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DEGLI STUDI
FIRENZE
NEUROFARBA
DIPARTIMENTO DI NEUROSCIENZE,
PSICOLOGIA, AREA DEL FARMACO
E SALUTE DEL BAMBINO

OPPIODI, L'ESPERIENZA CLINICA: EFFICACIA

QUANDO, QUANTO E PER QUANTO TEMPO

21.01.2019

Professor Guido Mannaioni

Uso di oppiacei nella gestione del dolore cronico. Dal 1917 al 2017

- Gli autori dello studio hanno esaminato l'uso degli oppiacei nella cura del dolore cronico e le leggi sugli oppiacei nell'anno 1917 e hanno mostrato che molte delle stesse problematiche presenti nel 2017 erano significative anche a quel tempo.

- Nel **1917 l'epidemia di abuso di oppiacei era in aumento**, in particolare tra i veterani della prima guerra mondiale e le preoccupazioni di prescrivere gli oppiacei erano molto diffuse. Queste preoccupazioni e sfide rimangono attuali ancora nel 2017.

- Più di 100 anni fa, la **produzione di massa di eroina è stata interrotta** e gli scienziati hanno prima sintetizzato l'ossicodone nella speranza di ridurre la dipendenza dagli oppiacei.

- Nel 1917, il governo federale ha creato leggi e atti diretti contro l'uso, l'abuso e il controllo degli oppiacei.

- L'uso di farmaci oppiacei per la gestione del dolore cronico continua a presentare potenziali rischi per i pazienti con dolore cronico e il loro uso genera preoccupazione in molti clinici.

Duarte and Rosen, S32 *The Journal of Pain*, 2017

Prescrizione di Oppioidi. Da un estremo all'altro

vs

http://www.opidemic.org/

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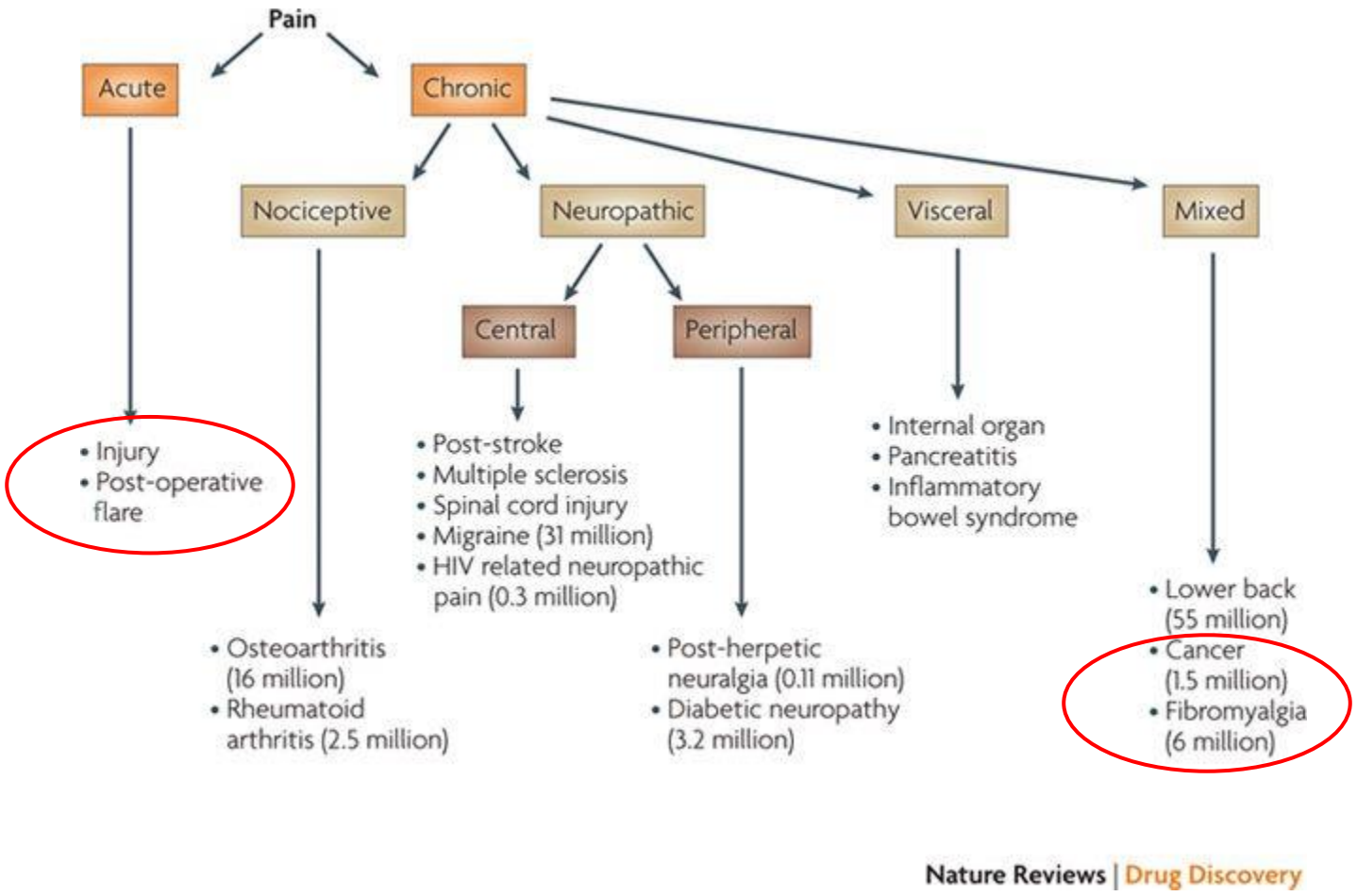
OPPIODI, L'ESPERIENZA CLINICA: EFFICACIA

QUANDO?

Professor Guido Mannaioni

CLASSIFICAZIONE DEL DOLORE



I. Melnikova, Nat Rev Drug Discov, 2010

CLASSIFICAZIONE DEL DOLORE

La IASP (International Association for the Study of Pain - 1986) definisce il dolore come "un'esperienza sensoriale ed emozionale spiacevole associata a danno tissutale, in atto o potenziale, o descritta in termini di danno. E' un esperienza individuale e soggettiva, a cui convergono componenti puramente sensoriali (nocicezione) relative al trasferimento dello stimolo doloroso dalla periferia alle strutture centrali, e componenti esperenziali e affettive, che modulano in maniera importante quanto percepito".

- **Dolore acuto**
- **Dolore cronico benigno**
- **Dolore cronico da cancro**

LA TERAPIA DEL DOLORE

Dolore acuto Il dolore acuto è causato da un trauma tissutale e dall'attivazione dei recettori periferici nel punto di lesione. Il trauma altera le risposte caratteristiche dei nocicettori e le loro connessioni centrali coinvolgendo il sistema simpatico. In genere i sistemi riparativi dell'organismo intervengono e portano alla guarigione della lesione con scomparsa del dolore.

- Post operatorio
- Trauma Viscerale (infarto, colica ad eccezione della biliare)
- Muscolare
- Parto
- Manovra diagnostica o terapeutica

Si utilizzano FANS ed oppiacei, a seconda della gravità del dolore

Tempo di somministrazione breve ed effetti collaterali trascurabili insorgenza acuta

IL DOLORE CRONICO

Dolore cronico **Anch'esso scatenato da un evento traumatico ma può continuare per fattori che, sia dal punto di vista patogenetico che da quello fisico, non sono direttamente correlati alla causa iniziale. Il trauma può superare la capacità di guarigione del corpo e il dolore diventa esso stesso malattia.**

DOLORE CRONICO BENIGNO

A differenza del dolore da cancro, il trattamento è di lunga durata e gli effetti collaterali sono importanti (SUD).

I farmaci utilizzati sono soprattutto i FANS (COX-1 e COX-2 inibitori), il paracetamolo e in patologie particolari bloccanti del TNF, gli antidepressivi e gli anticonvulsivanti.

Si sta facendo strada l'impiego di farmaci oppiacei anche nel dolore cronico benigno, soprattutto:

- quando gli effetti collaterali dei farmaci utilizzati sono inaccettabili (es. nel nefropatico)

- quando il dolore non risponde ad altri trattamenti (esempio METACEF)

IL DOLORE CRONICO da cancro

Il 35-45% dei pazienti prova dolore ad uno stato precoce o già al momento della diagnosi di tumore o di altre malattie degenerative.

- **Circa il 70% dei pazienti ha dolore in uno stadio avanzato della patologia.**
- **Quasi tutti i pazienti terminali hanno dolore.**

Si utilizza la scala OMS.

