

# Role of Ketamine and Methadone as Adjunctive Therapy in Complex Pain Management: A Case Report and Literature Review

Wasek Faisal, Judith Jacques<sup>1</sup>

Department of Medical Oncology, Ballarat Regional Integrated Cancer Centre, Ballarat, Victoria, <sup>1</sup>Department of Palliative Care, Central Coast Cancer Centre, Gosford, NSW, Australia

## Abstract

Assessment and management of complex cancer pain always remains a major challenge for any palliative care team, given its heterogeneity of underlying pathophysiology and limitations of any pharmacotherapy. Here, we present a case of complex pain management in a young patient with a life-limiting illness, highlighting the issues of organic and nonorganic contributors of pain and provide some insight into the role of ketamine and methadone as adjunctive therapy to opioid analgesics. A brief literature review is also done to provide the context of use of these adjunctive drugs in this setting.

**Keywords:** Ketamine, methadone, pain management

## INTRODUCTION

Pain management remains one of the major challenges in the practice of palliative medicine. This is not only because pain is one of the most predominant symptoms in cancer patients but also because there is a wide range of pathophysiological process that causes pain, which needs a comprehensive assessment and specialized management strategies. It is well documented in the literature that effective pain management does not only improve a patient's quality of life but it also significantly improves overall survival in cancer patients.<sup>[1]</sup> Therefore, it is imperative to realize that manifestation of pain in a patient with a life-limiting illness can have a number of underlying pathophysiological dysfunction including physical, psychosocial, and spiritual aspects. Therefore, a comprehensive/multimodality approach toward pain management can be conceived to be intuitively more effective than unimodal approaches, such as pharmacotherapy. A comprehensive review of different pain management strategies is beyond the scope of this case study; however, this case highlights the different aspects of manifestation of pain and the challenges that were faced in managing it effectively. Some of the recent thoughts and evidence (or the lack of it)

of ketamine and methadone in cancer pain management are also briefly reviewed.

## CASE REPORT

A 25-year-old male, with known family history of hereditary nonpolyposis colon cancer, was diagnosed with a *de novo* stage IV (T4N2M1) transverse colon cancer on surveillance colonoscopy and underwent a total colectomy and partial hepatectomy. Histology revealed poorly differentiated adenocarcinoma of the colon with lymphovascular and perineural invasion. Four of 27 resected lymph nodes were positive for tumor deposit; the tumor was RAS and BRAF mutant.

He did not have any other known medical condition at the time and was not on any regular medication. He was a current

**Address for correspondence:** Dr. Wasek Faisal,  
Department of Medical Oncology, Ballarat Regional  
Integrated Cancer Centre, Ballarat, VIC 3350, Australia.  
E-mail: wasek.faisal@bhs.org.au

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smoker with 10-pack-year smoking history and also smoked marijuana on a regular basis, but did not report using any other recreational drug in inhaled or injectable forms. Although born to Catholic parents, he did neither identify himself to be a strong believer in religion nor claim to be an atheist. At the time of diagnosis, the patient was living independently at his home with his girlfriend.

The patient underwent 5 cycles of adjuvant chemotherapy with FOLFOX (5-FU, Leucovorin, and Oxaliplatin), but unfortunately developed disease progression 3 months after initial diagnosis, with the development of right femoral, adrenal, and nodal metastatic disease. The chemotherapy regimen was changed to FOLFIRI (5-FU, Leucovorin, Irinotecan), and the patient underwent prophylactic intramedullary nailing of the right femur to prevent pathological fracture, followed by radiotherapy to the same area.

