IL TRATTAMENTO DEL DOLORE: CONFRONTO TRA OPPIOIDI A RILASCIO IMMEDIATO (SAO) E OPPIOIDI A LENTO RILASCIO (LAO)

Dipartimento Biotecnologie Mediche
e
Medicina Traslazionale
Università degli Studi di Milano

C.N.R. Istituto di Neuroscienze
Sezione di Farmacologia Cellulare e Molecolare
Milano

Milano, 23 marzo 2017

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POTENZIALI CONFLITTI DI INTERESSE

ALFA-SIGMA
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Clinical Review & Education

Special Communication

CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016

Deborah Dowell, MD, MPH; Tamara M. Haegerich, PhD; Roger Chou, MD

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Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2016, **41**, 592–593 doi: 10.1111/jcpt.12444

Commentary

The Centers for Disease Control and Prevention opioid guidelines: potential for unintended consequences and will they be abused?

J. V. Pergolizzi*† Jr., MD, R. B. Raffa‡§ PhD and J. A. LeQuang† BA

**Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, †NEMA Research, Inc., Naples, FL, ‡University of Arizona College of Pharmacy, Tucson, AZ, and §Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA*

Not mentioned in the new CDC guidelines is one thing that is urgently needed: better clinician education and training on pain, pain control, pain therapy options, and the risks and benefits of

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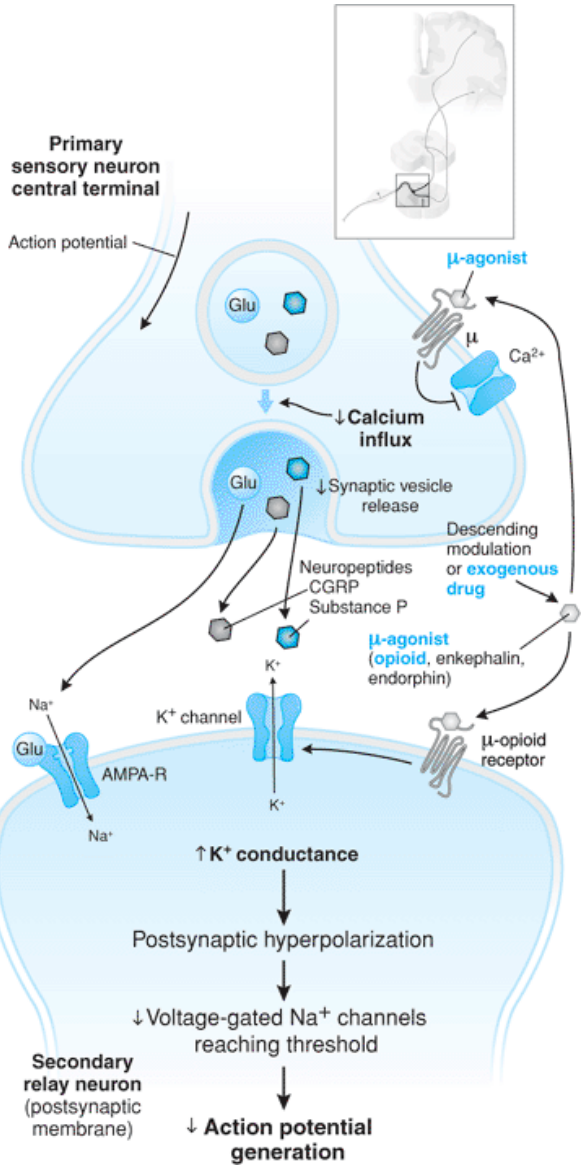

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Oppiacei deboli

Farmaco	Applicazione clinica	Reazioni avverse	Controindicazioni	Considerazioni terapeutiche
Codeina	Dolore da lieve a moderato	Come morfina		Profarmaco, necessita dell'attivazione da parte del CYP450 2D6 a morfina. Non è substrato dalla P-glicoproteina e quindi attraversa rapidamente la BBB. Attivazione anche nel SNC
Tramadolo	Dolore da lieve a moderato	Come morfina	In associazione con SSRI per rischio sindrome serotoninergica	Profarmaco, necessita dell'attivazione da parte del CYP450 2D6 a desmetil-tramadolo. Il tramadolo in quanto tale inibisce il reuptake della serotonina
Buprenorfina	Dolore da moderato a severo	Come morfina		Preferenzialmente somministrato per via sublinguale o per via transdermica. Ha lunga durata d'azione.

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Opioid Transport by ATP-Binding Cassette Transporters at the Blood-Brain Barrier: Implications for Neuropsychopharmacology