In relazione all'aumentare del dolore:

- **A) FANS**
- **B) Oppiodi deboli (codeina, buprenorfina, tramadolo)**
- **C) Oppiodi forti con o senza adiuvanti per il controllo degli effetti collaterali, del dolore incidente e per la qualità di vita**

I farmaci per la terapia del dolore

Analgesici Oppioidi

- Agonisti forti
- Agonisti deboli
- Agonisti / antagonisti
- Agonisti parziali

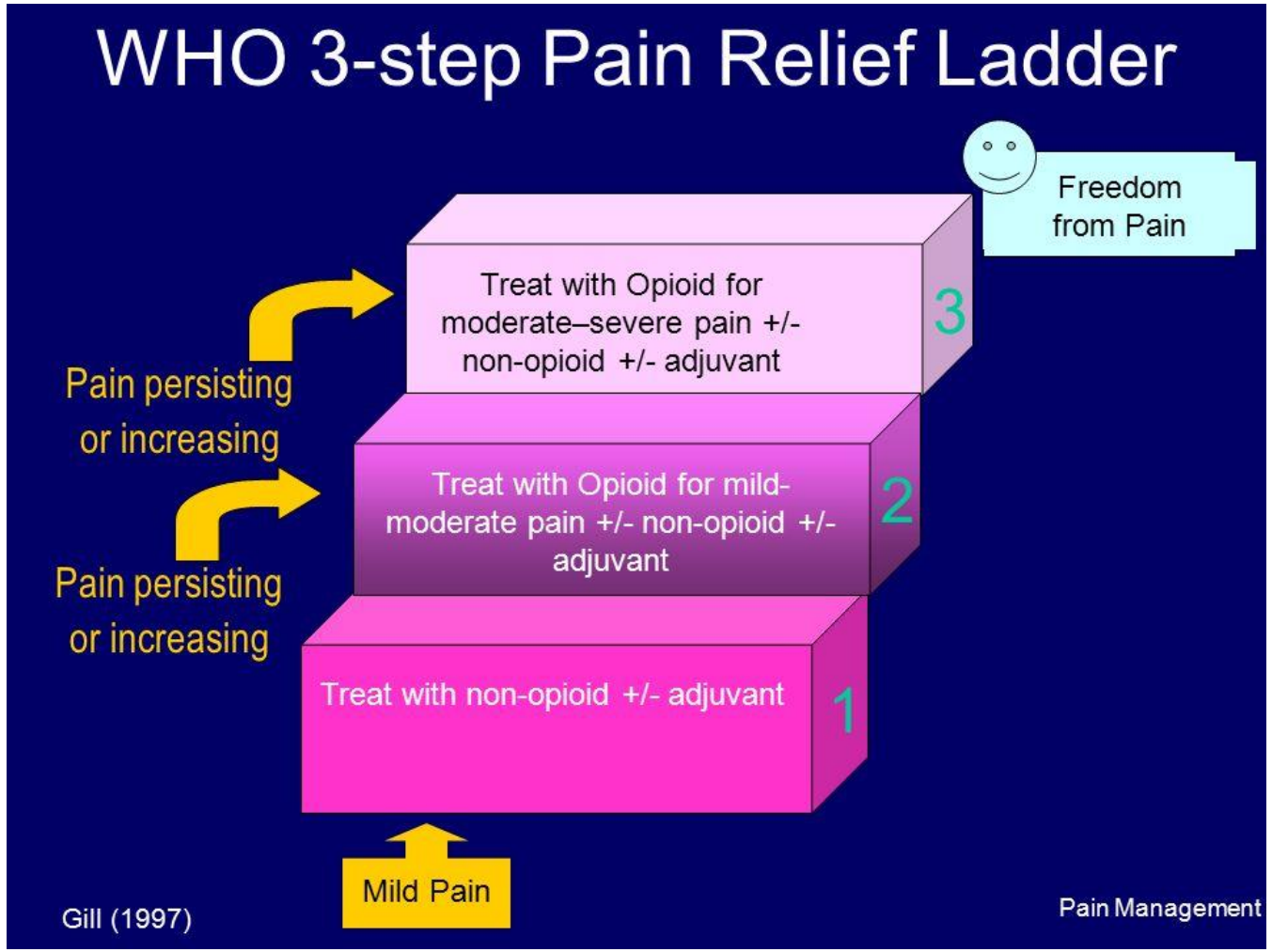
Analgesici Non Oppioidi

- Farmaci Antinfiammatori Non Steroidei (FANS)

Farmaci Adiuvanti

- Antidepressivi triciclici
- Antiepilettici
- Farmaci serotoninergici (SSRI, trazodone)
- Farmaci noradrenergici
- (clonidina, terazosina)
- Ansiolitici
- Neurolettici
- Miorilassanti
- Corticosteroidi
- Anestetici locali
- Altri (capsaicina, somatostatina)

Uso dei farmaci analgesici



Pain Treatment

Pain Treatment

Pharmacologic

Nonopioid analgesics: acetaminophen, NSAIDs

Opioid analgesics

Adjuvant analgesics or co-analgesics: a diverse group of drugs with primary indications for conditions other than pain, eg, anticonvulsants and antidepressants

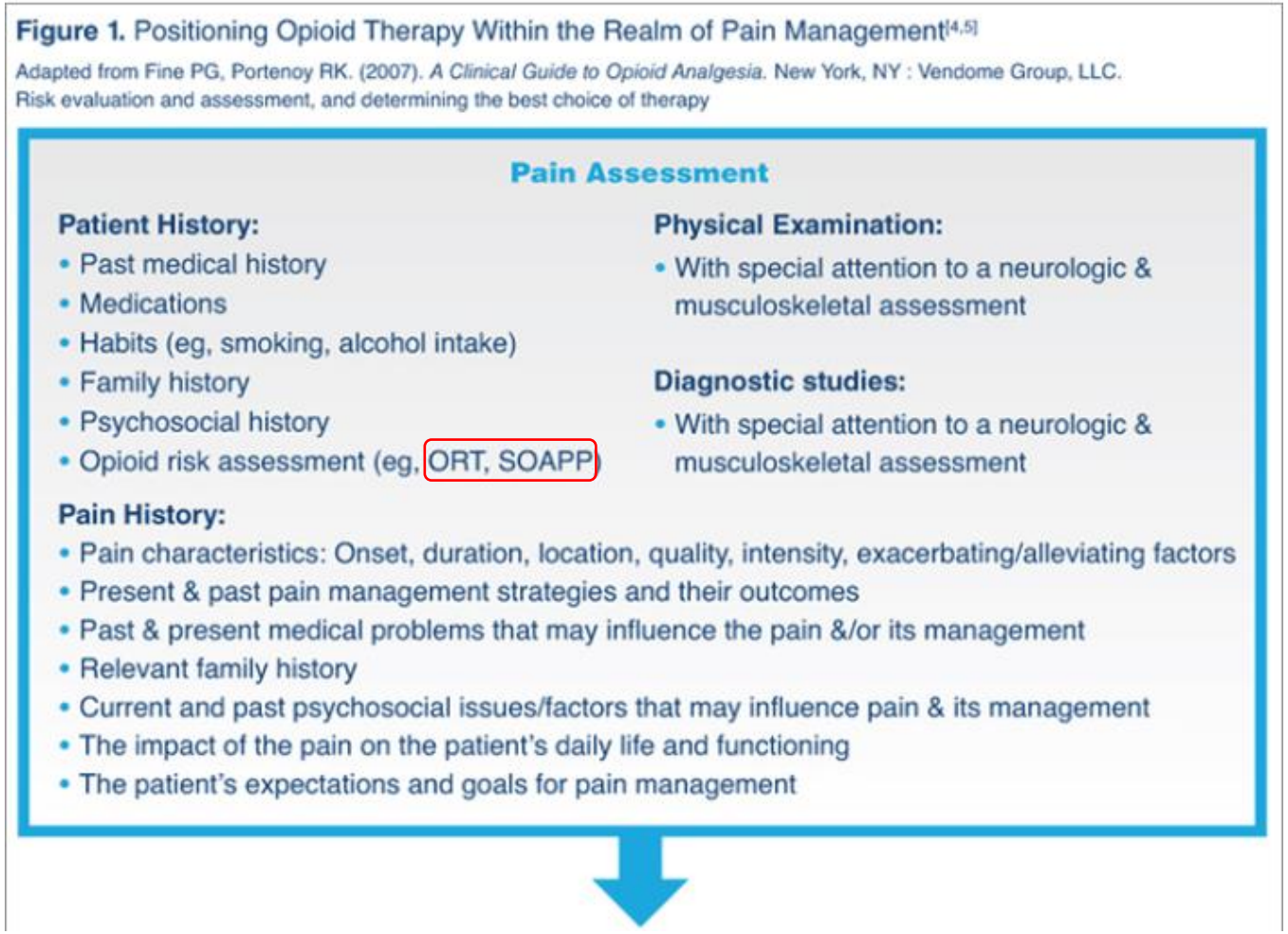
Disease-modifying therapies (eg, cancer chemotherapeutics, DMARDs)

Nonpharmacologic	
Rehabilitative approaches	Modalities (heat, cold, transcutaneous electrical nerve stimulation), physical therapy, occupational therapy
Psychologic approaches	Cognitive behavioral therapy, specific techniques (biofeedback, hypnosis, relaxation), other psychotherapies
Interventional therapies	
Injection therapies	Trigger point injections, joint injections, spinal injections
Neural blockade	Sympathetic nerve blocks, medial branch block, celiac plexus block
Implant therapies	Spinal cord stimulator, intrathecal pump
Surgical approaches	Cordotomy, neurectomy
Complementary and alternative medicine approaches	Acupuncture, chiropractic therapy, massage, nutritional approaches and nutraceuticals, energy therapies
Lifestyle changes	Weight loss, exercise

Positioning Opioid Therapy

Figure 1. Positioning Opioid Therapy Within the Realm of Pain Management[4,5]

Adapted from Fine PG, Portenoy RK. (2007). *A Clinical Guide to Opioid Analgesia*. New York, NY : Vendome Group, LLC.
Risk evaluation and assessment, and determining the best choice of therapy



Opioid Risk Tool

This tool should be administered to patients upon an initial visit prior to beginning opioid therapy for pain management. A score of 3 or lower indicates low risk for future opioid abuse, a score of 4 to 7 indicates moderate risk for opioid abuse, and a score of 8 or higher indicates a high risk for opioid abuse.

