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Pharmacovigilance of the Analgesic Therapy

Silvia Ussai

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Abstract

Analgesics, the cornerstone for the alleviation of both acute and chronic pain, represent one of the most used classes of medications. While they are essential for the improvement of patients' quality of life, analgesic use is often associated with adverse drug reactions (ADRs) that might affect their usability in particular clinical situations. This indicates that a detailed knowledge of analgesic-derived ADRs is essential for the planning of an efficient pain relief strategy. This chapter reviews the ADRs associated with the two most commonly used analgesic classes, opioid and nonsteroidal anti-inflammatory drugs (NSAID), discussing their common adverse effects and how these can influence their usability in clinical applications. With the publication in recent years of more and more long-term studies, this chapter also provides an overview of the potential risks of long-term analgesic use. This is particularly important for opioid analgesics, whose chronic use can lead to analgesic tolerance and addiction. A full description of potential problems deriving from analgesic use represents the first step in optimizing protocols for its safe application in clinical settings.

Keywords: Opioids, NSAID, ADRs, Analgesics, pharmacovigilance

1. Introduction

Pain relief, both for acute and chronic pain, is an important aspect of modern medicine and healthcare services [1]. Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' by the International Association for the Study of Pain (IASP) [2]: as such, it strongly worsens the quality of life of patients and remains one of the most common reasons for using health care services [1]. Pain relief drugs in the form of analgesics represent one of the most commonly used medications. While analgesics may include different therapeutic active compounds,

covering specific pain relief needs, opioid medications and nonsteroidal anti-inflammatory drugs (NSAIDs) remain the most commonly used analgesics [1, 3, 4].

Pain relief management teams have to be aware of the exact nature of the pain itself and its intensity, and must be able to differentiate between acute and chronic pain. These are not only essential factors for pain management itself, but this could also lead to the consideration of possible adverse drug reactions (ADRs) from analgesic use. Indeed, when implementing pain relief management, one must consider the best practice to alleviate pain directly, along with the possibility of having ADRs which would then defeat the purpose of analgesics use itself [5–8]. Additionally, chronic pain is associated with an increased incidence of mental health issues such as anxiety and depression [9]; thus, there is a need to extend the consequences of inefficient pain relief beyond pain management alone.

The proper use of analgesics, that is, targeted drug use against specific types of pain, can avoid or at least minimize ADRs. In this regard, scientific studies reporting on ADRs caused by analgesics become an invaluable tool to predict and prevent ADRs and to evaluate the safety of analgesics in different pain relief practices. While short-term side effects are generally easier to observe, long-term effects, particularly in chronic analgesic users, need specially designed studies or a careful review of previous literature. In the last few years, more literature has been made available that addresses ADRs of both the opioid and NSAID type, allowing for the re-evaluation of the safety of these two medication classes, including their chronic long term use [10–16].

In order to draw attention to analgesic an their risks and to minimize the negative consequences related to their use, the present review comprises a synthesis of the most important safety issues described in scientific literature. This stands as a broad overview of the topic, providing a basic understanding of safety issues associated with analgesics and a starting point for further understanding of the subject at hand.

The ADRs associated with the two most commonly used analgesic classes, opioid and nonsteroidal anti-inflammatory drugs (NSAID), discussing their common adverse effects and how these can influence their usability in clinical applications. In recent years, more and more long-term studies have been published providing an insight into the potential risks of long-term analgesic use, this chapter provides a thorough overview. This is particularly important when discussing opioid analgesics, whose chronic use can lead to analgesic tolerance and even addiction. A full description of the potential problems derived from analgesic use represents the first step in optimizing protocols for its safe application in clinical settings.

2. Opioids

The use of opioids has significantly increased during the last decade and concomitantly the occurrence of related ADRs has become more frequent [3, 17]. Opioids are, by definition, ligands for opioid neuroreceptors, thereby modulating them and their associated responses [3]. With opioid receptors controlling a variety of physiological processes, exogenous opioid

application results, therefore, in an imbalance in receptor activity and a potential plethora of side effects.