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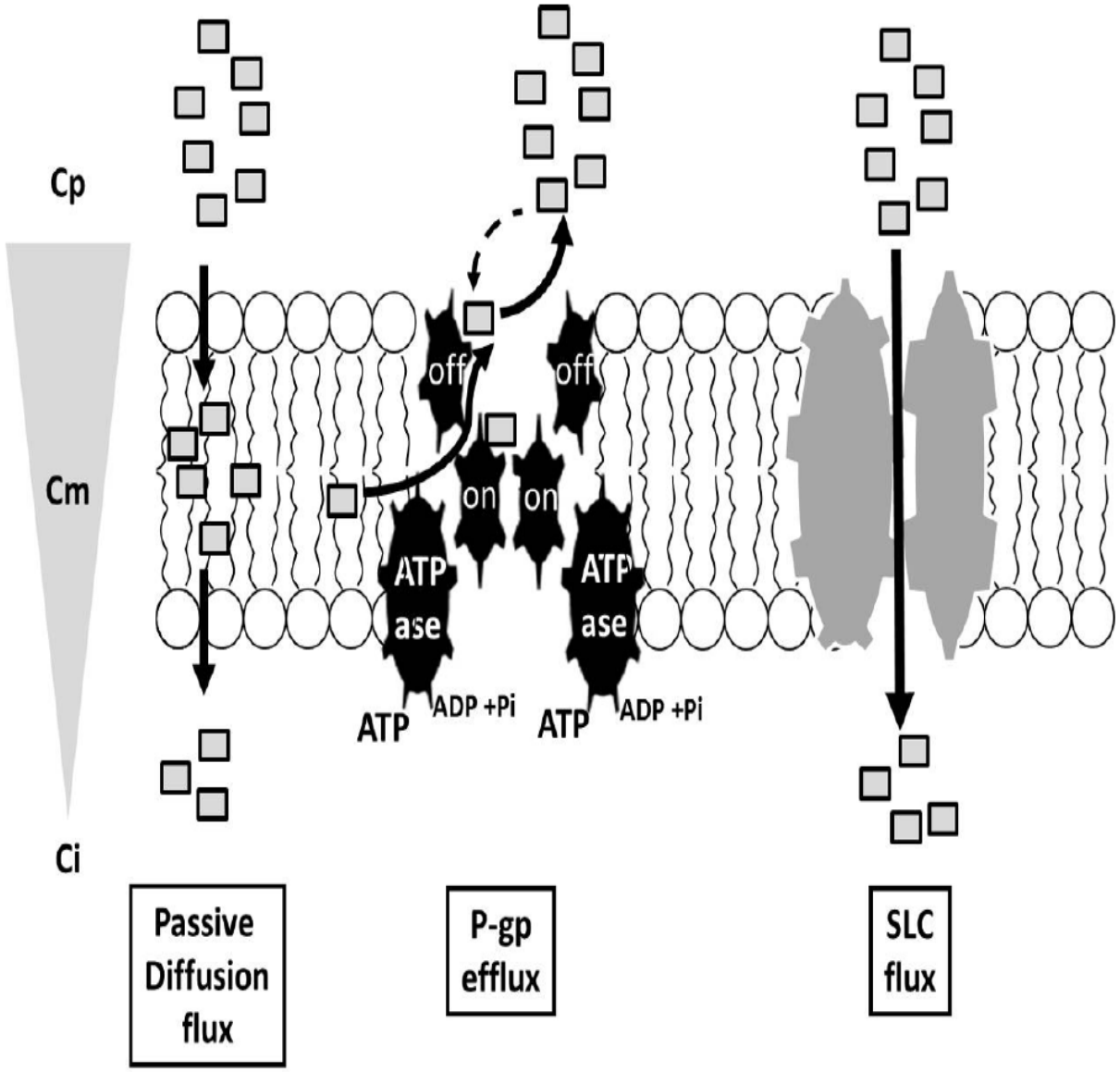

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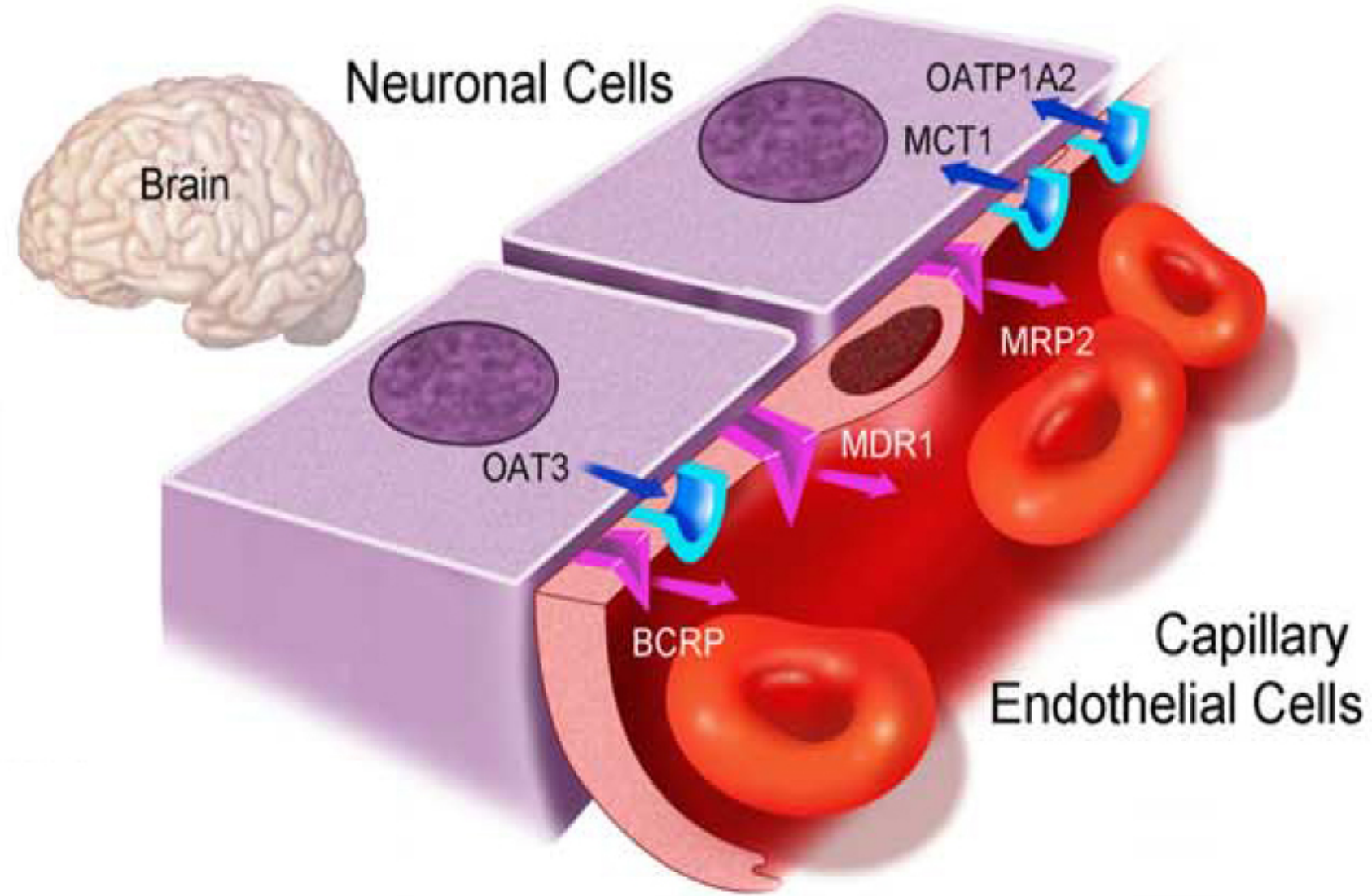