Mark each box that applies	Female	Male
Family history of substance abuse		
Alcohol	1	3
Illegal drugs	2	3
Rx drugs	4	4
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Rx drugs	5	5
Age between 16—45 years	1	1
History of preadolescent sexual abuse	3	0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	2	2
Depression	1	1
Scoring totals		

Screener and Opioid Assessment for Patients with Pain (SOAPP)

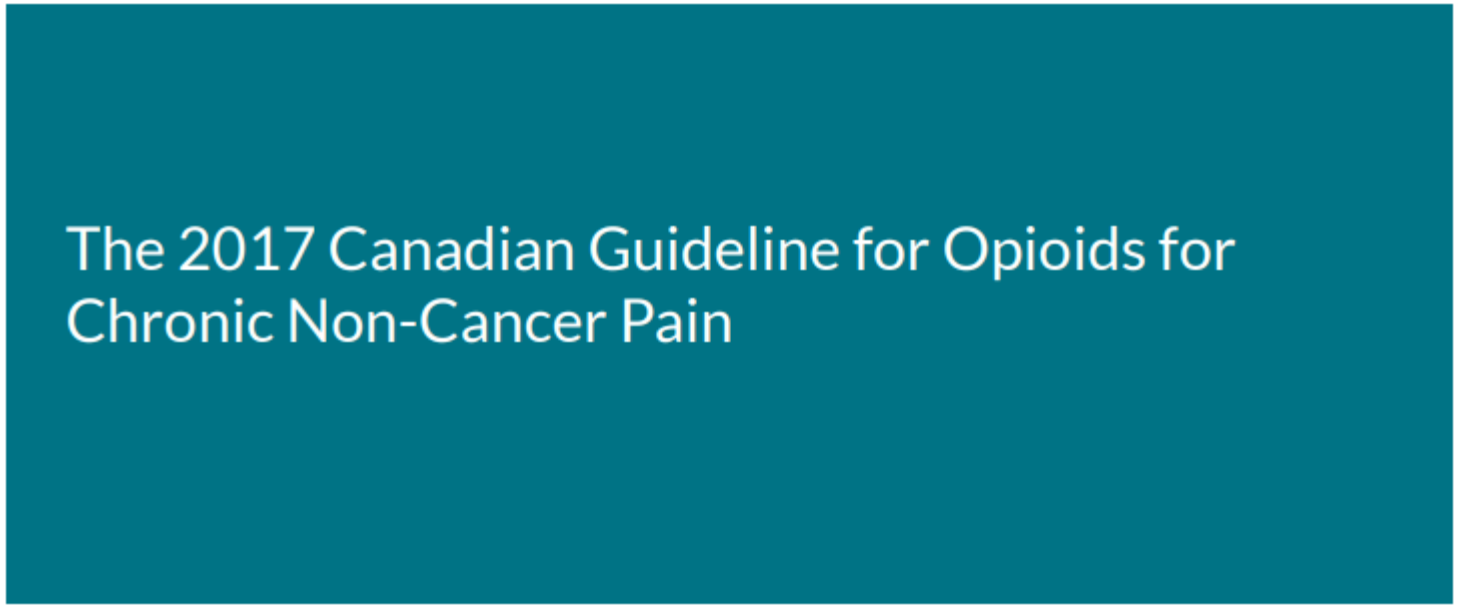
The following are some questions given to all patients at the Pain Management Center who are on or being considered for opioids for their pain. Please answer each question as honestly as possible. This information is for our records and will remain confidential. Your answers alone will not determine your treatment. Thank you.

Please answer the questions below using the following scale:

0 = Never, 1 = Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often

1. How often do you have mood swings?	0 1 2 3 4
2. How often do you smoke a cigarette within an hour after you wake up?	0 1 2 3 4
3. How often have you taken medication other than the way that it was prescribed?	0 1 2 3 4
4. How often have you used illegal drugs (for example, marijuana, cocaine, etc.) in the past five years?	0 1 2 3 4
5. How often, in your lifetime, have you had legal problems or been arrested?	0 1 2 3 4

Canadian Guideline for Opioids



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Canadian Guideline for Opioids, 2017

Canadian Guideline for Opioids

Initiation and Dosing of Opioids in Patients with Chronic Noncancer Pain

Recommendation 1: When considering therapy for patients with chronic non-cancer pain

Strong Recommendation

We recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids

Recommendation 2: For patients with chronic noncancer pain, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized nonopioid therapy

Weak Recommendation

We suggest adding a trial of opioids rather than continued therapy without opioids.

By a trial of opioids, we mean initiation, titration, and monitoring of response, with discontinuation of opioids if important improvement in pain or function is not achieved. The studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses. The mental illnesses identified in studies as risk factors for adverse outcomes were generally anxiety and depression, including ICD-9 definitions, as well as "psychiatric diagnosis", "mood disorder", and post-traumatic stress disorder.

Canadian Guideline for Opioids, 2017

Initiation and Dosing of Opioids

Recommendation 1: When considering therapy for patients with chronic non-cancer pain

Strong Recommendation

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Outcome Timeframe	Study results and measurements	Absolute effect estimates Optimization of therapy with NSAIDs.	 Trial of opioids.	Certainty in effect estimates (Quality of evidence)	Summary
Gastrointestinal side effects up to 6 months	Relative risk 2.52 (CI 95% 1.54 - 4.13) Based on data from 3,675 patients in 7 studies. (Randomized controlled) Follow up 6-26 weeks	**37** per 1000	**93** per 1000 Difference: **56 more** per 1000 (CI 95% 20 more - 116 more)	**High**	Opioid therapy results in a small increase in gastrointestinal side effects.
Pain 1-6 months	Measured by: 10-cm VAS Scale: 0-10 Lower better Based on data from: 2,250 patients in 13 studies. (Randomized controlled) Follow up 1-6 months	Difference: **MD 0.49 fewer** (CI 95% 1.24 fewer - 0.26 more)		**Low** Due to serious inconsistency, Due to serious imprecision	Opioid therapy may result in little or no difference in pain compared to NSAIDS.
Physical Function 1-4 months	Measured by: SF-36 Scale: 0-100 High better Based on data from: 1,972 patients in 8 studies. (Randomized controlled) Follow up 4-16 weeks	Difference: **MD 1.5 fewer** (CI 95% 3.08 fewer - 0.08 more)		**Moderate** Due to serious imprecision	Opioid therapy likely results in little or no difference in physical function compared to NSAIDS.

Canadian Guideline for Opioids, 2017

Initiation and Dosing of Opioids

Addiction FU not reported	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency.	Opioid therapy likely results in an important risk of addiction.
Fatal Overdose median 2.6 years	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy results in a rare but important risk of fatal overdose.
Non-fatal overdose up to 10 years	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Opioid therapy likely results in a small but important increase in the risk of non-fatal overdose.
Diversion 1 year	Based on data from 472,200 patients in 1 studies	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in 2013.	**Moderate** Due to serious risk of bias.	Opioid therapy likely results in an important increase in the risk of diversion.

Canadian Guideline for Opioids, 2017

Canadian Guideline for Opioids

Recommendation 3: For patients with chronic noncancer pain with an active substance use disorder

Strong Recommendation | AGAINST

We recommend against the use of opioids

Clinicians should facilitate treatment of the underlying substance use disorders, if not yet addressed. The studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

Recommendation 4: For patients with chronic noncancer pain with an active psychiatric disorder whose nonopioid therapy has been optimized, and who have persistent problematic pain

Weak Recommendation

We suggest stabilizing the the psychiatric disorder before a trial of opioids is considered

Recommendation 5: For patients with chronic noncancer pain with a history of substance use disorder, whose nonopioid therapy has been optimized, and who have persistent problematic pain

Weak Recommendation

We suggest continuing nonopioid therapy rather than a trial of opioids

The studies that identified a history of substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

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OPPIODI, L'ESPERIENZA CLINICA: EFFICACIA

Quali?

Quanto?

Professor Guido Mannaioni

Initiation and Dosing of Opioids

Table 3: Opioid options for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Morphine	Avoid in renal insufficiency
Oxycodone	~1.5x as potent as morphine. Available in a tamper-resistant formulation
Hydromorphone	~5x as powerful as morphine. Available in a tamper-resistant formulation
Oxycodone/Naloxone	Naloxone combination may minimize constipation and possibly act as an abuse deterrant
Buphrenorphine	Oral formulations preferred over transdermal for initial trial
Codeine	
Tapentadol	Available in a tamper-resistant formulation. Combined noradrenaline reuptake inhibitor and weak opioid
Tramadol	A prodrug (serotonin–norepinephrine reuptake inhibitor) that is converted to an opioid in a highly variable fashion.

Table 4: Opioids that are not recommended for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Methadone	Requires a specific Health Canada exemption to provide
Fentanyl (transdermal)	Not in opioid-naïve patients
Meperidine	Limited effectiveness; toxic metabolite accumulates in high doses or in renal insufficiency
Pentazocine	Limited effectiveness. High incidence of dysphoria

Canadian Guideline for Opioids, 2017

Canadian Guideline for Opioids

Recommendations 6 and 7: For patients with chronic noncancer pain who are beginning long term opioid therapy

Strong Recommendation

Recommendation 6: We recommend restricting the prescribed dose to less 90mg morphine equivalents daily rather than no upper limit or a higher limit on dosing

Weak Recommendation

Recommendation 7: For patients with chronic noncancer pain who are beginning opioid therapy, we suggest restricting the prescribed dose to less than 50mg morphine equivalents daily.

The weak recommendation to restrict the prescribed dose to less than 50mg morphine equivalents daily acknowledges that there are likely to be some patients who would be ready to accept the increased risks associated with a dose higher than 50mg in order to potentially achieve improved pain control.

Canadian Guideline for Opioids, 2017

Dosi equivalenti nella somministrazione orale degli oppioidi

Table 5: Opioid conversion table

Opioids*	To convert to oral morphine equivalent, multiply by:	To convert from oral morphine, multiply by:	50 MED equivalent dose	90 MED equivalent dose
Oral preparations (mg/d)				
Codeine	0.15 (0.1-0.2)	6.67	334 mg/d	600 mg/d
Hydromorphone	5.0	0.2	10 mg/d	18 mg/d
Morphine	1.0	1	50mg/d	90mg/d
Oxycodone	1.5	0.667	33 mg/d	60 mg/d
Tapentadol	0.3-0.4	2.5-3.33	160	300
Tramadol	0.1 -0.2	6	300	540**

*Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other drugs.
** The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.

