opioid not linked to an increased fracture risk due to falls.[32] Other advantages of buprenorphine are less constipating effects, in particular when administered transdermally, where it causes less constipation than even transdermal fentanyl.[6] Specific adverse effects of transdermal buprenorphine are local skin reactions, in particular erythema and pruritus, which are more common than with transdermal fentanyl and may be reduced by topical corticosteroid administration.[33]

Dependence, abuse potential and diversion

Buprenorphine is a partial mu-receptor agonist, which results in 'drug liking' and is therefore associated with abuse potential, withdrawal and diversion in its sublingual preparations.[34] However, buprenorphine is not as well 'liked' as full mu-receptor agonists. In particular, the transdermal preparation with stable plasma concentration seems to be unattractive for drug seekers. This is confirmed by US data showing that prescription-adjusted rates of intentional abuse and suspected suicidal

intent with transdermal buprenorphine were significantly lower than for morphine, oxycodone, oxymorphone, methadone and transdermal fentanyl.[22]

Physical dependence and withdrawal symptoms occur with buprenorphine, but are reported as milder than with conventional opioids, e.g. in a double-blind comparison with morphine;[35] however, to reduce these symptoms gradual dose reduction is recommended.[6]

Tramadol

Pharmacology

Tramadol is the prototype of the atypical opioid and the first compound to be described with this label in the literature.[1] Tramadol has analgesic effects based on three mechanisms: the mu-receptor agonist effect primarily of its main metabolite O-desmethyltramadol (M1), as well as noradrenaline reuptake inhibition and serotonin reuptake inhibition.[36] Both of the latter mechanisms strengthen descending pathways of pain control by increasing the synaptic concentration of inhibitory neurotransmitters.[37]

In animal experiments using appropriate antagonists, about 40% of the analgesic effect of tramadol was found to be based on mu-receptor agonism, about 40% on noradrenaline reuptake inhibition and about 20% on serotonin reuptake inhibition with synergism between these mechanisms.[38] However, this may be different in humans, partially because the contribution of the mu-receptor effect is mainly dependent on the active metabolite M1, which has about 200 times greater affinity for the mu-receptor than tramadol itself.[37] The O-demethylation of tramadol to M1 is catalysed by cytochrome P450 (CYP) 2D6; metabolisation is thereby dependent on the polymorphism of the gene encoding this enzyme. People who are poor metabolisers have significantly lower M1 plasma concentrations than extensive metabolisers.[39] This has been confirmed in studies showing that poor metabolisers required more tramadol to achieve the same analgesic effect and had a poorer analgesic response than extensive metabolisers.[40] There might also be an increased risk for mu-opioid receptor effects such as respiratory depression in ultra-fast metabolisers achieving high M1 plasma concentrations.[41]

Efficacy

In comparative trials with other opioids administered by patient-controlled analgesia, tramadol had comparable analgesic efficacy to conventional mu-receptor agonists such as morphine, fentanyl and oxycodone.[42] However, in clinical practice, it has limited efficacy partially due to a recommended maximum dose of 400 to 600 mg daily.

Tramadol has been successfully used in patients with cancer pain as a step-two drug on the WHO ladder, as well as in those with chronic noncancer pain, where it had also beneficial effects on physical function with reduced disability.[43-45] In osteoarthritis specifically, tramadol improved pain scores and function to some extent.[46] Tramadol is also an effective compound for the treatment of neuropathic pain with a number needed to treat of 3.8.[47] It is the only opioid listed as a second-line treatment for neuropathic pain in the guidelines from the Special Interest Group on Neuropathic Pain.[48]

Safety and adverse effects

Due to the difference in pharmacology from conventional opioids, tramadol's adverse effect profile also looks different. With regard to safety, the risk of respiratory depression is significantly lower than with the conventional opioids oxycodone and pethidine at equianalgesic doses.[49-51] Tramadol does not depress the hypoxic ventilator response.[52] However, it can cause respiratory depression, particularly with overdose, and fatalities have been reported, although the number of cases is very low.[53] In this context, it might be important to consider that the active metabolite M1 is excreted as a glucuronide via the kidney and therefore renal failure may lead to accumulation of this active metabolite.[41,54]

Tramadol lowers the seizure threshold, most likely by its serotonergic effects.[55,56] Therefore, it causes more seizures than conventional opioids, particularly with overdose.[53] This increased seizure risk was also shown in comparison with tapentadol in the US National Poison Data System.[57] However, comparative epidemiological studies have not confirmed a higher seizure rate for tramadol than those of conventional opioids in routine clinical use.[58,59]

