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CANNABIS AND OTHER ADJUVANTS: THEIR IMPLICATIONS IN MODERN MANAGEMENT OF PAINS

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ABSTRACTS

Pains have recently been defined as unpleasant sensory and emotional experiences associated with, or resembling that associated with actual or potential tissue damage. Pain may arise from a disease process or healthcare interventions and adversely affects multiple organ systems far from its site of location. Effective pain relief is highly desirable for the patients and healthcare providers as it impacts on outcome and improves quality of life. Conventional analgesics have traditionally been the mainstay of pain management, but unsatisfactory pain relief and troubling unwanted effects have led to the unending search for more efficacious and safer remedies. Adjuvant analgesics are drugs with beneficial analgesic effect but, primarily not developed as analgesics. The use of adjuvants in augmenting analgesia and in the management of refractory chronic pain is not new. Opioids have been the mainstay of severe acute postoperative pain associated with surgery but the troubling unwanted effects such as nausea, vomiting, respiratory depression, drowsiness, constipation and pruritis have continued to be of concern as they impair recovery and rehabilitation. Analgesic adjuvants enable better pain management with reduction in opioid dose and their concomitant unwanted effects. Neuropathic pain and other forms of chronic pain present a peculiar challenge to healthcare with their epidemiological enormity and associated disability thus, shortcomings of conventional analgesics are more glaring. Consequently, recommendations for multimodal analgesia have been widely canvassed with the understanding that their different mechanisms of action will provide coverage of a wider spectrum of pain inputs, enhancing efficacy by synergism. Conclusively, the current trends in surgical practice, especially the relentless expansion of ambulatory surgery and enhanced recovery after surgery (ERAS)/fast-track care pathways have profoundly impacted the choices in pain management. The direct and indirect effects of prescription opioid on the opioid epidemic and the sharp rise in deaths from opioid overdose is also of increasing concern and have necessitated a critical review of their risk-benefit analysis and ignited the search for more efficacious and safer alternatives. As clinical and research interests in patients' safety, satisfaction and quality of life evolve, further development of adjuvant analgesics will be expected to fill the existing gap in pain management. Expectedly too, as more jurisdictions approve a legal framework for its use, the intense interest in medicinal cannabis which is increasingly becoming popular in management of intractable chronic and neuropathic pains could be better explored.

KEYWORDS: Pains, Analgesics, Adjuvants, Opioids, Cannabis, Neuropathic pains.

INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[1]

Recently, this definition was revised to "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[2]

Pain is a subjective experience best described by subjects themselves. Pain may generally be described as acute pain or chronic pain, nociceptive and neuropathic. Acute pain is essentially nociceptive, arising from tissue injury and often serves as a protective response to an injury. The duration is often short, typically lasting less than 3 months; such as trauma pain or surgical pain. On the other hand chronic pain persists for more than 3 months or long after the trauma or surgical wound has healed. Chronic pain may be; (i) nociceptive from sustained inflammation following tissue injury or (ii) neuropathic following injury to nerve, spinal cord or brain. It includes osteoarthritis, cancer pain, chronic low back pain, post-herpetic neuralgia, trigeminal neuralgia, painful diabetic neuropathy, complex regional pain syndrome, neuropathic pain- trigger points/myofascial pain, surgical scar pain, chronic persistent pain and chronic non-specific pain syndrome.

Neuropathic pain could be caused by injury, lesion or diseases of the somatosensory system which may be peripheral or central. Neuropathic pains present a major challenge in healthcare afflicting about half of the patients attending pain clinics[3], yet only some 40-60% of these patients achieve partial relief with current treatment.[4]

Types of neuropathic pain are painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, phantom limb pain, neuropathic pain after surgery and human immunodeficiency virus (HIV) infection. It has also been reported with COVID-19 infection.[5] Neuropathic pain is commonly seen in cancers resulting from direct tumour compression on peripheral nerves, or as a complication of chemotherapy (chemotherapy-induced peripheral neuropathy), or radiation injury (radiation-induced peripheral neuropathy).

It has since been established that opioids which have been the mainstay of management of moderate to severe pain are insufficient for neuropathic and cancer pains.[6,7] Alarmed by the opioid epidemic and deaths from opioid overdose[8-11], the contribution of prescription opioid to the opiod crisis has come under focus.[12-14] Along with their potential for addiction and worrisome adverse effect profile the inappropriate medical use of opioids is being called to question, while the search for opioid-sparing analgesic alternatives has intensified.

