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Chronic Pain Management: Advance from Pharmaceutical, Technical and Digital Perspective

Osman Kamal Osman Elmahi[1], Manasi Dedhia[2], Jatin Dedhia[3*] and Zeyad Al-Moasseb[4]

[1]Department of Acute Medicine, Northern Lincolnshire and Goole NHS Foundation Trust

[2]Medical Student, 3rd Year, University College London (UCL), United Kingdom

[3]Consultant in Anesthesia and Chronic Pain, Mubadala Health, Dubai, UAE

[4]Department of Opthalmology, Hull University Teaching Hospitals NHS Trust, Hull, United Kingdom

[*]**Corresponding author:** Jatin Dedhia. Consultant in Anesthesia and Chronic Pain, Mubadala Health, Dubai, UAE

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Abstract

Pain is defined as an emotional or sensory experience which is unpleasant and often associated with tissue damage or injury. Many factors to patients' daily routine can be seriously affected by the presence of chronic pain, including activities of daily living, overall quality of life and physical/mental wellbeing (1-3). Chronic pain can be primary, independent of pain aetiologies and not linked to ongoing medical conditions, or secondary, encompassing chronic post-operative, neuropathic, cancer, musculoskeletal and visceral pains.

Keywords

Pain Medications; Aetiologies; Nociceptive Pain; Paraesthesia; Somatosensory; Anaesthesia

Introduction

Pain is defined as an emotional or sensory experience which is unpleasant and often associated with tissue damage or injury. Many factors to patients' daily routine can be seriously affected by the presence of chronic pain, including activities of daily living, overall quality of life and physical/mental wellbeing [1-3]. Chronic pain can be primary, independent of pain a etiologies and not linked to ongoing medical conditions, or secondary, encompassing chronic post-operative, neuropathic, cancer, musculoskeletal and visceral pains.

Chronic pain can also be classified within itself as nociceptive, nociplastic and neuropathic pain. Nociceptive pain is usually the result of actual or imminent injury to non-neurological structures. Neuropathic pain, by definition, involves neurological structures related to the somatosensory nervous system affected by tissue damage or injury. Common presentations may include paraesthesia, paroxysms of pain and focal neurological findings. However, although nociplastic pain results from altered pain signals, this occurs without any tissue injury or damage to the somatosensory system structures [4,5].

The overall disease burden of chronic pain globally is extensive. In the United States alone, chronic pain affects over 116 million people - a greater combined total than the disease burden of ischaemic heart disease, cancer and diabetes mellitus. Cost-effective interdisciplinary chronic pain management programmes have been affected following the introduction of the biopsychosocial model of pain, but multiple barriers have hindered the wider implementation of these programmes [6,7].

In this article, the authors review the advances in chronic pain management from a pharmaceutical, technical and digital perspective. Furthermore, the developments in chronic pain management through regenerative medicine are also discussed in this article.

Liposomal bupivacaine in chronic post-operative pain management

In the post-operative setting, pain is known to be a significant hindrance in post-operative recovery, culminating in prolonged post-anaesthesia care unit and hospital stays an increased risk of venous thromboembolisms and nosocomial infections and increased use of pro re nata opioid use.

Chronic post-operative pain is defined as the pain persisting post-surgery for over three months, absent prior or different to pre-operative pain, localised to the surgical site and has no other aetiology [8,9]. It is known tohave a high disease burden, impacting quality of life and contributing to economic hardships. The estimated incidence rate of chronic post-operative pain is approximately 10-50% for mild to moderate pain and 5-10% for severe pain. Certain procedures are also associated with higher incidence rates pf chronic post-operative pain, including amputation and coronary artery bypass grafts [10,11].

To date, multiple advances have played integral roles in both prevention and treatment of chronic post-operative pain, including the use of patient-controlled analgesia (PCA) and regional anaesthesia.

Patient-controlled analgesia is used to provide pain relief to patients following surgery and also during management of chronic pain and labour, encompassing various patient metrics for accurate calculations and typically given through intravenous lines. Regional analgesia consists of peripheral nerve infiltration to block transmission of nerve signals, thereby avoiding or relieving pain [12].

PCA has demonstrated its impact by giving patients more autonomy over their analgesia and considerably fewer hindrances in their recovery through improved mobility and physiotherapy. However, it has contributed a large economic burden to hospital budgets, owing to the cost of the medications used, often opioids, and of intravenous lines. Furthermore, there is also the cost of consulting anaesthetists responsiblefor management of patient-controlled analgesia [12,13].