Canadian Guideline for Opioids, 2017

Opioid Conversion Calculator

CAUTION: This calculator is intended for calculating the Morphine Equivalent Dose (MED) dose for a patient taking one or more opioid medications. It should not be used to determine doses when converting a patient from one opioid to another. Equianalgesic dose ratios are only approximations and do not account for genetic factors, incomplete cross-tolerance, and pharmacokinetics.

Instructions: Fill in the mg per day for the patient's opioid medications. The daily morphine equivalent dose is calculated automatically.

Opioid:	mg per day:	Morphine Equivalent Dose:
Codeine	0	0
Fentanyl transdermal (in mcg/hr)	0	0
Hydrocodone	0	0
Hydromorphone	0	0
Methadone	0	0
Morphine	0	0
Oxycodone	0	0
Oxymorphone	0	0
Tapentadol	0	0
Tramadol	0	0

Canadian Guideline for Opioids

Recommendation 8: For patients with chronic noncancer pain who are currently using opioids, and have persistent problematic pain and/or problematic adverse effects

Weak Recommendation

We suggest rotation to other opioids rather than keeping the opioid the same

Rotation in such patients may be done in parallel with, and as a way of facilitating, dose reduction

Recommendation 9: For patients with chronic noncancer pain who are currently using 90mg morphine equivalents of opioids per day or more

Weak Recommendation

We suggest tapering opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy.

Some patients are likely to experience significant increase in pain or decrease in function that persists for more than one month after a small dose reduction; tapering may be paused and potentially abandoned in such patients.

Strategia per il controllo degli effetti collaterali da oppioidi

Rotazione degli oppioidi o switching:

quando ?

- Dolore controllato, ma vi sono effetti collaterali intollerabili per il paziente.
- Il dolore non è adeguatamente controllato ed è impossibile aumentare la dose di oppioide a causa degli effetti collaterali.
- Il dolore non è adeguatamente controllato, nonostante il continuo incremento della dose di oppioide che comunque non produce effetti collaterali severi.

perché ?

- migliorare il rapporto analgesia/tollerabilità in relazione all'esistenza di una tolleranza crociata incompleta tra i diversi oppioidi.

Canadian Guideline for Opioids

Recommendation 10: For patients with chronic noncancer pain who are using opioids and experiencing serious challenges in tapering

Strong Recommendation

We recommend a formal multidisciplinary program.

Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration that includes several health professionals whom physicians can access according to their availability (possibilities include, but are not limited to, a primary care physician, a nurse, a pharmacist, a physical therapist, a chiropractor, a kinesiologist, an occupational therapist, an addiction specialist, a psychiatrist, and a psychologist).

Dosi equivalenti nella somministrazione di metadone

Dose di morfina	Ratio di conversione a metadone
<100 mg/24 h	1: 3 1 mg metadone ogni 3 mg di morfina
101– 300 mg/24 h	1: 5
301– 600 mg/24 h	1: 10
601– 800 mg/24 h	1: 12
801 - 1-1,000 mg/24 h	1: 15
> 1.000 mg/24 h	1: 20

B. Chabner et al, Harrison's Manual of Oncology, 2007

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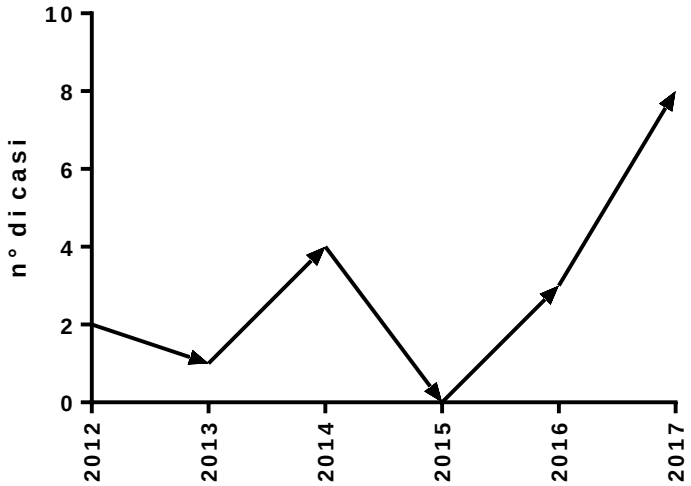
Per quanto tempo?

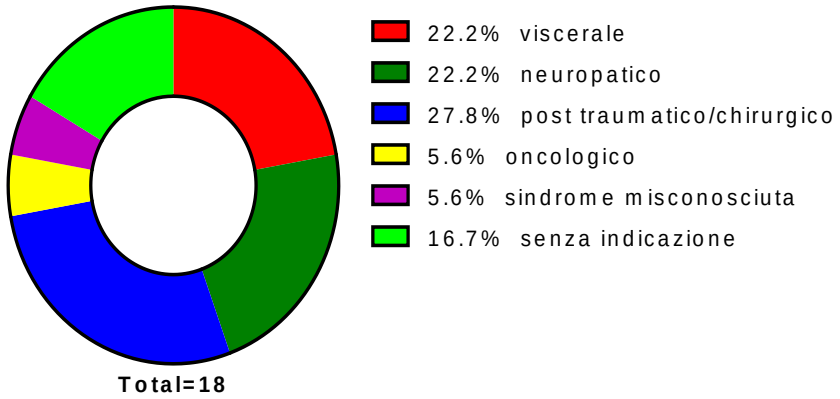
Professor Guido Mannaioni

ABUSO DI FENTANYL: UN PROBLEMA DI SALUTE PUBBLICA IN CRESCITA

NUMERO DI CASI ANNUO



INDICAZIONE TERAPIA CON FENTANYL



SWITCH DA FENTANYL A METADONE

OUTCOME

A 6 mesi	**n**	**%**
Buon compenso tossicologico e VAS <3	14/18	77.7%
	2 drop out e 2 insuccessi	

I due insuccessi terapeutici sono da ascrivere alla mancata compliance iniziale di un paziente e alla presenza di una concomitante grave problematica d'abuso di lormetazepam nel secondo caso.

METACEF STUDY

Aim of the study

To evaluate effectiveness, safety, and tolerability of low doses of methadone in patients affected by refractory chronic daily headache with medication overuse headache, after 12 months of treatment?

Patients were recruited and followed with good medical practice and applying the previously defined «English model»