The Pain Pathway

Pain originates through signaling pathway which begins in the periphery (The nociceptors sense thermal, mechanical and chemical insults and relay via alpha, delta and C fibres), ascend through the dorsal horn of the spinal cord and arrive in the thalamus before relaying in the cortex of the brain (See figure 1).

The basic processes in pain experience involves four components; transduction, transmission, pain modulation, and perception. The "free nerve endings" are the nociceptors which on activation transduce chemical and mechanical peripheral impulses to electrical signals that are transmitted through the first, second and third order neurons to the cerebral cortex for pain perception.[2]

However, peripheral, spinal and supraspinal modulation greatly modify the pain experience, through inhibitory or excitatory influences. The dorsal horn of the spinal cord is the principal site of pain modulation by both ascending and descending neural pathways; facilitated by excitatory(substance P, glutamate, aspartate) and inhibitory (noradrenaline, serotonin, endorphins, encephalins, glycine, γ-aminobutyric acid, acetylcholine) neurotransmitters. Most of the supraspinal descending fibres that inhibit pain in the spinal cord dorsal horn originate from the periaqueductal gray, reticular formation and nucleus raphe magnus, mediated by noradrenaline, serotonin, β-endorphins and encephalins.[2]

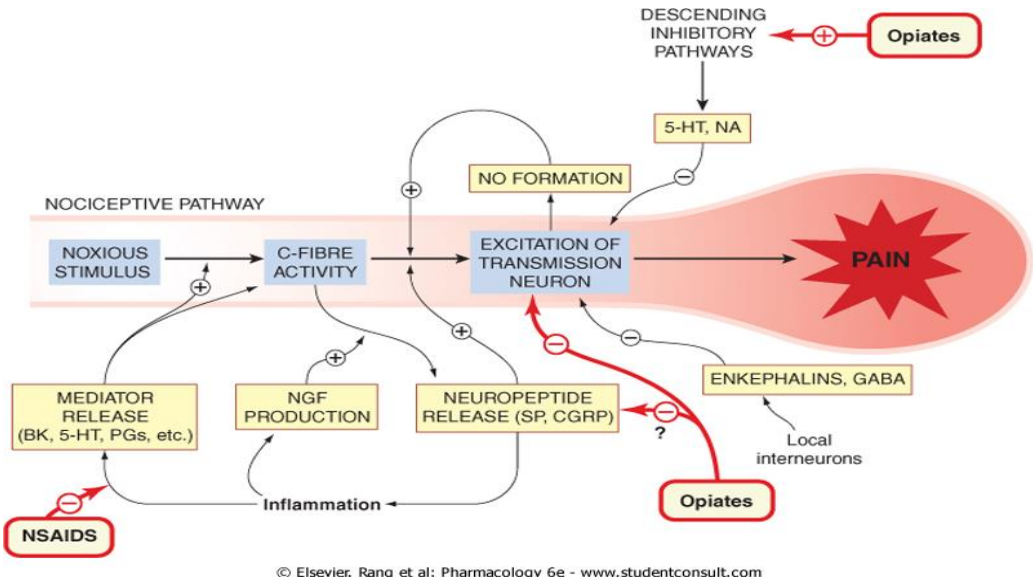

Fig 1: Pain pathway and site of analgesics. Adapted from Azikiwe., 2022.

Consequences of pain

The consequences of pain are widespread, and beyond the socially unpleasant discomfort associated with pain. It may involve several systems of the body with poor sleep, depression, poor appetite, delayed gastric emptying, hypertension, myocardial infarction, hypoventilation, cough suppression, atelectasis and hypoxia, constipation, ileus, urinary retention, nausea and vomiting. Others include anxiety, depression and decreased libido.

Poor wound healing, hypercoagulability of the blood with deep vein thrombosis and pulmonary embolism, immunosuppression and postoperative delirium in the elderly all contribute to the morbidity.

In many patients, a chronic pain syndrome may develop as a consequence of acute pain.[15] Chronic pain has been associated with psychosocial distress, worse limitations in activities of daily living and more rapid cognitive decline in the elderly. The association between pain and excess mortality has long been established, but this is even more pronounced with disabling pain in the elderly.

