Rapid Communication

A new mathematical approach to methadone conversion

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For the past 20 years, methadone has been experiencing resurgence in the palliative care community as a second-line opioid for the treatment of cancer pain.[1,2] Methadone is useful for refractory pain in cancer patients or in those who could not tolerate the side effects of other opioids; its positives are well cited in recent literature including dual elimination without active metabolites, N-methyl-D-aspartate antagonism, mu and delta receptor activity, multiple routes of administration, rapid onset of action, long half-life, low cost, and fewer adverse effects.[3,4] Despite the abundance of recent case reports and literature reviews demonstrating the effective use of methadone in cancer patients, there is a lack of consensus for an appropriate method for converting morphine (and by extension, other opioids) to methadone.[1-6]

It is generally agreed in the literature that the original conversion method proposed in 1977 suggesting a morphine-to-methadone ratio of 1:1 is not appropriate as methadone has since been shown to be more potent than was originally thought.[7] Using the 1:1 conversion could lead to respiratory depression and death, especially at high doses. This alone could have contributed to the unfavorable attitude of clinicians toward methadone in the past. Today, multiple approaches to a safer methadone conversion method have been proposed, some more complicated than others.[4,5,8]

In addition to the Morley-Makin method, which assumes a 10:1 morphine to methadone ratio at low doses, and an every 3 h prn regimen of methadone at higher doses,[4] two other commonly used methods are Plonk's method[8] and the Ayonrinde tables.[5]

The Plonk method is a linear equation of the form:

$$\text{Methadone (mg)} = \frac{\text{Morphine (mg)}}{15} + 15$$

This method assumes a linear relationship between methadone and morphine that likely does not exist and is useful in the lower range of morphine equivalent doses (300–600 mg).[6,7] The Plonk equation assumes a starting dose for opioid-naive patients of 15 mg/day or 5 mg per oral (PO) three times a day (TID) (i.e., the *y*-intercept of the equation is 15; therefore when morphine is zero, f [*x*] will be 15). At higher doses of morphine, the Plonk method is assumed to return overly high doses of methadone, theoretically to infinity, as illustrated in Graph 1.

The Ayonrinde method, on the other hand, is a changing ratio method that takes into account the need for lower relative doses of methadone with escalating morphine equivalent doses [Table 1].[5]

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This method moderates the doses in the higher range conversions but suffers from significant discontinuities at the ratio transition points. For example, the methadone dose at 300 mg of PO morphine equivalents would be 60 mg, but at 301 mg of PO morphine would be 30.1 mg, a 2-fold difference. These discontinuities can be most easily appreciated visually [Graph 2].

Note that after 1001 mg of PO morphine, the methadone dose again rises linearly with a slope of 1/20. In addition, the graph intercepts the *y*-axis at zero and therefore does not output a "starting dose," for opioid-naive patients, unlike the Plonk method (which outputs a starting dose of 15 mg/day, as noted above).

What is needed is a method that smoothly, without discontinuity, and without undue linearity outputs a reasonable and safe methadone dose for general use. In addition, outputting a starting dose when the patient is opioid naive (i.e., morphine dose = 0) would be helpful.

Noting that the Ayonrinde method in particular has the overall quality of rapid increase at low doses, with a more gradual increase at higher doses, the authors explored the possibility that the correct mathematical form would be a parabola with the form:

$$y = \sqrt{AX} + b$$

where *A* is a constant, *X* is the morphine dose, and *b* is the *y*-intercept (or starting dose). Empirically, *A* was found to be close to 2.3, a dimensionless constant. Substituting methadone for y, morphine for *X*, 15 for *b* gives the form:

$$\text{Methadone}(\text{mg}) = \sqrt{2.3 \times \text{morphine}(\text{mg})} + 15$$

The resulting graph appears to meet the criteria outlined above [Graph 3].

Moreover, when superimposed on the previous graphs, it shows reasonable agreement with both Plonk and Ayonrinde where they agree and a moderation of dose where they do not [Graph 4].

Note that the BJR method and Ayonrinde method intersect visually at approximately 1500 mg PO morphine. This can be confirmed by solving:

$$\frac{\text{Morphine}(\text{mg})}{20} = \sqrt{2.3 \times \text{morphine}(\text{mg})} + 15$$

which gives,

morphine (mg) =1458

An alternate form of the BJR method would use the Ayonrinde method for oral morphine doses >1500 mg. The graphical representation of this can be seen in Graph 5.

This may be reasonable as Ayonrinde's method has been used for years and gives higher doses of methadone at extreme values for PO morphine. For example, a patient on a daily dose equivalent to 7000 mg of oral morphine would be converted to 350 mg in both the Ayonrinde and BJR (Modified) methods, but only 142 mg methadone by the non-modified BJR method [Table 2].

