Adverse Effects of Opioid Therapy

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1. Introduction

The goal of opioid administration is to achieve effective analgesia, improve functional status and quality of life for the patient. As opioids act on opioid receptors distributed widely throughout the body, it has both central and peripheral effects. Opioids are neither universally effective nor universally well tolerated. Their effects are dose-dependent and can occur almost simultaneously with the intensity being dependent on the opioid and its dose, route of administration, duration and patient comorbidities.

Adverse effects associated with opioids play an important role in the success or failure of pain management. An adverse effect which is unpleasant and severe can contribute to discontinuation of therapy. In the postoperative patients, opioid-related adverse events are associated with increased risk of readmission, inpatient mortality, length of hospital stay and costs. Thus, identifying patients who are at a higher risk of opioid-related adverse effects is important.

Adverse effects therefore needs to be treated. For some effects, tolerance develops and continued use of an opioid is possible. Finding a balance between analgesia and side effects is important and the benefits of analgesia must outweigh its risks of side-effects.

This chapter will discuss general opioid adverse effects and classify them based on body systems, the mechanism of their generation and general management strategies.

2. General Principles of Management of Opioid-induced Adverse Effects

- When opioids are prescribed, the patient should be monitored for side-effects. In the acute pain setting, the patient's safety is paramount and should be monitored for signs of opioid toxicity, including monitoring for alertness and sedation levels, respiratory function (e.g. rate), oxygenation, pulse rate and blood pressure. Opioids should not be titrated solely to an arbitrary pain score. Other adverse effects which are not self-reported by the patient should be further enquired, especially if there is an index of suspicion.
- If pain is adequately controlled, opioid side-effects can be reduced by decreasing the dose of opioid by 25% or by changing the route of administration. This can also be assisted by the use of adjuvant and opioid-sparing analgesics.

- If opioid therapy needs to be maintained, the adverse effects can be treated by the opioid antagonist e.g. a small dose of naloxone, being careful not to antagonise the analgesia in the process.
- Targeting the generation of the adverse effect by blockade of its receptor-mediated action can also be taken e.g. opioid-induced nausea and vomiting due to dopaminergic stimulation can be treated by dopamine antagonist such as droperidol. Non-specific symptomatic relief of symptoms can also be employed.
- Some adverse effects are common and do not diminish with tolerance; and patients should be prescribed prophylactic agents to minimise the anticipated side-effects e.g. constipation.
- Some adverse effects can develop over the long term e.g. hypogonadism and potential for osteoporosis. These conditions should be monitored and treated if needed.
- Opioid adverse effects can also be potentiated by the patient's underlying comorbidities including being elderly. This should be considered and the underlying comorbidities should be corrected whenever possible.

Table 1: CNS adverse effects of opioids

Adverse effects	Mechanism	Incidence/risk	Management strategies
sedation	Decrease central cholinergic activity Opioid overdose; accumulation of opioid &/or metabolite	5% with PCA & IMI opioids 15-30% CNCP 20-60% in cancer pain Elderly; potentiation by other CNS depressants (benzodiazepine, antihistamines and antidepressants)	↓ opioid dose or ↑ interval of administration; ↓ use of CNS depressants; exclude organic causes (e.g. encephalopathy, dementia). If persistent consider psychostimulants e.g. dexamphetamine, methylphenidate
Cognitive impairment, confusion, delirium	?disturbance in central cholinergic function in modulation of cortical arousal, information processing and sleep-wake cycle.	? incidence Untreated pain; use of pethidine and tramadol (elderly); comorbidities (e.g. renal dysfunction, cognitive impairment); high dose opioids and other psychoactive drugs	Treat underlying causes and metabolic disturbance; discontinue non-essential centrally acting drugs; haloperidol;
Opioid-induced sleep disturbance	Opioids ↓ total sleep time, deep sleep, sleep efficacy, delta sleep & REM sleep. ↑ % time spent in light sleep. Modulation of GABAergic signaling	25%	? ↓ opioid dose

