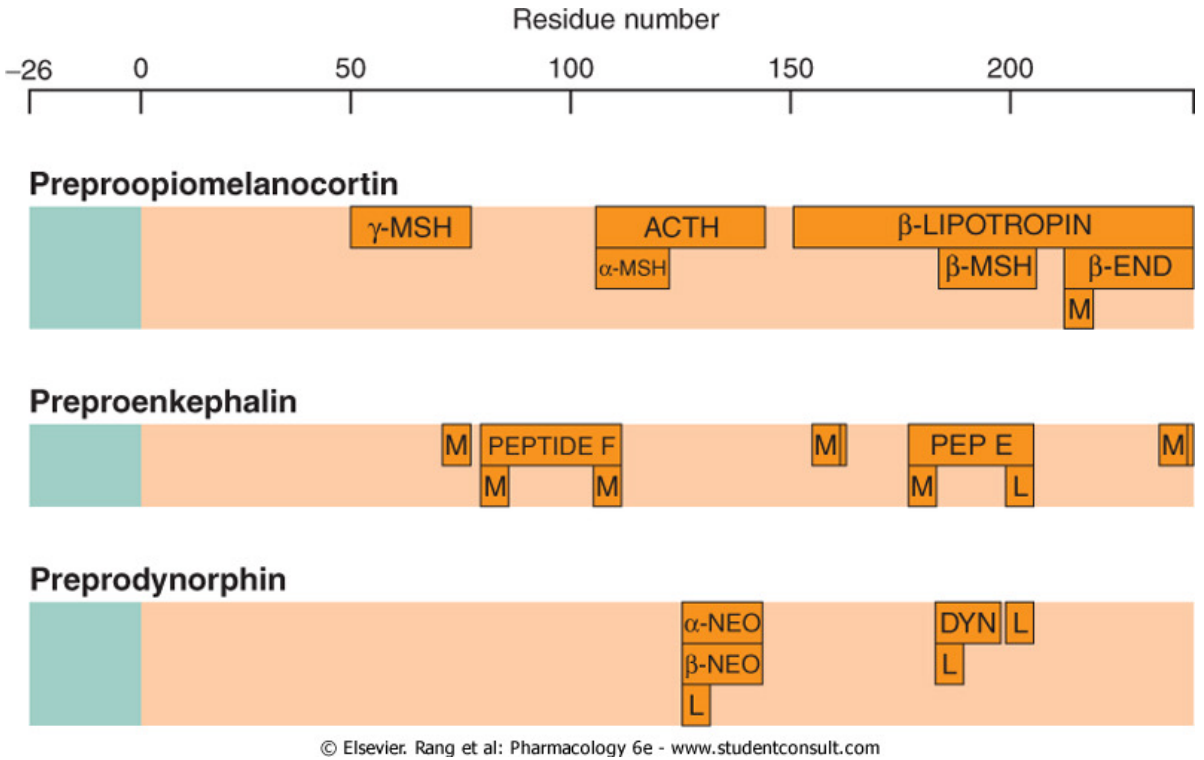
Analgesici centrali

- **Oppioide**: sostanza endogena o di sintesi che produce effetti morfino simili, che vengono bloccati da antagonisti specifici come il naloxone

Peptidi oppioidi endogeni

- Esistono tre principali famiglie di peptidi oppioidi endogeni, provvisti di attività analgesica e coinvolti in molte funzioni fisiologiche, ma non vengono utilizzati come farmaci.
- Sono i ligandi naturali dei recettori oppioidi
- Sono ampiamente distribuiti nel cervello, ma sono prodotti anche da altre cellule (ghiandole esocrine e endocrine, cellule del sistema immunitario)

Precursori polipeptidici



Recettori oppioidi

- **MOR (μ)**: sono responsabili della maggior parte degli effetti analgesici degli oppioidi e di alcuni dei più importanti effetti collaterali, come la depressione respiratoria, l'euforia, la sedazione e la dipendenza. La maggior parte degli oppioidi analgesici si comporta da agonista dei recettori μ.
- **DOR (δ)**: contribuiscono all'analgesia; gli agonisti disponibili sono peptidi e non attraversano la BBB.
- **KOR (κ)**: contribuiscono all'effetto analgesico a livello spinale e perferico, e possono promuovere sedazione e disforia; causano relativamente pochi effetti indesiderati e non contribuiscono alla dipendenza. Alcuni analgesici sono relativamente selettivi per il recettore κ.

	μ	δ	κ
Analgesia			
Sopraspinale	+++	-	-
Spinale	++	++	+
Periferica	++	-	++
Depressione respiratoria	+++	++	-
Miosi	++	-	+
Ridotta motilità GI	++	++	+
Euforia	+++	-	-
Disforia	-	-	+++
Sedazione	++	-	++
Dipendenza fisica	+++	-	+

