Special Review

Methadone for Pain Management: Past, Present and Future

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Abstract

Methadone for pain management in this article describes briefly pain, methadone as a Level 3 World Health Organization ladder opioid in the context of India and rest of the world, as well as the relationship to past, present, and future possibilities of pain management. Acute pain is proportional to the injury most of the times, and such proportionality may not exist in chronic pain. Pain management over decades has changed because of knowledge and availability of molecules and compounds to reduce chronic pain. Naturally occurring opioids from "poppy" such as morphine and heroin were available through cultivation and trade for pain management and recreational use in different parts of the world for centuries. Methadone has been a synthetic molecule discovered in the 1930s in Germany. It has been used for harm reduction for opioid use disorder in the form of "methadone maintenance treatment". This program exists since the 1950s while pain management started around the late 1970s in Europe and North America. More recently, the knowledge of acute and chronic pain at a molecular level, including ion channel modification, allowed the use of coanalgesics and opioids prudently. The concept of "total pain, neuroplasticity, and neurotransmitters" how they could be modified for better pain management with pharmaceuticals and nonpharmacological methods are being investigated, and evidence is being practiced clinically. In the present context, education for physicians, allied health professionals, patients, and family caregivers is important. Education to the physicians can skill and capacity build in the community and can be associated with educational research and peer-reviewed publications. The future remains promising, as innovations such as pharmacogenomics, nanotechnology, molecular, and quantum biology may create evidence, along with physical and psychological rehabilitation, to prevent and holistically better pain management.

Keywords: Future, India, methadone, pain management, past, present

Introduction

Opium poppy was cultivated in lower Mesopotamia around 3400 BC, the Sumerians called it "the joy plant," whereas, in 1300 BC, Egyptians cultivated *Opium thebacium* named for the capital city of Thebes. Hippocrates, the Greek physician, in 300 BC noted opium as an effective painkiller and a styptic (capable of stopping bleeding when applied to the wound). Opium was used in different forms for recreational use for centuries, leading to opium import/export, as well as opium wars. In England, artists, writers, and others experimented and addicted to opium in the early 1900s.[1]

In India, long-standing opium trade – the Opium Acts of 1857 and 1878 and the Dangerous Drugs Act of 1930 – was superseded by the Narcotic Drugs and Psychotropic Substances (NDPS) Act in November 1985. Acquisition or use of opioids for scientific and medicinal purposes became complex, requiring several licenses with major restrictions for physicians, pharmacists, and patients. When adequate opioids are not available in a community, underdosing becomes a reality with added suffering even in a tertiary care setting for cancer pain.[2,3]

The "Civil Society-Driven Drug Policy Reform for Health and Human Welfare-India" did convince the government to change the language of the NDPS Act and Essential Narcotic Drugs Federal NDPS Regulations 2015 amendment.[4] Public health strategy for palliative care has a value and can improve care in each nation.[5,6]

Past

Early part of 20th century, "consumption or tuberculosis" was being treated in sanatoria. Pain management in this group of patients along with fever and cough suppression was important. Hence, scientists were exploring semisynthetic

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and synthetics substances as antitussives and anti-pyrexias along with naturally occurring opioids and anti-inflammatory agents for pain management. Dr. Snow, at the Royal Brompton Chest Hospital in 1896, had used a mixture of morphine and cocaine to reduce the agony with advanced disease. Brompton cocktail with variety of ingredients in a fixed ratio but different combinations including heroin, morphine, cocaine, Benadryl, and Largactil were used to manage pain and suffering.[7,8]

Pain management around this time was like acute pain management following major surgery, and a designated dose was given when a patient had highest pain and half-life information of the molecule was not part of the practice. It was not until late 1977 Twycross suggested the used around the clock using half-life information. In a different study, Twycross explored the potency and equianalgesia between morphine and diamorphine.[9]

Eisleb and Schaumann, 1939, Hoechst scientists developed one of 105 antipyretics, antitussives, and analgesics #Va 10820: Later known as methadone.[10] Reports suggest that it was used during World War II with poor knowledge and consequences including death due to improper dose in German soldiers as an analgesic. Methadone, following World War II, was used for harm reduction methadone maintenance treatment (MMT), as a substitute for heroin. After the initial use of methadone for MMT, several deaths were reported, of which the majority were in combination with other prescribed and street psychotropic drugs, in North America and Europe.

