Equianalgesic doses of opioids – their use in clinical practice

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Opioid rotation is an established means of managing the side-effects of strong opioids.¹ From its origins in palliative care, the concept has moved into the fields of acute and chronic pain in cases where it is felt that changing a strong opioid may confer a benefit or if it becomes necessary in the context of co-morbidity. In an acute pain setting, for example, if a patient is undergoing an operation that may result in a reduction in their renal function then it may be necessary to change their opioid to one without metabolites that can cause problems with accumulation. In a pain clinic, it may be that a patient has developed tolerance over time to the analgesic effect of an opioid that was initially helpful, and the clinician believes that opioid rotation rather than dose escalation is an appropriate way to manage this. In a hospice, a patient may be receiving acceptable pain relief using a strong opioid, but may also be struggling with side-effects; therefore, a change to a different opioid, anticipated to have fewer side-effects, is planned.

The question, therefore, clinicians often find themselves asking is, 'If I am starting with "a" opioid at "b" dose, what dose of "x" opioid do I need to prescribe to have the same analgesic effect?'. This information can be derived from the equianalgesic dose, which is the dose of two opioids required to produce the same analgesic effect.² There are a number of sources of information available to guide clinicians. The British National Formulary (BNF) publishes tables comparing a number of strong opioids with morphine as the 'gold standard'.³ The Palliative Care Formulary provides more comprehensive information, and for some drugs information is given in the summary of product characteristics.⁴ In the wider literature there are summary tables,^{5,6} diagrams^{7,8} and now online resources including medically orientated smartphone applications.

Importantly, however, the BNF and most publications display notices of caution alongside such tables. The BNF notes, 'these equivalences are intended only as an approximate guide; patients should be carefully monitored after any change in medication and dose titration may be required'. There are a number of reasons why

caution is raised alongside the publication of such tables, and these relate to patient factors and issues surrounding the information used to create the tables.

Patient factors

Physiology and pathophysiology of the opioid systems

This subject has been reviewed in an International Association for the Study of Pain clinical update, 'Rethinking opioid equivalence',⁹ in which Lipowski and Carr describe the heterogeneity of opioid receptors, the variability of pharmacokinetics and pharmacodynamics of opioids, and differences in the opioid responsiveness of different types of pain. They suggested in the light of all these differences that a rethink is needed about how to interpret opioid equivalence information.

There are also physiological differences seen between short- and long-term opioid dosing in patients. The pathophysiology of opioid dependence has been reviewed detailing the adaptations at the receptor, synaptic, cellular and systemic levels, leading to widespread physiological changes in chronic opioid use.¹⁰ This points to reasons why switching opioids can be different in practice in terms of both dosing and withdrawal effects when undertaken in a chronically sensitised system. Buprenorphine, with its unique receptor profile, and methadone, with its potential effects via the *N*-methyl-d-aspartic acid (NMDA) receptor, have different characteristics from the more commonly used strong opioids. It has been noted that it may not be accidental that over time they have become the drugs

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Table 1. Sources of information for equianalgesic doses of opioids.

British National Formulary ³	Tables providing information comparing oral morphine with the equivalent doses of oral hydromorphone and oxycodone, intramuscular diamorphine and subcutaneous infusions of morphine and diamorphine
Palliative Care Formulary 3 ⁴	Table of approximate opioid dose conversions: 1. Oral to oral 2. Oral to transdermal 3. Oral to subcutaneous/intravenous 4. Subcutaneous/intravenous to subcutaneous intravenous 5. Information on opioid rotations involving methadone
<i>The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care</i> , 2nd edition ⁵	Tables of opioid conversion factors for morphine and diamorphine Opioid dose equivalence table
<i>Textbook of Pain</i> , 5th edition ⁶	Table of equianalgesic doses of common opioids compared with oral morphine
Drug Conversion Chart, St Gemma's Hospice, Leeds ⁷	Diagram detailing a method of converting between doses of oral morphine, hydromorphone and oxycodone; subcutaneous infusions of alfentanil, diamorphine and oxycodone; and buprenorphine and fentanyl transdermal patches It recommends first calculating the equivalent dose of morphine and then, from this, the morphine dose to any other proposed new opioid as a second step
Opioid Potency Converter ⁸	Visual 'target wheel' giving information on dose ranges of oral morphine equivalents for fentanyl patches and from morphine to oxycodone

used in the field of opioid addiction because their inherent differences may provide advantages in this context. However, undertaking changes in prescribing in addiction can be complex and is outside the remit of this review.¹¹

Co-morbidity and other medical factors

The patient's current age, weight, co-morbid medical and mental state and other medications they are prescribed (and which they are purchasing over the counter) are key features to be taken into account when prescribing strong opioids.