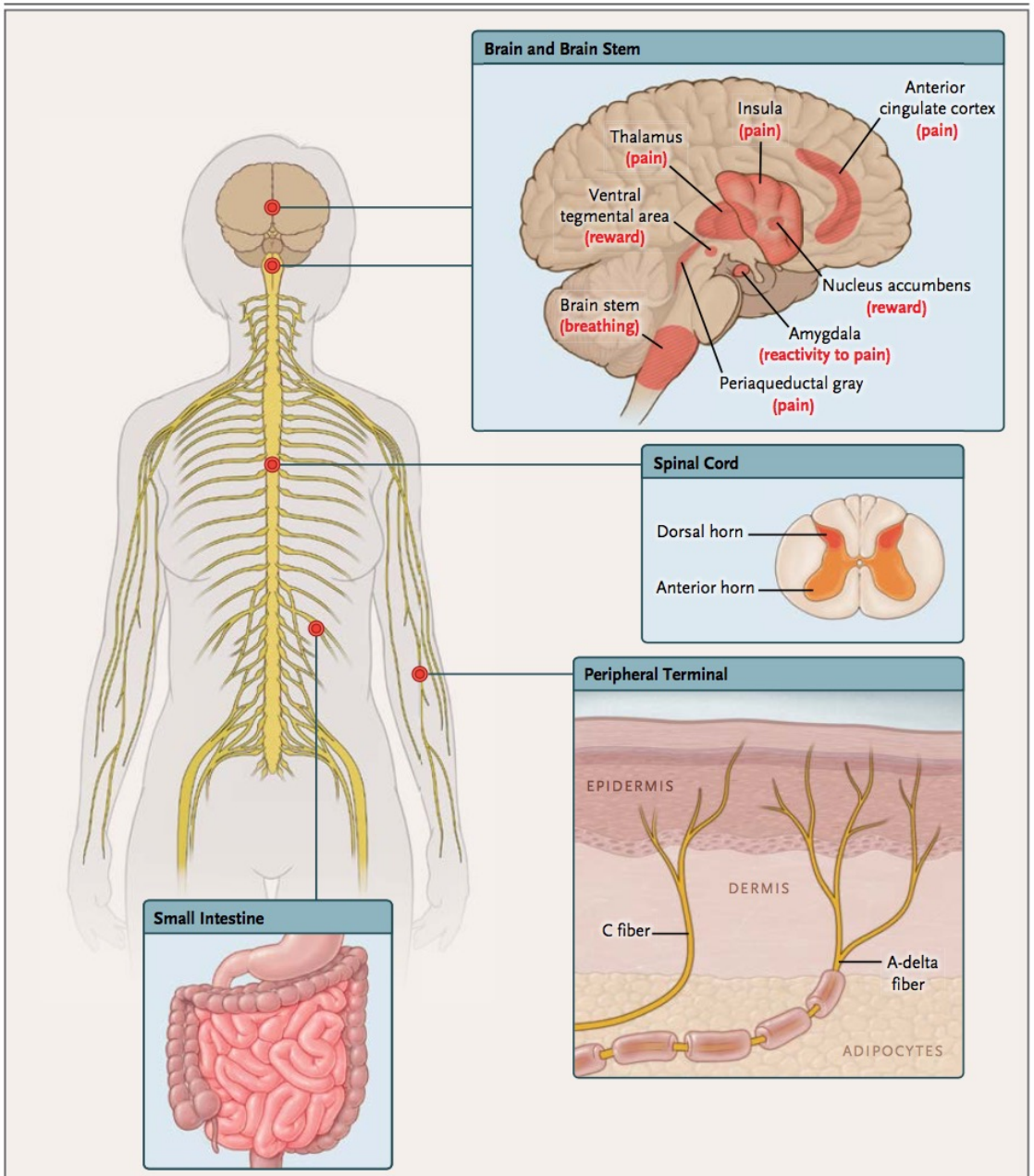
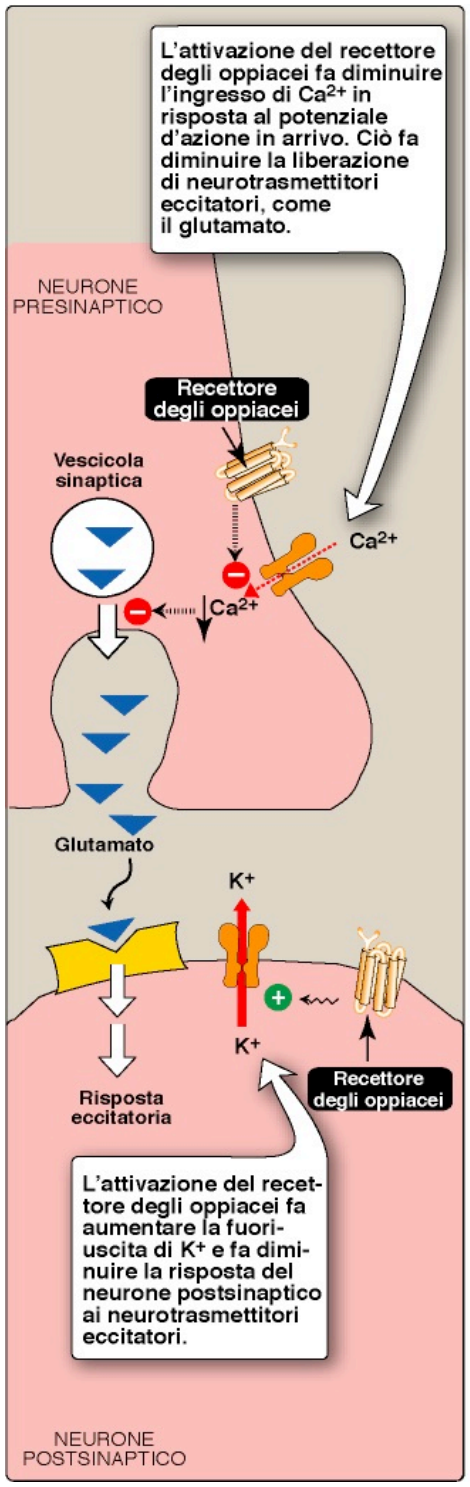


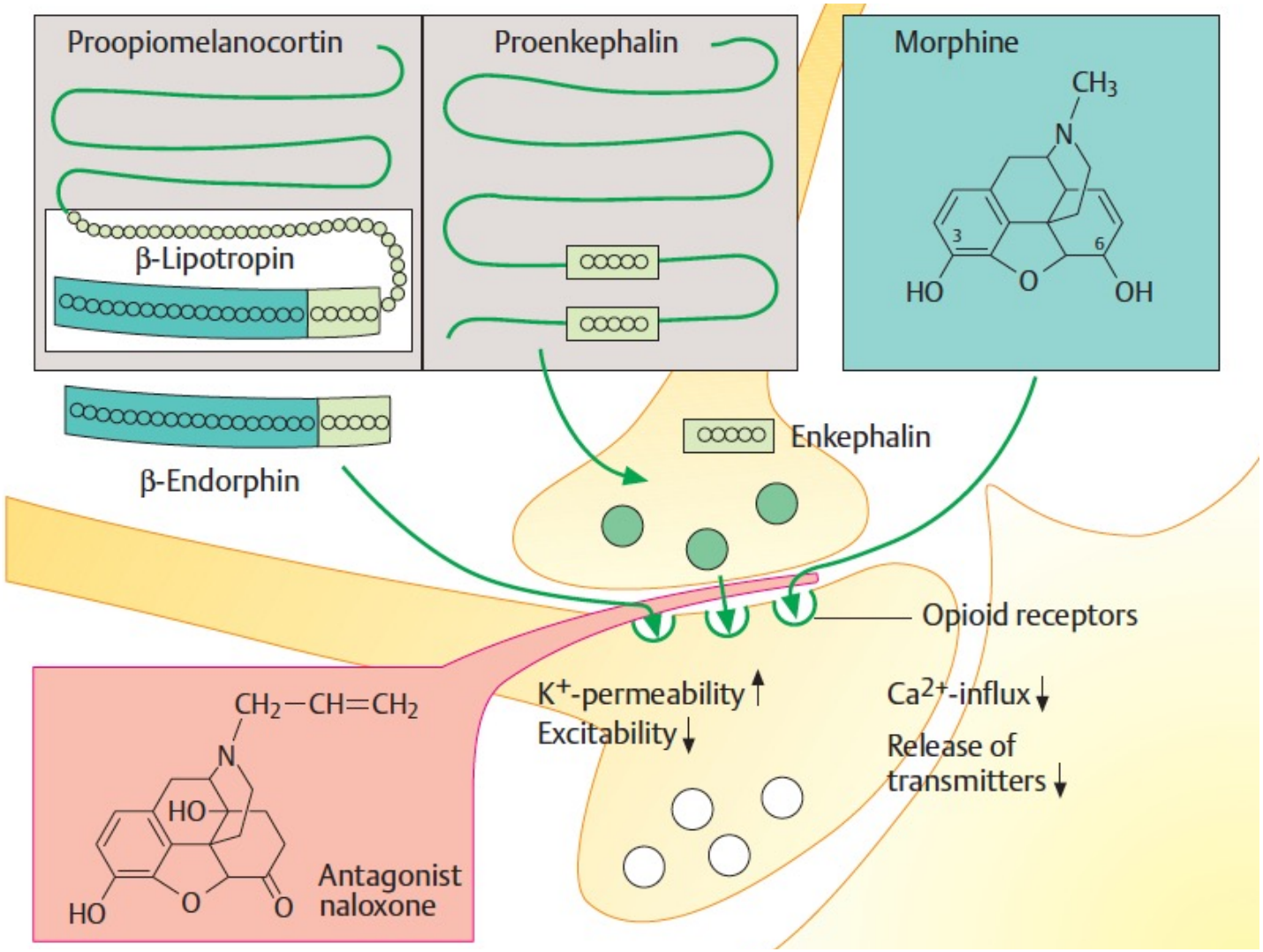
Figure 1. Location of Mu-Opioid Receptors.

Shown are the locations of mu-opioid receptors in the human brain, with high concentration in the thalamus, periaqueductal gray, insula, and anterior cingulate (regions involved with pain perception), in the ventral tegmental area and nucleus accumbens (regions involved with reward), in the amygdala (a region involved with emotional reactivity to pain), and in the brain stem (nuclei that regulate breathing). In the spinal cord, a high concentration of mu-opioid receptors is located in the dorsal horn. Mu-opioid receptors in peripheral terminals modulate the perception of pain, and receptors in the small intestine regulate gut motility.