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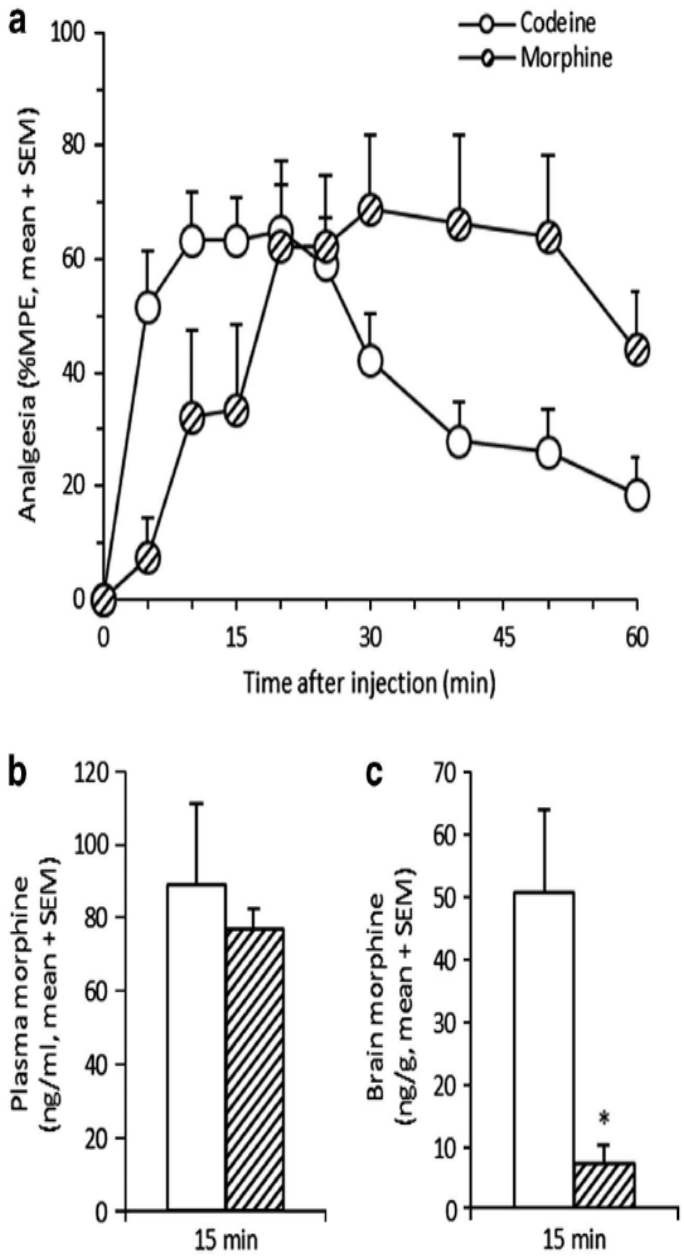

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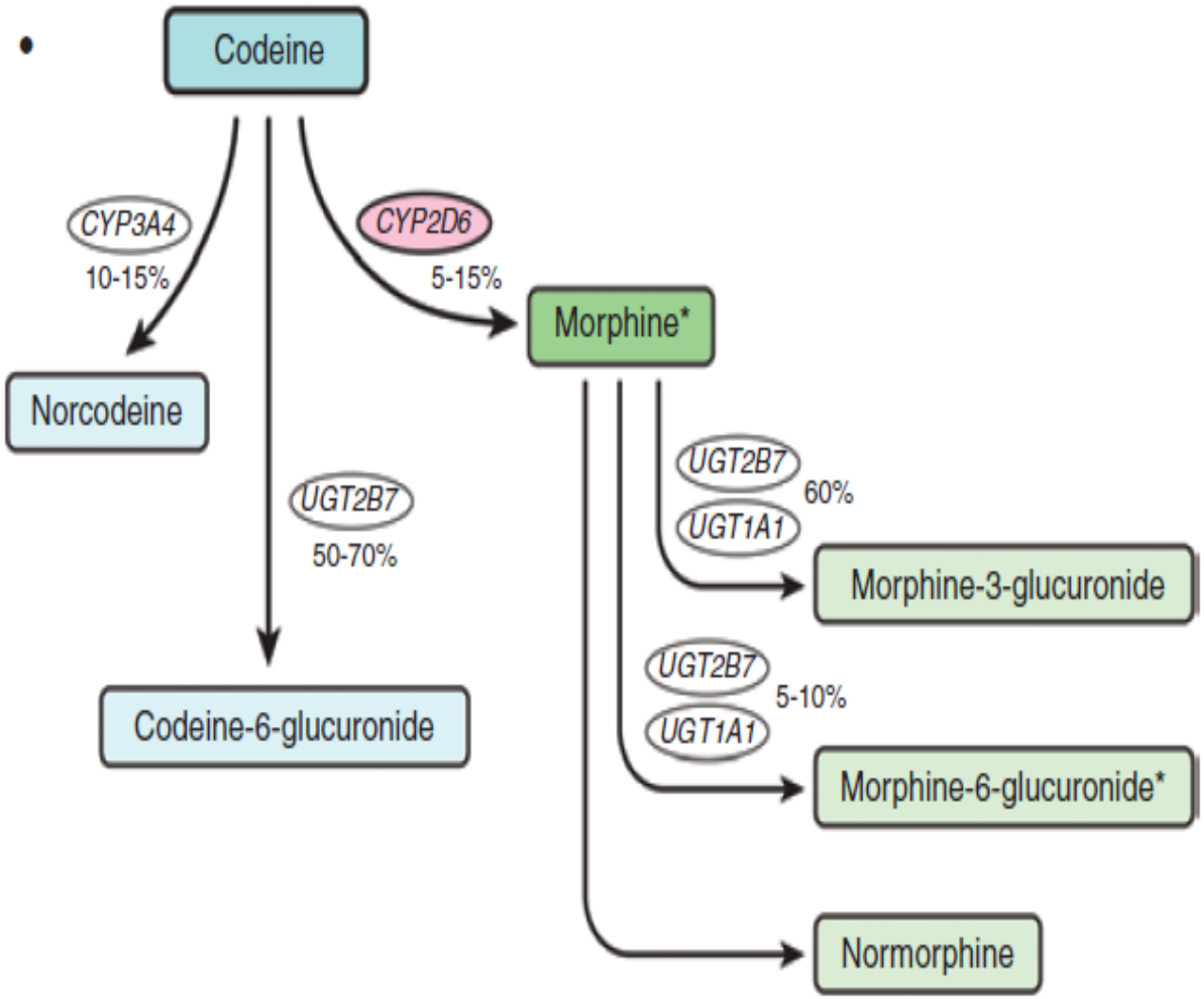

