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OPTIMIZING PAIN MANAGEMENT

Pain assessment and patient-specific factors in individualizing analgesic selection

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Mr. X is an 88-year-old retired healthcare professional with a history of heart disease, chronic kidney disease, and glaucoma. His medications include brimonidine/timolol eye drops, acetylsalicylic acid, and metoprolol. He recently suffered a hip fracture after a fall at home and required surgery. During the early postoperative period, Mr. X was prescribed acetaminophen 325 mg–tramadol 37.5 mg/tablet (1–2 tablets po q4h prn) to control his moderate postsurgical pain. After receiving three doses, Mr. X reported seeing vivid detailed pictures and spiders on his hospital room wall. The following day, Mr. X continued to receive additional doses of acetaminophen–tramadol to control his pain. In addition to developing agitation and confusion, Mr. X also reported hearing disturbing voices.

Pain can cause significant patient suffering. It has an underlying physical component and also a mental element that can impact all psychosocial components of the patient's life. Untreated pain can lead to long-term negative effects in patients of all ages, and is linked to increased use of the healthcare system, an increase in morbidity and

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mortality, the development of hyperalgesia, and impaired normal development.[1,2] In order to minimize short- and long-term negative outcomes, it is essential to recognize and treat pain as soon as it occurs,and to select the most appropriate pain medication based on patient-specific factors. Pharmacists can contribute significantly to helping patients achieve these important goals in collaboration with other members of the healthcare team.

Pain assessment

Pain assessment is the first step in effective pain management and a crucial component in quality patient care. Pain can be measured by self-report, behavioural, or physiological approaches.[3] The *self-report approach* involves understanding the patient's subjective experience, which may not be directly visible to the healthcare provider. This approach involves the patient's own assessment of feelings, images, or statements about their pain as they experience it.[3] The *behavioural approach* involves observing the patient for any physical or mental distress.[3] The *physiological approach* examines how the patient's body reacts when it is in pain.[3] In addition to these three pain assessment approaches, the following dimensions must be considered: type of pain, onset and frequency of pain, location (including radiation), intensity at rest and activity, quality (eg, continuous, intermittent, throbbing), associated symptoms, temporal or seasonal variations, impact on daily living, factors that precipitate or aggravate the pain, factors that relieve the pain, and culture, ethnic, or religious background.[3]

Currently there is no objective way to measure a patient's pain

The above considerations are essential components of pain assessment because currently there is no objective way to measure a patient's pain. The sensation of pain is subjective and the existence of pain cannot be proved or disproved.

Pain assessment techniques can be used to help healthcare professionals understand the patient's current pain situation. The current gold standard of pain measurement is the self-reporting approach using various types of scales.[3] A nationally accepted scale—the numerical rating scale—is based on pain intensity.[3] This assessment tool consists of a 10-point scale, where 0 is no pain and 10 is the worst pain imaginable. The rating requires a subjective report from the patient. The result is recorded by the healthcare professional in the patient's chart or profile and is used to track changes in trends.[3]

Other self-reporting pain assessment scales include the verbal rating scale (pain intensity based on a list of simple word descriptors or phrases), faces scale (drawings of facial expressions representing increasing levels of pain intensity), and the visual analogue scale (selecting a point on a vertical or horizontal line, usually 10 cm long, measuring from no pain to the worst pain).[3]

The use of a scale should incorporate different components of pain such as the functional capacity of the patient.[3] For example, in postoperative patients, assessing the patient's pain at rest and during movement (eg, pain on standing or coughing) would help assess overall pain.

