Equianalgesia, opioid switch and opioid association in different clinical settings: a narrative review

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Abstract. – Emergency or postoperative pain often represents an authentic challenge in patients who were already on opioid treatment for chronic pain. Thus, their management requires not only the physician's ability to treat acute pain, but also competence in switching the opioid that lost efficacy. Different aspects should be considered, such as opioids titration, switching, association and equianalgesia.

The objective of this paper is to provide a narrative review, which has been elaborated and discussed among clinicians through an iterative process involving development and review of the draft during two web-based meetings and via email. This expert opinion aims to facilitate the correct opioid use through appropriate practices with a focus on pain treatment in emergency and postoperative pain.

Equianalgesia tables were reviewed and integrated by clinicians and researchers with expertise in anesthesia, postoperative medicine, intensive care, emergency medicine pharmacology and addiction medicine. Special populations (liver/kidney failure, elder, pediatric, pregnancy/lactation) are discussed in detail along with other critical scenarios, such as: (i) rapid pain worsening in chronic pain (aggravating pain due to disease progression or tolerance development to analgesic therapy); (ii) acute pain on maintenance treatment; and (iii) pain management of complicated patients in emergency care.

Extended and updated equianalgesia tables and conversion rates for 17 different opioid formulations (of 9 different molecules) are presented as follows.

Opioids remain the class that best suits clinical needs of emergency and post-operative medicine. However, it should be stressed that equianalgesia can be affected by drug-to-drug interactions and pharmacological imprecision, in a complex field where clinical experience may be the main guiding principle.

Key Words:
Equianalgesia, Opioids, Opioid rotation, Opioid switching, Conversion rates, Special populations, Pain, Conversion table.

Abbreviations

ATC, around the clock; IM, intramuscular; IV, intravenous; OS, oral form; PD, peridural; SA, subarachnoid; SC, subcutaneous; SL, sublingual; TTS, transdermal system; FBT, fentanyl buccal tablet; FPNS, fentanyl nasal pectin spray; INFS, intranasal fentanyl; IV, intravenous; OTFC, oral transmucosal fentanyl citrate; SLF, sublingual fentanyl; OME, oral morphine equivalents; RASS, Richmond agitation-sedation scale; SAS, Riker sedation-agitation scale; COWS clinical opiate withdrawal scale; NAS, neonatal abstinence syndrome; OUD, opioid use disorder; BTcP breakthrough cancer pain; ROOs rapid onset opioids; NSAIDs non-steroidal-anti-inflammatory-drugs; MMT, methadone maintenance therapy; BMT buprenorphine maintenance therapy.

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Introduction

Despite the advances made over the last 50 years in the pharmacological management of acute and chronic pain, few helpful tools exist for chronic pain opioid daily management, opioid switch following acute emergency, postoperative pain, opioid hyperalgesia, or chronic intractable pain. These clinical settings often represent authentic urgencies, and their management requires not only the physician's ability to treat acute pain but also competence in switching the opioid that has lost efficacy. Coping with these medical needs involves different scenarios: equianalgesia, opioids titration, switching, rotation and association either with other opioids or different analgesics.

The term equianalgesia indicates the amount of different opioid formulations producing equal analgesic effect[1,2], while opioid titration means adapting the drug dose to the individual's need[3]. Opioid rotation and switching are defined as the process of changing from one opioid to another in order to obtain a satisfactory clinical balance between analgesia and adverse effects[1]. Rotation is the term preferably used when indicating the change from a first to a second opioid in a pre-set schedule to prevent potential adverse effects and limit dose escalation[4]. Opioid switching is more correctly referred to an opioid conversion in acute clinical phases with inadequate analgesic effect and/or dose-limiting side-effects[4-6].

The assessment of equianalgesic doses is important also when acute pain (e.g., trauma or surgery) occurs in patients on chronic opioid therapy. Acute pain treatment in chronic opioid therapy often ends up with the adding of a second opioid to the ongoing chronic therapy or opioid switching. In both cases, the computation of oral morphine equivalents (OME) is recommended and is supported by equianalgesia tables[4,7].

The concept of equianalgesia originated in the 1950s, comparing the potency of morphine-related substances in depressing the twitch and tetanus of stimulated guinea-pig ileum by reducing acetylcholine release from cholinergic nerves[8]. Since then, comparative analgesic studies[8,9] have been morphine-centered and, in the following years, equianalgesia tables have been structured on data derived from pre-clinical pharmacological sources rather more than clinical trials. Therefore, the task of studying differences in clinical setting (e.g., acute *vs.* chronic pain, cancer *vs.* non-cancer pain), in pharmaceutical substances and formulations (e.g., administration route, pharmacodynamic and pharmacokinetic characteristics), and in patient subjective parameters (e.g., age, gender, morbidities, ongoing treatments) was not deeply investigated[9-11].

Notwithstanding, conversion tables handiness and apparent ease of application often need clinicians' expertise in daily clinical practice. This is due to their partial completeness in terms of available compounds, routes of administration, or dosages (especially for low range, which is of particular interest for patients with older age or hepatic/kidney failure). Finally, conversion data are based on inhomogeneous studies (observational, retrospective, on a few patients, seldom bidirectional…) throughout the literature[2,6,12-15].

Nevertheless, opioid switching (both drug and route of administration) is common in clinical practice for several reasons, such as poor analgesic response regardless of dose increase, pain crisis or post-operative pain in chronic opioid patients.

