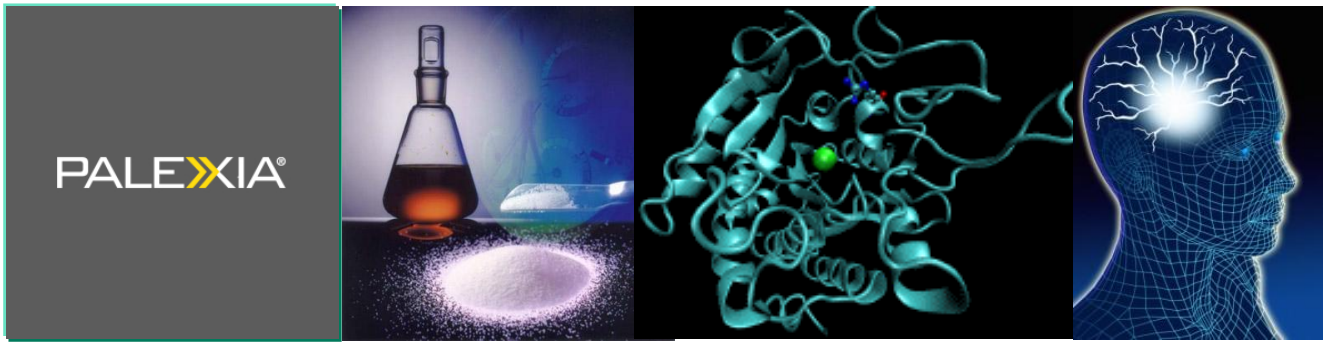
Rio de Janeiro, January 27th, 2015



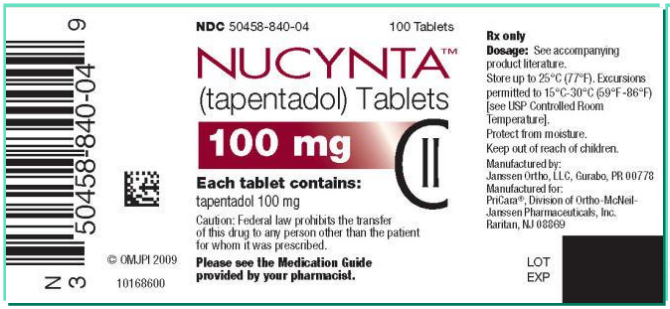
Pain Research Today: from Morphine to Tapentadol

&

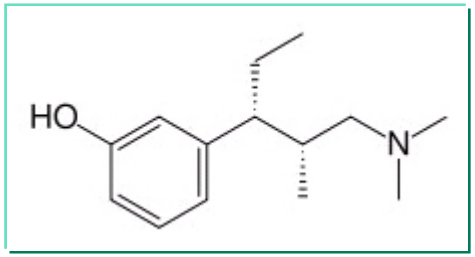
Some Refelections on the Pharmaceutical Industry

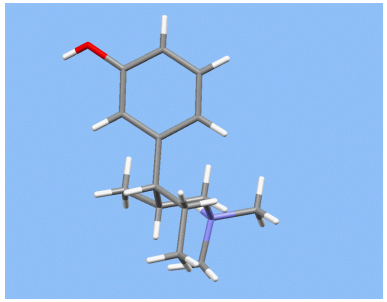
Helmut Buschmann
RD&C

PALEXIA®
TAPENTADOL



PALEXIA®

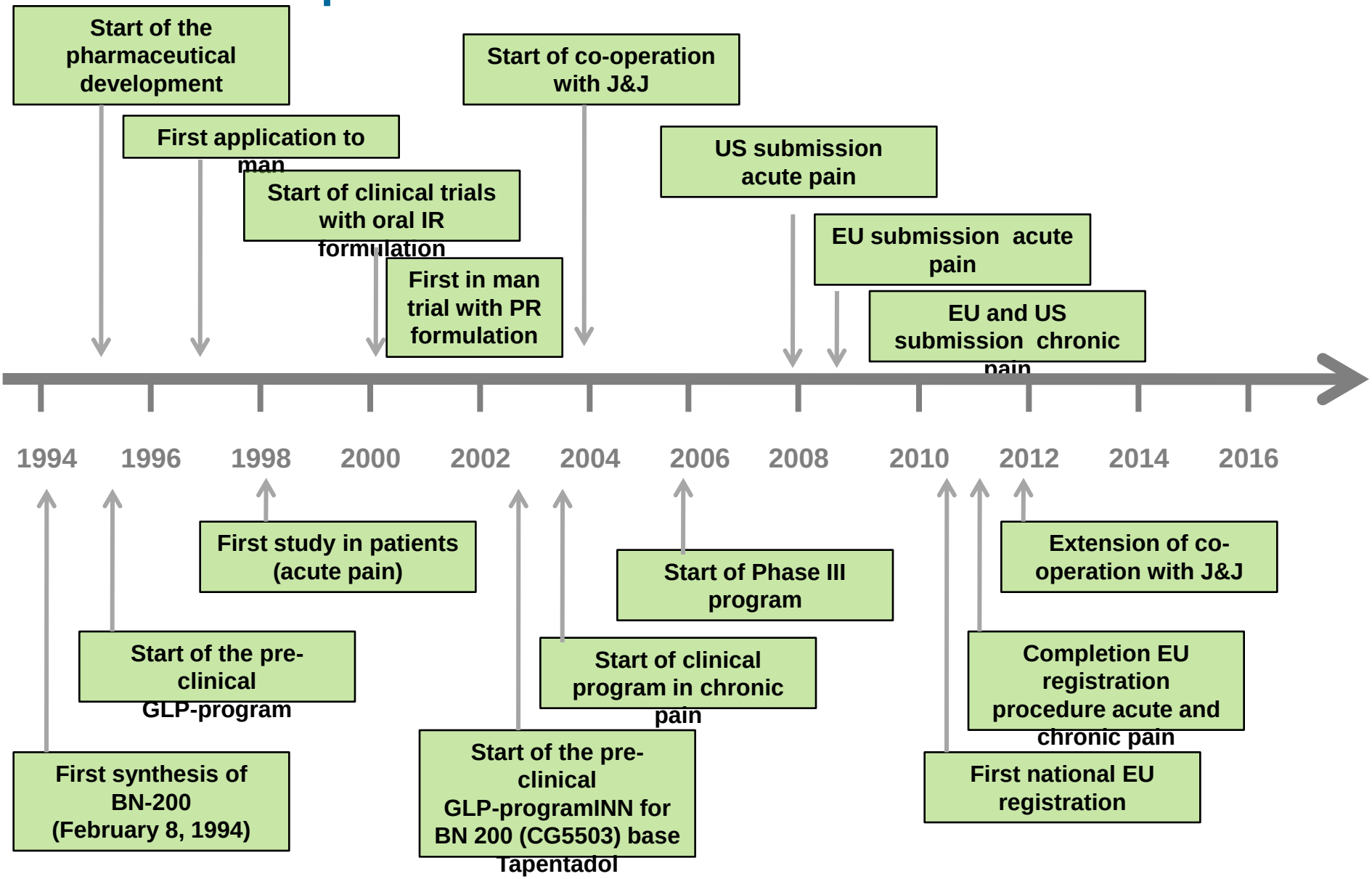




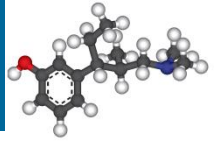
How it all started

In the mid-1990s, Grünenthal scientists in Aachen were asked to develop novel centrally acting analgesics.
February 8th 1994 was the birthday of PALEXIA®: for the first time, chemist Helmut Buschmann and his coworkers succeeded in synthesizing a few gram of a new active substance. At that time PALEXIA® was a drug candidate named by his inventor “BN200”.

Tapentadol – The Path To The Market



Tapentadol



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 0 693 475 B1**

(12) **EUROPÄISCHE PATENTSCHRIFT**

(45) Veröffentlichungstag und Bekanntmachung des Hinweises auf die Patenterteilung:
11.02.1998 Patentblatt 1998/07

(21) Anmeldenummer: **95110864.6**

(22) Anmeldetag: **12.07.1995**

(51) Int Cl.[6]: **C07C 217/72**, C07C 215/54, C07C 215/62, C07C 215/30, C07C 217/74, C07C 219/22, C07C 271/58, C07C 323/32, C07D 319/18, C07D 307/79, A61K 31/135

(54) **1-Phenyl-3-dimethylamino-propanverbindungen mit pharmakologischer Wirkung**

1-Phenyl-3-dimethylamino-propane derivatives having pharmacological activity

Dérivés propane 1-phényl-3-diméthylamino à activité pharmocologique

(84) Benannte Vertragsstaaten:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
Benannte Erstreckungsstaaten:
LT LV SI

(30) Priorität: **23.07.1994 DE 4426245**

(43) Veröffentlichungstag der Anmeldung:
24.01.1996 Patentblatt 1996/04

(73) Patentinhaber: **Grünenthal GmbH**
D-52078 Aachen (DE)

(72) Erfinder:
- **Buschmann, Helmut, Dr.**
  D-52066 Aachen (DE)
- **Strassburger, Wolfgang, Prof. Dr.**
  D-52146 Würselen (DE)
- **Friderichs, Elmar, Dr.**
  D-52223 Stolberg (DE)

(56) Entgegenhaltungen:
EP-A- 0 176 049 **DD-A- 124 521**

- **CHEMICAL ABSTRACTS, vol. 54, no. 20, 25.Oktober 1960 Columbus, Ohio, US; abstract no. 20963c, I.N. NAZAROV ET AL. 'Synthetic analgesic substances.' Seite 20963; Spalte 1;**
- **JOURNAL OF PHARMACEUTICAL SCIENCES, Bd. 57, Nr. 9, September 1968 Seiten 1487-1493, N.D. POTTI ET AL. 'Use of 3-Azabicyclo(3.2.1)octane in the Mannich Reaction'**
- **JOURNAL OF PHAMACEUTICAL SCIENCES, Bd. 59, Nr. 7, Juli 1970 Seiten 1038-1041, PYARE PARIMOO ET AL. 'New Compounds: Some potential chemotherapeutic agents derived from aralkyl ketones'**

Bemerkungen:

Die Akte enthält technische Angaben, die nach dem Eingang der Anmeldung eingereicht wurden und die nicht in dieser Patentschrift enthalten sind.

Pain Research Today: from Morphine to Tapentadol

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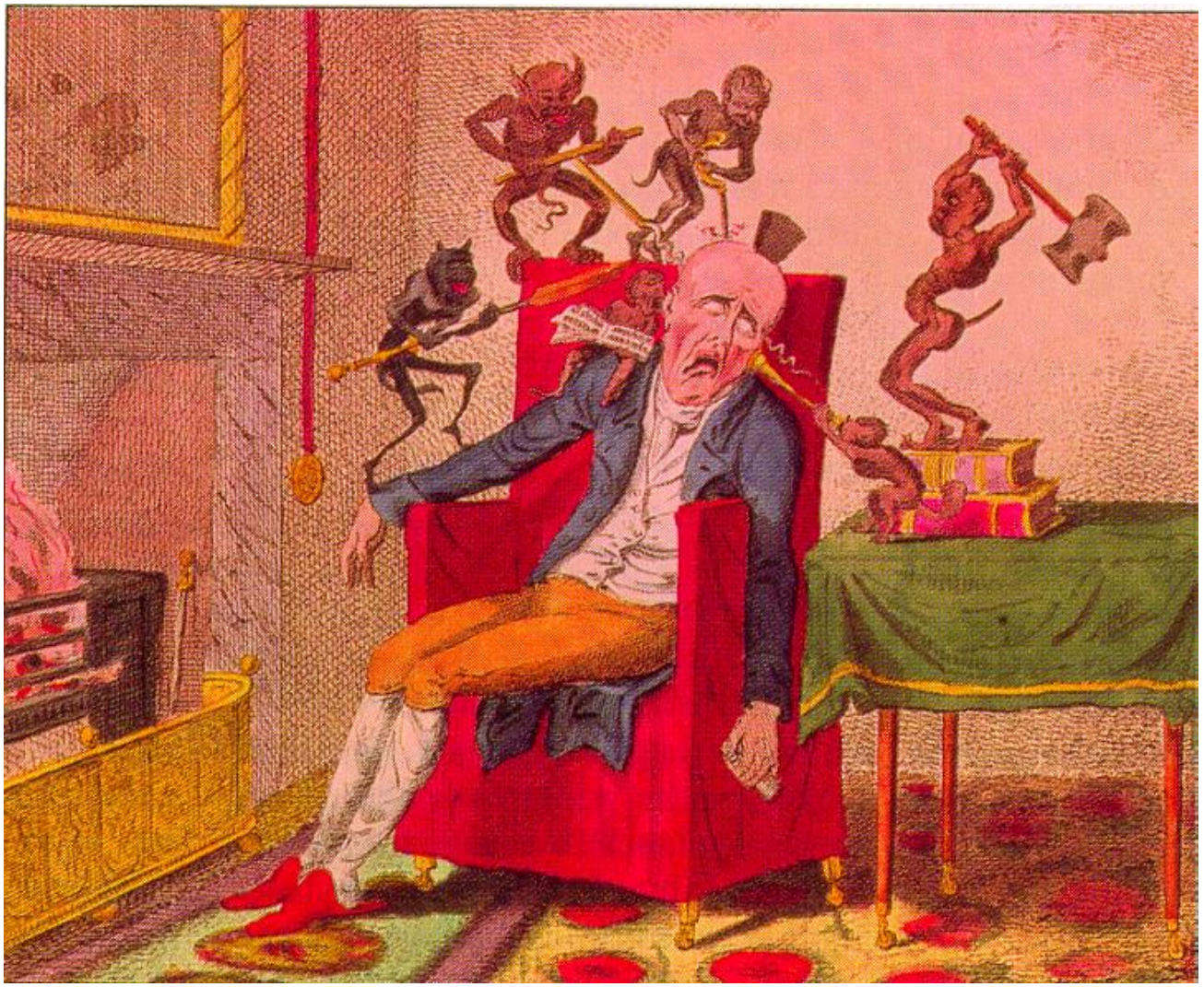
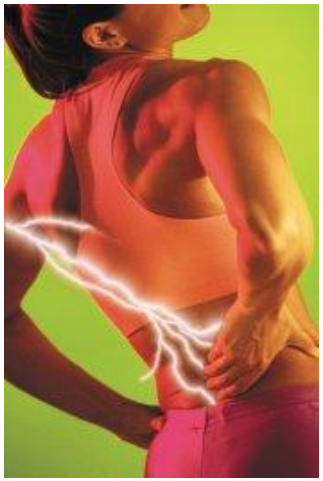
  - **Clinical Development**

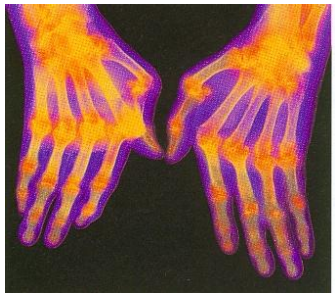
Pain



Le Mal de Tete

Facts About Pain and Pain Treatment



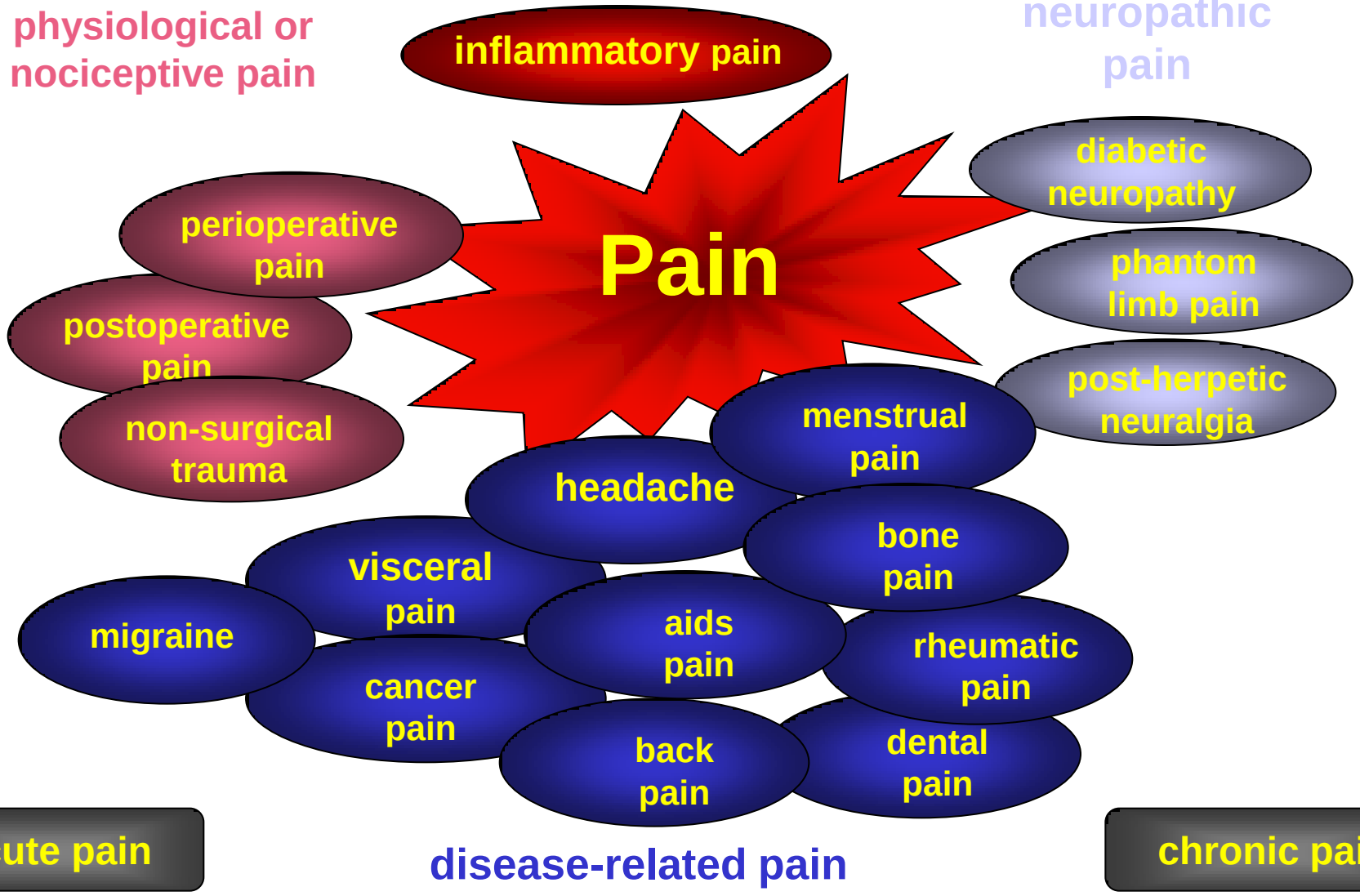


Facts about Pain

- Pain is a highly complex, heterogeneous and dynamic process that involves multiple interrelated neurotransmitter and neuromodulator systems in the spinal cord, ascending and descending spinal pathways and supraspinal sites
- **It is experienced as an unpleasant sensory and emotional experience associated with potential or real tissue damage.**
- It constitutes the body's mechanism of self-preservation; it serves as a warning to indicate harm or impending danger to body tissues and the need to avoid injury and/or take care of oneself.
- Pain has both sensory and emotional aspects, and emerges when there is a discrepancy between what an individual expects of himself and what he really is or does
- According to the International Association for the Study of Pain's Taxonomy Task Force, pain is a subjective experience that is learned by the individual through experiences relating to injuries in early life

Pain Transduction

Overview of the Different Types of Pain



Pain Transduction

Focus on Neuropathic Pain

Neuropathic pain encompasses a wide range of pain syndromes

NEUROPATHIC PAIN
Initiated or caused by a lesion or dysfunction in the nervous system (PNS or CNS)

MIXED PAIN
Pain with neuropathic and nociceptive components

NOCICEPTIVE PAIN
Pain caused by injury to body tissues

- Diabetic neuropathy
- Chemotherapy-induced neuropathic pain
- Posttraumatic neuropathy
- Trigeminal neuralgia
- Postherpetic neuralgia
- Low back pain (radiculopathy)
- CRPS
- Cancer neuropathy
- Cervical radiculopathy
- Postsurgical neuropathy
- Phantom limb pain
- Carpal tunnel syndrome
- Central post-stroke pain
- HIV neuropathy
- MS pain
- …

UNMET NEED FOR TREATMENT

Signs and symptoms:

➢Allodynia

Pain from an innocuous stimulus* that normally does not evoke pain

➢Hyperalgesia

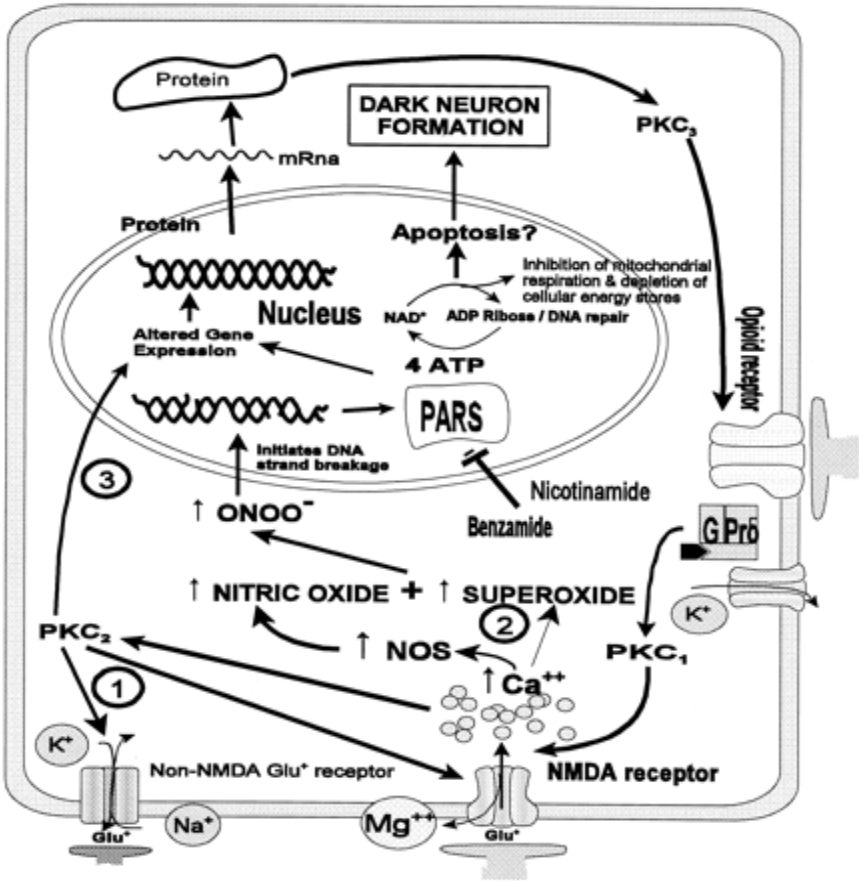
Exaggerated response to a normally painful stimulus*

* The stimulus may be mechanical or thermal

Pain Transduction

The Evolution in Pain Research

Descartes (1644)



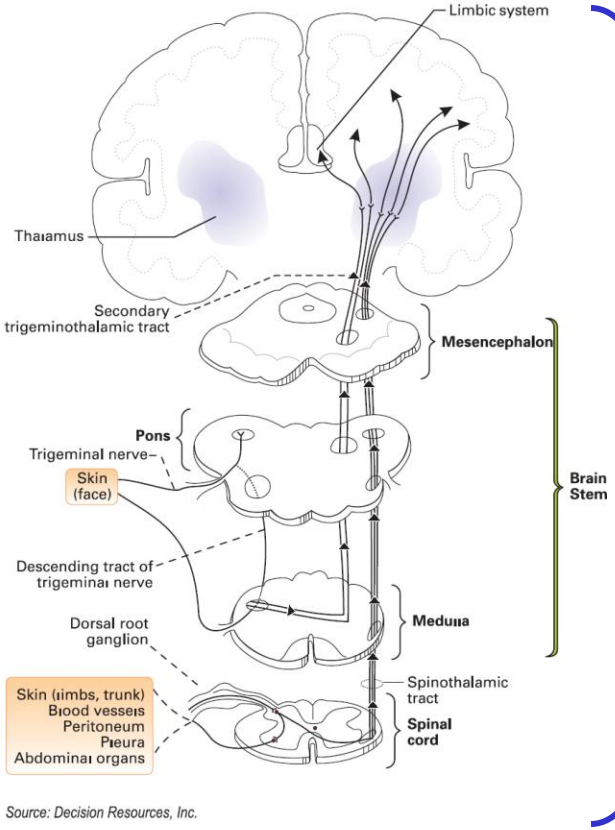
Mayer et al. (1999)

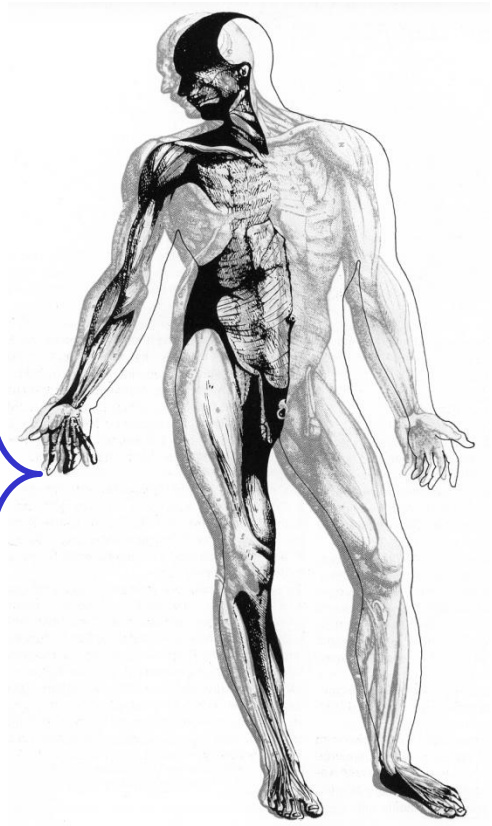
Pain Transduction

Many Targets for one Disease

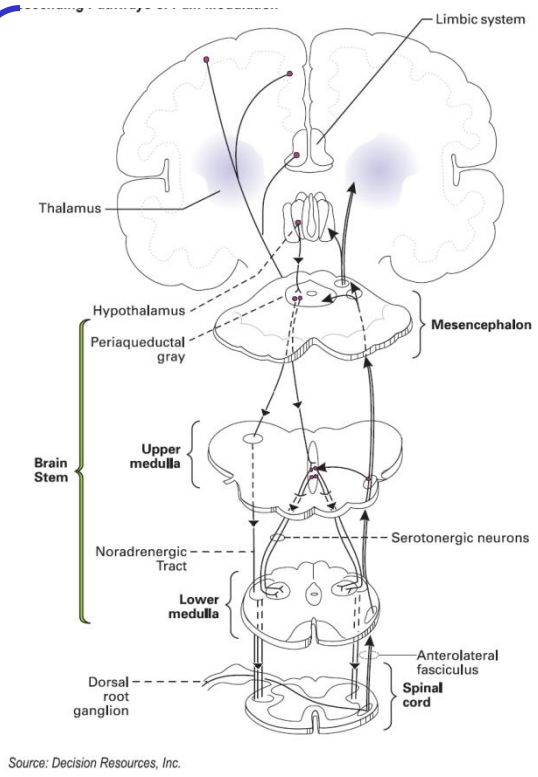
Multiple Mode of Actions for Analgesics

Ascending Pathways of Pain Perception





Descending Pathways of Pain Modulation



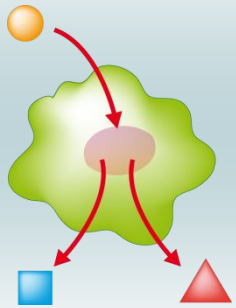
One Disease

Source: Decision Resources, Neuropathic Pain Report, 2004.

