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BOLOGNA 20-22 Febbraio 2023 Pericolo, rischio e rapporto rischio-beneficio

Meccanismi farmacologici degli oppioidi: analgesia e *addiction*, due facce della stessa medaglia?

Diego Fornasari

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Università degli Studi di Milano- La Statale

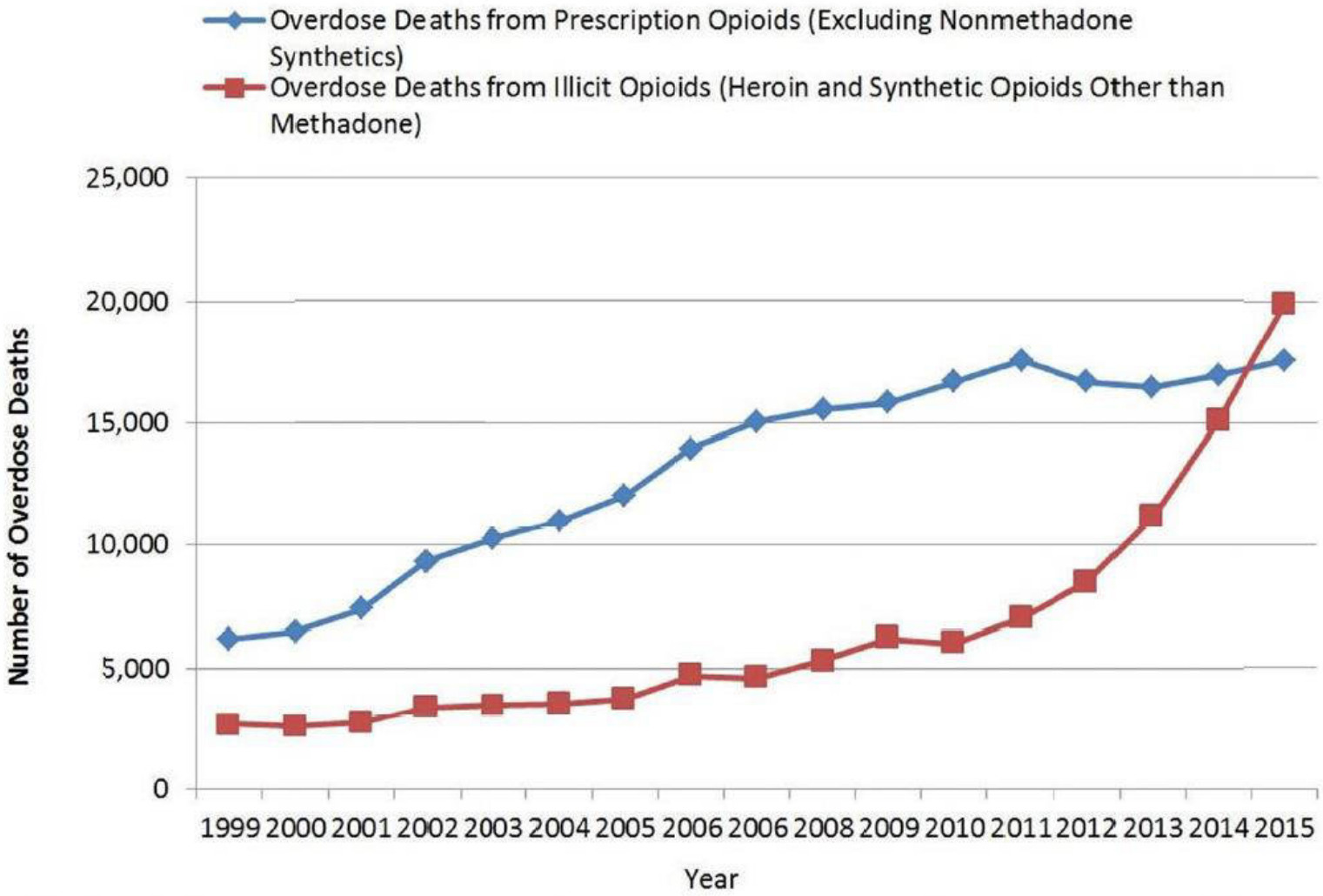

FIGURE S-1 Number of overdose deaths from prescription and illicit opioids, United States, 1999–2015.

The confluence of:

- social mandates (all pain should be treated),
- scientific discovery (chronic nonmalignant pain is real)
- clinician na¨ıvet´e (little training, lacking data)

Journal of Pain & Palliative Care Pharmacotherapy. 2015;29:102–114.

resulted in the dramatic increase in the number of opioid prescriptions written in the United States:

from approximately 76 million in 1991
to nearly 207 million in 2013.

Journal of Pain & Palliative Care Pharmacotherapy. 2015;29:102–114.

By 2007, 12.5 million Americans reported using a prescription opioid analgesic nonmedically (up from 11 million in 2002), making it the second-most abused class of drug behind marijuana.

Birnbaum HG, White AG, Schiler M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med*. 2011;*12*:657–667.

ONLINE PHARMACIES

Nel 2004 negli Stati Uniti esistevano 1400 farmacie online che dispensavano oppioidi.

Il 79% di esse fino alla fine del 2005 non richiedeva ricetta

Ryan Haight Online Pharmacy Consumer Protection Act del 2008 vieta l'acquisto di oppioidi online

Journal of Pain & Palliative Care Pharmacotherapy. 2015;29:102–114.

Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time (15).
Physical Dependence	A state of adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (15).
Addiction	A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving (15).
Aberrant drug-related behavior	A behavior outside the boundaries of the agreed-on treatment plan which is established as early as possible in the doctor-patient relationship (16).
Misuse	Use of a medication for nonmedical use, or for reasons other than prescribed (DSM IV TR 2000). Misuse can be willful or unintentional use of a substance in a manner not consistent with legal or medical guidelines, such as altering dosing or sharing medicines, which has harmful or potentially harmful consequences. It does not refer to use for mind altering purposes (17).
Abuse	Misuse with consequences (DSM IV TR 2000). The use of a substance to modify or control mood or state of mind in a manner that is illegal or harmful to oneself or others. Potentially harmful consequences include accidents or injuries, blackouts, legal problems, and sexual behavior that increases the risk of human immunodeficiency virus infection (17).
Diversion	The intentional transfer of a controlled substance from legitimate distribution and dispensing channels into illegal channels or obtaining a controlled substance by an illegal method (17).

Journal of Pain Research

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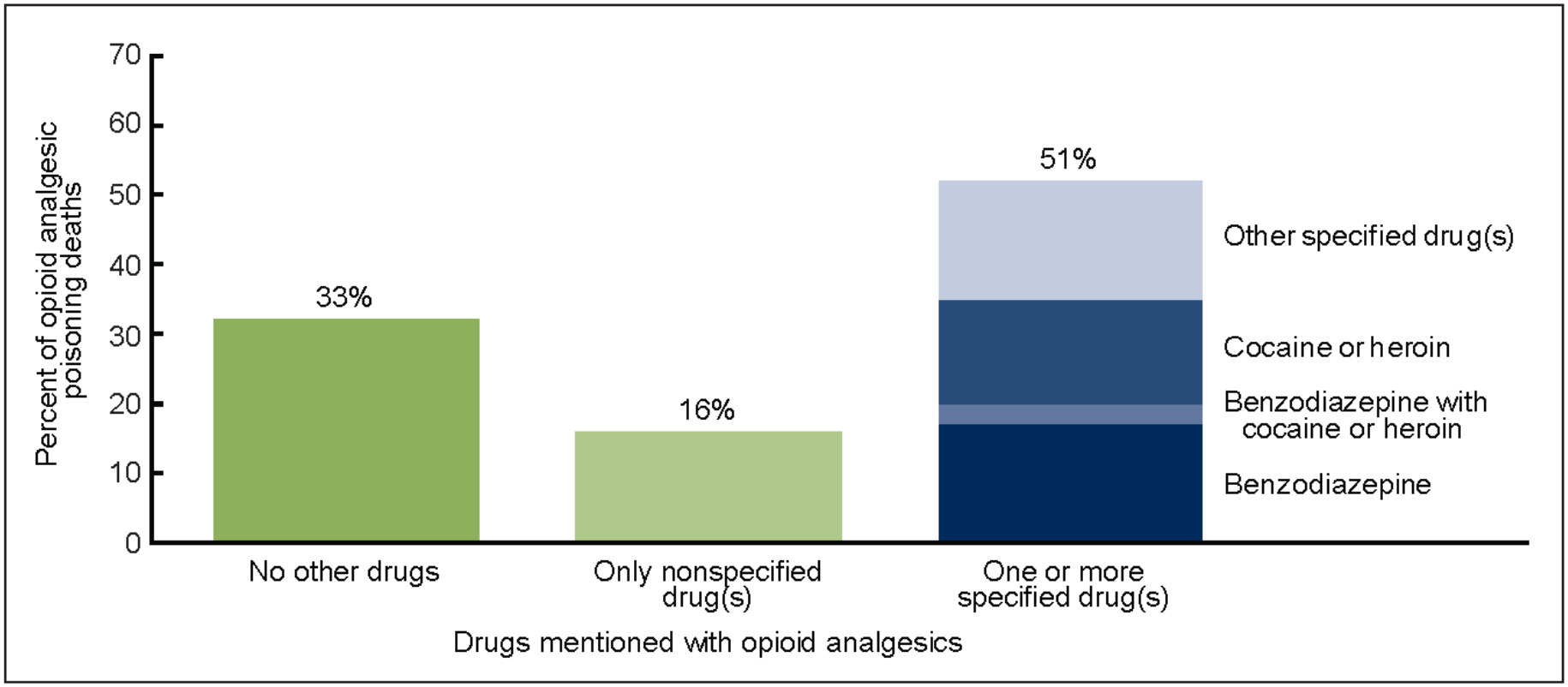
EDITORIAL

Pain management, prescription opioid mortality, and the CDC: is the devil in the data?

