MHRA - UK work in development of MME tables

Justin Pittaway-Hay, PhD, Senior Pharmacokinetics Assessor

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

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

Overview

Role of MHRA, Opioid Expert Group

Problem statement

Objective and approach

Results

Discussion and limitations

Medicines and Healthcare Products Regulatory Agency (MHRA)

MHRA

- regulates medicines, medical devices and blood components for transfusion in the UK

Commission on Human Medicines (CHM) [US: Committee]

- advises ministers on the safety, efficacy and quality of medicinal products

Opioid Expert Working Group [US: Panel]

- set up in early 2019, in light of growing concerns about overuse and misuse, particularly in non-cancer indications, leading to a growing problem of dependence and addiction.

https://www.gov.uk/government/news/opioid-expert-working-group-meets-at-mhra

Opioid Expert Working Group: Remit

To review available evidence on opioid dependence and addiction, recommend ways to strengthen risk minimisation measures and to improve communication and the education of healthcare professionals and patients.

Opioid Expert Working Group (EWG)

Made up of experts in relevant scientific disciplines:

- pain management
- general practice
- nursing
- pharmacy
- psychiatry and substance abuse
- anaesthesia
- toxicology and pharmacology
- geriatric medicine
- paediatric medicine
- rheumatology
- epidemiology
- a lay member

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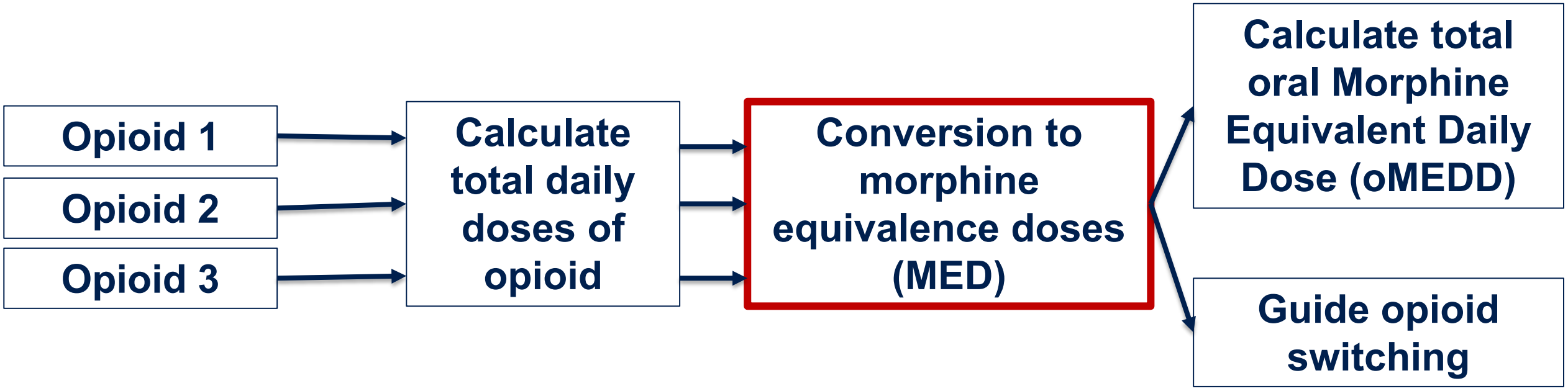
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/902455/HMR_CHM_BPC_Annual_report_2019.pdf

Problem statement

The EWG considered that further research was 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.



Objective and Approach

The objective of this research was to:

- **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.

A literature review and online search was performed for

1. **Opioid conversion tables**
2. MED thresholds was conducted.

Literature based on palliative care or cancer-related pain was generally **not** included. The source data for the conversion tables was **not** critically reviewed.