Pain Transduction

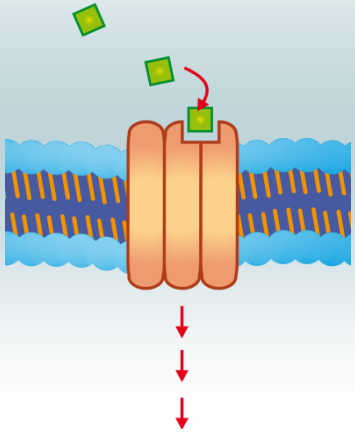
Function of the Target Location

Enzymes



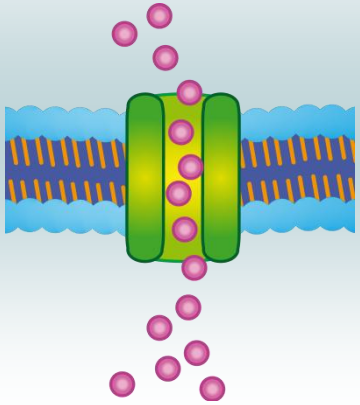
Inhibition of Formation of Pain Mediators

Receptors



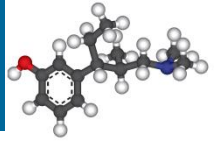
Activation of the endogene Pain Inhibition

Ion Channels / Transporters



- Change of Action Potential
- Blockade of Reuptake of Neurotransmitters

Pain Transduction



Physiology and Pathophysiology of Pain

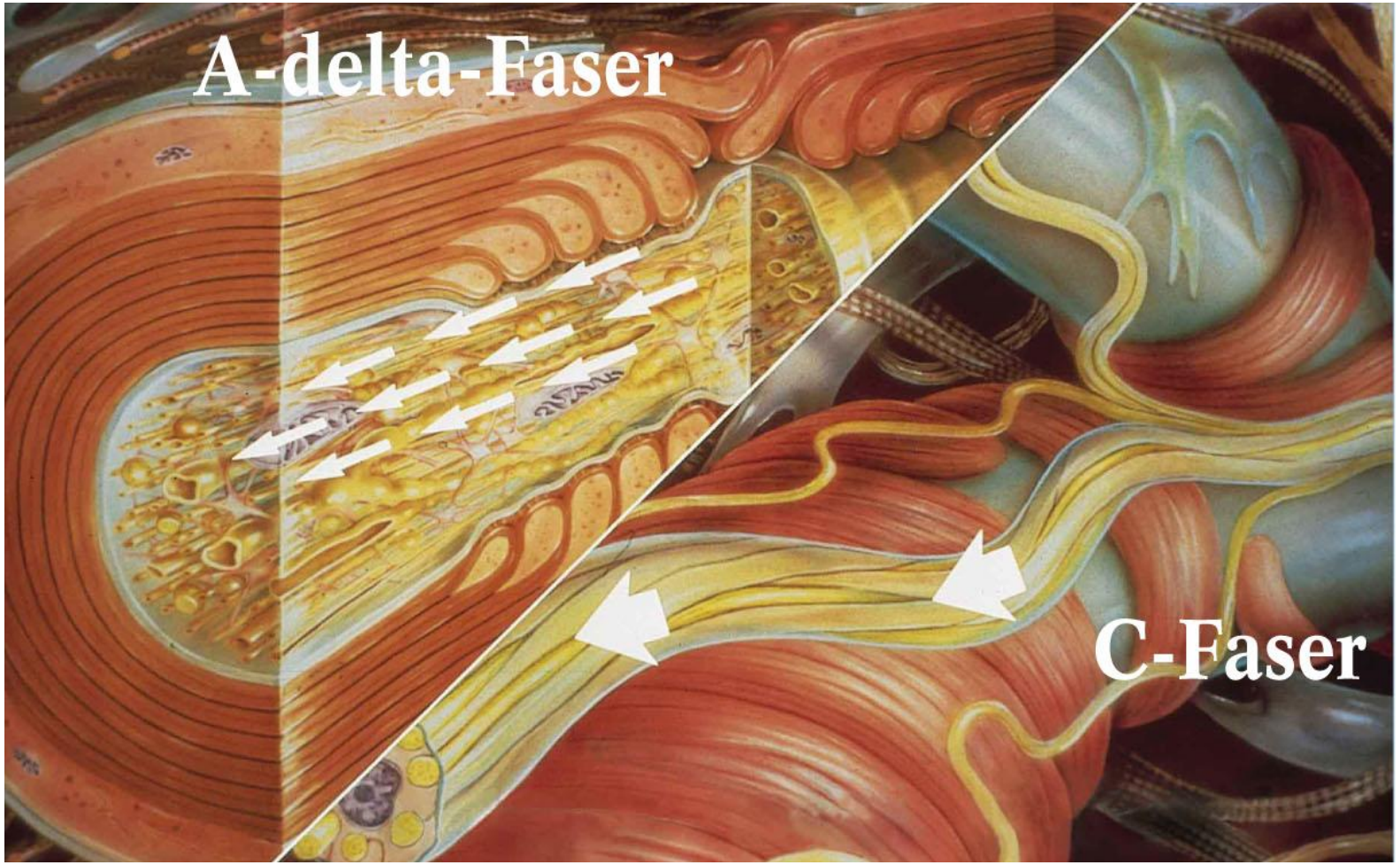
- **C-Fibre Activation**
  - **The physiological aspects of lasting pain can be described as when a *mechanical, thermal, chemical or electrical stimulus* strong enough to damage tissue or affect cellular metabolism, stimulates the nociceptive free nerve endings of the C-fibres, which are found all over the surface of the body and its organs.**

- **Aδ-Fibre Activation**
  - **Several subtypes of A-fibres also carry afferent nociceptive impulses. The damaged tissue sends out nerve impulses through nerve tracts in the spinal cord to the brain (cerebral cortex) where the stimulus becomes a conscious feeling of pain.**

- **Endogenous Pain Mediators**
  - **In addition to nervous pain impulses, injured tissues produce inflammatory pain-producing substances, including bradykinin and other kinins, serotonin, histamine, acetylcholine, excesses of potassium ions, proteolytic enzymes and prostaglandins, which can act in synergy to increase pain levels.**

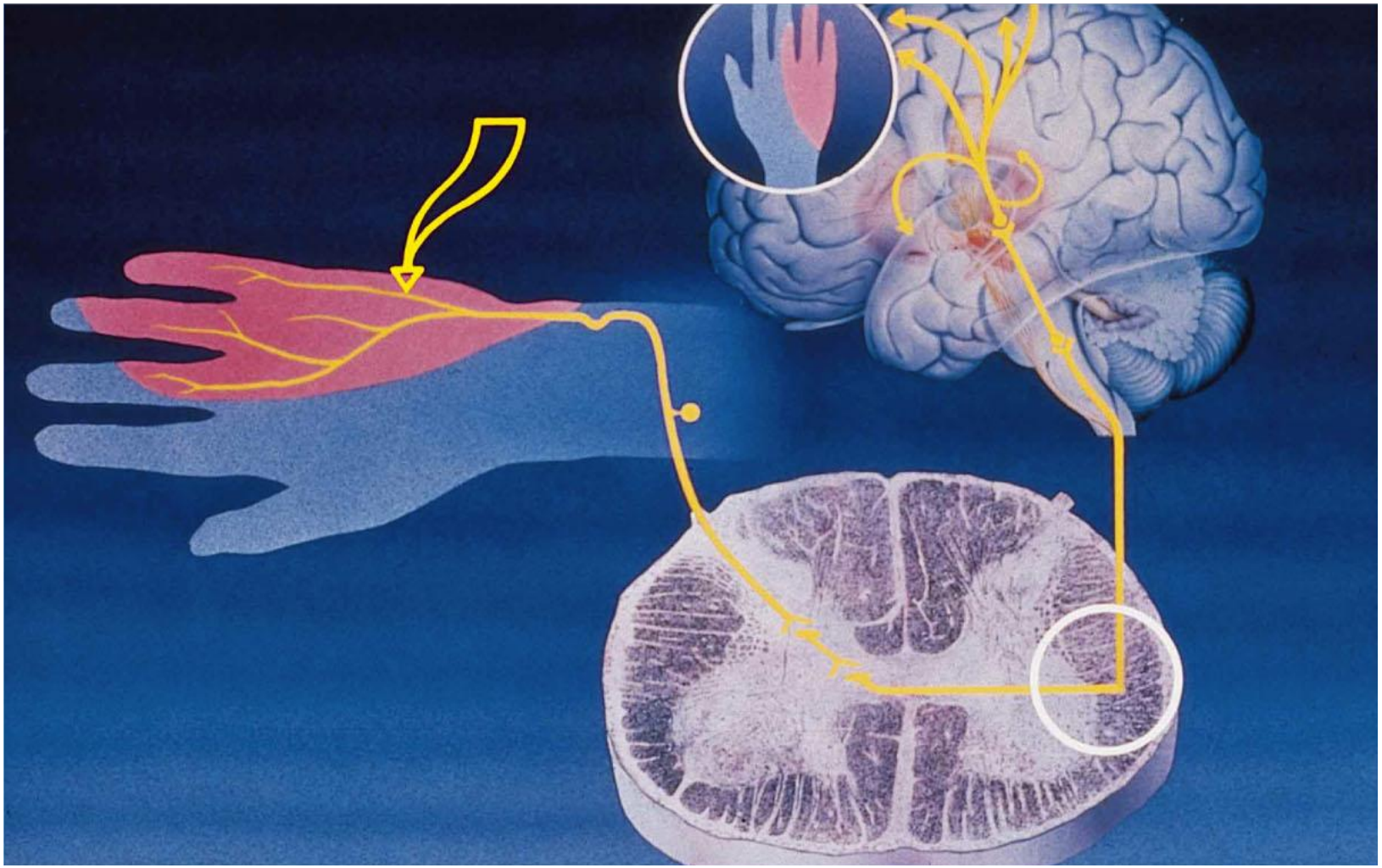
Pain Fibres

Aδ and C-Fibres



Pain Transduction

Pain Signal Transduction



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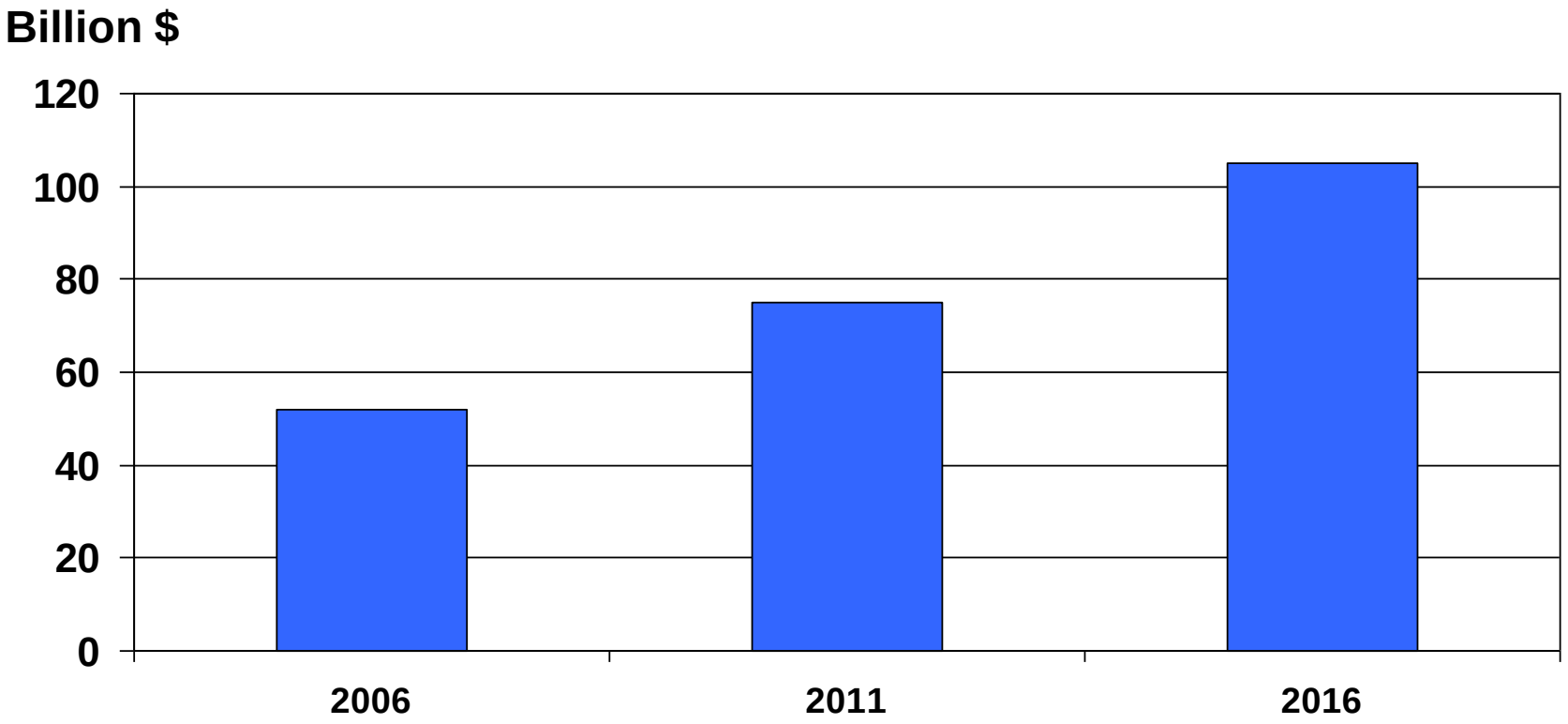
Analgesic Market

The Total Pain Market

2006-2015

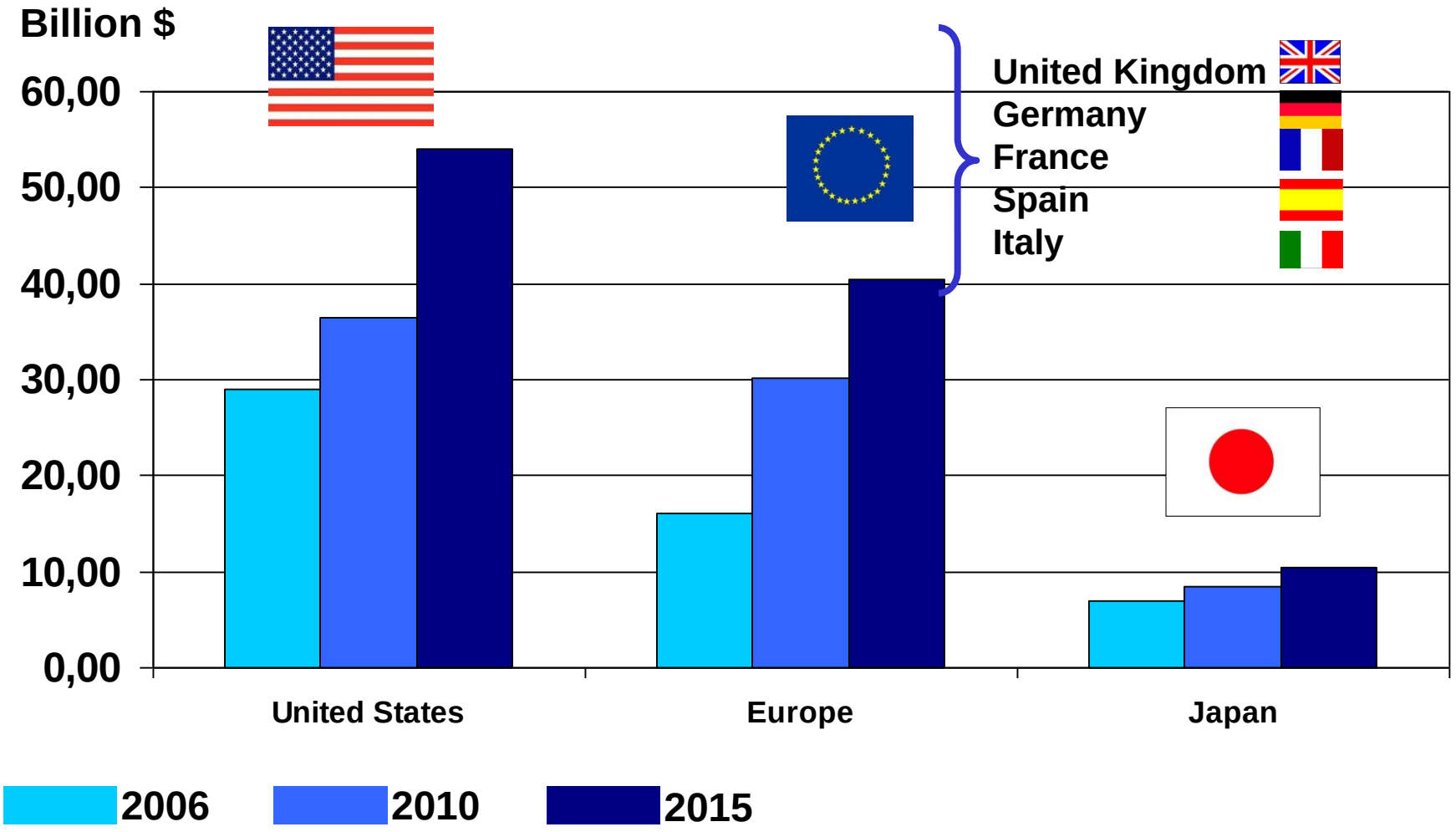


Jain PharmaBiotech Report, Pain Therapeutics – Drugs, Markets & Companies, K.K. Jain, October 2007

Analgesic Market

Pain markets according to geographical areas

Distribution of values of pain therapeutics in major markets 2006-2015

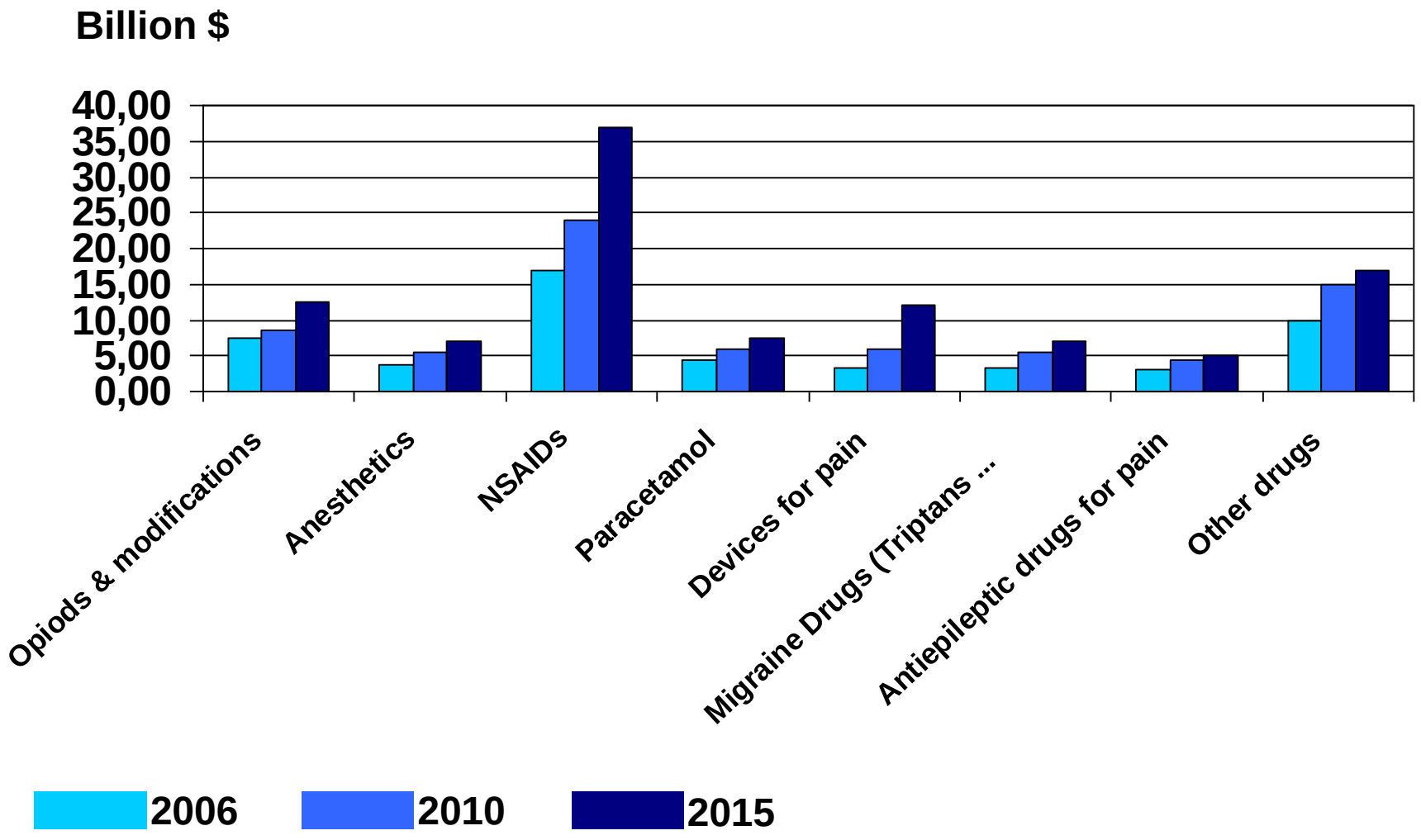


Jain PharmaBiotech Report, Pain Therapeutics – Drugs, Markets & Companies, K.K. Jain, October 2007

Analgesic Market

Pain markets based on drugs

Markets for pain according to therapies 2006-2015



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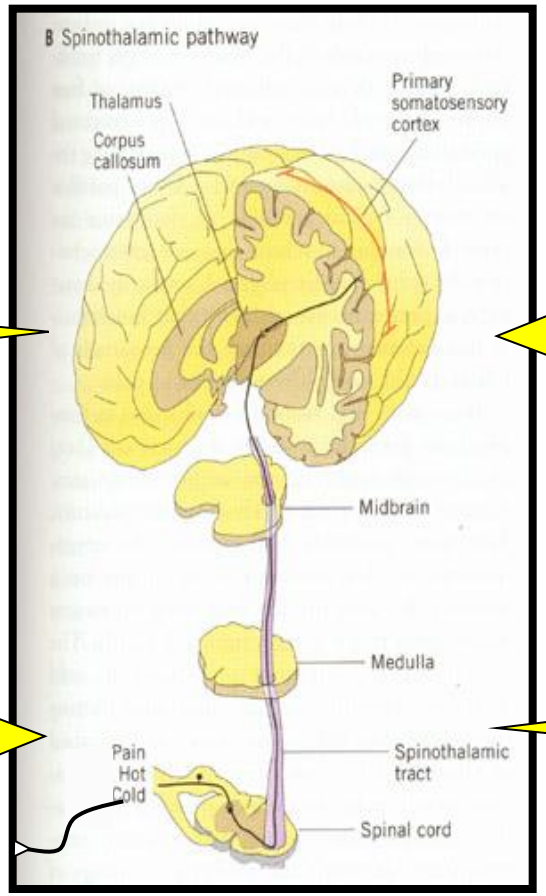
Current Analgesic Treatment Options

Most analgesics are based on two principles

Salicylates

inhibit prostaglandin synthesis



Opioids

Activate inhibitory systems

COX2- inhibitors (*Celebrex* or *Vioxx*)

Selective ligands Delivery techniques

Current Analgesic Therapy

NSAIDs

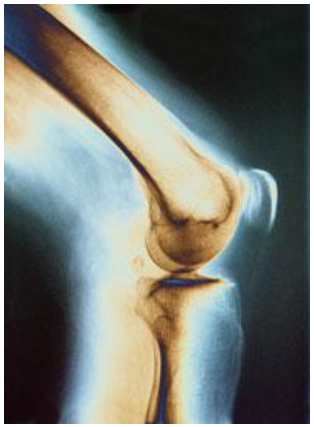
- Unselective COX inhibitors
- Selective COX-2 inhibitors
- Acetaminophen

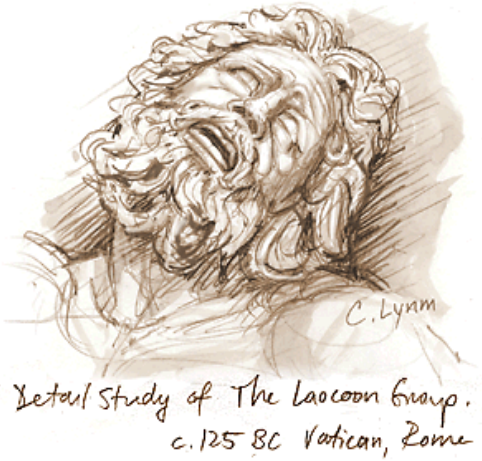
Opioids

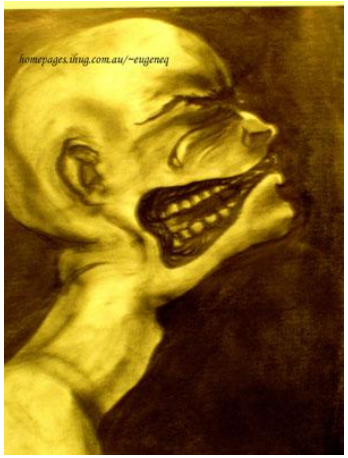
- Opiates
  - morphin, codein
- Opioids
  - N-methyl piperidines
  - 4-amido piperidines
  - 3,3-Bisarylprpylamines
  - cyclohexyl amimes

Adjuvants

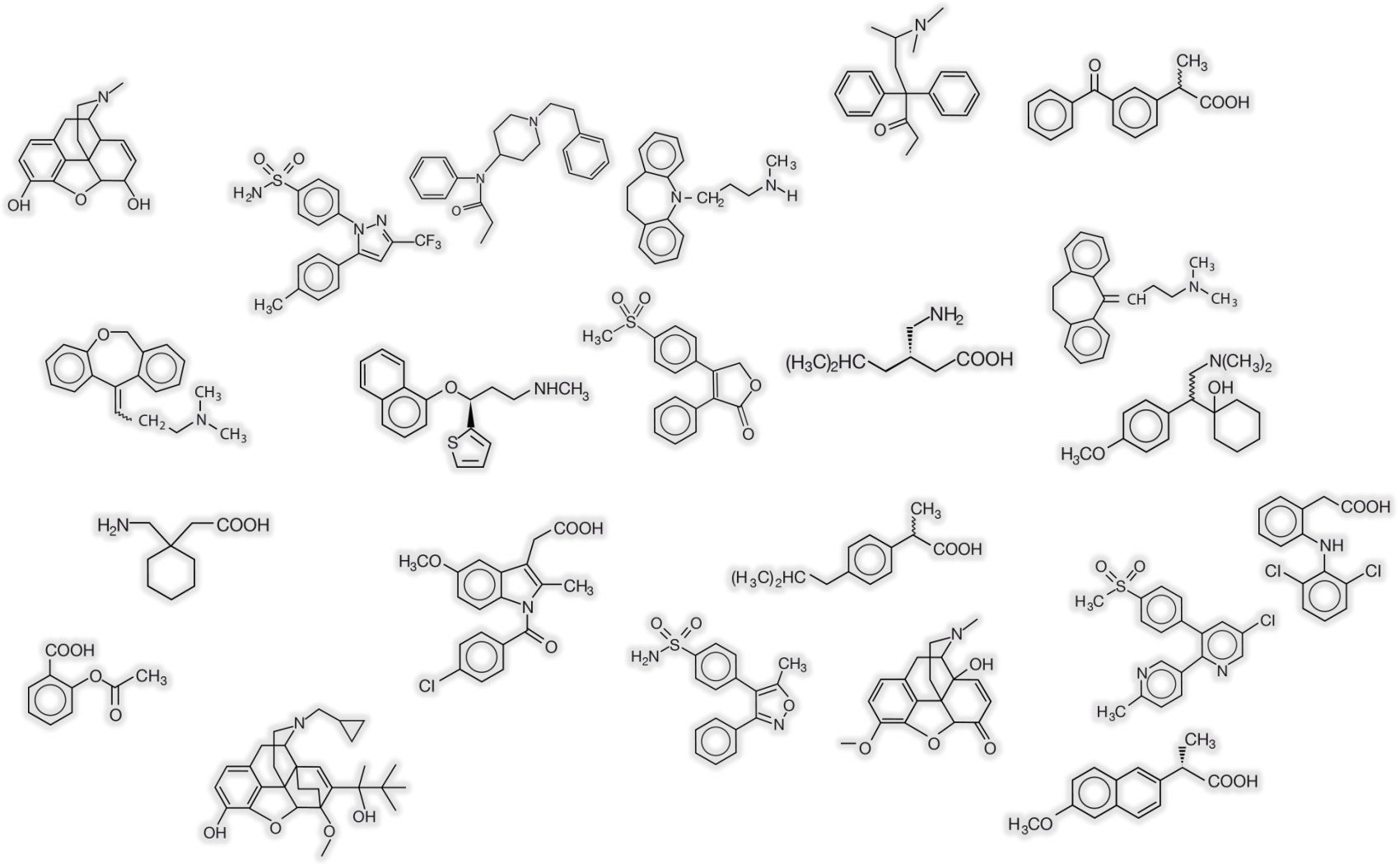
- Antidepressants
- Anticonvulsants
- Local anesthetics





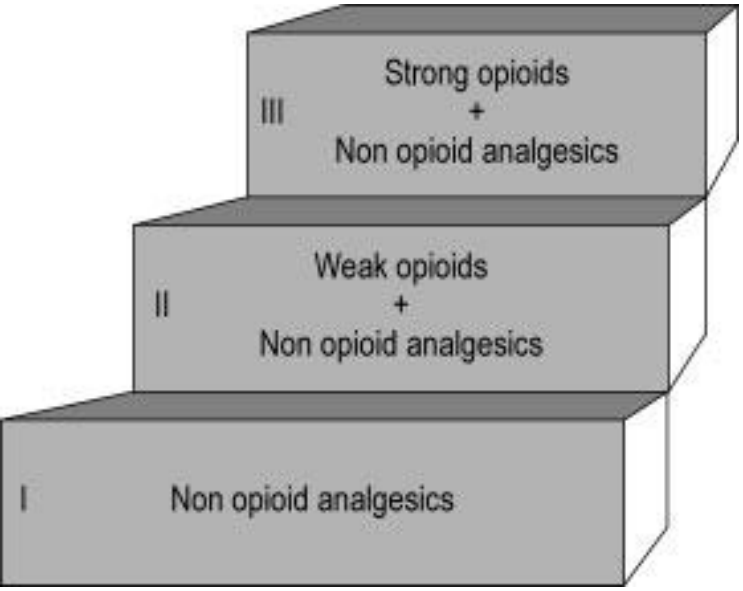


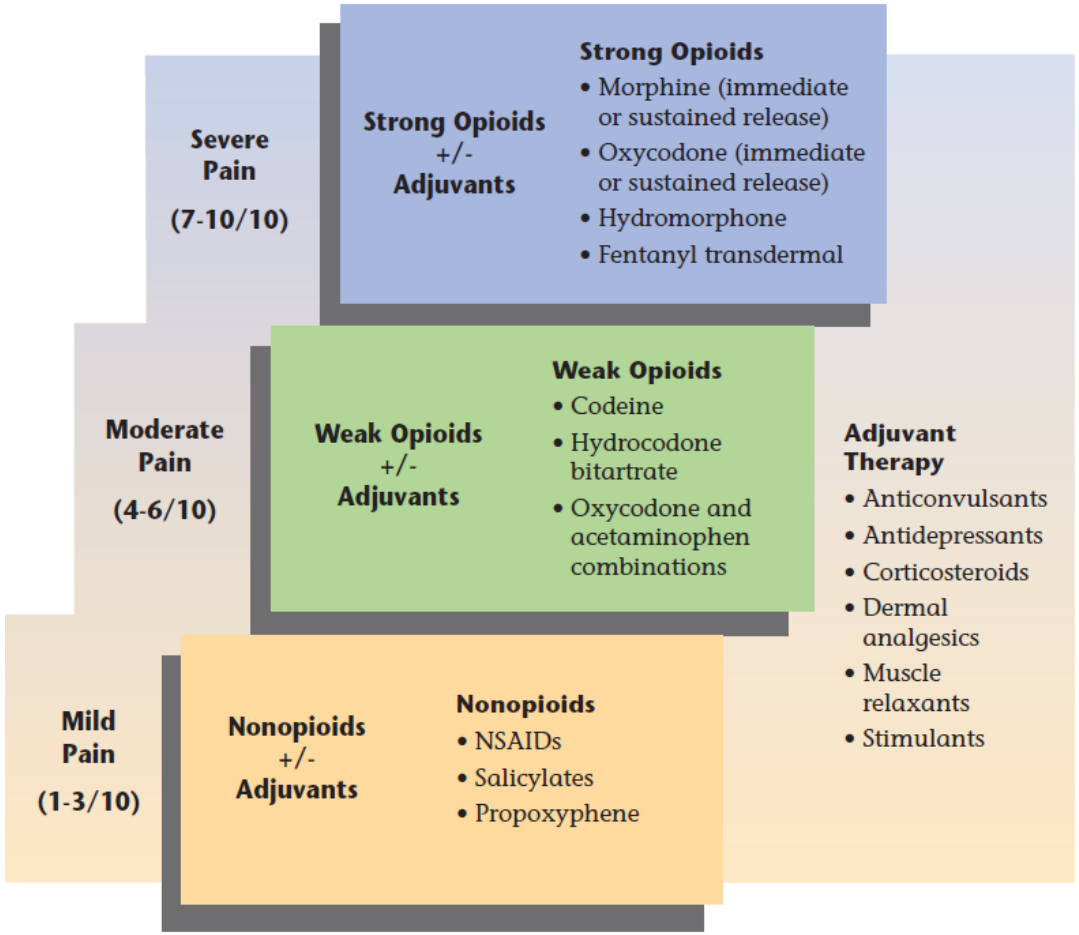
Different Structures of Current Analgesic Drugs