Methadone use for pain management did not commence until the late 1970s in a clinical setting the use had increased slightly, following HIV/AIDS crisis in the mid-1980s. Peripheral sensory neuropathy was thought to be "opioid resistant pain" and coanalgesics such as tricyclics, antiepileptics, and antiarrhythmics were used along with opioids. Around this period, palliative care was improving in different parts of the world. Cancer patients were treated with opioids, and it was suggested that there was no ceiling for opioids. A decade after, similar principles were applied to noncancer patients with chronic pain.

Present

There is a considerable amount of variation in the pain management in different countries, and several published articles suggest politics, policies, resources, education, knowledge, and coordination may be the major issues. World Health Organization (WHO) Pain Policy and Palliative Care has been working with developing countries to improve such disparity and opioid consumption.[11,12]

"Opiophobia" of caregivers and the general public all over the world and more so in the developing countries remains and educational endeavors are desperately required to "balanced and safe use of opioids" for pain management. von Gunten in his editorial "The pendulum swings for opioid prescribing" briefly describes the issue.[13] The present-day "opioid crisis is a double-edged sword" as in developed countries, the substance use disorder not only misunderstood, mismanaged, and blamed for the clinical use of opioids, but also most importantly in developing countries, the lack of opioids leading to increased suffering of patients, caregivers, and the community. It requires political will, resources with good education of the caregivers, and the public. Cleary *et al*.[12] reported formulary availability and regulatory barriers to accessibility of opioids for cancer pain, especially in India.

Neuropathic pain, which is resistant to conventional opioids, and molecular biology has shown along with functional magnetic resonance imaging peripheral sensitization and central excitation "wind up," the nervous system amplifies pain signals in chronic pain. Glutamate, a neuroexcitatory molecule release due to N-methyl-D-aspartate (NMDA) receptor activation, is likely cause of amplification of pain signals in the body.[14] Neurobiological mechanisms, in relation to posttraumatic stress disorder or negative experiences and poor coping, are associated with changes in neuroanatomy and function. Thus, balance of neurotransmitters is inefficient, leading to anxiety and depression along with increased perception and expression of pain.[15] Not all caregivers are aware of these mechanisms and require education and skill building.

Methadone has a reputation of being used for harm reduction; however, most individuals are reluctant to use it for pain management. "MMT in India – A Feasibility and Effectiveness Report has been published in 2014 through United Nations Office on Drugs and Crime." Community pharmacies, friends, family, and other caregivers may not be aware of its use for pain management; hence, patient and family education can assist for safe use.

Methadone in the present formulation has two racemic mixtures (R-Levo and S-Dextro) with clinical efficacy relates to R methadone as mu, delta agonist and S methadone as NMDA antagonist, norepinephrine, and serotonin reuptake inhibitor with a long half-life (7–150 h). Thus, on the positive side, it reduces nociceptive pain and improves neuropathic pain, unlike other opioids. However, such efficacy in relieving pain is associated with deep sleep and sleep apnea is a possibility.[16-18]

Methadone in clinical studies through neurobiological mechanisms has a value in reducing opioid-induced tolerance and hyperalgesia, independently and with other opioids.[19]

Adverse effects when methadone is used for pain relief, are similar to conventional, Mu agonistic opioids. Serotonin syndrome with other sertogenic medications and QT/QTc prolongation due to metabolic or other molecules prolong QT/QTc, are unique to methadone. Free methadone in the body is the analgesic and any other agents administered (nutritional, allopathic, homeopathic, or ayurvedic) change alpha-1-globulin or alter tissue reservoirs of methadone, will have implications toward adverse effects or efficacy.

Use of opioids, in general, requires a good education, and methadone, specifically, requires knowledge relating to both racemic mixtures, especially in titration phase and when the dose is being increased.