Drugs management of pains: Drugs used in pain can broadly be classified into steroidal and non steroidal analgesics. Non steroidal can further be divided into NSAIDS, Acetaminophen and paracetamol. The steroidal essentially consists of opioids. The individual members of the various classes may be used independently or as component of broad multimodal analgesic regime. Two members of the same class may not be used together as toxicity and intolerable adverse effects readily occur.

The NSAIDs provide pain relief and suppress inflammation by inhibiting the cyclo-oxygenase (COX) pathway and preventing the conversion of arachidonic acid to prostaglandins. While the older NSAIDs such as aspirin, ibuprofen, diclofenac, indomethacin and piroxicam are non-selective, inhibiting both COX-1 and COX-2 enzymes, the newer NSAIDs (celecoxib, parecoxib, valdecoxib, etoricoxib) selectively inhibit COX-2. The NSAIDs may be used orally, parenterally or topically, but the non selective COX inhibitors have been implicated in gastrointestinal bleeding and analgesic nephropathy. The COX-2 inhibitors were developed in the hope that by inhibiting inflammatory prostaglandins derived from COX-2 while sparing gastroprotective prostaglandins primarily formed by COX-1 they would offer better gastrointestinal tolerability. But they too have been implicated in cases of gastrointestinal bleeding and perforation, but of a lower incidence compared to the older NSAIDs. There is also safety concern with the COX-2 inhibitors regarding thromboembolic incidents such as heart attacks and stroke, especially in patients with pre-existing cardiovascular risk factors.[15] With the sulfonamide group present in celecoxib and valdecoxib, these COX-2 inhibitors should be avoided in patients that react to sulfur-containing drugs.[15]

Opioids are drugs that act on opioid receptors; μ, δ, κ and nociceptin opioid receptors. Opioid analgesics include morphine, pethidine, fentanyl, remifentanil, sufentanil, tramadol, pentazocine, codeine, dihydrocodeine, hydromorphone, oxycodone, methadone and dextromethorphan. Opioids are principally used for pain management but some are also used as anti-tussives and in the symptomatic control of diarrhoea. The potent opioids such as morphine, fentanyl and pethidine are widely used for the management of acute perioperative pain and sedation in critically ill patients. The common side effects of opioid analgesics include sedation, euphoria, respiratory depression, pruritis, constipation, nausea and vomiting.[16]

Naloxone, a non-selective and competitive opioid receptor antagonist is the antidote for opioid respiratory depression and opioid overdose but also antagonizes the analgesic effect of the drugs. Since the effect of naloxone is short-lasting, multiple doses may be necessary as the duration of action of most opioids is longer than that of naloxone. Opioid addiction has become a major public health menace.[16]

Adjuvant analgesics: Adjuvant analgesics are medications originally developed and used for indications other than pain control but which have beneficial analgesic effects. They may have independent analgesic effect or additive analgesic properties when used with conventional analgesics. Adjuvant analgesics reduce the dose and side effects of conventional analgesics, while increasing analgesic efficacy. They are widely used, especially in the management of chronic pains where they are frequently first-line. Adjuvant analgesics include some classical antidepressants, classical antipsychotics, anticonvulsants, anxiolytics, methyl xanthenes, corticosteroids, centrally acting skeletal muscle relaxants, centrally acting antihypertensives and now cannabis.[2,17]

The evolution of chronic pain often involves alteration of the pain modulatory pathways, with an imbalance between the descending facilitatory systems and the descending inhibitory systems. Impairment of the modulation by endogenous analgesic descending noradrenergic pathways is associated with pain chronicisation, and the TCAs, serotonin and noradrenaline reuptake inhibitors and gabapentinoids exert their analgesic effect for neuropathic pain through enhancement of descending noradrenergic inhibition, and similar pathways. In recent times, the use of adjuvants in the management of acute pain is gaining prominence, with ever increasing prospects. Adjuvant analgesics comprise of a diverse group of pharmacological agents of different classes; Glucocorticoids (dexamethasone, methylprednisolone), Anticonvulsants (carbamazepine, gabapentin, pregabalin), Tricyclic antidepressants (nortriptyline, amitriptyline), Serotonin norepinephrine reuptake inhibitors(duloxetine, venlafaxine), Atypical antipsychotics (olanzapine, quetiapine), Muscle relaxants

