

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.

June 7, 2021

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.

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)

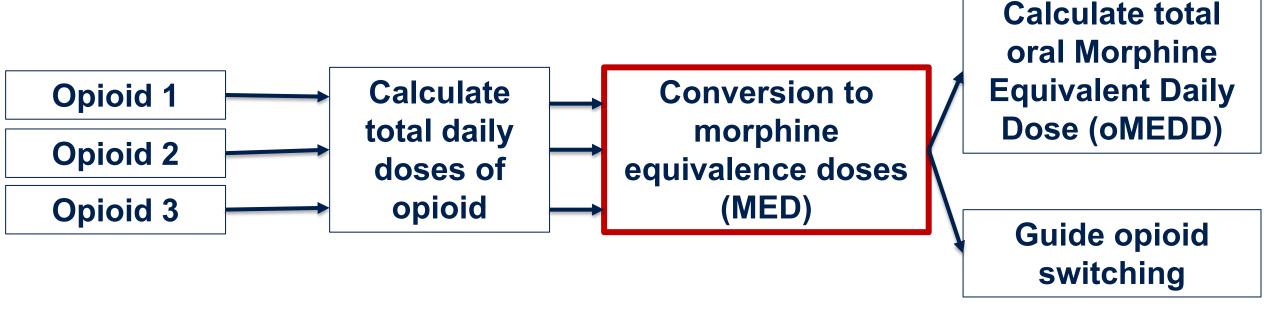
Made up of experts in relevant scientific disciplines:

- pain management
- general practice
- nursing
- pharmacy
- psychiatry and substance abuse
- anaesthesia

- toxicology and pharmacology
- geriatric medicine
- paediatric medicine
- rheumatology
- epidemiology
- a lay member

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.

	Curtis	(2)	'Opioids Aware'	UKMi (4)	SIGN (5)^	BNF (6)	FPM ANZCA (7)	MIMS (8) (9)	Glos. Hospitals (10) ^æ	SmPC	AMDG (11)	Online RPH (12) ²⁰	Easy Calculation (13)
			(3)			OI	RAL						
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 Methadone	5 3	4	7.5 SA	3.5-10	[7.5]	5	5 SA	5-7.5 Variable	5-10		4 4 – SA (14)	4 15 - SA [#]	4
1-20 mg/day 21-40 mg/day 41-60 mg/day		4 8 10									4 8 10		
≥ 61-80 mg/day Morphine	1	12 1	1	1		1	1	1			12 1	1 [20]	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 [2§] 1.5	1.5
Oxymorphone		3								_ (,	3	3 ^E	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
Dextropropoxyphe ne	0.1						0.1						
Pethidine	0.1							0.1	0.1-0.125				
Levorphanol												7.5 ^E	
Propoxyphene						CLIDA	NCHAL					0.23 ^E	
Buprenorphine (sublingual)	60	NR	NR	80		SUBL	MGUAL 40	80	80-100				
						RE	CTAL						
Oxycodone							1.5						
F		0.4	0.0.0.7			TRANS	DERMAL		0.4.0.5		0.4		0.4
Fentanyl (mcg/hr) Buprenorphine		2.4	3.6-3.7* 2.4*				3 2		2.4-2.5* 1.8-2.8*	1.8-	2.4		2.4
(mcg/hr)			2.4				2		1.8-2.77*	2.8*			
										1.8- 2.77* (18)			
							NTERAL						
Diamorphine	3					3.3		3	3			•	
Morphine (HCI/Sulf) Oxycodone	2					2	3	2	2-3			3	
ON COUCHE							15		2-3			20	
Hydromorphone Codeine	0.04						0.25		0.4				
Codeine Pethidine Fentanyl (mcg)	0.24						0.25 0.4 0.2		0.4 0.15			0.3	
Codeine Pethidine Fentanyl (mcg) Sufentanil	0.24						0.25 0.4	Variable				0.3	
Codeine Pethidine Fentanyl (mcg) Sufentanil Methadone	0.24						0.25 0.4 0.2	Variable					
Codeine Pethidine Fentanyl (mcg) Sufentanil Methadone Codeine	0.24						0.25 0.4 0.2	Variable				0.3 0.25 15 ^E	
	0.24						0.25 0.4 0.2	Variable				0.25	

