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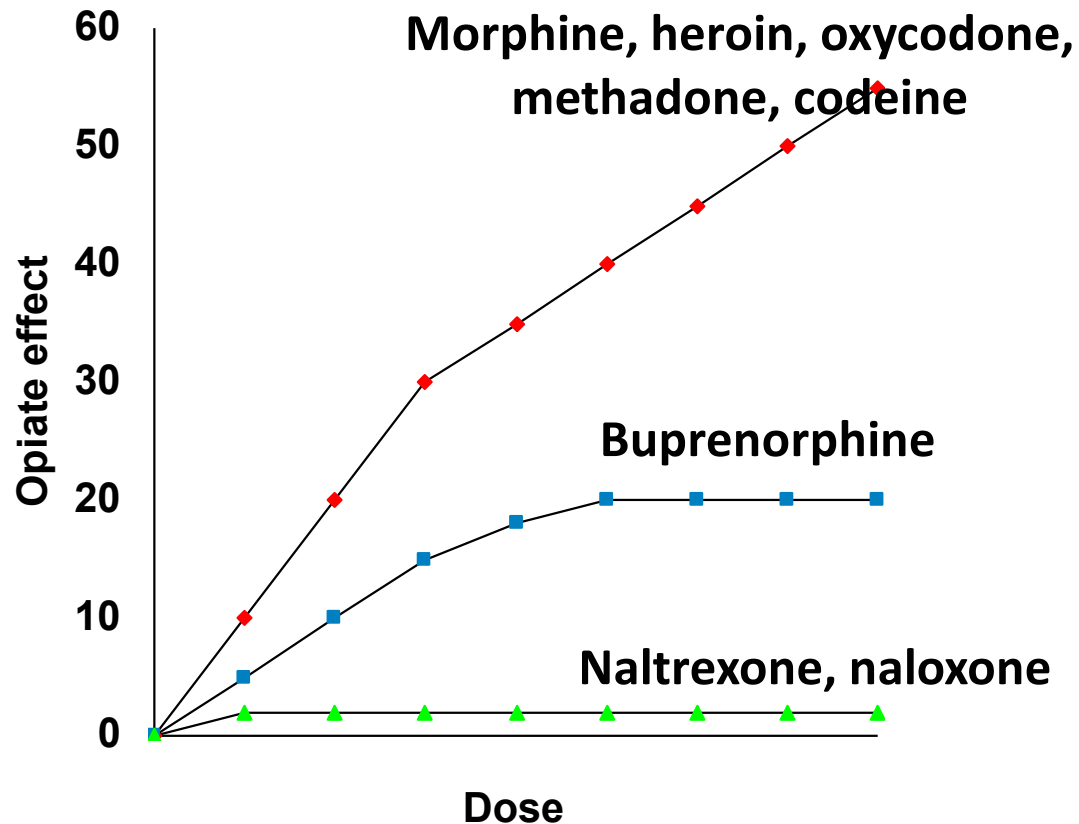
Gabapentinoids and Opioids

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Opioids – full or partial

- Full Agonists - bind completely and strongly to receptors creating maximum effect.
 - *These include oxycodone, heroin, fentanyl*
- Partial Agonists – are similar to full agonists at low doses, however cause less receptor activation, and at high doses analgesic effects plateau.
 - *These include buprenorphine and tramadol*
- Antagonists – Bind and **block** receptors and therefore biological response.
 - *This includes naloxone and naltrexone*

Effect of Opioids





Gabapentinoids

- Gabapentin and Pregabalin
- PBS listed for neuropathic pain, partial epileptic seizures
- Mechanism of action: block the $\alpha 2\delta$ subunit of specific voltage gated calcium channels. Inhibits inward calcium currents and reduces neurotransmitter release.
- Doesn't bind well to plasma protein and is not metabolized – excreted unchanged in urine. Dosing requires modifications if impaired renal function.
- Systematic review showed 30% of patients had 50% relief from pain compared with placebo of 20%
- Significant side effect profile

