Editorial Comment

Stephen H. Butler

Some controversies related to questionable clinical uses of methadone for chronic non-cancer pain and in palliative care

https://doi.org/10.1515/sjpain-2020-0178
Published online March 16, 2021

> "Where there is much desire to learn, there of necessity will be much arguing, much writing, many opinions: for opinion in good men is but knowledge in the making". John Milton 1644.

Introduction

Methadone has become popular as an alternative to other opioids in the treatment of chronic pain and pain associated with cancer. It has also become fashionable to add low dose methadone to other opioids in the mistaken belief that this will increase the analgesic effects by interaction with not only opioid receptors but also *N*-methyl-D-aspartate (NMDA) receptors and receptors for other neurotransmitters. This critique of some current practices is in response to many questions on the use of methadone that surface in discussions in Scandinavian pain clinics concerning complex and often difficult pain management issues. The commentary will not address the use of methadone in the perioperative setting as reviewed by E. Kharasch [1].

1) What dose of methadone is necessary to reach maximal receptor occupancy?

Receptor occupancy would seem to be at the crux of this discussion and many researchers have attempted to assess this with varying success. If mu (MOR, MOP) receptor occupancy by methadone or other opioids is sufficiently high, this will prevent additional opioid from reaching the receptors to produce an added clinical effect. Attempts to assess receptor occupancy in humans so far have been difficult. In a study by Melichar et al. [2], eight patients in a methadone maintenance program for opioid abuse with methadone doses from 18–90 mg daily were assessed for opioid receptor occupancy. Positron Emission Tomography (PET) with a radio-ligand was used. Receptor occupancy by this method was negligible at all doses but further studies have shown that this tracer is not sensitive, even for morphine [3, 4]. The inference, however, is that there was significantly high receptor occupancy at all doses since a parallel study in rats showed no decrease in radio-ligand binding by increasing the methadone dose from 0.35 mg/kg iv to 1.0 mg/kg, a three-fold increase. A further clinical study by Kling et al. [5] using PET but a different radio-ligand, again showed low receptor occupancy by methadone and concluded "adequate doses of methadone fully protected against any perception of superimposed short-acting opiates". The methadone doses here were from 30 –60 mg methadone per day. Another theory is that methadone produces receptor changes significant enough to block the effects of adding other opioids [6] but again, this indicates high occupancy.

The dose/response curve for most mu agonists is exponential at high receptor occupancy and appears to flatten at or slightly above the equivalent of 20 mg/day methadone, either due to receptor occupancy alone or possibly also to receptor desensitization. Escalating methadone doses (also other opioids) ad infinitum as is commonly done clinically, is based on the assumption that the dose/response curve is arithmetic – a straight line – for all doses. This is the basis for the belief that "more is better". Studies of cell cultures for opioid occupancy of mu opioid receptors show a logarithmic curve for all commonly used opioids and also for DAMGO, the standard experimental reference mu agonist [7]. Do not expect an improvement in analgesia with even doubling or tripling the methadone dose, or the dose of any other opioid agonist. This finding is in line with the experience of the University of Washington pain clinic [8]. In the detoxification program which occasionally led to low dose methadone maintenance, the maximum dose of methadone used was 20 mg/day with the experience that higher doses did not have a greater effect.

In another study by Melichar et al. [9], 18 mg methadone was sufficient to block the majority of the effects of

Stephen H. Butler, MD, Academic Hospital, Uppsala, Sweden, E-mail: stephen.butler@pubcare.uu.se

Open Access. © 2021 Stephen H. Butler, published by De Gruyter. This work is licensed under the Creative Commons Attribution 4.0 International License.

high-dose hydromorphone (5, 10 mg sc = approx. 20/40 mg morphine sc). However, this blockade was somewhat dose-dependent with doses above 60 mg methadone being slightly more effective for the 10 mg hydromorphone challenge. As an aside, it was obvious that all doses of methadone were adequate to prevent abstinence since the subjects in this Melichar et al. study were in a methadone maintenance program for drug abusers. Admittedly, this study has very few participants and the data need to be supported by further research.

2) What methadone dose is sufficient to prevent abstinence in a maintenance program for chronic pain?