This article was published in the following Dove Press journal:
Journal of Pain Research
20 October 2017
Number of times this article has been viewed

Figure 4. Drugs mentioned in opioid analgesic-related poisoning deaths: United States, 2006



NOTE: Opioid analgesic deaths classified as involving cocaine, heroin, or benzodiazepine may also involve other drugs; deaths classified as involving other specified drug(s) do not involve cocaine, heroin, or benzodiazepine.

SOURCE: CDC/NCHS, National Vital Statistics System.

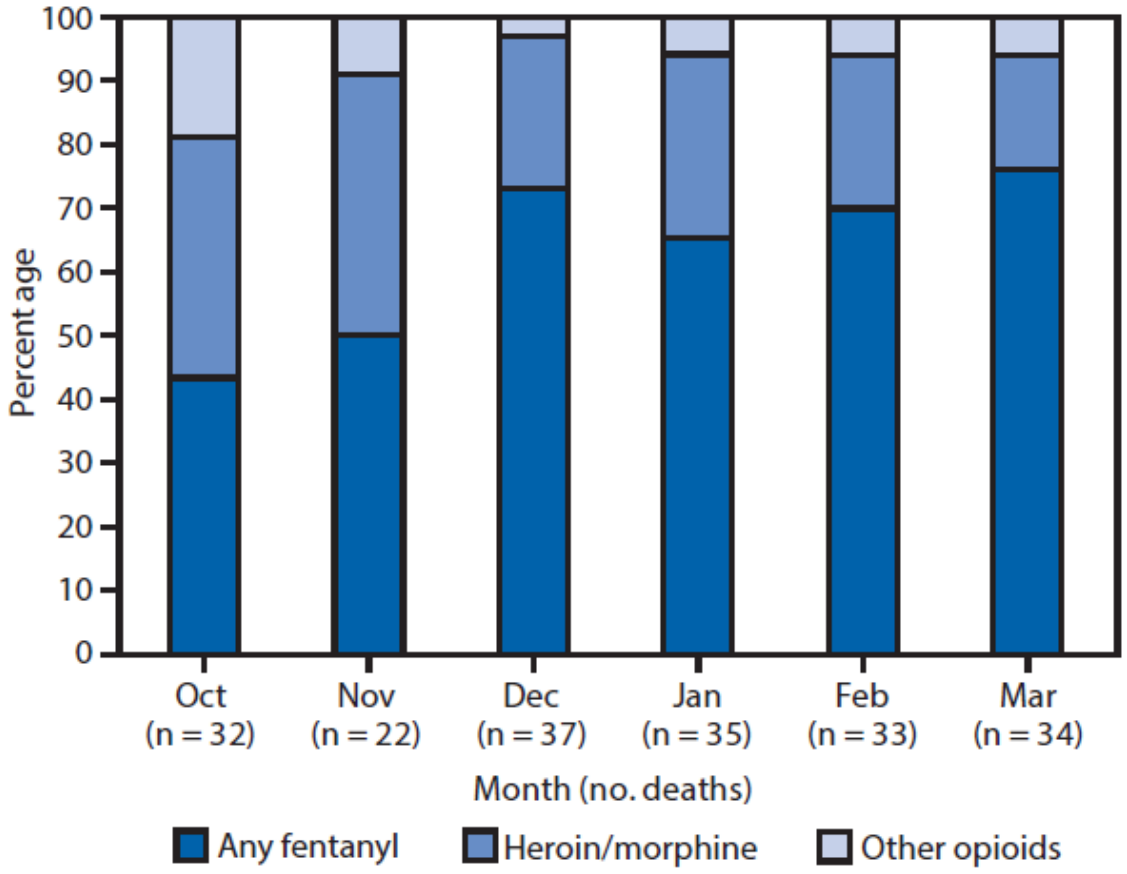
Morbidity and Mortality Weekly Report

Characteristics of Fentanyl Overdose — Massachusetts, 2014–2016

US Department of Health and Human Services/Centers for Disease Control and Prevention

MMWR / April 14, 2017 / Vol. 66 / No. 14

FIGURE. Percentage of opioid overdose deaths involving fentanyl, heroin/morphine (without fentanyl), and other opioids (without fentanyl, heroin/morphine) — Barnstable, Bristol, and Plymouth counties, Massachusetts, October 2014–March 2015



March 2015 (Figure). Eighty-two percent of fentanyl deaths were suspected to involve IMF, 4% were suspected to involve prescription fentanyl, and 14% involved an unknown source of fentanyl. Thirty-six percent of fentanyl deaths had evidence of an overdose occurring within seconds to minutes after drug use, and 90% of fentanyl overdose decedents were pulseless upon emergency medical services arrival (Table). Ninety-one percent of fatal fentanyl overdoses occurred in a hotel, motel, or private residence. Only 6% of fentanyl overdose deaths had evidence

According to the National Survey on Drug Use and Health, between 2011 and 2012, 68.9% of those aged 12 and older who reported PO abuse obtained them free, bought, or stolen from either a friend or relative. A majority of PO abusers, then, were abusing POs sold legally. Other sources of PO availability include drug theft, prescription forgery, and doctor shopping, particularly targeting doctors willing to prescribe without examinations. The elderly selling their pain medications to supplement their income has been reported as another source of prescribed opioids in the community.

