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Introductory Chapter

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1. Pain

Pain is one of the most common ailments which drive patients to a clinic, and pain alleviation is a key factor in the understanding of the well-being. There is a heightened awareness of pain as the “fifth vital sign,” therefore it should be monitored as cautiously as blood pressure, temperature, respiratory rate, and pulse. This also entails a change in paradigm, which means pain treatment has shifted from decisions taken by an individual physician with an unspecified follow-up to more systematic approach by multidisciplinary teams [1, 2].

Pain is defined by WHO as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” The inclusion of the word “emotional” is crucial for the understanding of the implications of pain perception by a subject. The obvious consequence of this is that that pain perception is unique to each individual, as well as pain threshold is different in subjects. Cultural aspects should also be considered as it is nowadays preconized that no one should experience pain, not even when giving birth. Pain is culturally determined and cannot be defined so coarsely when it has so many influencing factors on how it is apprehended and expressed, being culture one of the most efficacious ones [3–6]. The clinician should then make a great effort to conceptualize pain in the search for pain alleviation because pain relieving is one of the main goals in practice.

Even though it is an ailment common to many diseases and medical procedures and in many cases, an illness in itself, it is not common to find a specialization on pain in medical schools. In general, pain management or pain medicine should entail, though not always does, a multidisciplinary approach for easing the suffering and improving the quality of life of those patients suffering from it [2, 7–9].

Although it may not be correct, it is possible to distinguish between acute and chronic pain. The first one has gained more attention because the success in its treatment, due to advances in pharmacology, and also because it is generally easily associated with a biomedical pathological cause. It is also in this kind of pain that neurophysiological explanations are fundamental for its understanding [10].

In acute pain, a pharmacological approach is usually successful in the treatment because in general a biological approximation to the matter is acceptable. Collectively, non-steroidal anti-inflammatory agents (NSAIDs) and acetaminophen (paracetamol) are the most commonly used pain medications, followed by opioids generally used in moderate to severe pain [11, 12].

The definition aforementioned is not adequate for chronic pain because chronic pain does not only entail a biological state but also a psychological one, which in many cases is able to control patients' lives. An ordinary approximation to chronic pain would give us a false impression that it can be successfully treated by the ample arsenal of drugs available; however, in many aspects, chronic pain is still an enigma for medicine. Chronic pain may be defined then as a state of sensitized perception of pain that exceeds the simple sensorial experience. Medicine treats injury and pathology to support and speed healing and treats distressing symptoms such as pain to relieve suffering during treatment and healing. When a painful injury or pathology is resistant to treatment, when pain persists after the injury or pathology has healed, and when medical science cannot identify the cause of pain, the task faced is much more difficult. The obvious consequence of this is that treatment approaches to chronic pain not only include pharmacologic measures, such as analgesics, tricyclic antidepressants, and anticonvulsants but also interventional procedures, physical therapy, and psychological measures [10, 13–16]. As a consequence of this, the typical chronic pain management team includes anesthesiologists, occupational therapists, physiotherapists, clinical psychologists, and pain nurses. Together the multidisciplinary team can help create a package of care suitable to the patient. While acute pain usually resolves once the underlying trauma or pathology has healed and is treated by one practitioner, effective management of chronic pain frequently requires the coordinated efforts of multiple disciplines [14].

2. Pain treatment

In the last decades, the understanding of the multiple mechanisms and molecules that underlie pain perception have turned its treatment into a puzzle formed by therapies that involve not only the common substances considered as analgesics (NSAIDs and opioids) but also a wide array of other drugs such as anticonvulsants and antidepressant and not less important manual techniques, together with psychological follow-up, which has also proved to be successful in containing patients emotionally [10, 12–14]. The understanding of the different routes involved in this complex phenomenon has opened its therapy not only to drugs, not previously considered as analgesics, but also to the development of pharmaceutical forms able to alleviate pain for long periods of time as well as electrical techniques for the interruption of pain signal transduction [13, 14, 17].

Even though medicines seem to be the most common resource for pain relief, and despite all the advances in pain understanding, many people still restore to nontraditional or alternative medicine, some forced by the high costs of health care and others pushed by the inefficacy of conventional treatments [18].

2.1. Analgesics

The word analgesic derives from Greek an- (ἀν-, “without”), algos (ἄλγος, “pain”), and -ikos (-ικός, forming adjectives). Such drugs were usually known as anodynes before the twentieth century.

Both broader classes of analgesics have a natural origin. Salicylic acid extracted from the bark of Willow tree gave birth to NSAIDs, whereas *Papaver somniferum* is the origin of opioids [19, 20].

The mechanism of action shown by acetylsalicylic acid was at first generalized to all NSAIDs; however, nowadays this group comprises diverse classes of structures which have demonstrated different potential as anti-inflammatory, antipyretic, and analgesic drugs. In the last century, acetaminophen has gained field in treatment of mild pain, but it is still nowadays studied regarding its mechanism of action as it seems not to be like any other kind of analgesic [21].

The long use of these substances has allowed a thorough study of their efficacy as well as their safety profile; however, in many countries NSAIDs being sold as over-the-counter drugs, give the false impression of innocuous products when in fact they are not [22, 23].