Social context and psychological distress

Pain is recognised as a multidimensional phenomenon. The placebo effect does not seem to be simply a curious phenomenon noted in clinical studies; rather, it is likely to reflect some of the brain's complex mechanisms for modulating pain.¹² Whether, in fact, it is reasonable to extrapolate the outcomes of studies, for example from patients with cancer, to perioperative care without controlling for social and psychological distress has been questioned.²

Equianalgesic doses – data sources

There are few studies that involve patients who have been prescribed strong opioids for more than 3

months.¹³ Studies used to derive equianalgesia information show a wide variation in individual response. Some contain small numbers of patients, involve single doses and use patients with limited opioid exposure. In others, dosing information is not the primary endpoint of the study. Incomplete cross-tolerance can be seen and equianalgesic doses are not always found to stable in different directions as they can be affected by both the dose and duration of the primary opioid.^{2,14} Caution is therefore needed when extrapolating information out of the context from which it was derived.

What impact does this have on clinical practice?

1. Tables of equianalgesic opioid doses need to be treated as 'loose guidance at best' and used only to 'avoid significant under- or overdosing if opioid rotation is undertaken'.⁹ An equianalgesic dose can be derived or calculated from available sources. Beware of confusion if dose ratios, rather than equianalgesic doses, are listed. The 'equianalgesic ratio' is the ratio of the dose of two opioids required to produce the same analgesic effect, but the 'relative potency ratio' is, in pragmatic terms, the inverse of the equianalgesic dose ratio.²
2. It is recommended not to target the equianalgesic dose but to take such a dose and make a

Table 2. Questions to ask when considering opioid rotation.

Initial questions	Is this change necessary? Has the patient consented to the change and is he or she aware of any potential problems? What is the fallback position if it is unsuccessful?
Practicalities	What is the safest environment to undertake this (inpatient vs. community)? Who is going to oversee the change, monitor for complications, provide breakthrough medication and provide advice and support to the patient during the process? How rapidly is the opioid switch to take place? How rapidly will the first opioid be reduced? Will there be a period of cross-prescribing and, if so, for how long?
Calculating a target dose	1. Find or calculate an equianalgesic dose using an authoritative source 2. Reduce this by 30–50% taking into account age, weight, co-morbid medical and mental states, and other medications used/prescribed 3. Decide on a plan for breakthrough medication
Ongoing review	Monitor the change carefully and be prepared to change tack if the initial plan is unsuccessful

30–50% reduction as a initial target.^{2,4,5} Breakthrough medication should be used for rescue analgesia. In cases where dose ranges, rather than equianalgesic doses, are quoted it may be prudent to consider a dose reduction from the lowest point of the dose range.¹⁵ If the dose of the starting opioid has been escalated very recently after a prolonged period of stability then a dose closer to the previous stable level may be a more appropriate place to start.⁴

3. Any dose regimen has to be taken in context of the patient's age, weight, co-morbid medical and mental state, as well as concurrent medication (both prescribed and over the counter).
4. The timescale over which the change is to be made needs to be planned – is there to be a period of crossover prescribing with a tapered reduction of the initial opioid?
5. Be aware of the different pharmacokinetics of cutaneous opioid patches, including onset and offset times, and take these into account when making any changes.¹⁶
6. Patients who have been using opioids in the medium term or longer have undergone physiological adaptations to chronic use. This may impact not only on subsequent analgesic requirements but also on withdrawal symptoms, as can be seen sometimes in clinical practice.
7. Switching between very high-dose opioids or switching to methadone is recommended for inpatients.⁴ Serious adverse events have been reported involving methadone, and there does not seem to be a single equianalgesic dose ratio between morphine and methadone – only one that seems to be altered by both the dose and the direction of the switch.^{2,17} If you do not have experience of switching a drug such as

methadone, then seek advice from a person or a clinical team who has experience in using this drug before considering a change. Be wary of patients who are prescribed high doses of methadone or buprenorphine chronically for addiction. Formulations such as Subutex®, when used in the addiction setting for analgesia, are often prescribed in milligrams of buprenorphine rather than micrograms, and few clinicians outside of the field of addiction have experience in their use.

Currently, clinicians have limited, if any, pharmacogenetic information to help guide their decision-making, and much of the art of opioid rotation relates to how well the clinicians know their patients' previous responses to medication change as well as their own experience in prescribing different strong opioids. Table 1, which is not exhaustive, lists some tables and diagrams providing equianalgesic data for common opioids and Table 2 provides some questions to consider before starting an opioid rotation.

Summary

There are a variety of sources of information providing data on equianalgesic doses for opioids. This information can be used to help plan an opioid switch or rotation if there is a clinical indication to change. In clinical practice it is not advised to use these data as direct dose targets but as the starting point for a calculation. The dose of a substitute opioid needs to take into account a number of factors pertinent to patient co-morbidity and medication, and in practice it is normally advised to target a reduction in the equianalgesic dose of around 30–50%. This is because studies used to derive equianalgesic dose data show wide

variability between individuals in opioid analgesic efficacy and incomplete cross-tolerance. Tables and diagrams are often constructed using information from studies of different quality and the data quoted may have been derived from a different clinical context. Any changes in strong opioid prescribing need to be undertaken in a safe environment for the patient with access to breakthrough medication and a fall-back plan. Changes involving high doses of strong opioids or methadone are recommended to be undertaken for inpatients.

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Conflict of interest statement

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