

Opioids and antidepressants: which combinations to avoid

SUMMARY

Some opioids such as tramadol, pethidine, dextromethorphan and tapentadol increase serotonergic activity. Fentanyl and methadone also do this but to a lesser extent.

These opioids may increase the risk of serotonin toxicity when combined with antidepressants.

Some selective serotonin reuptake inhibitors block the metabolism of opioids. This may reduce the concentrations and analgesic effect of some opioids such as codeine and tramadol, and increase the concentrations and risk of adverse effects of other opioids such as methadone.

Fluoxetine and irreversible monoamine oxidase inhibitors – tranylcypromine and phenelzine – have prolonged actions and may interact for weeks after they have been discontinued.

Introduction

Opioid dispensing increased fourfold in Australia from 1990 to 2014 and prescribing of antidepressants doubled from 2000 to 2016. The prescribing of both classes in combination is therefore increasingly common.^{1,2} While many combinations have minimal risk, some may increase the risk of serotonergic effects and other toxicity, or reduce analgesic efficacy. The simplest preventive strategy is to generally avoid prescribing opioids associated with higher risks of interaction.

Opioids and serotonergic activity

The analgesic effect of opioids is mediated through three major opioid receptors – mu, delta and kappa. However, many opioids have actions on other targets, for example blocking serotonin and noradrenaline reuptake and N-methyl-aspartate (NMDA) receptors.³ This is mostly a phenomenon with synthetic opioids. These additional actions may be beneficial or harmful and occur peripherally and in the central nervous system.³ Serotonin in the neuronal synapse is tightly regulated via multiple mechanisms – a key one involves the serotonin transporter. Some opioids inhibit the serotonin transporter which increases concentrations of serotonin in the synaptic cleft and therefore postsynaptic serotonin signalling.^{4,5}

Toxicity

Serotonin toxicity or syndrome results from excessive serotonin and its severity depends on the amount of excess serotonin. The three main groups of features are:⁶

- neuromuscular hyperactivity – clonus, myoclonus, tremor, hyperreflexia, rigidity

- autonomic hyperactivity – fevers, tachycardia, diaphoresis, tachypnoea
- altered mental state.

Serotonin toxicity generally only occurs when serotonergic opioids are given with another serotonergic drug such as an antidepressant, even at therapeutic doses (see Box).³ The highest risk opioid drugs are tramadol, pethidine and dextromethorphan.⁷ The highest risk serotonergic drugs are the irreversible monoamine oxidase inhibitor (MAOI) antidepressants, tranylcypromine and phenelzine.⁸ The risk and precautions with different combinations are summarised in the Table.^{3,6,7,9} The highest risk for serotonin toxicity by far is with irreversible MAOIs and pethidine, tramadol or dextromethorphan.

There have been occasional case reports of serotonin toxicity with low-risk opioid and antidepressant combinations, such as oxycodone and buprenorphine/naloxone (Suboxone) with other serotonergic medicines.¹⁰⁻¹³ Many of these reports have very obvious alternative medical explanations for all the signs of the alleged severe serotonin toxicity.¹⁴ However, it also seems likely that moderate serotonin toxicity may occasionally be precipitated by any opioid in susceptible individuals taking an antidepressant, perhaps due to indirect effects of opioids on serotonin release. A high index of suspicion is therefore needed.⁸ Similarly, antidepressants such as agomelatine, mianserin and reboxetine have a very low risk of serotonin syndrome but caution still might be warranted in combination with very high-risk serotonergic drugs.^{3,5,7}

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Box Drugs likely to increase the risk of serotonin toxicity when combined with serotonergic opioids³

<p>Monoamine oxidase inhibitors</p> <ul style="list-style-type: none"> irreversible inhibitors (phenelzine, tranylcypromine) reversible inhibitors of monoamine oxidase (moclobemide) non-antidepressant monoamine oxidase inhibitors (linezolid, methylene blue, lamotrigine) <p>Serotonin-releasing drugs</p> <ul style="list-style-type: none"> appetite suppressants (fenfluramine, sibutramine) amphetamines (methamphetamine, methylphenidate, phentermine) synthetic stimulants (MDMA, cathinones) <p>Serotonin reuptake inhibitors</p> <ul style="list-style-type: none"> selective serotonin reuptake inhibitors serotonin noradrenaline reuptake inhibitors tricyclic antidepressants (clomipramine, imipramine) serotonin modulators (vortioxetine) <p>Miscellaneous</p> <ul style="list-style-type: none"> lithium St John's wort tryptophan bupirone triptans
MDMA 3,4-methylenedioxymethamphetamine

Table The risk of serotonergic toxicity with combinations of antidepressants and opioids^{3,6,7,9}

	Antidepressants	
	Low-intermediate risk SSRIs, SNRIs, TCAs, St John's wort, lithium	High risk MAOIs (or previous history of serotonin toxicity)
Opioids		
Low risk Morphine, codeine,* buprenorphine, oxycodone, hydromorphone, oxycodone	Should be safe	Possible rare interaction. Use with caution
Medium risk Fentanyl, tapentadol, methadone	Possible rare interaction. Use with caution	Increased risk of serotonin syndrome
High risk Tramadol,* pethidine, dextromethorphan	Increased risk of serotonin syndrome	Contraindicated

* risk of decreased analgesic effect
SSRI selective serotonin reuptake inhibitor
SNRI serotonin noradrenaline reuptake inhibitor
TCA tricyclic antidepressant
MAOI monoamine oxidase inhibitor