This work aims to provide a narrative review, elaborated and discussed among clinicians through an iterative process involving development and review of the draft during two web-based meetings and *via* email. This expert opinion aims to facilitate correct opioid use through appropriate practices (*i.e.,* equianalgesia, opioid switching and addition of opioids) in different clinical scenarios, with a focus on pain treatment in emergency and postoperative scenarios. Therefore, we propose an updated and comprehensive equianalgesia table combining conversion rates extrapolated from the literature with expert advice and recommendations as to overcome the intrinsic limits of the tables, enhancing their applicability with attention to a safety margin.

For the same reason and a safer approach, we also intend to focus on special populations (liver/kidney failure, elder, pediatric, pregnancy/lactation). Furthermore, recurring critical issues are presented with scenarios, such as: *(i)* rapid pain worsening in chronic pain (aggravating pain due to disease progression or tolerance development to analgesic therapy); *(ii)* acute pain on maintenance treatment; and *(iii)* pain management of complicated patients in emergency care.

Materials and Methods

This paper is a narrative review that addresses the updated and comprehensive equianalgesia table extrapolated from the literature with ex-

pert advice and recommendations to overcome the intrinsic limits of the tables. Literature was searched in PubMed and Embase from 2000 to November 2020 for articles with the following keywords: equianalgesia, opioid switching, and opioid rotation. Data from 19 literature articles and from the summaries of product characteristics were used in filling the tables.

The topic was discussed among 8 clinicians and researchers with expertise in anesthesia, postoperative medicine, intensive care, emergency medicine, addiction medicine, and pharmacology. Consensus was reached through an iterative process involving development and review of the draft during two web-based meetings and *via* email between July and December 2020.

Due to the nature of the paper, the ethical statement is not required.

Table I reports the equianalgesic doses extrapolated from the literature[1,2,13,16-32], integrated with authors' expertise in acute and chronic pain treatment and with data from the summaries of product characteristics[33-39]. Values below 30 mg OME, not found in previous papers, were arithmetically calculated assuming linearity with authors' consensus. Maximum daily doses were verified according to the summary of product characteristics of each drug.

Morphine was used as the reference molecule according to WHO40 and since titration with morphine is recommended by the Guidelines[7,18,41].

All data were validated according to authors' expertise. Nonetheless, equianalgesia tables need to be used cautiously (Table I).

The main issues encountered in the use of opioids in emergency and post-operative medicine are addressed below.

Opioid Pharmacology

Opioid receptors are normally stimulated by endogenous peptides produced in response to noxious stimulation. Mu (μ), kappa (κ), and delta (δ) opioid receptors represent the originally classified receptor subtypes, whereas opioid receptor like-1 (ORL1 aka nociceptin/opioid peptide receptor NOP) is the least characterized and supposedly fundamental in antinociception and anti-hypersensitivity regulation[42-44].

Supplementary Table I summarizes pattern of receptor activation (μ, κ, δ receptors with the additional action on NMDA receptor) that results in pain relief and other opioid related effects[45-48].

Opioids generally undergo extensive first-pass metabolism in the liver through two major enzyme systems, CYP450 (with more than 50 isoforms already known) and, to a lesser extent, UDP-glucuronosyltransferases (UGTs). The major opioid metabolic pathways are synopsized in Table II[16].

One of CYP450 isoenzymes, CYP2D6, exhibits a polymorphism that leads to clinical phenotypes showing either extensive or poor drug metabolism (mainly codeine and tramadol). In 5-10% of patients, CYP2D6 is inactive while, in a small percentage of patients, enzyme duplications were found, leading to its overexpression and ultra-rapid bioactivation activity. Besides, the activity of CYP-enzymes may be compromised by interactions with inducers or inhibitors. Table III summarizes a selection of drugs with CYP450 interference, to underline the importance of drug-on-drug interactions and the resultant pharmacological imprecision forcedly affecting equianalgesia conversion in polytherapy[49-55].

The genetic background of metabolic enzymes and the presence of other drugs that influence drug metabolism are important factors that can greatly modify opioid response[16].

Practical recommendations:
– Individual genetic variability in enzymatic expression can dramatically influence response to different opioids;
– Metabolic pathways should be considered in patients with hepatic or renal impairment;
– In chronically treated patients experiencing inadequate pain relief, interaction with other drugs known as enzymatic inducers or inhibitors should be scanned for.

Equianalgesia

Equianalgesia indicates the dose ratio of different opioids and/or different route administrations of the same opioid producing equal analgesic effect[1,2]. Table I reports the equianalgesic doses extrapolated from literature[1,2,13,16-32] and from the summaries of product characteristics[33-39]. Conversion rates are summarized in the **Supplementary Table II**. Given the peculiarity of methadone and buprenorphine, their conversion is discussed in a dedicated paragraph.

As a general rule in clinical practice, it is advisable to start the switch by applying a 25-50% reduction of the entering opioid amount resulting from the arithmetic calculation so as to titrate the dose[1,56]. The rationale for this reduction relies on the experience proving that the calculated equianalgesic dose commonly under-

Table I. Equianalgesia table.