Adverse effects	Mechanism	Incidence/risk	Management strategies
Hallucination	Overactivation of the mesolimbic dopaminergic system. ? role of opioid metabolites	About 4%. ↑ risk with tramadol (OR 6.3), morphine (OR4.4)	Discontinue opioid, ↓ dose or switch to another opioid; opioid antagonist naloxone; antipsychotics e.g. haloperidol; benzodiazepines (↓ agitation and anxiety)
Myoclonus – involuntary jerking of various muscle groups in limbs	? accumulation of neuroexcitatory metabolites e.g. M3G ? opioid effect on GABA in spinal cord ?central serotonergic and dopaminergic effect of opioids	? incidence High dose opioids; Patients with neurological disorders; patients on antidopaminergic drugs (haloperidol)	Opioid rotation; ↓ opioid dose; Muscle relaxants – benzodiazepines, baclofen
Muscle rigidity – usually in the chest wall	Opioid induced blockade of cortical inhibitory pathways with lower centres exhibiting excitability, ?abnormal motor activity from subcortical seizures	?incidence Rapid administration of opioids usually IV and intraoperatively	Prevented by slow administration of opioids; neuromuscular blockers during anaesthesia; naloxone
Seizure	Changes in catechoamines in dopaminergic pathways, ↑ glutamate-activated currents, ↑ release of excitatory neurotransmitters, or opioids and neuroexcitatory metabolites (e.g. M3G, H3G, norpethidine)	Uncommon High dose opioids (morphine, hydromorphone, fentanyl, pethidine); patients with epilepsy	Prevention – opioid rotation; ↓ dose. ? benzodiazepine; avoid use of pethidine

Adverse effects	Mechanism	Incidence/risk	Management strategies
Opioid induced hyperalgesia – paradoxical increase in pain sensitivity with opioids	Activation of excitatory NMDA receptors; neuroexcitatory effects of metabolites,; ↑ spinal dynorphins; release of CGRP	?incidence High dose opioids	↓ opioid dose, opioid rotation, NMDA receptor antagonist e.g. ketamine, consider α2-agonist e.g. clonidine
Tolerance – decrease in analgesic effect with time or need to increase dose for same effect	Activation of NMDA receptors, inactivation of opioid receptors and other mechanisms	Common Usually long term opioid intake, but can develop after continuous intake of opioid for a week or more.	Increase opioid dose; Coadministration of antihyperalgesics e.g. ketamine in acute pain.
Opioid dependence and addiction	Stimulation of the neural reward circuits on the mesolimbic system (VTA, NAc, amygdala) leading to the release of dopamine in NAc. (NAc=nucleus accumbens, VTA= ventral tegmental area)	2-26% (higher in primary care settings than pain clinic settings). ↑ risk with patients with substance use disorder, younger age, mood disorder and use of psychotrophic medications	See Chapter on Substance Use disorders and Aberrant behaviours.

3. Central Nervous System Adverse Effects (see Table 1)

CNS effects include sedation, cognitive dysfunction, delirium, hallucinations, sleep disturbance, myoclonus, hyperalgesia and seizure.

Sedation usually occurs at initiation of opioid therapy or when the dose is increased significantly. It can be associated with cognitive impairment and delirium. Opioids may also cause potential sleep disturbance which may contribute to sedation and fatigue.

Acute administration of opioids will impair motor coordination, attention and short-term memory. During long term stable opioid dosing, there is generally

no impairment of psychomotor abilities although impairment of cognitive function including memory shows a variable effect. If other sedative drugs e.g. benzodiazepines are taken concurrently, psychomotor abilities will be impaired. However, unrelieved pain itself also impairs both psychomotor and cognitive abilities. Memory and concentration deficits are commonly reported, in about 20% of patients, taking long term opioids.

4. Respiratory Adverse Effects (see Table 2)

Opioids act on the respiratory centres of the brain stem to produce dose dependent respiratory depression to the point of apnoea; and this

Table 2: Respiratory adverse effects of opioids

Adverse effects	Mechanism	Incidence/risk	Management strategies
OIVI – respiratory depression, ↑ PaCO2, depressed consciousness & upper airway obstruction.	Activation of MOR. ↓ responsiveness of respiratory centre in medulla to CO2 and hypoxia to depress respiratory drive. ↓ MV - ↓RR and ↓TV	Wide range of incidence dependent on definition used. 1-11% Female, obesity, sleep-disordered breathing, renal impairment, pulmonary disease, CYP450 polymorphisms.	Careful titration of opioid to effects; regular observation & monitoring. Supplemental oxygen; Opioid antagonist naloxone
Sleep-disordered breathing: Obstructive sleep apnoea (OSA) Central sleep apnoea (CSA) Hypoxaemia Ataxic breathing	↓ respiratory drive to upper airway dilating muscles (OSA) and respiratory pump muscles (CSA)	70% (40-85%). ↑ risk with increased opioid dose (threshold: 200mg oMEDD) 40% 24%	Cessation of opioid & other depressant drugs; ↓opioid dose; opioid rotation to partial agonist e.g. buprenorphine; ↑ use of non-opioid analgesics; supplemental oxygen; positive airway pressure ventilation e.g. CPAP, BPAP, servo-controlled ventilation.

is potentially the most serious of opioid side effects and requires close monitoring. Increases in PaCO2 is the most reliable way of detecting respiratory depression (monitored by measuring transcutaneous CO2) but sedation is its best indicator. Respiratory depression is uncommon in patients on long term opioids as tolerance usually develops within days to weeks.