METACEF STUDY

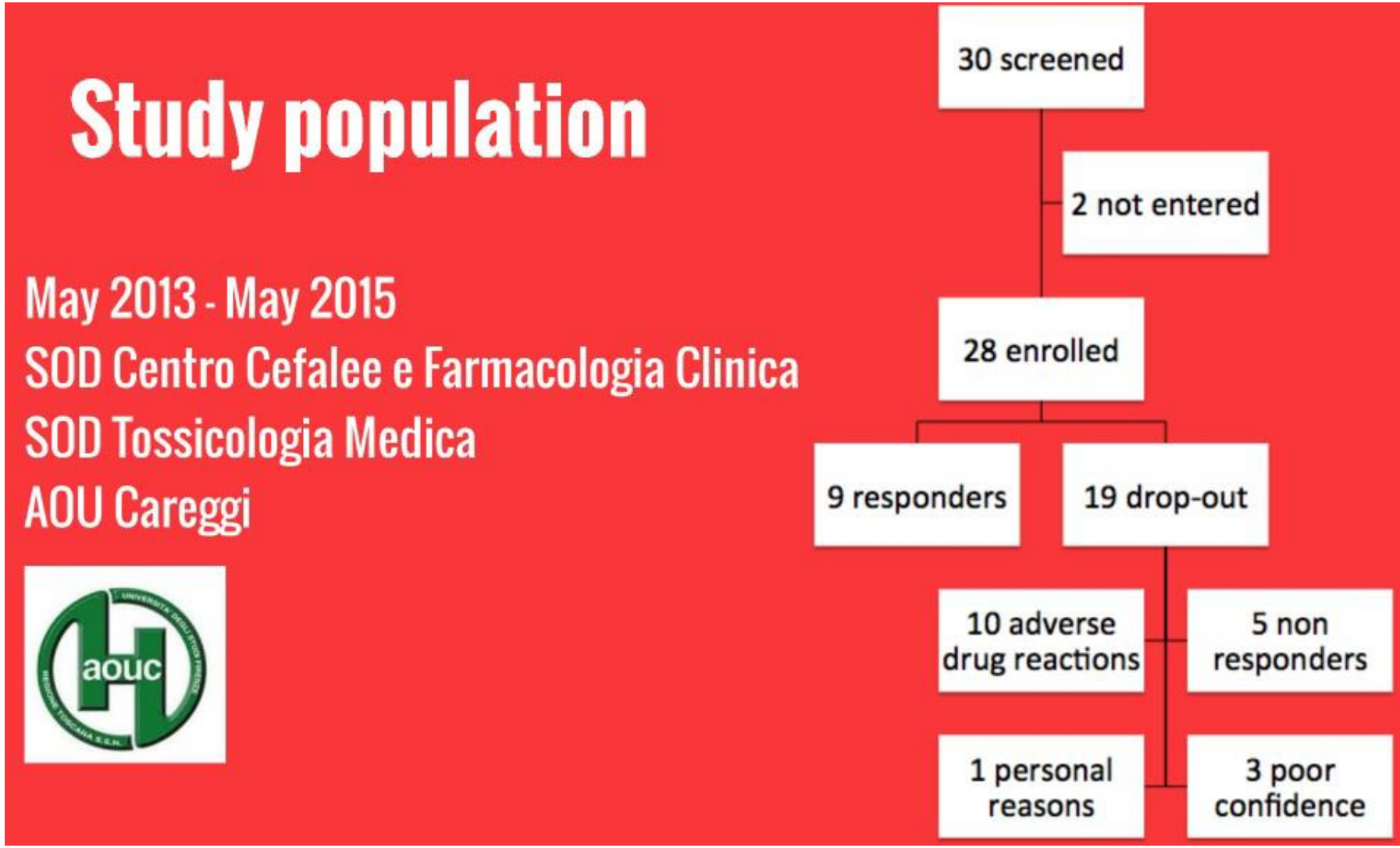
Study population

May 2013 - May 2015

SOD Centro Cefalee e Farmacologia Clinica

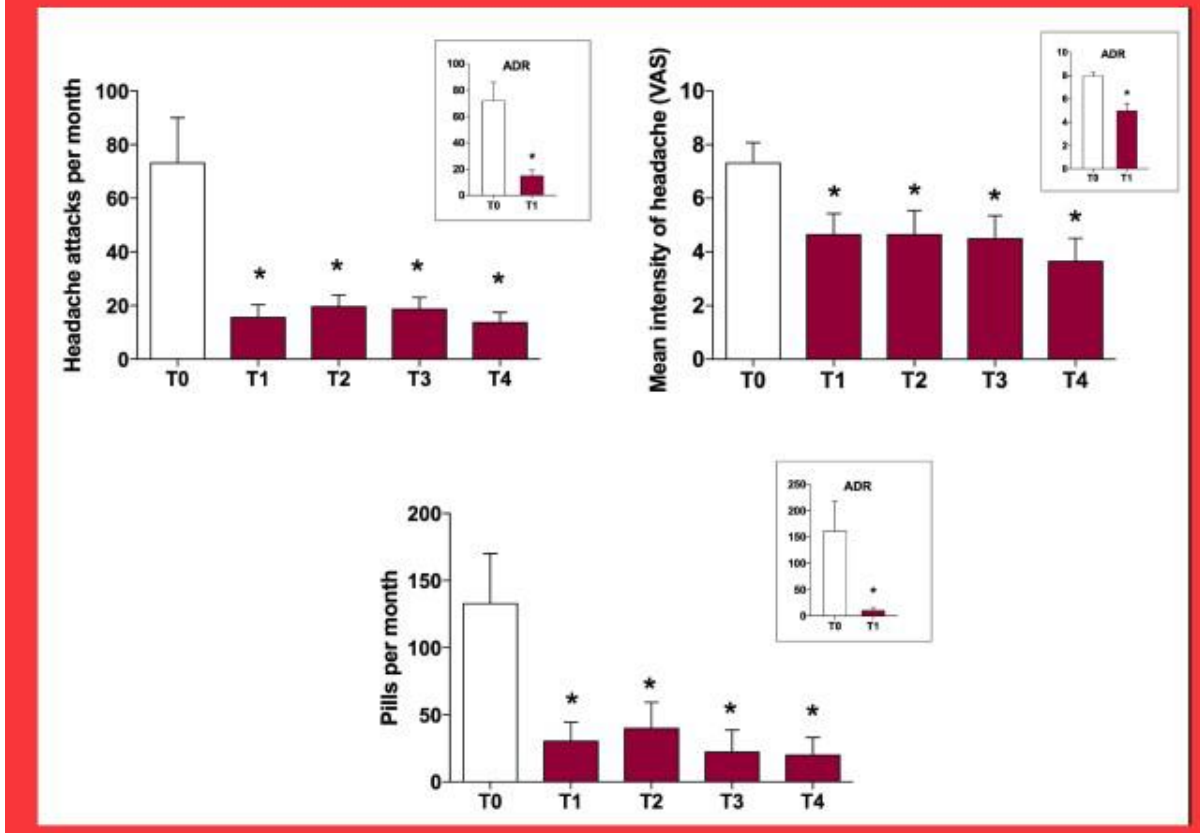
SOD Tossicologia Medica

AOU Careggi



METACEF STUDY

Effectiveness and safety



ADR

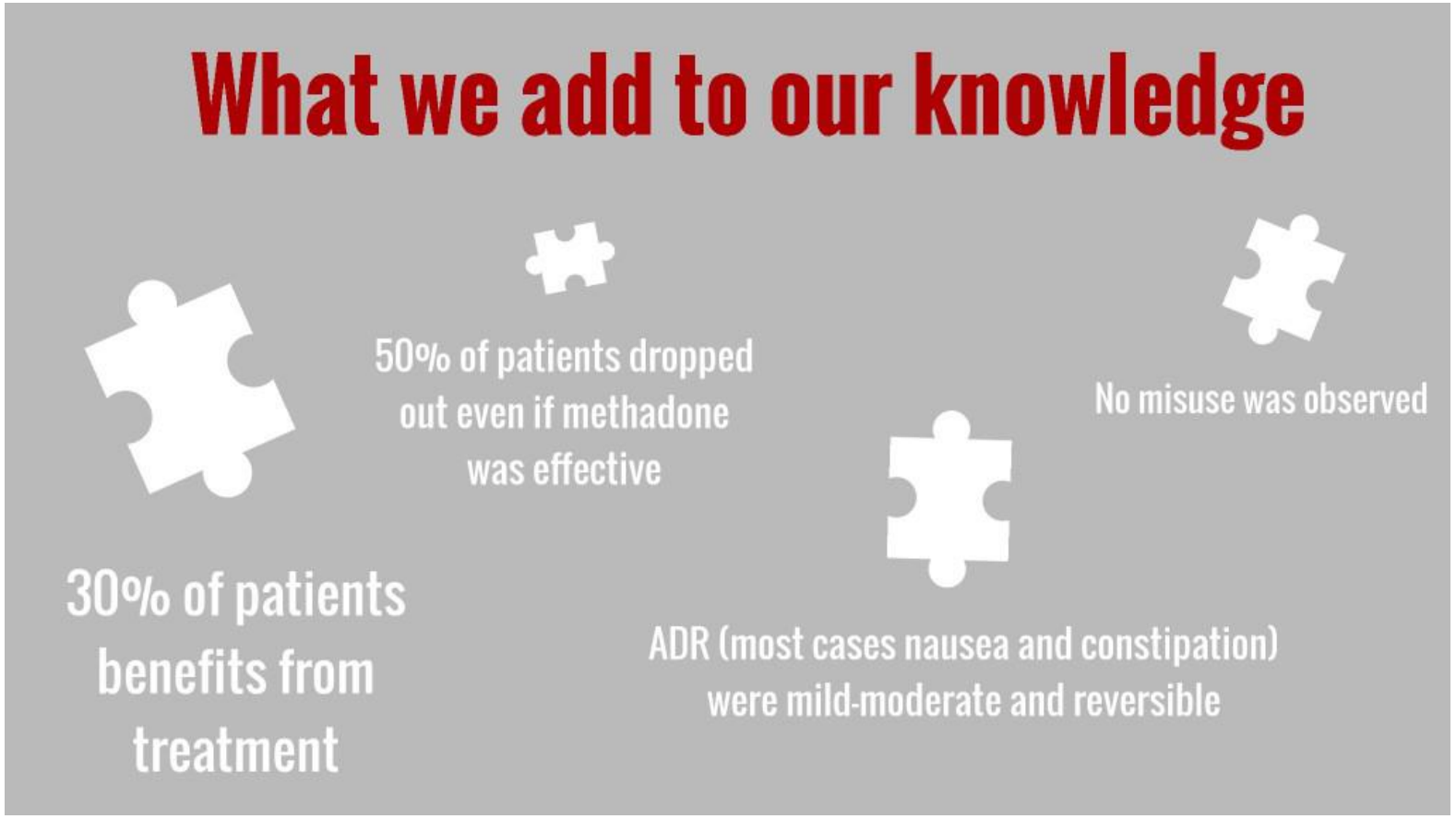
nausea (n:5, 50%)

emesis (n:3, 30%)