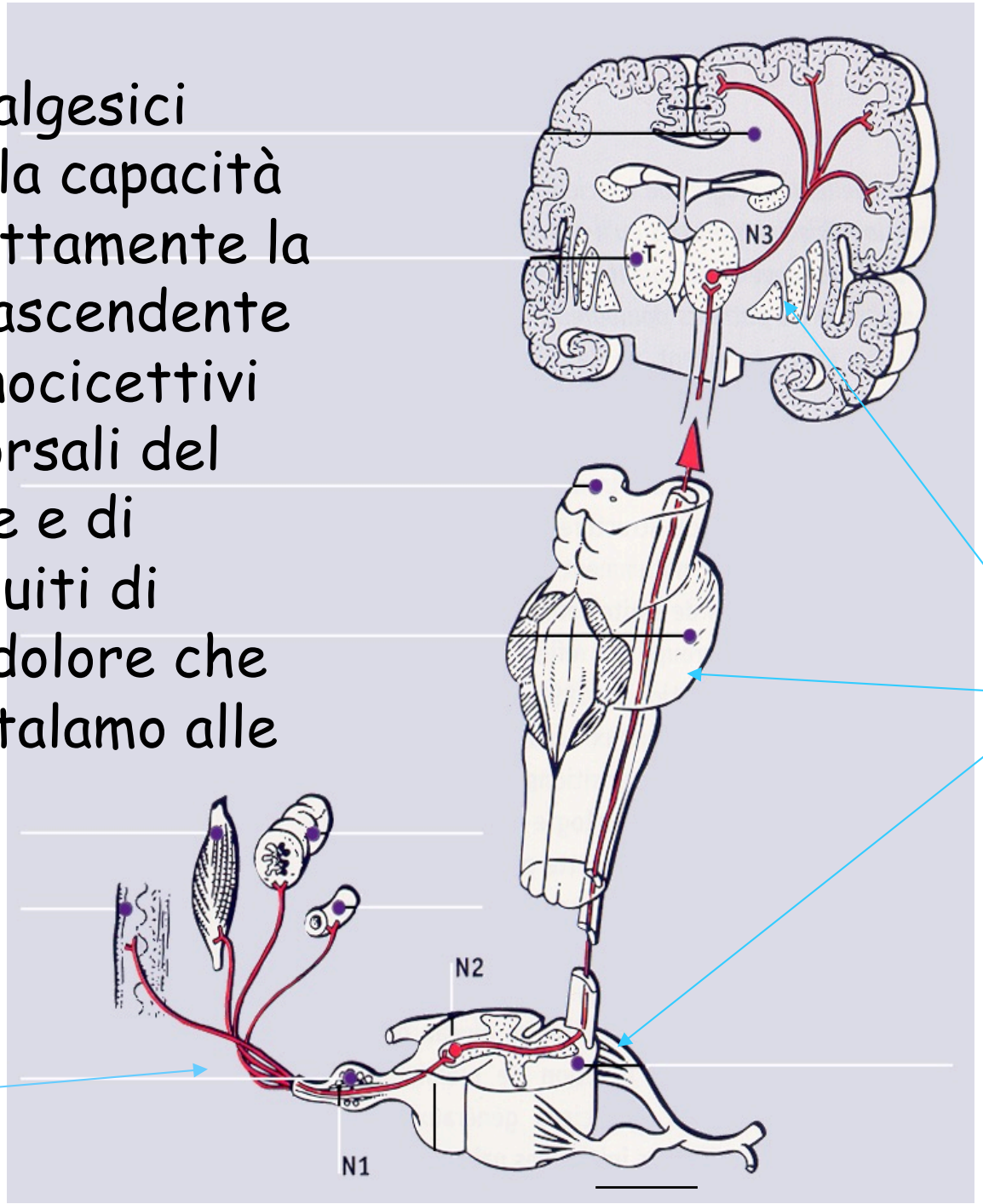
Recettori oppioidi

- Tutti i recettori oppioidi sono accoppiati alle proteine G e inibiscono l'adenilato ciclasi.

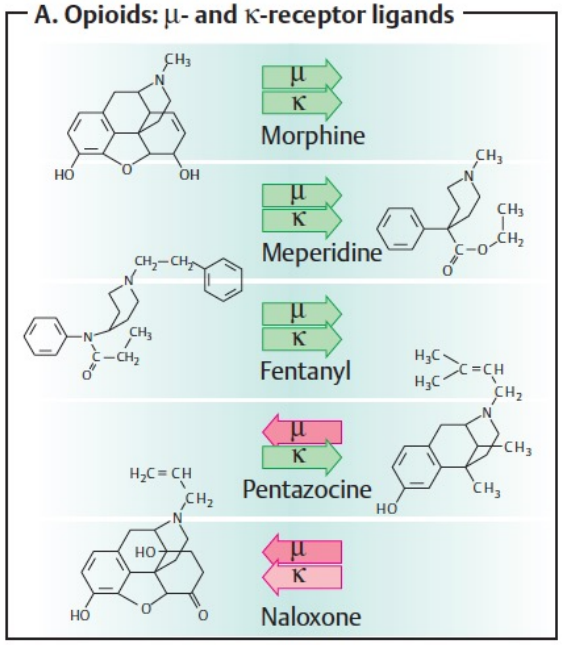


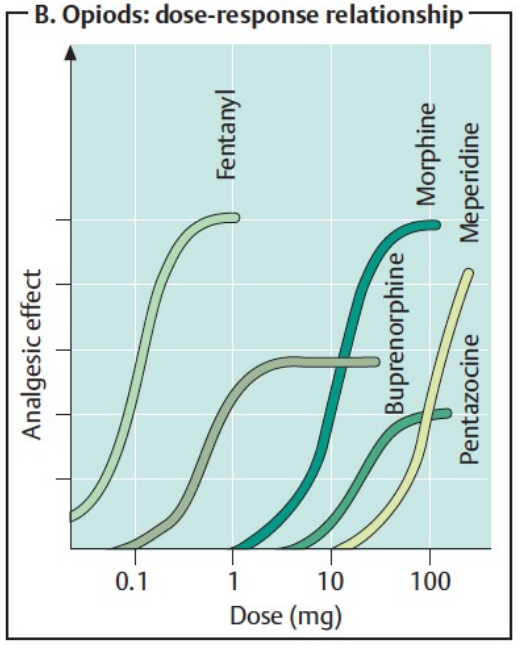


Gli effetti analgesici sono dovuti alla capacità di inibire direttamente la trasmissione ascendente degli impulsi nocicettivi dalle corna dorsali del midollo spinale e di attivare i circuiti di controllo del dolore che scendono dal talamo alle corna dorsali



Agonisti e antagonisti





- **Agonisti puri**: la maggior parte dei morfino-simili. Hanno un'affinità elevata per i recettori μ e affinità variabili per i recettori δ e κ. Alcuni (codeina, destropropossifene) vengono definiti **agonisti deboli**, perchè i loro effetti massimali sono molto inferiori a quelli della morfina e non causano dipendenza.
- **Agonisti parziali**: (nalorfina e pentazocina) sono caratterizzati da un certo grado di attività sia agonista che antagonista, esercitata su recettori differenti
- **Antagonisti**: provocano effetti trascurabili se somministrati da soli, ma bloccano gli effetti di altri oppioidi (naloxone e naltrexone)