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Neuropsychopharmacology (2015), 1–9

www.neuropsychopharmacology.org

Nicotine Increases Codeine Analgesia Through the Induction of Brain CYP2D and Central Activation of Codeine to Morphine

Douglas M McMillan[1] and Rachel F Tyndale[*,1]

[1]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health (CAMH) and Departments of Psychiatry, Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada

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Oppiacei forti

Farmaco	Applicazione clinica	Reazioni avverse	Controindicazioni	Considerazioni terapeutiche
Morfina	Dolore da moderato a severo	Nausea, vomito stipsi, sonnolenza, confusione, depressione respiratoria	Asma severa, BPCO, Ileo paralitico	Direttamente glucuronata a livello epatico, non subisce metabolismo da parte del sistema del cyp450. Il metabolita 6-glucuronide ha attivita' farmacologica come la morfina. Il 3-glucuronide potrebbe contribuire agli effetti eccitatori
Idromorfone	Come morfina	Come morfina	Come morfina	Direttamente glucuronato a livello epatico, non subisce metabolismo da parte del sistema del cyp450. Disponibile una formulazione a rilascio controllato che consente un'unica somministrazione giornaliera
Ossicodone	Come morfina	Come morfina	Come morfina	Metabolizzato dal CYP2D6 e da l CYP3A4. Disponibile un'associazione con naloxone in opportuni rapporti per il controllo della stipsi

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Oppiacei forti

Farmaco	Applicazione clinica	Reazioni avverse	Controindicazioni	Considerazioni terapeutiche
Tapentadolo	Dolore da moderato a severo	Come ossicodone, ma con minori effetti avversi gastrointestinali	Come morfina inibitori delle MAO	Duplice meccanismo d'azione (agonista recettori mu, inibitore reuptake della noradrenalina). Direttamente glucuronato a livello epatico, non subisce metabolismo da parte del sistema del cyp450. No metaboliti attivi.
Fentanyl	Dolore da moderato a severo	Come morfina	Come morfina	Più potente di morfina. Diverse vie di somministrazione (transmucosale, transdermica) formulazioni a lento rilascio
Metadone	Dolore severo	Come morfina. In aggiunta tossicità cardiaca	Come morfina	Duplice meccanismo d'azione. Lunga durata d'azione

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SAO OR LAO?