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	UKMi (4)	SIGN (5)^	BNF (6)	FPM ANZCA (7)	MIMS (8) (9)	Glos. Hospitals (10) ²⁰	SmPC	AMDG (11)	Online RPH (12) ²⁰	Easy Calculation
		(=)	Aware'				(,,		(10)			(12)	(13)
Codeine	0.1	0.15	0.1	0.08-	0.1	0.1	0.13	0.1	0.1		0.15	0.15	0.15
Codellie	0.1	0.15	0.1	0.00-	0.1	0.1	0.13	0.1	0.1		0.13	0.13	0.13
Dihydrocodeine	0.1	NR	0.1	0.1		0.1		0.1	0.1		,		
Hydrocodone Hydromorphone	5	1	7.5	3.5-10	[7 5]	-	5	5-7.5	5-10		1	1	1 4
Methadone	3	4	SA	3.5-10	[7.5]	5	SA	Variable	5-10		4 – SA (14)	15 - SA#	4
1-20 mg/day		4									4		
21-40 mg/day		8									8		
41-60 mg/day ≥ 61-80 mg/day		10 12									10 12		
Morphine	1	12	1	1		1	1	1			12	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								2 (10)	3	3 ^E	3
Tapentadol	0.4	0.4	0.4	0.3-			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
Dextropropoxyphe ne	0.1						0.1						
Pethidine	0.1							0.1	0.1-0.125				
Levorphanol Propoxyphene						OUBL	NOUAL					7.5 ^E 0.23 ^E	
Buprenorphine (sublingual)	60	NR	NR	80		SUBL	NGUAL 40	80	80-100				
						RE	CTAL						
Oxycodone							1.5						
Fantand (manufact		2.4	3.6-3.7*			TRANS	DERMAL		2.4-2.5*		2.4		2.4
Fentanyl (mcg/hr) Buprenorphine		2.4	2.4*				3 2		1.8-2.8*	1.8-	2.4		2.4
(mcg/hr)			2.7						1.0-2.0	2.8*			
									1.8-2.77*	(17)			
										1.8- 2.77* (18)			
							NTERAL						
Diamorphine Morphine	3					3.3	3	3 2	3 2-3			3	
(HCI/Sulf) Oxycodone	2					2	3	2	2-3			3	
Hydromorphone							15		2-0			20	
Codeine							0.25						
Pethidine	0.24						0.4		0.4				
Fentanyl (mcg)							0.2		0.15			0.3	
Sufentanil Methadone							2	Variable					
Methadone Codeine								variable				0.25	
Levorphanol												15 ^E	
Oxymorphone												30	
Alfentanil									30-40				
Tramadol									0.2-0.4				

- 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

	Curtis	CDC	FPM UK	UKMi (4)	SIGN (5)^	BNF (6)	FPM ANZCA	MIMS (8) (9)	Glos. Hospitals	SmPC	AMDG (11)	Online RPH	Easy
		(2)	'Opioids	(' '	(5)	(5)	(7)	(5) (5)	(10) ²⁰		(,	(12) æ	Calculation
			Aware'										(13)
			(3)			0	RAL						
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 Hydromorphone	5	1	7.5	3.5-10	[7.5]	5	5	5-7.5	5-10		1	1	1 4
Methadone	3	4	SA	3.3-10	[7.5]	3	SA	Variable	3-10		4 – SA (14)	15 - SA#	4
1-20 mg/day		4									4		
21-40 mg/day 41-60 mg/day		8 10									8 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	3 ^E	3
Tapentadol	0.4	0.4	0.4	0.3-	0.0	0.4	0.3	0.4	0.33		0.4	0.0	0.367
Tramadol Dextropropoxyphe	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
ne	0.1						0.1						
Pethidine	0.1							0.1	0.1-0.125				
Levorphanol Propoxyphene						OUBL	NGUAL					7.5 ^E 0.23 ^E	
Buprenorphine	60	NR	NR	80		SUBL	40	80	80-100				
(sublingual)													
Oxycodone						RE	1.5						
Oxycodolie						TRANS	DERMAL						
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)			
							NTERAL			()			
Diamorphine	3					3.3		3	3				
Morphine (HCI/Sulf) Oxycodone	2					2	3	2	2-3			3	
Hydromorphone							15	2	2-3			20	
Codeine							0.25						
Pethidine	0.24						0.4		0.4				
Fentanyl (mcg) Sufentanil							0.2		0.15			0.3	
Methadone								Variable				0.05	
Codeine Levorphanol												0.25 15 ^E	
Oxymorphone												30	
Alfentanil									30-40				
Tramadol									0.2-0.4				