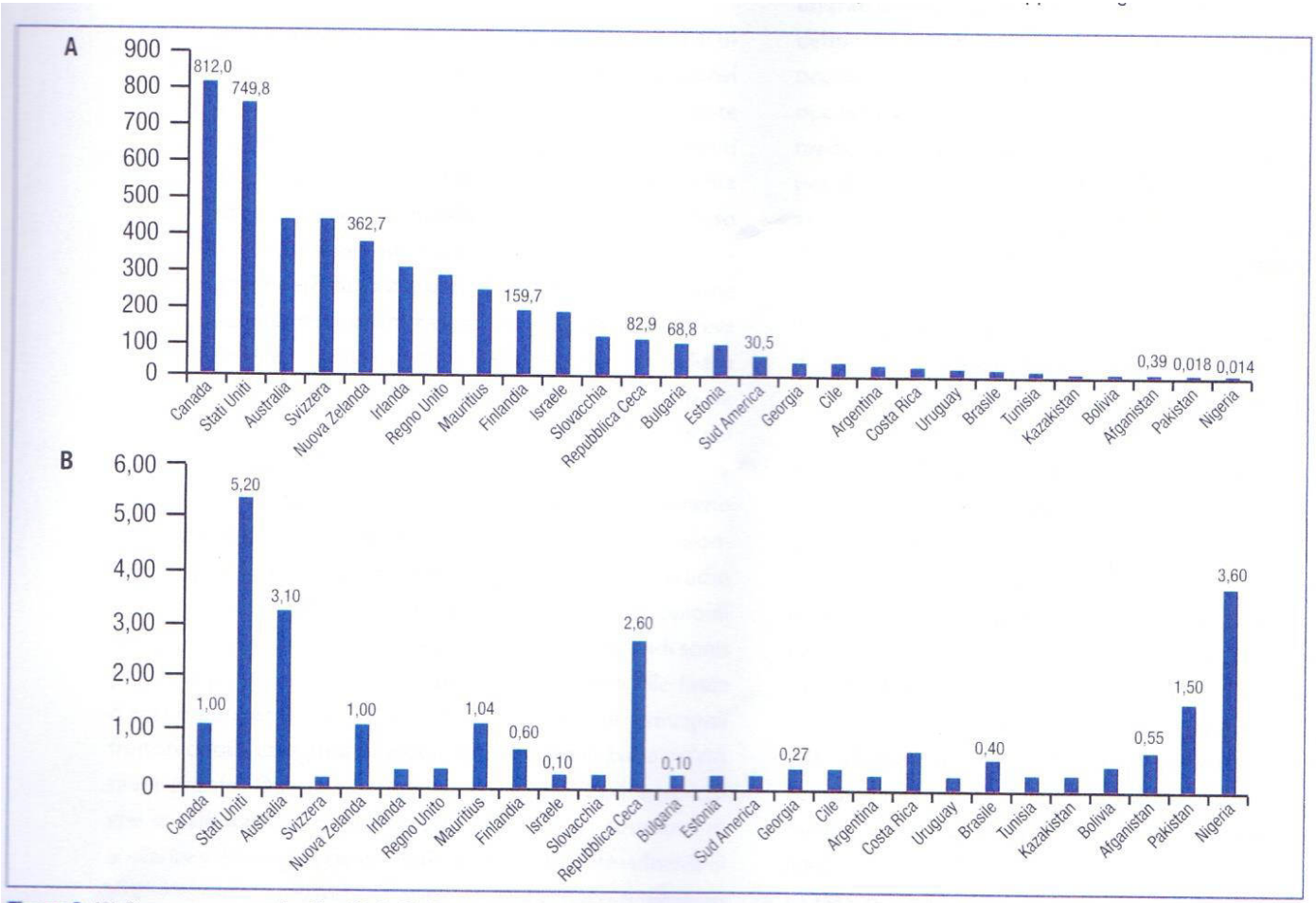
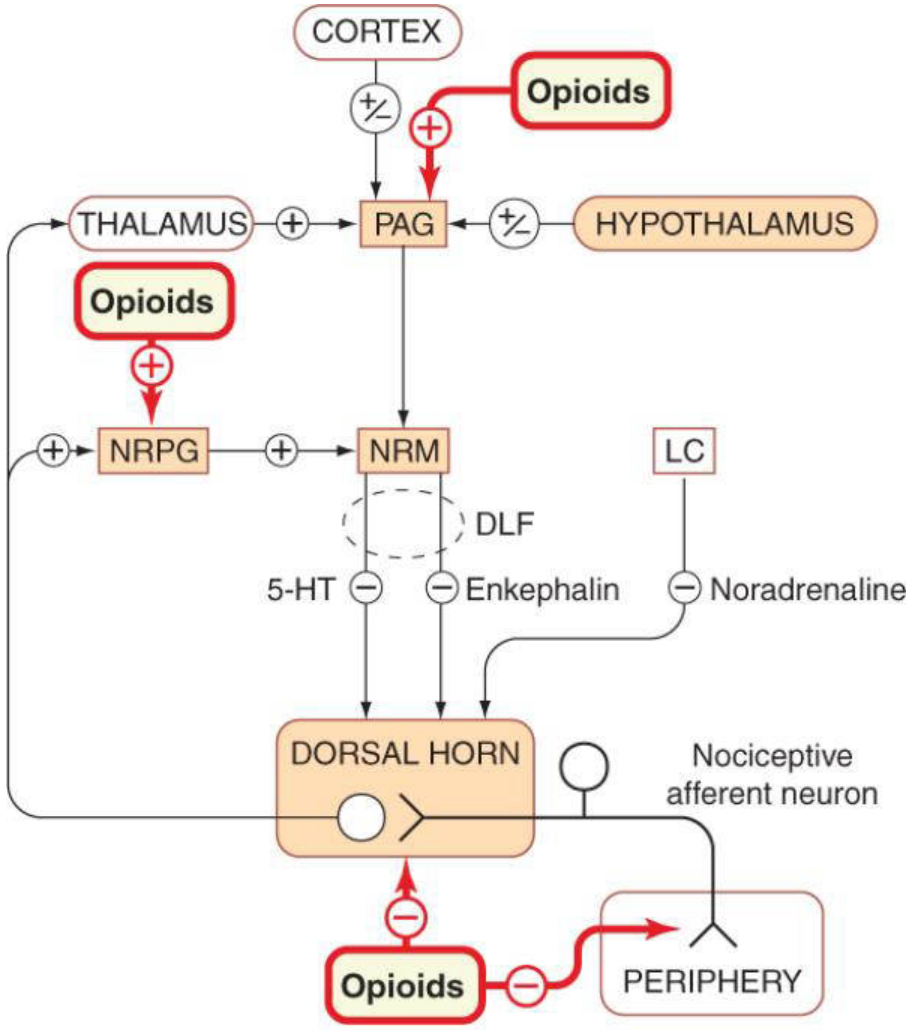
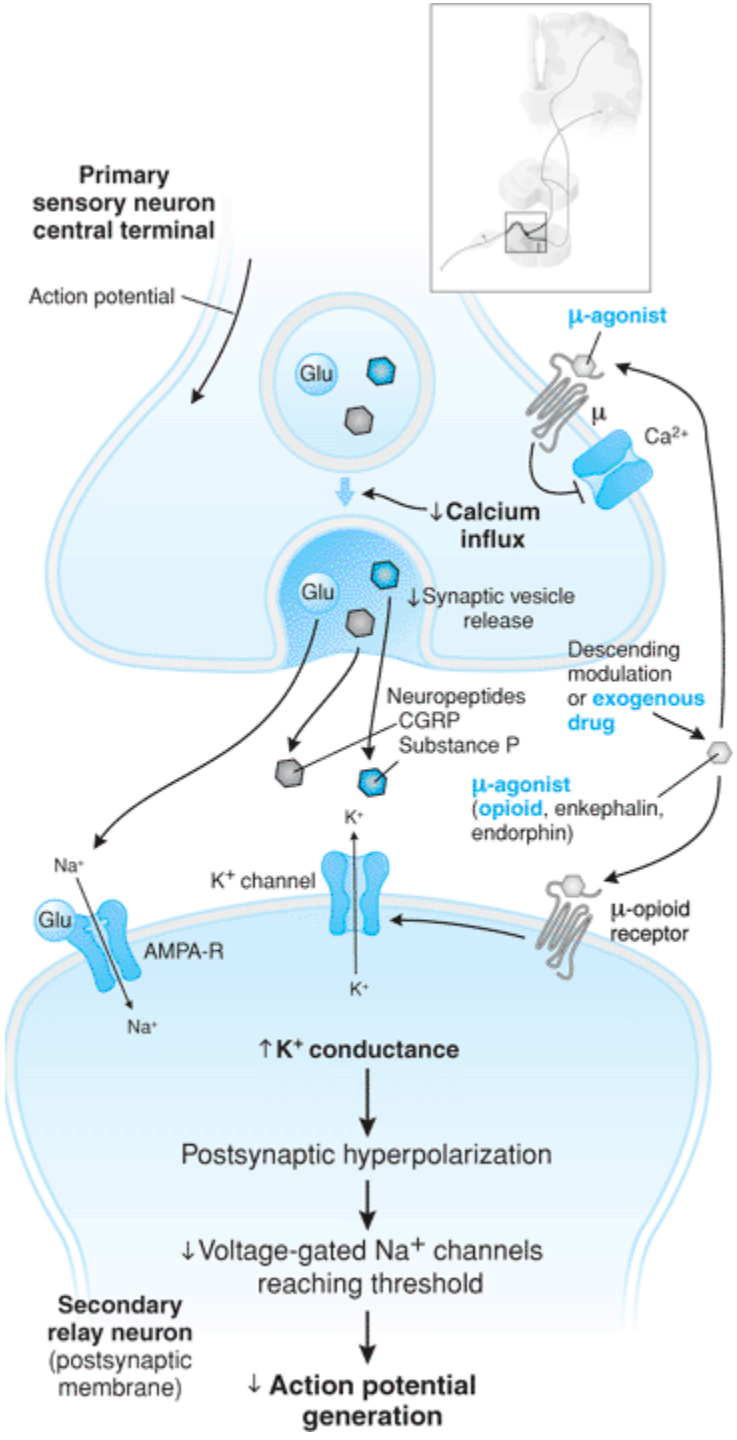


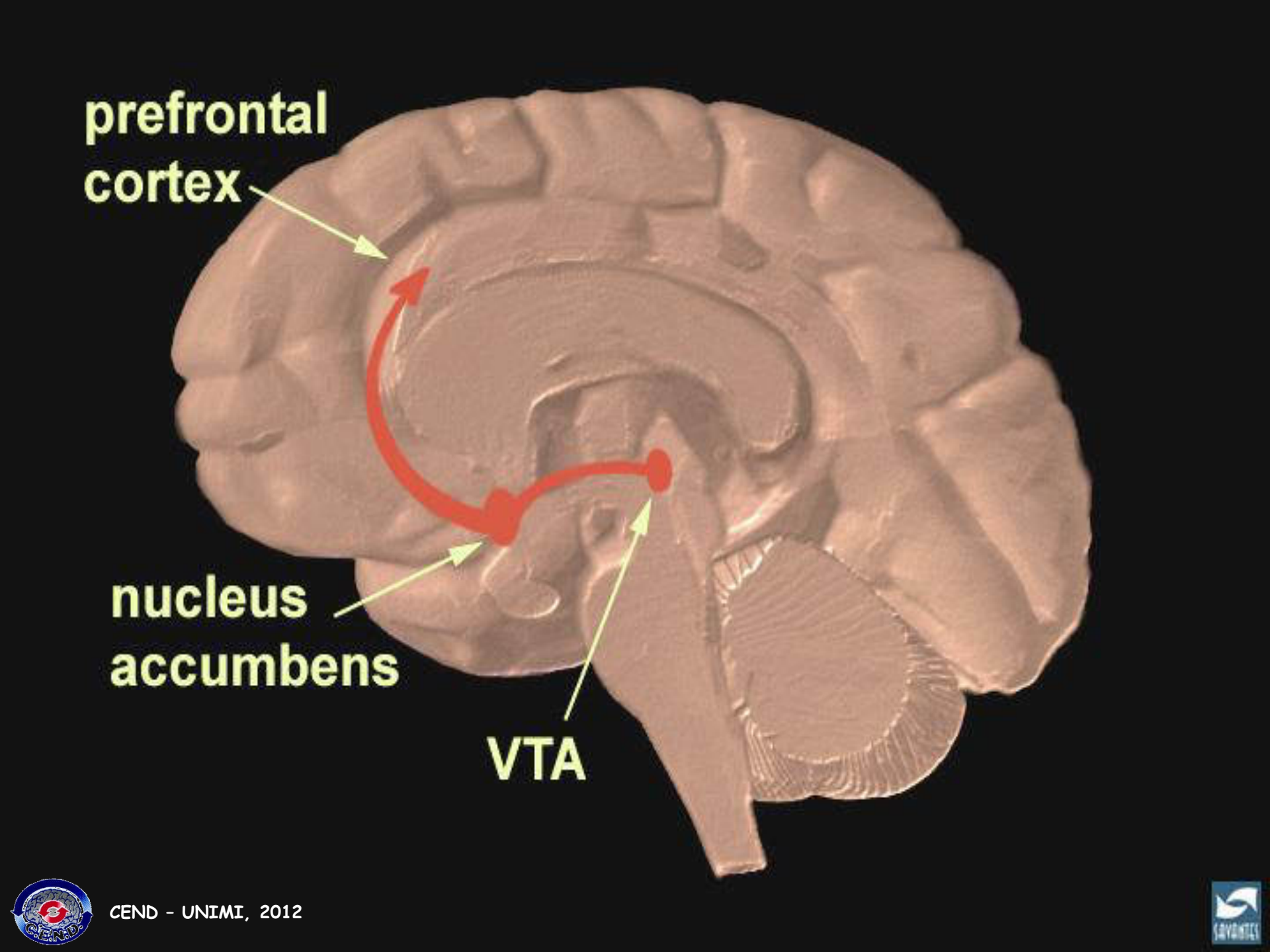
Figura 2. **(A)** Consumo pro capite di antidolorifici in equivalenti di morfina (mg ME/cap). **(B)** Prevalenza annuale di misuso di oppioidi prescrivibili (%).