Gabapentinoids

Side effects

- approx 60% of patients affected by side effects.
- **Most common side effects:**
 - Dizziness
 - Somnolence
 - Water retention
 - Gait and balance issues
 - Impaired concentration
 - Respiratory depression (in certain circumstances)

Interaction between

- Opioids slow the GIT leading to increased absorption and plasma levels of gabapentinoids.
- Leads to increased likelihood of side effects.
- Additionally, the central nervous system depression from opioids can be augmented by the concomitant use of gabapentinoids.
- Gabapentinoids potentiate the effects of opioids leading to higher effects from lower doses (particularly concerning for patients who take methadone as well as a gabapentinoid)

Benefits of use

Role of gabapentinoids in the reduction of the use of opioids (in the context of pain)?

Due to the interaction and potentiation of the opioid effect by the GABA agent.

Limited evidence

- 2020 Systematic Review and Meta analysis (Verret M et al) – 281 RCTs reviewing the role of gabapentinoids in acute post-operative pain. Small opioid-sparing effect with no clinically significant analgesic effect. Increased rate of adverse events.
- 2017 Systematic review (Shanthanna et al) – 8 RCTs evaluating the role of gabapentinoids in chronic lower back pain. Minimal analgesic or opioid-sparing effect identified.

Small studies show some possible benefit in post-operative pain management, however these results have not been reliably replicated.

Some evidence to support the role of gabapentinoids in the management of postherpetic neuralgia, diabetic neuropathy and post-traumatic neuropathy (vs placebo)



Gabapentinoid misuse

Gabapentin dose effects may include:

600mg:

Stumbling, disorientation, increased awareness, slurred speech, visual/audio changes, disinhibition

900mg:

Feeling of intoxication, mobility issues, euphoria, colour perception changes

1200mg:

Drowsiness, euphoria, empathetic feelings (Like MDMA)

>1500mg:

Hallucinations, dissociative events, behavioural inhibition, anxiety

Risks of concomitant use



The effects of both agents (opioids and gabapentinoids) are increased with concomitant use.

Significant case-control study published in 2017 examined the interactions between gabapentinoids and opioids and the risks of death. (Case = those where opioids were implicated in the death, control = deaths not attributed to opioids)

Study examined deaths in Ontario that were attributed to opioids. Suicides or homicides were excluded.

Patients were grouped into low medium and high dose ranges for gabapentin and oral morphine equivalent

Opioid related deaths



12.3% of cases and 6.8% of controls were prescribed gabapentin.

Odds of opioid related death 49% higher in patients receiving gabapentin compared to opioids alone.

Study showed that moderate and high dose gabapentin (>900mg/day and 1800mg/day) increased odds of an opioid related death by nearly 60%

Large database studies have further characterised this risk:

US database of >5 million adults who underwent major surgery

- Opioid overdose occurred in 14 per 100,000 patient who received gabapentinoids plus opioids
- Opioid overdose occurred in 4 per 100,000 patients who received opioids alone

SafeScript updates



2019 review of monitored medications based on 2017 literature review:

Evidence of harm only with combination of pregabalin and opioids or benzodiazepines. Not when prescribed in isolation.

Not included on SafeScript for monitored medications.

2021 review following recommendation made by Coroners Court of Victoria to include pregabalin in SafeScript

Why the position change?

- Overall metrics related to deaths not remarkable – this finding has been stable since last review
- Gabapentinoids as a surrogate to flag high-risk opioid use



Take away points

Concomitant use of Opioids and Gabapentinoids should be avoided unless absolutely necessary.

Increased risk of CNS and respiratory depression when used together.

Each agent potentiates the other and opioid use results in elevated serum gabapentinoid.

Risk of opioid related death when using gabapentinoids increased by 50% at any dose and nearly double when gabapentinoids used in high dose.

Gabapentinoids efficacy only proven in a limited number of conditions, but used widely outside these conditions with limited/no evidence.



Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W (2017) Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study. PLoS Med 14(10):e1002396.

<https://doi.org/10.1371/journal.pmed.1002396>