Opiate	Morphine[17]	Morphine[13,17]	Morphine[17]	Morphine[17]	Morphine[17]	Codeine[17]	Tramadol[17,33]	Tramadol[33]	Tapentadol[16,34]	Oxycodone[2,13,16-18,25-26,35]	Oxycodone[2,13,16-18,25-26,35]	Hydromorphone[2,13,16,17,32]	Fentanyl[13,36]	Buprenorphine[27,37]	Fentanyl[1,2,17,28-31]	Buprenorphine[17,27,37]	Sufentanil[39]
Form	OS ATC	SC	IV	PD	SA	OS	OS	IM/IV	OS	OS	SC/IV	OS	IV	IM/IV	TTS	TTS	SL
Unit	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	µg/h	µg/h	µg
	7.5	3.75*	2.5*	0.38*	0.04*	30*	37.5*	25*	25*	3.75*	1.88*	1.5*	0.1*		3*	5	7.5*
	15	7,5*	5*	0.75*	0.08*	60*	75*	50*	50	7.5*	3.75*	3*	0.2*		6*	10	15*
	22.5	11.3*	7.5*	1.13*	0.11*	90*	113*	75*	75	11.3*	5.63*	4.5*	0.3*		9*	15	22.5*
	30	**15**	**10**	**1.5**	**0.15**	**120**	**150**	**100**	**100**	**15**	**7.5**	**6**	**0.4**	**0.3**	**12**	**20**	**30**
	60	30	20	3	0.3	240	300	200	200	30	15	12	0.8	0,6	25	35	60
	90	45	30	4.5	0.45	#	#	300**	300	45	22.5	18	#	0.9	37.5*	52.5	90
	120	60	40	6	0.6	#	#	400**	400	60	30	24	#	1.2	50	70	120
	180	90	60	9	0.9	#	#	#	600	90	45	36	#	1.8	75	#	180
	240	120	80	12	1.2	#	#	#	#	120	60	48	#	2.4	100	#	240
	300	150	100	15	1.5	#	#	#	#	150**	75	60**	#	#	#	#	300

*Arithmetically extrapolated, below therapeutic range. **Arithmetically extrapolated, within therapeutic range. #Above therapeutic range. *Abbreviations:* ATC, around the clock; IM, intramuscular; IV, intravenous; OS, oral form; PD, peridural; SA, subarachnoid; SC, subcutaneous; SL, sublingual; TTS, transdermal system.

Table II. Major opioid enzyme pathways, modified from Mercadante 2015[16].

	CYP2D6	CYP3A3/4	CYP2B6	UGT
Morphine				++
Codeine	++			+
Tramadol	++	++		
Tapentadol				++
Oxycodone	+	++		
Hydromorphone				++
Methadone		++	+	
Fentanyl		++		
Buprenorphine		++		+
Sufentanil		++		

states the actual potency of the new opioid. This can be due to individual variation or to the impact of incomplete cross-tolerance. The 25-50% reduction helps in compensating potential incomplete cross-tolerance, differences in opioid receptors expression and other factors affecting the response.

Equianalgesia tables represent a very advantageous tool in the hands of the clinician, but they need to be used cautiously. Indeed, patient characteristics as well as pharmacodynamics, pharmacokinetics and pharmacogenetics should be taken into account.

Practical recommendations:
– Patients presenting pain characteristics involving defined receptors should be treated with molecules active on those receptors, e.g., investigating the quality of pain (visceral pain involving κ receptors, presence of neuropathic component);
– Starting opioid switching with a lower dose (-25-50% than the amount reported in equianalgesia table) and titrating to the effective dose is recommended;
– Careful monitoring of the patient after switching or starting a new opioid is strongly recommended, both for overdose (through Richmond agitation-sedation scale RASS[54] or Riker Sedation-Agitation Scale_SAS[55] and O$_2$ saturation) or opiate withdrawal (through Clinical Opiate Withdrawal Scale_COWS[52,53] every 4 hours).

Methadone
Equianalgesia can be difficult to achieve with methadone due to its nonlinear pharmacokinetics. Also, its high liposolubility, long plasma half-life (24-36 hours up to 130 hours in some patients)[57,58] and its high tissue accumulation make the binary conversion back to morphine even more problematic. Steady-state levels for

methadone can require several days up to two weeks, hindering fast pain control. For the above reasons, methadone should be only chosen when other opioids are not efficient in controlling pain anymore.

Many authors[47,59-61] proposed different scales of conversion from oral morphine to methadone, but all of them use different ratios and raise an issue of discontinuity when converting high morphine doses at the ratio transition points. Moreover, linear equations were proposed for converting racemic or levomethadone[19] to slow-release oral morphine, but none of these have been validated yet and doubts about the safety of this approach must be taken into account. Some authors[62,63] proposed new scales with a mathematical approach, by creating hyperbolic or mixed models of conversion. These could overcome the discontinuity problem but, again, none of these new models presents sufficient validation in literature to be proposed as a practical option in this article.

Our expert practical advice is to start equianalgesia by dividing the converted daily amount of methadone obtained through Storey scale[61] (Table IV) into 3 doses q8H. Storey scale is regularly chosen due to its easier conversion factors and multiple ratio steps. For non-tolerant opioid patients an initial 75% down-titration of the calculated dose should be considered as proposed in the literature[56]. Proper monitoring for overdose (through RASS[54] or SAS[55]) and opiate withdrawal (through COWS[52,53]) should be regularly performed to balance up or down titration in the following days (Table IV).

Levomethadone, used for opioid maintenance treatment, is an effective alternative to racemic methadone, given its less adverse effects and higher potency compared to its racemic counterpart with a 1:2 ratio[64]. Our advice is to avoid lin-

Table III. Selection of drugs with CYP450 interference[108-110].