This is difficult to glean from the literature in that most data come from the abuse population, not a chronic pain population, as do the above studies. The usual primary outcome in abuse treatment programs assessing the effectiveness of treatment with methadone substitution is the prevention of concomitant "recreational" use of heroin by the patients. The aim of the methadone dosing is to prevent craving for heroin and/or to block the "high" from heroin supplementation, not to prevent abstinence. The two endpoints are very different [10]. The mistaken assumption that the dose of methadone sufficient to block a heroin "high" is also the dose needed to prevent abstinence is not borne out by the evidence. Data from many studies do separate the two endpoints since the concomitant use of heroin with methadone is based on the abuser's desire to get "high", not to avoid abstinence [9, 10]. Heroin self-administration is less in patients in abuse treatment on higher methadone doses. Older studies compare doses from as low as 20 mg to higher levels to assess retention levels and show that the retention level (i.e., drop-out prevention) is better with high methadone doses (80 mg and up) but all doses are sufficient to prevent abstinence [9]. These high methadone doses and the opioid challenge doses would fall on the flat trajectory of the dose/response curve. Also note that the "high" does not equal analgesia.

There is another explanation for high dose methadone use in maintenance programs based on the dosing system which is standard in abuse treatment but not in chronic pain treatment. Almost all methadone maintenance programs use once-a-day dosing on site. Patients need to report daily to the program for their methadone dose and it would be inconvenient for staff and patients for them to come 3–4 times a day as is routine for methadone dosing for chronic pain. In a study by Donny et al. [10], heroin abuser volunteers, not in a treatment program, were tested using a step-wise increase in methadone dosing (30–60–120 mg/day). They were then given a heroin challenge (10 & 20 mg) at each step and their ability to assess the effects of the heroin plus physiological variables were the outcome criteria. Note that the challenges were given 4, **28**, and **52** h after the methadone dose. After three weeks of once-a-day dosing, all methadone doses were equally effective in the preventing abstinence in the opioid abusers in this study. Again, it is important to note that the participants were recruited from a cohort of street abusers. They represent what would be seen in pain patients beginning methadone substitution as the primary opioid (switch) to stabilize a difficult clinical situation or when entering a detoxification program.

3) Why higher dosing in methadone maintenance programs for opioid abusers?

Think of the previous information. High dose use is primarily to prevent abusers from supplementing their methadone with their abuse opioid of choice, often heroin. From the above studies, it is apparent that a "low dose" of methadone is 20–30 mg/day. A "high dose" would be 60 mg and above. One explanation, again, for why higher doses in these programs are necessary lies in the dosing schedule which is once-daily. In the Donny et al. study [10], heroin challenges were given 4, 28, and 52 h after the methadone. A more appropriate timing would be 24 h to mimic the clinical situation in methadone maintenance programs and 4–6 h for a pain population. Obviously, the 28 h and especially the 52 h timing would necessitate a much higher methadone dose to have significant receptor occupancy to block the heroin. At these later time points, blood levels of methadone would be much lower than at 6 h and, theoretically, lower at the mu receptors but, unfortunately, studies of receptor occupancy dynamics are not available to verify this. Would this be the same if the abuse subjects were receiving methadone 3–4 times a day and were challenged 4–6 h after the last dose?

With regard to this last point, in a study by Jiang et al. [11] in opioid abusers receiving a single methadone dose daily, methadone plasma levels were measured just before and just after their daily dose. Those that had a greater difference between these measures ("peak-to-trough" difference) were more likely to relapse. This is an indication that daily plasma fluctuations also mean fluctuations in receptor occupancy throughout the day. This is the reason behind high once-daily methadone doses in drug abuse treatment programs. Keep the just-before-dosing serum/CSF/brain levels high. The same study in pain patients receiving 3–4 doses of methadone per day would not have the same peak-to-trough fluctuations. This is presumptive evidence that even lower total daily doses on a 3–4/day

dosing schedule would be adequate to prevent abstinence when converting from another opioid to methadone. Perhaps this would also prevent supplementation in opioid abusers.

4) Are methadone serum levels useful in assessing dosing for chronic pain patients (or for drug abusers)?