The pain became an issue for the first time at this point. The patient reported gradual onset, constant, dull pain in the right inguinal and thigh area. It did not have any neuropathic feature to it. This bony pain correlated to the known metastatic site in the right femur and was partially helped with the palliative radiotherapy. The patient, who was opiate naïve at the time, was commenced on long-acting oxycodone 10 mg BID with the immediate release of oxycodone 5 mg as breakthroughs with good clinical efficacy. Three months after commencing second-line chemotherapy, the patient developed further progression of the disease as evidenced by new bony metastatic sites including right iliac crest, left femoral neck, and sacral ala as well as widespread liver metastases. He underwent prophylactic intramedullary nail insertion of the left femur followed by radiotherapy and an increase in his analgesic regimen with variable effects. Over the following 3 months, the patient's bony pain became a significant issue with multiple painful sites secondary to bony metastases which needed an escalation of his opioid doses by his medical oncologist, from long-acting oxycodone dose of 20 mg BID to ultimately 160 mg BID along with single fractions of palliative radiotherapy to the painful sites with partial but short-lived benefit.

Nine months after original diagnosis, the patient presented to the hospital with an acute pain crisis and this is when the patient was referred to the hospital palliative care team. The pain, as described by the patient, was widespread over multiple bony sites with a fluctuating pattern of intensity. The patient was mostly wheelchair bound at this stage as minimal amount of movement/weight-bearing seemed to exacerbate the pain. An increasing amount of oral breakthrough usage did not seem to alleviate the pain as reported by the patient. The patient also showed a significant amount of anxiety, frustration, and despair regarding the fact that his disease was progressing with no meaningful response to anticancer therapy. The patient felt that his increasing pain was a manifestation of his worsening disease status. On review, at least three different reasons for the suboptimal pain control were identified. First, a pattern of early satiety

and postprandial vomiting in the patient was noted, which, on investigation by barium swallow and gastric emptying studies, was confirmed to be gastroparesis (possibly related to platinum drugs in the chemotherapy regimen), suggesting that poor absorption of oral long-acting opioid drugs was contributing to poor pain control. Second, opioid tolerance was postulated to be contributing toward poor pain control, and finally, it was felt that the patient had significant existential distress, possibly manifesting as a pain syndrome.

With these working hypotheses, the acute pain crisis was managed by stopping all oral opioid analgesics and commencing the patient on regular 4<sup>th</sup> hourly subcutaneous hydromorphone including hydromorphone breakthroughs, and doses were up-titrated until an acceptable level of pain control was achieved. A therapeutic trial of dexamethasone 8 mg/day was also tried with minimal benefit and, therefore, ceased after 5 days. The delivery method of the analgesics was then changed to a continuous subcutaneous infusion through a syringe driver with 110 mg hydromorphone over 24 h with the provision of 15 mg as breakthroughs as a subcutaneous injection. Although this controlled the patient's pain optimally for 4 weeks, the pain became resistant to it again being evident by an increasing number of breakthroughs required in any given 24-h period (ranging from 12 to 20 breakthroughs). At this stage, in the absence of other therapeutic options (the patient had already exhausted radiotherapy options and an intrathecal block was deemed unacceptable to the patient), ketamine was added to the analgesic regimen. He was commenced on 300 mg of ketamine over 24-h through the syringe driver with 2 mg haloperidol to counteract the neuropsychiatric side effects with modest clinical improvement in pain control. The ketamine dose was further increased to 500 mg/24 h in the following 2 weeks with ongoing clinical benefit. Interestingly, this clinical improvement of pain control was also short-lived with further precipitations of pain crisis, when the ideas of disease progression, opioid tolerance, opioid-induced hyperalgesia, and psychosomatic aspects of pain manifestations were all considered and discussed with the patient. Low-dose methadone at 10 mg BID was added to the pain regimen at this stage with the dose increased up to 30 mg TDS with moderate therapeutic benefit.

Throughout the entire duration of palliative care team's involvement, other allied health professionals were invited to the case management, including clinical psychologist, social worker, and occupational therapist. Although the patient was receptive of the recommendations and suggestions of these teams in his overall management plan, he remained mostly reliant on his girlfriend for psychosocial support. Pastoral care visits were declined.

The patient's final hospital presentation was due to a combination of disease progression, progressive functional decline, and psychospiritual distress, which remained difficult to manage despite a concerted effort by palliative care, medical oncology, clinical psychology, and allied health teams. The

patient passed away peacefully in hospital 11 months after his original diagnosis.