	Inducers	Inhibitors*	Other known substrates
CYP3A4	STRONG: -Anti-androgens -Phenytoin Others: -Carbamazepine -Oxcarbazepine -Topiramate -Barbiturates -Glitazones -Modafinil -Dexamethasone	STRONG: -Protease inhibitors -Clarithromycin -Erythromycin -Chloramphenicol -Azole antifungals MODERATE: -Amiodarone -Ciprofloxacin -Cyclosporine -Fluvoxamine WEAK: -Cimetidine -Ranitidine -Tacrolimus -Gabapentin -Amlodipine -Valproic acid	-Glucocorticoids -Taxanes -Doxycycline -Etoposide -Other macrolides -Benzodiazepines -Z Drugs -Statins -Calcium channel blockers -Sex hormones
CYP2B6	-Carbamazepine -Phenytoin -Phenobarbital -Rifampicin	-Ethinylestradiol -Raloxifene -Fluoxetine -Fluvoxamine -Paroxetine -Sertraline -Itraconazole -Ketoconazole -Clotrimazole -Ticlopidine -Clopidogrel	-Verapamil -Bupropion -Cyclophosphamide -Ifosfamide -Valproic acid -Ketamine -Propofol
Clinical effects**	Opioid withdrawal syndrome[111]	Overdose symptoms	
CYP2D6 (Bioactivation)	-Dexamethasone -Rifampicin -Glutethimide	STRONG -Paroxetine -Fluoxetine -Bupropion -Quinidine -Ritonavir MODERATE -Sertraline -Paroxetine WEAK -Buprenorphine -Cimetidine -Amiodarone	-Tricyclic antidepressants -Other SSRI-SNRI -B-blockers -Promethazine -Chlorpromazine -Dextromethorphan -Class I antiarrhythmics -Anti H1 and H2 -Ondansetron
Clinical effects**	Overdose[111] symptoms	Opioid withdrawal syndrome	

*STRONG = >5-fold increase in plasma concentrations; MODERATE = >2-fold increase in plasma concentrations; WEAK = 1,25-2-fold increase in plasma concentrations. **For opioid withdrawal syndrome use Clinical Opiate Withdrawal Scale (COWS)[32,33] and check patient symptoms every 4-6 hours. For overdose use Richmond agitation-sedation scale (RASS)[30] or Riker Sedation-Agitation Scale (SAS)[31] and frequently check for GCS, saturation, and respiratory rate.

ear conversion scales from morphine but, instead, it is safer to calculate racemic oral methadone dose from morphine and use half a dose of the conversion for levomethadone.

Parenteral methadone shows different bioavailability compared to oral route, with about a 1:2 intramuscular ratio of correction[65]. It can be employed for patients with persistent nausea, vomit or who underwent massive upper/abdominal surgery with following oral intake difficulties. It might also be considered in terminal patients who do not respond to other opioids anymore[66,67]. We

Table IV. Different scales used for morphine-methadone conversions.

Daily oral morphine dose	Morphine: methadone	
	Mercadante[27]	
30-90 mg 90-300 mg > 300 mg	4:1 8:1 12:1	
	Ayonrinde[36]	**Gazelle[37]**
< 100 mg 101-300 mg 301-600 mg 601-800 mg 801-1000 mg > 1000 mg	3:1 5:1 10:1 12:1 15:1 20:1	4:1 6.7:1 13.3:1 15.4:1 20:1 26.7:1
	Storey[38]	
< 30 mg 30-100 mg 100-299 mg 300-499 mg 500-999 mg > 1000 mg	2:1 4:1 8:1 10:1 15:1 20:1	

suggest using half of the calculated oral methadone dose and divide this amount into two up to four equals daily administrations[68]. It is advisable to regularly check the injection area for possible local adverse effects.

Practical recommendations:
– Start equianalgesia by dividing the converted daily amount of methadone into 3 doses;
– For non-tolerant opioid patients consider an initial 75% down titration of the calculated dose;
– Proper monitoring for overdose (RAS or SAS and O2 saturation) and opiate withdrawal (through COWS every 4 hours) should be regularly performed to modulate the dose;
– With levomethadone, calculate racemic oral methadone dose from morphine and use half a dose of the conversion;
– With parenteral methadone, use half a dose of the calculated oral methadone dose and divide this amount into 2-4 equal daily muscular administrations.

Buprenorphine

Buprenorphine has a more linear profile compared to methadone despite having completely different pharmacokinetics and pharmacodynamics from morphine (partial versus full MOR agonist). Thus, due to buprenorphine's higher affinity for μ receptor along with its potential for precipitating a withdrawal syndrome among patients on opioids with lower affinity, many authors removed its conversion ratios from tables[69] and suggest not to consider this drug as a first option for opioid switching[70]. Nevertheless, latest evidence in literature retrieved buprenorphine as a valid alternative in acute pain management either alone or with the addition of a short-acting full μ agonist, since it has ceiling effect for respiratory depression but not for analgesia[71,72] and withdrawal symptoms for its concomitant use with low OME (<80 mg/die) should not significantly be feared[73,74].

Sublingual tablets are the most commonly used formulations for substitution therapy in opioid use disorder (OUD) whereas transdermal patches are frequently chosen for analgesia purposes[7,75]. Buccal microgram films, despite being not easily available in many countries worldwide, are becoming more and more considered by authors for their use in pain medicine[76,77].

Different conversion factors have been proposed for buccal and sublingual formulations19, ranging from 1:30 in former (until 2017) CDC guidelines[78] up to a different approach of 1:100 in a 2016 study[74].

Transdermal patches conversions are usually built with the rationale of 1:75 ratio between

parenteral buprenorphine and oral morphine and different derived multiplying factors for daily and weekly amount needs[17,78,79].

New formulations have lately been introduced (*i.e.,* depot injection gels, sub-dermal implants) but literature lacks information about conversion ratios back to morphine, given the extreme inhomogeneous pharmacokinetics of these products. If symptoms of toxicity or overdose are present, sub-dermal implants can be surgically removed and the opioid should be changed with proper adjustment. On the contrary, depot injection gels are not removable from the body.