The serotonergic effects of tramadol lead to an increased risk of serotonergic reactions, and in rare cases serotonin syndrome, when combined with medications also having a serotonergic effect such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs).[56,60] The risk is higher in people who are CYP2D6 poor metabolisers and those taking SSRIs that inhibit CYP2D6 such as sertraline, paroxetine or fluoxetine, as both scenarios lead to increased tramadol concentrations.[60,61] Another relevant drug interaction is between tramadol and 5-HT(3) receptor antagonist antiemetics, described in particular for ondansetron.[62] The interaction is most likely pharmacokinetic (via CYP2D6) and pharmacodynamic (via opposite effects on serotonin effects) leading to reduced efficacy of both drugs.[60,63,64]

The serotonergic effects of tramadol resulted in an increased rate of nausea and vomiting in several comparative trials with other conventional opioids such as morphine, fentanyl and oxycodone.[42] An increased rate of confusion and delirium in elderly patients has also been described.[65]

Tramadol causes significantly less constipation than conventional opioids primarily due to a less inhibitory effect on gastrointestinal motor function.[37] Animal data support less immunosuppressive effects of tramadol, which is not surprising in view of the low mu-receptor agonist effect of this compound.[66] Human data confirm this, but again there are no clinical outcome data in line with these findings.[67]

Dependence, abuse potential and diversion

Tramadol can cause physical dependence, but with a lower incidence and lower severity of withdrawal symptoms than conventional opioids.[68] Atypical withdrawal symptoms similar to those observed with SSRIs or SNRIs can also occur.[69] Tramadol has been used successfully in opioid withdrawal and was found to be superior to clonidine and comparable with buprenorphine in reducing withdrawal symptoms.[70]

Although abuse of tramadol has been reported, the abuse potential is much lower than that of conventional opioids.[37] These findings are in line with US data, which show tramadol to have a comparable rate of diversion to tapentadol and a significantly lower rate than conventional opioids.[71] This is also supported by several extensive studies, performed in particular in the US, leading to a lower scheduling of tramadol than conventional opioids in most countries;[72,73] this assessment has been confirmed by expert committees, such as in Germany.[74]

Tapentadol

Pharmacology

The analgesic effect of tapentadol is based on its combined effect as a mu-opioid receptor agonist and a noradrenaline reuptake inhibitor.[75] The affinity of tapentadol for the human mu-receptor is about 18 times lower than that of morphine (but tapentadol is only three times less potent than morphine), whereas the reuptake inhibition of noradrenaline is similar to that of an SNRI such as venlafaxine. The high analgesic efficacy is explained by the extensive synergy between the two mechanisms of action as shown in site-specific administration studies.[76] This mechanism of action explains that tapentadol potentiates descending pain inhibition.[77]

Although often regarded as being similar to tramadol, tapentadol differs with regard to its almost complete lack of a serotonergic effect and the fact that metabolites do not contribute to its analgesic effect.[78,79] This explains why no causal relationship between tapentadol and serotonin syndrome has been established and there are no clinically relevant drug interactions between tapentadol and antidepressants.[80]

Efficacy

In settings of osteoarthritis, chronic low back pain, neuropathic pain due to diabetic polyneuropathy and cancer pain, tapentadol provides equianalgesic efficacy to conventional opioids such as oxycodone and morphine, the main comparators.[81-83] This efficacy can be shown across a spectrum of nociceptive and neuropathic pain states as well as mixed nociceptive-neuropathic pain.[84] In neuropathic pain states tapentadol improves neuropathic pain symptoms and quality of life.

Similarly, in contrast to conventional opioids such as oxycodone, tapentadol significantly improves the quality of life of patients with chronic pain due to osteoarthritis and low back pain as shown in a large pre-planned meta-analysis.[81] This effect is seen across most domains of the SF-36 quality of life questionnaire and thereby offers significant outcome advantages in comparison with conventional opioids. In comparative trials, 5 mg oral tapentadol was equianalgesic to 1 mg oxycodone and 1 mg to 3.3 mg morphine.[81,85,86] However, as these are equianalgesic rates and tapentadol has a much lower mu-receptor affinity than conventional opioids, change from a conventional opioid to tapentadol has to be performed slowly over time. Direct immediate opioid rotation leads to opioid withdrawal symptoms. The rotation from tramadol to tapentadol, however, can be performed in one step and leads to better outcomes in most patients.[87]