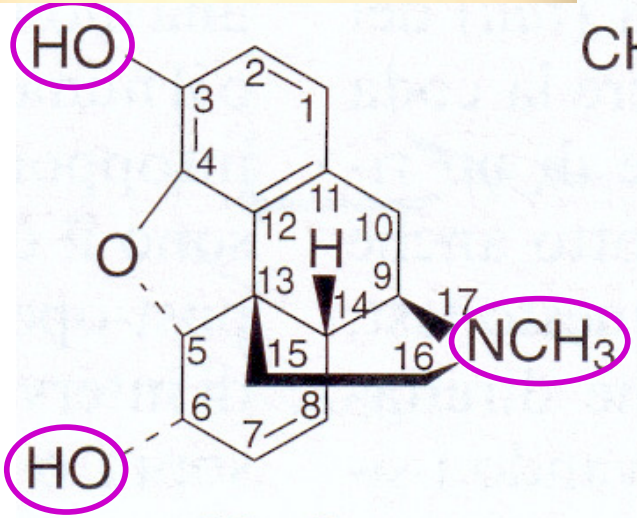
	μ	δ	κ
Peptidi endogeni			
β-endorfina	+++	+++	+++
Leu-encefalina	+	+++	-
Metencefalina	++	+++	-
Dinorfina	+	+	+++
Farmaci oppioidi			
Agonisti puri			
Morfina, codeina	+++	+	+
Metadone	+++	-	-
Fentanil	+++	+	-
Agonisti parziali			
Pentazocina	+	+	++
Nalorfina	++	-	(++)
Buprenorfina	(+++)	-	++
Antagonisti			
Naloxone	+++	+	++
Ligandi per ricerca			

+: attività agonista; (+): agonisti parziali; +: attività antagonista;
-: attività debole o nulla;

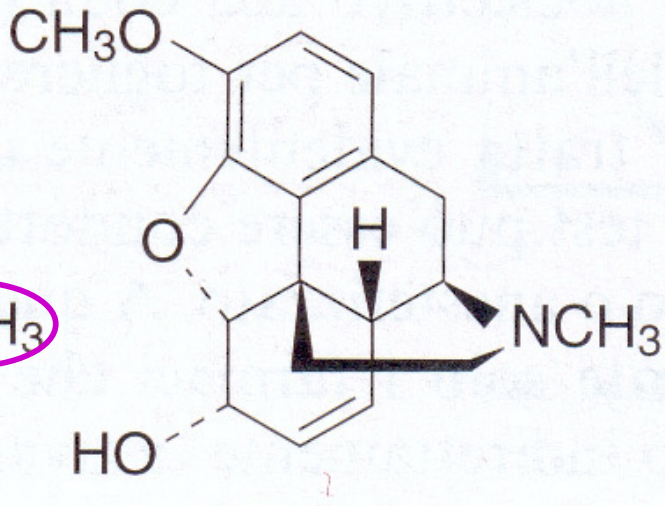
Papavero da oppio
(*Papaver somniferum*)

Alcaloidi:

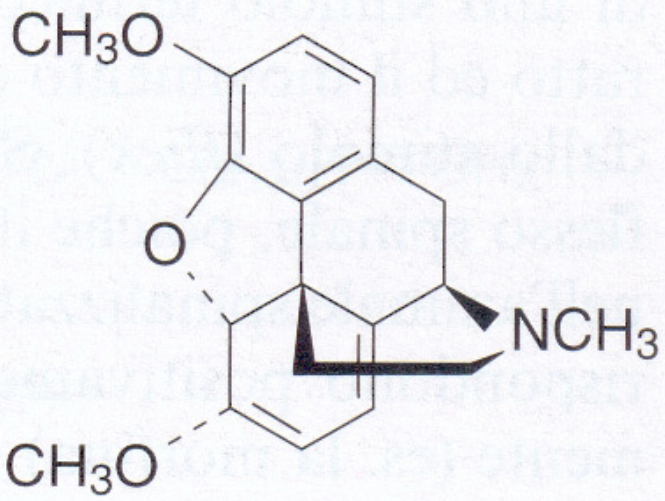
- Benzilisochinoline (papaverina)
- Fenantreni



Morfina (10%)
isolata nel 1803 da Serturner



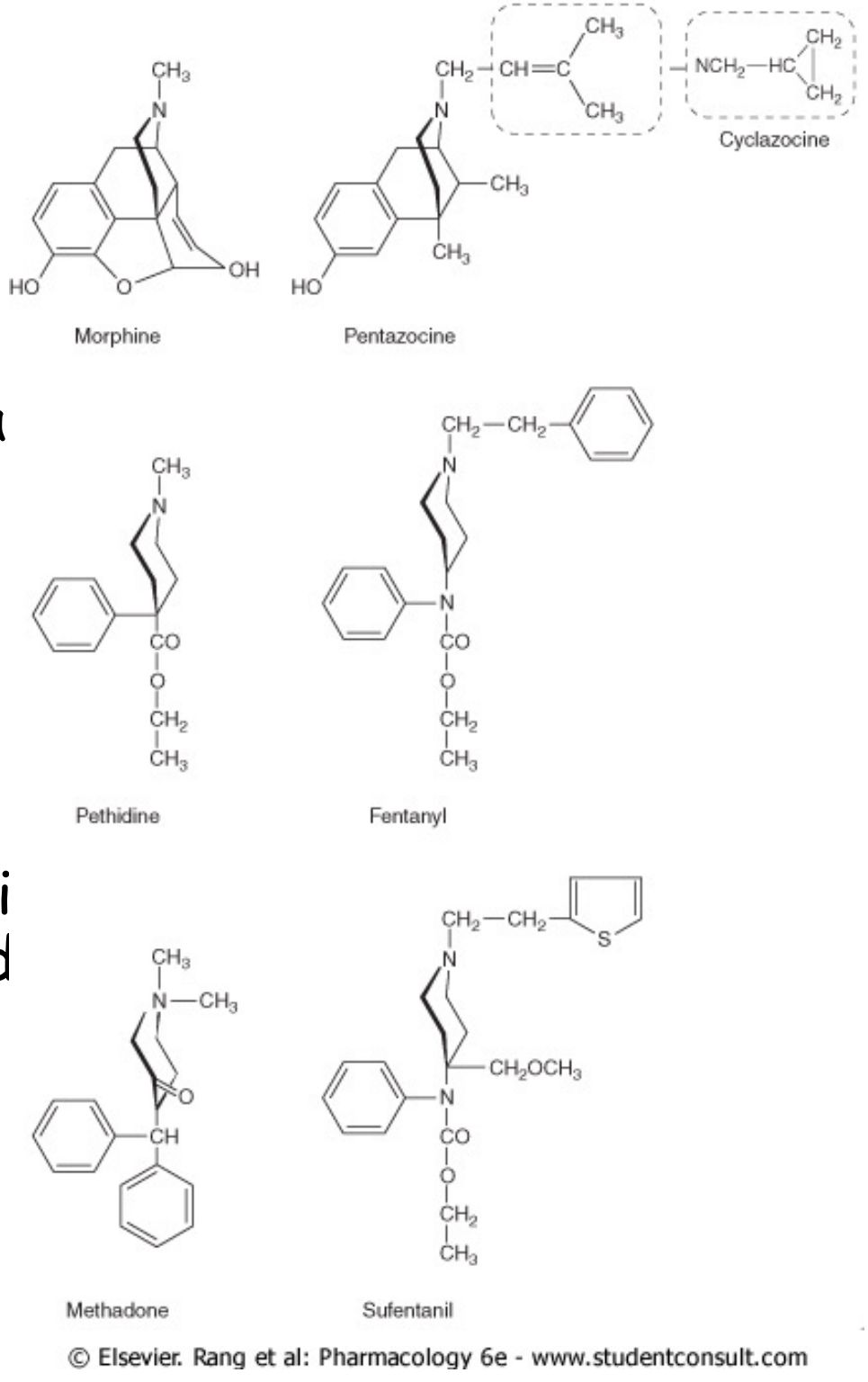
Codeina (0.5%)



Tebaina (0.2%)

