Pruritus or severe itching of the skin occurs frequently with opioid analgesic use. Although not life threatening, pruritus is discomforting and may decrease quality of life. Opioid-induced pruritus affects 2% to 10% of people on oral opioids and up to 100% of people receiving epidural and intrathecal (neuraxial) opioids.

Symptoms
Pruritus is an unpleasant side effect leading to patient discomfort, decreased quality of life, and discontinuation of medication. It can be described as an unpleasant sensation of the skin and mucous membranes that provokes a desire to scratch or rub.

The intensity of pruritus ranges from mild to severe, and it can have a significant psychosocial impact on patients, by interfering with their sleep and daily activities.

Severe itching is also seen in patients with advanced disease associated with uraemia (chronic renal failure) and cholestasis (decrease in bile flow). Dry skin also may be present in many of these conditions.

Incidence
Symptoms vary with type of opioid, dose and administration route. In most cases, higher doses correlate with a higher incidence of pruritus. Lipid soluble opioids such as fentanyl have a shorter duration of action of pruritus and usually respond to decreases in dosage.

Chronic use of oral opioids has a low incidence of pruritus (2% to 10%) compared to injectable opioids. Extended-release oral opioids have a higher incidence than immediate-acting oral drugs, because of prolonged activation of the opioid receptors.

Transdermal patches (buprenorphine, fentanyl) may cause pruritus in 3% to 15% of patients. It is primarily a local reaction.

Injectable formulations of morphine, buprenorphine, fentanyl, hydromorphone, methadone, and pethidine have a higher incidence of opioid-induced pruritus of 10% to 50%. Epidural or intrathecal opioids have a much greater incidence rising to 20% to 100%. People who have received major orthopaedic surgery are most susceptible. The highest prevalence is associated with intrathecal morphine (up to 100%).

Mechanism
Even though the mechanism of opioid-induced pruritus is not yet fully understood, both peripheral and central-acting pathways appear to be involved.

Peripherally induced pruritus occurs due to the release of histamine from mast cells, resulting in local itching and hives. Opioid agonists (morphine, methadone) are thought to produce pruritus through this mechanism.

However histamine is not the sole cause of opioid-induced pruritus. Activation of central mu-opioid receptors is likely to also contribute to a centrally mediated reaction. Pretreatment with naloxone, a mu-receptor blocker, is more effective than antihistamines in preventing pruritus.

Serotonin and dopamine D₂-receptors, prostaglandins and spinal inhibitory pathways may also be involved in the genesis of pruritus.

As there is a high concentration of opioid receptors in the trigeminal nerve and spinal cord, itching of the face is common.

Management
Prevention by using the lowest effective doses of opioids is the best management strategy.

Several strategies have been suggested to reduce the incidence of opioid-induced pruritus:
- Opioid rotation
- Dose reduction
- Changing the route of administration
- Symptomatic management

Switching to hydromorphone (Jurnista) or fentanyl may provide some relief from the itching. These medicines have less histamine-releasing properties.

Non-drug treatments include cool compresses or moisturisers. Emollients should be liberally applied.

continued over
after bathing. Topical preparations containing menthol also provide a cooling sensation. When the itch is localised, topical corticosteroids can also be useful. Soap substitutes should be used, and hot showers should be avoided. Vasodilating food and drinks (e.g., coffee, alcohol, spices) should also be avoided.

Treatment
Several pharmacological agents have been used, both for the treatment of established pruritus and in its prevention, including:

- Pure opioid receptor antagonists
- Mixed opioid receptor agonist-antagonists
- Serotonin 5-HT₃ receptor antagonists
- D₂-receptor antagonists
- Propofol
- NSAIDs
- Antihistamines
- Gabapentin
- Mirtazapine

Antihistamines are often used as first-line treatment. They have little if any effect on centrally induced pruritus, but are effective for the peripherally induced pruritus of morphine or methadone. Sedating antihistamines may be more effective; however, they may cause oversedation and an increased risk of respiratory depression. Non-sedating antihistamines are not effective for pruritus except where histamine is clearly the mediator of itch.

The Therapeutic Guidelines recommends:

- promethazine (Phenergan) 10 to 25 mg orally, 2 or 3 times daily (maximum 100 mg/24 hours), or
- trimeprazine (Vallergan) 10 mg orally, 3 or 4 times daily

Opioid receptor antagonists such as naloxone and naltrexone have some benefit in the prevention and treatment of opioid-induced pruritus. They do not cause additional sedation. Naloxone has a short half-life and does not provide long-lasting relief. It does have a rapid onset within 2 to 5 minutes providing potent antipruritic effects. A meta-analysis of studies has shown that for every four patients receiving naloxone, one patient would not experience pruritus. When used in higher doses opioid receptor antagonists will reverse analgesia activity.

D₂-receptor antagonists such as droperidol (Droleptan Injection) may be effective in a few patients. Metoclopramide, another D₂-receptor antagonist, has not been proven effective.

5-HT₃ receptor antagonists (ondansetron, dolasetron) can significantly decrease the incidence and intensity after neuraxial opioid administration, especially with morphine. They cause both central and peripheral 5-HT₃ receptor blockade. Ondansetron is an antiemetic, non-sedative and has no anti-analgesic effect.

Ondansetron (Zofran) is available as tablets, oral disintegrating tablet, oral liquid, suppository, wafer and injection. Dolasetron (Anzemet) is available as a tablet and injection.

Use of these medications is still controversial, with limited evidence; and they are only registered for cytotoxic chemotherapy/radiotherapy-induced prevention and treatment of nausea and vomiting. Parenteral ondansetron is also indicated for the prevention and treatment of postoperative nausea and vomiting (PONV).

Mirtazapine, an antidepressant, has been studied for the prevention of intrathecal morphine-induced pruritus. It acts both centrally and peripherally. Other antidepressants such as paroxetine or doxepin may also be useful. Treatment should begin with low doses, and an effect is usually seen within 1 to 2 days.

The Therapeutic Guidelines recommends:

- doxepin (Deptran, Sinequan) 10 to 50 mg orally, at night
- paroxetine (Aropax) 20 mg orally, in the morning

Gabapentin, an antiepileptic agent and useful in the treatment of neuropathic pain, has been shown to be effective in many cases of chronic pruritus.

Summary
Pruritus is a well-recognised adverse effect of opioids. When intolerable, it may lead to discontinuation of the opioid and loss of its beneficial effects on pain. Several treatment options are available.

References
Canadian Family Physician 2011;57:1010-3.