Sedation is a common short-term ADR because of the anticholinergic effect of opioids. Drowsiness, sedation, nausea and vomiting could all be seen after treatment with opioids, and usually occurs in dosage transition states. Sedation represents the best early clinical indicator of respiratory depression [18]. A number of blind studies confirm this effect which seems particularly evident for methylphenidate [19–21].

On the other side of the spectrum, opioids also appear to disturb the normal sleep cycles. This is likely due to the interference of this class of molecules with the action or binding of sleep-related neurotransmitters, such as noradrenaline, serotonin, acetyl choline, dopamine, histamine and gamma-aminobutyric acid [22]. Although this effect appears to be limited to the depth of sleep and duration of the REM (Rapid eye movement) phase rather than the quality of sleep itself [23, 24], this factor might be worth considering when opioid treatments worsen sleep disturbances derived from an underlying condition.

Constipation is also a common side effect reported in opioid users, due to the activation of mu receptors and the consequent modulation of gut motility [25]. Opioid-induced constipation is very diffused, with a single opioid treatment alone being able to induce constipation [26], this condition does not improve over time, and so its management should be planned in advance before the start of an opioid regimen. In recent studies, the naloxone-oxycodone combination has been shown to reduce constipation [25, 26], which favours an improved quality of life for patients.

Long-term use of opioids may also lead to additional complications, for example a hormonal imbalance [27, 28]. These ADRs are well known in the medical arena, to the point where the terms opioid endocrinopathy (OE) and opioid-induced androgen deficiency (OPIAD) both appear in the literature. Opioid users often display an imbalance in estrogen, testosterone, adrenocorticotropin, cortisol, and corticotropin-releasing hormone, luteinizing hormone, gonadotrophin-releasing hormone, dehydroepiandrosterone and dehydroepiandrosterone sulphates. This accounts for the increase reports of depression and sexual dysfunction among both sexes, while women are also at risk of a potential loss in bone mineral density [27, 28].

A well-known complication of opioid use is the potential development of physical addiction and opioid tolerance [29]. Both short- and long-term opioid use can induce these problems and due to the fact that they particularly affect chronic pain patients, incorrect use of opioids in this group of users could become both dangerous and ineffective.

Opioid tolerance is dependent on both the patient and the specific opioid employed [30]. This means that tolerance developed for a specific opioid does not automatically affect the efficacy of another opioid medication. However, in conjunction with the risk of hyperalgesia [31], which is, an increase in pain sensitivity also present in opioid users, this might still lead to an abuse of prescription medication, a particularly sensitive topic in opioid research.

Pruritus is another common adverse effect of opioids, more frequent with the parenteral route than oral. Opioid-induced pruritus is primarily mediated by mu-opioid receptors, serotonin

receptors and to a lesser extent by histamine. The first-line treatment for pruritus should include low-dose nalbuphine, low-dose naloxone and ondansetron; antihistamines are less efficient. In addition to these common side effects, there are also ADRs for specific opioids. The most common ones are summarized in **Table 1**.
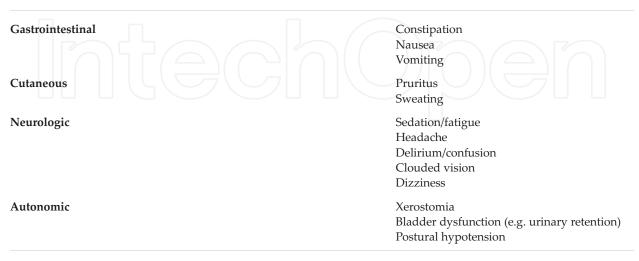
Gastrointestinal	Constipation
	Nausea
	Vomiting
Cutaneous	Pruritus
	Sweating
Neurologic	Sedation/fatigue
	Headache
	Delirium/confusion
	Clouded vision
	Dizziness
Autonomic	Xerostomia
	Bladder dysfunction (e.g. urinary retention)
	Postural hypotension

Table 1. Most commonly reported opioid-induced side effects [3].