Regional anaesthesia plays an integral preventive role in providing opioid-free anaesthesia through multiple techniques, in the form of neuraxial or peripheral nerve blocks. Many targets and risk factors of chronic post- operative pain from surgical incisions are amenable to intervention with regional anaesthesia. These include peripheral nerve and central sensitisation (gabapentin, pregabalin; NMDA recepter antagonists), local inflammatory response (NSAIDs) and cortical pain processing. In addition, regional anaesthesia has also demonstrated a longitudinal reduction in vulnerability to pain, thus potentially acting as a potential means ofreducing chronic pain development [14].

The potential of liposomal bupivacaine has also been examined in treatment and prevention of chronic pain. In the United States, cost-effectiveness of liposomal bupivacaine (Exparel) was observed in prospective cohort studies on patients following cardiothoracic surgery. In the cohort receiving Exparel, the overall cost of achieving the same was considerably less than patients receiving PCA [12]. Studies have also shown superior analgesia and less opioid use through using liposomal bupivacaine following total knee arthroplasty; in a meta-analysis encompassing five clinical trials - three randomised and two non- randomised - and 1214 patients, liposomal bupivacaine has demonstrated superior analgesia in comparison to standard bupivacaine. However, although potential has been demonstrated by liposomal bupivacaine over conventional local anaesthetics on surgical sites, its potential as a regional block may be questionable at present. Liposomal bupivacaine initially releases a limited amount of its active ingredient following its administration, but its concentration gradient across connective tissues surrounding neurons may be insufficient to achieve a blockade comparable to regional anaesthesia. Although, higher doses may be required to achieve this, liposomal bupivacaine has demonstrated no cardiac toxicity at higher concentrations (approx. 30mg/kg) [15].

Spinal cord stimulators in chronic pain management

In the midst of pharmaceutical advances in treatment and prevention of chronic pain, it remains a global health problem due to high incidence rates of refractory chronic pain and drug resistance. The prevalence of these may be considerably higher with certain pain syndromes; an example of which is chronic pelvic pain with drug resistance prevalence rates ranging between 20-65%. Patients with these pain syndromes eventually develop tolerance to pain medications, requiring higher doses with inadequate effects. Recent studies have also demonstrated that the average daily dose gabapentin among the top 5% of users is 9,534mg - almost three times the recommended daily dose [16-18].

Fortunately, following the advent of technical advancements in the form of spinal cord stimulation (SCS) in 1967, it is now the most performed procedure for treatment of chronic pain worldwide. Since then, further developments including high-frequency and burst stimulation have supplemented SCS. Although the exact mechanism of SCS is yet to be fully understood, it is perceived to follow the gate-control theory developed by Melzack and Wall, in which the stimulation of larger nerve fibres blocks transmission of neuropathic pain signals from small afferent fibres. It has also been demonstrated on animal models that SCS' effect on tissue excitability is linked to a decreased intracellular glutamate concentration [19,20].

Significant benefits have been shown with conventional SCS in patients with chronic lower back and leg pain - significant pain relief was observed in 50-90% of patients after 12 months of follow-up after implantation. However, the introduction of new stimulation techniques - high-frequency and burst stimulation - was prompted by a non-uniform response to tonic stimulation. These stimulation paradigms dramatically improved analgesia rates among patients with chronic pain syndromes in many investigations. A study performed by Deer et al. In 2018 demonstrated a preference to burst simulation by 70.8% of patients with chronic regional pain syndrome, whereas the Lambru et al. Study in 2018 demonstrated complete pain regression in patients with chronic neuralgiform headache attacks [21-24].

The role of regenerative medicine in management of chronic pain

Regenerative medicine is playing a progressively integral role in non-pharmacological chronic pain management, owing to its use in treating chronic pain secondary to degenerative bone and joint diseases, neuropathic pain, malignancy and other chronic conditions. This has encompassed the use of biologically active materials, engineered tissues and natural polymers. Recent advances within regenerative medicine have been successful in treatment of chronic low back pain, e.g. secondary to degenerative intervertebral discs, through the use of hyaluronic acid, collagen and synthetic polymers specifically acting in repair andhealing of injured bone, cartilage and nervous tissue [25].

Further promise has been demonstrated through use of bioactive tissue components and growth factors,including platelet-rich plasma (PRP) and mesenchymal stem cells. PRP is usually harvested through prior venipuncture and subsequently centrifuged to isolate PRP from platelet-poor plasma, red blood cells and white blood cells. From an initial sample of 20-60mL of autologous blood, 3-6mL of PRP is isolated. Musculoskeletal disorders including osteoarthritis, shoulder and spinal disorders and intractable wounds have demonstrated effective response to treatment with PRP [26].