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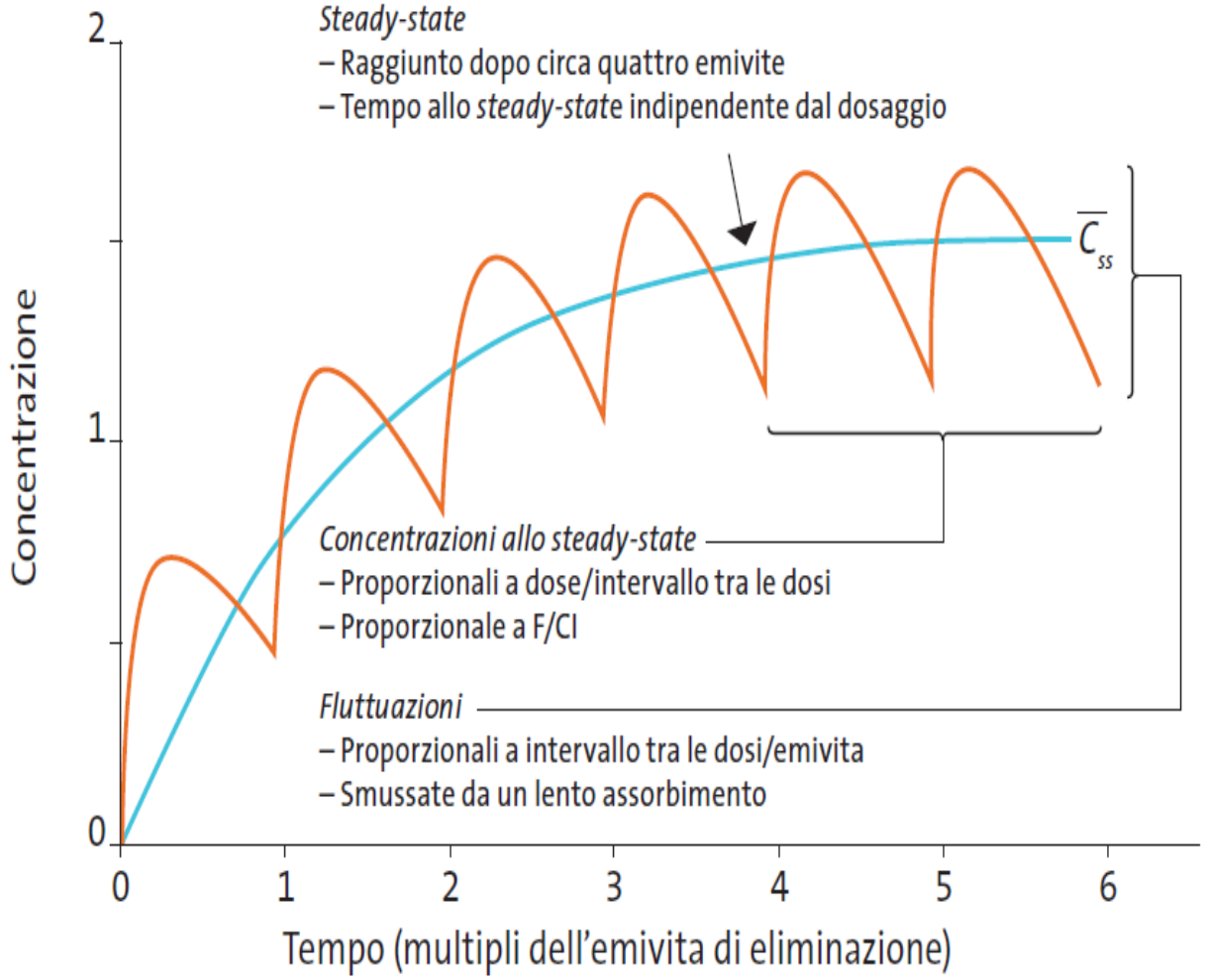
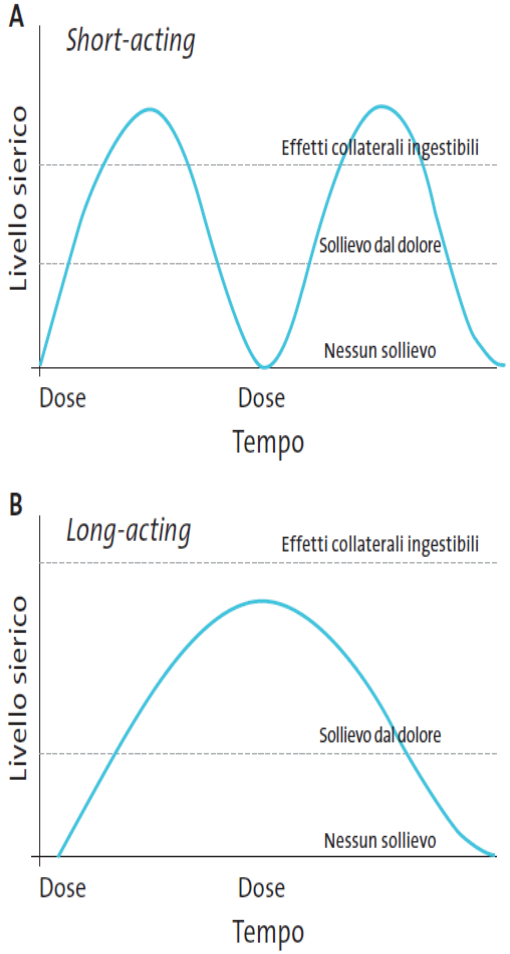
CLASSIFICAZIONE SECONDO FDA DELLE FORME FARMACEUTICHE A RILASCIO IMMEDIATO O MODIFICATO

Immediate release forms	
– Standard release	**= SAO**
– Faster release	
Modified release forms	
– Extended release	
– *Sustained release*	**= LAO**
– *Pulsatile release*	
– Delayed release	
– *Time release*	
– *Site release*	
Hybrid release forms	