The Jiang et al. study mentioned above shows that the timing of sampling is important. The literature talks about "steady state" in discussing the PD/PK situation with chronic dosing o f methadone. The Jiang et al. study shows that the plasma levels of methadone are not at all "steady state" with some very wide swings in some individuals. The mean peak-to-trough differences varied up to 70% and standard deviations of measurements were in the 50% range, even in those sampled. The evidence also in this study is that the plasma levels were not closely related to dosage due to variability in pharmacokinetics. Studies show [1, 12] that there are fast metabolizers and slow metabolizers. Peak serum concentrations occur between 2.5 and 4 h after dosing because of highly variable inter-subject metabolizing of methadone. Another aspect is the effect of other drugs taken concomitantly. This is especially so in pain patients who often take tricyclic anti-depressants or other psychotropics and medications for comorbid conditions that also alter liver enzyme degradation [1, 12]. Methadone serum levels between subjects on similar doses vary widely and therefor random sampling not related to the metabolizing rate of the individuals or the timing of dosing of methadone may not be very helpful. Studies in pain patients on 3–4 daily doses of methadone are needed.

A review by Fonseca et al. [13] delves more deeply into the pharmacogenetics of methadone metabolism and explains much of the confusion in the literature over serum levels and dosing. We have little evidence for the correlation of serum levels to cerebrospinal fluid levels or, more importantly, the correlation of serum levels to brain receptor occupancy of methadone. Leavitt et al. [14] recommend tailoring the dose of methadone in drug abuse treatment programs to compensate for fast metabolizers who will need higher once-a-day doses so that the trough will not be so low.

5) Should we expect any analgesic effect from adding other opioids to a baseline of methadone or, conversely, from adding low dose methadone to a baseline of another opioid?

The origin of this practice is obscure but it probably evolved from the use of "opioid switching", "opioid rotation" in cancer patients with pain. The initial studies of opioid switching were case series in patients where side effects prevented a dose increase of opioid when pain was not controlled [15]. Since many patients had better pain control (only for about two weeks) on the second opioid at lower equivalent doses with fewer side effects, the initial reason for the switch was lost. The focus became better pain control, not control of side effects. Many paradigms for the switch/rotation involve tapering down the initial opioid while tapering up the second and therefore, two opioids were administered together with better effect than with the initial opioid. The next step in the reasoning was to invoke the principle of incomplete cross-tolerance, i.e., opioid receptors respond differently to different opioids since there are many sub-classes of opioid receptor types [16]. The theory is that higher total receptor occupancy can be achieved with two opioids than with one. It is possible that this could be the case with low dose opioids but it seems unlikely with high receptor occupancy. Think of the logarithmic dose-response curve. The heroin challenge data from the Donny et al. [10] study is evidence that adding another opioid to a high dose of methadone will have little effect.

Is there any clinical or pre-clinical data to support the addition of low dose methadone to other opioids for better effect? Some evidence does exist for the addition of methadone to a base of morphine. Tolerance to morphine is felt to be due to its weak ability to cause internalization of the mu receptor from the cell membrane. In an animal model, methadone caused internalization of the mu receptor in morphine-tolerant mice with the reversal of tolerance [17]. This could improve analgesia but that evidence is lacking. The addition of methadone to other opioids would not have the same effect since other opioids in common use, other than oxymorphone (metabolite of oxycodone, used clinically in the United States of America [USA]), cause internalization of mu receptors. What dose of methadone is needed to produce this effect is unknown. Studies in volunteers and then a patient population are needed to test this hypothesis. The basis for the practice seems to be "expert opinion". With the logarithmic dose-response curve of opioids, is it reasonable to expect that a low dose of methadone can actually reach any receptors?

6) Is there any evidence that methadone has a clinical effect due to its interaction with NMDA receptors?

In theory, this seems possible from animal studies [18] and the studies show that it is the D-stereoisomer of methadone that has the strongest NMDA antagonistic effect in rats. Some countries only use the L-stereoisomer clinically since this has the strongest effect at the mu receptors and the

NMDA antagonism is very low with this stereoisomer. The theory is often applied and an NMDA effect is also imputed for the clinical use of the less affective L-stereoisomer.