Headline results

	Curtis	CDC (2)	FPM UK 'Opioids Aware' (3)	UKMi (4)	SIGN (5)^	BNF (6)	FPM ANZCA (7)	MIMS (8) (9)	Glos. Hospitals (10) ab	SmPC	AMDG (11)	Online RPH (12) ab	Easy Calculation (13)
ORAL													
Codeine	0.1	0.15	0.1	0.08-0.1	0.1	0.1	0.13	0.1	0.1		0.15	0.15	0.15
Dihydrocodeine	0.1	NR	0.1	0.1		0.1		0.1	0.1				
Hydrocodone		1									1	1	1
Hydromorphone	5	4	7.5	3.5-10	[7.5]	5	5	5-7.5	5-10		4	4	4
Methadone	3		SA				SA	Variable			4 – SA (14)	15 - SA#	4
1-20 mg/day		4									4		
21-40 mg/day		8									8		
41-60 mg/day		10									10		
≥ 61-80 mg/day		12									12		
Morphine	1	1	1	1		1	1	1			1	1 [2§]	1
Oxycodone	2	1.5	2	1.5-2	[2]	1.5	1.5	1.5-2	1.3-2	1.5-2 (15) 2 (16)	1.5	1.5	1.5
Oxymorphone		3									3	3E	3
Tapentadol	0.4	0.4	0.4	0.3-0.8			0.3		0.33		0.4		0.367
Tramadol	0.1	NR	0.15	0.1-0.17	0.2	0.1	0.2	0.1	0.1-0.2		0.1	0.2	0.2
Dextropropoxyphene	0.1						0.1						
Pethidine	0.1							0.1	0.1-0.125				
Levorphanol												7.5E	
Propoxyphene												0.23E	
SUBLINGUAL													
Buprenorphine (sublingual)	60	NR	NR	80			40	80	80-100				
RECTAL													
Oxycodone							1.5						
TRANSDERMAL													
Fentanyl (mcg/hr)		2.4	3.6-3.7*				3		2.4-2.5*		2.4		2.4
Buprenorphine (mcg/hr)			2.4*				2		1.8-2.8* 1.8-2.77*	1.8-2.8* (17) 1.8-2.77* (18)			
PARENTERAL													
Diamorphine	3					3.3		3	3				
Morphine (HCl/Sulf)	2					2	3	2	2-3			3	
Oxycodone							3	2	2-3				
Hydromorphone							15					20	
Codeine							0.25						
Pethidine	0.24						0.4		0.4				
Fentanyl (mcg)							0.2		0.15			0.3	
Sufentanil							2						
Methadone								Variable					
Codeine												0.25	
Levorphanol												15E	
Oxymorphone												30	
Alfentanil									30-40				
Tramadol									0.2-0.4				

Table **not** intended to be legible, explanatory foot notes and sources **not** included.

Headline results
Routes of administration

ORAL – by MOUTH

SUBLINGUAL – UNDER THE TOUGUE

RECTAL - VIA THE BOTTOM

TRANSDERMAL - VIA THE SKIN

PARENTERAL - INJECTION

	Curtis	CDC (2)	FPM UK 'Opioids Aware' (3)	UKMi (4)	SIGN (5)^	BNF (6)	FPM ANZCA (7)	MIMS (8) (9)	Glos. Hospitals (10) ab	SmPC	AMDG (11)	Online RPH (12) ab	Easy Calculation (13)
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Hydrocodone		1									1	1	1
Hydromorphone	5	4	7.5	3.5-10	[7.5]	5	5	5-7.5	5-10		4	4	4
Methadone	3		SA				SA	Variable			4 – SA (14)	15 - SA#	4
1-20 mg/day		4									4		
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41-60 mg/day		10									10		
≥ 61-80 mg/day		12									12		
Morphine	1	1	1	1		1	1	1			1	1 [2§]	1
Oxycodone	2	1.5	2	1.5-2	[2]	1.5	1.5	1.5-2	1.3-2	1.5-2 (15) 2 (16)	1.5	1.5	1.5
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Buprenorphine (sublingual)	60	NR	NR	80			40	80	80-100				
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TRANSDERMAL													
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Levorphanol												15E	
Oxymorphone												30	
Alfentanil									30-40				
Tramadol									0.2-0.4				