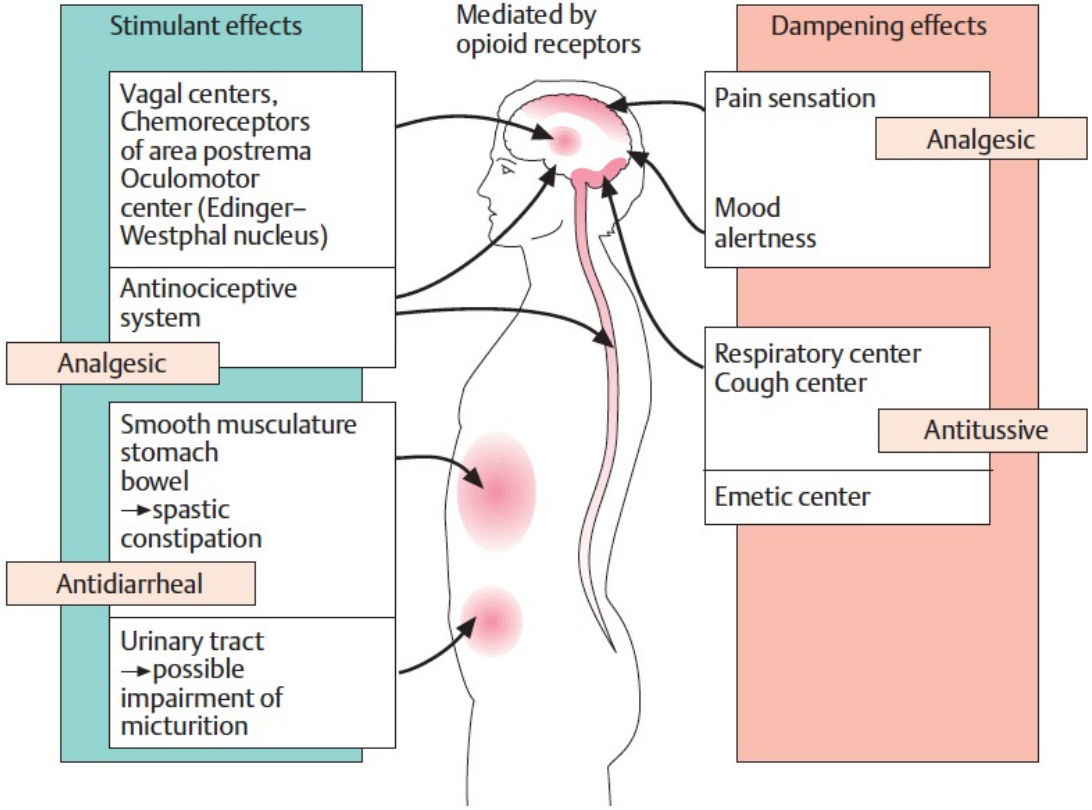
Oppioidi

- derivati fenantrenici, strutturalmente correlati alla morfina. Possono essere agonisti (eroina), agonisti parziali (nalorfina) o antagonisti (naloxone).
- composti sintetici, aventi struttura chimica diversa ma analoghi effetti farmacologici Comprendono le piperidine (ad es. petidina e fentanil), il metadone, i benzomorfani (ad es. pentazocina) e i derivati della tebaina (ad es. buprenorfina).

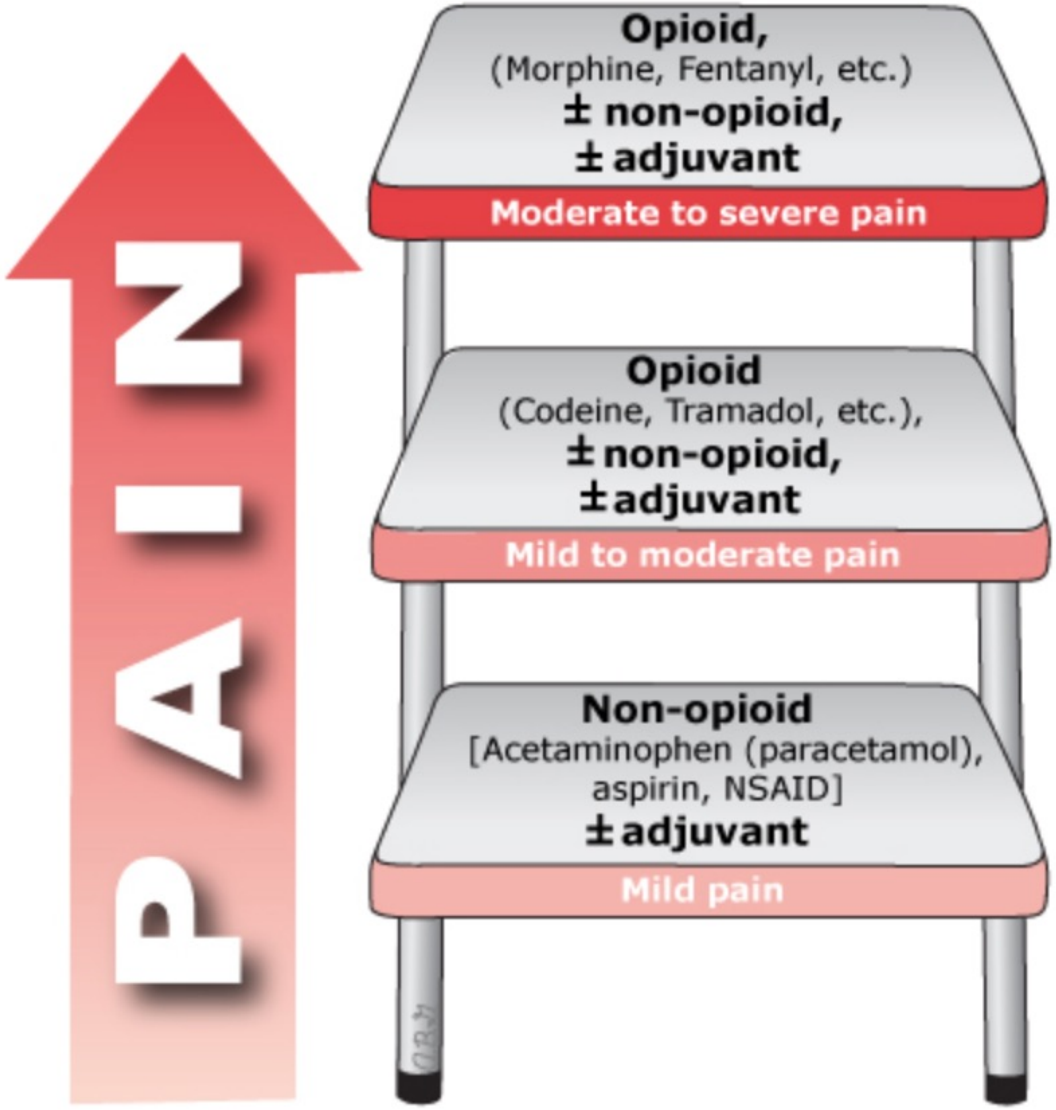


Azioni della morfina

- **Analgesia; riduce anche la componente emotiva del dolore (sistema limbico)**
- si manifesta senza perdita di coscienza. E' attiva soprattutto sul dolore cronico. Abolisce il dolore nocicettivo. Riduce anche il dolore neuropatico derivante da lesione di strutture neurofisiologiche; in questo caso riduce la sensazione del dolore inteso come sofferenza. In tale azione è importante anche l'attività sedativa o euforizzante del farmaco. Ha attività sia spinale che sopraspinale.



World Health Organization (WHO) analgesic ladder



LEGGE 15 marzo 2010, n. 38

Disposizioni per garantire l'accesso alle cure palliative e alla terapia del dolore.