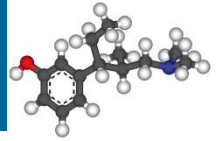
Current Analgesic Treatment Options

WHO Analgesic Ladder





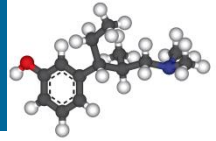
Combination of drugs are used to enhance the analgesic efficacy of opioids, treat concurrent symptoms that exacerbate pain, and provide independent analgesia for specific types of pain. They may be used in all stages of the pain magnagement



NSAIDs

Nonsteroidal Antiinflammatory Drugs

- **NSAIDs are used in the treatment of mild to moderate pain**
  - **with *analgesic, antiinflammatory, and antipyretic* activity**
  - **NSAIDs are used to relieve the pain associated with headache, tooth extraction, musculoskeletal trauma, especially arthritis,**
- **NSAIDs are also used as adjuvants to opioids in the management of moderate to severe pain**
- **NSAIDs act by inhibiting the prostaglandin biosynthetic enzyme cyclooxygenase (also known as COX or PGHS, prostaglandin H_2 synhase)**
  - **The liberation of these arachidonic acid pathway products following local tissue injury contributes to peripheral sensitization and hyperalgesia**
  - **NSAIDs block prostaglandin production and thus attenuate the peripheral sensitization process**
- **NSAIDs have a ceiling effect in terms of their analgesic efficacy such that complete pain relief cannot be achieved even with dose escalation**



NSAIDs

Nonsteroidal Antiinflammatory Drugs

NSAID side effects

- **Therapeutic effects and side effects of NSAIDs are closely related to thei biochemical mechanism of action**
- **The side effects associated with the clasical NSAIDs include**
  - ***gastrointestinal bleeding***
  - ***ulceration*, *lesions*, and *perforation***
  - ***inhibition of platelet aggregation***
  - ***Nephrotoxicity***
  - **a severe side effect of NSAIDs is *bronchoconstriction* with resultant *asthmatic events***
- **and in 10 % of those experiencing such side effects, death**
  - **every year it is estimated that 16.000 NSAID-related deaths occur in the US alone, with 75.000 patients hospitalised**
  - **because of this problems, a major target of drug research is the development of NSAIDs with anti-inflammatory and analgesic activity but without side-effects**

Opioid market definition today

The opioids are divided into short- and long-acting opioids according to these molecular classes:

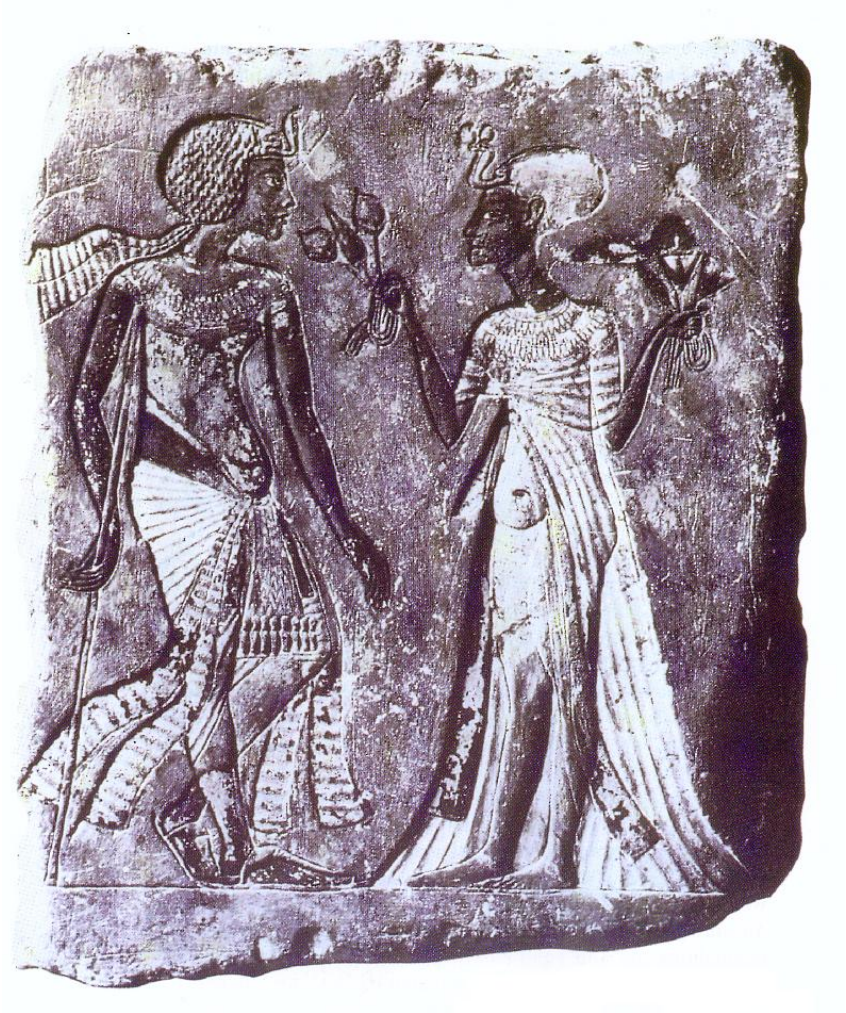
- **fentanyl;**
- **morphine;**
- **oxycodone;**
- **others.**

Short-acting opioids:
Opioids with a rapid onset of action to treat short episodes of pain (e.g. oral fentanyl).

Long-acting opioids:
Opioids with a sustained release to treat chronic pain (e.g. oxycodone controlled release).

Datamonitor Report: Commercial and Pipeline Insights: Opioids, Puplication Date 03/2008, Reference Code: DMHC2377

Opioids in History



Nofretete

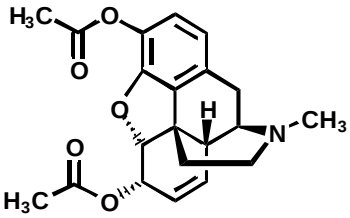
Babylonian God

Opioid Receptors

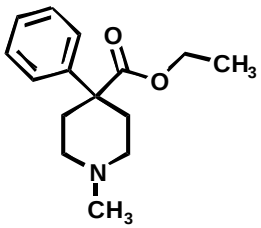
Historical Overview

Opium is the Greek term for the juice of the poppy plant

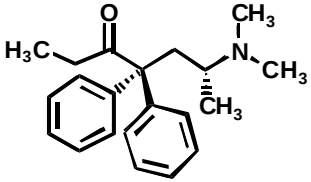
- since 3000 BC use of the *pain relieving* and *euphoric effect* of opium in Egpt, India, and China;
- 3000 BC cultivation of *Papaver somniferum* by the Sumerians in the area between *Euphrates* and *Tigris*
- 1st century AD mention of opium by the greek doctor *Pendanicus Dioscorides* (De Materia Medica)
- 1806 isolation of Morphine by *Adam Sertürner*
- 1874 synthesis of Heroin (Diacetylmorphine)
- 1939 synthesis of Pethidine (Meperidine)
- 1946 synthesis of Methadone



Heroin



Pethidin

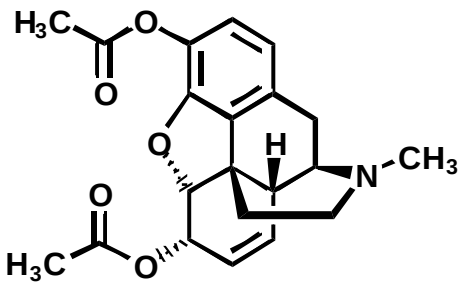


(*Levo*-)Methadon

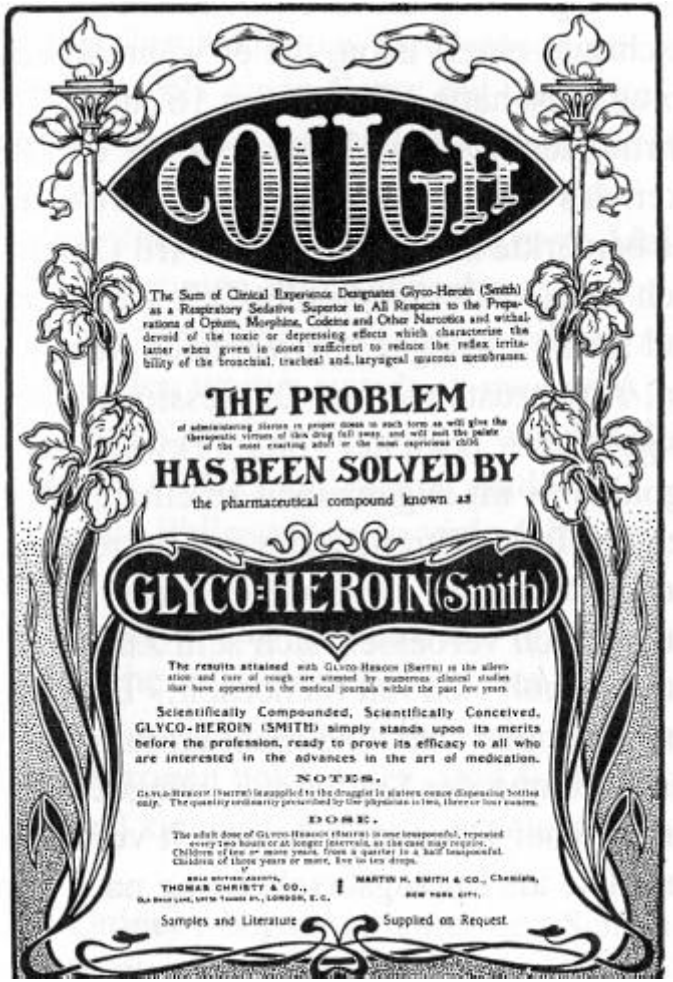
Adam Sertürner

Opioids

Historical Overview



- 1874 discovery of heroin
- 1898 introducing of heroin as a sure and non addicting antitussivum

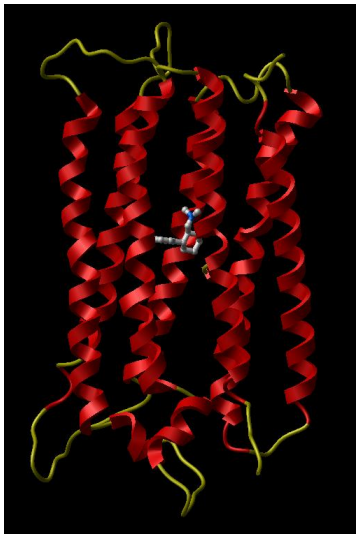


Mrs. Winslows Soothing Syrup

"For children teething. Greatly facilitates the process of Teething, by softening the gums, reducing all inflammation; will allay ALL PAIN and spasmodic action, and is SURE TO REGULATE THE BOWELS. Depend on it, Mothers, it will give rest to yourselves and RELIEF AND HEALTH TO YOUR INFANTS. Sold by all chemists, at 1s 1/2d per bottle."

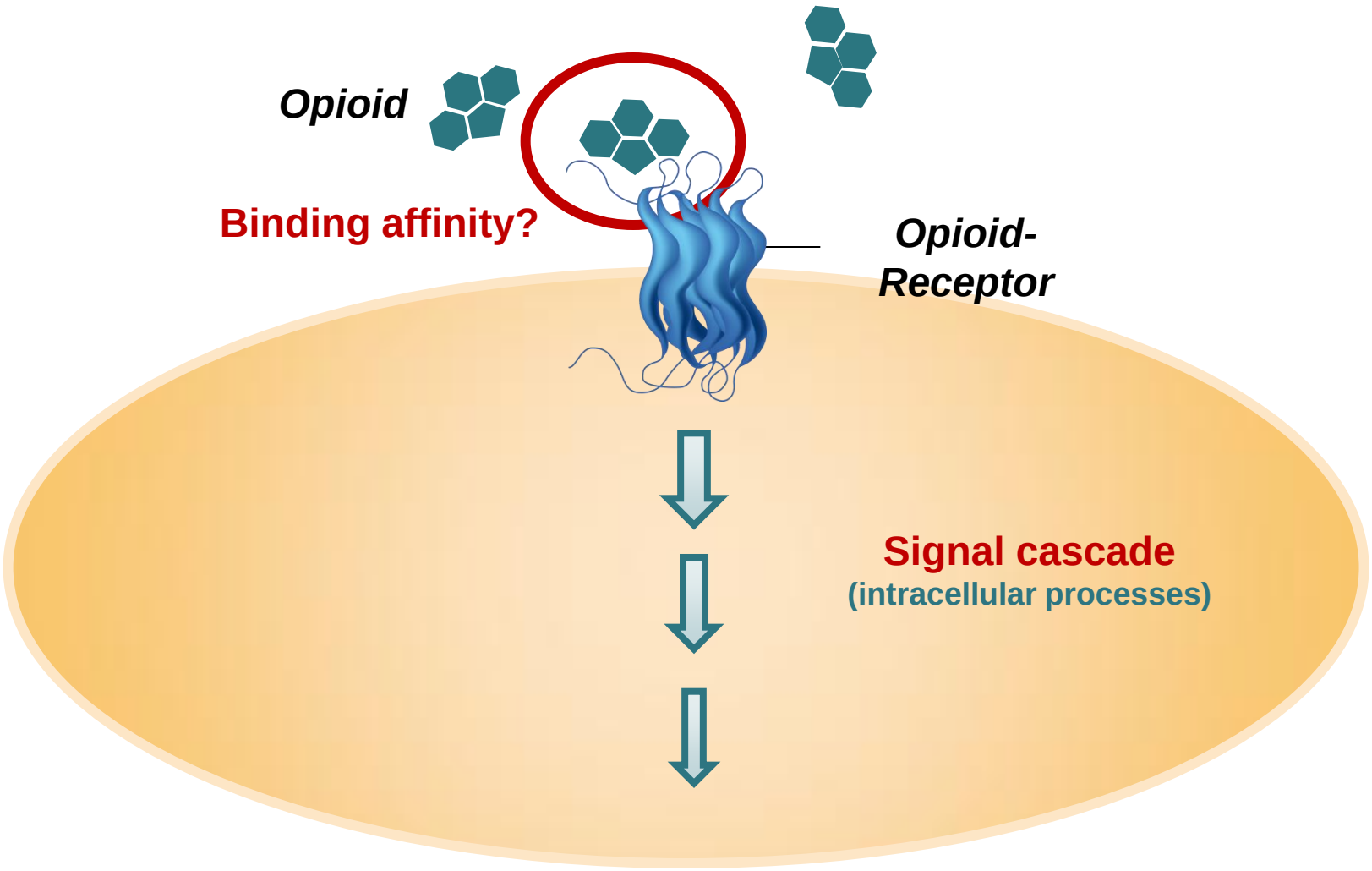
Opioid Receptors

Subtypes

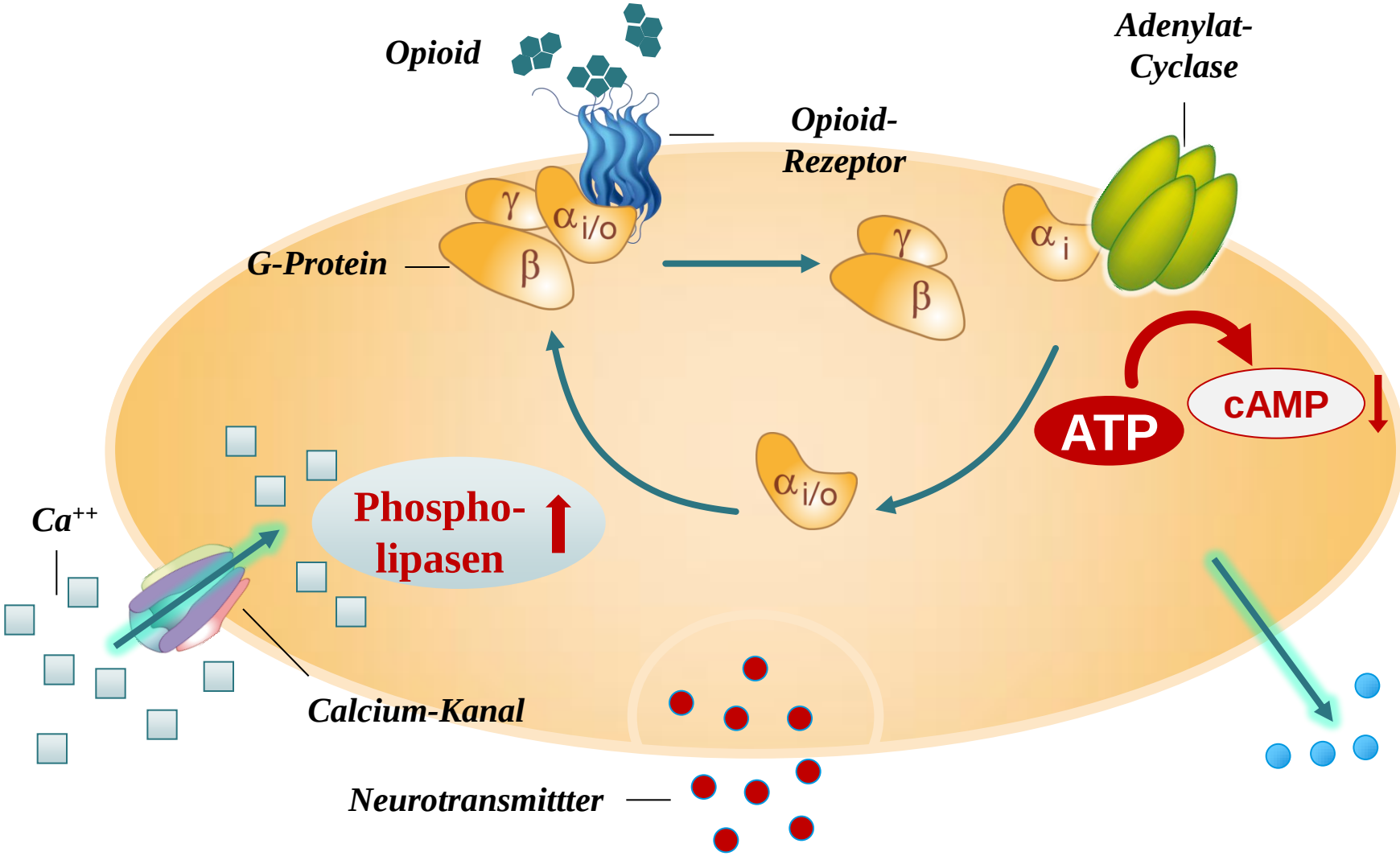


- opioids produce their effects by activating receptors in the brain and spinal cord
- the opiod receptor family is a G-protein-coupled receptor (GPCR) superfamily, characterized by a heptahelical structural motif
- opioid receptors were designated as μ, κ, and δ subtypes based on the synthetic ligands originally used to classify them
- an orphan member of the opioid receptor family, ORL-1, has also been identified
- opioid-receptor subtypes
  - *mü-receptor:* *μ1, μ2*
  - *delta receptor:* *δ1, δ2*
  - *kappa receptor:* *κ1, κ2, κ3*
  - *orphan receptor:* *ORL-1*
- morphine is the gold standard opioid and it is the analgesic of choice for terminal pain
  - pharmacologically, morphine is a complete agonist at the μ-receptor
  - it is the standard against which all other analgesics are compared

Wirkung der Opioide auf intrazelluläre Prozesse

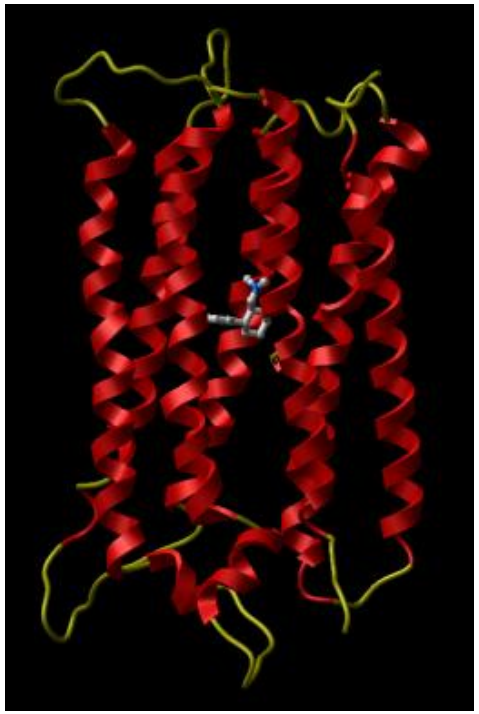


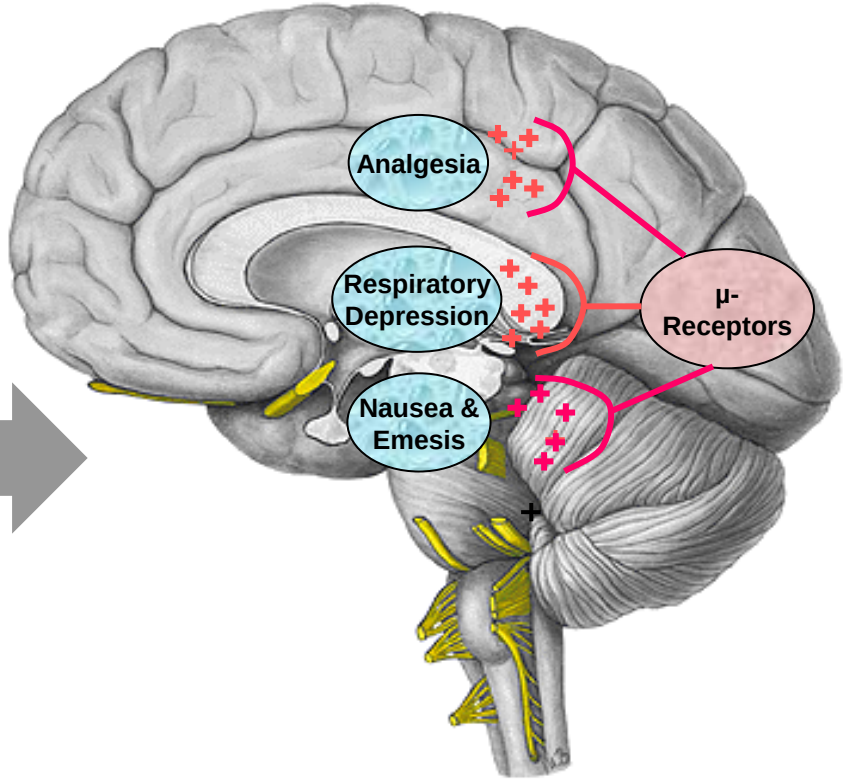
Action of Opioids on Intracellular Processes



Current Analgesic Treatment Options: Opioids

Side effects associated with clinical use of opioids

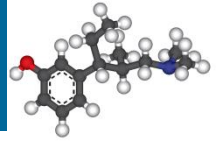




Analgesic Profile

Side Effect Profile

Current Analgesic Treatment Options: Opioids



Side effects associated with clinical use of opioids

Constipation

- due to inhibition of gut motility
- constipation is a significant side effect that is often underestimated
- and in many instances, leads the patient to choose pain over the GI side effects of opioids

Respiratory depression

- due to activation of opioid receptors in the respiratory centers of the brain stem

Cardiovascular effects

- bradycardial effects are induced by nearly all opioids

Emesis

- nausea and vomiting are often observed by opioid application, but due to the tolerance these effects normally increase

Addiction

- The social and legal issues related to use, and regulatory constraints contribute to an underutilization of opioids, particularly for the management of chronic nonmalignant pain
- In 25.000 cancer patients taking narcotics, only 7 became addicted

Tolerance

- **associated with drug dependence, this phenomenon may occur with chronic administration of a drug.**
- **it is characterised by the necessity to progressively increase the dose of the drug to produce its original effect. Tolerance is mainly caused by neuroadaptive changes in the brain**

The Discovery of Tapentadol – A New Option for Pain Treatment

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- The Analgesic Market
- Current Analgesic Treatment Options
- **Pain Research Today - The Unmet Needs**
- Tramadol – History and Pharmacology
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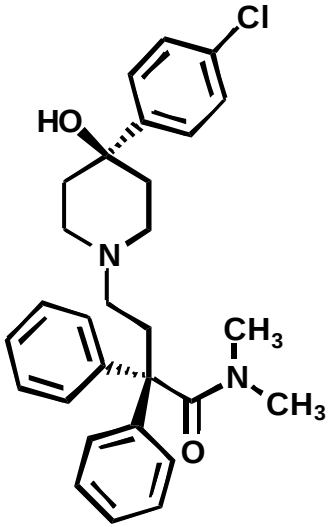
  - Metabolism
  - Synthesis

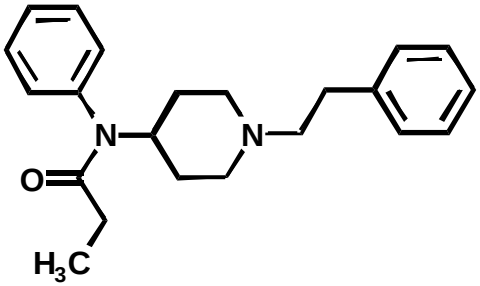
Pain Research in 1999

"Despite an intensive research effort over the past two decades involving many innovative approaches in the global academic community and by the pharmaceutical industry, the latter representing an aggregate investment in excess of $ 2.5 billion, the only new opioid-based pain medications either in clinical development or on the market are alternative dosage forms of the classical opioids, *morphine*, *loperamide*, and *fentanyl*, or compounds such as *tramadol*."

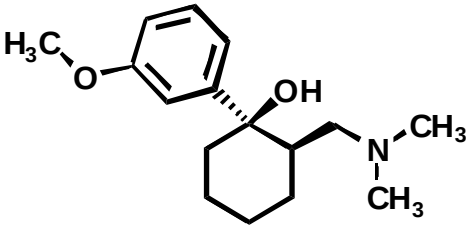
M. Williams et al., *J. Med. Chem.* 1999, *42*, 1481-1500.



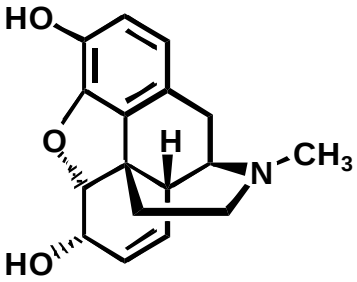
Loperamide



Fentanyl



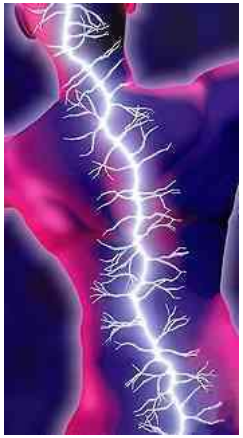
Tramadol



Morphine

Pain Tratment Today…

J.A. Butera, *Current and Emerging Targets To Treat Neuropathic Pain*, J. Med. Chem. 2007. *50*, Miniperspectives-2543-2596

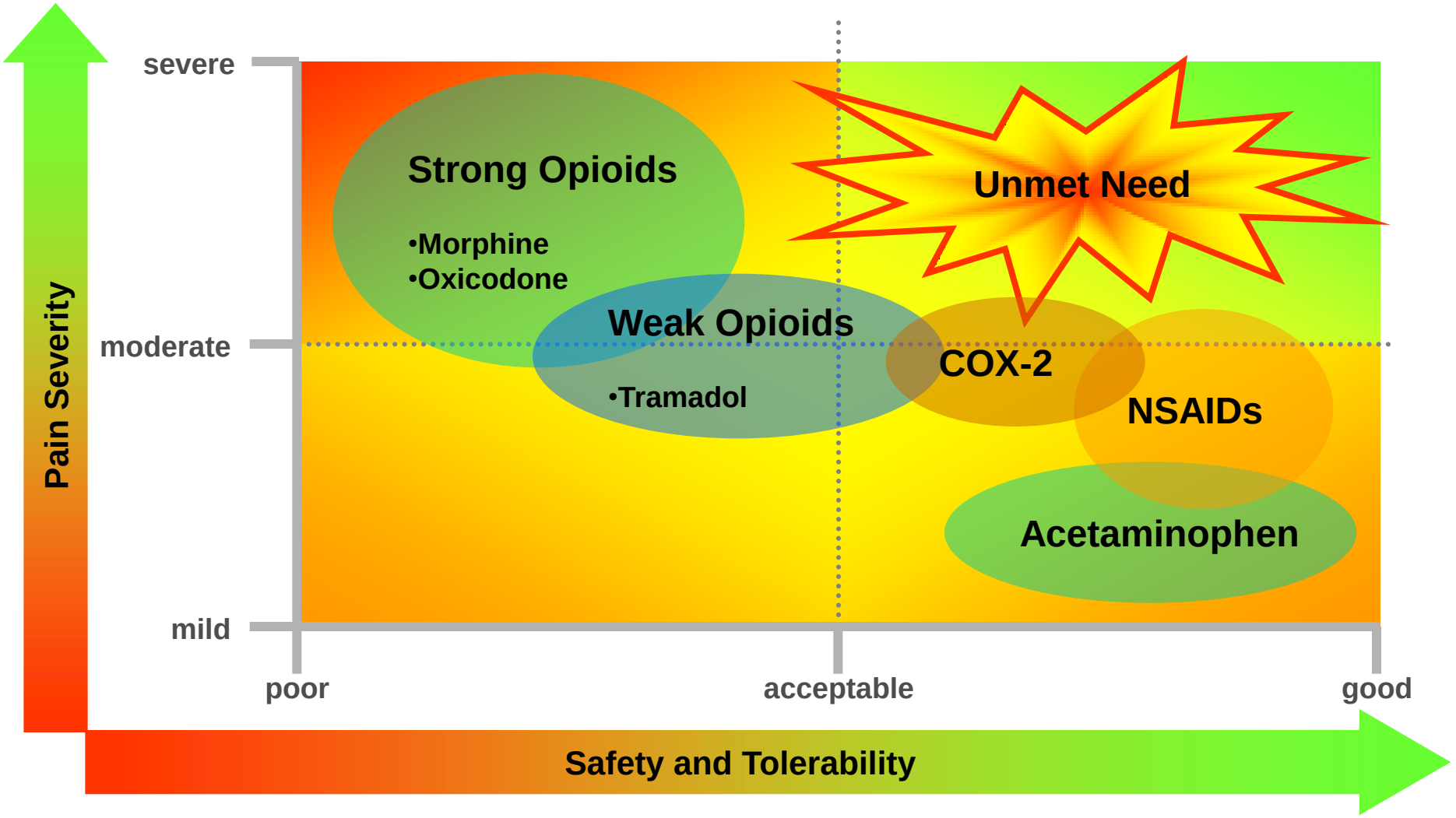


- It is estimated that neuropathic pain affects over **6 million patients in the U.S. and Europe and over 26 million patients worldwide**,
- resulting in a worldwide healthcare cost of over $3 billion per year, with a significant portion of this money paid for drug therapies that were originally developed for other medical conditions
- As physicians are faced with an **increasing number of patients** with numerous neuropathic pain symptoms most likely stemming from multiple etiologies, they are forced to resort to the **polypharmacia approach** as the mainstay therapy.
- Current pharmacological treatment for neuropathic pain will typically include some combination of agents from several of the following drug classes: *opioids, tricyclic antidepressants, anticonvulsant agents, or nonsteroidal anti-inflammatory drugs (NSAIDs)/analgesics.*
- Ironically, even with such an impressive arsenal of powerful drugs, these approaches only provide an approximate **30-50% reduction in pain in about 50% of patients**.
- Coupled with this limited efficacy, there are **low levels of compliance** due to intolerable side effect profiles associated with some of these drugs.
- These results profoundly illustrate **that treatment of neuropathic pain is a hugely unmet medical need**, and they underscore the importance of considering, validating, and pursuing alternative targets to treat refractory neuropathic pain.