In 1947, Eli Lilly, US following world war II, seemed to have obtained the rights to methadone for a nominal sum of a dollar as spoils of war since the "patent rights" to Hoechst was no longer protected and now registered to Roxane Laboratories. Hence, the cost of methadone is relatively low, and developing countries can afford this medication, better than some of the conventional opioids.

At present, research and clinical trials are in progress, relating to genetic or stem cells, epigenetics, ion channel modification, and NMDA antagonism to reduce the presence of glutamate in the nervous system to improve pain management. Similarly, education and nonpharmacological approaches including "gate theory" are being investigated with promising early results for pain management. The changes in the central nervous system are being labeled as part of "neuroplasticity," and evidence suggests that such neuroplasticity may be reversible by interventions, in a variety of ways.

Not all countries require a special license to prescribe methadone and other opioids. In India as estimated by the WHO Collaborating Centre in 2012, the use of opioids is around 0.24 mg/person, Kaur *et al*. in an open-access article also stated that the NDPS Regulations 2015 Amendment has requirements with regard to procuring narcotic license.[20]

Health Services in India have been improving; however, caregiver coordination between different services can be difficult. Patient autonomy is respected, but different services such as medical college hospital, government hospital, private, homeopathic, and ayurvedic services may confuse the patient, while poor compliance can affect the outcome of an intervention.

The Trivandrum Institute of Palliative Sciences (TIPS) the WHO, Collaborating Centre for Training and Policy on Access to Pain Relief and Extension for Community Health Outcome (TIPS) Certificate Courses in pain and palliative medicine for doctors and nurses www.palliumindia.org/courses with timetable, in major cities in India, are great resource.

There are opportunities in relation to educational research along with clinical research in India; specially their experience in developing countries. Indian physicians, Pallium India, Indian Medical Association, and Indian Palliative Care Association jointly or individually can explore further the "point of care" material, in the form of tools like "apps" for android or iPhone for education and caregiving.

Future

Academics, clinicians, universities, and corporations are investing time and money to improve pain management all over the world. Methadone, when used safely, seems to have advantage over other opioids in relation to good pain management and reduced adverse effects.

Good education to the patient in groups or one on one seems to empower the individual and helps the coping process. Nonpharmacological interventions such as cognitive behavioral therapy, distraction, radiofrequency, laser, phototherapy, and other interventions are being used with benefit.

NMDA receptors, ion channels such as sodium (Na), potassium, and calcium are being investigated to alter peripheral sensitization and central excitation. Puffer fish toxin has been investigated as a gated sodium channel modifier with early mixed results. Novel pharmaceuticals to alter ion channels to improve pain management are being investigated.[21] Similarly, ion-channel modification is being investigated to improve pain management and reduce the use of opioids.

Genomics, pharmacogenomics, and epigenetics are being investigated, but it is early to predict the outcomes. Early results with nanotechnology using nanoparticles to transport pharmaceuticals to reduce adverse effects and improve efficacy are being investigated.

The availability of medications and services along with the cost of pain management in palliative care in developing countries has been an issue. Confidentiality along with electronic medical records and electronic health records may improve coordination between caregivers, thus improving safety.

In the future, electronic devices such as android and iPhone not only can be used for education but also simple investigations such as Electrocardiography at "point of care" along with advanced tests are possible.[22]

Conclusions

India is a populous and developing country. Recent NDPS Regulations 2015 Amendment allows better use of Level 3 WHO ladder opioids to alleviate pain in palliative care patients. Physicians, caregivers, and patients require good education and understanding of safe use of opioids.

The protocol and approach is different for pain management and MMT. Physicians and other caregivers who have received education for MMT not only may have good knowledge of the use of methadone in relation to addiction but also require a good understanding of pain management.[23]

Methadone is a "long-acting" opioid, relatively inexpensive, and has properties that could reduce neuropathic along with nociceptive pain in palliative care patients better than conventional opioids. However, caution must be exercised as added adverse effects relating to methadone use require specific education, mentorship, and skill building for safe use.

A minor caution, methadone may not solve all the problems associated with pain management in India or elsewhere but used safely will add value to the care of patients with cancer and noncancer pain. Nonpharmacological approaches in the

form of physical and psychological rehabilitation will enhance care.