La Camera dei deputati ed il Senato della Repubblica hanno approvato;

IL PRESIDENTE DELLA REPUBBLICA

promulga

la seguente legge:

Pain control—a basic kindness

Annie Cavanagh, Wellcome Images

Morphine crystals

For **information on nurse and pharmacist prescription of analgesics** see http://www.dh.gov.uk/health/2012/04/prescribing-change/

For more on **NICE guidelines on opioid prescription in palliative care** see http://www.nice.org.uk/CG140

When pain is reduced, so too is at least some of the distress associated with serious illness. The correct amount of analgesia given at the right time has a considerable positive effect on the quality of life of a patient in palliative care. Thus the introduction of independent prescribing of opioid analgesia by appropriately qualified nurses and pharmacists in the UK in April, 2012, was a welcome move, as was the publication on May 23 of new guidance on palliative pain management from the UK's National Institute for Health and Clinical Excellence (NICE). *Opioids in Palliative Care* is particularly commendable for its emphasis on the need to communicate the risks and benefits of opioid drugs to patients and their relatives, and for its call for further research into patients' concerns and the best ways of delivering information.

Prescribers, too, need information and reassurance. In launching the guidelines, NICE highlighted evidence suggesting "that pain caused by advanced disease remains under-treated", as well as the "reservations" that some health-care professionals have about giving strong opioids. The reasons why health-care workers are reluctant to prescribe opioids to patients who need them are unclear. It has been suggested that the lethal use of opioids by Harold Shipman might be a factor, as well as the well-publicised role of opioid over-prescription in medical negligence cases. In other words, opioid drugs are suffering from guilt by association. But there is nothing intrinsically wrong with giving opioid drugs: it is all a question of appropriate use.

Health-care workers may also be worried that, even if they prescribe responsibly, opioid painkillers lend themselves to misuse. This is a legitimate concern: but physicians must read the evidence, and apply it humanely for the individual patient's benefit. Prescription drug misuse should be prevented, but the comfort of seriously ill patients cannot be sacrificed for fear of it. Though some patients may be beyond hope of cure, they are not beyond care. Opioid prescription in such cases is not just medical treatment: it is basic human kindness. ■ *The Lancet* 2 giugno 2012

Azioni della morfina

- Euforia e sensazione di benessere
- Sedazione (sonnolenza e obnubilamento mentale più frequente nell'anziano)
- Depressione respiratoria (ridotta sensibilità alla CO_2)
- Soppressione del riflesso della tosse
- Nausea e vomito
- Costrizione pupillare
- Riduzione della motilità gastrointestinale (stipsi) metilnartrexone; loperamide (imodium)
- Contrazione dello sfintere di Oddi
- Liberazione di istamina (prurito e orticaria)
- Effetto immunosoppressore

Tolleranza

- La tolleranza si sviluppa rapidamente (ma clinicamente dopo 2 – 3 settimane); riguarda tutte le azioni della morfina con l'eccezione della stipsi e della miosi.
- Tolleranza crociata spesso parziale o incompleta (rotazione dell'oppioide)
- I meccanismi biochimici non sono chiari, ma potrebbero implicare alterazioni di tipo adattativo a carico dell'adenilato ciclasi.
- La tolleranza non è di origine farmacocinetica.

Dipendenza

- La dipendenza è causata dagli agonisti dei recettori μ, e la sindrome da astinenza viene precipitata dagli antagonisti di questi recettori.
  - Dipendenza fisica, sindrome d'astinenza
  - Dipendenza psichica, associata al craving; ramente si manifesta in pazienti che assumono gli oppioidi come analgesici.
- Gli agonisti dei recettori μ a lunga durata d'azione, come il metadone, possono essere utilizzati per alleviare i sintomi dell'astinenza.

Dipendenza fisica

E' una condizione che si sviluppa conseguentemente all'adattamento prodotto da un riequilibrio di meccanismi omeostatici in risposta all'uso ripetuto di farmaci.

Qualora la somministrazione del farmaco venga interrotta repentinamente si manifesta un nuovo sbilanciamento e i sistemi interessati devono nuovamente passare attraverso un processo di riadattamento e riequilibrio.

La comparsa di una sindrome di astinenza quando il farmaco viene sospeso repentinamente, è l'unica reale evidenza di dipendenza fisica.

I pazienti che assumono farmaci per le corrette indicazioni terapeutiche e a dosi appropriate possono anch'essi mostrare segni di tolleranza, dipendenza fisica e sindrome di astinenza nel caso che l'assunzione del farmaco venga interrotta repentinamente e non gradualmente.
Ciò non significa che siano tossico dipendenti; questi ultimi utilizzano le sostanze in senso d'abuso, a scopo non terapeutico e vanno incontro anche ad astinenza di tipo psichico.

Sindrome d'astinenza da oppioidi

Sintomi:

- Craving
- Irriquietezza, instabilità
- Aumentata sensibilità al dolore
- Nausea e crampi
- Dolori muscolari
- Umore disforico
- Insonnia
- Ansia

Segni:

- Dilatazione pupillare
- Sudorazione
- Piloerezione
- Tachicardia
- Vomito e diarrea
- Ipertensione arteriosa
- Sbadigli
- Febbre

Intossicazione acuta da oppioidi

- I pazienti che hanno assunto una dose troppo elevata di oppioidi, entrano in uno stato di stupore
- Se la dose è ancora più elevata si va incontro al coma
- La frequenza respiratoria diminuisce e può comparire cianosi
- La pressione arteriosa cala
- Le pupille divengono intensamente miotiche
- Compare midriasi quando vi è un intenso stato di ipossia
- Si riduce la formazione delle urine
- La temperatura corporea cala, la cute diventa umida e fredda
- La muscolatura scheletrica si rilassa
- Compaiono i segni dello shock
- La morte può avvenire per insufficienza respiratoria
- Anche quando vi è una ripresa della respirazione vi può essere morte del paziente dovuta alle complicazioni irreversibili venutesi a creare.

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Farmacovigilanza, Aifa: no all'utilizzo di oppioidi per dolore lieve

TAGS: ANALGESICI OPPIOIDI, OPPIO, AIFA , OPPIOIDI, INDICAZIONI

ARTICOLI CORRELATI

18-06-2020 I Oppioidi, Aifa: nuove avvertenze su etichette. Possono dare dipendenza

27-02-2020 I Farmaci oppioidi, raddoppiato l'uso in un quarto di secolo. Lo studio

26-02-2020 I Oppioidi, l'allarme Ame: in aumento la dipendenza. Rischio malattie endocrine

No all'utilizzo di **farmaci oppioidi** per dolore lieve e no a un uso oltre i 30 giorni per quelli a base di tramadolo. A precisarlo è l'Agenzia italiana del farmaco (Aifa) che, con una nota sul portale, precisa di voler "veicolare un messaggio corretto che richiami le indicazioni appropriate senza rischiare di penalizzare l'utilizzo degli oppioidi nella terapia del dolore".

Coinvolti da uno scandalo di sovraprescrizione negli Stati Uniti, gli oppioidi sono potenti antidolorifici ma possono dare dipendenza e effetti collaterali come sonnolenza e confusione mentale. L'Aifa richiama pertanto "l'attenzione degli operatori sanitari sulle indicazioni terapeutiche autorizzate dei medicinali oppioidi, con particolare riferimento a quelli contenenti fentanile e tramadolo, sottolineando che esse non comprendono il dolore di lieve entità". A seguito di una recente disposizione, inoltre, ricorda Aifa, "è stata introdotta la limitazione della durata massima di terapia a 30 giorni per medicinali contenenti il principio attivo tramadolo da solo e/o in associazione". Pochi giorni fa l'Aifa aveva inviato anche una comunicazione alle aziende titolari di Autorizzazione all'immissione in commercio (Aic) di oppioidi, indicando che quelli vendibili al pubblico devono contenere in etichetta informazioni precise "in considerazione del fatto che alcuni pazienti potrebbero non essere consapevoli del contenuto del medicinale, soprattutto se esso ha un nome di fantasia". Pertanto, le confezioni dovranno prevedere, in modo ben visibile, un rettangolo contenente l'avvertenza "contiene oppioide, può dare dipendenza".