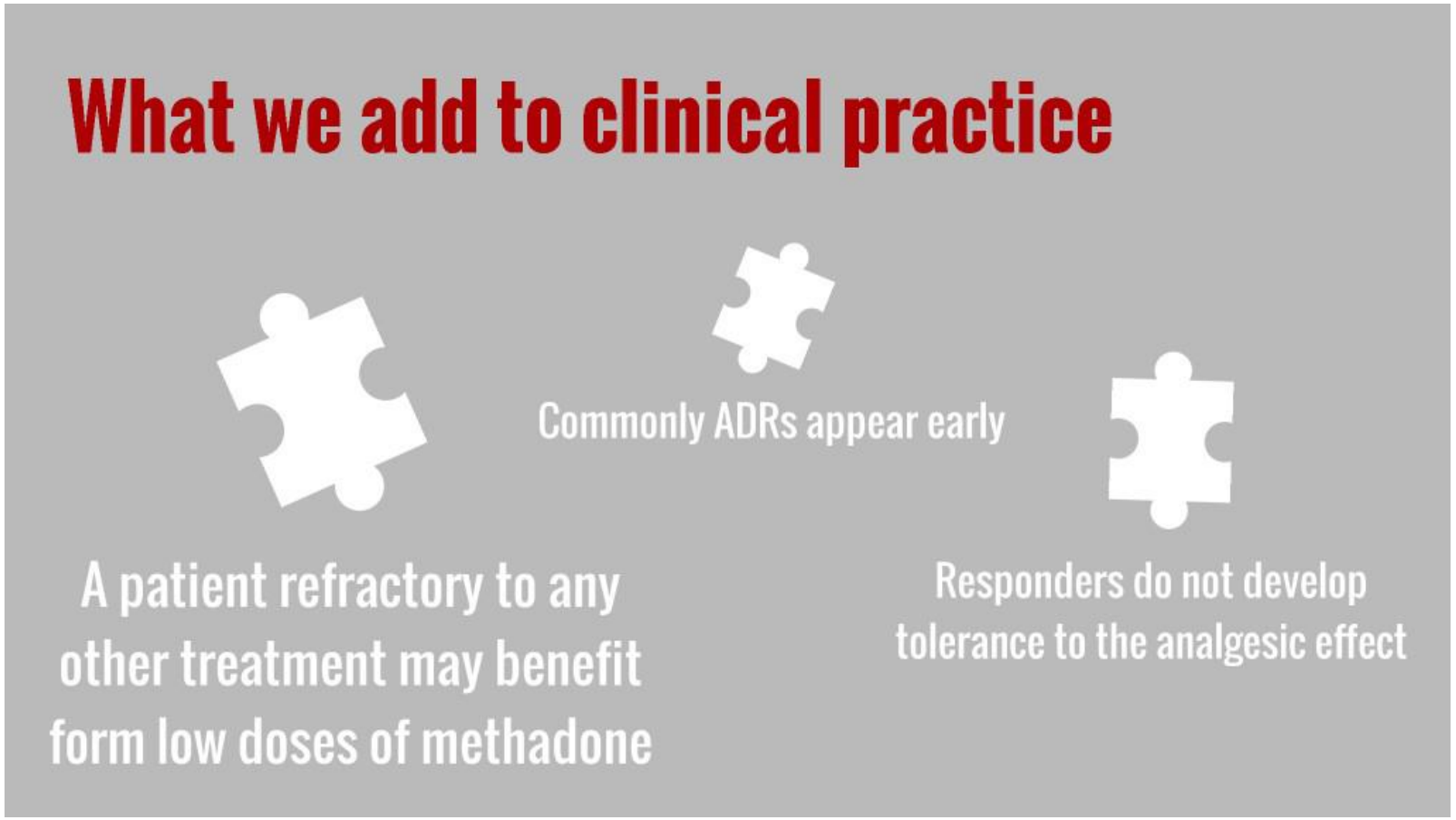
constipation (n:2, 20%)

Low-moderate grade

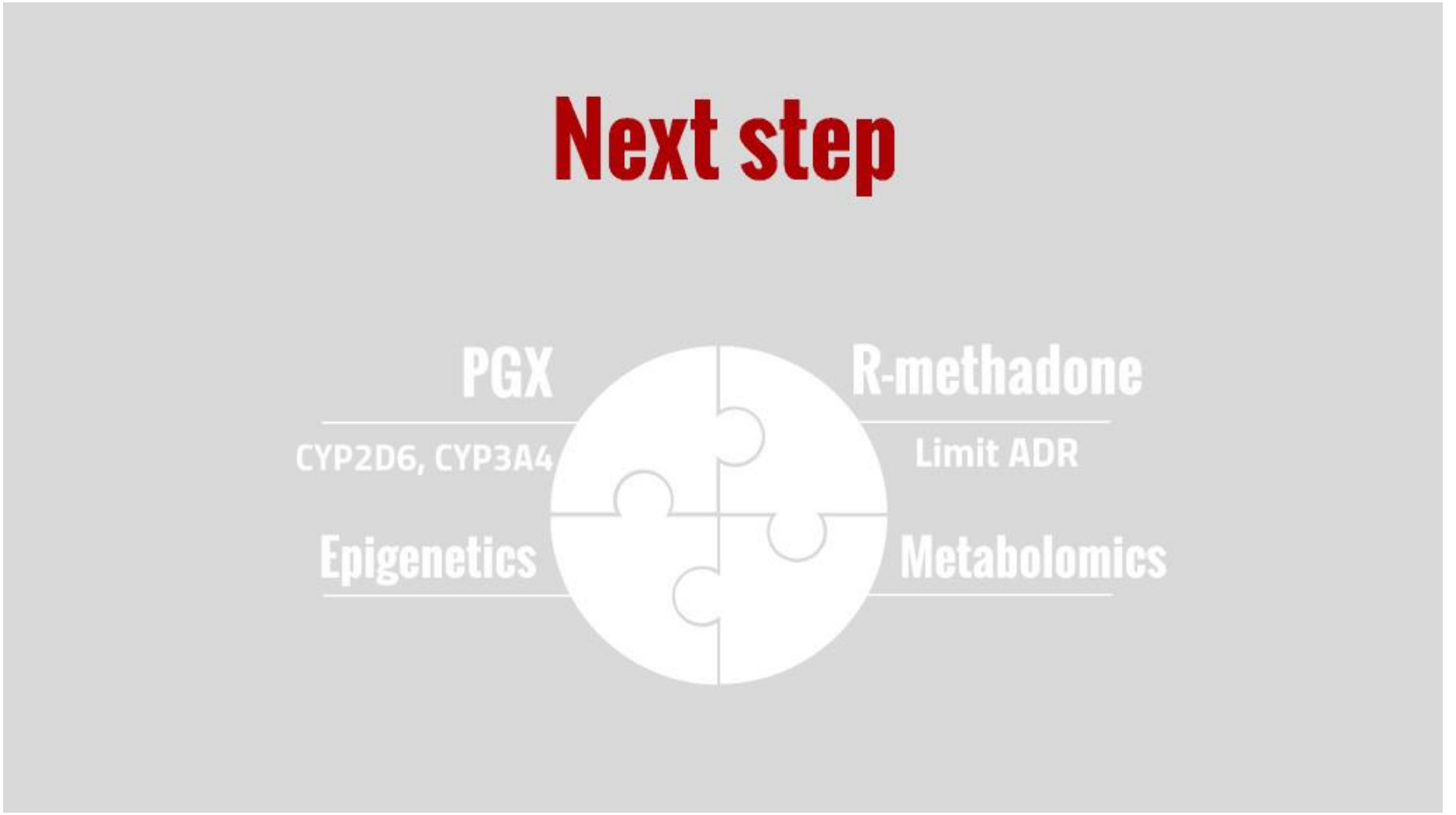
METACEF STUDY



METACEF STUDY



METACEF STUDY



Conclusioni

- E’ fondamentale creare una **cultura condivisa** tra i professionisti coinvolti nella gestione del malato con dolore
- Nei pazienti con dolore cronico in terapia con oppioidi è raccomandata una **periodica revisione** delle strategie terapeutiche:
  - Uso appropriato degli oppioidi
  - Implementare l’uso di altri farmaci in combinazione (risparmio degli oppioidi)
  - Preferire oppioidi con formulazioni abuso-deterrenti (es. Suboxone)
  - Programmare controlli seriati e frequenti
  - Evitare di sotto-trattare il dolore cronico
  - Evitare le prescrizioni multiple e centralizzare le prescrizioni ad un’unica figura di riferimento
  - Evitare prescrizioni non necessarie
  - Rivalutare periodicamente la strategia terapeutica con il paziente (rischi/benefici)
  - Screenare i pazienti potenzialmente a rischio di sviluppare un disordine da uso di sostanze con scale adeguate

Maremmani et al., 2015 e SIF position paper

Classificazione degli oppiodi

Agonisti forti

- morfina
- meperidina
- metadone
- ossicodone e idrocodone
- fentanil e suoi derivati (alfentanil, sufentanil, remifentanil)

Agonisti deboli

- codeina
- destropropossifene
- tramadolo

Agonisti/antagonisti e Agonisti parziali

- pentazocina
- buprenorfina

Recettori per gli oppiodi

	Recettore	Effetto
Analgesia sopraspinale spinale	m, k, d k, m, d N/OFQ	Analgesico
Respirazione	m	Depressione respiratoria
App. gastroenterico	m, k	Stipsi
Psiche	m k	Euforia Disforia
Alimentazione	m, k, d	Aumento
Sedazione	m, k	Sedativo
Neuroendocrina prolattina GH	m m	Inibizione release

Recettori per gli oppiodi

Tabella 11.2 **Effetto della stimolazione dei vari tipi di recettori degli oppiacei**

Tipo di recettore	δ	κ	μ	σ (non viene più compreso nel gruppo dei recettori degli oppiacei)
Effetto	Effetto analgesico			Disforia, Allucinazioni Stimolazione del centro circolatorio e respiratorio
		Depressione respiratoria		
		Sedazione	Euforia	
			Dipendenza	
	Inibizione da naloxone			**Nessuna** inibizione da naloxone

Recettori per gli oppiodi

Farmaco	Recettore		
	m	d	k
Morfina	+++		+
Metadone	+++		
Fentanil	+++		
Ossicodone	+++	+	
Meperidina	++		
Codeina	+-		
Tramadolo	+-		
Buprenorfina	AP		--
Pentazocina	-	AP	+

Tolleranza

Necessità di aumentare la dose di un farmaco nel tempo per ottenere lo stesso effetto ottenuto in precedenza

Tolleranza cronica (classica)

Si manifesta nell'uso prolungato. E' causata dall'aumento dell'attività dell' adenilato ciclasi in risposta alla cronica inibizione apportata dagli oppioidi (agonisti m in particolare). In aggiunta si può manifestare tolleranza metabolica.

Tolleranza acuta

Si può manifestare anche dopo poche somministrazioni. E' causata sia dalla fosforilazione del dominio intracellulare del recettore da parte della protein kinasi C, con inattivazione funzionale (desensitization), sia dalla endocitosi del complesso agonista recettore (m e d ma non k) (down regulation).