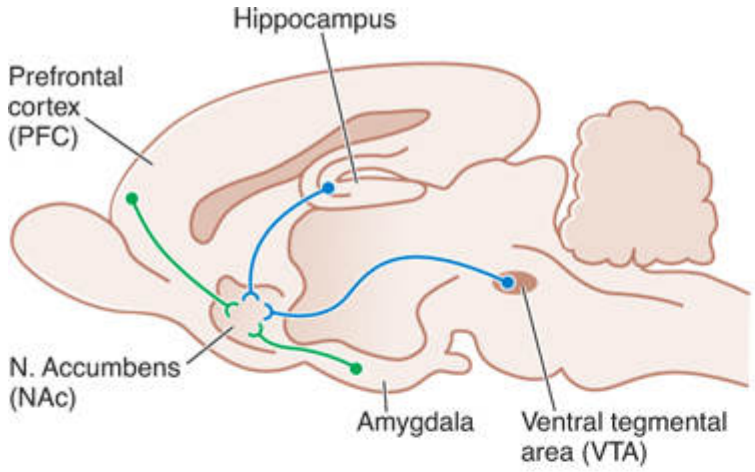
da Gilberto Gerra

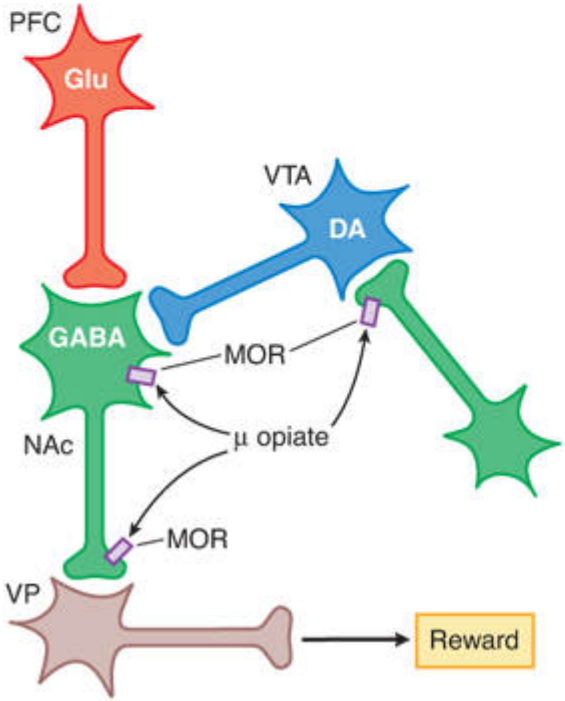
37° Congresso SIF, Napoli 27-30 ottobre 2015



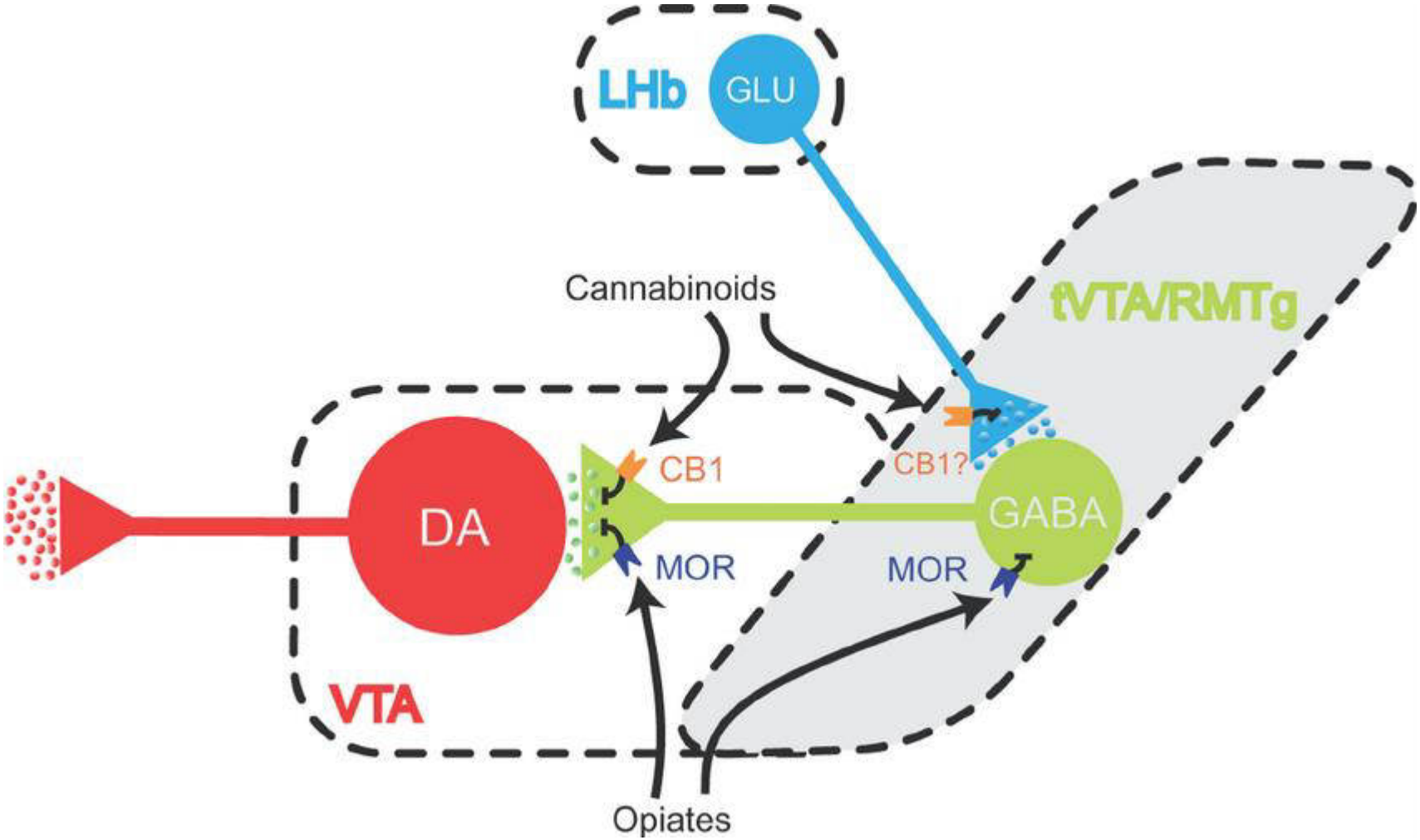

Primary sensory neuron central terminal
Action potential
Glu
μ-agonist
μ
Ca2+
↓Calcium influx
Glu
↓Synaptic vesicle release
Descending modulation or exogenous drug
Neuropeptides
CGRP
Substance P
μ-agonist (opioid, enkephalin, endorphin)
K+
Na+
K+ channel
μ-opioid receptor
Glu
AMPA-R
K+
Na+
↑K+ conductance
Postsynaptic hyperpolarization
↓Voltage-gated Na+ channels reaching threshold
Secondary relay neuron (postsynaptic membrane)
↓ Action potential generation