Oppioidi in odontoiatria

Uso ospedaliero

Fentanil

- Oppioide sintetico molto liposolubile
- Rapida insorgenza e breve durata d'azione
- 50-100 volte più potente della morfina
- Non rilascia istamina, meno effetti cardiovascolari della morfina
- Analgesia e depressione respiratoria dose-dipendente
- Peri indurre sedazione cosciente in interventi di estrazione chirurgica del terzo molare

Tramadolo e codeina nel secondo gradino della scala del dolore:
per alleviare il dolore dopo estrazione di 2 o più terzi molari o interventi di chirurgia dento alveolare.
in associazione con FANS

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies

Nora D. Volkow, M.D., and A. Thomas McLellan, Ph.D.

CHRONIC PAIN NOT CAUSED BY CANCER IS AMONG THE MOST PREVALENT and debilitating medical conditions but also among the most controversial and complex to manage. The urgency of patients' needs, the demonstrated effectiveness of opioid analgesics for the management of acute pain, and the limited therapeutic alternatives for chronic pain have combined to produce an overreliance on opioid medications in the United States, with associated alarming increases in diversion, overdose, and addiction. Given the lack of clinical consensus and research-supported guidance, physicians understandably have questions about whether, when, and how to prescribe opioid analgesics for chronic pain without increasing public health risks. Here, we draw on recent research to address common misconceptions regarding the abuse-related risks of opioid analgesics and highlight strategies to minimize those risks.

From the National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD (N.D.V.); and the Treatment Research Institute, Philadelphia (A.T.M.). Address reprint requests to Dr. Volkow at the National Institute on Drug Abuse, National Institutes of Health, 6001 Executive Blvd., Bethesda, MD 20892, or at nvolkow@nida.nih.gov.

N Engl J Med 2016;374:1253-63.
DOI: 10.1056/NEJMra1507771

SOURCE OF THE OPIOID EPIDEMIC

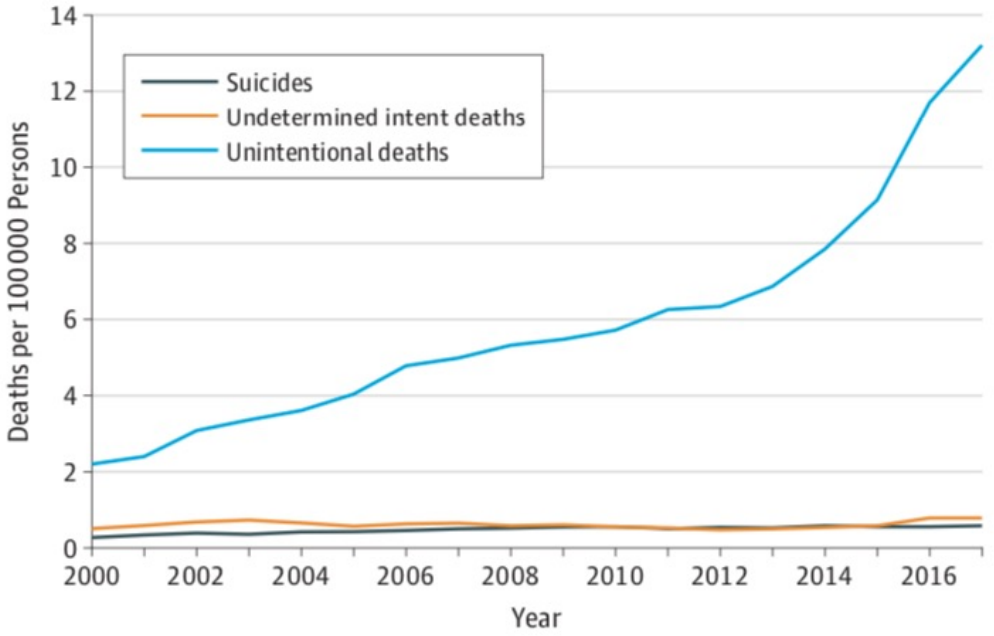
More than 30% of Americans have some form of acute or chronic pain.[1,2] Among older adults, the prevalence of chronic pain is more than 40%.[2] Given the prevalence of chronic pain and its often disabling effects, it is not surprising that opioid analgesics are now the most commonly prescribed class of medications in the United States.[3] In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers.[4,5] Of these prescriptions, 65% were for short-term therapy (<3 weeks),[6] but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy.[7] Although opioid analgesics rapidly relieve many types of acute pain and improve function, the benefits of opioids when prescribed for chronic pain are much more questionable.[8]

However, two major facts can no longer be questioned. First, opioid analgesics are widely diverted and improperly used, and the widespread use of the drugs has resulted in a national epidemic of opioid overdose deaths and addictions. More than a third (37%) of the 44,000 drug-overdose deaths that were reported in 2013 (the most recent year for which estimates are available) were attributable to pharmaceutical opioids; heroin accounted for an additional 19%. At the same time, there has been a parallel increase in the rate of opioid addiction, affecting approximately 2.5 million adults in 2014.[9] Second, the major source of diverted opioids is physician prescriptions.[10,11] For these reasons, physicians and medical associations have begun questioning prescribing practices for opioids, particularly as they relate to the management of chronic pain. Moreover, many physicians admit that they are not confident about how to prescribe opioids safely,[12] how to detect abuse or emerging addiction, or even how to discuss these issues with their patients.[13]

This review is not intended as clinical instruction in chronic pain management;

Negli USA 49,860 morti da overdose nel 2019 (70.6% di tutte le morti da overdose da farmaci).

Figure. Trends in Drug Overdose Deaths Involving Opioids in the United States per 100 000 Persons by Intent, 2000-2017



Data are from the National Center for Health Statistics National Vital Statistics System and exclude assaultive overdose deaths. The linear trend is 9.19 for unintentional deaths ($P < .001$), 0.30 for suicide ($P < .001$), and 0.02 for undetermined intent deaths ($P = .64$).

Table 3. Factors Associated with the Risk of Opioid Overdose or Addiction.

Factor	Risk
Medication-related	
Daily dose >100 MME*	Overdose,[8] addiction[8]
Long-acting or extended-release formulation (e.g., methadone, fentanyl patch)	Overdose[14,41]
Combination of opioids with benzodiazepines	Overdose[42]
Long-term opioid use (>3 mo)†	Overdose,[43] addiction[44]
Period shortly after initiation of long-acting or extended-release formulation (<2 wk)	Overdose[45]
Patient-related	
Age >65 yr	Overdose[46]
Sleep-disordered breathing‡	Overdose[47]
Renal or hepatic impairment§	Overdose[48]
Depression	Overdose, addiction[49]
Substance-use disorder (including alcohol)	Overdose,[50] addiction[49]
History of overdose	Overdose[51]
Adolescence	Addiction[52]

* The risk of opioid overdose increases in a dose–response manner at opioid doses of more than 20 morphine milligram equivalents (MME).
† Although addiction is associated with long-term but not short-term opioid use, the prescription of a higher quantity of opioids than is needed for acute pain contributes substantially to the availability of opioids for diversion and abuse.
‡ Sleep-disordered breathing refers to conditions that manifest as abnormal breathing patterns during sleep and includes obstructive sleep apnea and central sleep apnea.[53]
§ Patients with these disorders are at increased risk because the disposition of various opioid drugs is affected by hepatic and renal impairments, which reduce drug clearance and increase bioavailability.[54-56]

Summary of CDC Recommendations for Prescribing Opioids for Chronic Pain

Determining When to Initiate or Continue Opioids for Chronic Pain
• Nonpharmacological therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, combine them with nonpharmacological therapy and nonopioid pharmacotherapy, as appropriate. • Before starting opioid therapy for chronic pain, establish treatment goals with the patient, including realistic goals for pain and function. Consider how therapy will be discontinued if benefits do not outweigh risks. Continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety. • Before starting and periodically during opioid therapy, discuss with patient the known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Summary of CDC Recommendations for Prescribing Opioids for Chronic Pain

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation
• When starting opioid therapy for chronic pain, prescribe immediate-release opioids instead of ER/LA opioids. • When opioids are started, prescribe the lowest effective dosage. Use caution when prescribing opioids at any dosage. Reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 MME/d. Avoid increasing dosage to ≥ 90 MME/d or carefully justify a decision to exceed this limit. • Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, prescribe the lowest effective dose of immediate-release opioids and in no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed. • Reevaluate benefits and harms of opioids with the patient within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation and thereafter every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, optimize other therapies and work with the patient to taper opioids to lower dosages or to taper and discontinue opioids.