### Role of ketamine in pain management

Ketamine hydrochloride is a dissociative anesthetic agent, commonly given intravenously or intramuscularly for surgical anesthesia. During the last decade, it has become apparent that low, subanesthetic doses of ketamine may improve opioid analgesia and has been widely used off label as an adjunct to opioid agents for poorly controlled cancer pain. Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. It interacts with NMDA receptor complexes, interrupts cholinergic transmissions, and inhibits the reuptake of noradrenaline and 5-hydroxytryptamine. There is good evidence from experimental animal models, human volunteer studies, and small clinical trials that NMDA receptor antagonists relieve some types of neuropathic pain.<sup>[2]</sup> However, their use is restricted by unpleasant adverse effects, including cardiac (hypertension and tachycardia, especially of concern in patients with ischemic heart disease) and neurologic (e.g., hallucinations, a sense of disconnection, vivid dreams).<sup>[3]</sup> There is also emerging evidence on the deleterious effect of ketamine on bladder function.<sup>[4]</sup> The NMDA receptor also seems to play a role in the development of opioid tolerance.<sup>[5,6]</sup> Ketamine in low doses (e.g., 1 mg/kg/24 h as a subcutaneous infusion) has been suggested to reverse or partially reverse opioid tolerance.<sup>[7]</sup>

There has been a general paucity of high-level clinical evidence of efficacy of ketamine in managing cancer-related pain. Evidence to support the use of ketamine in chronic cancer pain has mostly been extrapolated from other settings and has been justified primarily from case series and uncontrolled studies.<sup>[8-10]</sup> A randomized, controlled trial, although not in cancer pain, also reported the lasting effect of a single ketamine infusion in patients with ischemic pain.<sup>[11]</sup> Two randomized control trials of sufficient quality have also returned broadly positive conclusions.<sup>[12,13]</sup> On the contrary, a recent, well-powered, randomized, double-blind placebo-controlled study to assess the efficacy and toxicity of ketamine in the management of cancer pain concluded that no net clinical benefit exists for ketamine in this setting.<sup>[14]</sup> Although this is a major finding to refute the role of ketamine in cancer pain management, it is unlikely to influence the current clinical practice unless the results are reproduced in further well-designed, robust studies. Therefore, although the evidence base for ketamine as an adjuvant to opioids for cancer pain remains weak, the available literature allows for a cautious conclusion that there is a promise in the potential efficacy of ketamine as an adjuvant to opioids for cancer pain.

### Role of methadone in pain management

Methadone is a lipophilic and highly protein bound synthetic opioid with a 50%–80% oral bioavailability and a half-life of 72 h. Methadone has many attractive features as an analgesic, such as the high bioavailability, lack of known metabolic

products that produce neurotoxicity, and multiple receptor affinities. Most of its oral dose is absorbed and active within 30 min. Not only methadone has activity at the mu-opioid receptor but also it is an inhibitor of serotonin reuptake and a moderate antagonist at the NMDA receptor. These properties have raised interest in using methadone for neuropathic pain as well as for opioid tolerance and opioid-induced hyperalgesia.<sup>[15,16]</sup> The pharmacoeconomic benefit of methadone has also prompted a reappraisal of this medication since it is much less costly than proprietary sustained-release opioids. However, methadone undergoes N-demethylation through the cytochrome P450 group of enzymes to such a variable extent that there can be interindividual variability in steady-state serum levels. Thus, there are multiple potential drug interactions with medications commonly employed in pain management. There is also potential instability in methadone's effects related to variability in protein binding, excretion, and equianalgesic potency. The most significant risk of parenteral administration of methadone, which is unique to this medication, is QT prolongation, which can lead to potentially fatal arrhythmias including *torsades de pointes*. Close monitoring is especially needed in the presence of other risk factors such as electrolyte abnormality, structural cardiac disease, or some congenital diseases.<sup>[17]</sup> All of these have led to a divergence between the supporters and critics of methadone utilization.