Practical recommendations:
– Buprenorphine is a valid alternative in pain management in clinical practice;
– Buprenorphine conversion ratios were not updated in guidelines after 2016 and are here reported as an aid only for healthcare providers in peculiar settings;
– Consider the need of reducing opioid MME to a safer range before the switch and withdrawal risk (through COWS every 4 hours).

We suggest consulting an addiction specialist/pain therapist when switching to methadone or sublingual buprenorphine from other opioids. We suggest performing switching only for inpatients in a monitored environment.

Opioids Associations

Patients in chronic treatment with opioids *via* an oral or transdermal formulation that reached stable serum concentration may experience pain as they became tolerant to the compound, for increased pain or disease exacerbation. In this case, these patients are typically switched to the intravenous form using equianalgesia tables for conversion, especially in hospital inpatient.

As an alternative, a second opioid can be added to the ongoing therapy, so that treatment consists of an opioid association. As an addition, 1/6 (roughly corresponding to 15%) of the daily dose of the first opioid should be administered[7] as a rescue dose. Inevitably, the rescue dose will increase proportionally to the 24 hours dose increment, when needed.

Fentanyl in specific formulations, known as rapid onset opioids (ROOs, including: buccal tablet, nasal spray, intranasal, oral transmucosal, and sublingual formulations), is already indicated for the management of breakthrough cancer pain (BTcP) in patients on other opioids for background pain. The identification of BTcP is an issue of paramount importance in emergency setting. In case of patients with uncontrolled pain on ROOs treatment, the total amount of opioids used for background pain and opioids taken for BTcP should be taken into account. Table V reports the equianalgesic doses among ROOs and oral morphine. Table I and V are intended to facilitate the calculation of the total OME intake in patients simultaneously treated with an opioid for background pain and with a ROO for BTcP.

Practical recommendations:
– When adding a second opioid to the ongoing therapy, 1/6 (roughly corresponding to 15%) of the daily dose of the first opioid should be administered.

Table V. Equianalgesia table relative to BTcP, data from Mercadante 2018[91].

Morphine OS on demand mg	Morphine IV on demand mg	Fentanyl OTFC µg	Fentanyl FBT µg	Fentanyl FPNS µg	Fentanyl SLF µg	Fentanyl INFS µg
10	3.3	200	100	100	100	50
15	4.95	300				75
20	6.6	400	200	200	200	100
30	9.9	600	300	300	300	150
40	13.2	800	400	400	400	200
50	16.5	1000	500	500	500	

Abbreviations: FBT, fentanyl buccal tablet; FPNS, fentanyl nasal pectin spray; INFS, intranasal fentanyl; IV, intravenous; OS, oral form; OTFC, oral transmucosal fentanyl citrate; SLF, sublingual fentanyl. When switching between different fentanyl containing products, independent dose titration is required due to significant differences in formulations bioavailability.

Special Populations

Liver Failure

Metabolism and elimination largely depend on liver and kidney function, so that patients with hepatic or kidney impairment can experience a serious worsening of the opioid's toxic effects.

A critical aspect is the treatment of patients with hepatic failure. In these cases, opioids whose metabolic pathway mainly relies on CYP450 should be avoided and morphine, which mainly undergoes glucuronidation, should be preferred.

In patients with hepatic impairment, an opioid dosing regimen should be carefully established, with an individual titration approach with short-acting opioids to achieve optimal doses for pain relief avoiding adverse effects[80].

Practical recommendations:
– Opioids whose metabolic pathway mainly relies on CYP450 (Table II) should be avoided.

Kidney Failure

Fentanyl and buprenorphine should be preferred in patients with kidney failure[81,82]. Fentanyl is primarily oxidized in the liver with no active metabolites. Buprenorphine is primarily metabolized to norbuprenorphine and N-dealkylbuprenorphine, poorly excreted by the kidney[73,81].

Oxycodone (that is extensively metabolized in the liver but excreted primarily by the kidney) and methadone (that has a long elimination half-life as well as being poorly removed by hemodialysis) are useful in patients with chronic kidney disease, but require careful monitoring[81,82].

Morphine, tramadol, codeine should be avoided[81,82].

Practical recommendations:
– Fentanyl and buprenorphine should be preferred in patients with renal failure.

Elderly Patients

Age-related differences in perception and response to pain are well-known in the elderly since response to mild pain is often diminished, but higher sensitivity to severe pain is as well reported[83]. Response to different opioids has been shown to be variable in the elderly[83,84].

However, physiological impairment (e.g., kidney, hepatic) can affect opioids pharmacokinetics while comorbidities and concurrent therapies increase drug interactions, as well as reduced response and adverse events[83]. In older patients,

in consideration of the possibility of developing tolerance, unremitting opioid-induced sedation/fatigue limiting the quality of life, necessity of performing dose escalation for optimum pain control, a start with 50% to 75% of the new opioid equianalgesic dose is recommended. By doing so, compensation for incomplete cross-tolerance and individual variation will be granted[83].

Careful slow dose titration based on individual response is always required in older people, in consideration of the individual tolerability profiles and in order to reduce the incidence of initial adverse events (e.g., nausea or vomiting)[83,84].

Practical recommendations:
– Start with 50% to 75% of the published equianalgesic dose of the new opioid to compensate for incomplete cross-tolerance and individual variation;
– Careful slow dose titration based on individual response is always required.