To further reduce the ADRs caused by opioid administration, several measures have been suggested in the form of guidelines to ensure that an effort is being made on the part of the health care providers to reduce the amount of ADRs that occur with opioid drug administration.

The health care provider must ensure that before prescribing opioids to a patient, one has thoroughly documented the patient's diagnosis, medical well-being at the time and more importantly their psychological, psychiatric and social state, including whether or not the patient has abused any drugs in the past.

A patient who is now presenting with a pain condition should be asked questions regarding any previous medical or surgical treatments that may have been performed, along with clarifying and quantifying the present intensity of pain and how this may be affecting their daily activities of living.

Along with the patient's present physical state of health, a health care provider would also find it beneficial to inquire on the patient's living conditions, whether or not the patient has easy access to family and/or social support, and if the patient currently has a job or any domestic duties.

The psychiatric status of the patient is especially important. Knowing whether or not there has been a diagnosis of any psychiatric disorders in the past and how they were treated can greatly reduce the chances of the related ADRs or opioid addiction; some guidelines suggest to initiate with a low opioid dose and monitor the patient daily [32] when dealing with a patient who has a co-morbid psychiatric condition or a family history of psychiatric disorders.

Furthermore, substance use history is vital to formulate a comprehensive knowledge of the patient. A physician should inquire on the patient's history of substance use, abuse and addiction, namely marijuana, tobacco, benzodiazepines, opioids themselves, cocaine, amphetamines, barbiturates, hallucinogens and solvents.

After gathering all the information necessary to formulate a management plan, the physician should use this information to perform risk screening for the patient, assessing the potential for opioid drug misuse, overdose and addiction, looking at aberrant drug-related behaviours and if necessary, employing a urine drug screening.

Patients and their health care providers should then initiate goal setting in order to find out what the patient's goals are and how feasible the treatment could be, along with fully documenting what specific goals have been agreed on by the patient with the health care provider.

Additionally, documented informed consent for the use of opioids is suggesting, enabling the doctor and patient to explore the benefits, adverse effects. Medical complications and risks that may be encountered during the course of opioid treatment should also be determined and discussed with the patient, especially with high risk groups including the elderly, adolescent, pregnant, breastfeeding and those with co-morbid psychiatric conditions and those on long-term opioid treatment.

Moreover, one should verify and confirm that they have selected the most appropriate opioid for treatment of their patients, this should be done using peer-reviewed evidence which specifies which drug and what dose is used for first, second and third line treatment for the specific pain condition that the patient has.

After reviewing current data on the topic and starting a treatment regimen, one should continuously monitor the dose of opioid being given. If the patient is taking a dose on the higher end of the scale, the health care provider should re-asses the patient's pain condition to note if the medication is effective at reducing the pain (at least 30% reduction), and are there any non-opioid treatment options available.

Also, the doctor should clarify that all mental health disorders are adequately treated, that any ADRs are being managed and lastly if there is any sign of abnormal drug-related behaviours, the physician should then taper or switch the medication appropriately. After all these precautionary measures are taken, one should remember that arranging a consultation with an expert in pain or addiction management is always an option that could only benefit the patient greatly [33].

Health care providers should also consider alternative recommendations to replace long-term opioid treatment. Over the counter alternatives include acetaminophen and low dose NSAIDS. Although NSAIDs carry the well-known risk of organ failure and ulcer formation, NSAIDs at high doses are effective means of pain relief. Corticosteroids, serotonin inhibitors and norepinephrine inhibitors are all pharmacologic agents that can help alleviate pain.

Other measures which could be employed to reduce pain, with little to no risk to the patient, include the use of steroid injections for musculoskeletal pain, physical therapy, massage, exercise and chiropractic care [34].

3. NSAIDs

NSAIDs are generally considered non-specific analgesic medications and these are commonly prescribed for inflammation-derived acute pain. This class of drugs acts mainly through the inhibition COX (cyclooxygenase) synthesis, this then leads to a decreased in the synthesis of prostaglandin [35]. Being widely diffused, NSAIDs are often used in combination with further on-going treatments, leading to final effects dependent on drug-drug interactions [1]. However, prescribers should take into account the intrinsic risk of NSAIDs' ADRs (**Table 2**).