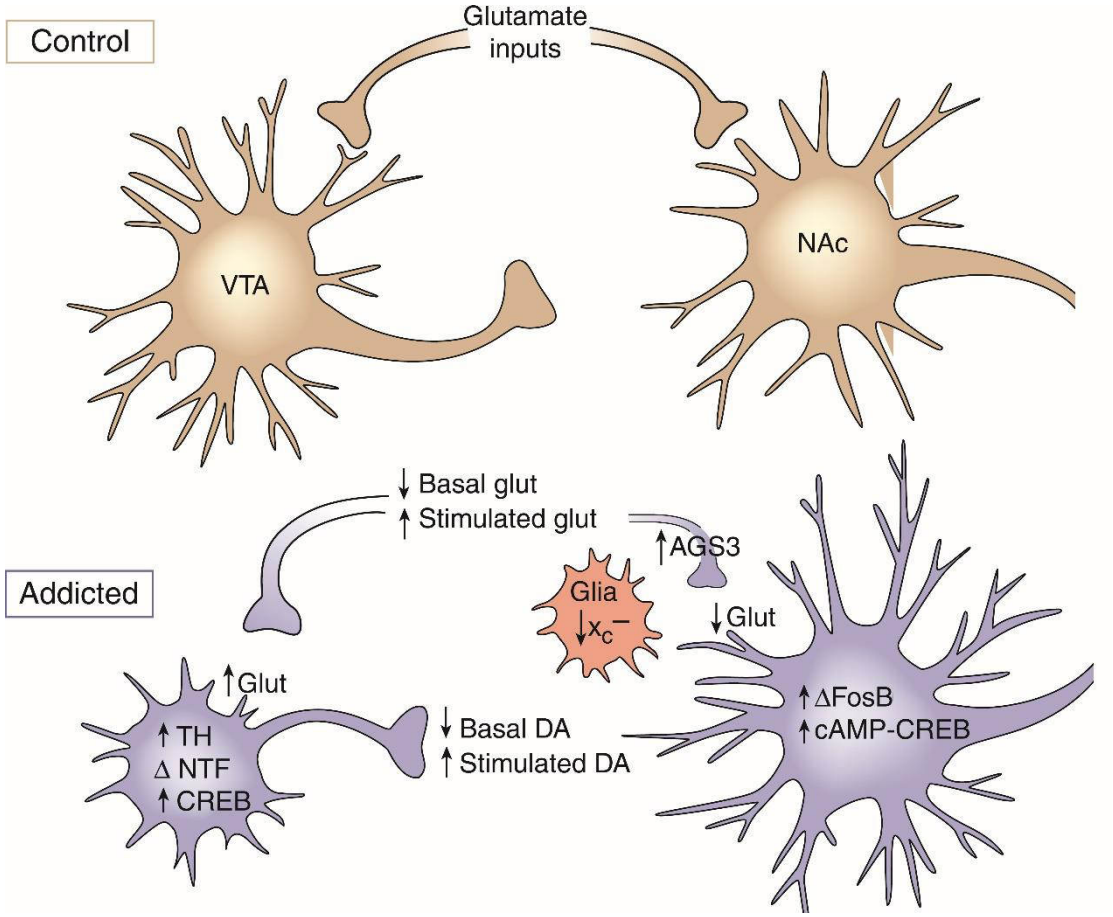

prefrontal
cortex
nucleus
accumbens
VTA



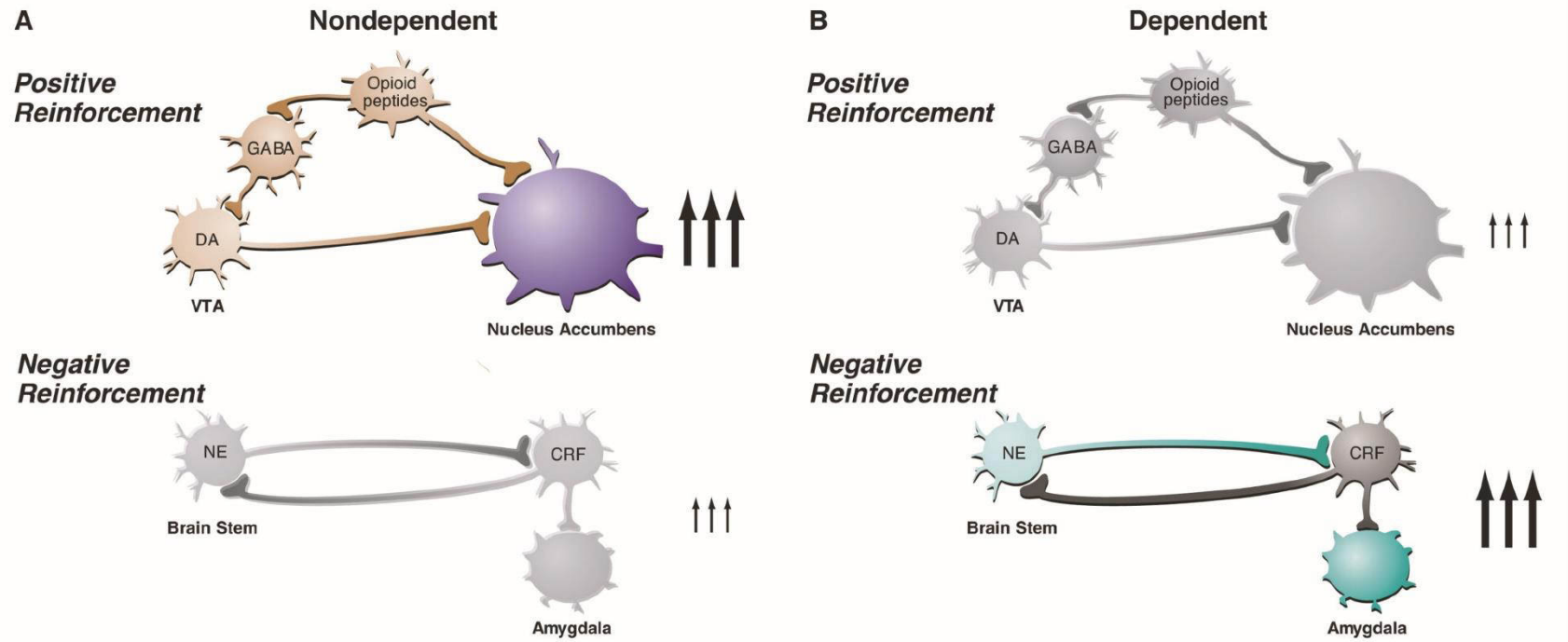


Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com


LHb
GLU
Cannabinoids
tVTA/RMTg
CB1
CB1?
DA
GABA
MOR
MOR
VTA
Opiates



Nat Neurosci, 2005



Alcohol Res Health. 2008 ;31(3): 185–195.