Inhibition of opioid metabolism

The two most commonly used 'weak opioids' codeine and tramadol require cytochrome P450 (CYP) 2D6 for conversion to an active opioid agonist. They consequently have less abuse potential which allows less restrictive scheduling in most countries. However, many antidepressants are CYP2D6 inhibitors (fluoxetine, paroxetine, and to a lesser extent duloxetine, fluvoxamine, sertraline, desvenlafaxine and escitalopram). This means combinations of codeine or tramadol with these antidepressants may lead to reduced analgesia.¹⁵

Conversely, inhibition of metabolism of other opioids (via a variety of enzymes) may lead to increased risks of opioid adverse effects. The combinations that are particularly of concern are specific to individual drugs such as tramadol, tapentadol, fentanyl and methadone.

Tramadol

While tramadol's main metabolite is an opioid agonist, it is remarkably similar in structure to venlafaxine, with similar inhibitory effects on noradrenaline and serotonin reuptake.^{16,17} The combination of tramadol with an antidepressant is by far the most common serotonergic drug-drug interaction.^{18,19}

As tramadol inhibits serotonin and noradrenaline reuptake, combinations with selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) are likely to have additional adverse effects without added benefits. Inhibition of CYP2D6 by common antidepressants such as paroxetine and fluoxetine²⁰ not only reduces conversion of tramadol to an opioid agonist, it also results in higher concentrations of tramadol. Thus, these antidepressants both directly and indirectly increase the serotonergic and other adverse effects of tramadol, while potentially reducing analgesic efficacy.^{16,21}

Seizures are a key adverse effect of tramadol and can occur in overdose.²² Tramadol is also commonly implicated in new onset seizures with therapeutic use.²³ This risk is further heightened when it is co-administered with SSRIs, tricyclic antidepressants, venlafaxine and bupropion.^{21,24-26}

Tapentadol

Tapentadol has different pharmacology to tramadol. It is an opioid agonist without active metabolites and a noradrenaline reuptake inhibitor with only weak effects on serotonin reuptake.²⁷ MAOI use is contraindicated with tapentadol and there have been many reports to regulatory agencies of serotonin toxicity with this combination.⁷ MAOIs were also excluded from most tapentadol trials.⁹ Currently, it is unclear if tapentadol has a greater risk of serotonin toxicity than other opioids.

Fentanyl

Fentanyl is a high-potency opioid agonist with no effect on serotonin reuptake and low affinity (relative to opioid receptor affinity) for postsynaptic serotonin receptors (5-HT_{1A} and 5-HT_{2A}).⁵ Co-administration with an SSRI has been reported to cause an agitated delirium consistent with serotonin toxicity.²⁸ However, in a retrospective analysis of 4583 people who received fentanyl and another serotonergic drug, only 23 of them had adverse events and only four (0.09%) met the criteria for serotonin syndrome.²⁹ It is also unclear how fentanyl compares to other opioids in terms of the risk of serotonin syndrome. However, its combination with an MAOI is contraindicated.

Methadone

Methadone is largely used in the management of opioid dependence. It also has potential serotonergic effects with serotonin and noradrenaline reuptake inhibition and high affinity for serotonin receptors (5-HT_{2A} and 5-HT_{2C}).⁵ Methadone has been associated with serotonin toxicity when given with other serotonergic medicines but the risk appears low.⁷

Methadone also has highly variable hepatic clearance via CYP3A4, CYP2B6 and CYP2D6. Most SSRIs and SNRIs inhibit one or more of these enzymes and might then precipitate methadone toxicity. Methadone and (es)citalopram both cause QT prolongation, thus providing yet another potential interaction.

Antidepressants and duration of risk

Avoiding high-risk combinations can be difficult and this is further complicated by three factors:

- many antidepressants have prolonged durations of action so patients may be at risk of interactions for two weeks after an irreversible MAOI is discontinued and five weeks after fluoxetine is discontinued^{4,6,7}
- sudden cessation of short-acting antidepressants commonly causes withdrawal phenomena, which might even be misinterpreted as serotonin toxicity
- there are high rates of substance dependence and concomitant depression.

Other drug interactions

Sedating antidepressants such as tricyclics, tetracyclics (mirtazepine and mianserin) and agomelatine in combination with opioids can exacerbate drowsiness which can increase the risk of falls and respiratory depression.³⁰

Serotonergic drug interactions are not confined to antidepressants and opioids. For example, very severe interactions may occur with methylene blue and linezolid which inhibit monoamine oxidase and care should be taken when these are prescribed with opioids or antidepressants.

The combination of an opioid and drugs with anticholinergic effects can increase the risk of constipation, urinary retention and delirium.

Conclusion

Co-administration of antidepressants and opioids, deliberate or unplanned, is common. The risk of serotonin toxicity should be evaluated routinely but by far the highest risk is with MAOIs and pethidine, tramadol or dextromethorphan. Avoiding the routine use of any of these higher risk drugs is the simplest prescribing strategy. If there is an urgent need for opioids in someone taking an MAOI, using a non-synthetic opioid like morphine is preferred.

There are many kinetic interactions, adverse effects and withdrawal phenomena from all of these drugs. Clinicians should not assume that problems from combining these drugs can be explained by serotonin toxicity, and other obvious alternative medical explanations should also be considered. ◀

Conflicts of interest: none declared

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