(tizanidine,methocarbamol), N-Methyl D-Aspartate (NMDA) -antagonists (ketamine), Antihypertensive (clonidine), Anxiolytics (dexmedetomidine) and Stimulants (caffeine).[18] In recognition of the glaring shortcomings inherent in the management of both acute and chronic pain with conventional analgesics, the World Health Organization (WHO) recommended the incorporation of adjuvant analgesics as part of the regimen in every step of the analgesic ladder.[19] Adjuvant analgesics such as gabapentin, pregabalin, nortriptyline, amitriptyline, duloxetine and venlafaxine have also become the recommended first-line pharmacological treatment for neuropathic pains, over and above the conventional analgesics, by the International Association for the Study of Pain.[20]

Caffeine

Caffeine is an unregulated stimulant which is a component of widely available beverages such as coffee, tea and cola drinks. It is a naturally occurring plant alkaloid, and with its xanthine structure it inhibits phosphodiesterase enzymes, with elevation in cellular cyclic adenosine monophosphate (cAMP) levels. Its stimulant effect is thought to derive from adenosine receptor antagonism which promotes the release of neurotransmitters such as noradrenaline, serotonin, dopamine and acetylcholine. Caffeine may not be better than placebo, if administered alone for analgesia.[21] However, caffeine has proven adjuvant analgesic properties, and for over half a century it has been formulated with acetaminophen, aspirin, codeine and non-steroidal anti-inflammatory drugs for use in acute pain management.[22-25] A recent systematic review and meta-analysis of randomized clinical trials compared the efficacy and adverse effects profile of 17 oral analgesic combinations for pain control following third molar surgery.[26] The satisfactory analgesic efficacy with fewer side effects reported for the ibuprofen-caffeine combination when compared to the other combinations further testifies to the importance of caffeine as an adjuvant in the management of acute post-operative pain. The potential for caffeine use as analgesic adjuvant in the management of some types of chronic pain is currently being explored, with some promise.[27,28,29]

Corticosteroids

Corticosteroids are potent anti-inflammatory agents, which reduce pain by inhibiting prostaglandin synthesis, reducing inflammation, vascular permeability and tissue edema. They were designed for the suppression of harmful inflammatory conditions and autoimmune diseases such as allergic reactions, asthma, septic shock and rheumatoid arthritis. There is increasing use of corticosteroids such as dexamethasone and methylprednisolone in the management of acute pain. The efficacy of systemic corticosteroid in this respect is thought to be dose-dependent, as attested to in a meta-analysis.[30] Until recently, corticosteroids were not being used during surgery owing to concerns regarding immunosuppression, wound infection and poor wound healing. But all that has changed; with both systemic and local infiltration of the surgical site with corticosteroid injections being extensively used as components of multimodal analgesia in critical surgeries such as total knee and hip replacements, without increase in complications.[31,32,33] Historically, corticosteroids have been used extensively in chronic pain management with as much as 41% of cancer patients in a palliative care setting receiving them.[36] They have also demonstrated considerable effectiveness in the treatment of neuropathic pain owing to their ability to reduce spontaneous discharge in injured nerves. Corticosteroids have many potential side effects with long term use; such as hypertension, avascular necrosis of the head of femur, proximal myopathy, cushings syndrome, gastric bleeding, osteoporosis and infections. Consequently, corticosteroids are best used in the short term at the lowest effective dose. As adjuvants they are not used in combination formulation with other analgesics, but as single drug component of multimodal analgesia. Discontinuing corticosteroids used for longer than 2 weeks should involve tapering off to reduce the risk of steroid withdrawal syndrome.

Alpha-2 adrenoceptor agonists

Clonidine

This antihypertensive agent is a partial alpha-2 adrenoceptor agonist. Owing to its central sympatholytic action, it produces anxiolysis and sedation, obtunds cardiovascular response to endotracheal intubation, reduces anaesthetic requirement during surgery and controls perioperative shivering. In the acute setting, it has proven an effective adjunct in enhancing the quality of neuroaxial anaesthesia during surgery and for postoperative pain management, when used with local anaesthetic agents, opioids or corticosteroids. Similarly, it has found extensive use in the management of chronic pains.[37] Troubling perioperative hypotension however remains a problem with its use.