1. Gastrointestinal bleeding

2. Cardiovascular disease

3. Stroke

4. Thrombotic disease

5. Arrhythmia

Table 2. The intrinsic risk of ADRs associated with NSAIDs [7, 40].

Complications involving the gastrointestinal tract as a consequence of NSAID use are common, especially in combination with the presence of risk factors [36]. NSAIDs exert their effects through the inhibition of COX and the pharmacological inhibition of COX (both 1 and 2 isoenzymes) works to provide relief from the symptoms of inflammation and pain.

This NSAID-induced decrease in prostaglandin synthesis is responsible for side effects such as dyspepsia, abdominal pain, nausea, vomiting, heartburn, haemorrhage (NSAIDs could also lead to prolongation of bleeding time and a significantly increased risk of haemorrhage by altering vascular homeostasis), ulceration, perforation or obstruction [37].Therefore, COX-2 specific inhibitors, for example celecoxib, have a lower risk of causing gastrointestinal related ADRs [38].

NSAIDs are also a cause of renal complications. Acute renal failure is a possible consequence of NSAID use. While this is an intrinsic risk of NSAID medications, it is more likely to occur in geriatric patients and in patients using enzyme inhibitors (ACEIs) or angiotensin receptor II blockers [39]. NSAIDs are the class of medicines that are most commonly associated with hypersensitivity reactions. Because of this, it is generally not recommended to use NSAIDs even after having an unrelated hypersensitivity reaction or having positive allergy tests. NSAID-triggered hypersensitivity reactions can result in respiratory complications or in dermatological problems [40, 41].

Long-term NSAID use is often associated with cardiovascular complications such as strokes and myocardial infarctions, especially with COX-2 inhibitor therapy. This is an important factor to consider in patients with pre-existing cardiovascular diseases, where the use of NSAIDs could potentially worsen their condition, especially in combination with other drug treatments [42, 43]. Liver toxicity is also commonly associated with NSAID use, in particular nimesulide, making this medication particularly unsuitable for long-term applications in patients affected by chronic conditions [44].

Health care providers should also ensure that NSAIDs are prescribed properly and monitored closely considering the aforementioned ADRs; this can be done by precision treatment of patients.

Physicians should first consider prescribing the lowest effective dose of NSAIDs to those who have not found alleviation of pain after taking paracetamol. Patients who require NSAIDs have to be treated according to their gastrointestinal risk profile, because the use of NSAID is associated with increased ADRs of the entire GI tract, thus increasing mortality. Therefore, a gastro-protective pharmacologic agent such as misoprostol should be prescribed along with the NSAID even though it may not completely eradicate the risk of ADRs such as bleeding, the incidence of ulcer disease will be reduced [45].

Furthermore, physicians should be precise when evaluating patients for NSAID therapy especially in patients with existing cardiovascular conditions as the use of these medications could increase the risk of cardiovascular events occurring. Namely, celecoxib carries the highest risk of coronary artery events at high doses and thus one should consider an alternative like naproxen in place of its use [45].

4. Acetaminophen

Acetaminophen is often used as the first-line treatment for pain relief for many diagnoses across the fields of medicine, globally. As an over the counter medication, it is either prescribed by a doctor or bought by patients. The patients either complete the course as directed or they continue buying and self-treat with the medication, managing the doses on their own and subsequently increasing the dose with increasing pain. This behaviour, which is encouraged by some physicians, can be fatal and has been proven to be useless in most cases of long-term chronic pain management [46].

It is now known that acetaminophen is not effective in substantially reducing chronic pain conditions such as osteoarthritis, back pain or post-operative pain [47, 48]. A careful, systematic and thorough review of acetaminophen use becoming a public health and ethical concern must be gauged in depth across the globe. When one considers the ADRs associated with its use, acetaminophen as a first-line treatment for chronic pain seems to call for further evaluation; ADRs such as liver failure can occur in any patient demographic regardless of pre-existing conditions ranging from abnormal liver enzyme profiles to requiring liver transplantation.