Effetti clinici degli oppioidi

Analgesia

Effetto di sollievo sia sul dolore acuto che su quello cronico, con notevole attenuazione o scomparsa completa e sensazione di sollievo psichico. Efficacia minore sul dolore neuropatico.

Siti e meccanismi di azione

Inibizione diretta del sistema nocicettivo ascendente (k, m)
Attivazione del sistema di controllo del dolore discendente (k, m)
Inibizione della trasmissione algica a livello talamico (m)
Inibizione periferica della liberazione di mediatori infiammatori dalle cellule immunitarie (m)

Effetti collaterali degli oppioidi

Alterazioni dell'umore

Sensazione di euforia (m) o disforia (k) – corteccia cerebrale

Effetto gratificante

Liberazione di dopamina nel nucleus accumbens septi dell'ipotalamo (d) a partire da neuroni dell'area ventrale tegmentale (k) del mesencefalo

Depressione respiratoria

Inibizione diretta dei centri respiratori del midollo allungato e del centro della tosse (m)

Miosi

Azione eccitatoria sull'innervazione parasimpatica del muscolo costrittore della pupilla (m, k)

Effetti collaterali degli oppioidi

Nausea e vomito

Stimolazione della chemoreceptor trigger zone nell'area postrema del midollo allungato

Ipotensione ortostatica

Inibizione dei riflessi barocettivi (m), vasodilatazione periferica per liberazione diretta di istamina

Diminuzione del precarico, effetto inotropo e cronotropo negativo

Raramente azione cardiodepressiva, effetto utile nella terapia dell'infarto acuto del miocardio (d?).

Effetti collaterali degli oppioidi

Apparato gastroenterico

Diminuzione della secrezione gastro-bilio-pancreatica (m) e della motilità gastro-intestinale (m, d, rallentato svuotamento e transito), spasmo dello sfintere di Oddi (m)

Altra muscolatura liscia

Spasmo sfinterico (m, d, stipsi e ritenzione urinaria)

Cute

Vasodilatazione cutanea, prurito, orticaria, tutti riferibili alla liberazione diretta di istamina

Sistema immunitario

Effetto immunosoppressivo diretto (m, d) o mediato dal sistema nervoso simpatico (acuto) e dall'attivazione dell'asse ipotalamo-ipofisi-surrene (cronico)

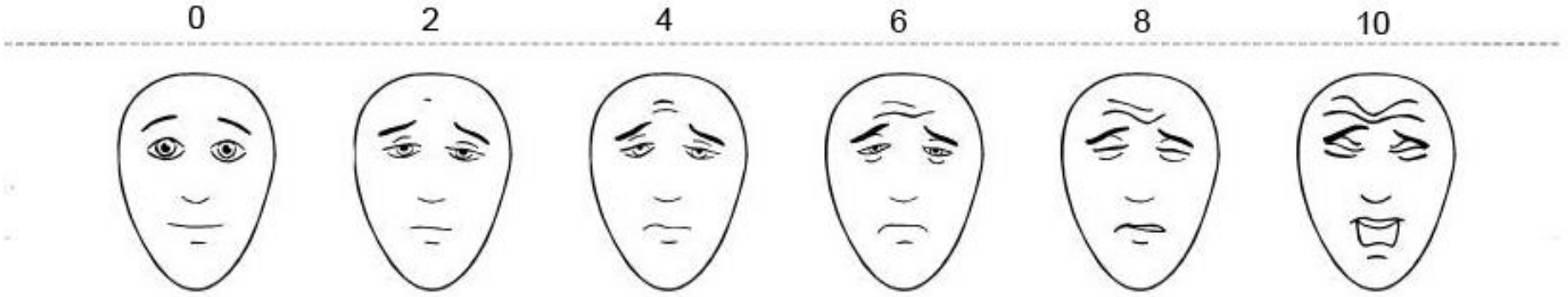
Faces Pain Scale – Revised

Faces Pain Scale – Revised (FPS-R)

In the following instructions, say "hurt" or "pain," whichever seems right for a particular child.

"These faces show how much something can hurt. This face *[point to left-most face]* **shows no pain.**
The faces show more and more pain *[point to each from left to right]* **up to this one** *[point to right-most face]* **–**
it shows very much pain. Point to the face that shows how much you hurt [right now]**."**

*Score the chosen face **0**, **2**, **4**, **6**, **8**, or **10**, counting left to right, so '**0**' = 'no pain' and '**10**' = 'very much pain.'*
Do not use words like 'happy' and 'sad'. This scale is intended to measure how children feel inside, not how their face looks.



Avoid affective descriptors (eg. "Point to the face that shows how you are feeling")

- **May be misinterpreted as "are you happy/sad?"**

Canadian Guideline for Opioids

The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

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Canadian Guideline for Opioids

Initiation and Dosing of Opioids in Patients with Chronic Noncancer Pain

Recommendation 1: When considering therapy for patients with chronic non-cancer pain

Strong Recommendation

We recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids

Recommendation 2: For patients with chronic noncancer pain, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized nonopioid therapy

Weak Recommendation

We suggest adding a trial of opioids rather than continued therapy without opioids.

By a trial of opioids, we mean initiation, titration, and monitoring of response, with discontinuation of opioids if important improvement in pain or function is not achieved. The studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses. The mental illnesses identified in studies as risk factors for adverse outcomes were generally anxiety and depression, including ICD-9 definitions, as well as "psychiatric diagnosis", "mood disorder", and post-traumatic stress disorder.

Canadian Guideline for Opioids

Recommendation 3: For patients with chronic noncancer pain with an active substance use disorder

Strong Recommendation | AGAINST

We recommend against the use of opioids

Clinicians should facilitate treatment of the underlying substance use disorders, if not yet addressed. The studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

Recommendation 4: For patients with chronic noncancer pain with an active psychiatric disorder whose nonopioid therapy has been optimized, and who have persistent problematic pain

Weak Recommendation

We suggest stabilizing the the psychiatric disorder before a trial of opioids is considered

Recommendation 5: For patients with chronic noncancer pain with a history of substance use disorder, whose nonopioid therapy has been optimized, and who have persistent problematic pain

Weak Recommendation

We suggest continuing nonopioid therapy rather than a trial of opioids

The studies that identified a history of substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

Canadian Guideline for Opioids

Recommendations 6 and 7: For patients with chronic noncancer pain who are beginning long term opioid therapy

Strong Recommendation

Recommendation 6: We recommend restricting the prescribed dose to less 90mg morphine equivalents daily rather than no upper limit or a higher limit on dosing

Some patients may gain important benefit at a dose of more than 90mg morphine equivalents daily. Referral to a colleague for a second opinion regarding the possibility of increasing the dose to more than 90mg morphine equivalents daily may therefore be warranted in some individuals.

Weak Recommendation

Recommendation 7: For patients with chronic noncancer pain who are beginning opioid therapy, we suggest restricting the prescribed dose to less than 50mg morphine equivalents daily.

The weak recommendation to restrict the prescribed dose to less than 50mg morphine equivalents daily acknowledges that there are likely to be some patients who would be ready to accept the increased risks associated with a dose higher than 50mg in order to potentially achieve improved pain control.

Recommendation 8: For patients with chronic noncancer pain who are currently using opioids, and have persistent problematic pain and/or problematic adverse effects

Weak Recommendation

We suggest rotation to other opioids rather than keeping the opioid the same

Rotation in such patients may be done in parallel with, and as a way of facilitating, dose reduction

Canadian Guideline for Opioids

Recommendation 9: For patients with chronic noncancer pain who are currently using 90mg morphine equivalents of opioids per day or more

Weak Recommendation

We suggest tapering opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy.

Some patients are likely to experience significant increase in pain or decrease in function that persists for more than one month after a small dose reduction; tapering may be paused and potentially abandoned in such patients.

Recommendation 10: For patients with chronic noncancer pain who are using opioids and experiencing serious challenges in tapering

Strong Recommendation

We recommend a formal multidisciplinary program.

Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration that includes several health professionals whom physicians can access according to their availability (possibilities include, but are not limited to, a primary care physician, a nurse, a pharmacist, a physical therapist, a chiropractor, a kinesiologist, an occupational therapist, an addiction specialist, a psychiatrist, and a psychologist).

Initiation and Dosing of Opioids

Recommendation 1: When considering therapy for patients with chronic non-cancer pain

Strong Recommendation

We recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids

Outcome Timeframe	Study results and measurements	Absolute effect estimates Optimization of therapy with NSAIDs.	 Trial of opioids.	Certainty in effect estimates (Quality of evidence)	Summary
Gastrointestinal side effects up to 6 months	Relative risk 2.52 (CI 95% 1.54 - 4.13) Based on data from 3,675 patients in 7 studies. (Randomized controlled) Follow up 6-26 weeks	**37** per 1000	**93** per 1000 Difference: **56 more** per 1000 (CI 95% 20 more - 116 more)	**High**	Opioid therapy results in a small increase in gastrointestinal side effects.
Pain 1-6 months	Measured by: 10-cm VAS Scale: 0-10 Lower better Based on data from: 2,250 patients in 13 studies. (Randomized controlled) Follow up 1-6 months	Difference: **MD 0.49 fewer** (CI 95% 1.24 fewer - 0.26 more)		**Low** Due to serious inconsistency, Due to serious imprecision	Opioid therapy may result in little or no difference in pain compared to NSAIDS.
Physical Function 1-4 months	Measured by: SF-36 Scale: 0-100 High better Based on data from: 1,972 patients in 8 studies. (Randomized controlled) Follow up 4-16 weeks	Difference: **MD 1.5 fewer** (CI 95% 3.08 fewer - 0.08 more)		**Moderate** Due to serious imprecision	Opioid therapy likely results in little or no difference in physical function compared to NSAIDS.