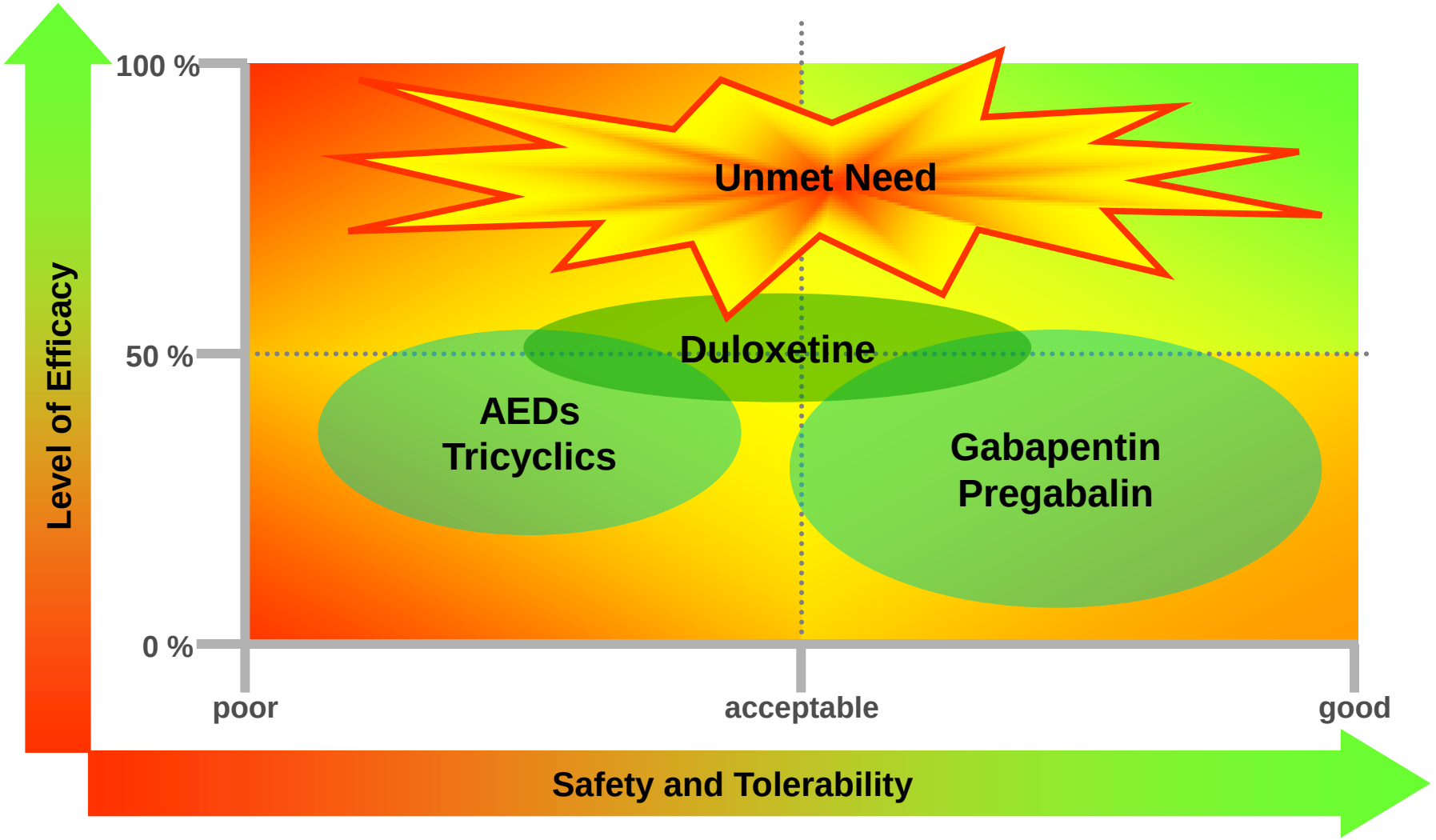
Datamonitor: Pipeline Insight: Neuropathic Pain (Publication Date: 09/2007)

Pain Research Today - The Unmet Needs

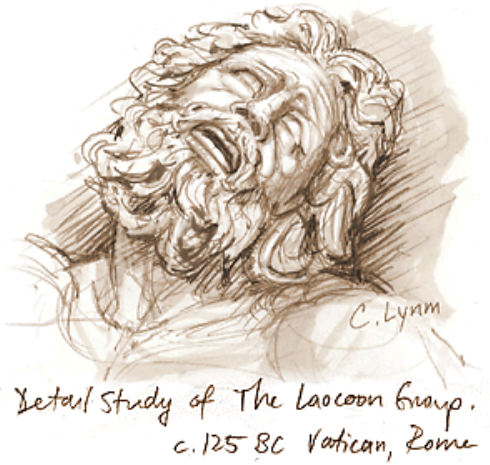
Significant Unmet Needs in Inflammatory/Nociceptive Pain Treatments

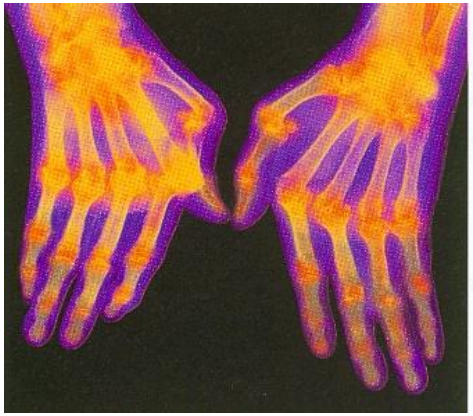


Significant Unmet Needs in Neuropathic Pain Treatments



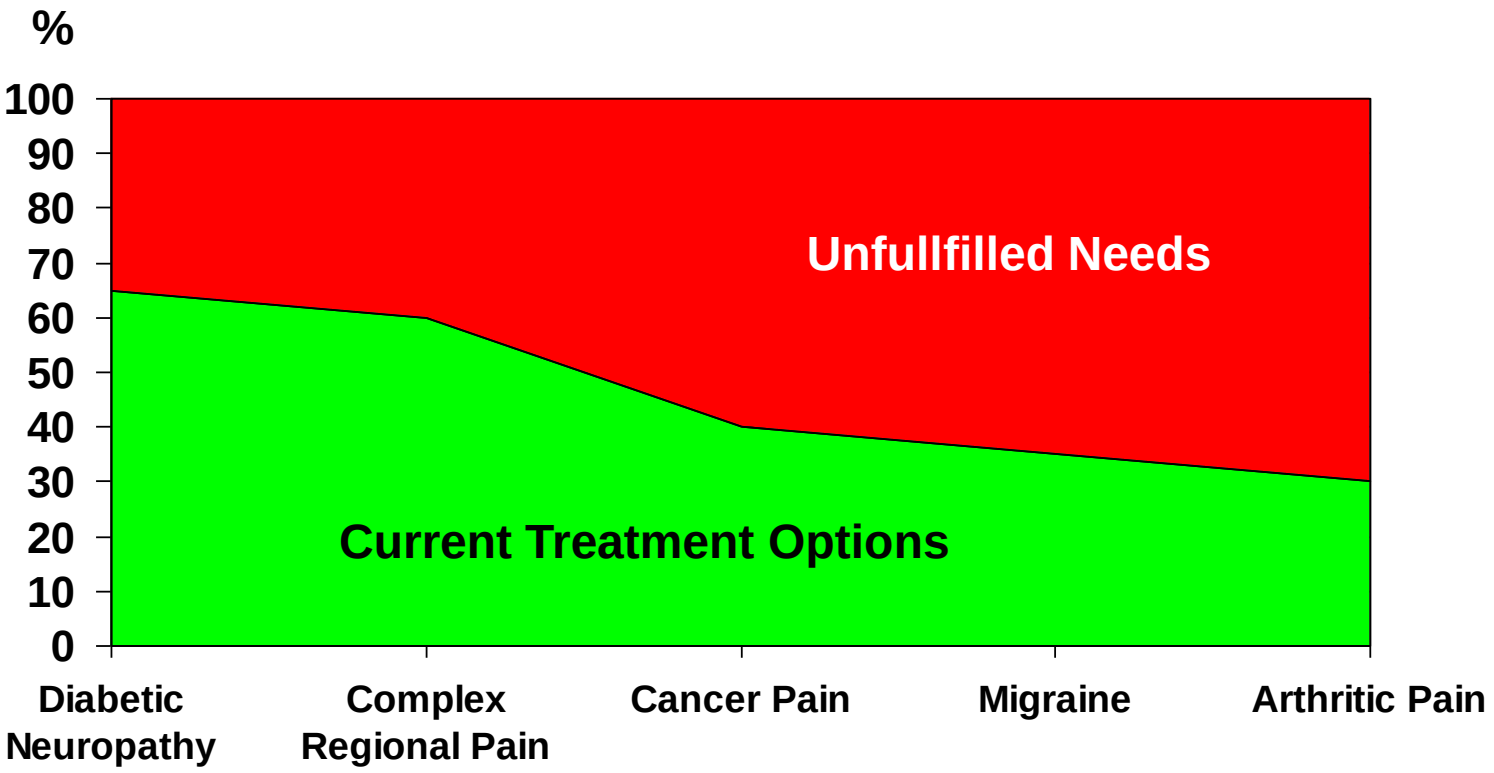
Key Needs in Pain Treatments



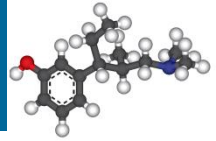


Neuropathic Pain	Inflammatory & Nociceptive Pain
▪ Greater Efficacy ▪ Faster Onset of Action	▪ New Drugs with Efficacy of Opioids but Greater Tolerability/Safety

Unfullfilled Needs In The Treatment For Chronic Pain



Jain PharmaBiotech Report, Pain Therapeutics – Drugs, Markets & Companies, K.K. Jain, October 2007



Efficacy and Tolerability of Pain Management

Efficacy

Low Dosage

High Dosage

Insufficient Efficacy

Sufficient Efficacy

+

+

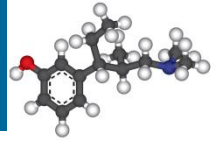
Acceptable Tolerability

Non Acceptable Tolerability

Low Dosage

High Dosage

Tolerability



Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol

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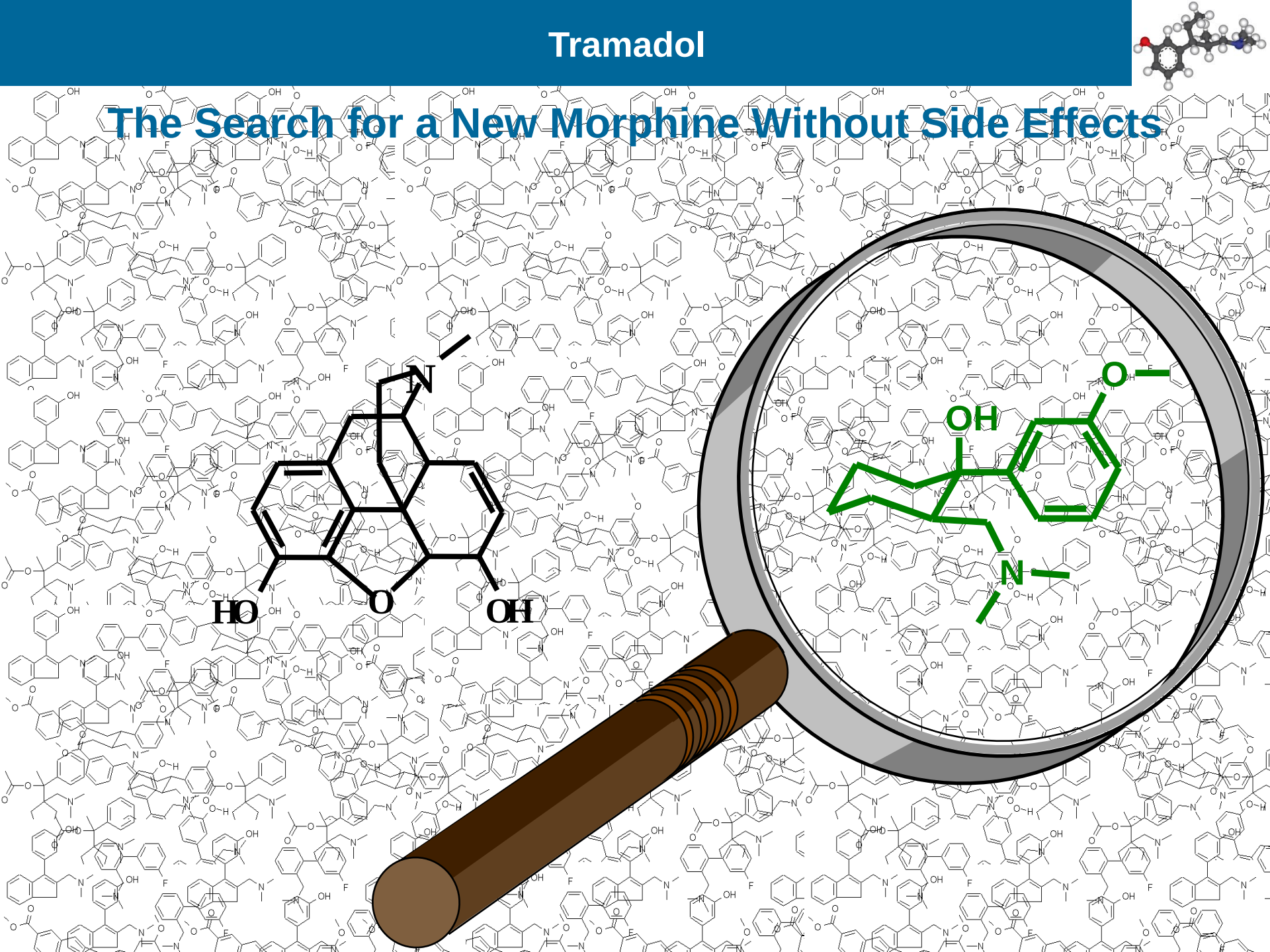
  - Synthesis

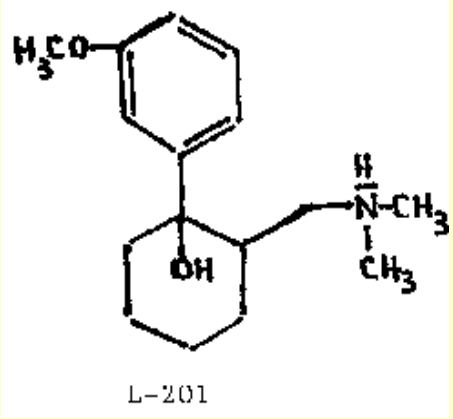
Tramadol

The Search for a New Morphine Without Side Effects



Tramadol – The History

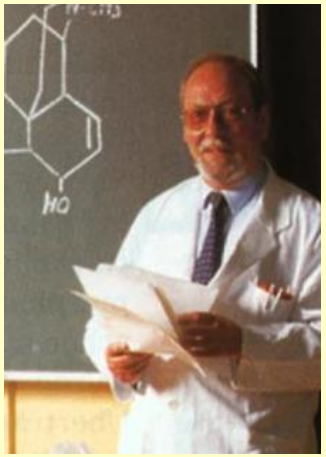
Synthesis of L 201

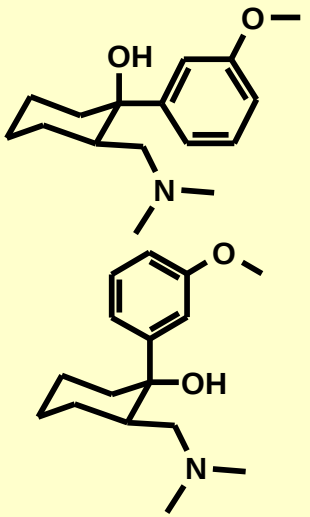


L-201

K. Flick (1962)

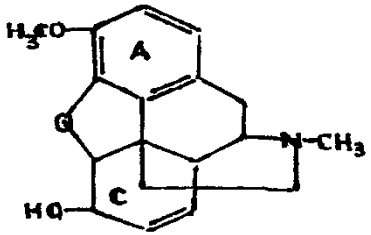
Characterization of Tramadol



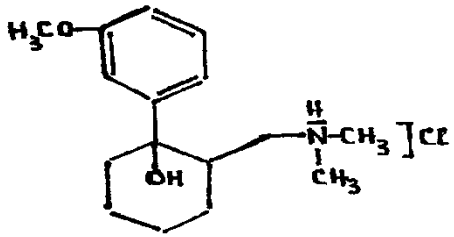


E. Frankus(1963)

mir im Frühjahr 1962 die Idee kam, die Codein-Struktur als Modell für ein neues Hustenmittel anzusehen und die komplizierte Struktur durch Abwandlung zu vereinfachen. Meine Überlegungen ließen sich verwirklichen und so entstand schließlich die chemische Verbindung: 1-(m-Methoxyphenyl)-2-dimethylaminomethyl-cyclohexan-1-ol-hydrochlorid, die unter der Bezeichnung L-201 zur pharmakologischen Testung mit dem Hinweis "Verbindung mit vermutlich antitussiven bzw. analgetischen Eigenschaften" weitergeleitet wurde.



