Review Article

Methods of Rotation From Another Strong Opioid to Methadone for the Management of Cancer Pain: A Systematic Review of the Available Evidence

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Abstract

Context. Up to 44% of patients with cancer-related pain require opioid rotation (OR) because of inadequate analgesia or side effects. No consensus exists regarding the most efficacious method for rotation to methadone.

Objectives. To define the available evidence regarding methods of rotation to methadone and to determine if sufficient evidence exists regarding the superiority of one method.

Methods. A predefined search strategy, using Medical Subject Headings (MeSH) search terms and keywords combined using Boolean operators, was performed. Study selection was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance. Data were extracted, quality of studies assessed, and narrative synthesis undertaken.

Results. A total of 3214 potentially relevant studies were identified. Twenty-five studies were included: 15 retrospective and 10 prospective ($n = 1229$). One trial compared three-day switch (3DS) and rapid conversion (RC) methods; two, 3DS; 10, RC; nine, ad libitum (AL). Success rates were as follows: 3DS—93%, RC—71.7%, and AL—92.8%. The single clinical trial and retrospective studies demonstrated poorer analgesia and an excess of adverse events (AEs) in the RC group (five dropouts because of AEs) compared with the 3DS group (no severe AEs). Time to stable analgesia was as follows: RC <4.3 days and AL <6 days.

Conclusion. Evidence identified was mainly from uncontrolled observational studies, making causality difficult to establish. Studies were heterogeneous in methodology and outcome measures. There was a trend toward excess AEs using the RC method, in comparison to the AL and 3DS methods. The methodological quality of the AL studies was low. A direct comparison of AL and 3DS methods would be informative. J Pain Symptom Manage 2015;50:248–259. © *2015 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words
Methadone, opioid rotation, cancer pain, review, three-day switch, rapid conversion, ad libitum

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage,[1] experienced by 50%–90% of cancer patients.[2] Pain may be caused by the direct effects of tumors, cancer therapies, or comorbidities.[1] An association has been demonstrated between increased cancer pain severity and increased psychological and spiritual distress.[3]

Opioids have been found to be effective in controlling cancer-related pain.[4] It is estimated that between 71% and 100% of patients achieve adequate control of cancer pain when the World Health Organization approach is used appropriately.[5] However, up to 30%

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of patients prescribed strong opioids will experience inadequate pain relief, intolerable side effects, or a combination of the two.[6]

Opioid rotation (OR) describes the practice of changing opioid choice, or route of administration, with the goal of either improving analgesic control or minimizing opioid-related adverse events (AEs).[7] The biological mechanisms for the observed beneficial effect of OR are explained by a combination of factors, including incomplete cross-tolerance,[8] genetic polymorphisms,[9] and interindividual variation in receptor types, interactions, density, and binding.[10] OR is necessary in 20%–44% of patients with cancer-related pain[11] and results in clinical improvement in 40%–80% of cases.[12,13]

Methadone is a unique synthetic opioid with activity at both μ-receptors, and *N*-methyl-D-aspartate receptors,[14] which are implicated in the development of neuropathic pain. Two systematic reviews[15,16] have examined the use of methadone for cancer-related pain. Four studies that compared methadone to other oral or transdermal strong opioids[17–20] found that methadone provides similarly effective analgesia as morphine sulfate, oxycodone, and hydromorphone and is associated with no more side effects than these opioids. The European Association for Palliative Care has recommended that methadone may be used as a first-line strong opioid for moderate-severe cancer pain.[13,21] Furthermore, methadone has several characteristics that make it an attractive option in cancer pain: it is relatively inexpensive; its metabolites are inactive[4] and do not accumulate in renal failure;[22] and it may be administered either orally, rectally, or parenterally.[22] Challenges surrounding the use of methadone for cancer pain include an association with QTc-interval prolongation[14] and a historical stigma surrounding the use of methadone as a treatment for opioid addiction.[4]

Much of the published research regarding the use of methadone for cancer-related pain has focused on identifying safe conversion ratios that can be used to rotate to methadone from other strong opioids. This is a complex topic as methadone exhibits a complex pharmacodynamic/pharmacokinetic profile. The oral bioavailability of methadone is 80%, compared with morphine sulfate, which is approximately 30%.[23] Wide interindividual variation in metabolism occurs as a result of common genetic polymorphisms in the CYP3A4 and CYP2D6 enzyme families,[24] as well as within the CYP2B6 enzyme, which has more recently been found to be predominantly responsible for methadone metabolism.[25,26] This results in a wide and variable plasma half-life, ranging from 13 to 58 hours.[13,14] This can contribute to unpredictable accumulation of methadone during the early days and weeks of treatment, potentially leading to toxicity, including respiratory depression.[27] Dose conversion ratios from other strong opioids to methadone are affected by previous opioid use, and when rotating from higher oral morphine-equivalent doses, a higher conversion ratio is required.[6] The relative potency of methadone and other opioids varies depending on the direction of the rotation.[27]

There is increasing evidence that the use of opioid dose conversion ratios published in equianalgesic tables may be an important associated and contributing factor in adverse patient outcomes, in particular when rotating from opioids to methadone. Several reviews have recently drawn attention to the limitations inherent in the construction of such equianalgesic tables.[27] Such limitations are well described in the literature and include

- Study designs that used a single dose or limited range of doses via a specific route, which may not generalize to chronic dosing or alternative routes of administration;
- Studies performed in nonopioid-tolerant patients;
- Study populations that did not include patients with concurrent illness, organ dysfunction, or concomitant medication use;
- That most opioid equianalgesic dose studies were performed before recognition of significant opioid receptor polymorphisms, which has implications for major interindividual differences in opioid responsiveness.[27]

As a result of the challenges outlined previously, the recent European Association for Palliative Care guidelines did not provide firm recommendations regarding equianalgesic conversion ratios for methadone.[13] In a systematic review, Weschules and Bain[28] described the important distinction between rotation to methadone as a *care pathway* as opposed to a *dose calculation* and the need to take into account such factors as individual patient characteristics, individual therapeutic goals, and care setting, when rotating to methadone from other strong opioids.

In carrying out this care pathway when rotating to methadone, various methods of rotation are used in clinical practice.[29] The most commonly reported methods in the literature are the *stop and go* method, which itself may be categorized into the *rapid conversion* (RC) and the *ad libitum* (AL) methods, and the *three-day switch* (3DS) method (Table 1). It has been proposed that the 3DS method, by gradually replacing the original opioid with an equipotent dose of methadone, avoids methadone accumulation and toxicity, especially for patients on high opioid doses.[29] Advocates for the RC method argue that because of

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