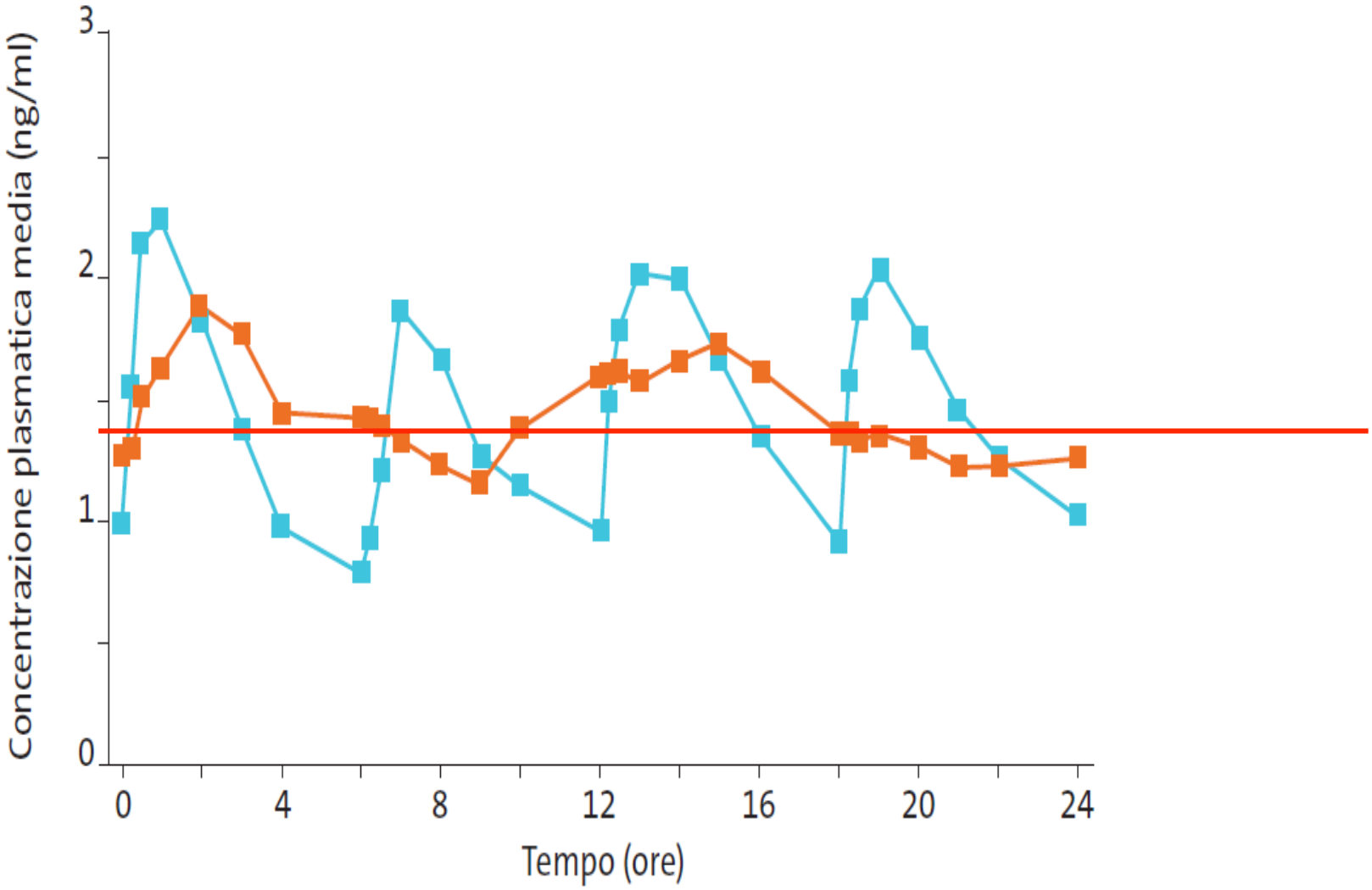
RAGGIUNGIMENTO DELLO STEADY STATE



PROFILO FARMACOCINETICO TEORICO DI UN SAO E DI UN LAO



IDROMORFONE LAO O SAO



Pain Physician 2010; 13:61-70 • ISSN 1533-3159

Randomized Trial

Dose Conversion Between Tapentadol Immediate and Extended Release for Low Back Pain

Mila S. Etropolski, MD, Akiko Okamoto, ScD, Douglas Y. Shapiro, MD, PhD, and Christine Rauschkolb, MD, PhD

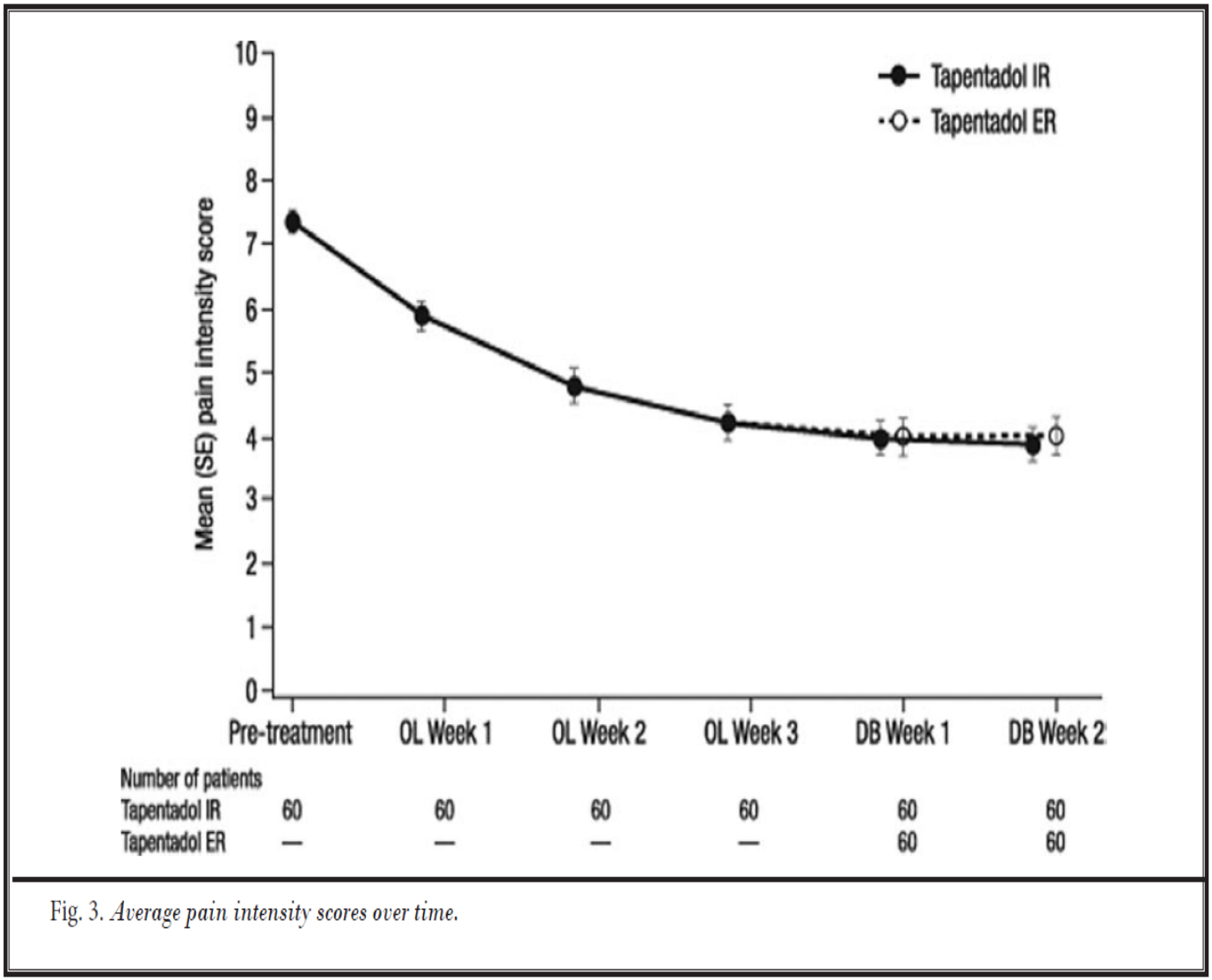


Fig. 3. *Average pain intensity scores over time.*

Table 2. *TEAEs Reported by ≥2% of patients during the double-blind treatment period.*