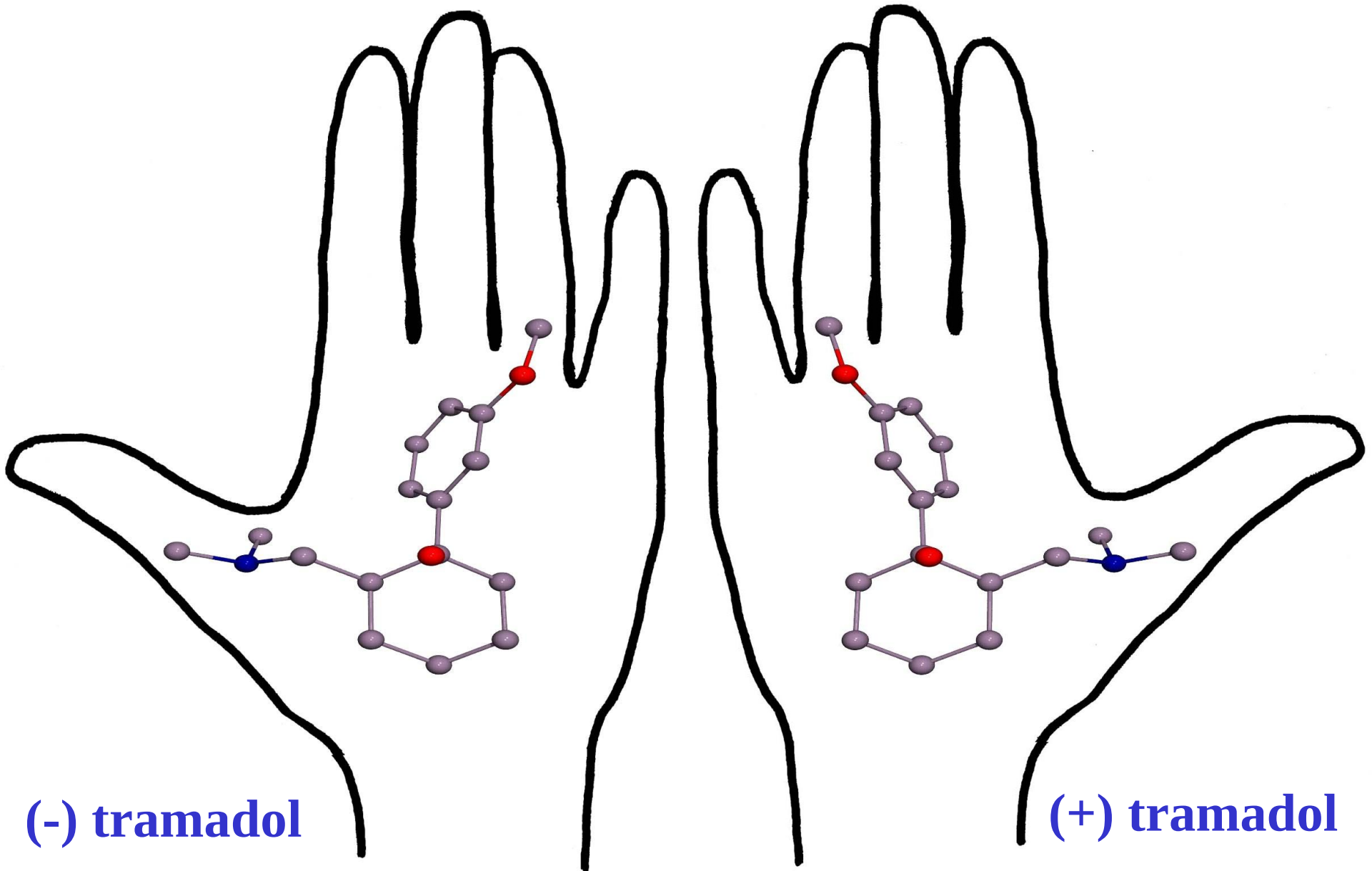
Codein



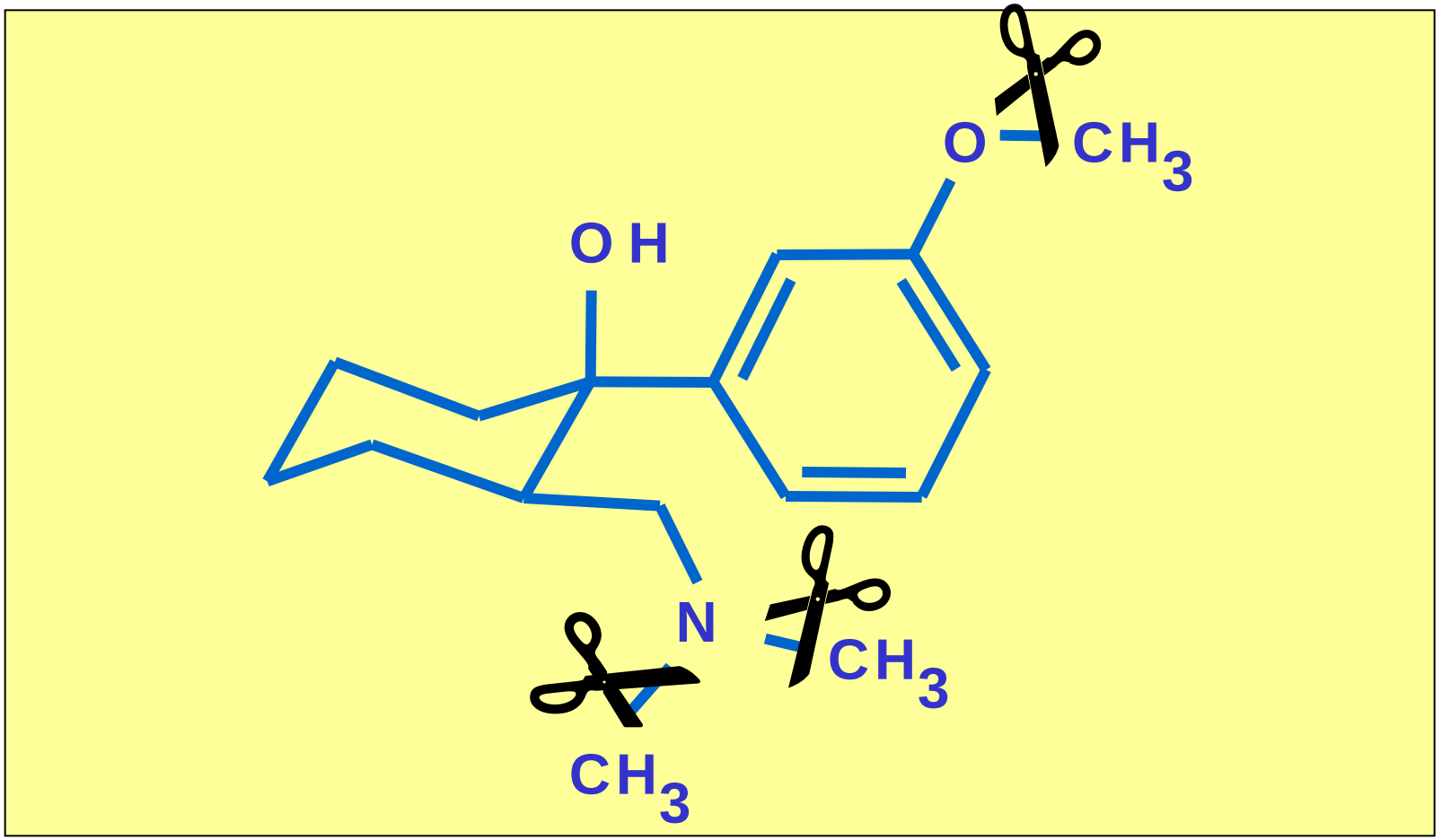
L-201

Tramadol – Pharmacological Profile

Tramadol is a racemate



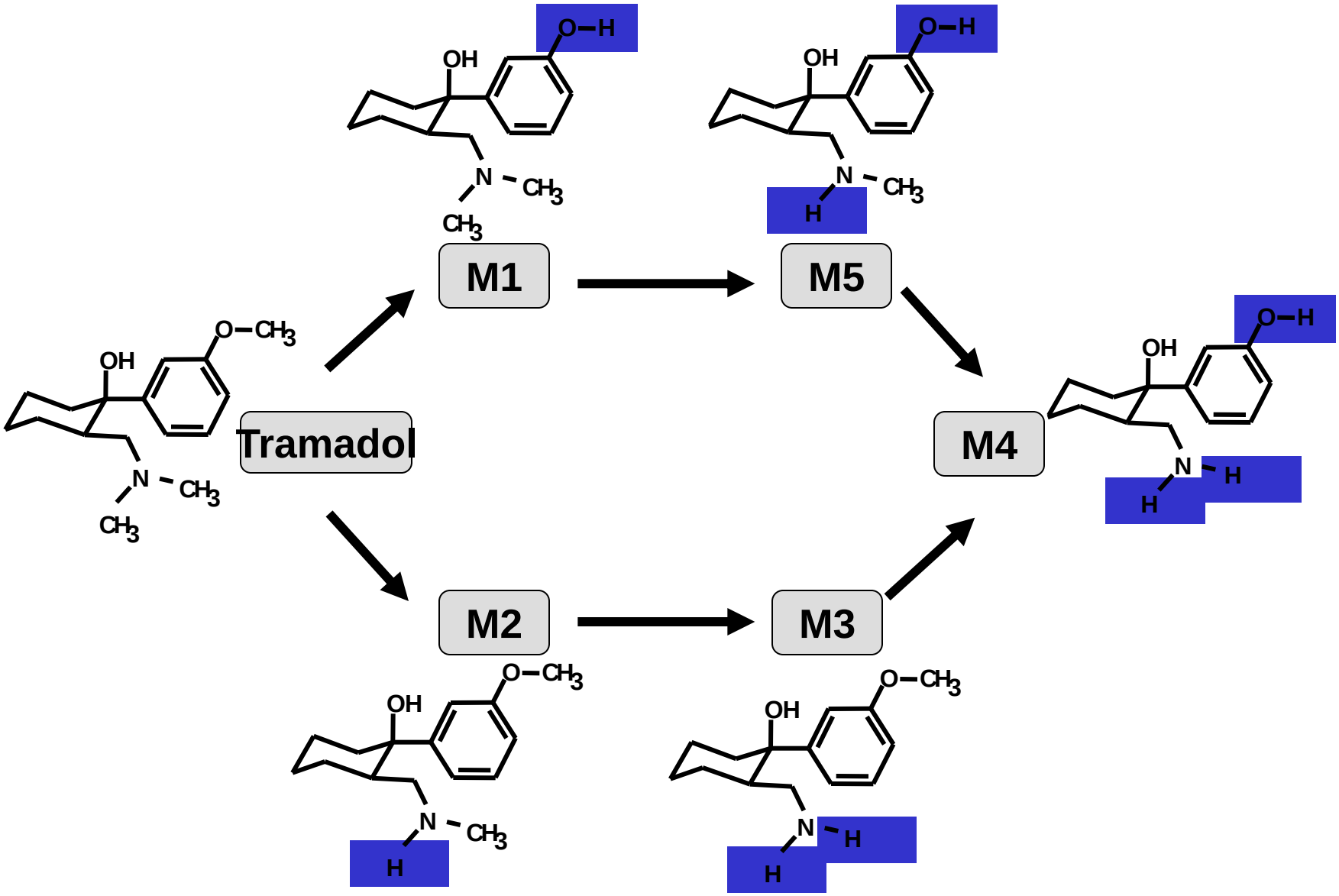
Metabolites of Tramadol



Metabolites are generated by O- or N-demethylation

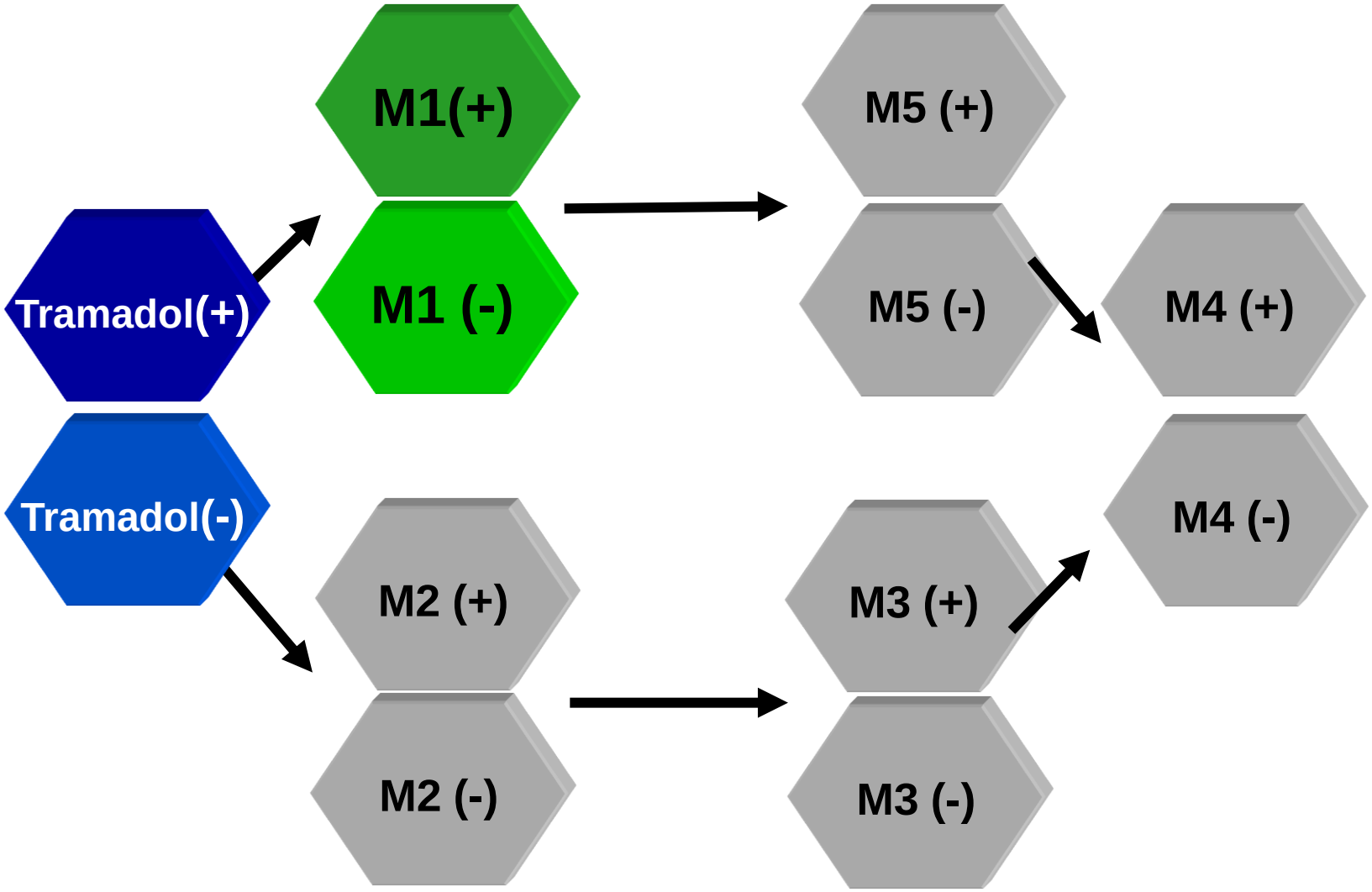
Tramadol – Pharmacological Profile

Metabolites of Tramadol

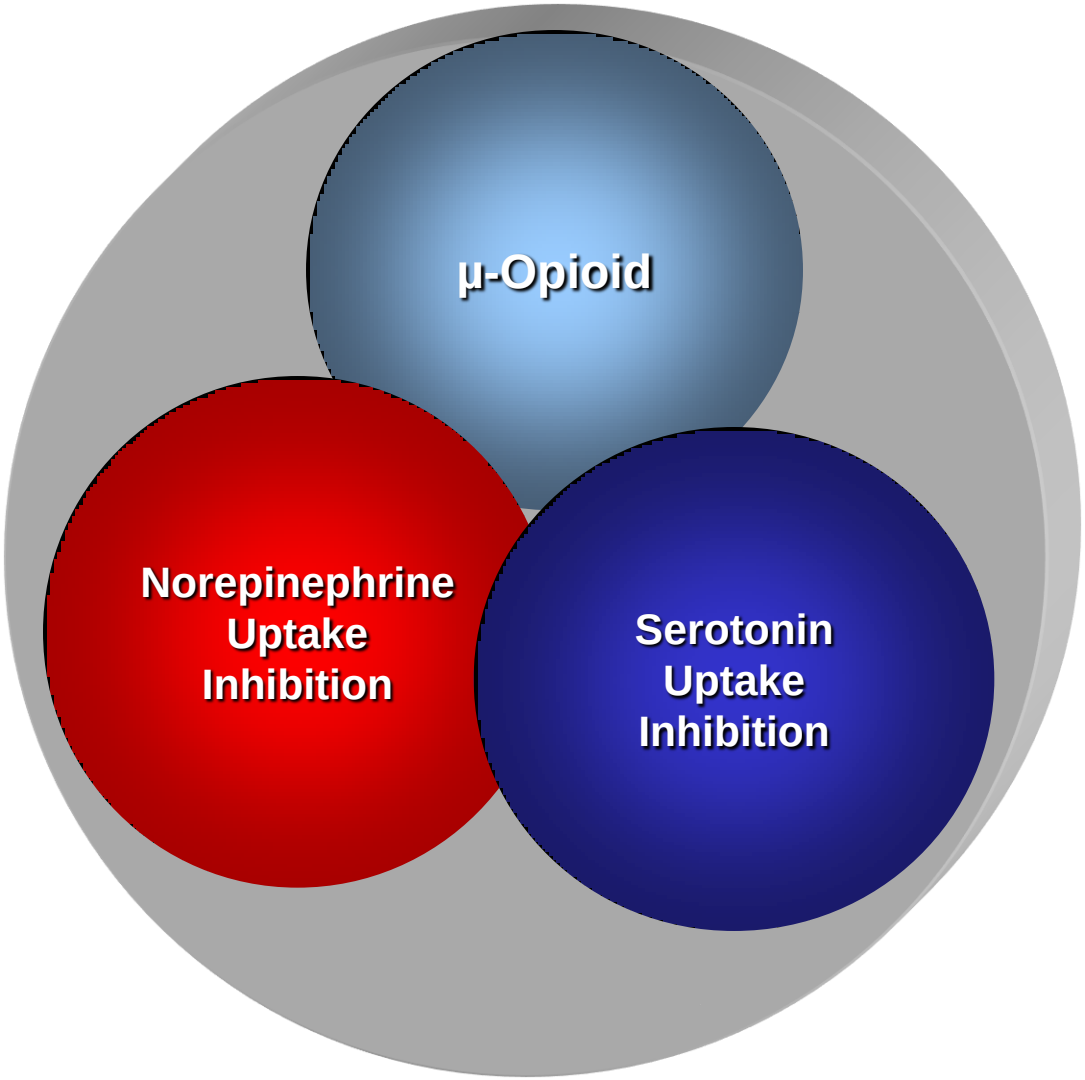


Tramadol – Pharmacological Profile

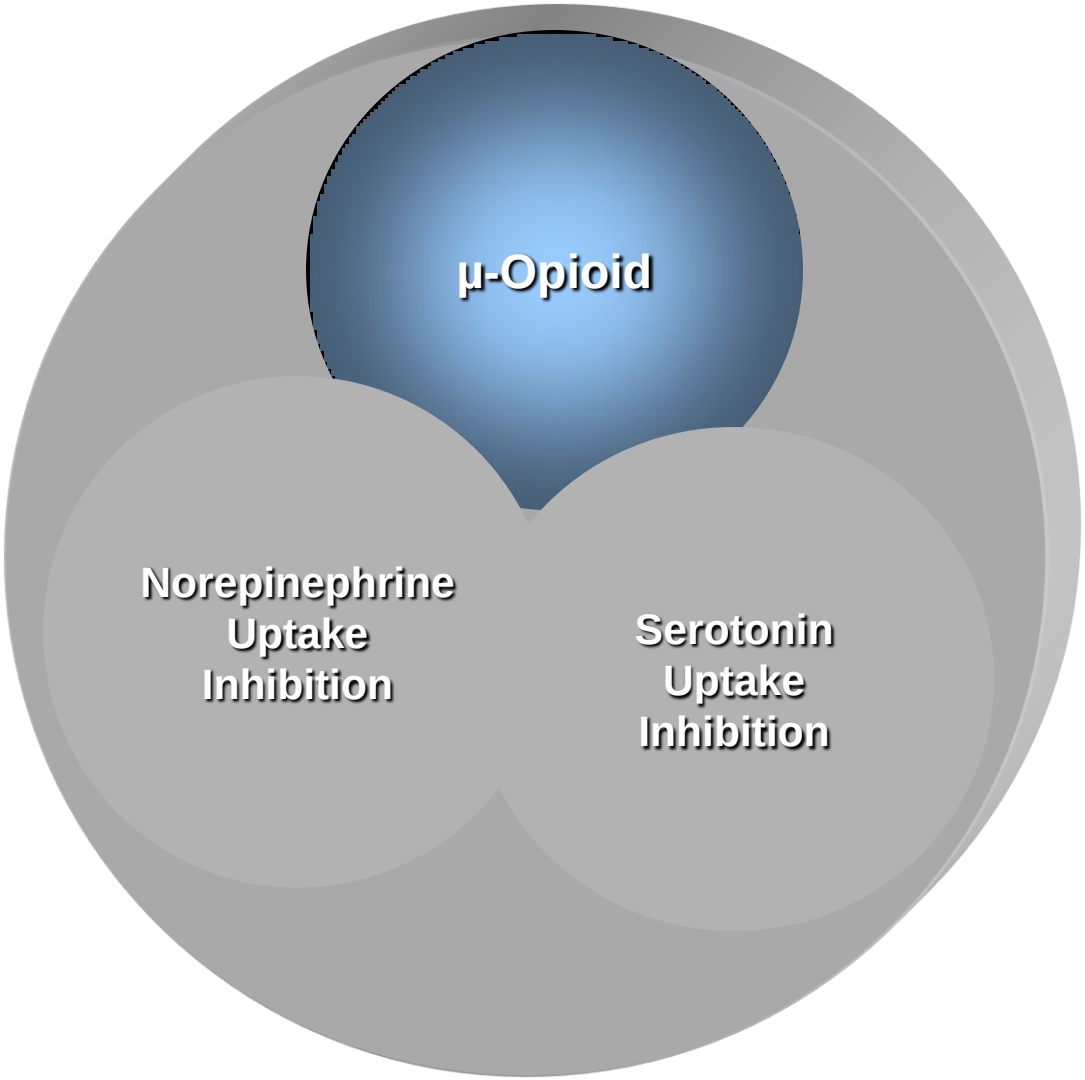
Metabolites of Tramadol



Tramadol‘s mode of action - biochemical profile

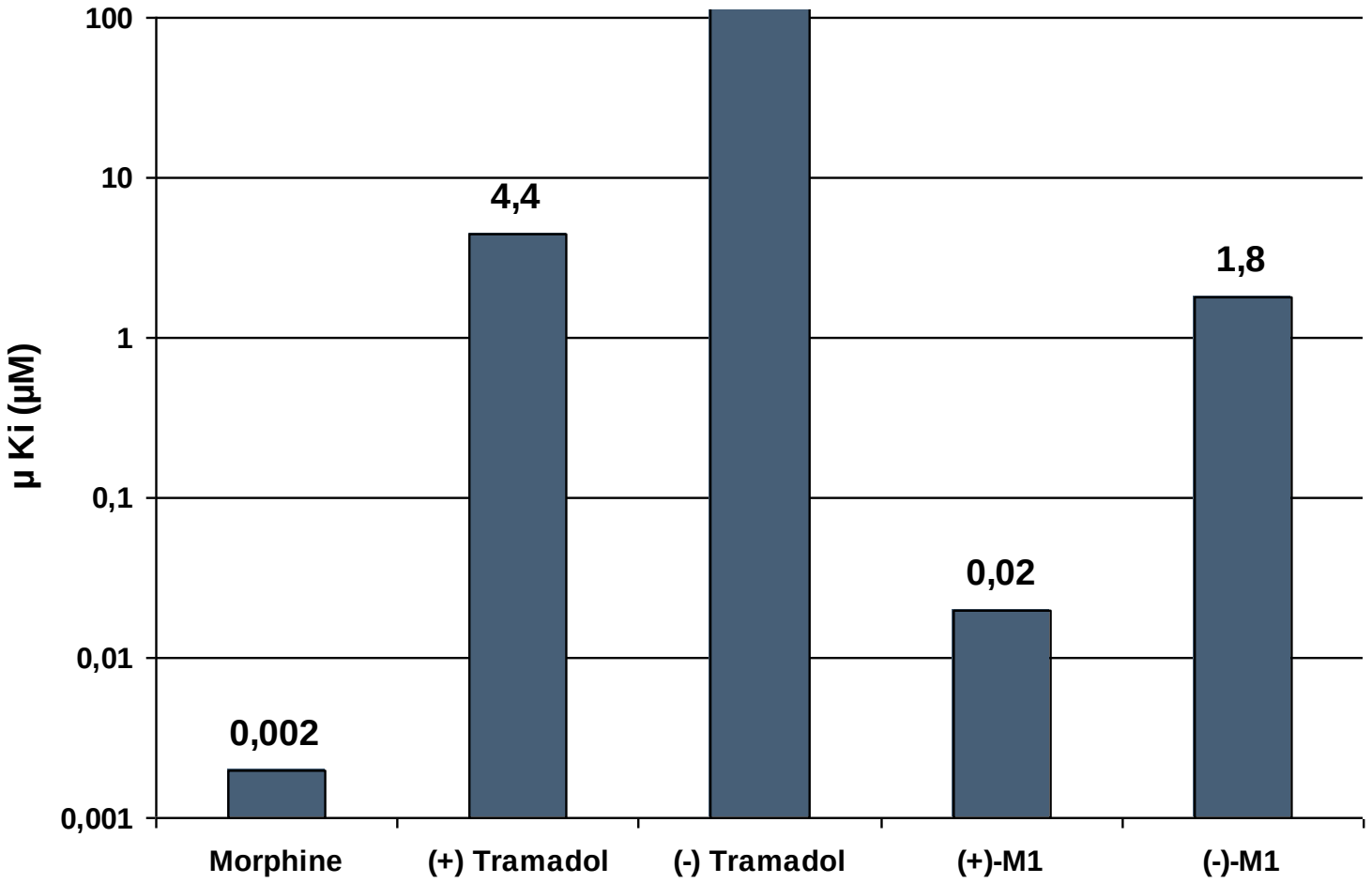


Tramadol‘s mode of action - biochemical profile

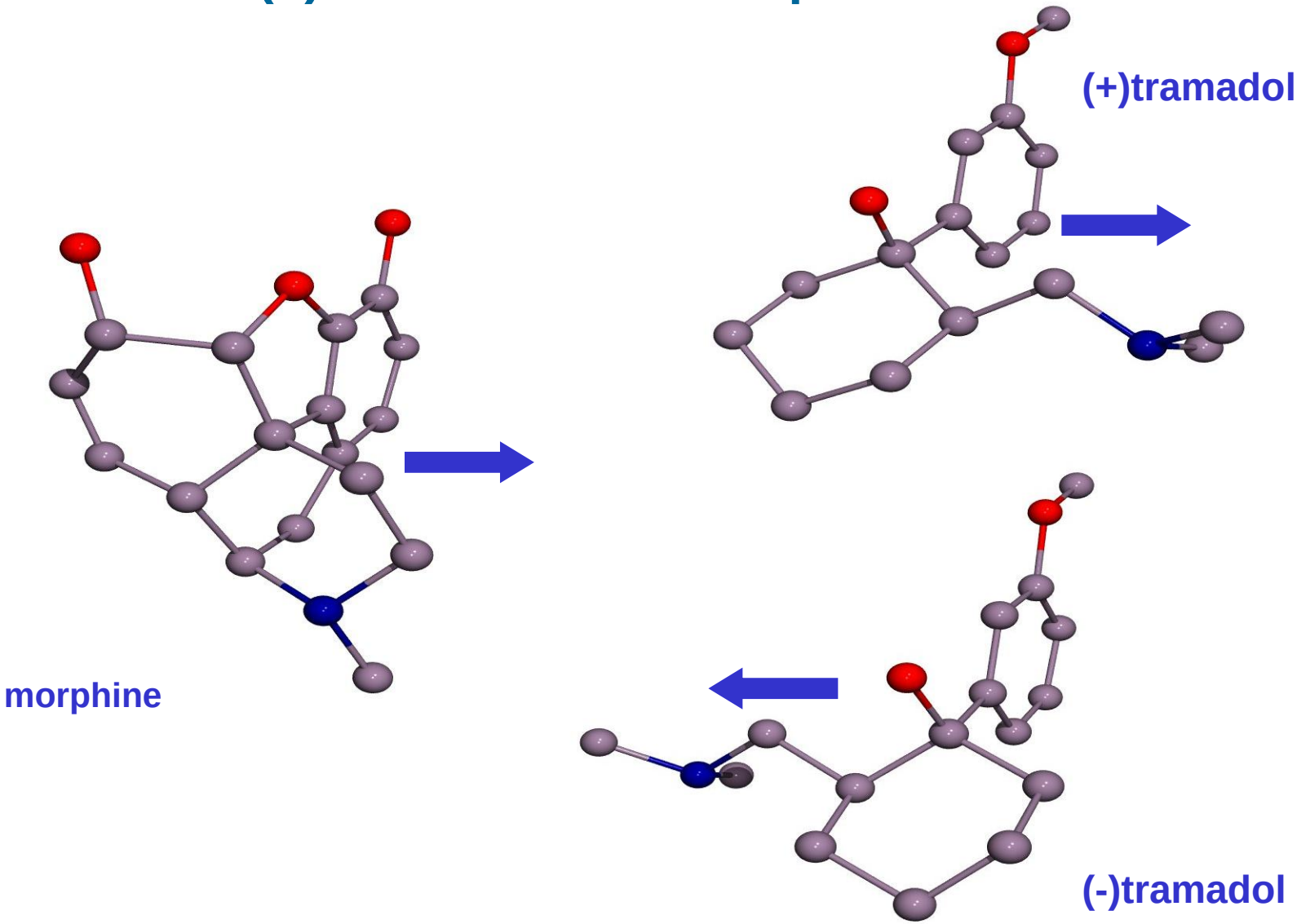


Tramadol – Pharmacological Profile

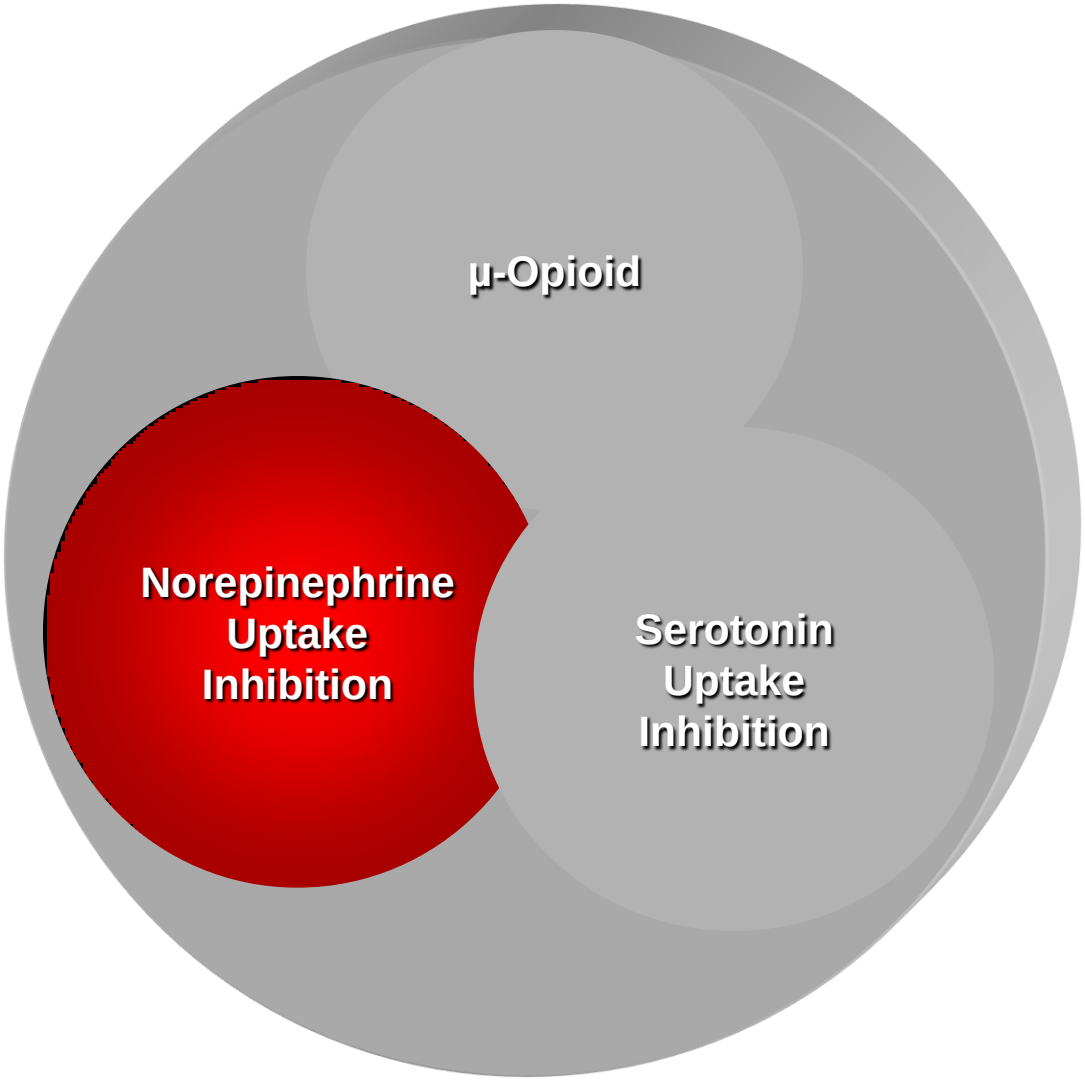
μ-Opioidbinding of tramadol and tramadol-M1



Comparison of molecular structures (+) Tramadol and Morphine

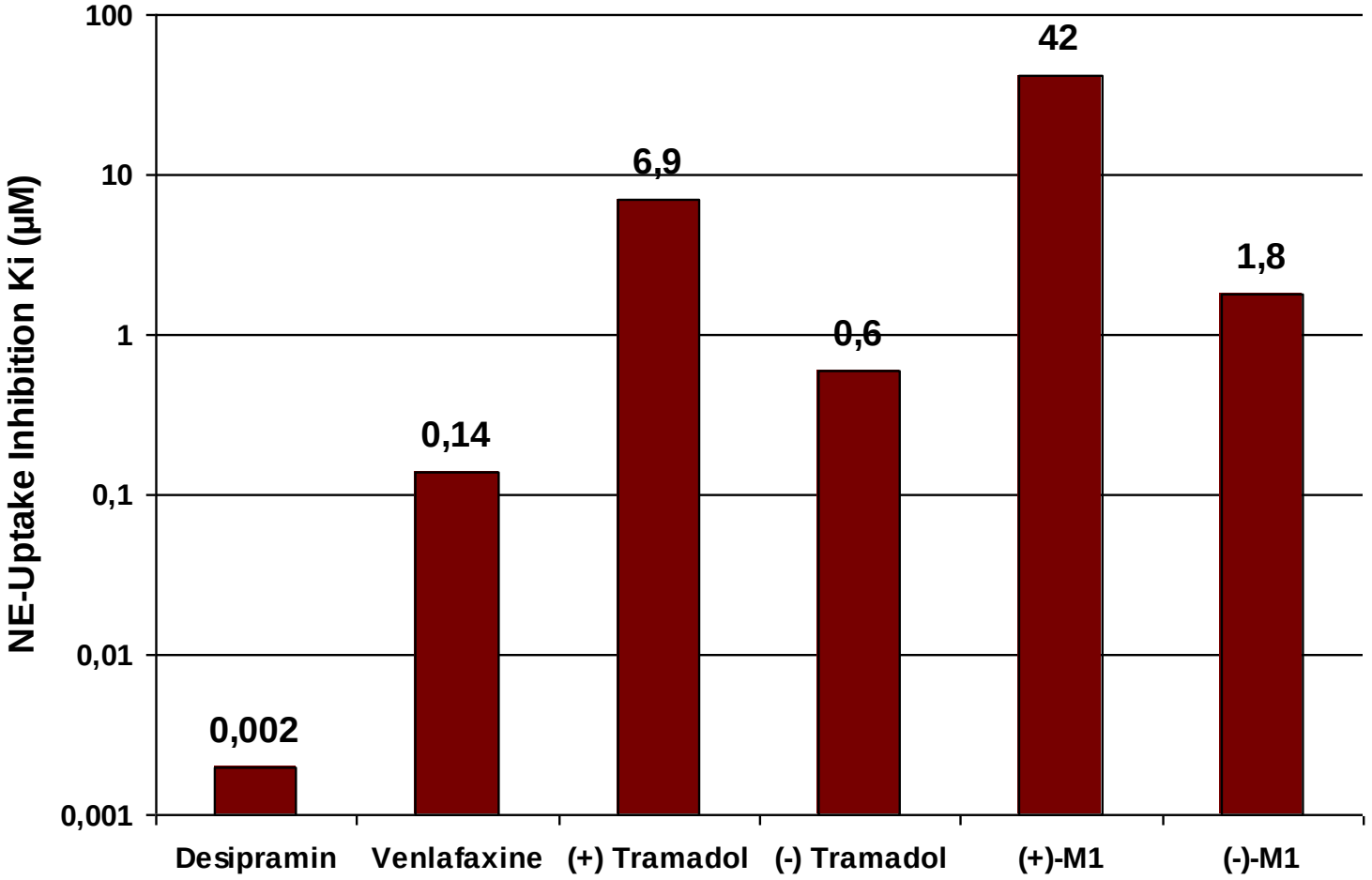


Tramadol‘s mode of action - biochemical profile

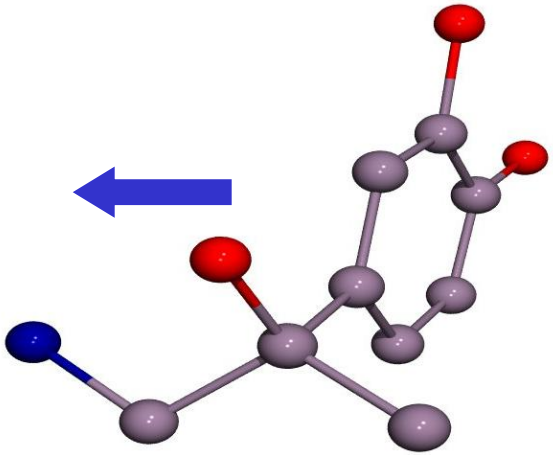


Tramadol – Pharmacological Profile

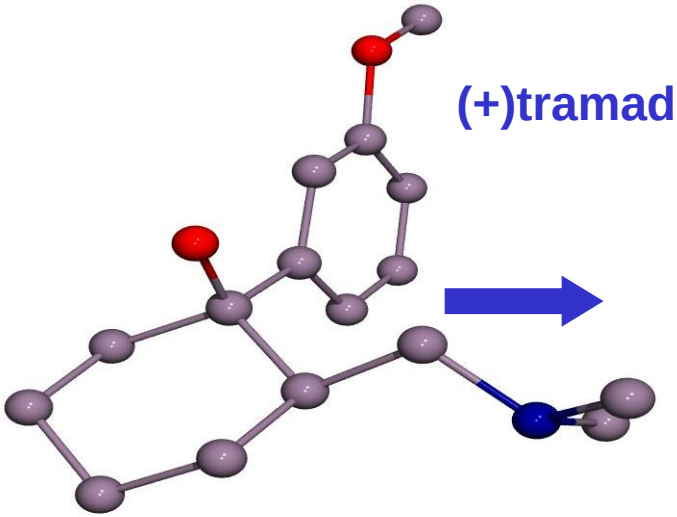
Norepinephrine-Uptake inhibition of tramadol and tramadol-M1