Naloxone in the dose of 100-400 mcg every 5 minutes can be used to reverse opioid-induced respiratory depression. But if higher doses are used, it can precipitate acute opioid withdrawal and reverse opioid analgesia, which can precipitate a pain crisis that is difficult to manage. Naloxone has a shorter half-life than most of the opioids and hence respiratory depression can re-emerge if only single doses are given. Any patient at risk of recurrent respiratory depression should be monitored closely and a continuous naloxone infusion used.

Opioids can affect all aspects of respiration (frequency, tidal volume, rhythm, upper airway patency, chemosensitivity and arousal to CO2 and O2, and cough reflex) by inhibition of respiratory neurons in the central and peripheral nervous system. It is manifested clinically by disturbance of breathing pattern (ataxia or irregular breathing), breathing interruptions (apnoea and hypopnoeas) and gas exchange (hypoxia and hypercapnoea).

Acute effects of opioids on ventilation generally lead to hypoxic and hypercapnoeic respiratory failure due to decreased respiratory drive and hypoventilation. Chronic effects are more complicated; they involve both peripheral chemoreceptors and its central effects e.g. inhibitory effect on upper airway muscles and depression of protective arousal responses.

5. Cardiovascular Effects

Administration of opioids e.g. morphine can lead to hypotension and bradycardia through reduction of sympathetic tone but also through its histamine releasing and direct effect on vascular smooth muscle causing vaso- and venodilation. It can result in postural hypotension. Hypotension as the result of opioid administration in the postoperative patient often indicates an underlying hypovolaemic state.

Prolongation of the QT interval is also of concern for some opioids such as methadone with the risk of development of torsades de pointes and cardiac arrest. This risk is increased with high doses of methadone used and in the presence of other risk factors (*see Chapter on Methadone*).

Table 3: Gastrointestinal adverse effects

Adverse effects	Mechanism	Incidence/risk	Management strategies
Nausea Vomiting	Stimulation of chemoreceptor trigger zone in medulla; gastric stasis; ↑ vestibular sensitivity.	25% (10-40%) Female, past history PONV and motion sickness, inhalational anaesthesia, non-smokers.	Antiemetics – droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, ganisetron, dexamethasone, cyclizine. PC6 point acupressure or acupuncture
Constipation; Postoperative ileus	Opioid binding to MOR in gut and CNS → delay gastric emptying, ↑ small & large bowel transit times, ↓ intestinal secretion	40-45% Comorbidities e.g. spinal cord injury; inactivity; dehydration; concurrent medications (e.g. antidepressants, antacids, anticholinergics)	Stool softeners; bulk and stimulating agents. Peripheral opioid antagonist – methylnaltrexone, alvimopan, naloxegol
Biliary spasms	Spasm of sphincter of Oddi & increase biliary tract pressure	?incidence	Naloxone; Atropine; Nitroglycerin

Long term opioid therapy has been associated with an increased risk of about 30% for myocardial infarction compared to non-opioid users. The opioids implicated are mainly morphine, pethidine and dextropropoxyphene even though the cause is unknown.

6. Gastrointestinal Adverse Effects (see Table 3)

Opioids have the propensity of causing nausea and emetic effects apart from a range of opioid-induced bowel dysfunction due to its activation on the opioid receptors in the gut. This includes delayed gastric emptying causing nausea and loss of appetite, increased absorption of fluid from bowel lumen causing dry stools and decreased propulsive peristalsis causing constipation.

There is also increased circular muscle contractions leading to abdominal cramps, pain and constipation.

Constipation is the most commonly occurring adverse effect of chronic opioid therapy and few patients develop tolerance to it. It is associated with significant impairment of quality of life, higher emergency room and hospital admissions and longer hospital stays. When severe, it increases the risk of bowel obstruction. It should therefore be routinely treated prophylactically. In cancer pain, reversible comorbidities such as hypercalcaemia and nausea related to other drugs e.g. digoxin, antibiotics and cytotoxic chemotherapy should be treated.