Pediatric Patients

According to WHO Guidelines on persisting pain management in children, switching opioids and/or administration route is strongly recommended in the presence of inadequate analgesic effect and/or intolerable side-effects. Still, optimal titration is crucial before starting switching and routine rotation is not recommended[40]. Safety, concerning the risk of opioid overdose in particular, should always be ensured[4].

Conversion from oral morphine to fentanyl TTS (1:0.01), oral hydromorphone (1:0.2), and oral oxycodone (1:0.67, instead of 1:0.5) are similar to those reported in Supplementary Table II. However, titration is recommended considering previous opioid treatments, bioavailability of the formulation, interactions with other therapies and kidney/hepatic clearance[4].

Practical recommendation:
– Titration is recommended considering previous opioid treatments, bioavailability of the formulation, interactions with other therapies, and renal/hepatic clearance.

Pregnancy and Lactation

Chronic use of non-steroidal-anti-inflammatory-drugs (NSAIDs) should not be the first analgesic choice during pregnancy, as it could increase the risk of first-trimester spontaneous abortion, oligohydramnios after the 20th week of gestation and pre-term labor after the 28-30th

week[85,86]. All opioids used for analgesia can be a good alternative since they are not related to an increased teratogenic risk[87,88]. On the contrary, the mother will benefit from proper pain management (titrated to avoid withdrawal or overdose) resulting in a better continuation of pregnancy, despite the possible risk for delayed delivery, longer hospitalization[89], and small for gestational age newborns[87,88].

If opioids are maintained during the last month of pregnancy, it is advisable to monitor the newborn for sedation or neonatal abstinence syndrome (NAS)[87,88], the latter up to 72 hours after birth. NAS can be evaluated through Finnegan Scale (multiple modified versions are available in literature, e.g.,[90,91]).

If opioids are chronically used throughout pregnancy, lactation should not be simplistically discouraged. Instead, the safest opioid should be selected to reduce the risk of NAS[87,88]. To this aim, breastfeeding should be carefully considered following opioid pharmacokinetic characteristics, such as: *i)* opioid half-life in the mother; *ii)* mother milk/plasma ratio (M/P); and *iii)* opioid infant oral bioavailability and reported infant dose (RID) after nursing.

Morphine and fentanyl are drugs of choice during lactation[92-95]. Fentanyl seems to be the safest option given its short half-life (4 hours) and low passage into milk. Many studies and case reports[94,96] found insufficient justifications for interrupting breastfeeding after a single use of intravenous fentanyl for analgesia or its chronic transdermal use. Nevertheless, if prolonged therapy with opioids is planned, a more conservative approach is advisable (*i.e.*, using pumped and bottled milk before taking a new opioid dose or mixed feeding with formula).

Drugs going through CYP2D6 bioactivation (*i.e.*, codeine, tramadol) are strictly contraindicated for the risk of rapid metabolizers newborns[87,92,94].

Women on maintenance therapy with methadone or buprenorphine might keep these two drugs during breastfeeding as they are considered safe (methadone RID 3% up to 150 mg/die, buprenorphine RID is less than 2.3%)[93,95,97]. A medically assisted up-titration of these drugs can be a reasonable option in case of severe acute pain if the OUD is safely stabilized.

Nevertheless, both the mother and the pediatrician should regularly monitor the baby if opioids are chronically maintained[92] and specific considerations must be taken in case of prematurity.

Practical recommendation:
– For detailed information and suggestions about medications during pregnancy and lactation a teratology or perinatal-toxicology service should be consulted.

Critical Scenarios

To widen the overview of special cases and populations, a few emblematical scenarios of acute pain treatment in complex patients on chronic opioid therapy are exemplified as follows.

Rapid Pain Worsening in Chronic Pain

In patients on chronic opioid therapy, rapid dose escalation can be required for aggravating pain or tolerance development, both associated with a negative prognosis[98]. Considering that a rapid increase in pain may also be due to lack of drug absorption or failure in therapy adhesion, it is primarily important to take patients detailed medical history. Once it has been defined that pain is related to disease progression or a new cause to be studied, a response to acute pain must be given. An intravenous/intramuscular dose with the same molecule can be chosen (tramadol, morphine, buprenorphine, fentanyl, and oxycodone are also available in intravenous formulation), if the patient was previously on oral or transdermal treatment. In alternative, an association of different drugs is also possible (intravenous morphine in a patient treated with oral hydromorphone or tapentadol). As these patients could be opioid tolerant, a proportional dose may be predictably effective, averting the risks of adverse effects[49].

Following acute pain management guidelines in chronic pain patients[7], intravenous analgesic opioid dose should be one-sixth of the daily dose and administration route changes could also be taken into account, based on the equianalgesia table. Considering the numerous variables related to the response to the new analgesic drug, both in terms of efficacy and side effects, careful titration of the intravenous analgesic drug is required.

After the first intravenous dose, if effective, it is possible to maintain a continuous infusion with a dose of analgesic that takes into account the previous oral/transdermal therapy and the necessary increase compared to it.

If the intravenous drug is the same administered for background pain and it is not effective, tolerance to the analgesic has probably occurred. In this case, it is advisable to use different drugs or methods (multimodal analgesia). It may be useful to try an intravenous NSAID (if not contrain-

dicated), an anesthetic drug (methoxyflurane)[99] or going with locoregional anesthetic/analgesic block[41], immediately followed by the use of a different opioid.