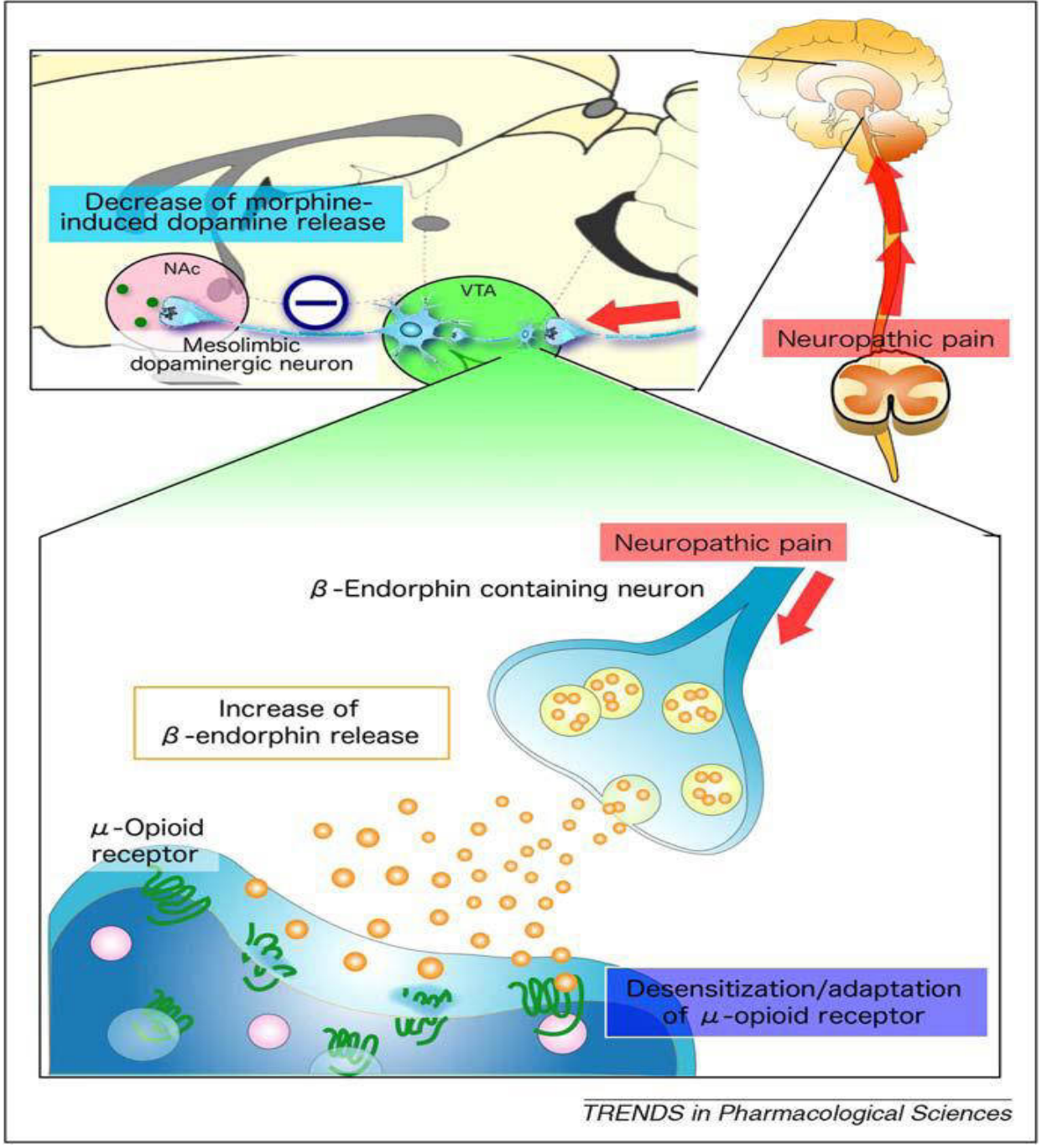
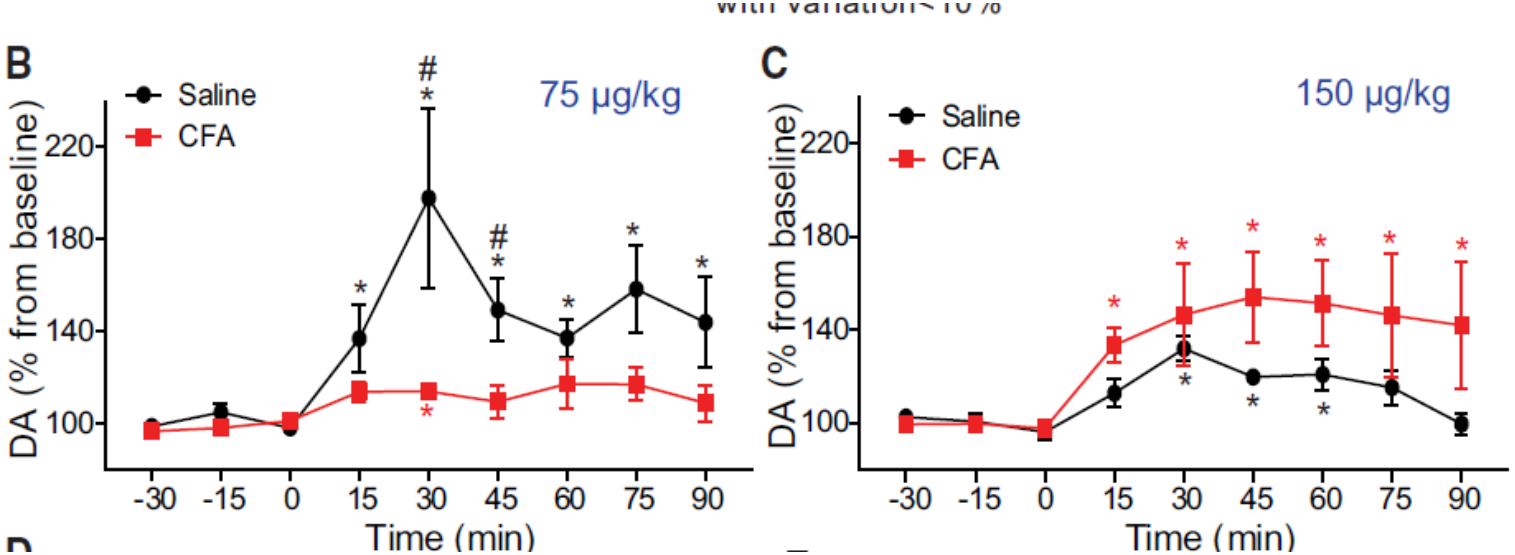


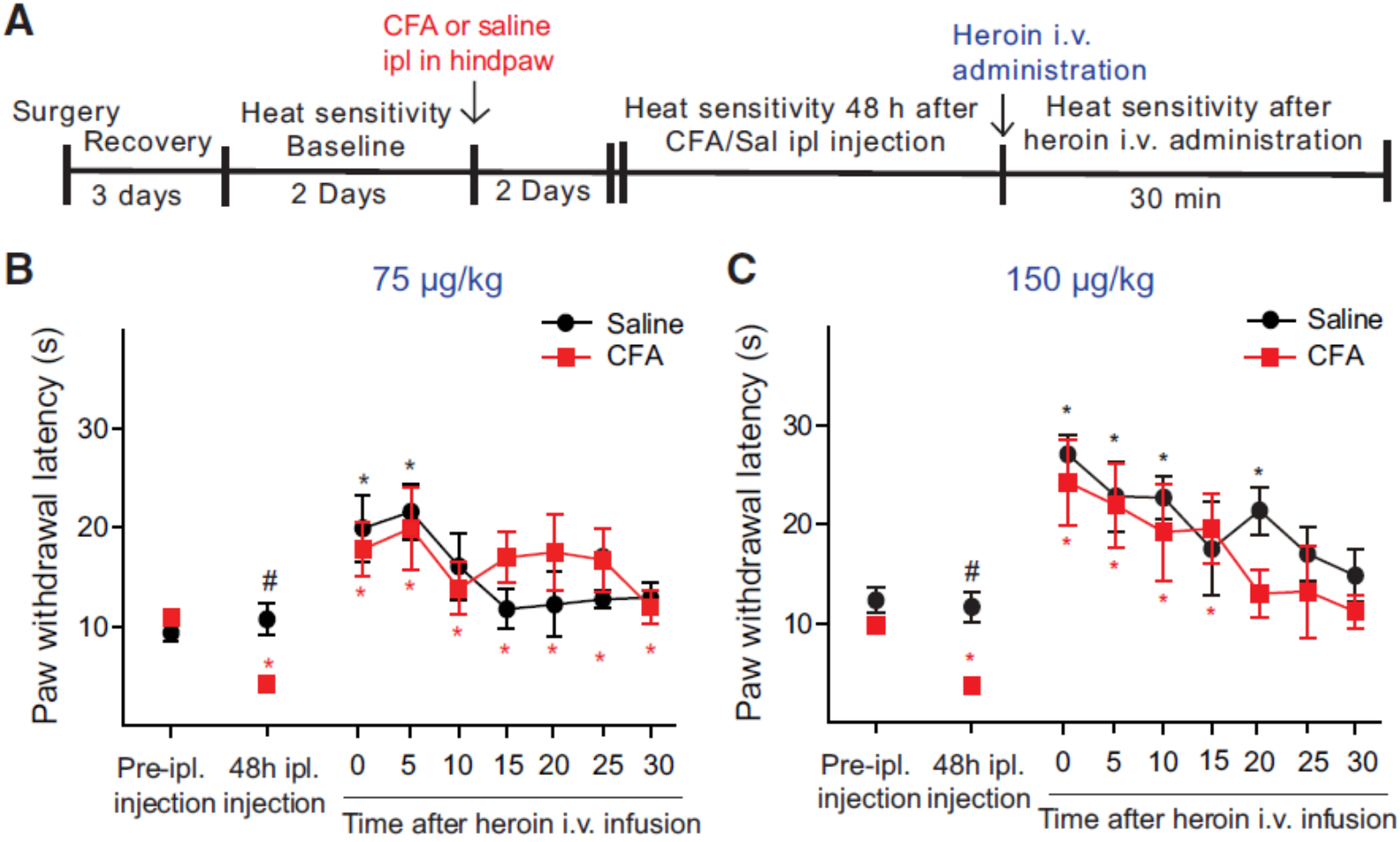
Figure 1. Model of the mechanism of suppression of m-agonist-induced reward in neuropathic pain. Peripheral nerve injury can cause sustained activation of the endogenous b-endorphinergic system in the brain. b-Endorphin released by chronic nociceptive stimuli can continuously activate m-opioid receptors in the VTA, thus leading to downregulation of m-opioid receptor function and resulting in a decrease in dopamine release in the NAc. This phenomenon could explain the mechanism that underlies the suppression of m-opioid reward under neuropathic pain-like states observed in animal models .