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

	Curtis	CDC	FPM UK	UKMi (4)	SIGN (5)^	BNF (6)	FPM ANZCA	MIMS (8) (9)	Glos. Hospitals	SmPC	AMDG (11)	Online RPH	Easy
		(2)	'Opioids	(+)	(5)	(0)	(7)	(0) (3)	(10) ²⁰		(1.1)	(12) ²⁰	Calculation
			Aware'										(13)
			(3)										
Codeine	0.1	0.15	0.1	0.08-	0.1	0.1	RAL 0.13	0.1	0.1		0.15	0.15	0.15
Codellie	0.1	0.15	0.1	0.00-	0.1	0.1	0.10	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 Hydromorphone	5	1 4	7.5	2 5 10	[7.5]	5	5	5-7.5	5-10		1 4	1	1 4
Methadone	3	4	SA	3.3-10	[7.5]	5	SA	Variable	3-10		4 – SA	15 -	4
otilaaoiio	Ŭ		0,1				0, 1	variable			(14)	SA#	·
1-20 mg/day		4									4		
21-40 mg/day		8 10									8 10		
41-60 mg/day ≥ 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	1.5	1.5	1.5
										(15)			
										2 (16)			
Oxymorphone Tapentadol	0.4	3 0.4	0.4	0.3-			0.3		0.33		3 0.4	3 ^E	3 0.367
rapentadoi	0.4	0.4	0.4	0.3-			0.3		0.33		0.4		0.307
Tramadol	0.1	NR	0.15	0.1-	0.2	0.1	0.2	0.1	0.1-0.2		0.1	0.2	0.2
				0.17									
Dextropropoxyphe	0.1						0.1						
ne Pethidine	0.1							0.1	0.1-0.125				
Levorphanol	0.1							0.1	0.1-0.125			7.5 ^E	
Propoxyphene												0.23 ^E	
						SUBL	NGUAL						
Buprenorphine (sublingual)	60	NR	NR	80			40	80	80-100				
(aubilitgual)						RE	CTAL						
Oxycodone							1.5						
						TRANS	DERMAL						
Fentanyl (mcg/hr) Buprenorphine		2.4	3.6-3.7* 2.4*				3 2		2.4-2.5* 1.8-2.8*	1.8-	2.4		2.4
(mcg/hr)			2.4				2		1.0-2.0	2.8*			
(meg/m)									1.8-2.77*	(17)			
									1.0 2	(,			
										1.8-			
										2.77*			
						DARE	NTERAL			(18)			
Diamorphine	3					3.3	TEIVAL	3	3				
Morphine	2					2	3	2	2-3			3	
(HCI/Sulf)									0.5				
Oxycodone Hydromorphone							3 15	2	2-3			20	
Codeine							0.25					20	
Pethidine	0.24						0.23		0.4				
Fentanyl (mcg)							0.2		0.15			0.3	
Sufentanil							2						
Methadone								Variable				0.05	
Codeine Levorphanol												0.25 15 ^E	
Oxymorphone												30	
Alfentanil									30-40			- 50	
Tramadol									0.2-0.4				
													_

- 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.

	Curtis	CDC	FPM UK	UKMi (4)	SIGN (5)^	BNF (6)	FPM ANZCA	MIMS (8) (9)	Glos. Hospitals	SmPC	AMDG (11)	Online RPH	Easy
		(2)	'Opioids	(-)	(0)	(5)	(7)	(0) (0)	(10) ^æ		(• •)	(12) æ	Calculation
			Aware'										(13)
			(3)										
Codeine	0.1	0.15	0.1	0.08-	0.1	0.1	RAL 0.13	0.1	0.1		0.15	0.15	0.15
				0.1									
Dihydrocodeine Hydrocodone	0.1	NR 1	0.1	0.1		0.1		0.1	0.1		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 21-40 mg/day		4 8									4 8		
41-60 mg/day		10									10		
≥ 61-80 mg/day		12									12		
Morphine	1	1	1	1		1	1	1			11	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								2 (10)	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
Dextropropoxyphe ne	0.1						0.1						
Pethidine	0.1							0.1	0.1-0.125				
Levorphanol												7.5 ^E	
Propoxyphene						SUBI	INGUAL					0.23 ^E	
Buprenorphine (sublingual)	60	NR	NR	80			40	80	80-100				
Oxycodone						RE	CTAL 1.5						
Oxycodone						TRANS	DERMAL						
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)			
Diamorphine	3					PARE 3.3	NTERAL	3	3				
Morphine	2					3.3	3	2	2-3			3	
(HCI/Sulf)													
Oxycodone Hydromorphone							3 15	2	2-3			20	
Codeine							0.25					20	
Pethidine	0.24						0.4		0.4				
Fentanyl (mcg)							0.2		0.15			0.3	
Sufentanil Methadone							2	Variable					
Codeine								· aabis				0.25	
Levorphanol												15 ^E	
Oxymorphone Alfentanil									30-40			30	
Tramadol									0.2-0.4				

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

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