Type of TEAE, n (%)	Tapentadol IR (n = 81)	Tapentadol ER (n = 84)
Patients with ≥ 1 TEAE	28 (34.6)	28 (33.3)
Infections and infestations	5 (6.2)	4 (4.8)
Gastroenteritis viral	2 (2.5)	0
Upper respiratory tract infection	2 (2.5)	1 (1.2)
Musculoskeletal and connective tissue disorders	4 (4.9)	5 (6.0)
Arthralgia	2 (2.5)	1 (1.2)
Pain in extremity	1 (1.2)	2 (2.4)
Nervous system disorders	4 (4.9)	7 (8.3)
Headache	2 (2.5)	4 (4.8)
Somnolence	2 (2.5)	1 (1.2)
Skin and subcutaneous tissue disorders	4 (4.9)	0
Rash	3 (3.7)	0
General disorders and administration site conditions	3 (3.7)	7 (8.3)
Pyrexia	2 (2.5)	4 (4.8)
Fatigue	0	3 (3.6)

TEAE, treatment-emergent adverse event; IR, immediate release; ER, extended release.

Double-Blind, Randomized Comparison of the Analgesic and Pharmacokinetic Profiles of Controlled- and Immediate-Release Oral Oxycodone in Cancer Pain Patients

John E. Stambaugh, MD, PhD, Robert F. Reder, MD, Michael D. Stambaugh, MD, Heather Stambaugh, MD, and Maureen Davis

Journal of Clinical Pharmacology, 2001;41:500-506

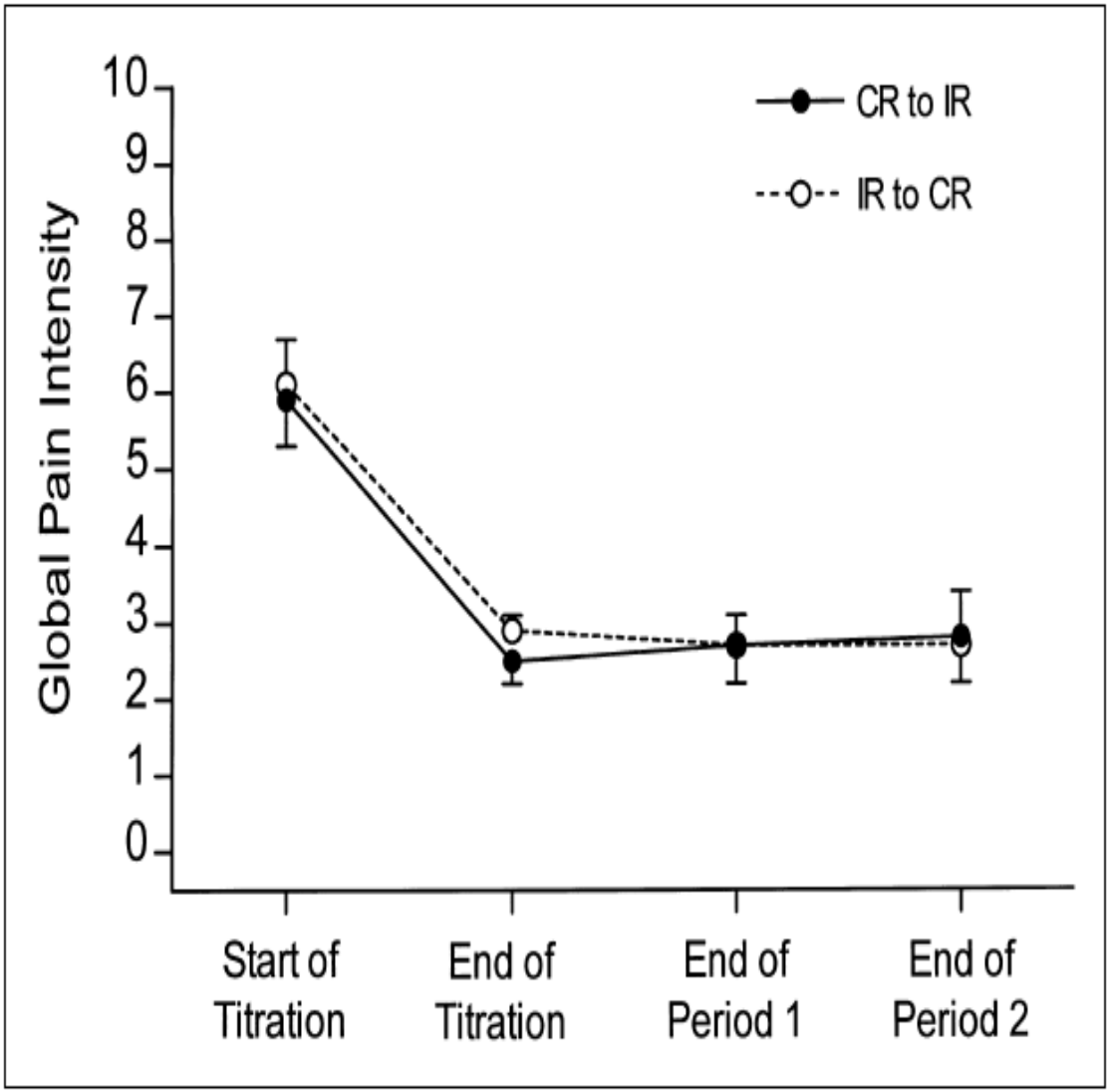

Global Pain Intensity
10
9
8
7
6
5
4
3
2
1
0
CR to IR
IR to CR
Start of Titration
End of Titration
End of Period 1
End of Period 2