Musculoskeletal disorders - in particular, back pain secondary to degenerative intervertebral discs - are also amenable to treatment using mesenchymal stem cells. Mesenchymal stem cells are located abundantly in bodily tissues but are most often harvested from bone marrow and adipose tissue. Once isolated, these cells are cultured to ensure homogeneity of the cell population. Once isolated from the culture vessels, these cells are then centrifuged, trypsinised, pelleted and res-suspended in a fibronectic gel consisting of ice-cold collagen. Target tissues are then treated with the resultant gel by direct injection. Following the developmentof mesenchymal stem-cell and PRP preparations, disc injections

have demonstrated level 3 evidence in providing long-term relief of chronic back pain; lumbar facet, epidural and sacroiliac joint injections have also demonstrated level 4 evidence in treating facet joint and sacroiliac arthralgia [25,26].

Wireless peripheral nerve stimulation in chronic pain management

Following the introduction of the pain theory by Melzak and Wall in 1965 and subsequent conceptualisationof peripheral nerve stimulation (PNS) by Sweet and Wall in 1967, PNS was used with great enthusiasm in management of chronic pain, but with various outcomes arising from technical issues and substandard selection criteria. However, despite its difficult advent, PNS has the potential today to treat chronic somatic pain as well as autonomic and visceral disorders, e.g. refractory epilepsy and diaphragm palsy [27,28].

The process of peripheral nerve stimulation involves a very specific nerve supplying a very distinct area or internal structure, whereby unidirectional paraesthesia is applied. This can be achieved using two methods - the surgical method or the minimally invasive percutaneous stimulation technique. In the former, the nerve is exposed to the external environment and electrodes are placed directly. The percutaneous stimulation technique involves a skin puncture through which electrodes are guided to the target location where maximum effect is achieved [29].

Since its advent, PNS has rapidly evolved following developments in technology leading to the innovation of minimally invasive, wireless peripheral nerve stimulation. Traditionally, spinal cord stimulation involved the use of long extension wires and implantable electrodes enclosed by a catheter, which were all implantedsurgically and therefore associated with complications arising from multiple surgical procedures. These challenges had been subsequently alleviated following the use of wireless neuromodulation through micro- implant wireless power generators (WPGs). Through a radiative electric field operating at microwave frequencies, the micro-implant WPG has the ability to deliver the appropriate stimulation from within a diameter of 800-1350 micrometers. As a result of its minimalistic design concept, micro-implant WPGs mitigate the complexity and subsequent surgical complications associated with implanting considerably larger spinal cord stimulators [30]. Furthermore, whilst providing analgesia to patients, it may also provide comfort to surgeons and reduce the economic burden of treating intractable neuropathic pain and adverse effects associated with pharmacological pain control. As a result of its minimally invasive implantation in comparison to SCS, it may also be applied in patients with a variety of chronic pain syndromes, including complex regional pain syndromes, herpetic neuralgia in immunocompromised patients, fragile skin conditions related to psoriasis and chronic pain associated with malignancy [31,32].

Telemedicine

In the midst of pharmacological and technical advances in chronic pain management, telemedicine plays an ever-increasing role in creating a patient-centred approach to chronic pain management. Telemedicine is integrating rapidly into healthcare and includes applying digital modes of communication to present health interventions, extending from text-based emails to multi-agent systems (MAS). MAS' modalities communicate and co-operate between various agents, which are

often considered autonomous units, and mayconcurrently involve many common applications including the internet, medical applications and even robotics [33].

Cost-benefit ratios in recent years have proven to be extremely high in managing chronic pain, especially in remote communities. Recent studies have demonstrated that integrating telemedicine in chronic pain management led to lower costs for both hospitals and patients, a reduction in missed appointments and a highsatisfaction rate amongst healthcare professionals and their patients [34].

In a study performed by Gailano-Castillo et al, the use of telemedicine in chronic pain management amongbreast cancer survivors yielded higher satisfaction rates with their pain management, through the use of internet-based exercise programmes. These were found to improve overall mental health and wellbeing, cognitive functioning and arm symptoms in patients. A further study by Bailey et al, through use of digitalcare programmes, also demonstrated that its patients had decreased levels of anxiety and depression.

Conclusion

The economic burden of chronic pain worldwide remains extensive, with particular emphasis on certain cohorts such as post-operative and cancer patients. Owing to pain among these patients, further complications may arise including lengthy hospital stays, leading further to hospital-acquired pneumonia an exposure to other hospital-based infectious diseases. Further complications arising from chronic pain in these patients include those resulting from decreased mobility, such as venous thromboembolism, circulatory compromise and musculoskeletal issues.

Developments in chronic pain management have augmented rapidly in the last few decades, demonstrating high patient satisfaction levels, cost-effectiveness and mitigation of previously commonplace surgical complications. Furthermore, with the advent of telemedicine, the concept has revolutionised the practice of chronic pain management in multiple respects, including patient satisfaction, mitigation of patient hardship, greater coverage to include marginalised and remote communities and improvement of overall physical health and wellbeing among chronic pain patients.

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