While morphine has long been the “gold standard” by which other opioid analgesics have been compared, methadone has been proposed as a suitable alternative because of its lower potential for opioid-induced neurotoxicity, absence of active metabolites, and NMDA-receptor-antagonist activity. Unfortunately, this concept has not been widely studied, and a recent systematic review only found two studies comparing methadone to morphine and transdermal fentanyl, which showed comparable efficacy but increased toxicity and dropout rates for methadone. The evidence, however, was considered poor based on the quality of the studies and inconsistent results.<sup>[18]</sup> Another theoretical advantage of methadone might be mitigation of opioid-induced tolerance. Recent data support the conclusion that S-methadone (d-isomer), by virtue of its NMDA-receptor-antagonist activity, affects the development of morphine-induced tolerance and hyperalgesia. Using animal models of neuropathic pain, Davis and Inturrisi examined the ability of S-methadone to attenuate the development of morphine tolerance and to modify NMDA-induced hyperalgesia.<sup>[19]</sup> Administration of intrathecal S-methadone reversed tolerance induced by intrathecal morphine. In a related series of experiments, these investigators demonstrated an S-methadone-mediated reduction in hyperalgesia following administration of NMDA by d-methadone.<sup>[19]</sup> These results support the inhibitory effect of S-methadone on the development of morphine tolerance as a result of its NMDA-receptor-blocking activity. Notwithstanding, there remain limited clinical data relating to methadone's potential advantage in treating neuropathic pain, hyperalgesia, and



tolerance. Thus, its potential role in these conditions remains a compelling concept that requires further investigation.

There are several other settings where methadone may be advantageous. Methadone may be ideal for those patients with renal impairment as it does not accumulate in renal failure and is insignificantly removed during dialysis. Because of its intrinsic extended analgesic effects, methadone may also have an advantage over sustained-release formulations in those with rapid bowel transit times or in those with “short gut syndrome.”<sup>16</sup> Unfortunately, the dosing frequency required in such cases is unclear.

## DISCUSSION

Conducting scientifically sound clinical trials in palliative care patient population is a considerable challenge, reflected by the small number of published trials. The difficulty is due to the fact that the patient population is diverse in age, diagnosis and prognosis, and comorbidities, often with multiple concurrent medications, with unstable, deteriorating clinical states. Furthermore, given the heterogeneity of the patient population, pooled response data are often meaningless. Therefore, although evidence-based medicine remains a very attractive concept, its practical implication in palliative medicine remains challenging. The paucity of good clinical data for the use of ketamine and methadone in cancer pain management is reflected by this fact.

The patient presented here highlights the complexity of pain management at several different levels. First, this is a young patient with no premorbid medical condition being presented with a diagnosis of a life-limiting illness. This alone is sufficient to cause severe anxiety, psychospiritual and existential distress. The manifestation of this mental anguish can vary widely between individuals, and as described in the case vignette, compounded and impacted on patient’s pain threshold, perception, and coping mechanism. It is interesting to note that every time there was a documented disease progression and treatment failure episode, this was soon followed by an acute pain crisis and more curiously; every time a new analgesic drug was introduced, there appeared to be a therapeutic response. In the eye of a skeptic, this could partly be explained by an overwhelming desire to continue to search for hope and remedy to the dire situation. Second, opioid tolerance and poor absorption due to gastroparesis appeared to play a significant role in the early stages of pain management in this patient. Although the clinical evidence of ketamine in alleviating opioid tolerance is not robust, anecdotally, this certainly was deemed useful. The other issue of opioid-induced hyperalgesia is a diagnosis by exclusion, which merits further research. In the present case, an active attempt was made to explain this possibility to the patient with a view to limiting the total number of permissible breakthroughs in any 24-h period. Despite the patient being compliant with this strategy, it did not significantly improve the pain management, thereby questioning the validity of this diagnosis. The case also highlights the emotional, professional, and personal challenges

palliative care teams face when looking after a young patient who is facing an untimely death at the prime of their life.

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## Conflicts of interest

There are no conflicts of interest.

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