NSAIDs differ from acetaminophen in that they possess anti-inflammatory properties and are associated with a different side effect profile that includes bleeding, gastrointestinal ulceration, renal dysfunction, and an elevated risk of adverse cardiovascular events. On the other hand, paracetamol, though a widespread option for mild pain, rises concerns regarding its safety in people with impaired hepatic function, alcoholics, etc. [24–26].

Morphine derivatives are in general more cautiously used, and in the last decades, attitude toward opioids has shifted from willingness to fear of their use especially because of their potential for addiction which leads to the prescription of lower than effective doses.

In many settings, morphine is still the standard of care in active cancer because of its short half-life, which allows a more flexible administration regimen. The availability of multiple pharmaceutical dosage forms and, last but not least, economic reasons have maintained morphine as a current option [27–29]. In contrast, the long-term administration of an opioid for the treatment of chronic noncancer pain continues to be controversial accompanied by the folk knowledge that sustains the use of opioids in terminal illnesses [30–32]. In this setting, opioids, such as tramadol, methadone, and oxycodone, have gained field to morphine because of either their more advantageous pharmacokinetics parameters or the addition of adjunctive mechanisms of action (serotonin, norepinephrine reuptake inhibition, and NMDA antagonism).

Even though opioids are the first-line approach for moderate or severe pain in populations with active cancer, the comprehensive management of pain in this kind of patient also requires expertise in the use of the nonopioid analgesics, such as acetaminophen (paracetamol), non-steroidal anti-inflammatory agents (NSAIDs), and drugs referred to as “adjuvant” analgesics or coanalgesics [33].

The knowledge that serotonin and norepinephrine play an important role in pain has influenced the incorporation of serotonin-norepinephrine reuptake inhibitor (SNRI) drugs in the

wide array of drugs for pain alleviation. SNRIs are commonly used in conjunction with opioids (especially tapentadol and tramadol) with greater success in pain relief. This is the case of chronic pain syndromes, which usually require the use of this “adjuvant analgesics.” The treatment of neuropathic pain has changed with time. At the beginning it included tricyclic antidepressants and anticonvulsants such as carbamazepine. Nowadays, the arsenal has spread with the use of gabapentinoids and SNRI antidepressants, such as duloxetine which in recent years has acquired approved indications for pain. For migraine pain, anticonvulsants such as valproic acid and topiramate are also used [34, 35]. And last but not least the T-type calcium channel blockers have also been included in pain treatment protocols in animals and human models [36–39].

2.2. Other targets and techniques for pain alleviation

When Western medicines seem not to be effective, many people restore to nontraditional or alternative medicine. There is some evidence that some treatments using alternative medicine can relieve some types of pain more effectively than placebo [40, 41]. Medicinal plants (MPs) have been used for centuries by many cultures to treat pain and this knowledge has been embraced by the pharmaceutical industry which has used it to synthesize and elaborate analgesics commonly used in traditional Western treatments. The scientific verification process of this tradition is ongoing. The natural origin of MPs may lead to the false impression of innocuity and ample safety [42, 43], but despite presenting a wide therapeutic range, MPs are not exempt of adverse effects and interactions [44]; phytovigilance should be performed as for conventional medicines and should be sustained on a scientific basis regarding their toxicity and its allergenic potential [44]. Despite all this evidence, MPs use should not be discouraged, because for certain population, they are not only the adequate option but may be the only one available or affordable.

As it has been stated that the two main systems addressed in pain treatment are the routes involving COXs enzymes and opioids receptors and lately the inhibition of monoamines reuptake. Seeking for other options, lately, the endocannabinoid/vanilloid systems have also been studied regarding their effect on pain alleviation [45–47]. Although cannabis has proved to be useful in pain alleviation, there are two drawbacks for this option. First, cannabis is still a prohibited plant in many countries and second, as with many other plants, it is troublesome to identify the substance responsible for the action. To make matters worse, what raises concerns in this case is that tetrahydrocannabinol (THC) which is responsible for pain alleviation is also responsible for the psychoactive effects of marijuana. THC is not the only natural occurring substances capable of agonizing the endocannabinoid receptors and efforts are being made to find synthetic derivatives with a safer profile. The entourage effect is also a problem when extracting substances from biological matrixes, as sometimes the final effect of a treatment depends on a group of substances and not just an isolated one.

Local anesthetics have also proven to be a useful tool in acute and chronic pain relief; lidocaine presents good results in this regard because of the rapid alleviation obtained after administration, though cardiovascular adverse effects should also be taken into consideration [48, 49].

In newborns, sweet solutions have also presented analgesic properties showing promising results at very low cost and placing babies at minimum risk of side effects. There is also ongoing research over different forms of administration including patient-controlled analgesia, different pharmaceutical forms for a more effective pain control as well as electrical techniques for disrupting pain signal.

3. Conclusion

It has been clearly stated that pain treatment is a challenge difficult to face. Health care teams have to articulate the resources available and patients' needs in a particular scenario where previous experiences are sometimes difficult to extrapolate. This book intends to give those involved in pain management a proper idea of the tools available for pain relief, comprising pharmacological ones and adjuvant techniques, as well as presenting late research on analgesics, their benefits and security profile.

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