The past may not be changed, but as we move forward, innovations and new discoveries may assist further in relation to communication, coordination, and care. Modern public health approaches to palliative care may compliment good care and community engagement further and hopefully, costs remain affordable.

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Conflicts of interest

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References

1. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: Controversies, current status, and future directions. Exp Clin Psychopharmacol 2008;16:405-16.
2. Khosla D, Patel FD, Sharma SC. Palliative care in India: Current progress and future needs. Indian J Palliat Care 2012;18:149-54.
3. Thota RS, Jain P, Bakshi SG, Dhanve CN. Opioid-prescribing practices in chronic cancer pain in a tertiary care pain clinic. Indian J Palliat Care 2011;17:222-6.
4. Vallath N, Tandon T, Pastrana T, Lohman D, Husain SA, Cleary J, *et al.* Civil society-driven drug policy reform for health and human welfare-India. J Pain Symptom Manage 2017;53:518-32.
5. Sallnow L, Richardson H, Murray SA, Kellehear A. The impact of a new public health approach to end-of-life care: A systematic review. Palliat Med 2016;30:200-11.
6. Stjernswärd J, Foley KM, Ferris FD. The public health strategy for palliative care. J Pain Symptom Manage 2007;33:486-93.
7. Clark D. The Brompton Cocktail, 2014: 19 Century Origins to 20th Century Demise, End of Life Studies. Available from: http://bit.ly/2oqMLhn. [Last accessed on 2017 Dec 24].
8. Mount BM, Ajemian I, Scott JF. Use of the brompton mixture in treating the chronic pain of malignant disease. Can Med Assoc J 1976;115:122-4.
9. Twycross RG. Choice of strong analgesic in terminal cancer: Diamorphine or morphine? Pain 1977;3:93-104.
10. Gerlach R. A Brief Overview on the Discovery of Methadone. Available from: http://bit.ly/2BzUXkx. [Last accessed on 2017 Dec 24].
11. Opioid Consumption: A Global Indicator for Palliative Care?Posted by Pain Policy and Palliative Care; 11 April, 2012. Available from: http://bit.ly/2kGbKIy. [Last accessed on 2017 Dec 24].
12. Cleary J, Simha N, Panieri A, Scholten W, Radbruch L, Torode J, *et al.* Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in India: A Report from the Global Opioid Policy Initiative (GOPI). Ann Oncol 2013;24 Suppl 11:xi33-40.
13. von Gunten CF. The pendulum swings for opioid prescribing. J Palliat Med 2016;19:348.
14. Zhuo M. Ionotropic glutamate receptors contribute to pain transmission and chronic pain. Neuropharmacology 2017;112:228-34.
15. aan het Rot M, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. CMAJ 2009;180:305-13.
16. Gagnon B, Almahrezi A, Schreier G. Methadone in the treatment of neuropathic pain. Pain Res Manag 2003;8:149-54.
17. Lynch ME. A review of the use of methadone for the treatment of chronic noncancer pain. Pain Res Manag 2005;10:133-44.
18. Parsons HA, de la Cruz M, El Osta B, Li Z, Calderon B, Palmer JL, *et al.* Methadone initiation and rotation in the outpatient setting for patients with cancer pain. Cancer 2010;116:520-8.
19. Arout CA, Edens E, Petrakis IL, Sofuoglu M. Targeting opioid-induced hyperalgesia in clinical treatment: Neurobiological considerations. CNS Drugs 2015;29:465-86.
20. Kaur G, Kaur G, Bajwa SS. Inside preview of procuring narcotic license. Indian J Anaesth 2015;59:385-6.
21. Hagen NA, du Souich P, Lapointe B, Ong-Lam M, Dubuc B, Walde D, *et al.* Tetrodotoxin for moderate to severe cancer pain: A randomized, double blind, parallel design multicenter study. J Pain Symptom Manage 2008;35:420-9.
22. Eric Topol, TED Ideas worth Spreading. Available from: http://bit.ly/2Cs7Wlt. [Last accessed on 2017 Dec 24].
23. MMT in India. Available from: http://bit.ly/2CsrDtj. [Last accessed on 2017 Dec 24].