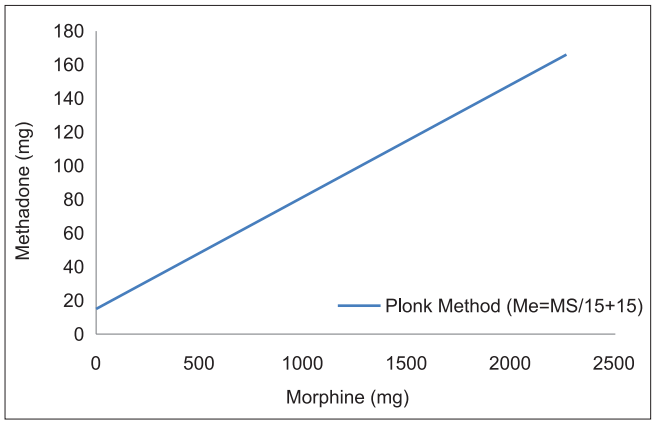
Using the BJR (modified) method would give a simple formulaic approach for the vast majority of conversions to

Table 1: Ayonrinde methadone conversion table

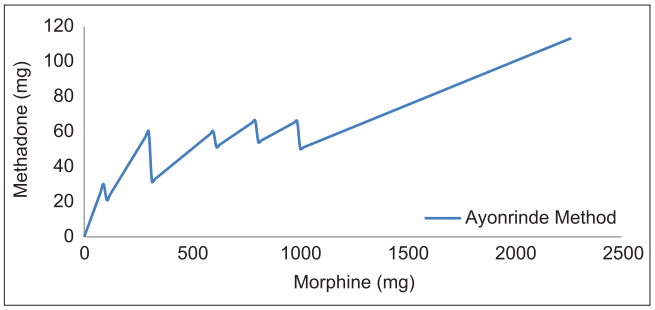
Ratio morphine to methadone (morphine: methadone)	Oral morphine equivalents (mg/day)
3:1	<100
5:1	101-300
10:1	301-600
12:1	601-800
15:1	801-1000
20:1	>1000

Table 2: Example results at 7000 mg PO morphine

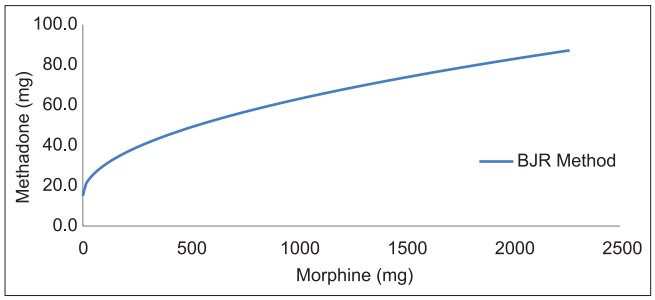
Method	Total daily methadone dose (mg)
Plonk	481
Ayonrinde	350
Morley–Makin	30 mg q 3 h prn (maximum 240)
BJR	142
BJR (modified)	350



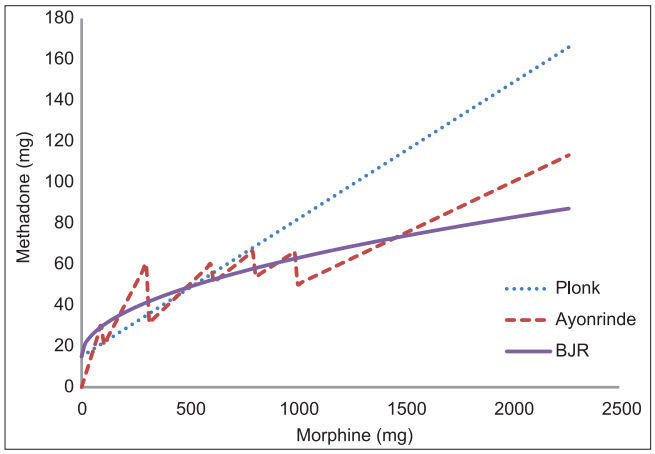
Graph 1: Plonk method $\text{Methadone}(\text{mg}) = \frac{\text{Morphine}(\text{mg})}{15} + 15$



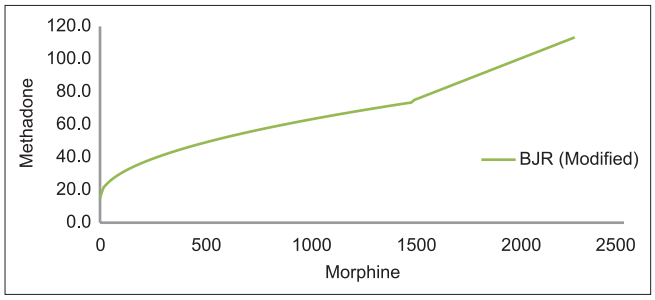
Graph 2: Ayonrinde method



Graph 3: BJR method



Graph 4: Superposition of Plonk, Ayonrinde, and BJR



Graph 5: BJR (modified)

methadone, with the "modified" aspect used only in special circumstances when the morphine dose is exceptionally high, i.e., >1500 mg of oral morphine equivalents per day.

The half-life of methadone can vary from patient to patient, depending on various host factors including age and urinary pH[9] and methadone should be administered only by providers skilled in its use. The authors do not propose that this new method can be used clinically until it can be studied in a controlled manner, but a simple conversion method that is safe and renders a reasonable methadone dose without resorting to tables,[5] protocols,[4] or special-case equations[7] would be a very useful tool in palliative medicine.

In the future, if this method can be validated, it would be interesting (but not necessary) to determine the metabolic pathways that determine the shape of the curve and the constant, A.

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Conflicts of interest
There are no conflicts of interest.

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