The World Health Organization pain ladder

Once the quality and severity of pain have been assessed, the pharmacist can select pain medications that will be appropriate to treat acute or chronic pain, as well as prevent anticipated pain. The World Health Organization's (WHO) pain ladder captures an approach to pain management.[4] This simple and effective ladder for escalation of analgesic drug therapy was developed by the WHO in 1986.[5] While the ladder was initially intended to assist with the treatment of chronic cancer pain in adults, a similar approach can be used when treating acute pain.[5]

For patients experiencing mild-to-moderate pain, analgesics found at the bottom of the ladder such as nonopioids (eg, acetaminophen or nonsteroidal anti-inflammatory drugs [NSAIDs]) should be promptly initiated.[5] If these analgesics do not sufficiently control the pain or the pain escalates, or if the initial pain is moderate in nature, mild opioids (eg, codeine) should be started with or without a nonopioid.[5] If pain is still uncontrolled or escalates, or is initially severe in nature, stronger opioids (eg, morphine, oxycodone, or hydromorphone) may be tried with or without a nonopioid.[5]

For effective treatment of difficult-to-manage pain, patients may also require adjuvant analgesic agents, such as tricyclic antidepressants or anticonvulsants for neuropathic pain.[4,6] The idea of combining nonopioids with opioids for moderate or severe pain as outlined in the WHO pain ladder is based on the concept of multimodal or balanced analgesia.[7] This approach involves using more than one class of analgesic, each with a different mechanism of action, in order to improve pain control and minimize dose-related side effects.[7]

Considerations in individualizing analgesic therapy

Several factors should be considered when personalizing analgesic therapy, including assessing and managing postoperative pain, managing pain in special patient populations, and polymorphisms and drug interactions.

Managing postoperative pain

Acute moderate-to-severe pain can be a major symptom during the postoperative period and is one of the risk factors for developing ongoing chronic pain.[8] When developing a therapeutic care plan for treatment of postoperative pain, it is important to remember that its maximum intensity occurs within the first 24 hours, then progressively declines over time.[9] Therefore, early effective postoperative pain control is crucial in the initial stages of surgical patient care.[10] Following this proactive approach to effective management of postoperative pain can lead to increased patient comfort and satisfaction, earlier mobilization, fewer

table1 Common medication classes with serotonergic properties[22-26]

Antidepressants
- Selective serotonin reuptake inhibitors (eg, sertraline, fluoxetine)
- Serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine)
- Norepinephrine-dopamine reuptake inhibitors (eg, bupropion)
- Noradrenergic and specific serotonergic antidepressants (eg, mirtazapine)
- Tricyclic antidepressants (eg, imipramine, clomipramine)
- Monoamine oxidase inhibitors (eg, phenelzine)
- Other antidepressants (eg, trazodone)

Other psychoactive drugs
- Atypical antipsychotics (eg, olanzapine, risperidone, aripiprazole)
- Anxiolytics (eg, buspirone)
- Mood stabilizers (eg, lithium)
- Anticonvulsants (eg, valproate, divalproex)

Analgesics
- Opiates (eg, morphine)
- Opioids (eg, fentanyl, meperidine, tramadol)
- Migraine agents (eg, sumatriptan)

Other drug classes
- Anti-infectives (eg, linezolid)
- Antiemetics (eg, ondansetron, granisetron, metoclopramide)
- Herbals (eg, Panax ginseng, tryptophan, St. John's wort)
- Illicit drugs (eg, lysergic acid diethylamide (LSD, 3,4-methylenedioxy-N-methamphetamine [MDMA, Ecstasy])
- Intravenous dyes (eg, methylene blue)
- Over-the-counter drugs (eg, dextromethorphan)
- Weight loss agents (eg, sibutramine)

pulmonary and cardiac complications, reduced risk of deep vein thrombosis or pulmonary embolism, faster recovery with decreased chance of developing neuropathic pain, faster return to normal activities of daily living, shortened hospital stay, and reduced hospital costs.[9-12]

Postoperative pain management should not be standardized for all patients. Optimal pain management requires a multimodal or balanced analgesia approach.[7] In the postoperative setting, a multimodal approach involves the combination of nonopioid and opioid analgesics, as well as special analgesic techniques (eg, regional analgesia, patient-controlled analgesia), which act on different sites within the central and peripheral nervous systems.[9,11] The overall goal with this multimodal approach is to provide greater analgesia with fewer side effects.[9] The decision as to which analgesic technique to employ depends on the type of surgery and the intensity of postoperative pain expected. Overall, evidence in the literature demonstrates that multimodal analgesia provides a clear preventive effect for residual pain for up to one year and improves patient outcomes related to pain control.[8,11]

Special patient populations

When evaluating possible analgesic options, other important factors to consider include age, renal function, concurrent mental health conditions and medications (and the potential for developing serotonin syndrome), and the occurrence of postoperative delirium.