Dexmedetomidine

This novel anxiolytic agent is used primarily for anaesthetic premedication prior to surgery, and for sedation in the intensive care unit. It is a selective alpha-2 adrenoceptor agonist. It reduces anaesthetic requirement during surgery, attenuates cardiovascular response to laryngoscopy and intubation, reduces postoperative nausea and vomiting and controls perioperative shivering. Dexmedetomidine is popular for procedural sedation during colonoscopy, transesophageal echocardiography and awake fibreoptic intubation.[37] Its preference over other sedative agents in the perioperative and intensive care settings is in part due to its property of maintaining cardiovascular and respiratory stability. It is also used in the management of alcohol, opioid and benzodiazepine withdrawal. Its analgesic effect is mediated through activation of alpha-2 adrenoceptors in the spinal cord with reduction in nociceptive transmission. Dexmedetomidine is increasingly used as adjuvant analgesic in several multimodal analgesia

regimen to optimise perioperative pain control, with opioid-sparing benefits. Preoperative, intraoperative, and postoperative administration of dexmedetomidine, via the oral, intravenous, intramuscularly, intranasal or neuroaxial routes have all recorded commendable efficacy in perioperative pain management, with attractive safety profile; in diverse surgical procedures. Hypotension and bradycardia are seldom side effects, but they are much less severe compared with another alpha-2 adrenoceptor agonist, clonidine. Its ever increasing utility has become more pronounced with the recent trend towards Enhanced Recovery After Surgery (ERAS) care pathway.

Antidepressants

Antidepressants are used primarily in the treatment of major depressive disorder and anxiety disorders; such as post-traumatic stress disorder, general anxiety disorder, obsessive-compulsive disorder and panic disorder. The major classes are (i) Tricyclic antidepressants (TCAs); amitriptyline, nortriptyline, clomipramine (ii) Monoamine oxidase inhibitors (MAOIs); phenelzine, isocarboxazid (iii) Selective serotonin reuptake inhibitors (SSRIs); paroxetine, fluoxetine, fluvoxamine, sertraline (iv) Selective serotonin- noradrenaline reuptake inhibitors (SSNRIs); duloxetine, venlafaxine. Antidepressants have become increasingly popular in the management of chronic pain, especially the TCAs and SSNRIs. The greater success recorded with these agents over the SSRIs in chronic pain management may further allude to the relative role of the noradrenergic pathways and serotonergic pathways in chronic pain.

Tricyclic antidepressants relieve neuropathic pain by their non-selective ability to inhibit presynaptic reuptake of serotonin and noradrenaline, with limited effect on dopamine, thereby increasing their concentration in the brain and spinal cord. They also possess NMDA-receptor antagonist activity[38] which may contribute to their analgesic activity in neuropathic pain, since these receptors are involved in the sensitization leading to development of neuropathic pain. There is also evidence for the role of δ -opioid (but not μ- or κ-opioid) receptors in the antidepressant mechanism against neuropathic pain.

While the efficacy of antidepressants and anticonvulsants in the treatment of neuropathic pain may generally be deemed comparable, the adverse effect profiles differ with each group and the individual drugs. Tricyclic antidepressants are categorized as secondary (nortriptyline, desipramine) or tertiary amines (amitriptyline, imipramine). The secondary amines show relatively selective inhibition of norepinephrine reuptake, while the tertiary amines show more balanced inhibition of norepinephrine and serotonin, but they also have greater anticholinergic side effects such as dry mouth, constipation, urinary retention, sedation, weight gain and cognitive impairment; and therefore may be contraindicated in elderly patients. Amitriptyline and nortriptyline have the best documented efficacy in the treatment of neuropathic and non-neuropathic pain syndromes. The SSNRIs have balanced inhibition of serotonin and norepinephrine reuptake, but without blockade of other neuroreceptors that are responsible for tertiary amine TCA side effects. The efficacy of SSRIs for pain treatment is relatively low. A TCA may be preferred for neuropathic pain with coexisting psychiatric morbidity, or if cost is a consideration; but may be avoided in the elderly, or patients with cardiac conduction abnormalities.