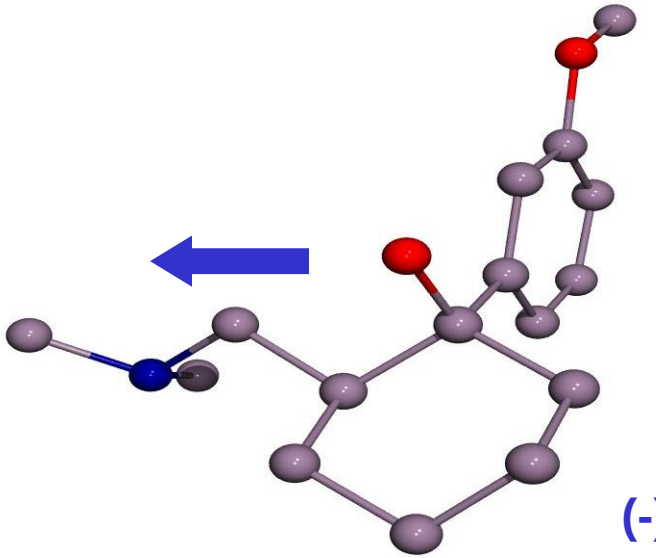
Comparison of molecular structures



norepinephrine

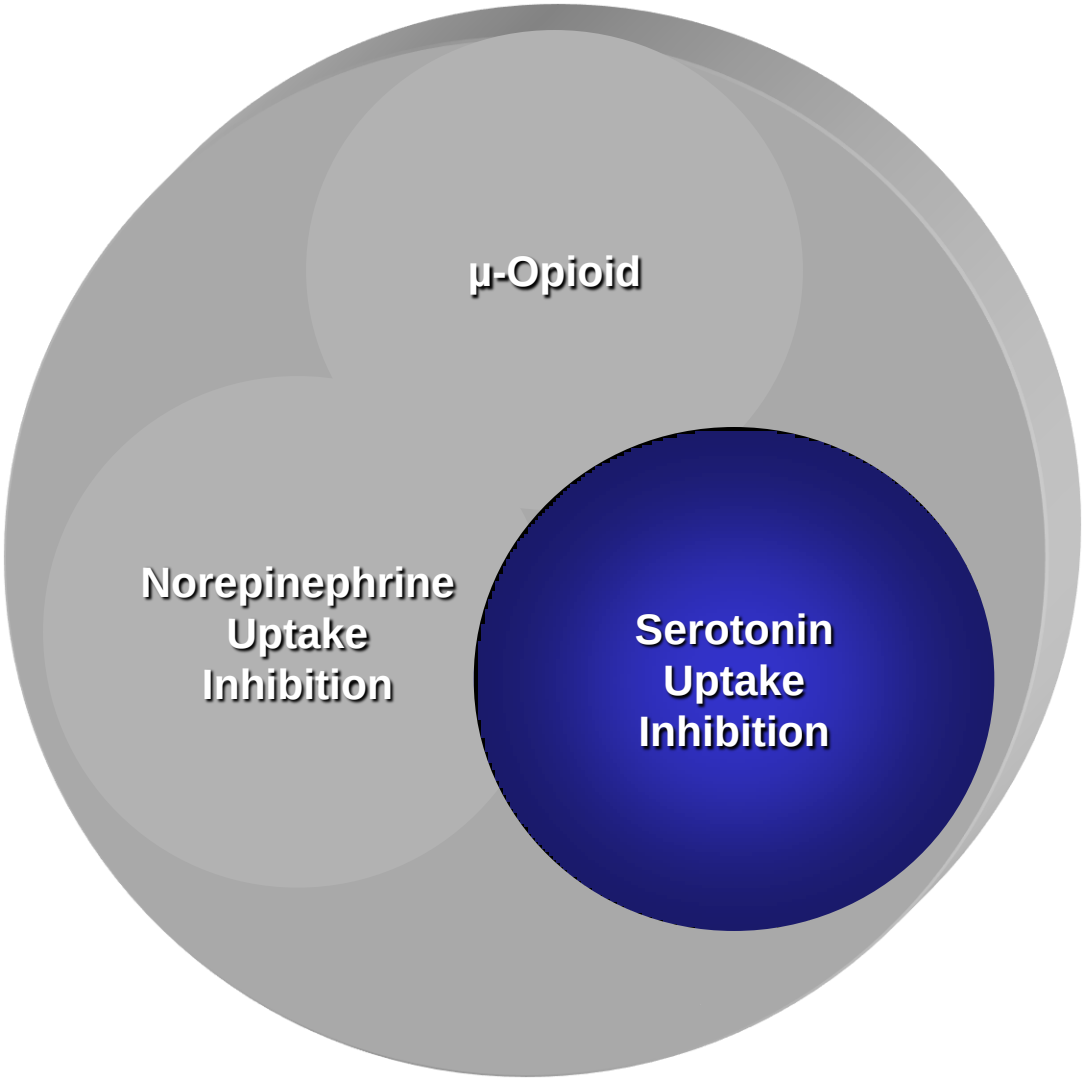


(+)tramadol



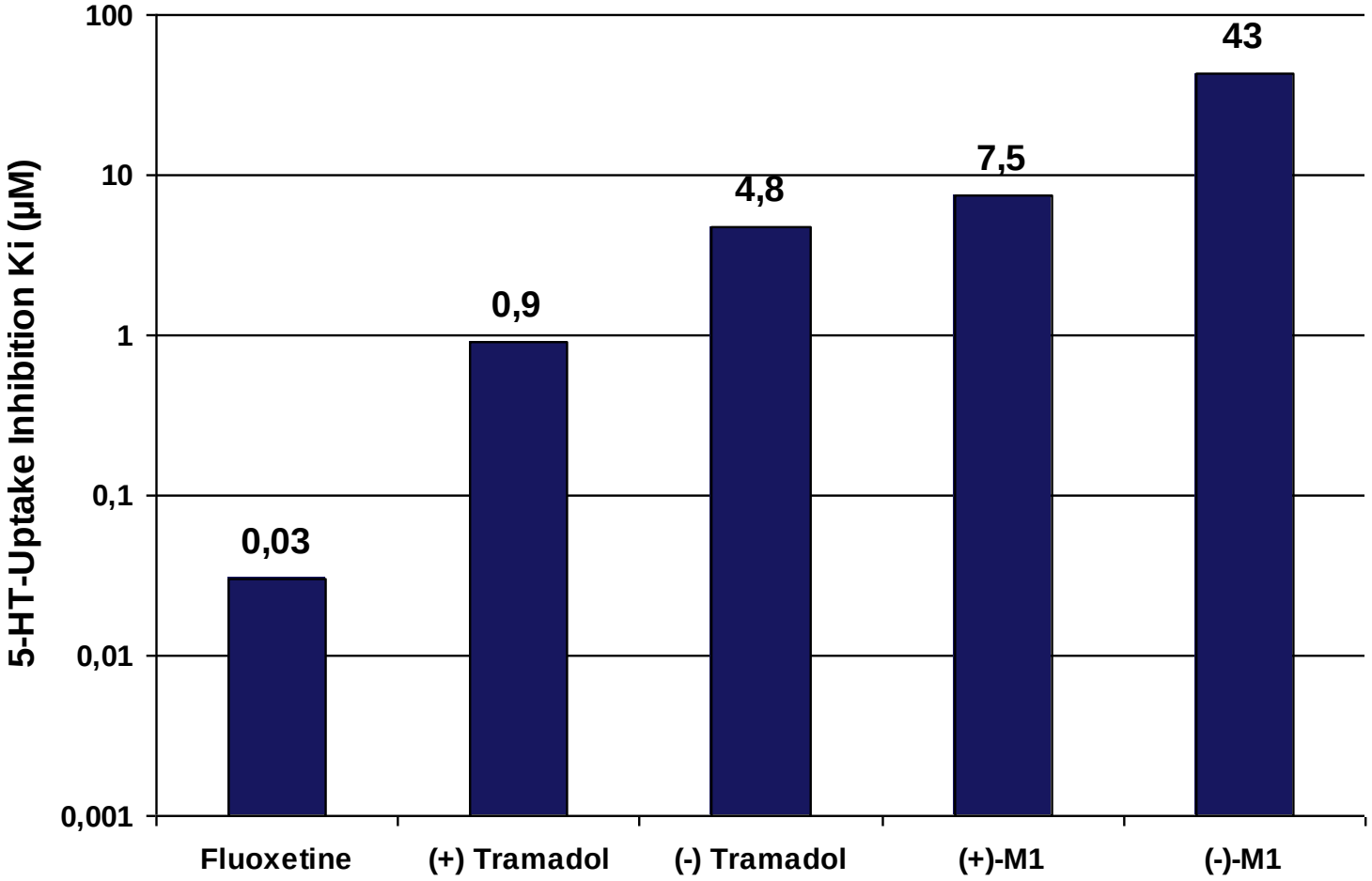
(-)tramadol

Tramadol‘s mode of action - biochemical profile

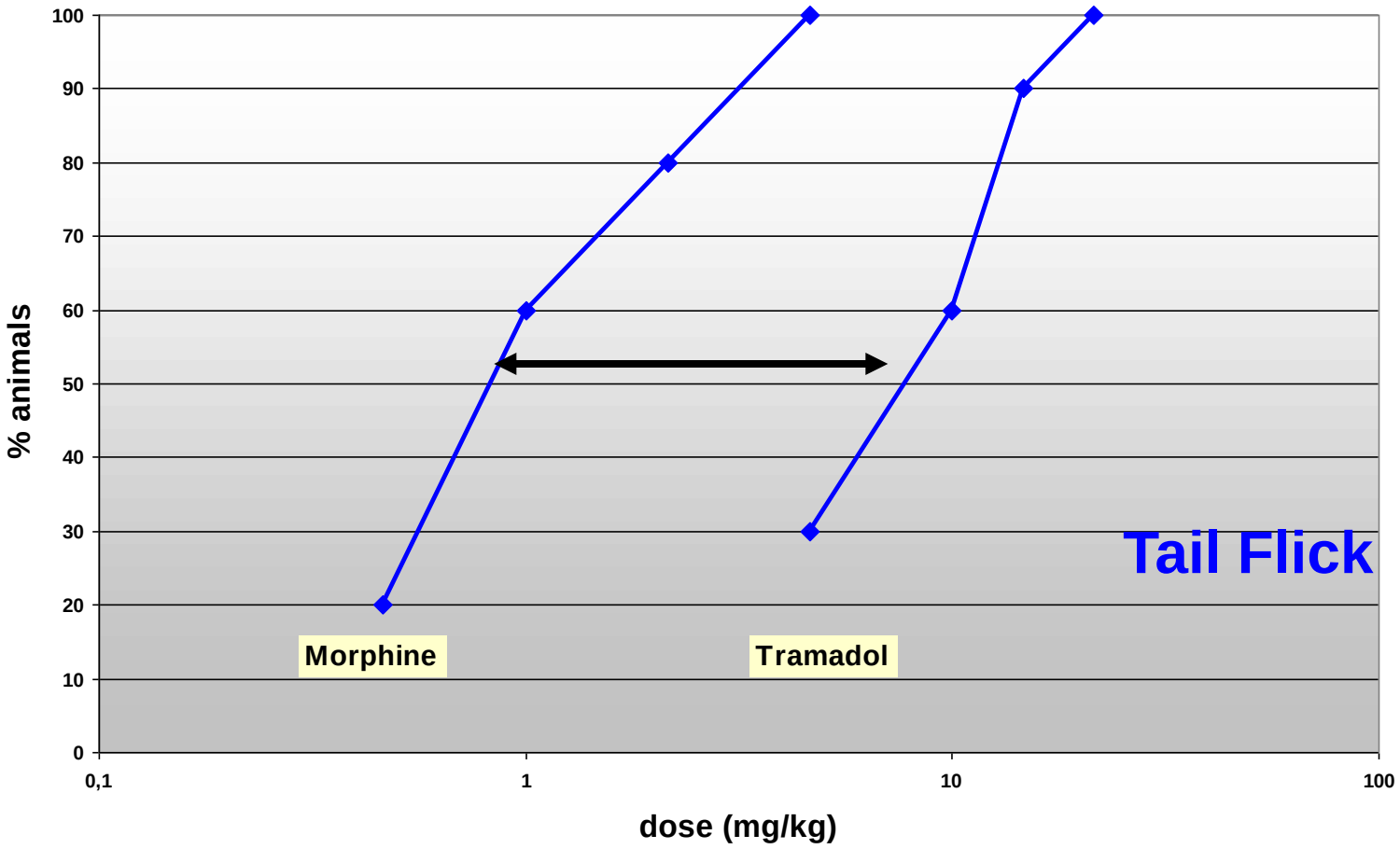


Tramadol – Pharmacological Profile

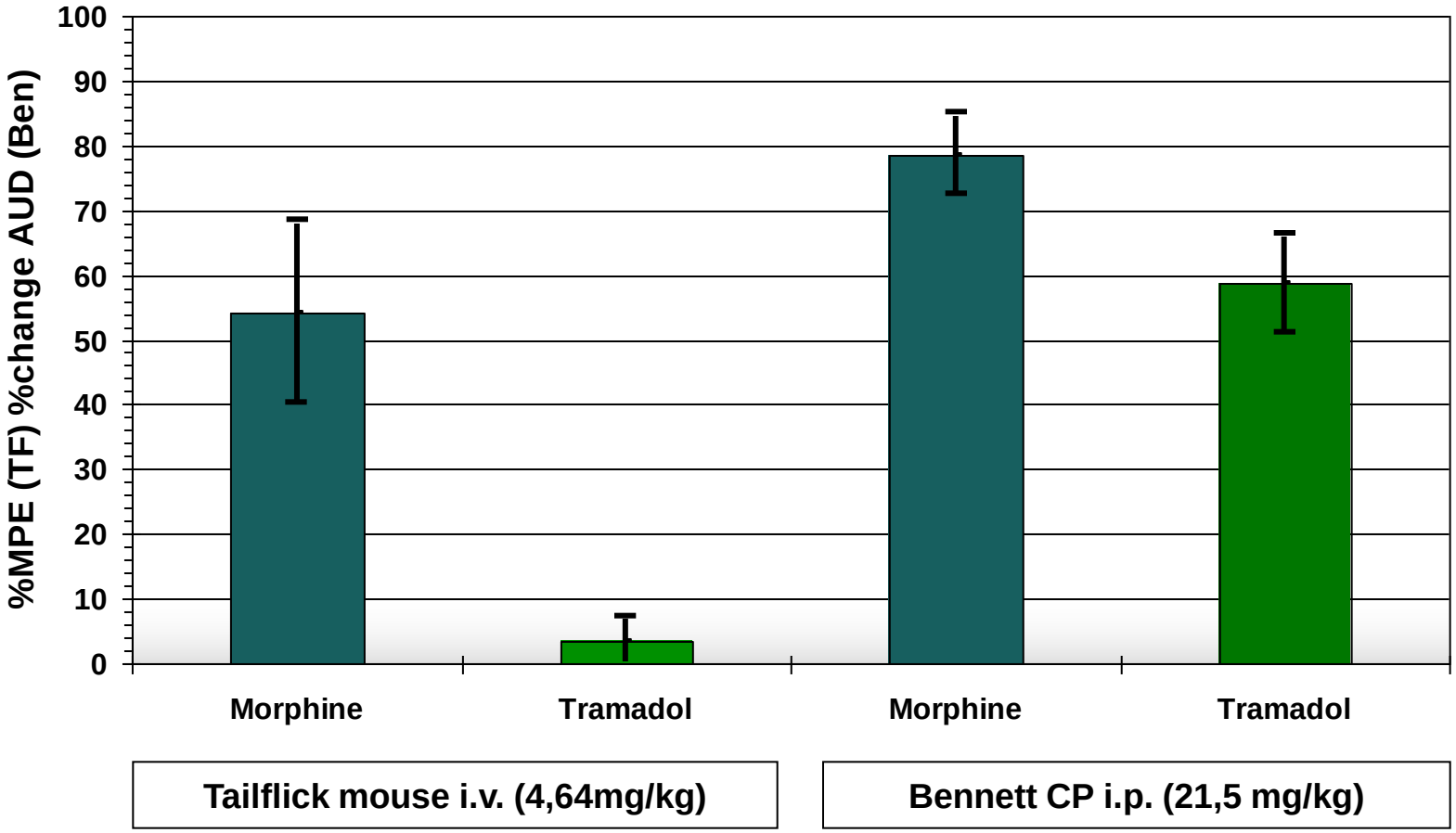
5HT-Uptake inhibition of tramadol and tramadol-M1



Comparison of acute pain (Tail Flick) and chronic inflammatory pain (Randall Selitto)

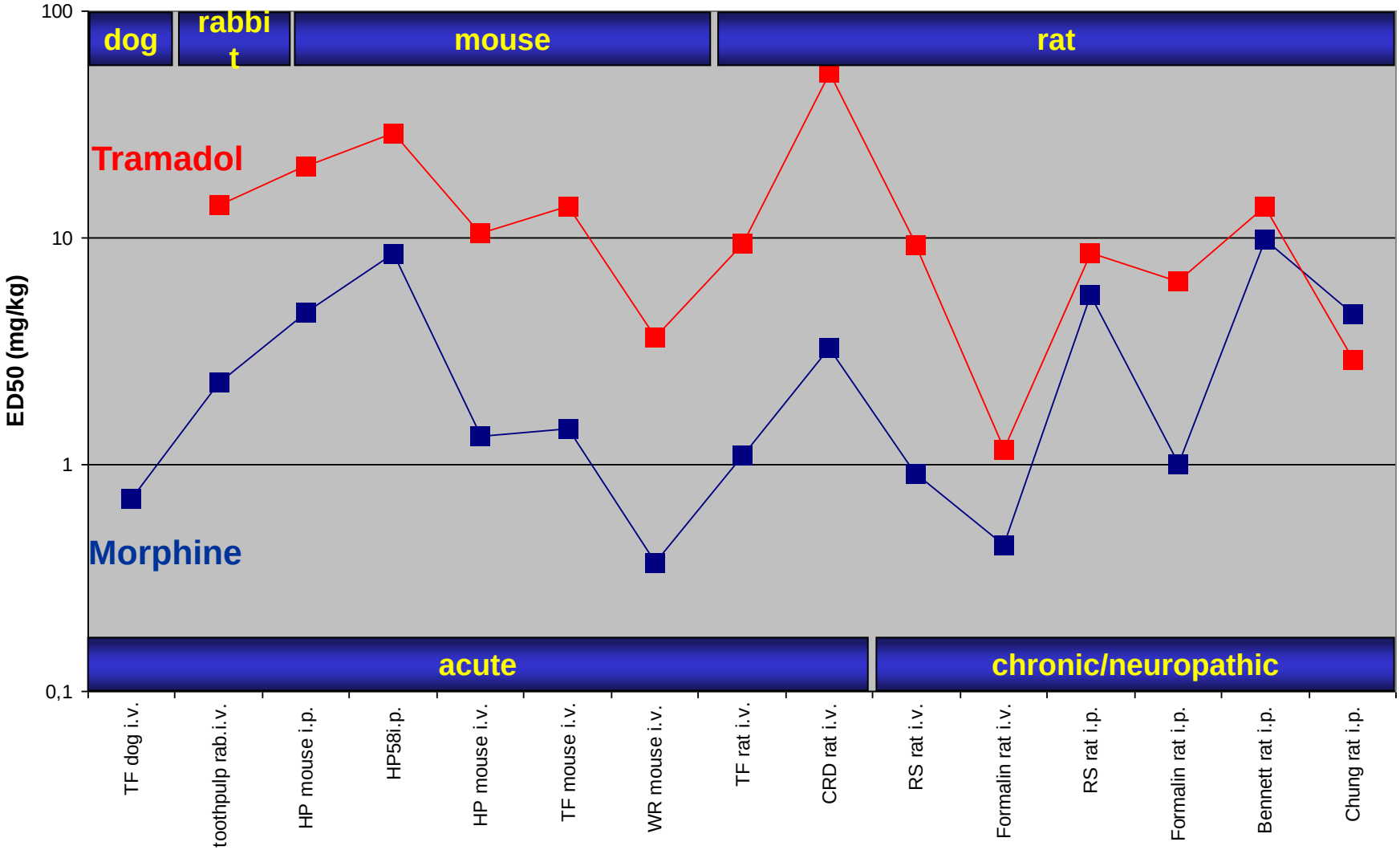


Comparison of acute pain (Tail Flick) and neuropathic pain (Bennett)

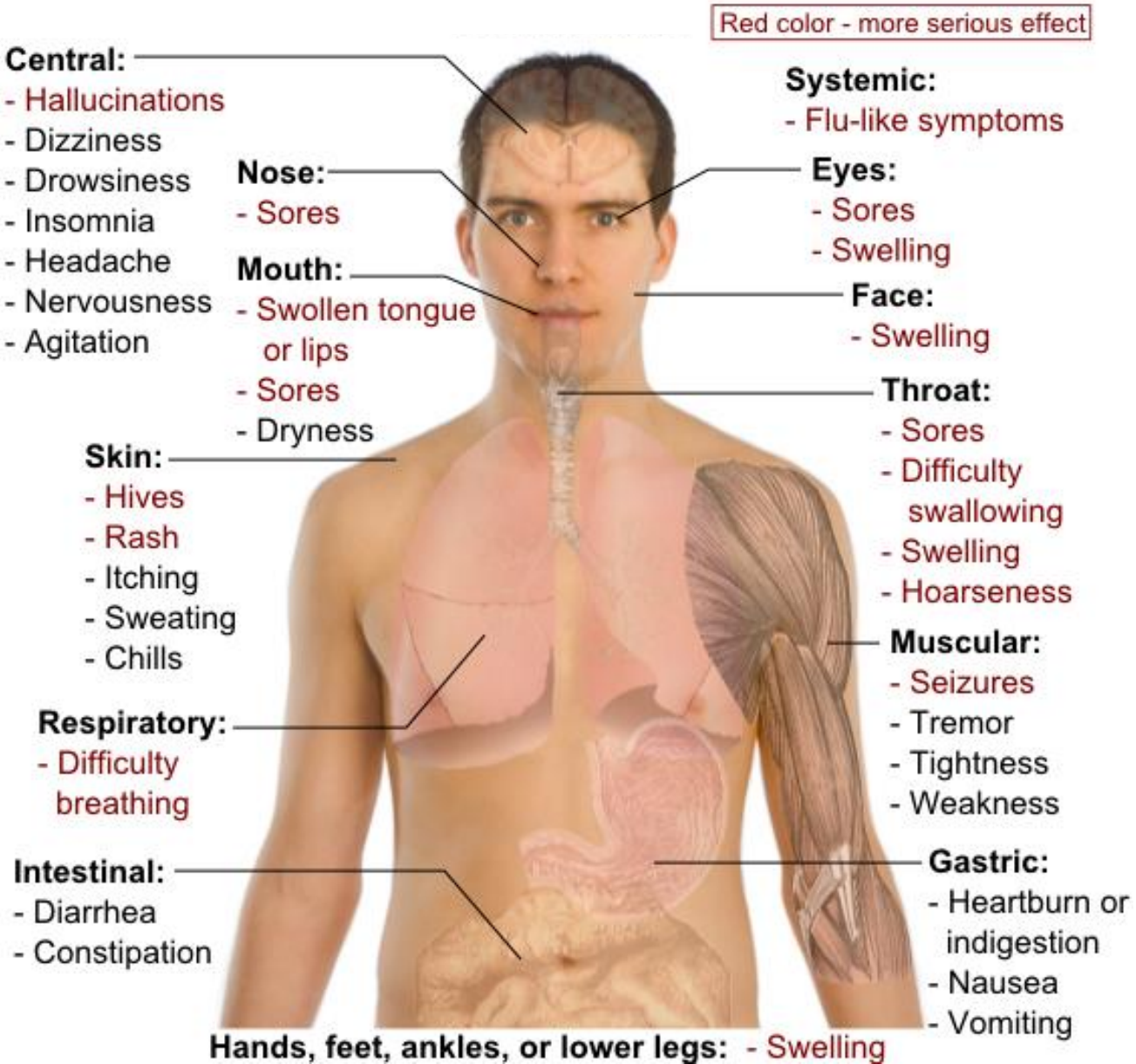


Tramadol – Pharmacological Profile

Antinociceptive Potency Profile
Comparison Morphin - Tramadol



Side Effects of Tramadol



Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant

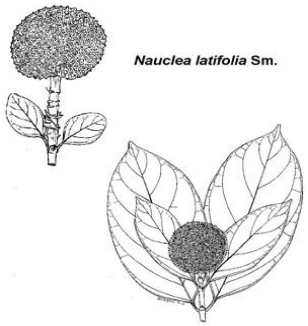
Angewandte Chemie

Natural Products

DOI: 10.1002/ange.201305697

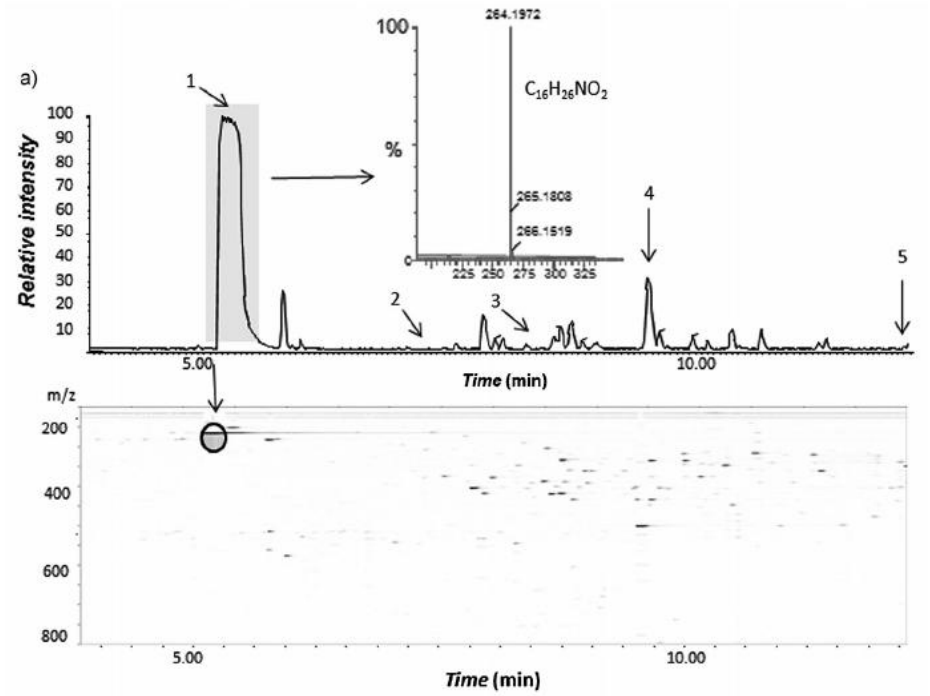
Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant**

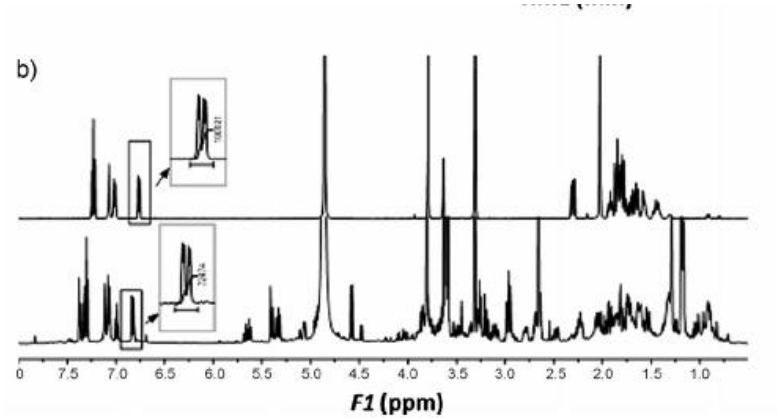
Ahcène Boumendjel, Germain Sotoing Taïwe, Elisabeth Ngo Bum, Tanguy Chabrol, Chantal Beney, Valérie Sinniger, Romain Haudecoeur, Laurence Marcourt, Soura Challal, Emerson Ferreira Queiroz, Florence Souard, Marc Le Borgne, Thierry Lomberget, Antoine Depaulis, Catherine Lavaud, Richard Robins, Jean-Luc Wolfender, Bruno Bonaz, and Michel De Waard**



Tramadol – A Natural Product?

NMR analysis and UHPLC-TOF-MS profiling of the crude extract from *N. latifolia* for identification and quantification of tramadol.





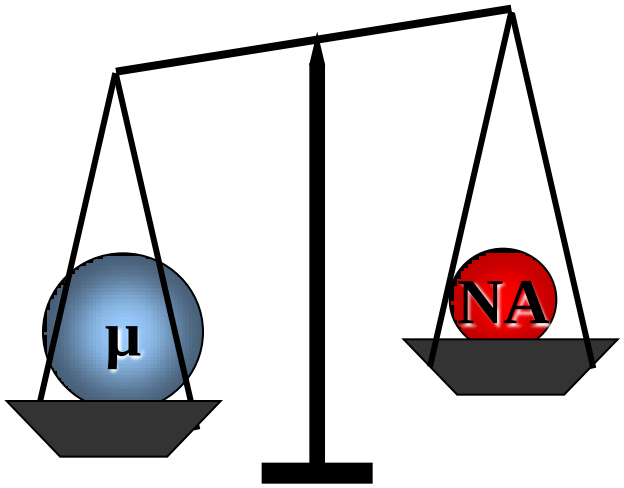
UHPLC-TOF-MS profiling of the crude ethanolic extract of N. latifolia with a label for compounds dereplicated (zoomed into the 0–12 min retention domain). Top panel: TOF-MS spectra of tramadol in the crude extract. Bottom panel: 2D ion map of the crude extract of N. latifolia displaying all recorded ions.

The absolute integration of the 1H NMR signal at dH=6.77 (ddd, 8.0, 2.6, 0.9 Hz, H-4') of commercial tramadol in a CD3OD solution at 263.4 mm was used as an external reference (top panel) to quantify the amount of natural tramadol in an ethanolic extract of N. latifolia (bottom panel) using the PULCON method.

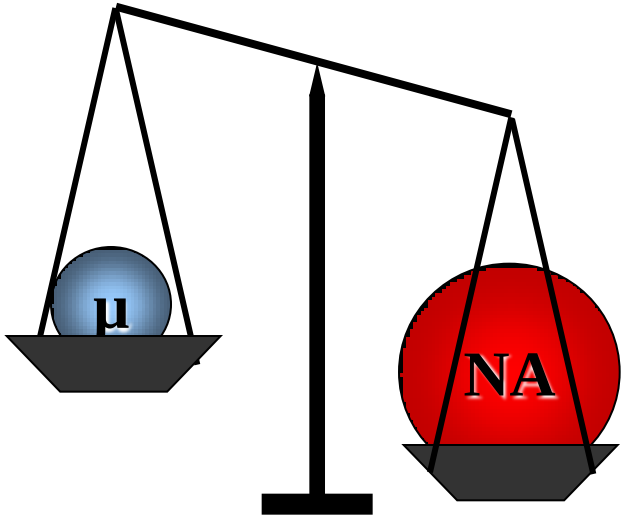
Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol

- Pain Transduction
- The Analgesic Market
- Current Analgesic Treatment Options
- Pain Research Today - The Unmet Needs
- Tramadol – History and Pharmacology
- **Tapentadol – A New Analgesic With a Dual Mode of Action**
  - **Structure-Activity-Relatioship**
  - ***In vitro* Profile**
  - ***In vivo* Pharmacology**
  - **Metabolism**
  - **Synthesis**

What have we learned from the Tramadol story?