Geriatric patients

When selecting an analgesic for an elderly patient, consider the following factors: age, weight, drug allergies, kidney function, medical conditions, concurrent medications, compliance factors, and ability to chew or swallow oral dosage forms. Age and weight should be considered when selecting the analgesic dose because a lower opioid dose should be used for an elderly frail patient. This is due to the fact that the efficiency of hepatic drug metabolism via CYP450 enzymes decreases rapidly beyond the age of 65 years.[13] Consequently, older patients may not metabolize opioid analgesics as efficiently and, therefore, may be more sensitive to usual adult doses and experience more side effects (eg, sedation, respiratory depression).[13]

Increasing age may also correlate with decreasing renal function, which is another factor to consider when selecting an analgesic.

Acute or chronic renal insufficiency

A patient's renal function should be carefully considered when selecting the most appropriate analgesic because NSAIDs, codeine, tramadol, and morphine are renally cleared.[14] Important considerations include the patient's age, degree of renal impairment, whether the drug is primarily removed from the body via the kidneys, and the risk of drug-induced nephrotoxicity.[15] In general, if a patient's creatinine clearance is <30 mL/min, it is preferable to avoid or minimize the use of NSAIDs because they are inherently nephrotoxic agents. Hydromorphone is the agent of choice for patients with acute or chronic renal insufficiency who require an opioid for moderate to severe pain.[14] For mild pain, where a nonopioid is acceptable, acetaminophen should be selected over NSAIDs.[12]

Concurrent mental health conditions

There appears to be a relationship between pain and psychiatric conditions, where worsening of one seems to aggravate the other.[16] Pain may be a precursor to, aggravator of, or appear during a psychiatric condition. In patients with pain caused by inflammatory bowel disease, for example, the frequency of concurrent psychological and psychiatric disturbances is 50% higher than in the general population.[17]

As pain and depression or other affective mood disorders have a high degree of prevalence and reciprocity, it is essential for pharmacists to demonstrate competency in this area. The mechanisms of action of analgesics medications and psychiatric medications often overlap strongly, as they affect similar neurotransmitters such as serotonin, dopamine, or norepinephrine.[18] For example, fentanyl increases serotonin levels, and tramadol acts as a serotonin-norepinephrine reuptake inhibitor and is structurally similar to venlafaxine.[19,20] In addition, pain medications such as most opioids and opiates can have an indirect impact on dopamine and acetylcholine.[18] Therefore,

Pain may be a precursor to, aggravator of, or appear during a psychiatric condition

the patient's concurrent psychiatric medications and potential drug-drug interactions must be considered when selecting an analgesic in order to prevent negative outcomes, such as serotonin syndrome. A final point for pharmacists to recognize is that in patients with pain and concurrent psychiatric conditions, the emotional symptoms of pain management, including well-being and nonsomatic depressive symptoms, are more resistant to treatment.[21] This may make it more difficult to find an analgesic to appropriately prevent or treat acute or chronic pain.