Treatment aims include effective relief of acute pain, prevention of drug withdrawal, assistance with any related social, psychiatric, and behavioral issues, and ensuring continuity of long-term care. Pharmacological approaches include continuation of usual medications (or equivalent), short-term use of higher opioid doses than average and prescription of non-opioid and adjuvant drugs, all aiming to improve pain relief and attenuate opioid tolerance and/or opioid-induced hyperalgesia[100].

Practical recommendations:
– Rapid pain worsening due to clear nociceptive etiology among patients with chronic pain in opioid therapy can be treated with a dose equivalent to 1/6 the total daily dose.
– Titration of the new opioid or the previously increased dose may be medically evaluated as soon as the pain is stabilized, with different tapering programs according to patients' clinical and surgical needs.
– In case of failure of short-acting i.v. opioids a different approach is appropriate, with multimodal analgesia: NSAIDs, methoxyflurane, local anesthetic blocks to immediately manage the crisis followed by a different opioid for the background pain.

Acute Pain on Maintenance Treatment

Acute pain can be challenging for health providers when a patient with OUD is affected, either in active abusers or in patients with controlled methadone or buprenorphine maintenance therapy (MMT or BMT).

OUD patients ought to be considered pathophysiologically similar to patients under chronic opioid treatment, but even more careful decisions need to be taken in this population when choosing the proper drug to treat acute pain crises.

Before increasing MMT or BMT or inserting an extra opioid, a proper selection of non-opioid drugs should be considered, especially for mild pain crises. If the non-opioid strategy is not enough (especially in moderate or severe pain), we suggest keeping the non-opioid drugs and consider either increasing maintenance therapy or adding an oral or parenteral short-acting (SA) full μ agonist, on a schedule if necessary[68,101,102]. Patients with OUD are opioid-tolerant and might need higher doses of short acting opioids to control pain.

When active abusers without MMT or BMT are taken into consideration, it is advisable to perform a toxicological urine screening and ask for toxicologist evaluations. It is advisable to agree with the patient on which opioid to choose in order to obtain better compliance after pain crisis resolution. To this aim, methadone should be considered at first, for its better control of withdrawal and degree of analgesia[103].

It is important not to be afraid of opioid therapy as analgesic either in MMT/BMT or in active abusers without MMT/BMT since it does not worsen OUD as long as it is promptly tapered after pain resolution.

We propose a possible management algorithm (Figure 1) for the above scenarios, as proposed by some authors[104]. It must be stressed that literature lacks evidence of pain management in OUD patients and only expert opinions have been proposed so far.

Careful monitoring should be provided throughout the up-titration process and the algorithm proposed doses should be properly modified based on the patient's personal history and their risk factors.

We suggest that health providers should always develop a taper plan with the outpatient addiction specialists' team, as soon as the pain crisis is resolved.

Practical recommendations:
– Non-opioid strategy should be evaluated first. If not sufficient, keep the non-opioid drugs and consider either increasing maintenance therapy or adding an oral or parenteral short-acting full μ agonist;
– Patients with OUD are opioid-tolerant and might need higher doses of short-acting opioids to control pain.

Pain Management of Complicated Patient in Emergency Care

In emergency care, the use of ROOs for the treatment of acute pain seems to be a necessity, but also a therapeutic solution. ROOs allow rapid achievement of the analgesic effect using non-invasive and easy-to-use routes of administration, practicable also in challenging circumstances. Fentanyl formulations developed for rapid onset action are only authorized for the treatment of BTcP, even though they could be valuable in several circumstances, from traumatic events in patients with difficult venous access, to painful complications as vaso-occlusive crisis[105].
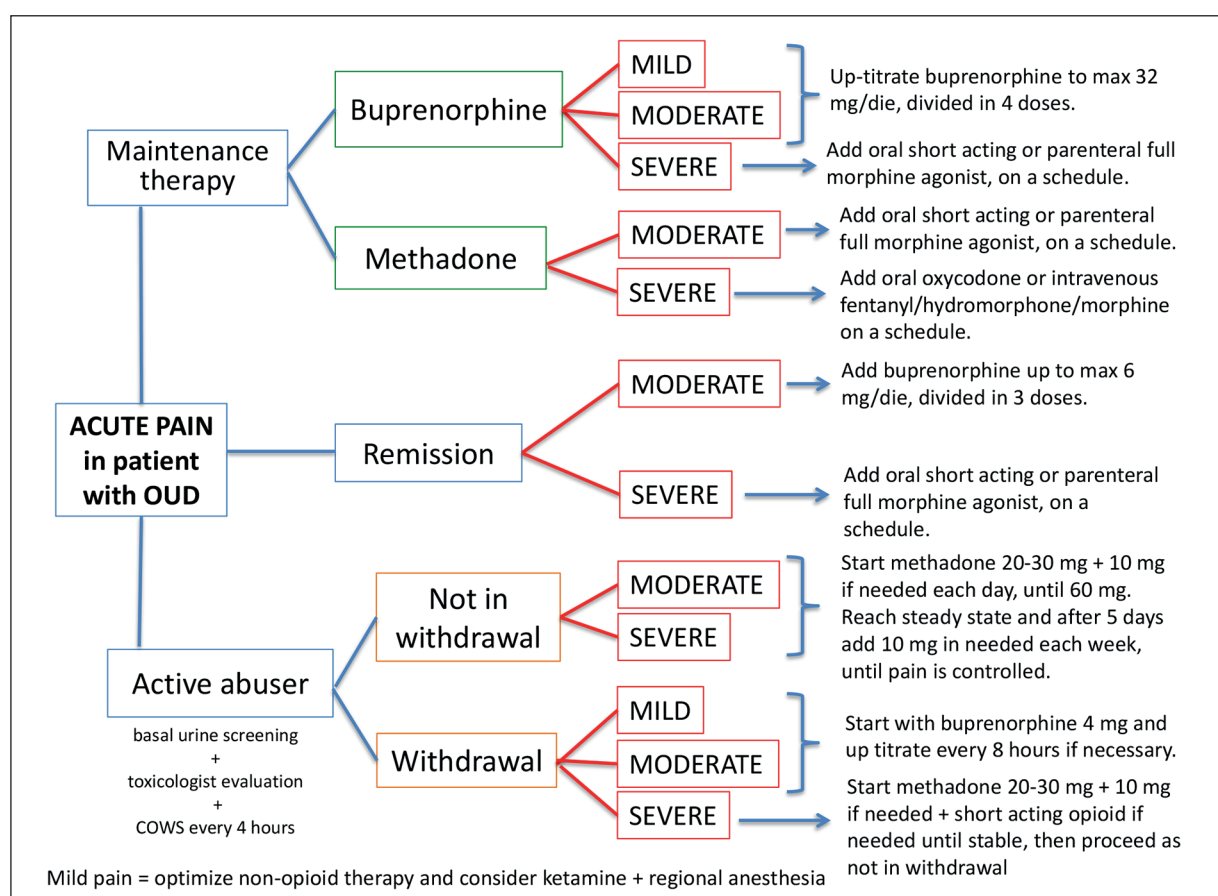
Figure 1. Clinical practice exemplifications of acute pain management in patients with opioid use disorder. Abbreviation: COWS, clinical opiate withdrawal scale; OUD opioid use disorder.