Anticonvulsants

Carbamazepine, sodium valproate, gabapentin and pregabalin are anticonvulsants used in the management of seizure disorders. Anticonvulsants limit neuronal excitation and enhance inhibition. Relevant sites of action include voltage-gated ion channels (i.e., sodium and calcium channels), ligand-gated ion channels, the excitatory receptors for glutamate and N-methyl-D-aspartate, and the inhibitory receptors for γ-aminobutyric acid (GABA) and glycine. The first-generation anticonvulsants; carbamazepine and sodium valproate have extensively been used for the treatment of a variety of neuropathic pains, but tolerability and adverse event profile have remained a concern. Carbamazepine is thought to act by enhancing GABA and blockade of sodium channels. Adverse effects include drowsiness, marrow suppression and suicidal ideation. Sodium valproate is thought to increases levels of γ-amino butyric acid in the brain through the inhibition of an enzyme γ-amino butyric acid transaminase. It is also thought to block sodium and calcium channels. Sodium valproate is contraindicated in pregnancy, owing to its teratogenic properties. It is also associated with suicidal ideation and hepatotoxicity, but is generally less sedating than carbamazepine.[37]

Gabapentin and pregabalin are gabapentionoids, the latter having been recently developed as a successor to the former. These second-generation anticonvulsants are both γ-aminobutyric acid analogues and act by inhibiting presynaptic voltage gated-calcium channels widely distributed in the spinal cord and brain, inhibiting calcium release and preventing the release of excitatory neurotransmitters involved in the pain pathways, such as substance P and glutamate. They are recommended first-line treatment for post-herpetic neuralgia and painful diabetic neuropathy (Fornasari, 2017) With their proven opioid-sparing effect and variable analgesic efficacy in the postoperative period, gabapentinoids are increasingly being used too in the management of acute pain.[37,38] In the elderly, or patients with cardiac conduction abnormalities, a gabapentinoid may be preferred on account of better adverse effect profile.

Lamotrigine, another second generation anticonvulsant is not in reckoning as an analgesic adjuvant, but has shown some benefit in patients with trigeminal neuralgia and human immunodeficiency virus-associated neuropathy.

The use of lamotrigine has been limited by potentially life-threatening rashes.

Low-dose antidepressants and anticonvulsants for pain management

It is imperative to note that the analgesic benefits derivable from adjuvants such as antidepressants and anticonvulsants occur at dosages lower than those typically used for their primary indication. For instance, the usual dose of amitriptyline for treatment of depression in adults is 50mg to 150mg per day whereas 25mg to 75 would suffice for its use as analgesic adjuvant. Even, amitriptyline dose as low as 10mg at night provides satisfactory pain relief for chronic neck pain.[39] For carbamazepine 400-800mg/day is used for treating neuropathic pains, as against 800-1200mg/day for epilepsy. Sodium valproate 200 mg daily, or twice daily is used for treating neuropathic pains, as against 400mg twice daily, or more for epilepsy. Gabapentin is titrated from 300mg on day 1 to 300mg thrice daily by day 3 for treating neuropathic pains, as against 300mg thrice daily on day 1, till 600mg thrice daily by day 3, or more for epilepsy. At such low doses the adverse effect associated with the adjuvants are minimal.

Skeletal muscle relaxants

There is high quality evidence that muscle relaxants provide clinically significant pain relief in the short term for acute low back pain. Recent guidelines recommend skeletal muscle relaxants as an option in the pharmacological management of acute and subacute low back pain. As observed with the other classes of analgesic adjuvants, only specific muscle relaxants have been credited with useful analgesic benefits in specific painful states. Skeletal muscle relaxants are a heterogeneous group of medications which are generally well-tolerated, with sedation, blurred vision, dry mouth and weakness being the most common adverse effects. Serious complications are infrequent, but they should be generally avoided in geriatric patients due to the increased risk of injury.

Tizanidine is a central α_2-receptor agonist closely related to clonidine and dexmedetomidine whose role in multimodal analgesia is well established. It has muscle relaxant properties, being commonly used in the treatment of muscle spasms. Tizanidine is thought to principally affect spinal polysynaptic reflexes through its noradrenergic α_2-receptors, resulting in direct impairment of excitatory amino acid release from spinal interneurons. The antinociceptive property of tizanidine had earlier been demonstrated along with clonidine, in rats and dogs. Later studies were to prove that tizanidine has commendable adjuvant analgesic properties in the treatment of acute postoperative pain, acute low back pain and neuropathic pain. Tizanidine is well tolerated, with minimal adverse effects.