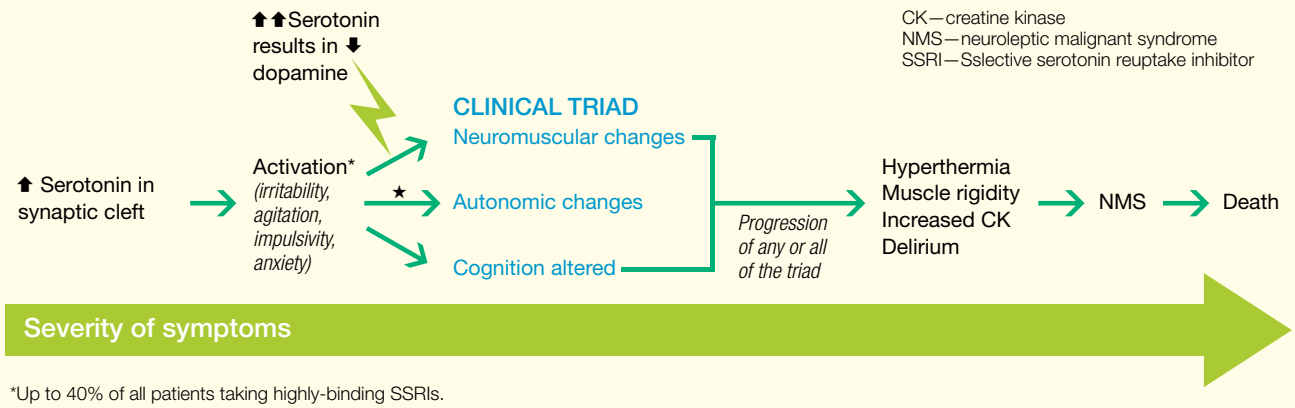
Serotonin syndrome

Serotonergic agents are used in psychiatry, medicine, and infectious diseases, as well as in pain management. Serotonin syndrome can occur when a patient with or without a pre-existing psychiatric history is treated with three or more serotonergic agents (Table 1[22-26]).[22] Tightly-binding serotonergic agents (eg, escitalopram, citalopram) may cause an increase of serotonin at the synaptic cleft within two hours of administration, with a downstream decrease in serotonin and a corresponding decrease in dopamine and increase in norepinephrine (Figure 1[23]).[22] Patients with serotonin syndrome experience a classic triad of symptoms including autonomic instability (eg, increased heart rate and blood pressure, diaphoresis), cognitive changes (eg, agitation, confusion), and neuromuscular changes (eg, arm, leg or eye twitching).[22] About 0.3% of patients with serotonin syndrome will die if they are not treated.[27] Agents with the highest serotonin release appear to be fentanyl and tramadol, while the lowest incidence of serotonin syndrome occurs with hydromorphone.[20,28,29] Pharmacists can use the mnemonic SCANDIAN as an easy way to remember what happens with serotonin syndrome. Patients experience Serotonin increase, altered Cognition, Autonomic changes, Neuromuscular changes, Delirium, Irritability/Impulsivity, Agitation, and Neuroleptic malignant syndrome.[23] It is paramount for pharmacists to minimize exposure to analgesics with serotonergic properties in patients who are already being treated with three or more serotonergic agents.

Delirium

Patients who develop delirium or a decline in cognition and attention have a high incidence of morbidity and mortality. This is a life-threatening, but potentially treatable complication in the postoperative setting.[30] Morbidity may be associated with an escalation of the underlying medical condition itself or, less

FIGURE 1 Serotonin syndrome[23]



*Up to 40% of all patients taking highly-binding SSRIs.
★Increases in norepinephrine secondary to effects of accelerated breakdown of dopamine via β-hydroxylase (hypothesized).

Figure 1 originally appeared in Lamoure J, Stovel J. Serotonin syndrome: a perfect storm. How to prevent, recognize and manage serotonin syndrome. Pharm Pract 2011;27(1):22-26,30-1.

likely, due to the decline in cognition and attention.[31] The incidence of postoperative delirium cannot be exactly quantified, as a subclinical presentation occurs, in which patients exhibit confusion and altered cognition.[30] It is estimated that 10%–30% of postoperative patients will develop delirium after hospital discharge, and 15%–53% of elderly patients in an outpatient surgical setting will experience delirium.[30,32]

Delirium is a transient, usually reversible, cause of cerebral dysfunction; it manifests clinically with a wide range of neuropsychiatric abnormalities.[33] It is commonly mistaken for dementia, depression, mania, acute schizophrenic reaction, or simply "old age."[32] An imbalance in neurotransmitters is believed to cause postoperative delirium. This imbalance may be secondary to dehydration or altered renal function (from the surgery itself) or medications that have anticholinergic effects (eg, dimenhydrinate), sedatives that act on gamma-aminobutyric acid, or analgesics that act on dopamine or serotonin (which overlaps with the neurotransmitters involved in depression and psychosis).[34]

A final point for pharmacists to recognize is that in patients with pain and concurrent psychiatric conditions, the emotional symptoms of pain management, including well-being and nonsomatic depressive symptoms, are more resistant to treatment.