Is there any research evidence, basic or clinical, that there is a strong NMDA antagonistic effect of methadone? Evidence shows that the effect is minimal and may not be significant clinically except at very high doses. One study [19] trained rats to discriminate between methadone and saline and then exposed the rats to MK-801, a potent NMDA antagonist, and saline in the same test. The rats could not distinguish between MK-801 and saline, implying that the methadone discrimination could not have been related to NMDA antagonism. Not a good study. It would have been more interesting if the rats used were a neuropathic pain model. However, the same group went further and looked at the ability of D-methadone to displace MK-801 from NMDA receptors and found little effect. More pre-clinical studies need to be done but the evidence is that even the D-stereoisomer of methadone is not a strong NMDA antagonist.

A recent Cochrane Review [20] to examine the efficacy of methadone in neuropathic pain found little evidence for a positive effect. In one study, morphine was superior to methadone. The studies were not rated very highly. There was no significant improvement in pain at the 30% or the 50% level when combining data from all the studies. This information refutes the use of methadone as an NMDA antagonist in neuropathic pain as has been suggested in the literature [21].

7) Should we expect that the putative serotonergic effects of methadone are clinically relevant?

There are many case reports about the occurrence of the serotonergic syndrome in association with opioid use. Occasionally, methadone has been implicated. There is some basic science evidence that this is possible but is it clinically relevant? Some clinicians propose that methadone is the opioid of choice in patients with neuropathic pain who are also being treated with anti-depressants that increase serotonin levels due to methadone's minimal effects on serotonin.

8) Is there any evidence that increasing the dose of any opioid for chronic pain beyond recommended levels is helpful?

A recent study in Pain [22] retrospectively analyzed the difference in pain control in two groups of chronic pain patients. This study, in a large sample of 53,187 patients with a variety of pain conditions, compared a stable dose of opioids with doubling the dose over several months. There was a trend to lower pain scores in the stable opioid users and no change in pain scores with doubling the dose. This study may be criticized since it is retrospective and the various pain diagnoses are lumped together. However, the size of the study population and the variables analyzed call into question, as do the above studies, simply continuing to increase the dose of opioids when there is little effect at the recommended levels. All chronic pain is not opioid sensitive. One possible explanation for the difference in the two groups could be that those on stable doses of opioids were opioid sensitive and those in the opioid escalation group was not. The fact that the pain levels were similar at study start and this was chronic administration, not newly instituted opioid treatment negates this. The supposition that "more is better" is part of the reason for the opioid epidemic in the USA.

9) Adverse events

Although a discussion of adverse events is not a part of this article, adverse events are always of concern with any opioid, methadone included [23, 24]. Adverse events are dose related and many are not trivial. Some, torsade de pointes (primarily the D-stereoisomer) and respiratory depression, are life threatening. Increasing the opioid dose in the belief that "more is better" does not apply to side effects. The effects on the hypothalamic-pituitary-adrenal axis and other hormones are also not trivial and lead to a decrease in quality of life for many on chronic opioid therapy.

In conclusion, there are many practices in the use of methadone in the treatment of patients with complicated pain problems that are based more on "expert opinion" than on solid research in opioid pharmacology. Many practices use information from methadone maintenance programs treating drug abuse with the belief that this is appropriate for chronic pain patients on opioids. If chronic pain patients are not opioid abusers, most of this cross-over information does not apply. If these pain patients are drug abusers, they do not belong in the pain clinic.

A wise clinician once advised me to "never prescribe in the hope rather than the belief that the drug will work". I propose a modification: never prescribe in the hope that the drug will work without basing prescribing on data from research". Primum non nocere. Pain is a biopsychosocial phenomenon but opioid prescribing remains in the "bio" realm.

Finally, some advice from Francis Bacon (1551–1626), arguably the father of modern science. He cautioned against "idols and false notions" that impede the march of science [25].

Research funding: None declared.

Author contributions: The author has accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: The author declares that he has no competing interests.

