

FAST FACTS AND CONCEPTS #171 METHADONE FOR NEUROPATHIC PAIN

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Background Prescriptions for methadone have greatly increased in the past decade (1). The reason for this increase is likely related to two factors: reduced cost relative to other potent opioids and basic science data suggesting that methadone may be particularly useful in treating neuropathic pain. Two previous *Fast Facts* (#75, 86) reviewed methadone's pharmacological properties. This *Fast Fact* examines the research base regarding methadone and neuropathic pain and reviews the rise in methadone-related deaths.

Historical Context

- Prior to 1985, when long-acting morphine preparations were introduced, methadone was commonly prescribed for cancer-related pain as it had a longer duration of action than morphine. However, it was well appreciated that methadone had a higher risk of respiratory depression due to drug accumulation with chronic dosing – an effect not associated with other opioids, for which there is no drug accumulation in the setting of normal renal function.
- Prior to 1990 there was a widespread belief that opioids were relatively ineffective in treating neuropathic pain. Since then, there has been a much greater understanding that opioids are an effective part of neuropathic pain treatment.

Basic science data Methadone inhibits reuptake of norepinephrine and serotonin in a similar manner to newer anti-depressants, some of which are effective against neuropathic pain (e.g. duloxetine, venlafaxine). Also, methadone binds to the NMDA receptor, a known modulator of neuropathic pain. Finally, methadone has demonstrated efficacy in animal models of neuropathic pain (2).

Patient data Small non-controlled case series and two small randomized study (methadone vs. placebo) have demonstrated that methadone can reduce neuropathic pain in both cancer and non-cancer patients (3-6). There is no data, for or against the proposition, that methadone is superior to other opioids for neuropathic pain. A 2007 Cochrane Collaborative review found, “*there is no trial evidence to support the proposal that methadone has a particular role in neuropathic pain of malignant origin*” (7). Furthermore, the review cautioned clinicians about the danger of methadone-induced respiratory depression due to its long terminal half-life.

Methadone deaths There is a growing awareness that the increased prescription of methadone is being paralleled by a similar increase in methadone-related deaths. Methadone has been implicated in 30% to 40% of opioid related deaths in the US, even though methadone remains a small minority of opioids prescribed (8). The US Department of Health and Human Services convened an expert panel in 2003 to investigate the rise in methadone deaths and concluded that the rise was largely due to the increasing use of methadone as an analgesic (9). The Center for Disease Control published a report detailing data from Utah in 2005, suggesting that part of the problem was due to increased prescribing (10). The current data seem to suggest that the general increased supply of methadone, via legitimate prescribing, is leading to deaths due to accidental overdose through improper prescribing or illicit diversion/recreational use. In addition to concern about respiratory depression, there has been an observation that methadone, unlike morphine or hydromorphone, can prolong the QTc interval and lead to serious cardiac conduction abnormalities especially when coadministered with antiretrovirals in HIV patients (11). *Note:* the overall number of opioid-related deaths has increased, not just from methadone. *Note:* there are no data on untimely deaths related to methadone prescribing in hospice/palliative care patients.

Summary The renewed interest in an old drug holds exciting promise of benefit for the many patients with neuropathic pain. However, clinical research has yet to confirm or deny a unique clinical role for methadone compared to other opioids. The risk of respiratory depression should give clinicians pause before prescribing methadone based solely on the theory that it is a superior opioid in neuropathic pain. Coadministration of methadone with antiretrovirals may pose a particular risk for cardiac arrhythmias and therefore should be avoided if at all possible. Given that diversion of legitimate opioid prescriptions to the illicit market can occur, even in the practice of hospice and palliative care, physicians and hospice

agencies need to recognize they also have a larger social responsibility to the public welfare, and prescribe methadone with care and caution.

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