Oral formulations may have some limitations of use, as they are available at fixed dosages that cannot be adapted to the individual patient and their specific condition. Therefore, in these patients it might be useful to evaluate the intranasal route, which allows more precise titration of the fentanyl dose.

Table V reports the equianalgesia data for morphine on-demand and ROOs, including intranasal administration (INA), as found in the literature[17,106] in agreement with the summaries of the product characteristics.

INA is a growing option in emergency setting[107]. Two anatomical characteristics make INA reliable[108]: *(i)* the extensive vascularization of the nasal mucosa ensures diffusion through the capillary network and delivers the drug to systemic circulation, thus avoiding the absorption-limiting effects of first-pass metabolism; *(ii)* intranasal administration relies on the contact with the olfactory mucosa and the delivery *via* the olfactory nerve pathway directly to the cerebral spinal fluid

and brain bypassing the blood-brain barrier[109]. Intranasal administration can be accomplished with a variety of delivery methods, including topical preparations, sniffing, insertion of drops, spray formulations or drug atomization devices[110,111]. Atomization is the process of reducing a solution into a fine spray to expand the available surface area of drug molecules. A mucosal nebulizer device (MAD) is used to atomize drugs directly inside the nose.

Fentanyl intranasal administration has been described as a well-tolerated, non-invasive, safe and efficacious route of administration for the management of acute pain. Once intranasal fentanyl is distributed within the systemic circulation, it is expected to demonstrate the same pharmacokinetic and adverse-effect profile as intravenous fentanyl. Intranasal fentanyl has a bioavailability of 71% to 89%, and both maximal arterial blood concentration and onset of analgesia are reached in approximately 7 minutes[112,113].

In the emergency setting, the intranasal fentanyl is used extemporaneously at the recommended dose of 1-2 µg/kg[107,114]. Intranasal fentanyl in doses of 50, 100, and 200 µg are demonstrated as adequate analgesics in cancer patients with breakthrough pain[112]. Nausea, vomiting, and pruritus are the most commonly reported adverse effects, while nose mucosal irritation is rare[107,114].

Practical recommendation:
– Fentanyl formulations developed for rapid onset action allow rapid achievement of the analgesic effect using non-invasive and easy-to-use routes of administration.

Limitations

The lack of prospective/retrospective clinical trials to support the opinions expressed above and the narrative review form of this paper are a limitation to this article[115]. In addition, the discussion is limited to prescription opioids only. Illegal market drugs, other analgesic/anesthetics and adjuvant therapies were beyond the purpose of the authors. The pain generating effect of opioid dependence through neurobehavioral mechanisms (allostatic effects) and the effect of expectancy associated with opioids (placebo effect) was not discussed here due to the scope of this review and space limitations.

Last but not least, this review is imperfect because of the lack of data and the vastness of the topic. However, the aim was to start presenting a classification of scenarios and the recommendations in opioid switching/rotation. Many other experts might not agree with every recommendation, but this paper is meant to provide a baseline summary on which future efforts can build on.

Conclusions

Although awareness campaigns on the use of opioids in clinical practice are common, highlighting their addiction and overdose potential, these molecules seem to be the class that best suits clinical needs of emergency and post-operative medicine.

In this narrative review, several scenarios in which the use of opioids could be indicated have been analyzed. From the analysis of the literature, not always satisfactory for number and quality of studies, and from the opinion of the Authors, suggestions were made on how to use opioids in acute pain and how to integrate a chronic therapy with opioids with formulations and/or types of opioids more effective in acute pain.

Some considerations about equianalgesia of opioids are reported, translated into tables with the aim to simplify the clinical practice of any doctor in the setting of emergency or postoperative pain.

However, it should be stressed that equianalgesia can be affected by drug-to-drug interactions and pharmacological imprecision, in a field where clinical experience should always be the main driver.

Authors' Contribution
FDI and FM contributed to the conception of the work. All authors contributed to the design of the work, to the analysis and interpretation of data and have substantively revised it. All authors approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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