Methocarbamol is a centrally-acting muscle relaxant used to treat muscle spasms. Though the precise mechanism of action remains unknown it has no direct effect on the skeletal muscles or the peripheral nerve fibre, but possibly inhibits NMDA receptors. Its efficacy has been evaluated; as a sole analgesic agent, and in combination with conventional analgesics as part of a multimodal regimen. As a sole agent, methocarbamol has proven efficacy in pain control in patients with low back pain. Its use in combination with opioids and non-steroidal anti-inflammatory drugs enhances pain relief, with remarkable reduction in opioid requirements in acute painful muscular spasms, but has not been found useful in the treatment of other acute traumatic pain. It produces lesser degree of sedation than the other skeletal muscle relaxants, but brown or green urine discoloration may cause some concern. It is either prescribed as a sole drug, or in combination with NSAIDS, or paracetamol.

Baclofen (β-4-chlorophenyl gamma-aminobutyric acid) is a GABA analogue, and GABA-receptor agonist, approved for the treatment of spasticity and commonly used in the management of many types of neuropathic pain. Baclofen selectively activates $GABA_B$ receptors. Activation of presynaptic $GABA_B$ receptors decreases calcium conductance leading to a decrease in excitatory amino acid release, while postsynaptic $GABA_B$ receptors increase potassium conductance producing neuronal hyperpolarisation and inhibitory postsynaptic potentials. This combination of decreased excitatory transmission and increased inhibition results in facilitation of segmental inhibition. As baclofen preferentially blocks episodic than continuous pain, its main indication is for the treatment of trigeminal and ophthalmic post-herpetic neuralgia. It is also efficacious in the spasm-associated pain of acute low back syndrome. While it is commonly administered orally, intrathecal baclofen has offered benefit to patients with neuropathic pains where other intrathecal and oral analgesics and adjuvants were ineffective, providing satisfactory analgesia at doses that do not produce motor dysfunction.[39] Baclofen is generally adjudged to be safe but intoxication may manifest as disturbance of consciousness, seizures, respiratory depression, hypotonia and hyporeflexia, hallucination, memory deficits, catatonia, or acute mania. Patients with renal disease may develop toxicity even with low doses as baclofen is mainly excreted unchanged by the kidneys. Baclofen therapy must not be discontinued abruptly after prolonged use, as withdrawal syndrome manifesting as psychotic episodes, or seizures may occur.

Antipsychotics

Classical antipsychotics have been used sparingly over the years in the treatment of troubling, unremitting pain. But their use for this indication has been very limited owing to frequent adverse extrapyramidal symptoms such as parkinsonism, akathisia, akinesia, dystonic reactions, among others.[2,39] The atypical antipsychotics is a new class of antipsychotics with fewer extrapyramidal side effects and includes olanzapine, clozapine, quetiapine, sertindole and