References

1. Kharasch ED. Intraoperative methadone: rediscovery, reappraisal, and reinvigoration. Anesth Analg 2011;12:13–6.
2. Melichar JK, Hume SP, Williams TM, Daglish, Taylor LG, Ahmed R, et al. Using [11C] diprenorphine to image opioid receptor occupancy by methadone in opioid addiction: clinical and preclinical studies. J Pharmacol Exp Therapeut 2005;312:309–15.
3. Lingford-Hughes A. Human brain imaging and substance abuse. Curr Opin Pharmacol 2005;5:42–6.
4. Hume SP, Lingford-Hughes AR, Hataf V, Hirani A, Ahmed R, Davies A, et al. Low sensitivity of the positron emission tomography ligand [11C]diprenorphine to agonist opioids. J Pharmacol Exp Therapeut 2007;322:661–7.
5. Kling MA, Carson RE, Borg L, Zametkin A, Matochik JA, Schluger J, et al. Opioid receptor imaging with positron emission tomography and [18F]cyclofoxy in long-term, methadone-treated former heroin addicts. J Pharmacol Exp Therapeut 2000;295: 1070–6.
6. Rodriguez-Martin I, Braksator E, Bailey CP, Goodchild S, Marrion NV, Kelley E, et al. Methadone: does it really have low efficacy at u-opioid receptors? Neuroreport 2008;19:589–93.
7. Volpe DA, Tobun GA, Mellon RD, Katki AG, Parker RJ, Colarsky T, et al. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol 2011;59:385–90.
8. Halpern L. Substitution-detoxification and its role in the management of chronic benign pain. J Clin Psychiatr 1982;43:10–4.
9. Melichar JK, Myles JS, Eap CB, Nutt DJ. Using saccadic eye movements as objective measures of tolerance in methadone dependent individuals during the hydromorphone challenge test. Addiction Biol 2003;8:59–66.
10. Donny EC, Walsh SL, Bigelow GR, Eissenberg T, Stitzer ML. High-dose methadone produces superior opioid blockade and comparable withdrawal suppression to lower doses in opioid dependent humans. Psychopharmacology 2002;161:201–12.
11. Jiang H, Hillhouse M, Du J, Pan S, Alfonso A, Wang J, et al. Dose, plasma level, and treatment outcome among methadone patients in Shanghai, China. Neurosci Bull 2016;32:538–44.
12. Eap CB, Bertschy G, Baumann P, Finkbeiner T, Gastbar M, Schebaum N. High interindividual variability of methadone enantiomer blood levels to dose ratios. Arch Gen Psychiatr 1998; 55:88–90.
13. Fonceca F, Torrens M. Psychogenetics of methadone response. Mol Diagn Ther 2018;22:57–78.
14. Leavitt SB, Shinderman M, Maxwell E, Eap CB, Paris P. When “enough” is not enough: new perspectives on optimal methadone maintenance dose. Mt Sinai J Med 2000;67:404–11.
15. Mercadente S. Opioid rotation in cancer pain. Rational and clinical aspects. Cancer 1999;86:1856–66.
16. Pasternak GW. Incomplete cross-tolerance and multiple mu-opioid peptide receptors. Trends Pharmacol Sci 2001;22:67–70.
17. Posa L, Accarie A, Noble F, Marie N. Methadone reverses analgesic tolerance induced by morphine pretreatment. Int J Neuropsychopharmacol 2016;19:1–11.
18. Gorman AL, Elliott KJ, Inturrisi E. The d- and l-isomers of methadone bind to the noncompetitive site on the N-methyl-D-aspartate (NMDA) receptor in the rat forebrain and spinal cord. Neurosci Lett 1997;223:5–8.
19. Doi S, Mori T, Uzama N, Arima T, Takahashi T, Uchida M, et al. Characterization of methadone as a β-arrestin-biased u-opioid receptor agonist. Mol Pain 2016;12:1–9.
20. McNichol ED, Ferguson MC, Schumann R. Methadone for neuropathic pain in adults. Cochrane Database Syst Rev 2017;5: CD0112499.
21. Brown R, Kraus C, Fleming M, Reddy S. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. Postgrad Med 2004;80:654–59.
22. Hayes CL, Krebs EE, Hudson Y, Brown J, Li C, Martin B. Impact of opioid dose escalation on pain intensity: a retrospective study. Pain 2020;161:979–88.
23. Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence in collaboration with the Heart Rhythm Society. J Pain 2014;15:321–34.
24. Benyamin R, Trescot AM, Datta S, Buenevantura R, Adlaki R, Sehgal N, et al. Opioid complications and side effects. Pain Physician 2008;11:S105–20.
25. Weinfurt K. Vanquishing false idols, then and now. Science 2020; 367:1312.