Initiation and Dosing of Opioids

Addiction FU not reported	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency.	Opioid therapy likely results in an important risk of addiction.
Fatal Overdose median 2.6 years	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy results in a rare but important risk of fatal overdose.
Non-fatal overdose up to 10 years	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Opioid therapy likely results in a small but important increase in the risk of non-fatal overdose.
Diversion 1 year	Based on data from 472,200 patients in 1 studies	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in 2013.	**Moderate** Due to serious risk of bias.	Opioid therapy likely results in an important increase in the risk of diversion.

Initiation and Dosing of Opioids

Table 3: Opioid options for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Morphine	Avoid in renal insufficiency
Oxycodone	~1.5x as potent as morphine. Available in a tamper-resistant formulation
Hydromorphone	~5x as powerful as morphine. Available in a tamper-resistant formulation
Oxycodone/Naloxone	Naloxone combination may minimize constipation and possibly act as an abuse deterrant
Buphrenorphine	Oral formulations preferred over transdermal for initial trial
Codeine	
Tapentadol	Available in a tamper-resistant formulation. Combined noradrenaline reuptake inhibitor and weak opioid
Tramadol	A prodrug (serotonin–norepinephrine reuptake inhibitor) that is converted to an opioid in a highly variable fashion.

Table 4: Opioids that are not recommended for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Methadone	Requires a specific Health Canada exemption to provide
Fentanyl (transdermal)	Not in opioid-naïve patients
Meperidine	Limited effectiveness; toxic metabolite accumulates in high doses or in renal insufficiency
Pentazocine	Limited effectiveness. High incidence of dysphoria

Recommended Opioid Analgesic Doses (> 6 Months Age)*

Agent	Intermittent Dose		Parenteral Infusion Dose
Codeine	Enteral	0.5 – 1.0 mg/kg q4h	Not recommended parenterally
Morphine Sulfate	Enteral	0.2 – 0.3 mg/kg q 4h	0.05 mg/kg IV load over 10 min then 0.01 – 0.03 mg/kg/hr
	IV/SQ	0.05 – 0.2 mg/kg q 2-4h	
Hydromorphone	Enteral	30 – 80 micrograms/kg q4h	10 – 20 micrograms/kg IV load over 10 min then 2 – 8 micrograms/kg/hr
	IV/SQ	15 micrograms/kg q 2 – 4h	
Oxycodone	0.05 – 0.15 mg/kg po q4h		N/A
Fentanyl Citrate	0.5 – 2 micrograms/kg IV		0.5 – 2 micrograms/kg/hr IV

* For infants < 6 months start with ¼ of the pediatric starting dose and titrate

1. Valutare la possibilità di ricorrere ad una terapia multimodale con trattamenti farmacologici diversificati che abbiano meccanismi d'azione differenti ed eventualmente integrare con la medicina complementare e con l'utilizzo di presidi fisioterapici.

2. Rivalutare con il paziente gli esiti di una terapia farmacologica non soddisfacente proponendo in alternativa i) la rotazione degli oppiacei e delle via di somministrazione, ii) l'integrazione di altri farmaci non oppiacei, iii) formulazioni abuso-deterrenti/transdermiche, iv) un adeguato uso di farmaci indicati per il dolore cronico neuropatico (gabapentinoidi, antidepressivi SNRI e SSRI, antiepilettici, anestetici locali, cannabinoidi).

3. Monitorare il rischio di uso compulsivo (addiction) con test validati come l'Opioid Risk Tool per permettere una stratificazione dei pazienti in gruppi ad alto, medio e basso rischio di abuso/dipendenza ed indirizzare risorse diverse a chi ne ha più bisogno secondo necessità.

4. Valutare attentamente la terapia con oppiacei nei pazienti con una pregressa storia di disturbo da uso di sostanze (SUD), compreso l'alcool, o malattia mentale attiva. La terapia con oppiacei nei casi di SUD pregressa non deve essere criminalizzata o evitata a priori ma decisa congiuntamente agli esperti del SERT, in modo da valutare il dosaggio migliore di oppiaceo, la via di somministrazione (preferendo la transdermica), le formulazioni abuso-deterrenti, in modo da trattare il dolore e non indurre sindrome astinenziali. In caso di SUD attiva e di terapia sostitutiva con metadone adeguare il dosaggio per un corretto controllo del dolore.

5. Iniziare con dosi inferiori a 90 mg di equivalenti di morfina (*morphine milligram equivalents_MME*) al giorno nei pazienti naïve (quando possibile iniziare da dosaggi inferiori a 50 mg MME).

6. Intraprendere nei pazienti che ricevono una terapia con oppiacei ad alto dosaggio (≥ 90 mg MED) e hanno un soddisfacente controllo del dolore, una riduzione graduale della dose (*tapering*), offrendo loro un supporto multidisciplinare fino a interrompere il trattamento laddove possibile, con adeguato controllo del dolore.

Strategia per il controllo degli effetti collaterali da oppioidi

Rotazione degli oppioidi o switching:

quando ?

- Dolore controllato, ma vi sono effetti collaterali intollerabili per il paziente.
- Il dolore non è adeguatamente controllato ed è impossibile aumentare la dose di oppioide a causa degli effetti collaterali.
- Il dolore non è adeguatamente controllato, nonostante il continuo incremento della dose di oppioide che comunque non produce effetti collaterali severi.

perché ?

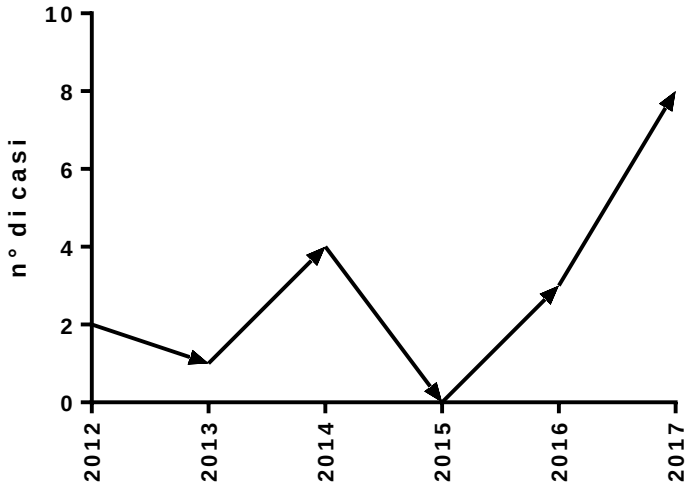
- migliorare il rapporto analgesia/tollerabilità in relazione all'esistenza di una tolleranza crociata incompleta tra i diversi oppioidi.

Dosi equivalenti nella somministrazione orale e parenterale degli oppioidi

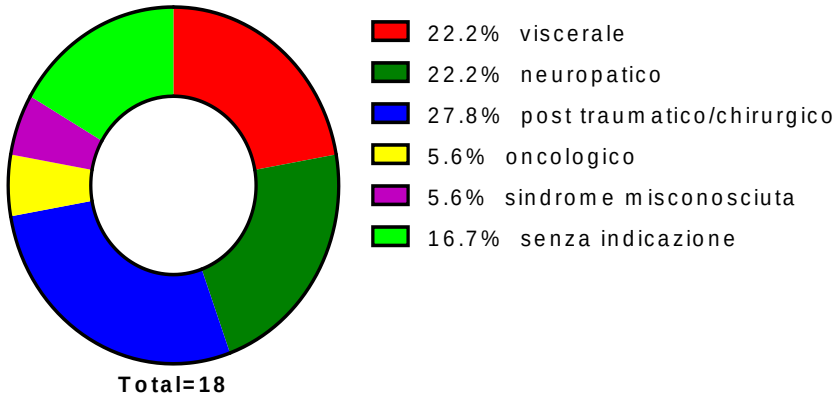
Oppioidi analgesici	Dose orale		Dose parenterale	
Codeina	100 mg	4h	50 mg	4h
Idrocodone	15 mg	4h	---	---
Ossicodone	7.5-10 mg	4h	---	---
Morfina	15 mg	4h	5 mg	4h
Idromorfone	4 mg	4h	0.75-1.5 mg	4h
Levorfanolo	2 mg	6-8h	1 mg	6-8h
Metadone	10 mg	6-8h	5 mg	6h
Fentanil	---	---	0.5 - 2 mcg/kg/h	72h transdermico

ABUSO DI FENTANYL: UN PROBLEMA DI SALUTE PUBBLICA IN CRESCITA

NUMERO DI CASI ANNUO

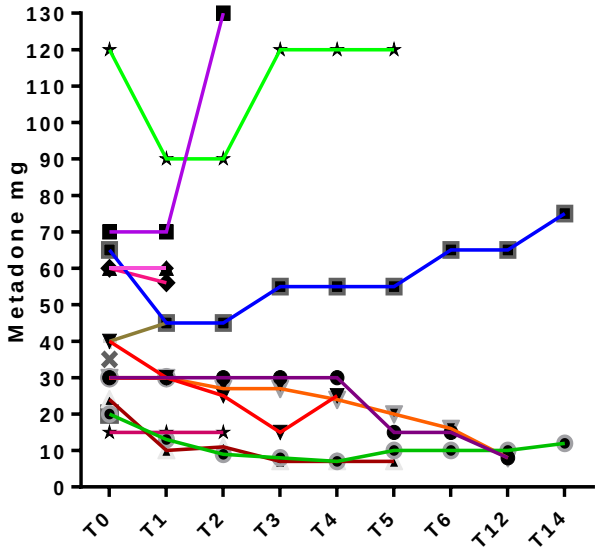


INDICAZIONE TERAPIA CON FENTANYL



SWITCH DA FENTANYL A METADONE

ANDAMENTO TERAPIA SOSTITUTIVA



COMPLIANCE AL FOLLOW UP