Summary of CDC Recommendations for Prescribing Opioids for Chronic Pain

Assessing Risk and Addressing Harms of Opioid Use
• Incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/d), or concurrent benzodiazepine use are present. • Review the patient's history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving opioid dosages or dangerous combinations that carry high risk for overdose. Review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months. • When prescribing opioids for chronic pain, use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications and other controlled prescription drugs and illicit drugs. • Avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. • Offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for a patient with opioid use disorder.

VIEWPOINT

Continued Increases in Overdose Deaths Related to Synthetic Opioids

Implications for Clinical Practice

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Viewpoint

The current overdose epidemic in the US that began in the late 1990s continues unabated. Since 2013, deaths involving synthetic opioids surged substantially, largely due to the rapid proliferation of illicitly manufactured fentanyl and fentanyl analogs (eg, acetylfentanyl, carfentanil).[1,2] More recently, overdose deaths involving stimulants, such as methamphetamine and cocaine, have increased with and without opioid co-involvement.[3,4] As illicitly manufactured fentanyl became more ubiquitous, drug overdose death rates increased in all age groups, among both sexes, across most races and ethnicities, within all urbanization levels, and in the majority of US states.[1]

Importantly, the increases in overdose deaths are occurring against a backdrop of overall stable or declining rates of illicit drug use other than cannabis, underscoring that the illicit drug supply is a key driver of the current overdose crisis.[5] Illicitly manufactured fentanyl, which is easier and less costly to make, distribute, and sell, is observed in a steadily increasing percentage of overdose deaths and has displaced heroin in the illicit drug market in some communities.[5] The increasing availability, geographic dispersion, mixing or co-use of illicitly manufactured fentanyl with other drugs, and presence of illicitly manufactured fentanyl in counterfeit prescription pills resembling commonly misused prescription drugs underscores the urgency to evolve the approach to prevention.[6]

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A report released by the Centers for Disease Control and Prevention (CDC) on February 11, 2021, highlights the scope of the problem.[7] In 2019, 70 630 drug overdose deaths occurred in the US (21.6 per 100 000 persons), representing a 4.3% increase over the 2018 rate.[7] Among all these deaths, approximately 71% involved opioids and 52% specifically involved synthetic opioids excluding methadone.[7] No state had a significant decrease in synthetic opioid death rate between 2018 and 2019, and the West census region experienced the largest relative (68%) and absolute (1.9 per 100 000) increase.[7] Nine states (Connecticut, Delaware, Massachusetts, Maryland, Maine, New Hampshire, New Jersey, Ohio, and Vermont) reported that more than 70% of all their overdose deaths involved synthetic opioids in 2019.[7]

From 2018 to 2019, the death rate involving any psychostimulant with abuse potential (eg, methamphetamine), increased 28%, from 3.9 to 5.0 per 100 000, and 24 states had statistically significant increases in rates.[7] Between 2013 and 2019, the overdose death rates for synthetic opioid co-involvement increased for prescription opioids (from 0.3 to 1.8 per 100 000), heroin (from 0.1 to 2.7 per 100 000), cocaine (from 0.1 to 3.2 per 100 000), and psychostimulants with abuse potential (from 0.1 to 1.8 per 100 000).[7] The increase in synthetic opioid–involved deaths in the western states (eg, Colorado, California, Washington) and in psychostimulant-involved deaths in the northeastern states (eg, Maine, New Jersey, New York) indicates new geographic spread of these substances.[7]

The risk of overdose is elevated with any use of illicitly manufactured fentanyl, given its potency, lethality, and the variability in the illicit supply, but risk is particularly high among persons who are opioid naive or whose tolerance to opioids has decreased following periods of abstinence.[5] The coronavirus disease 2019 pandemic has exacerbated the overdose crisis as individuals struggled to maintain access to essential harm reduction, treatment, and recovery support services, initiated or increased substance use to cope with the stressors and social isolation created, and likely used illicit drugs while alone more frequently.[6] These changing dynamics demand innovative clinical, health system, and community solutions.

Clinicians can increase screening for substance use disorder using validated instruments, initiate counseling for patients after a positive urine drug screen or drug-related clinical visit, and expand overdose prevention education among their patients. They also could prescribe naloxone to persons who use drugs, including those who are not knowingly using opioids, their friends, and others likely to witness, experience, or respond to an overdose.[6] Health systems and community partners could expand locations where these services are offered and co-locate services whenever possible, including via primary care settings, retail pharmacies, support groups, outpatient substance use disorder treatment programs, syringe services programs, and mobile outreach.[6] This diversification of prevention strategies is especially important for rural areas.[6]

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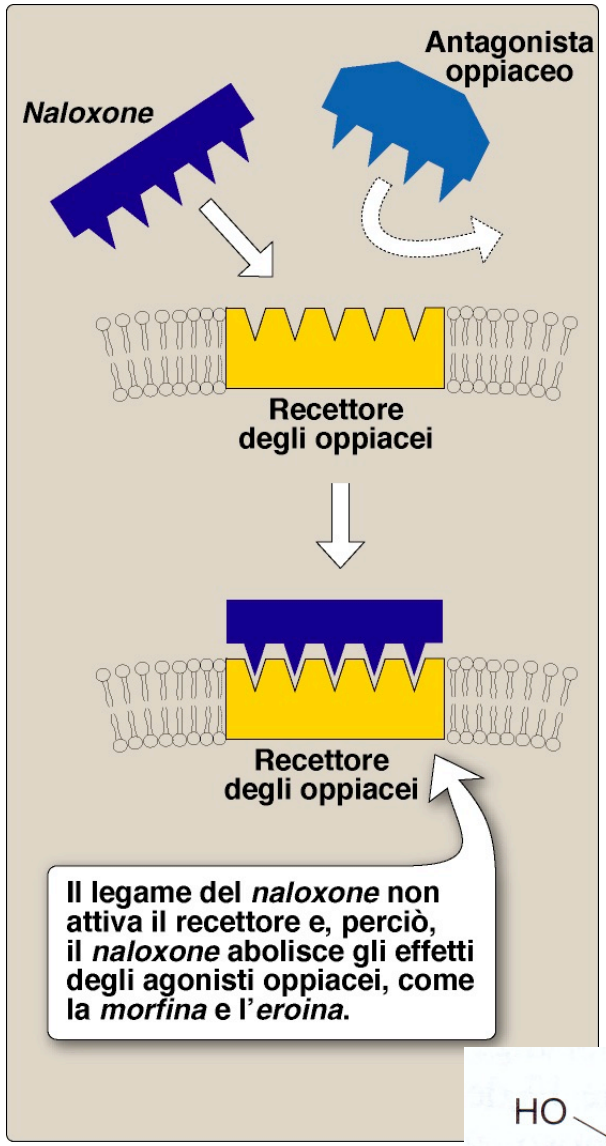
Antagonisti degli oppioidi: naloxone



- Il naloxone non attiva il recettore e perciò abolisce gli effetti degli agonisti come la morfina e l'eroina
- Nella depressione respiratoria da oppioidi (0,1 – 0,4 mg e.v., ripetuto se necessario, ha un'emivita breve)