Table III Patient Incidence and Number of Reports of Drug-Related Adverse Events during Double-Blind Periods

	Immediate-Release Oxycodone (n = 31)			Controlled-Release Oxycodone (n = 30)		
	Number	%	Reports	Number	%	Reports
Nausea	4	13	4	3	10	3
Dizziness	3	10	3	3	10	3
Somnolence	3	10	5	2	7	4
Asthenia	2	6	2	2	7	2
Pruritus	1	3	1	2	7	2
Sweating	2	6	2	1	3	1
Constipation	1	3	1	1	3	1
Dry mouth	1	3	1	1	3	1
Nervousness	0	0	0	1	3	1
Vomiting	2	6	2	0	0	0
Total	10	32	21	10	33	21

Use of long-acting, vs short-acting, opioids for chronic pain was linked to unintentional overdose

Miller M, Barber CW, Leatherman S, et al. ***Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy.*** *JAMA Intern Med. 2015;175:608-15.*

Association between use of long- vs short-acting opioids and unintentional overdose in veterans with chronic noncancer pain*

Duration of opioid use	Event rates/10 000 person-y		Adjusted hazard ratio (95% CI)†
	Long-acting	Short-acting	
Any	35	15	2.33 (1.26 to 4.32)
≤ 14 d	143	25	5.25 (1.88 to 14.72)
15 to 60 d	36	16	2.30 (0.67 to 7.90)
> 60 d	26	12	1.50 (0.68 to 3.33)

*CI defined in Glossary.

†Adjusted for all available covariates.

Association between use of long- vs short-acting opioids and unintentional overdose in veterans with chronic noncancer pain*

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*CI defined in Glossary.

†Adjusted for all available covariates.

Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study

Richard A. Deyo, MD, MPH[1,2,3], Sara E. Hallvik, MPH[4], Christi Hildebran, LMSW[4], Miguel Marino, PhD[1,2], Eve Dexter, MS[1], Jessica M. Irvine, MS[4,5], Nicole O'Kane, PharmD[4], Joshua Van Otterloo, MSPH[6], Dagan A. Wright, PhD, MSPH[6], Gillian Leichtling, BA[4], and Lisa M. Millet, MSH[6]

[1]Department of Family Medicine, Oregon Health and Science University, Portland, OR, USA; [2]Department of Public Health and Preventive Medicine, Oregon Health and Science University, Portland, OR, USA; [3]Department of Medicine and The Oregon Institute for Occupational Health Sciences, Oregon Health and Science University, Portland, OR, USA; [4]Acumentra Health, Portland, OR, USA; [5]OCHIN Inc., Portland, OR, USA; [6]Injury and Violence Prevention Program for the State of Oregon, Portland, OR, USA.

Table 3 Long-Term Opioid Use Among Opioid-Naive Patients, in the Selective Analysis*

Opioid prescriptions during initiation month	Number of patients	No. (%) who became long-term opioid users†	*p* value‡	Odds ratio (95 % CI) adjusted for urban or rural residence, categorical age
Short-acting opioids				
Number of prescriptions filled			<0.0001	
1	196,452	3905 (2.0 %)		Reference
2	34,244	2459 (7.2 %)		2.25 (2.17, 2.33)
3	8404	1129 (13.4 %)		2.62 (2.49, 2.76)
≥4	4327	953 (22.0 %)		3.32 (3.11, 3.53)
Morphine equivalents dispensed			<0.0001	
1–119	109,983	1988 (1.8 %)		Reference
120–279	88,190	2396 (2.7 %)		1.42 (1.37, 1.49)
280–399	18,859	968 (5.1 %)		2.22 (2.10, 2.34)
400–799	18,645	1490 (8.0 %)		2.96 (2.81, 3.11)
800–1599	5900	1002 (17.0 %)		4.63 (4.37, 4.92)
1600–2399	1163	326 (28.0 %)		6.78 (6.21, 7.40)
2400–3199	502	190 (37.8 %)		11.27 (10.04, 12.65)
3200–3999	185	86 (46.5 %)		16.30 (13.71, 19.37)
Long-acting opioids				
Number of prescriptions filled			<0.0001	
1	445	70 (15.7 %)		Reference
2	183	61 (33.3 %)		2.04 (1.31, 3.17)
3	83	29 (34.9 %)		1.88 (1.06, 3.33)
≥4	68	31 (45.6 %)		1.77 (0.96, 3.24)
Morphine equivalents dispensed			<0.0001	
1–799§	271	26 (9.6 %)		Reference
800–1599	252	50 (19.8 %)		1.99 (1.16. 3.42)
1600–2399	106	44 (41.5 %)		4.89 (2.70, 8.84)
2400–3199	87	42 (48.3 %)		6.84 (3.67, 12.75)
3200–3999	63	29 (46.0 %)		5.21 (2.57, 10.56)

Results stratified according to initial prescription for short-acting or long-acting opioid

**Selective analysis: excluding adults > 45 years old, children ≤ 11 years old, patients who died within 1 year of index prescription, those with any address outside Oregon*

†Long-term use defined as ≥ 6 opioid fills in the subsequent 12 months

‡Cochran–Armitage test for trend across increasing categories

§The 4 lowest dose categories were combined due to small patient numbers in the lowest 3 (each ≤ 42 patients) and failure of the logistic regression model

Nel dolore acuto e riacutizzato si dovrebbe utilizzare un SAO

Prima dell'inizio di una terapia con LAO per non-cancer pain si dovrebbe iniziare nel paziente naive, nelle prime 1-2 settimane, con un SAO.

Nel dolore ricorrente/persistente si dovrebbe utilizzare un LAO a basso dosaggio (in associazione con un adiuvante)

Nel trattamento del dolore cronico si dovrebbe usare un LAO e non un SAO

Nei buchi di analgesia del LAO si dovrebbe usare un SAO