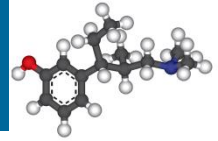
(+)-Tramadol



(-)-Tramadol

Can both principles be combined in one molecule (one enantiomer) ?

Tramadol – The Research Strategy



Gold -standard for the relief of moderate to severe pain

But: side effects

μ-Opioid

Noradrenalin Uptake Inhibition

Antidepressants and co-medication for chronic pain

Serotonin Uptake Inhibition

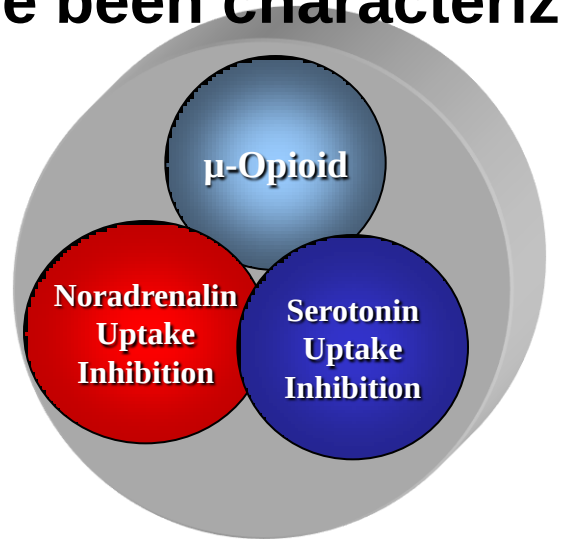
μ-Opioid

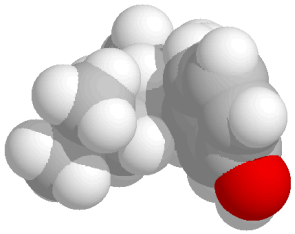
Noradrenali Uptake Inhibition

Serotonin Uptake Inhibition

Synergistic pain relief and less opioid side effects

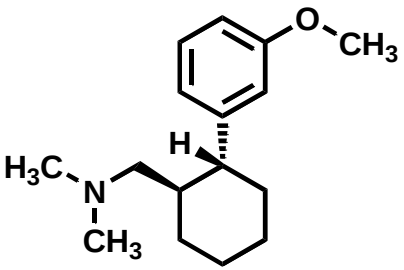
Several compounds with different biological profiles have been characterized

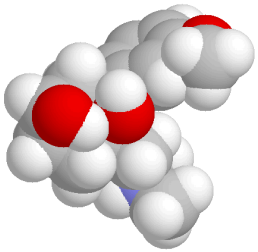




Faxeladol

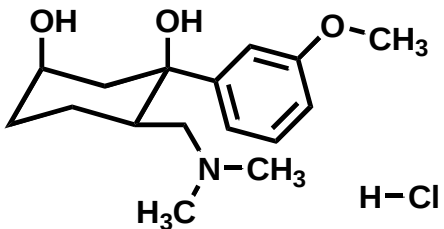
*03.12.1991

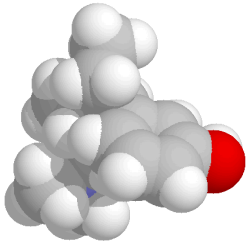




Axomadol

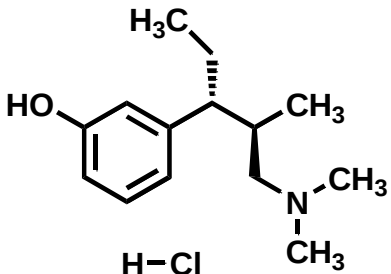
*16.07.1993





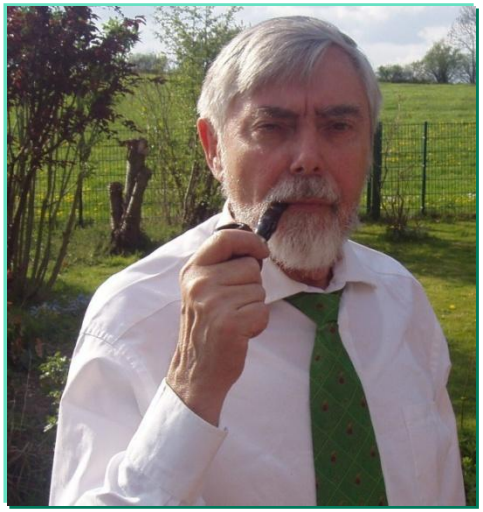
Tapentadol

*08.02.1994

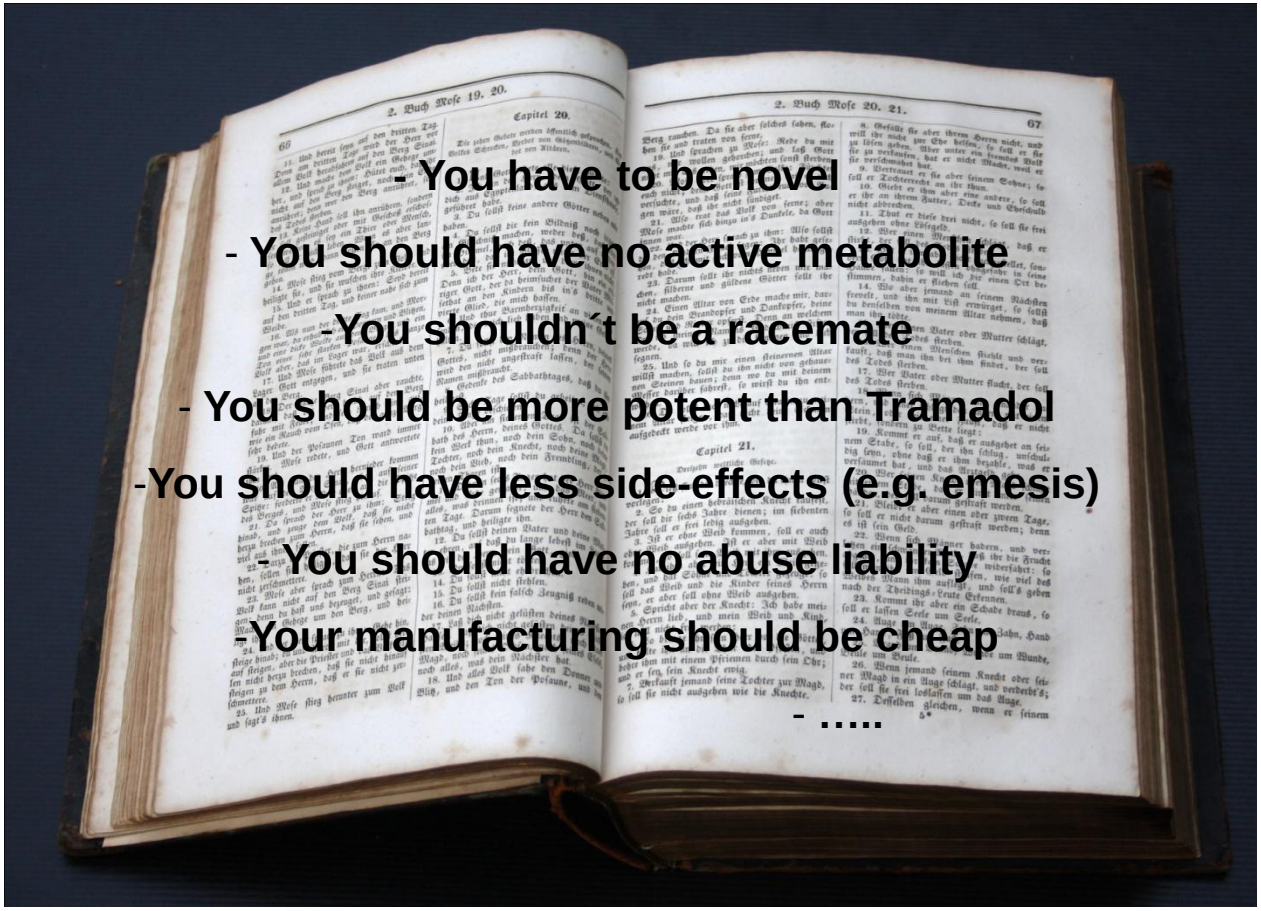


The Ten Commandments

The Golden Era of Research

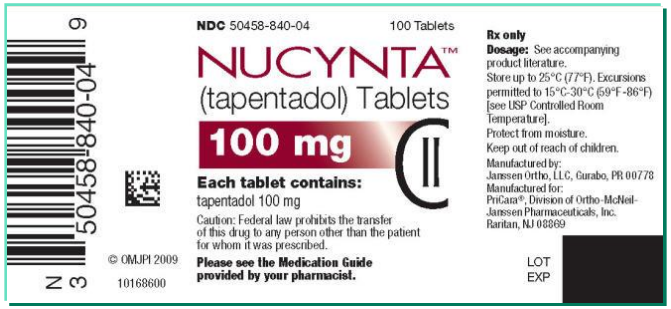


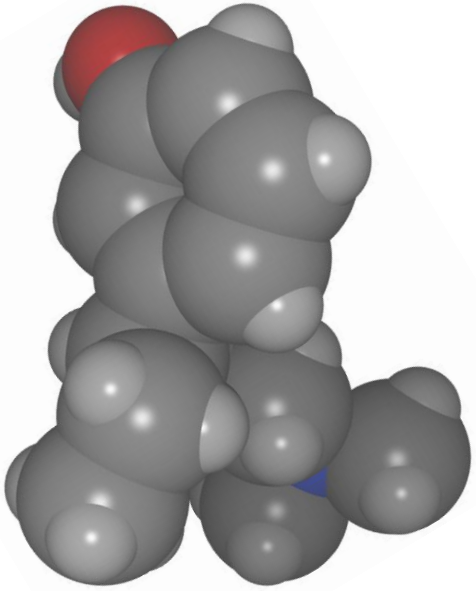
Prof. Werner Winter
(1980s – 1990s)

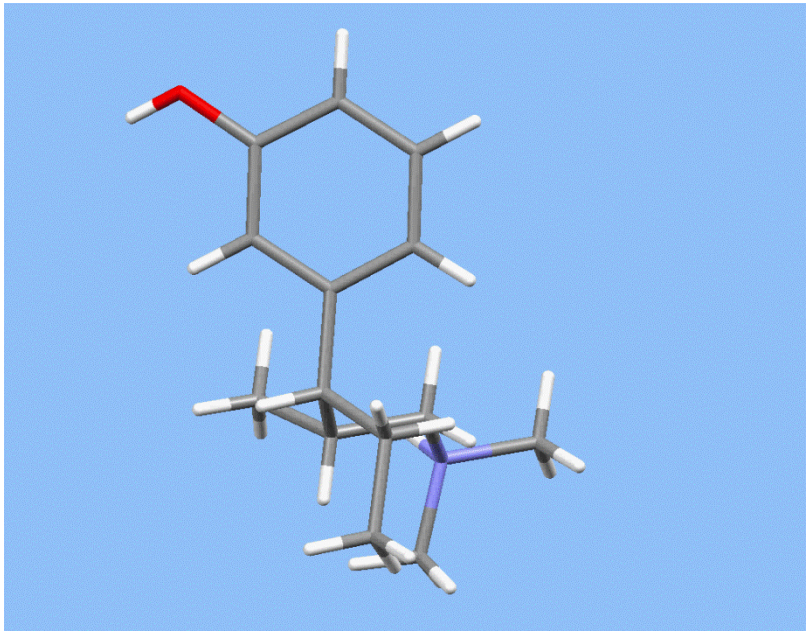


Tapentadol – A New Analgesic with a Dual Mode of Action

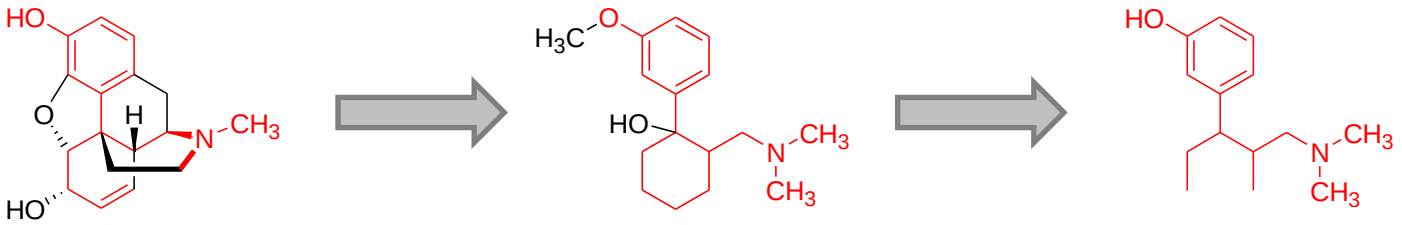
PALEXIA®
TAPENTADOL



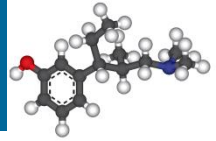




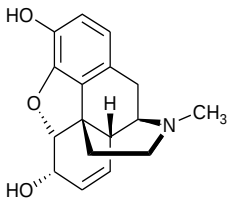
Tapentadol – A New Analgesic with a Dual Mode of Action

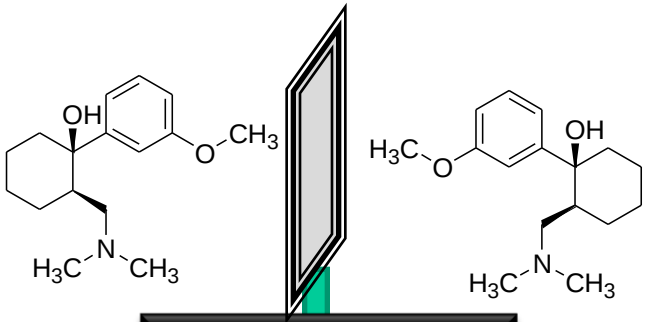


Tapentadol – A New Analgesic with a Dual Mode of Action

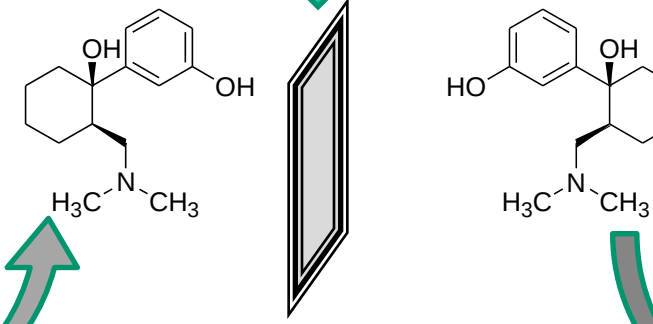


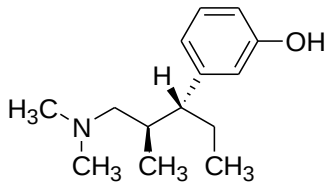
Morphine | **Tramadol** | **Tapentadol**

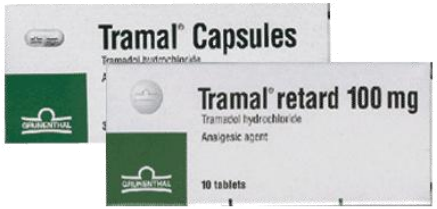




Metabolic Activation



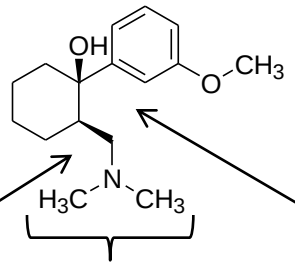




Tapentadol – A New Analgesic with a Dual Mode of Action

- Derivatisation of hydroxyl group: ester, ether, …
- Replacement of hydroxylgroup by N, H, halogen
- Elimination resulting in olefins

- Substitution of cyclohexane ring
- Size of ring system
- Introduction of hetero atoms (e. g. O, N, S)
- Aromatic rings

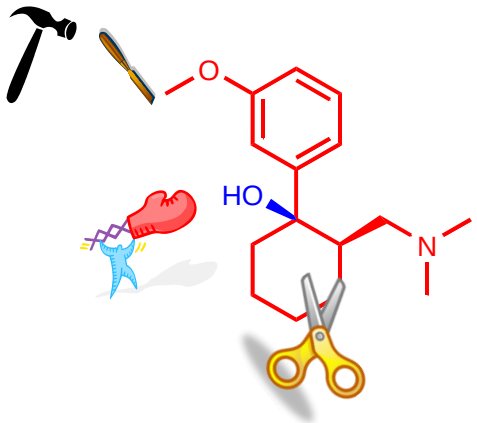


- Phenyl ring substitution
- Replacement by heterocyclic aryl rings
- Replacement by acyclic ring systems

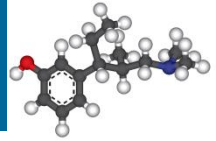
- Methylen group substitution

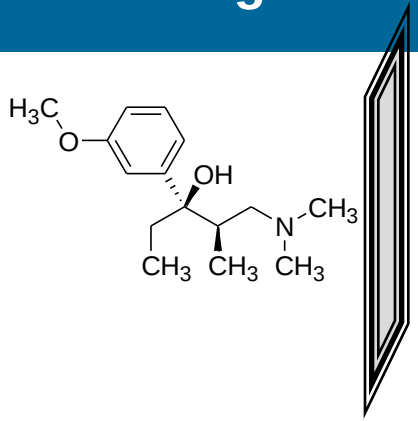
- N- Substitution
- N-containing ring systems

- Introduction of spacer groups between ring systems

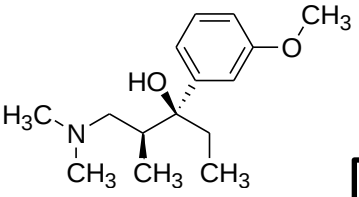


Tapentadol – A New Analgesic with a Dual Mode of Action

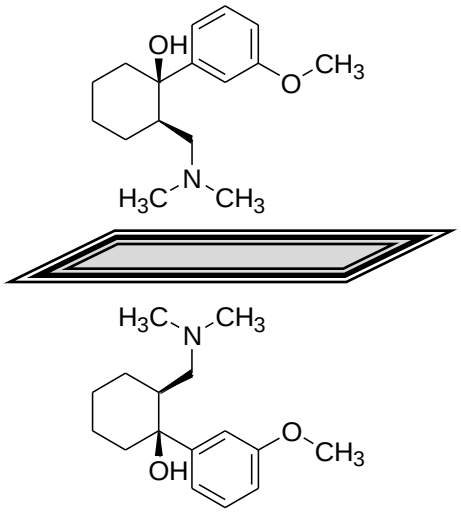




Opening of the cyclohexane ring

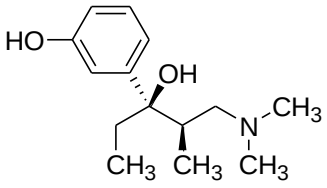


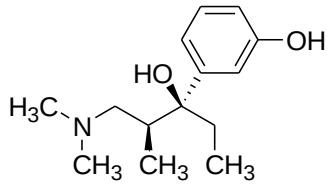
From Prodrug to direct acting drug



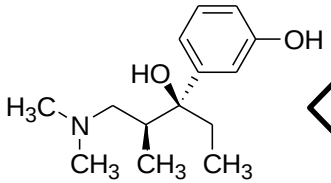
Tramadol

Racemate with relative stereochemistry cis

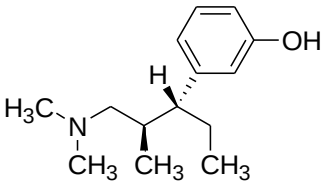




Selecting of one enantiomer

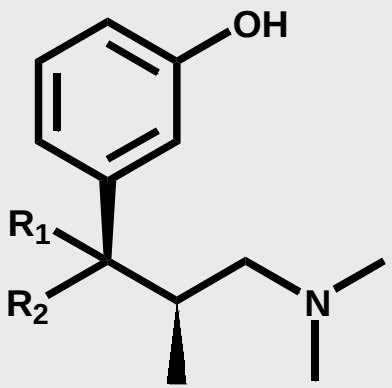


Replacement of *tert.* OH group



Tapentadol

CH_3 as replacement for C_2H_5

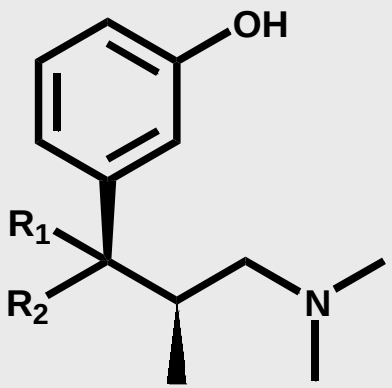


Code	R_1	R_2	μ Ki	5-HT Ki	NA Ki	TF mouse ED50
GRT6 (+)	OH	C2H5	0,009	75	4,4	0,32
GRT5 (-)	OH	C2H5	1,4	84	0,7	56,1
GRT8 (+)	OH	CH3	0,06	8,6	20	2,1
GRT7 (-)	OH	CH3	0,7	81	1	32,4

μ-binding:	**(+) Enantiomer**	**↓**
	(-) Enantiomer	**-**
5HT:	**(+) Enantiomer**	**↑**
	(-) Enantiomer	**-**
NA:	**(+) Enantiomer**	**-**
	(-) Enantiomer	**-**

For the (+)-enantiomer μ-binding decreased,
5-HT-binding increased

H, F as replacement for OH

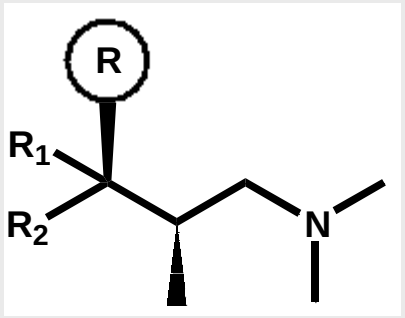


Code	R_1	R_2	μ Ki	5-HT Ki	NA Ki	TF mouse ED50
GRT6 (+)	OH	C2H5	0,009	75	4,4	0,32
GRT5 (-)	OH	C2H5	1,4	84	0,7	56,1
GRT2 (+)	H	C2H5	0,007	7,3	1,9	0,85
GRT1 (-)	H	C2H5	0,1	2,3	0,6	3
GRT4 (+)	F	C2H5	0,007	27,8	1,7	0,32
GRT3 (-)	F	C2H5	0,04	4,1	0,3	1,44

μ-binding:	**(+)**	**Enantiomer**	**-**
	(-)	**Enantiomer**	**↑**
5HT:	**(+)**	**Enantiomer**	**↑**
	(-)	**Enantiomer**	**↑**
NA:	**(+)**	**Enantiomer**	**-**
	(-)	**Enantiomer**	**-**

The (-)-enantiomers have μ-binding and NA-reuptake inhibition in a similar range

Phenol as replacement for naphtol



Code	R	R_1	R_2	μ Ki	5-HT Ki	NA Ki	TF mouse ED50
GRT10 (+)	Naphtol	OH	C_2H_5	0,02	17,4	0,2	0,6
GRT9 (-)	Naphtol	OH	C_2H_5	15%(1)	6,8	0,05	2an.(10)
GRT6 (+)	Phenol	OH	C_2H_5	0,009	75	4,4	0,32
GRT5 (-)	Phenol	OH	C_2H_5	1,4	84	0,7	56,1

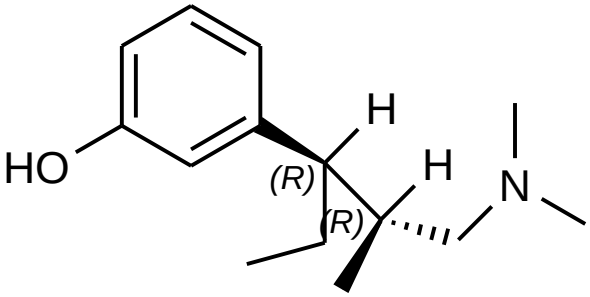
μ-binding:	**(+)**	**Enantiomer**	↑
	(-)	**Enantiomer**	↑
5HT:	**(+)**	**Enantiomer**	↓
	(-)	**Enantiomer**	↓
NA:	**(+)**	**Enantiomer**	↓
	(-)	**Enantiomer**	↓

μ-binding for both enantiomers increased,
5-HT and NA decreased

The „Birth Certificate“ of Tapentadol

…Is it boy or is it a girl?

Peter Jansen



STOLBERG IM RHEINLAND

Zentral-Analytik	Prüfsubstanz	Datum: 8.2.1994

Code-Nr.	Hersteller	Herst.-Datum	Charge	Vorh. Menge
BN-200	Labor Dr. Buschmann	01/94	0 Bu 322-1-1-I	1.0 g

Angenommene Struktur: (−)-(5,5)

Bezugssubstanz/Literaturangabe: BN-9

Summenformel: $C_{14}H_{24}ClNO$ (257.80) Fp: 123.1° (Zersetzung) Kp: /

Chemische Bezeichnung: (−)-(1S,2S)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol-Hydrochlorid

letzter Syntheseschritt: Darstellung des Hydrochlorids
Lösungsmittel: Ether

Dünnschichtchromatographie durchgeführt: ja ☒ nein ☐
Bedingungen:
Trennschicht: DC-TLC mit Fluoreszenzindikator
Fließmittel: Chloroform : Methanol = 4:1
Detektion: 1. Kammer: UV

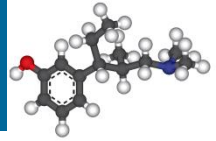
*) ^{1}H-NMR: 42852
^{13}C-NMR: 42883

**) ee > 99 %
Bu 68 #1 als Reagenz
chiral HPLC, Herr Wehr

$[\alpha]_D^{RT}$ = −27.5° (c=0.52, MeOH)

VORSICHT

Bemerkungen:
lichtempfindlich: ja ☐ nein ☐ hygroskopisch: ja ☐ nein ☐
feuchtigkeitsempfindlich: ja ☐ nein ☐ hautreizend: ja ☐ nein ☐
Sonstiges:



Morphin und Tapentadol

Vergleich der Affinität von Tapentadol und Morphin zu unterschiedlichen Opioidrezeptor-Subtypen, untersucht in Bindungsstudien an Rattenhirnmembranen (MOR, KOR,DOR) oder humanen rekombinanten Rezeptoren (NOP) (Tzschentke et al. 2006)

Substanz	K_i Wert (µM)			
	MOR	KOR	DOR	NOP
Tapentadol	0,1	0,9	1,0	>100
Morphin	0,002	0,17	0,002	>100

MOR: µ-Opioidrezeptor, KOR: κ-Opioidrezeptor, DOR: δ-Opioidrezeptor, NOP: ORL1- oder Nozizeptin-Rezeptor

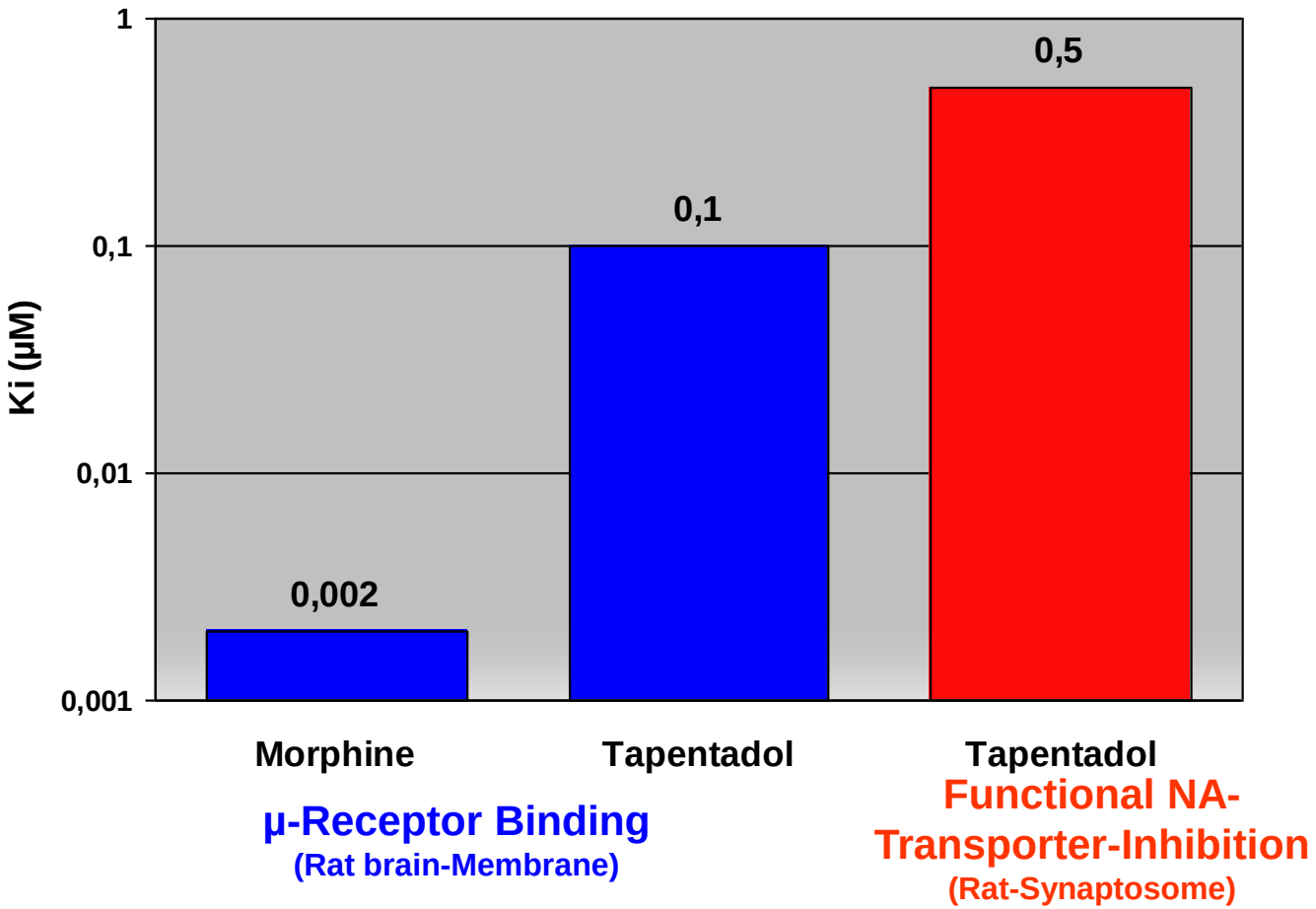
Vergleich von Tapentadol und Desipramin im Hinblick auf die Neurotransmitter-Wiederaufnahme-Hemmung, untersucht an Rattenhirn-Synaptosomen

Transmitter	K_i Wert (µM)	
	Tapentadol	Desipramin
Noradrenalin	0,5	0,001
5-HT	2,4	1,4
Dopamin	KE	KA
Cholin	39	KA

KE: kein Effekt (5 % Hemmung bei 1 µM), KA: keine Angabe.