Safety and adverse effects

In contrast to conventional opioids, tapentadol causes significantly less opioid-induced ventilatory impairment. This has been confirmed in head-to-head comparisons at equianalgesic doses with the conventional opioid oxycodone.[88] More relevantly, data from the US, where tapentadol has been available since 2009, report no fatalities from tapentadol use in a comparative analysis of the safety of various opioids.[89] The same study also showed that tapentadol had the lowest rate of major medical adverse effects, hospitalisations and serious adverse effects of all opioids on the US market, including tramadol. A systematic literature review identified four, possibly five, deaths from single-drug tapentadol overdose worldwide over nine years, which is in stark contrast to, and orders of magnitude lower than, the mortality caused by conventional opioids.[90]

With regard to adverse effects, slow-release tapentadol shows significant less gastrointestinal adverse effects, namely nausea, vomiting and constipation, than the slow-release preparation of the conventional opioid oxycodone.[81] These benefits remained when tapentadol was compared with the slow-release combination of oxycodone and naloxone in another study.[91] The medication is also extremely well tolerated in the elderly, with similar advantages seen in patients aged older than 75 years.[92,93] In a network meta-analysis of the tolerability of opioid analgesics for chronic pain, tapentadol was the top ranking analgesic due to the lowest incidence of overall adverse events, including constipation, and the lowest trial withdrawal rate.[94]

In a three-month study, tapentadol showed significantly less testosterone suppression than oxycodone, with only 11% of patients taking tapentadol compared with 46% of patients taking oxycodone presenting with testosterone levels below the normal range.[91] With regard to effects of tapentadol on immune function, data are currently still sparse, but, in contrast to conventional opioids, short- and long-term tapentadol administration seems to maintain splenic cytokines in animal experiments.[95]

Dependence, abuse potential and diversion

Physical dependence on tapentadol is limited and therefore withdrawal symptoms occur rarely and are mild to moderate,

even with abrupt cessation.[96] Tapentadol abuse has been described, but rates are lower than with conventional opioids such as oxycodone, suggesting a significantly lower potential for abuse.[71,97-99] This has been consistently shown for a considerable number of outcome parameters commonly used to identify issues of abuse with a medication.

An evaluation of the internet discussion among recreational drug users in the US, where tapentadol has been on the market for more than nine years, revealed the lowest proportion of all posts were discussing tapentadol and this was significantly lower by orders of magnitude than any other substance discussed.[99] Endorsement as a drug of abuse for tapentadol was also the lowest and similar to tramadol.

In a post-marketing study of patients assessed for substance-abuse treatment, tapentadol abuse was rare and lower than for most other scheduled analgesics.[98] Tapentadol resulted in significantly lower rates of doctor shopping (obtaining medication from multiple prescribers) than oxycodone.[100] Tapentadol has, together with tramadol, the lowest rate of diversion of opioid analgesics in the US and an extremely low black-market price.[101] These findings in the US have been confirmed in other markets including Australia.

Conclusion

The atypical opioids buprenorphine, tramadol and tapentadol show different profiles to conventional opioids with regard to efficacy, safety, tolerability and risk of abuse. With regard to the specific substances, buprenorphine has the highest mu-receptor effect of the three atypical opioids. This explains why sublingual buprenorphine with higher dosing carries an increased risk of problems found usually with conventional opioids, whereas the low-dose transdermal patch preparation is very safe and has low abuse risk.[6]

Tramadol is not scheduled as a full opioid in most countries of the world (S4, not S8, in Australia) because it was registered before the increased concerns about opioids and carries a relatively low risk of abuse. However, the disadvantages of tramadol are its reliance on a metabolite for its mu-receptor agonist effects and its serotonergic component; these properties make the analgesic effect less reliable and cause a number of adverse effects and drug interactions.

Tapentadol is currently the preferred atypical opioid for the treatment of chronic pain. Tapentadol is equianalgesic to potent conventional opioids and has the most convincing evidence for a positive effect on multiple domains of quality of life.[81] It also has the best tolerability and the lowest rate of fatalities and serious adverse events of all opioids, possibly with the exception of transdermal buprenorphine.[89,94] Finally, its abuse potential is much lower than that of conventional opioids.

It will be interesting to see how a fourth atypical opioid, cebranopadol, currently under development, will compare with these three established representatives of this interesting class of analgesics.[3]

The current literature supports the notion that if opioids are regarded as necessary and useful for the treatment of chronic pain states, atypical opioids should be preferred.[2] MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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