



Improving information for opioids prescribers on the safest possible effective dose of morphine or equivalent: a UK perspective

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FDA Virtual Public Workshop on Morphine Milligram Equivalents: Current Applications and Knowledge Gaps, Research Opportunities, and Future Directions.

June 7, 2021

The views expressed in this presentation are those of the speaker and are not necessarily those of the MHRA.

UK Opioids Expert Working Group (EWG) meeting outcome

- A number of conversion charts and opioid calculators are available that have shown significant differences in how they determined opioid conversion to morphine equivalence doses (MED).
- Lack on unanimity on what is the safest maximum morphine equivalent daily dose (MEDD).
- Further research required to investigate the benefits and risks behind the setting of a maximum MED, evidence supporting a preferred maximum daily dose for which benefit risk may be favourable, and calculation of morphine equivalences.

2nd Opioids EWG meeting

Title of paper: Comparison of opioid equivalence tables and maximum total daily opioid doses in chronic pain guidelines.

Objective :

- identify opioid conversion tables from regulatory and institutional guidelines and the online calculators and review dose-reduction recommendations, format and references;
- to review recommended maximum MED thresholds from regulatory agencies, advisory bodies or professional organisations.

Approach:

- A literature review and online search for
 - 1) opioid conversion tables and
 - 2) MED thresholds was conducted.

Literature reviewed was generally limited to non-cancer related pain. Literature based on palliative care or cancer-related pain was generally not included.

Maximum total daily opioid dose recommendations: published guidelines



2016. US Department of Health: *“the individual benefits and risks when increasing dosage to ≥ 50 mg Morphine Equivalent Dose (MED)/day and avoid increasing dosage to ≥ 90 mg MED/day or carefully justify a decision to titrate dosage to ≥ 90 mg MED/day”*.

2017. Canadian Practice guideline also restricted the prescribed dose to less than 90 mg morphine equivalents daily.

Australian and New Zealand guideline provides a >100 mg MME/day limit above which specialist advice should be sought.

2018 UK Opioids Aware: *‘max daily dose of morphine equivalent of 120 mg, above which there is an increased risk of harm without increase in benefit’*.

2019. Scottish Intercollegiate Guidelines Network (SIGN), new high limit of 90 mg, or even 50 mg.

3. Current maximum total daily opioid dose recommendations

Table 3: Max ME daily recommendations

Source	Opioids dose-equivalence table	Maximum daily dose
RCOA	Yes	Not given
Opioids aware	Yes	The risk of harm increases substantially at doses above an oral morphine equivalent of 120mg/day , but there is no increased benefit.
SIGN (2019)	Yes	<p>Pathway for chronic pain assessment, early management and care planning in non-specialist settings: Consider onward referral to specialist pain service if the opioid dose is greater than 180 mg morphine per day or equivalent. (Annex 2)</p> <p>Pathway for patients with neuropathic pain: Prescribe no higher than 180 mg morphine (or equivalent) without specialist advice. (Annex 3)</p> <p>Pathway for using strong opioids in patients with chronic pain: If >90 mg morphine equivalent dose/day seek specialist advice'. (Annex 4)</p>
ANZCA	Yes	>100 mg/day (with associated alert: seek specialist advice).
CDC (US)	Yes	Higher dosages of opioids are associated with higher risk of overdose and death—even relatively low dosages (20-50 morphine milligram equivalents (MME) per day) increase risk. Higher dosages haven't been shown to reduce pain over the long term.
MIMS	Yes	Not given
NICE	Yes	Not given
HERPC	Yes	Not given
West Suffolk CCG	Yes	<p>Dosages ≥ 120 mg oral MED the risk of harm is substantially increased without increased benefit. Opioid related overdose risk is dose dependent.</p> <p>Dosages of 50-<100 mg MED/d increases the risk for opioid overdose by factors of 1.9 to 4.6 compared with 1-<20 mg MED/d.</p> <p>Dosages ≥ 100 mg MED/d increases the risk of overdose significantly: 2.0-8.9 compared with 1-<20 mg MED/d.</p>
Nottsapc	Yes	Referring to Opioids Aware : The risk of harm increases substantially at doses above an oral morphine equivalent of 120mg/day , but there is no increased benefit.
Brighton and Hove CCG	Yes	Referring to Opioids Aware: The risk of harm increases substantially at doses above 120mg/day of oral morphine equivalent (e.g. oxycodone 60mg/day, fentanyl 50mcg/hr patches or a combination of opioid doses), but there is no increased benefit.
Glosh	Yes	Not given

Opioids EWG meeting outcome

The need of a ready available conversion table is necessary

A conversion table for every individual opioids would be helpful and facilitate prescribers.