Niikura K et al., TIPS, 2010

Behavioral/Cognitive

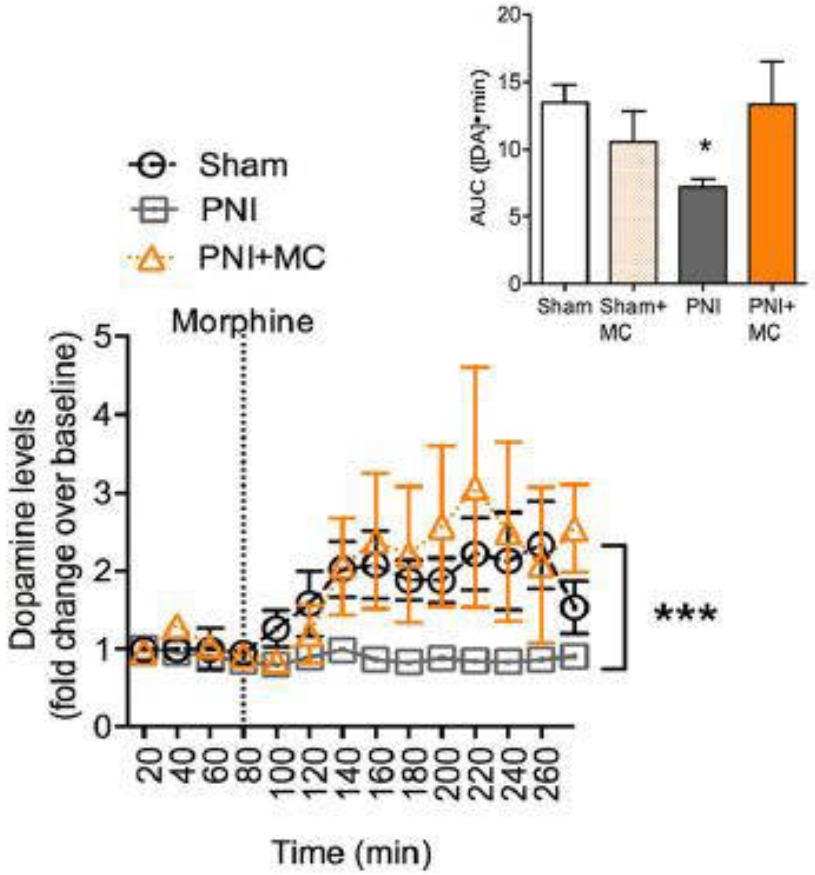
Inflammatory Pain Promotes Increased Opioid Self-Administration: Role of Dysregulated Ventral Tegmental Area μ Opioid Receptors




A
CFA or saline
ipl in hindpaw
Heroin i.v.
administration
Surgery
Recovery
3 days
Heat sensitivity
Baseline
2 Days
2 Days
Heat sensitivity 48 h after
CFA/Sal ipl injection
Heat sensitivity after
heroin i.v. administration
30 min
B
75 µg/kg
Saline
CFA
Paw withdrawal latency (s)
30
20
10
#
*
Pre-ipl. injection
48h ipl. injection
0 5 10 15 20 25 30
Time after heroin i.v. infusion
C
150 µg/kg
Saline
CFA
Paw withdrawal latency (s)
30
20
10
#
*
Pre-ipl. injection
48h ipl. injection
0 5 10 15 20 25 30
Time after heroin i.v. infusion

Neurobiology of Disease

Microglia Disrupt Mesolimbic Reward Circuitry in Chronic Pain



Drug and Alcohol Dependence 138 (2014) 202–208

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: Mathematical modeling using a database of commercially-insured individuals

Bryan N. Cochran[a,*], Annesa Flentje[b], Nicholas C. Heck[a], Jill Van Den Bos[c], Dan Perlman[c], Jorge Torres[c], Robert Valuck[d], Jean Carter[e]

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[e] Department of Pharmacy Practice, 32 Campus Drive, The University of Montana, Missoula, MT 59812, United States

Results: When compared to non-OUDs, OUDs were more likely to: (1) be male (59.9% vs. 44.2% for non-OUDs) and younger ($M = 37.9$ vs. 47.7); (2) have a prescription history of more opioids (1.7 vs. 1.2), and more days supply of opioids ($M = 272.5$, vs. $M = 33.2$; (3) have prescriptions filled at more pharmacies ($M = 3.3$ per year vs. $M = 1.3$); (4) have greater rates of psychiatric disorders; (5) utilize more medical and psychiatric services; and (6) be prescribed more concomitant medications. A predictive model incorporating these findings was 79.5% concordant with actual OUDs in the data set.

Table 1
Characteristics of a commercially insured opioid-using population ($n = 2{,}841{,}793$) with comparisons of non-OUDs ($n = 2{,}838{,}880$), and OUDs ($n = 2913$).

Demographics				
Variable	Entire Sample	Non-OUDs	OUDs	Comparison of non-OUDs and OUDs
Age	Mean (SD)	Mean (SD)	Mean (SD)	*t*-Value
	47.7 (18.2)	47.7 (18.2)	37.9 (14.8)	35.55*
	n (%)	*n* (%)	*n* (%)	X^2
Gender				291.77*
Female	1,586,335 (55.8)	1,585,167 (55.8)	1,168 (40.1)	
Male	1,255,458 (44.2)	1,253,713 (44.2)	1,745 (59.9)	
Region				218.60*
Northeast	267,379 (9.4)	266,915 (9.4)	464 (15.9)	
North Central	816,325 (28.7)	815,376 (28.7)	949 (32.6)	
South	1,255,249 (44.2)	1,254,255 (44.2)	994 (34.1)	
West	497,865 (17.5)	497,359 (17.5)	506 (17.4)	
Other/unknown	4,975 (0.2)	4,975 (0.2)	0.0 (0.0)	
Dependent status				653.65*
Dependent	341,637 (12.0)	340,865 (12.0)	772 (26.5)	
Employee	1,706,933 (60.1)	1,705,676 (60.1)	1,257 (43.2)	
Spouse	793,223 (27.9)	792,339 (27.9)	884 (30.3)	

* $p < 0.0001$.

Table 3
Mental health diagnoses of a commercially insured opioid-using population ($N = 2{,}841{,}793$), with comparisons of non-OUDs ($n = 2{,}838{,}880$), and OUDs ($n = 2{,}913$).

Variable	Non-OUDs n (%)	OUDs n (%)	Comparison of non-OUDs and OUDs X^2
Any anxiety disorder	156,110 (5.5)	842 (28.9)	3050.76*
Any mood disorder	259,375 (9.1)	1,588 (54.5)	7179.6*
Any pain disorder	2,534 (0.1)	59 (2.0)	1174.98*
Any personality disorder	825 (0.0)	23 (0.8)	538.30*
Somatoform disorders	1,805 (0.1)	22 (0.8)	206.08*
Psychotic disorders	4,930 (0.2)	56 (1.9)	498.05*
Any other substance use disorder	96,539 (3.4)	1,681 (57.7)	25,703.25*

* $p < 0.0001$.

Pathway 1: Inadequately controlled chronic physical pain leads to misuse

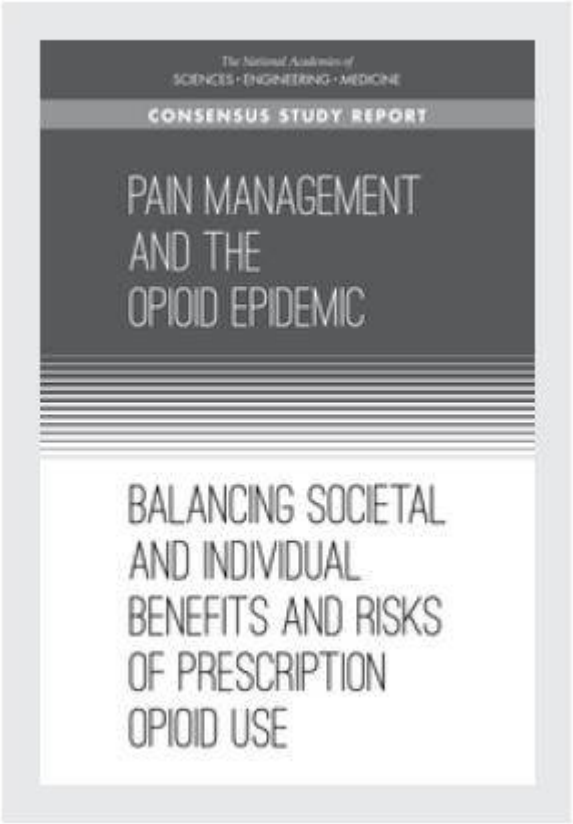
Pathway 2: Some individuals are vulnerable to opioid dependence even after brief opioid exposure

Pathway 3: Prior substance use problems and introduction of prescribed Opioids

Pathway 4: Relief from emotional distress reinforces misuse or abuse

Pathway 5: Recreational initiation or non-medically supervised use of opioids

Journal of Substance Abuse Treatment 73 (2017) 47–54



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Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2017. *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24781.