Pain management challenges in patients experiencing postoperative delirium include appropriate medication selection and the occurrence of an inflammatory response with increased cytokine and tissue necrosis factor production, which may be linked to an increased risk of depression, a change in functioning, and changes in blood-brain barrier permeability.[34,35] The updated Beers Criteria indicate that several medications should be avoided in delirium, and also in dementia. These include (but are not limited to) anticholinergics, which may be used for nausea postoperatively, meperidine, pentazocine, and benzodiazepines.[36]

Polymorphisms and drug interactions

Genetic polymorphisms are an emerging important factor to consider when optimizing analgesic therapy. White patients have a one in six probability of possessing a genetic polymorphism that impairs or induces their ability to metabolize medications through the CYP450 system.[37-39] The CYP drug-metabolizing enzymes include CYP1, CYP2, and CYP3. To date, genetic variations have been noted in the CYP2 and CYP3 systems.[39,40] The best studied variant is within the CYP2D6 system; 6%–10% of whites, 4% of African-Americans, and < 1% of Asians have allelic variants or duplications of the alleles that affect metabolism.[37]

When a patient who is a poor metabolizer of a CYP enzyme (eg, CYP2D6) is given a prodrug (eg, codeine or tramadol), the patient will not be able to metabolize the prodrug to its active analgesic form. This could lead to lower analgesic efficacy, resulting in acute pain and establishment of psychological fear surrounding the pain experience.[41] On the other hand, toxicity may result in a patient who is an ultrarapid metabolizer.[42] Other notable polymorphisms include the Han Chinese, who lack the CYP2B6 isozyme, and Southeast Asians (eg, Thailand, Burma) who are at an increased risk of missing the CYP2C19 isozyme.[43,44]

Since personalized medicine is in its early stages of development, we are often unable to access the resources needed to determine changes to the CYP450 or UDP-glucuronosyltransferase (UGT) systems. Even when these tests are available, it is difficult to determine the exact meaning of the altered drug metabolism and implications to the patient. Clinically, the authors use a combination of a good drug metabolism table, guidelines on polymorphisms, and patient questioning. In the patient interview, we ask about unusual side effects to medications. This helps to determine whether the patient has experienced an unusual response to a medication and increases our suspicion that there may be an underlying polymorphism. For example, patients who report no pain relief and just constipation with codeine may be poor CYP2D6 metabolizers, as only the

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component of codeine that is metabolized to morphine has analgesic properties while codeine in isolation is associated with constipation.

Mr. X's postoperative agitation, confusion, and development of visual and auditory hallucinations could be secondary to the buildup of higher than usual levels of serotonin from the tramadol in his acetaminophen–tramadol tablets. Contributing factors could be Mr. X's age and concurrent chronic kidney disease, which has resulted in decreased hepatic and renal clearance of tramadol. Consequently, it would be prudent to select an alternate analgesic for his moderate pain. Given Mr. X's history, the agent of choice for his postoperative pain control would be hydromorphone 0.25–0.5 mg orally q4h prn. Following the discontinuation of acetaminophen–tramadol and a switch to hydromorphone, Mr. X's agitation, confusion, and hallucinations resolve and he is able to partake in the physiotherapy required for his rehabilitation and return home.

Conclusion

Community and hospital pharmacists are well placed to help optimize pain management by considering patients' other medical or psychiatric conditions and the medications they are receiving for those conditions. Insufficient attention to analgesic selection may cause patients to experience both short-term and long-term negative outcomes in what is often already a challenging point in their lives. Short-term effects include impaired quality of life and acute pain, while longer term consequences include potential development of a pain-fear complex that can lead to anxiety or other complications. As such, effective pain medication selection should be preceded by a thorough medical and psychiatric history. Care must be exercised in special patient populations such as the young or elderly, or in situations of renal impairment, polymorphisms, polypharmacy, or a history of a psychiatric condition.

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