Information on a maximum daily dose for prescribers is necessary

Information on paediatric posology would be useful



CHM opinion on:

A proposed maximum daily dose of morphine and equivalent

Best conversion table available

Best way to inform prescribers

Points presented to the CHM (Commission of Human Medicine):

- No clear safe threshold for a maximum daily dose of morphine and equivalent could be defined or extrapolated from the references presented in the discussed guidelines.
- Limited evidence for the accuracy of dose equivalence tables is available and considerable variation between individuals affects the response to treatment.
- The risk of overdose is dose related as discussed in the studies below:
 - *Franklin (2014)* reported a nine-fold increased risk of overdose at doses exceeding 100 mg/d MED compared to doses below 20 mg/d MED in patients with CNCP.
 - *Chou R et al (2015)* found that compared to a baseline of ≤ 19 mg/day MED, the hazard ratio (HR) for overdose with a MED of 20 to 49 mg/day was 1.44 (95% CI 0.57 to 3.62), and the HR for a MED of ≥ 200 mg/day was 2.88 (95% CI 1.79 to 4.63).
 - *Dowell D, Haegerich TM and Chou R (2016)* and *Hegmann KT et al (2014)* recommend reassessing the benefits/risks associated with increasing dosage to 50 morphine milligram equivalents (MME) or more per day and to avoid increasing dosage to 90 MME or more per day if not carefully justified.
- All studies concur that there is a substantial increased risk associated with doses at or above **90-120mg/day**

PMEAG (Paediatric Medicines Expert Advisory Group)

The SmPCs [US: Prescribing Information] for opioids were reviewed for paediatric relevant information concerning maximum dose, posology in obesity, and information on conversion to alternative opioids for products which might be used in the setting of chronic non-cancer pain.

Findings:

- The SmPCs for various opioids licensed in the paediatric population either recommend dosing based on weight and/or by age. Where age ranges are used, an approximate dose/weight might be calculated, although there is no guidance provided on dosing at extremes of weight.
- Adolescent dosing tends to approximate that of adults, although for some products there is a lower suggested minimum dose or frequency of administration (for example codeine).
- There is limited information on posology in obesity.
- PK data in younger children are limited.
- In tramadol, the maximum dose for children and adolescents with a high BMI must not exceed the calculated maximum dose for a body weight at the 97.5 percentile for the given age.
- Where opioid conversion or equivalence is described in the SmPC there is no differentiation made between adult and paediatrics.



Conclusions

There is insufficient available evidence in the paediatric population to draw conclusions on safe maximum MEDD directly.

While extrapolation of the adult MEDD recommendations might be contemplated, there are too many uncertainties to recommend this approach.

It is also unknown whether the long-term safety of opioid use in the paediatric population (particularly addiction risk in adolescents) can be extrapolated from adults



Where to put new information (UK)?

Summaries of Product Characteristics (SmPCs)* is a description of a medicinal product's properties and the conditions attached to its use. It explains how to use and prescribe a medicine. It is used by healthcare professionals, such as doctors, nurses and pharmacists.

Proposed SmPC* Text

(endorsed by CHM and PMEAG)

Section 4.2 Posology and method of administration

Total morphine equivalent daily dose (calculated from a single opioid or multiple opioid administration) for patients with non-cancer chronic pain

- At dosages ≥ 90 -120 mg total morphine equivalent daily dose the risk of harm is substantially increased.
- Clinicians should prescribe the lowest effective dosage.
- Caution is advised when prescribing opioids at any dosage due to individual variability.

Paediatric population

The long-term efficacy of opioids has not been established and potential risk of harm cannot be excluded, therefore long-term opioid treatment should be managed under specialist supervision. No recommendation on maximum morphine equivalent daily dose can be made. Benefit risk should be assessed regularly by the prescriber.

What is next?

- Identify a suitable MME table/calculator that is reliable and easy to use.
- Contact Marketing Authorisation Holders (MAHs) [Companies]
- National variations to implement changes



Thank you