Of note, hepatotoxicity is considered when more than 4 gm of acetaminophen have been administered in 1 day [49], but there have been cases of liver injury occurring even at lower doses [50]; geared with this information, physicians should begin to re-evaluate their stance on acetaminophen being completely safe for use with patients at home, regardless of their liver health status and especially in the setting of long-term chronic pain management.

5. Adjuvant therapy

Adjuvant analgesics are defined as drugs with a primary indication other than pain that have analgesic properties in some painful conditions. The group includes numerous drugs in diverse classes. Although the widespread use of these drugs as first-line agents, the term "adjuvant" is a misnomer, they usually are combined with a less-than-satisfactory opioid regimen, in particular when administered for cancer pain. Some adjuvant analgesics are useful in several painful conditions and are described as multipurpose adjuvant analgesics (antidepressants, corticosteroids, α_2-adrenergic agonists, neuroleptics), whereas others are specific for neuropathic pain (anticonvulsants, local anesthetics, N-methyl-D-aspartate receptor antagonists), bone pain (calcitonin, bisphosphonates, radiopharmaceuticals), musculoskeletal pain (muscle relaxants) or pain from bowel obstruction (octreotide, anticholinergics).

Antidepressants, namely triclyclics (TCAs), which are used as adjuvants for pain management, can sometimes cause lethal cardiotoxicity as an ADR. In order to reduce the likelihood of this, the prescribing physician is advised to order an electrocardiogram in those patients with a history of heart disease, or simply provide a better tolerated alternative, such as desipramine and nortripltyline. Orthostatic hypertension, acute glaucoma and cognitive impairment are also ADRs caused by TCAs which can be avoided by screening patients for pre-existing conditions and previous episodes of these diseases in order to reduce the likelihood of a reaction [51].

Corticosteroids, although well tolerated at moderated doses, can cause ADRs such as increasing the risk of peptic ulcer disease at a higher prolonged dose. One way to ameliorate this side effect is by prescribing a gastro-protective formulation, hence reducing the possible damage to the gastric lining [51].

Medications in the α_2-adrenergic drug class (clonidine and tizanidine) are only used as a last resort adjuvant, due to their serious side effects [51] which include somnolence and hypotension.

Olanzapine, along with other neuroleptics, are also used as an adjuvant only in cases where the patient is being treated for dementia or agitation. ADRs caused by olanzapine including tardive dyskinesia and neuroleptic malignant syndrome greatly reduce the quality of life of patients, which is undesirable [51].

Anticonvulsant drugs are now widely used to treat cancer-related neuropathic pain. Gabapentin and lamotrigine have both been proven to improve the condition of patients with neuropathic pain but these also cause side effects such as somnolence, dizziness and unsteadiness [51].

Calcitonin, another adjuvant, may cause a hypersensitivity reaction at the onset of administration when given subcutaneously, this requires skin testing, but has been identified, along with nausea as a minor side effect when used as an adjuvant in palliative care [51].

Radionuclide pharmaceutical agents have been used to treat metastatic bone disease, namely strontium and samarium, but using these medications can lead to myelosuppression, a severe unwanted ADR [51].

Therefore, it can be said that adjuvants also present with their own pertinent adverse drug reactions that could damper the overall effectiveness in improving the condition of a patient with long-term use, which does not improve the patient's quality of life.

6. Conclusions

Analgesics are essential pain relievers in modern medicine. However, analgesic misuse and their adverse effects can affect the efficiency of pain treatment and the eventual outcome could reduce the quality of life of patients. This review aims to highlight the most common adverse drug reactions of analgesic treatments and the possible safety risks involved with their use. Drug-drug interactions can be sometimes responsible for the adverse effects. However, a significant proportion of analgesic ADRs are preventable, which would reduce the patients' suffering. Acknowledging potential safety problems represents the first step for health professionals in assuring a safe and efficient analgesic treatment with minimum risks to patients. But being aware of the potential risks of the drugs should not be an impediment for health professionals to initiate analgesic therapy when necessary.

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