From methadone to Methadose

Lessons learned from methadone formulation change in British Columbia

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In British Columbia (BC) in 2014, the Ministry of Health implemented a change in methadone formulation affecting approximately 15 000 patients receiving oral methadone for opioid agonist therapy. Instead of a pharmacy-compounded solution of methadone mixed with a flavoured drink (Tang), patients now received a premixed cherry-flavoured methadone syrup (Methadose) that was 10 times more concentrated. Despite the manufacturer's and the health officials' expectations that the 2 formulations would be clinically equivalent, many patients soon began voicing concerns that Methadose was an inferior treatment for their opioid use disorder. In this article, we review what happened in BC, report our success with a third alternative, and recommend precautions for future methadone formulation changes.

Three studies have investigated BC patients' responses to this change. The first, a qualitative study that interviewed 34 patients who were receiving oral methadone for opioid agonist therapy, found that many of the patients reported worsened withdrawal symptoms following the change to Methadose.[1] The second, a survey of 405 patients taking Methadose, found that more than half of the respondents experienced worse pain and withdrawal after the formulation change, and approximately one-third increased their dose of Methadose in response.[2] The third, a cohort study of 331 HIV-positive people who used drugs, demonstrated that heroin use increased by 11.5% (95% CI 5.6% to 17.4%) and antiretroviral therapy adherence decreased by 15.9% (95% CI 5.0% to 26.7%) immediately following the change.[3] These values represent higher heroin use and lower antiretroviral therapy adherence during the 2 months following the change than during any of the 15 months before the change.[3] This third study also measured methadone treatment enrolment and HIV viral load suppression, neither of which decreased in relation to the change.

As a whole, these studies' findings, along with numerous anecdotal reports of relapses and deaths, suggest that the change in methadone formulation led to destabilization of patients and a significant rise in opioid-related morbidity and mortality.

A new solution?

Many patients who believed that Methadose was ineffective have recently transitioned to a third formulation called *Metadol-D,* a liquid methadone solution diluted with an orange-flavoured drink (Tang). Metadol-D was made available in 2018 primarily as a result of advocacy on the part of patient-led organizations, including the BC Association of People on Methadone, which were seeking an effective alternative for patients who did not respond well to the 2014 formulation change. Anecdotally, we, as well as the community of practice in BC, have found overwhelmingly that Metadol-D is an effective alternative. Whereas patients were experiencing withdrawal symptoms such as cravings, malaise, nausea, and pain as early as 10 to 14 hours after their dose of Methadose, they are free from these uncomfortable symptoms for closer to 24 hours with Metadol-D, making stability on a once-per-day dosage more possible. The change to Metadol-D has created a substantial positive effect on patients' social stability and illicit drug use. Very few patients have asked to return to Methadose.

Why some patients deteriorated after switching to Methadose and now report improvement after switching to Metadol-D remains unclear. Patients often prefer one brand of a drug over another, and we often do not know why that is. Where possible, we should simply accommodate patient preference, as we should do with methadone formulations, even in the absence of clinical trials.

Seeking understanding of change intolerance

Additionally, understanding the possible mechanisms of methadone change intolerance could help clinicians and policy makers mitigate future harms caused by formulation changes.

Formulations might differ in bioavailability or in the ratio of the 2 enantiomers of methadone (R- and S-methadone). According to Mallinckrodt's product monograph for Methadose[4] and a Paladin Labs medical information representative's description of Metadol-D (personal oral communication, January 2020), however, both products are racemic mixtures (ie, containing equal proportions of R- and S-methadone). As well, the existing knowledge based upon controlled clinical comparison of methadone formulations is limited. We are aware of no clinical trials directly comparing the formulations in question in BC.[5] One double-blind randomized controlled trial conducted in 1999 by Gourevitch et al[6] has, however, compared liquid Methadose to 2 other formulations. The authors found no significant differences in either plasma concentrations or subjective opioid withdrawal scale scores among 18 patients.[6] Importantly, plasma concentrations do not differentiate methadone enantiomers, so isomer ratios might still have been different.

Mallinckrodt, the manufacturer of Methadose, used Gourevitch and colleagues' findings to justify their expectation that Methadose would be clinically equivalent to

the old methadone formulation in BC.[7] This expectation was inappropriate for at least 2 reasons. First, Gourevitch and colleagues' findings do not rule out pharmacologic differences in BC, where Methadose is being "compared" to different formulations than those used in their study. Second, the well documented history of real-world instances of methadone change intolerance—including observational studies in the United States and the United Kingdom that have found substantial increases in social instability and nonprescription drug use following methadone formulation change[8,9]—provides evidence of a pattern of destabilization events resulting from methadone formulation changes.

Psychological mechanisms might also be responsible. Patients might, for example, expect reduced drug effectiveness because of the reduced volume of Methadose or because of a distrust of health care providers. Relatedly, patients might experience stress due to a feeling of loss of control of their treatment or due to the disagreeable taste of the new formulation. These mechanisms are plausible, given the well-known influence of psychology on drug effects (eg, the placebo effect). A conditioning mechanism is also possible, whereby a sensorineural association might form between the vehicle (eg, orange-flavoured Tang) and the physiologic effect of the drug, such that changing the vehicle diminishes or alters the effect, irrespective of higher psychological processes. It is important to emphasize that, to the extent that psychological mechanisms are responsible for change intolerance, they create a real clinical effect on the population we treat and should not be dismissed as readily modifiable or as the fault of the patient.

Proceed with caution

Despite the currently limited evidence, clinicians and policy makers should take precautions if a methadone formulation change is proposed in the future. It is important that the reasons for the change are deemed important and in the best interest of the patients taking the drug. If a formulation change must go forward, we must ensure that manufacturers provide chiral identity to the previous formulation. Additionally, where possible, the vehicle ought to be similar or identical to that of the previous formulation so as to maintain psychological familiarity. Health care providers and drug manufacturers should exercise flexibility and patient advocacy in making alternative formulations accessible for patients who do not respond well to a formulation change. Last, a growing evidence base indicates that close involvement of community stakeholders in the planning and implementation of public health policies reduces costs and improves patient satisfaction.[10] For this reason, public health efforts should be made to extensively consult with and inform patients about intended changes and to proceed in collaboration.

The experience in BC should be a cautionary story for any jurisdiction considering a formulation change for methadone. The likelihood of harm to patients was underestimated before the change, and we were slow to respond with an alternative formulation after harm became clear. Fortunately, offering Metadol-D as an alternative to Methadose appears to be greatly beneficial. We encourage investigation of the mechanisms underlying change intolerance. With considerate planning and some continued study, we can prevent this pattern from recurring and protect patients from additional harm.

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Competing interests
None declared

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