risperidone, which are used primarily for the treatment of schizophrenia, bipolar disorder, refractory major depression and some anxiety disorders. The atypical antipsychotics led to renewed interest in investigating these more tolerable agents for the management of chronic pain. The principal difference between the typical and atypical antipsychotics lies in their receptor selectivity. The former principally block postsynaptic dopamine D_2- receptors in the brain, with some noradrenergic, cholinergic, and histaminergic blocking effects; while the atypical antipsychotics primarily block serotonin $5HT_{2A}$ -receptors in the brain, with limited post-synaptic dopamine D_2 receptors blockade, resulting in reduced risk of extrapyramidal side effects.
By mechanism of action, the atypical antipsychotics show varying individual affinity for multiple neurotransmitter receptors; including dopaminergic receptors, serotoninergic, histaminergic, adrenergic, and muscarinic acetylcholine receptors. In spite of their similar receptor heterogeneity to tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, the atypical antipsychotics have advantage of rapid onset of action compared to the antidepressants which may take weeks to improve symptoms. This is in addition to the beneficial effect on psychiatric comorbidities such as anxiety and depression that often accompany chronic pain conditions. Results for the use of atypical antipsychotics in pain management have been mixed, but among these olanzapine has shown remarkable efficacy in fibromyalgia, migraine and refractory headache management. Among the atypical antipsychotics clozapine has a lower propensity for causing extrapyramidal adverse effects, tardive dyskinesia and prolactinaemia. However its use has largely been limited by the significant risk of agranulocytosis, myocarditis, pancreatitis and remarkable weight gain. It is thus reserved for patients with schizophrenia or major depression that are unresponsive to conventional or other atypical antipsychotics. Other adverse effects associated with the atypical antipsychotics include weight gain, hyperglycaemia, dyslipidaemia and cardiac QT prolongation. Based on their relative receptor affinity clozapine, olanzapine, and quetiapine which have pronounced combined histamine H_1-receptor blockade and muscarinic M_1 – receptor blockade may produce sedation, weight gain and dry mouth; these side effects are not a problem with risperidone and sertindole. In the light of the foregoing, olanzapine may be the preferred adjuvant analgesic for patients with psychiatric features based on its proven efficacy and relative safety from cardiac QT prolongation, while being restrained in elderly, diabetic and overweight patients.[40]

Medicinal cannabis and cannabinoids for chronic pain

Cannabis is a psychoactive substance from the cannabis plant, frequently used illegally for recreational purposes.[2,41] Cannabinoids are the dozens of active extracts obtained from the cannabis; with cannabidiol (CBD) and tetrahydrocannabinol (THC) being the most abundant. While a few countries have legalized the recreational use of cannabis, many more have given legal approval for the medical use of cannabis and cannabinoids.[2,42] The predominant use of medicinal cannabis has been for the management of nausea and vomiting during chemotherapy in cancer patients, and in the treatment of resistant epilepsy. Possible mechanisms of analgesic action include modulation of descending inhibitory noradrenergic pathway on neurons in the dorsal horn.[43] Cannabinoids also act as allosteric modulator of the μ- and δ-opioid receptors. It is also thought that some analgesic effect of THC is derivable from its potentiationn of glycine receptors.[43] The management of intractable chronic pain and neuropathic pain is an area of intense interest for medical cannabis use. Available literature from Canada, United States of America and Australia indicate that medical cannabis and cannabinoids use for pain relief is gaining popularity among people living with chronic pain, with the patients reporting better pain relief with cannabis adjuvant compared with when opioids are used alone.[43,44,45] But this optimism has been tempered by the findings of the Pain and Opioids IN Treatment (POINT) study.[45] This prospective national cohort study conducted in Australia to examine relationships between cannabis use, prescription opioid use and pain outcomes among people living with chronic non-cancer pain had revealed a surge in interest in using cannabis for chronic pain treatment over the course of the study; despite a greater pain severity score in the cannabis users on follow-up, and with no reduction in prescription opioid use. Similarly, another prospective cohort study conducted in the United States among people living with HIV and chronic pain reported that cannabis use was not associated with improved pain control or reduced opioid use.[45] Unfortunately, clinical research in cannabinoids has been greatly constrained by legal restrictions to its use in most countries. However in the past 30 years, there have been a growing number of jurisdictions legalizing access to medicinal cannabis, with dozens of states in the United States legalising medical marijuana, or cannabidiol use. Currently many pain societies, among them German and Israeli pain societies recommend the use of cannabis-based drugs (plant-derived or synthetic) as third-line therapy for multimodal chronic pain management. With emerging evidence indicating that the concern for increased use of cannabis with marijuana legalization is after all unsupported, and as more jurisdictions approve a legal framework for its use, the medicinal potentials for these substances as adjuvant analgesics would be better explored.

CONCLUSION

The direct and indirect effects of prescription opioid on the opioid epidemic and the sharp rise in deaths from opioid overdose is also of increasing concern and have necessitated a critical review of their risk-benefit analysis and ignited the search for more efficacious and safer alternatives. As clinical and research interests in patients' safety, satisfaction and quality of life evolve, further

development of adjuvant analgesics will be expected to fill the existing gap in pain management. Expectedly too, as more jurisdictions approve a legal framework for its use, the intense interest in medicinal cannabis which is increasingly becoming popular in management of intractable chronic and neuropathic pains could be better explored.

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