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Headline results

- 13 sources identified
  - 10 tables (1 with associated app)
  - 3 calculators
  - SmPC [US: Prescribing Information]
- Quality of References
  - 1 had individual references
  - 5 ‘grouped’ references
  - 1 referenced another source
  - 6 provided none

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Methadone								Variable					
Codeine												0.25	
Levorphanol												15E	
Oxymorphone												30	
Alfentanil									30-40				
Tramadol									0.2-0.4				

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Headline results

- Consistency of conversion
- Known variability (methadone)
- Ranges
- Missing data (orange)

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Morphine	1	1	1	1		1	1	1			1	1 [2§]	1
Oxycodone	2	1.5	2	1.5-2	[2]	1.5	1.5	1.5-2	1.3-2	1.5-2 (15) 2 (16)	1.5	1.5	1.5
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Hydromorphone							15					20	
Codeine							0.25						
Pethidine	0.24						0.4		0.4				
Fentanyl (mcg)							0.2		0.15			0.3	
Sufentanil							2						
Methadone								Variable					
Codeine												0.25	
Levorphanol												15E	
Oxymorphone												30	
Alfentanil									30-40				
Tramadol									0.2-0.4				

Table **not** intended to be legible, explanatory foot notes and sources **not** included.

Headline results

- Dose reduction (when using to guide opioid switching)
  - 9 included warning
  - 3 gave warning for converting high doses
  - 1 guide stated that where equivalence is expressed as a range, the value that produces the lowest equivalent dose should be used
  - 1 calculator stated it should not be used when converting a patient from one opioid to another.

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Oxycodone	2	1.5	2	1.5-2	[2]	1.5	1.5	1.5-2	1.3-2	1.5-2 (15) 2 (16)	1.5	1.5	1.5
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Methadone								Variable					
Codeine												0.25	
Levorphanol												15E	
Oxymorphone												30	
Alfentanil									30-40				
Tramadol									0.2-0.4				

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Discussion & Limitations

Accompanying warnings: Most of the equivalence tables were accompanied with notes for consideration.

- Example issues:
  - caution needed when using for opioid switching
  - consider variability in pharmacokinetics (how the body handles the medicine) and pharmacodynamics (how the medicine affects the body) within and between patients
  - modified release formulation to be accounted for
  - data derived from pooled data
  - residual drug in the patient's system must be accounted for

Limitations

‘Directional inequality’

Many reviews noted that opioid conversion tables may be overly simplified (1), and note that ‘clinicians need to be aware that there are directional differences in opioid equivalents and that some ratios may not be “reversible” in direction.’ While the mechanism is not clear, it may be due to active metabolites. (2)

Limitations of opioid conversion tables (3), include

- Failure to standardise a reference opioid
- Failure to address bi-directional difference
- Inclusion of a wide range of doses
- Determined by single doses or acute pain
- Computations instead of clinical trial data

1. Treillet E, et al . Practical management of opioid rotation and equianalgesia. *J Pain Res.* Oct 29, 2018, 11:2587-2601.

2. Pereira J, et al. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. *J Pain Symptom Manage.* . Aug, 2001 , Vol. 22, (2):672-87.

3. Shaheen PE, et al.. Opioid equianalgesic tables: are they all equally dangerous? *J Pain Symptom Manage.* . Sep, 2009, Vol. 38, (3):409-17

Conclusion

Published opioid equivalence tables provide a clinically useful tool for clinicians but are beset with limitations namely in regard to the quality of the underlying data, issues of directionality, ease of use and wide variability in conversion factors between tables/studies. Subsequently this has an impact on recommending a maximum total daily opioid dose.

Significance for patients and prescribers

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

Dr Maria Molinari, Senior Clinical Assessor, MHRA, UK