7. Urological Adverse Effects

Opioids treatment for acute, postoperative pain, especially via intraspinal route, may lead to urinary retention. This may be due to decrease in detrusor tone and inhibition of the voiding reflex, and may be reversed by naloxone and methylnaltrexone. The incidence is reported to be 4-18% in the postoperative period.

8. Immunological Adverse Effects — Immunosuppression

Opioid administration can cause suppression of antibody and cellular immune responses, natural killer (NK) cell activity, cytokine expression and phagocytic activity. During chronic opioid administration, the activity in the hypothalamic-pituitary-adrenal axis is increased and this leads to the production of the immunosuppressive glucocorticoids and consequent decrease in natural killer (NK) cell activities.

Opioids used for treatment of chronic pain differ in their immunologic activities. Buprenorphine, oxycodone, hydromorphone and tramadol are relatively immunosparing. Due to its additional serotinergic activity, tramadol may have some immune-enhancing (NK cell activity, lymphocyte proliferation, IL-2 release) effect as well. Opioids with significant immunosuppressive actions include morphine, codeine, methadone and fentanyl.

Pain, as well as stress response generated from surgery, may be immuno-suppressive by reduction of natural killer cell activities and this should be balanced by the potential adverse effects of opioids. However, the immune effects of long-term administration of opioids has not been fully defined clinically.

9. Endocrinological Adverse Effects — Opioid Induced Hormonal Changes

Acute administration of opioids stimulates prolactin, growth hormone, thyroid stimulating hormone and adrenocorticotrophic hormone (ACTH) but inhibits lutenizing hormone (LH). With chronic administration, there is suppression of gonadotropin-releasing hormone (GnRH), LH and ACTH release leading to hypogonadism and hypoadrenalism. Testosterone levels in some men and oestrogen levels in women are reduced. The effects of opioids on testosterone may be dependent on the specific opioid used e.g. patients treated with buprenorphine had higher testosterone levels and less sexual dysfunction than those on methadone. The secretion of adrenal androgens is also reduced. Side effects include reduced libido, lethargy, depression, a/oligomenorrhoea, sexual dysfunction (erectile dysfunction in men) and potentially reduced bone mineral density. The reduced bone mineral density leads to osteoporosis and risk of fractures.

Testosterone replacement therapy improves indices of sexual function, mood and well-being but incompletely. Ostrogen replacement therapy may be useful to restore menses and maintain bone mineral density in younger women but the risk for older women has not been fully elucidated. These

Table 4: Dermatological adverse effects

Adverse effects	Mechanism	Incidence/risk	Management strategies
Pruritus Neuraxial induced pruritus	Histamine release Central effect – activation of opioid, ?dopamine and serotonin receptors in medulla and DH of spinal cord; activation of itch centre	3% (IMI) 14% (IV PCA) 10-15% (chronic use) 2-10% (cancer pain) 10-40%	Antihistamine – diphenhydramine, hydroxyzine, cyproheptadine 5HT3 antagonist- IV ondansetron 4 mg; opioid antagonist – naloxone 10-40 mcg; propofol, droperidol
Sweating	Histamine release; Central thermoregulatory mechanisms	Up to 30%	Antihistamines; Anticholinergics

side effects are reversible with the cessation of opioid therapy. Opioid rotation can also be considered. These adverse effects are uncommon, occurring in 5% of patients but with intrathecal opioid therapy, the incidence of hypogonadotrophic hypogonadism may be higher.

10. Dermatological Adverse Effects (see Table 4)

Pruritus is a relatively common side effect of opioid. It is generally widespread over the face, neck and truncal region. Increased sweating is also commonly reported.

11. Other Adverse Effects

11.1 Xerostomia

Opioid use is strongly associated with xerostomia from salivary gland hypofunction and the incidence can be as high as 40%. It causes difficulty with talking, chewing, swallowing and impairs taste sensation; and the symptoms tend to worsen with time. It can be exacerbated by the use of tricyclic antidepressants, anticholinergic drugs, cytotoxics and local radiotherapy treatment. The salivary gland hypofunction may cause alteration in oral microbial population, increased rate of plaque accumulation and periodontal disease. These will also be worsened by the immunosuppressive effects of opioids, poor diet and poor oral hygiene, in some patients, leading in many cases to loss of dentition.