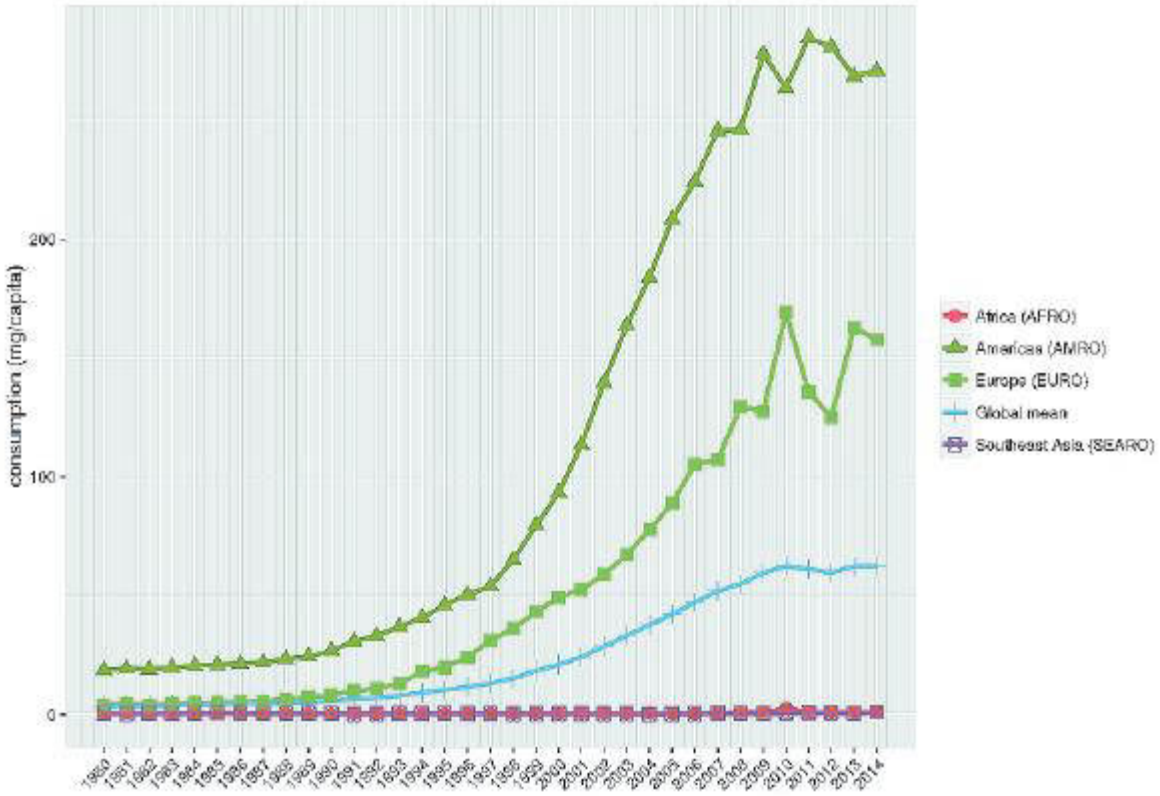
The vast majority of people who are prescribed opioids do not misuse them. However, opioids can produce feelings of pleasure, relaxation, and contentment, leading to an overreliance on these drugs in many patients and to misuse and OUD in others. Moreover, many lawfully dispensed opioids make their way into the hands of people for whom they were not intended, including participants in illicit markets. As a result, harms associated with use of prescription opioids affect not only patients with pain themselves but also their families, their communities, and society at large.

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2017. *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24781.

Recommendation 3-1. Invest in research to better understand pain and opioid use disorder. Given the significant public health burden of pain and opioid use disorder (OUD) in the United States, the National Institutes of Health, the Substance Abuse and Mental Health Services Administration, the U.S. Department of Veterans Affairs, industry, and other relevant research sponsors should consider greater investment in research on pain and OUD, including but not limited to research aimed at

- improving understanding of the neurobiology of pain;
- developing the evidence on promising pain treatment modalities and supporting the discovery of innovative treatments, including nonaddictive analgesics and nonpharmacologic approaches at the level of the individual patient; and
- improving understanding of the intersection between pain and OUD, including the relationships among use and misuse of opioids, pain, emotional distress, and the brain reward pathway; vulnerability to and assessment of risk for OUD; and how to properly manage pain in individuals with and at risk for OUD.

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2017. *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24781.



Bone Joint J 2017;99-B:856–64.

THE BONE & JOINT JOURNAL

■ INSTRUCTIONAL REVIEW

An epidemic of the use, misuse and overdose of opioids and deaths due to overdose, in the United States and Canada

IS EUROPE NEXT?

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■ T. Teunis, MD, PhD, Resident in Plastic, Reconstructive and Hand Surgery
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■ S. J. Janssen, MD, Resident Orthopaedic Surgery, Department of General Surgery Onze Lieve Vrouwe Gasthuis, Oosterpark 9, 1091 AC Amsterdam, The Netherlands.

■ D. Ring, MD, PhD, Associate Dean of Comprehensive Care, Professor of Surgery and Perioperative Care and Orthopaedic Surgeon, Department of Surgery and Perioperative Care, Dell Medical School
The University of Texas at Austin, 1912 Speedway, Austin, Texas, 78712, USA.

In conclusion, the general public and the medical and legal professions in Europe and the rest of the world need to be careful not to make the same mistakes made in the United States and Canada. Opioids relieve pain, but they are addictive and dangerous and do not provide peace of mind. Resilience is the best form of pain relief. Pain is generally managed in the rest of the world without the use of opioids. That is a much better strategy and worth preserving.

***Bone Joint J* 2017;99-B:856–64.**

SOCIETÀ ITALIANA DI FARMACOLOGIA

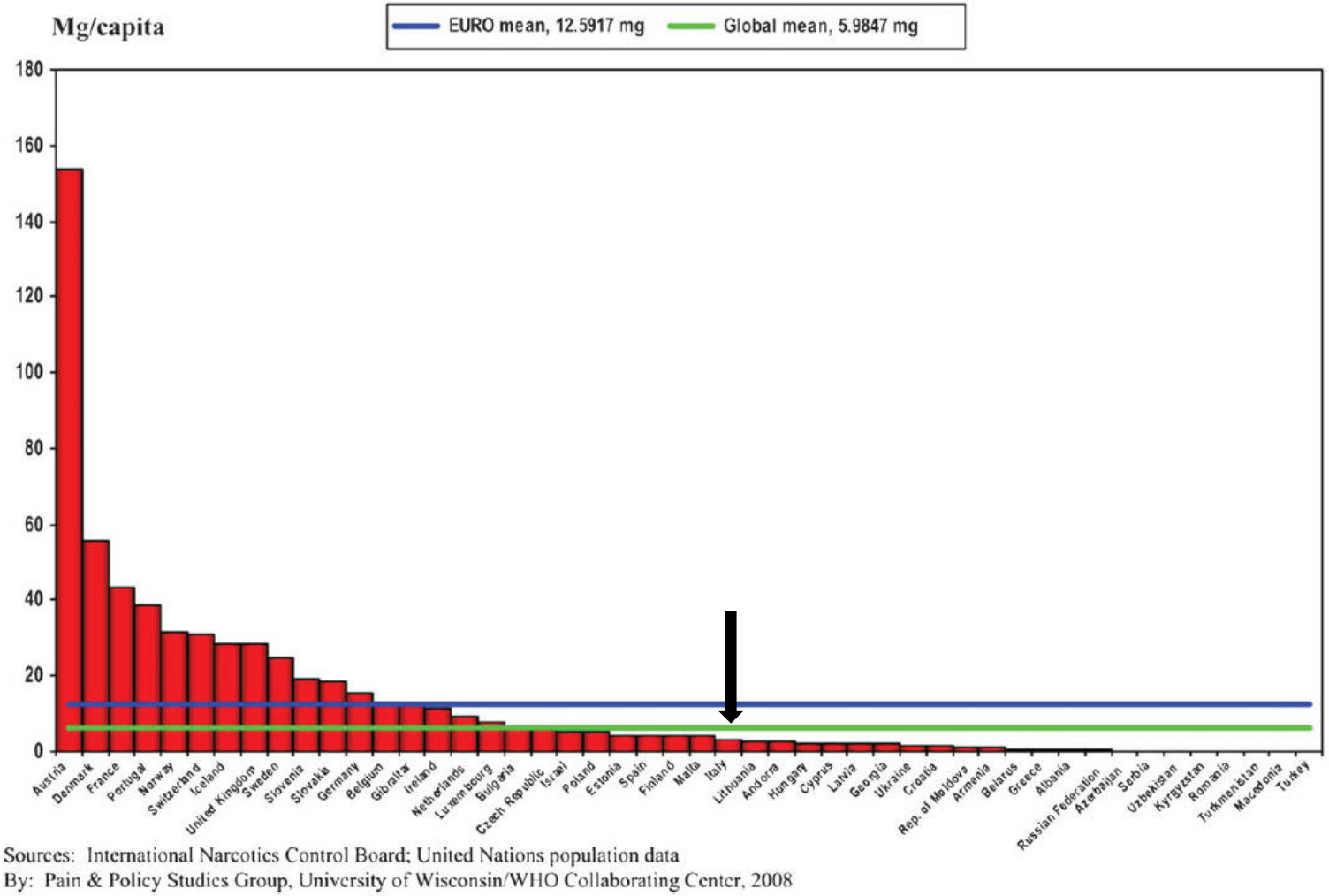
Trattamento del dolore cronico in Italia: appropriatezza terapeutica con oppiacei e timore di addiction: situazione italiana vs USA

a cura dei Proff. Diego Fornasari, Gilberto Gerra, Sabatino Maione, Guido Mannaioni (coordinatore), Alessandro Mugelli, Daniela Parolaro, Patrizia Romualdi (coordinatore) e Paola Sacerdote

Approvato dal Consiglio Direttivo 2015-2017 che l'ha commissionato e dal Consiglio Direttivo 2017-2019

La Società italiana di Farmacologia ritiene che, benché l'utilizzo di analgesici oppiacei in Italia sia di gran lunga inferiore al Nord Europa e agli USA, grande attenzione debba essere posta nell'evitare il rischio di abuso, pur garantendo a tutti i pazienti con dolore il diritto all'accesso alle cure, come previsto dalla legge 38/2010.

Diego Fornasari



Sources: International Narcotics Control Board; United Nations population data
By: Pain & Policy Studies Group, University of Wisconsin/WHO Collaborating Center, 2008

Figure 1. European consumption of morphine, 2006.