Patients require a well-structured delivery of oral health care including dental hygiene and dietary advice. When xerostomia is troublesome, sialagogues such as pilocarpine or saliva substitutes can be used.

11.2 Fluid Retention

Peripheral oedema especially in the lower limbs is known to occur with opioid therapy especially with long-term administration. The cause is unknown but may relate to stimulation of the release of antidiuretic hormone and increased sodium absorption in the renal tubules. Other causes of peripheral oedema should be excluded and management options include the use of elastic stockings, salt and fluid restrictions and use of diuretics.

11.3 Societal Harms

The trend to increased prescribing of opioid analgesics in Australia has caused increasing concerns of opioid abuse and non-medical use (opioid

dependence, recreational use and self-treatment) mainly through diversion of the drugs. This can lead to harm, including deaths due to overdose. In most cases, deaths are accidental but could be suicide related. They generally involve polypharmacy with sedatives (benzodiazepines, antidepressants and other CNS depressants), alcohol use, the opioid(s) being sourced from multiple sources and those in the lower socioeconomic groups. Recent opioid use in a patient is associated with a 5fold increase in overdose events and higher doses used will increase this risk. There is also a direct correlation between opioid dose and opioid-related death. Those taking 200mg or more of oral morphine equivalent daily dose (oMEDD) suffer from a nearly 3-fold increase in risk of opioid-related mortality, while those on 50-199mg oMEDD have about a 2 fold increase and those on 20-49mg oMEDD have about 1.3 fold increased risk relative to those taking less than 20mg oMEDD.

Aberrant drug taking behaviours such as medication agreement violations, returning positive urine drug tests, was well as opioid misuse which involves a whole range of problematic behaviours, are difficult to manage by the clinician. The rates range from 6-45%. There is a risk that it may evolve into problems with opioid abuse and diversion, as well as the development of dependence and addiction. The higher the doses of long term opioid therapy, the higher the risk of association with opioid abuse and dependence.

12. Some Differences in Adverse Effects of Opioids

Opioids may differ in the frequency of side effects e.g. transdermal fentanyl causing significantly less constipation than morphine. Pruritus may be more common with morphine than fentanyl and risk of respiratory depression higher with methadone than buprenorphine.

When opioid adverse events were determined from systematic review of RCTs, those studies using predominantly weak opioids seemed to have different incidences and types of adverse events from those using strong opioids. The strong opioids used studies were associated with higher rates of adverse events especially constipation, somnolence and nausea. Generally, 20-25% of patients withdraw from opioid studies due to adverse events (see Table 5).

It should also be noted that there may be age-related (e.g. risk of respiratory depression increasing with age); sex-related (e.g. women experiencing higher incidence of nausea and vomiting than men) and probably racial differences.

Table 5: Comparison of adverse effects with studies on predominantly weak opioids (codeine, tramadol) and strong opioids (morphine, oxycodone). *Adapted from Moore (2005) and Kalso (2004).*

Adverse events	Studies with predominantly weak opioids	Studies with strong opioids	Approximate NNH with strong oral opioids
Any adverse events	50%	80%	4
Drowsiness / somnolence	15%	30%	5.3
Dizziness	15%	20%	8.2
Nausea	20%	30%	5
Vomiting	10%	15%	8
Constipation	15%	40%	3.4
Pruritus	15%	15%	13
Dry mouth	25%	15%	Not calculated

13. Summary

This chapter summarises some of the more common adverse effects of opioid therapy that the clinician is likely to encounter when prescribing for acute, chronic non-cancer or cancer pain conditions. Most of these conditions should be monitored and treated appropriately. This will improve safety and enhance the quality of pain management for the patient.

Bibliography

1. Benyamin R, Trescot AM, Datta S, Buenaventure R, et al. Opioid complications and side effects. Pain Physician. 2008; 11:S105-S120.
2. Harris JD. Management of expected and unexpected opioid-related side effects. Clin J Pain. 2008;24:S8-S13.
3. Chou R, Turner JA, Devine EB, Hansen RN, et al. The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain. Annals of internal medicine. 2015;162(4):276-286.
4. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, et al. Opioid dose and drug-related mortality in patients with non-malignant pain. Arch Intern Med. 2011; 171(7):686-691.
5. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain. 2004; 112:372-380.
6. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of opal opioids. Arthritis Research & Therapy. 2005; 7:R1046-1051.