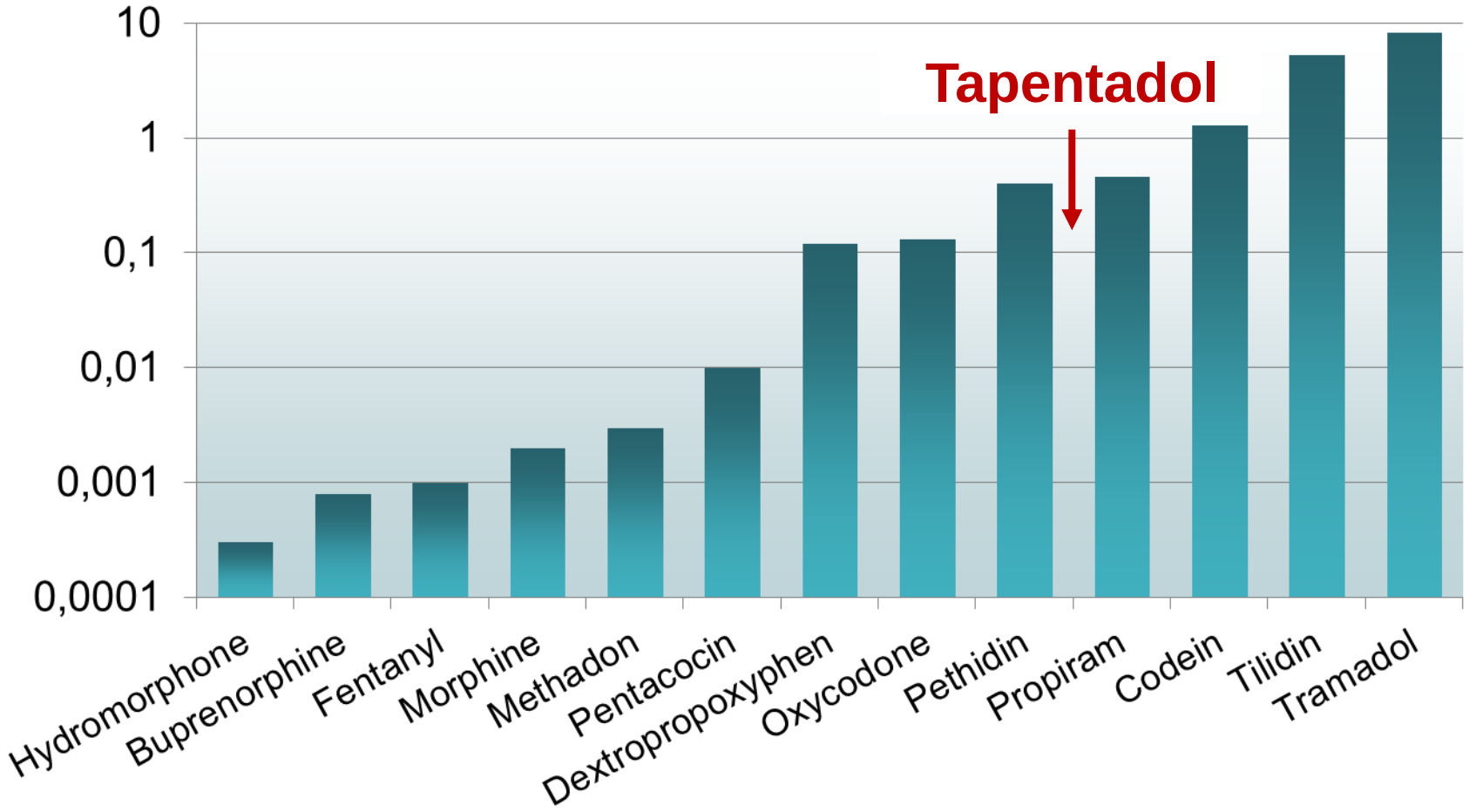
Tapentadol – A New Analgesic with a Dual Mode of Action

μ-Rezeptor-Agonism (MOR) and Noradrenalin Reuptake Inhibition (NRI)

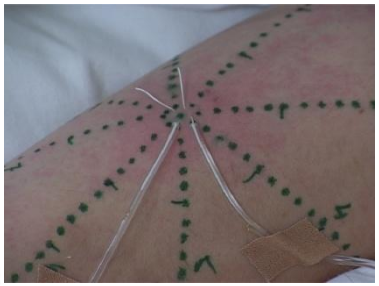


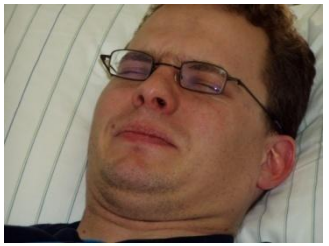
50-fold weaker μ-receptor binding in comparison to Morphine

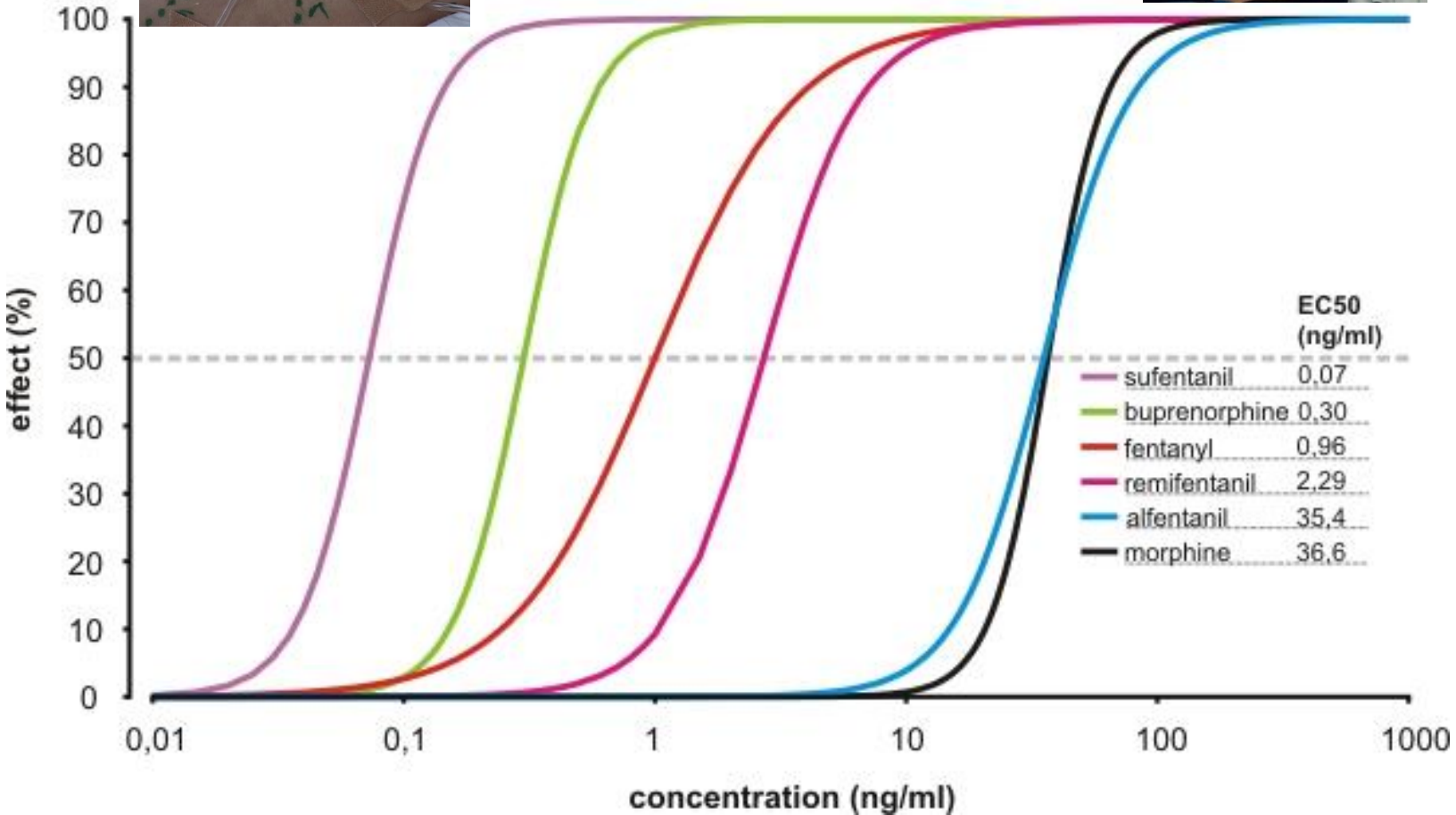
Binding Affinity of μ-Opioids



Analgetische Effekte von Opioiden

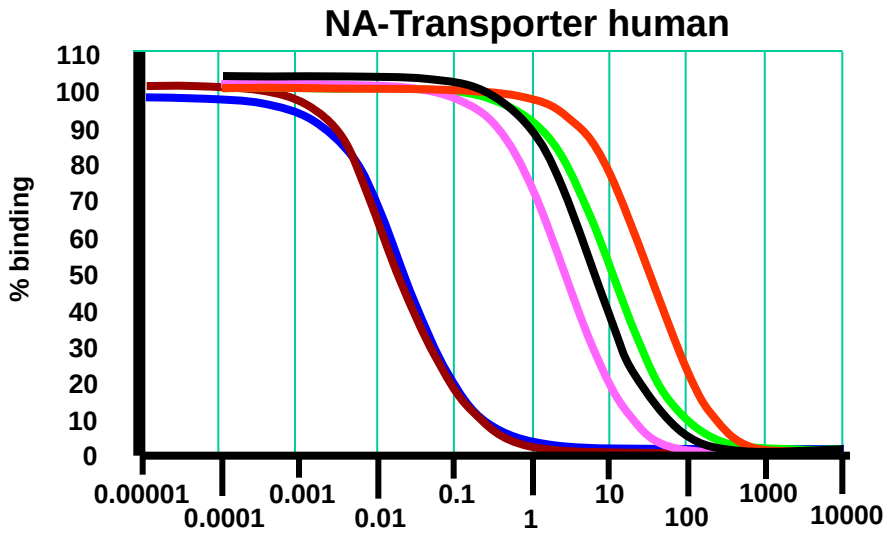


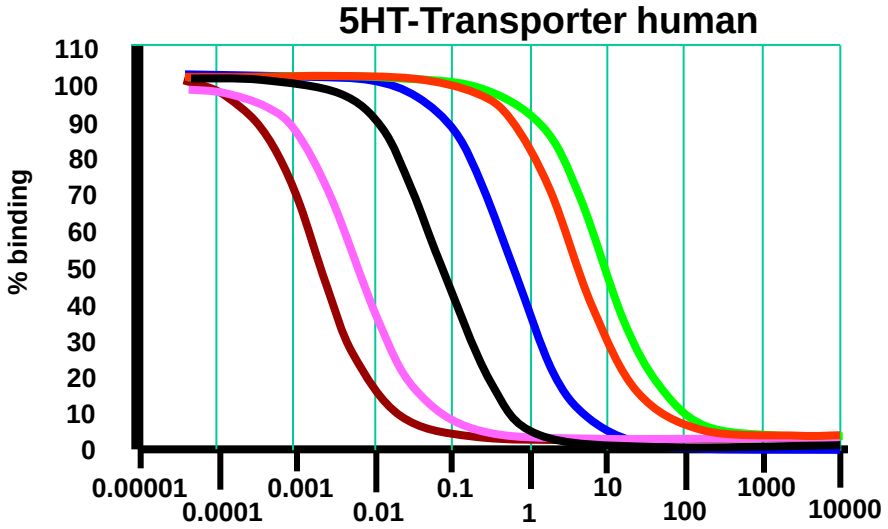


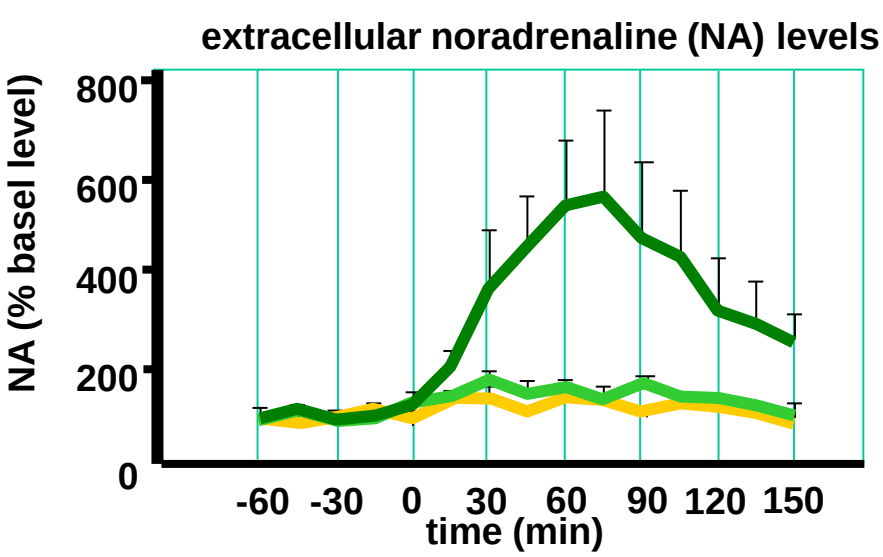


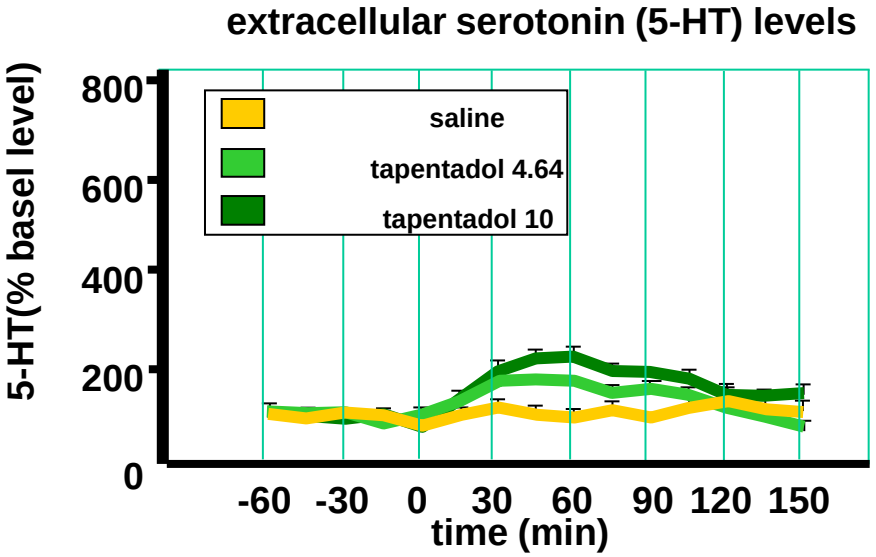
Tapentadol – A New Analgesic with a Dual Mode of Action

Effect on Noradrenalin- und Serotonin





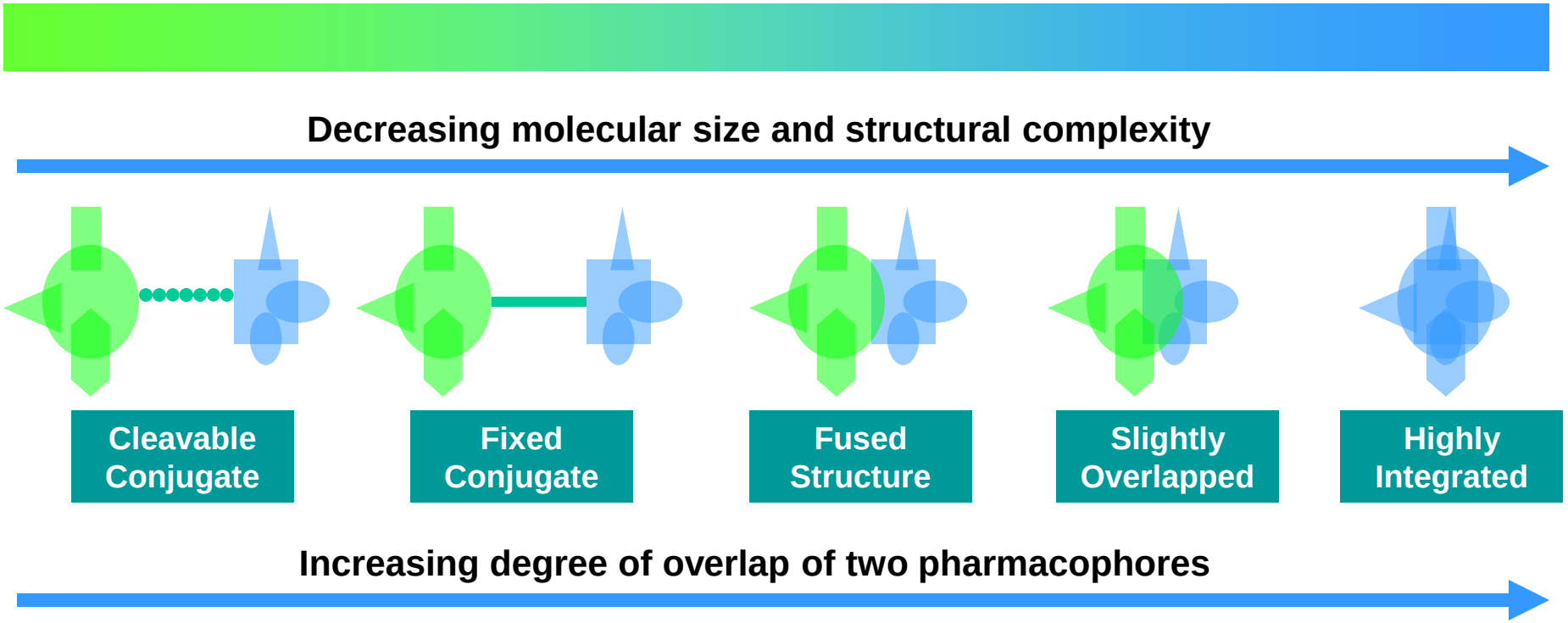




Tzschentke, JPET 2007

Tapentadol as a Multiple Ligand

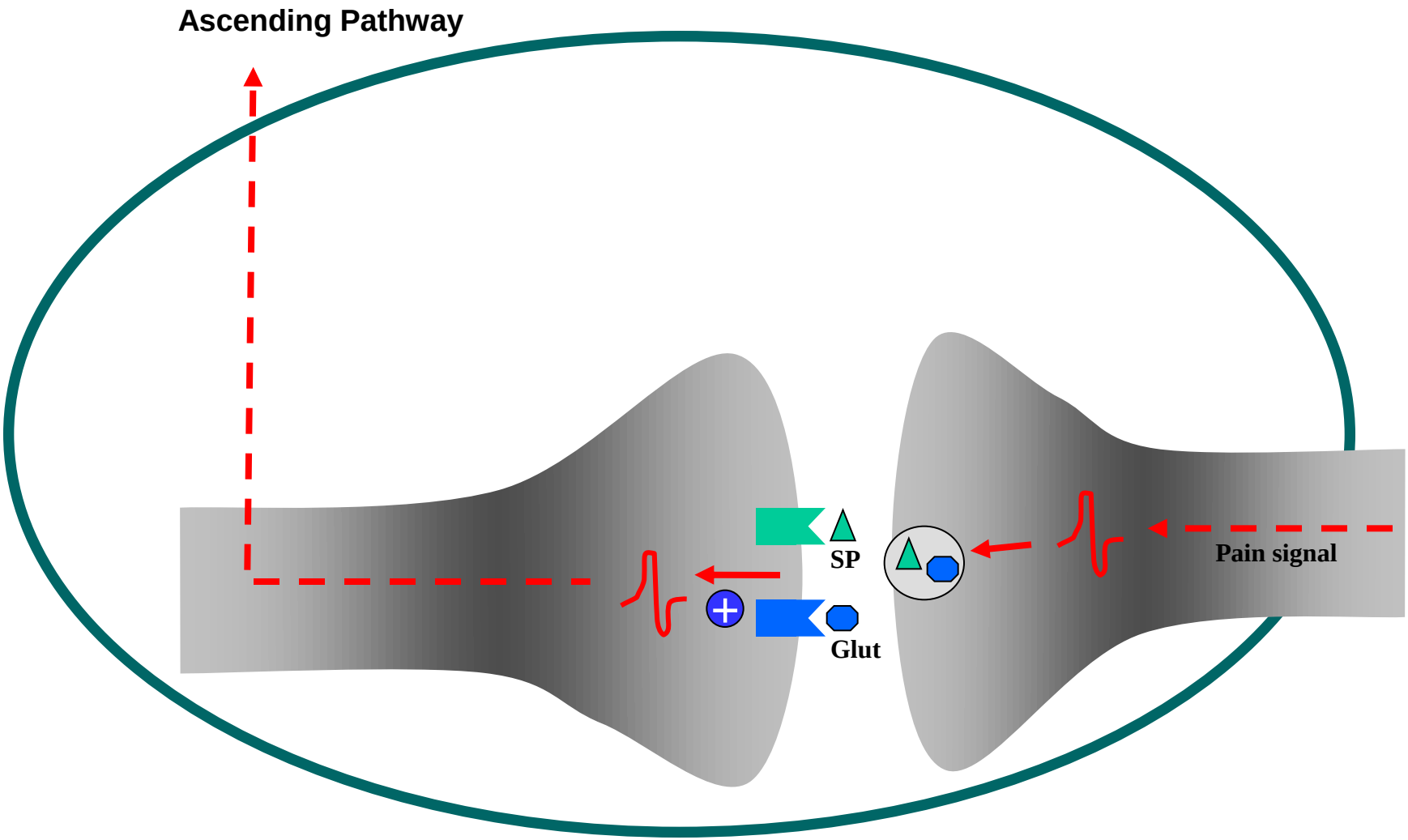
Designed Multiple Ligang Continuum*)**)



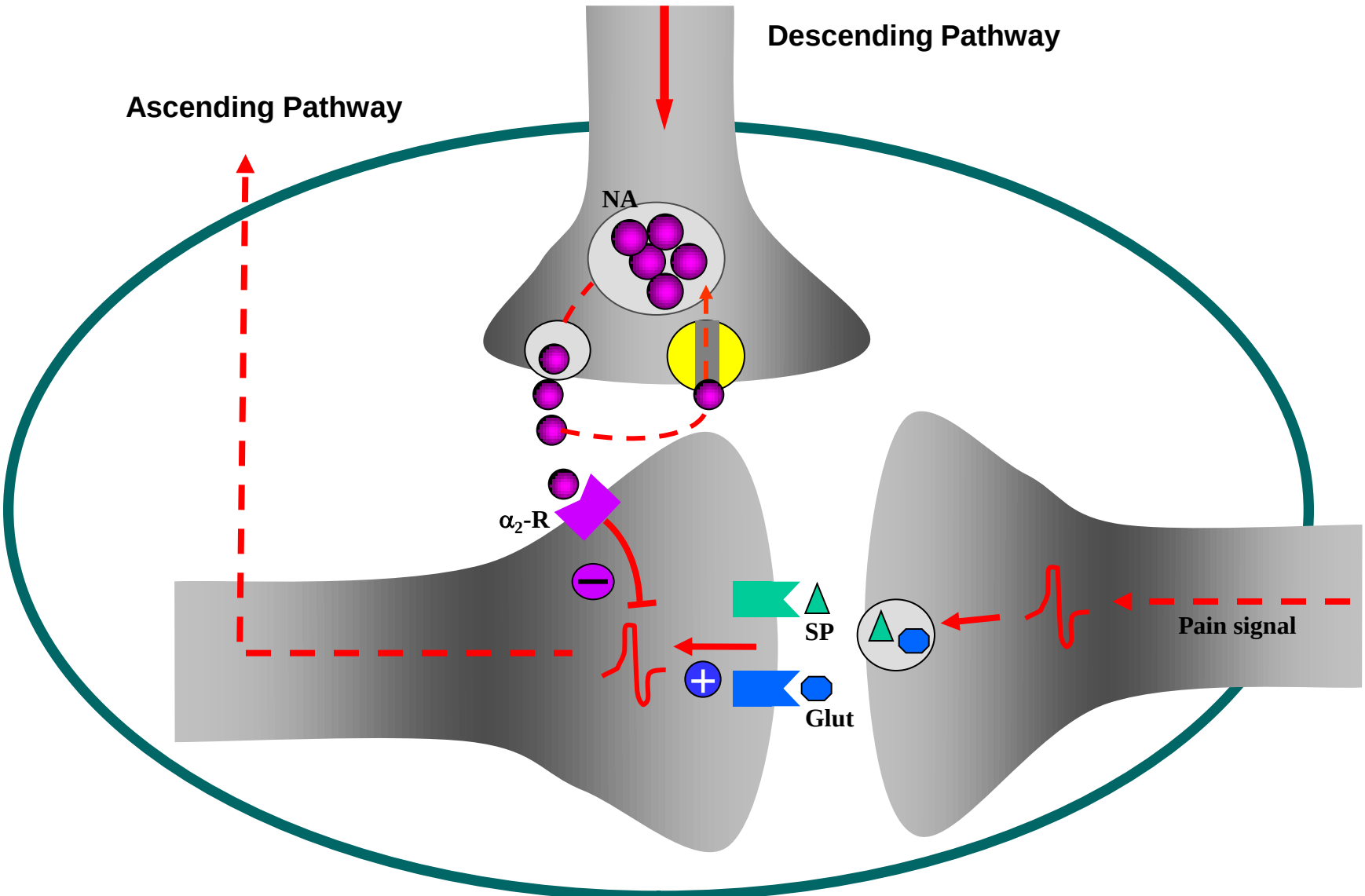
*) R. Morphy, Z. Rankovic, *Designed Multiple Ligands. An Emerging Drug Discovery Paradigm*, J. Med. Chem. 2005 (48), 6523-6543.

**) R. Morphy, C. Kay, Z. Rankovic, *From Magic Bullets to Designed Multiple Ligands*, Drug Discovery Today 2004 (9), 641-651.

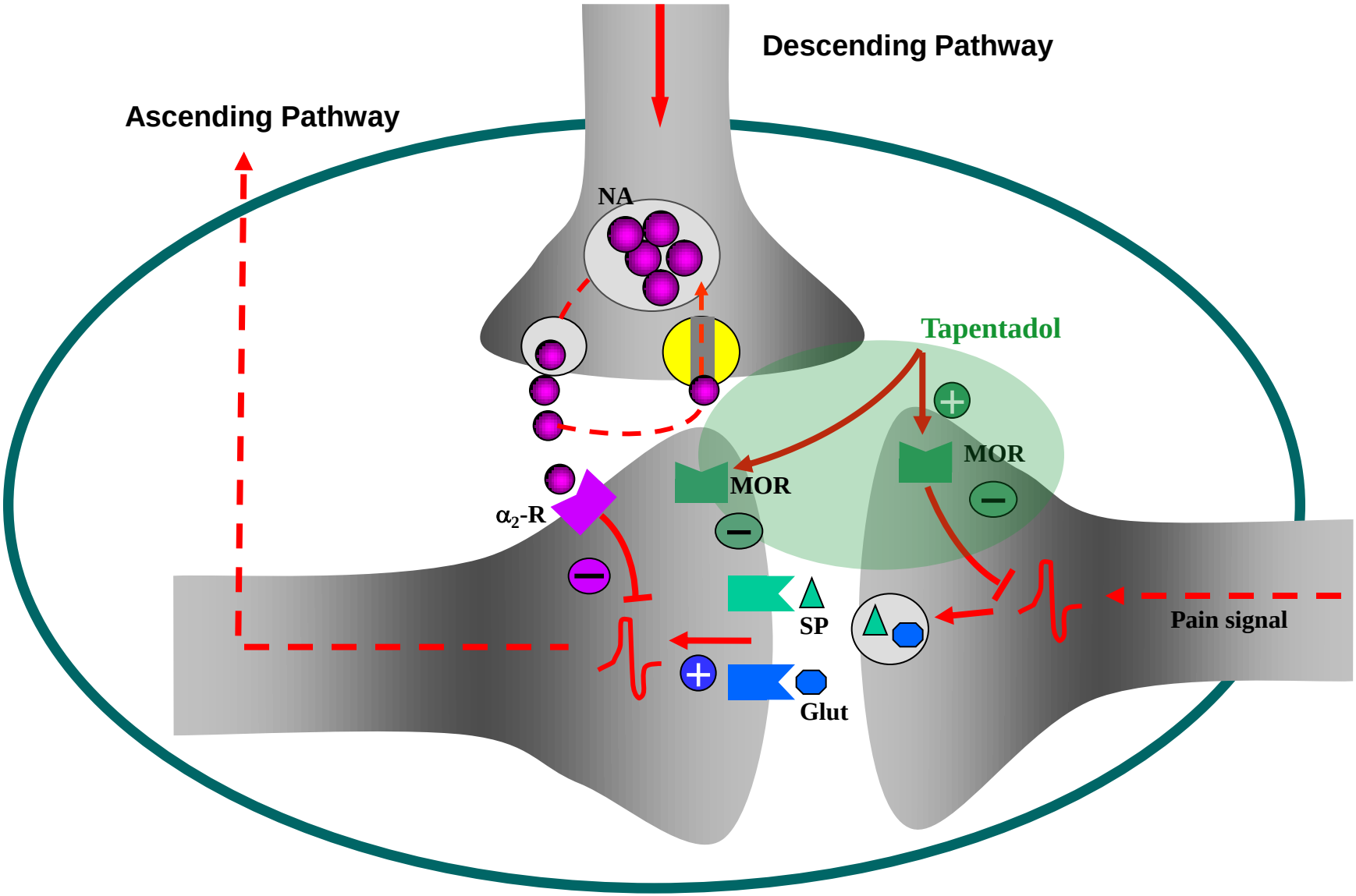
Spinal Mechanism of Action: MOR-NRI



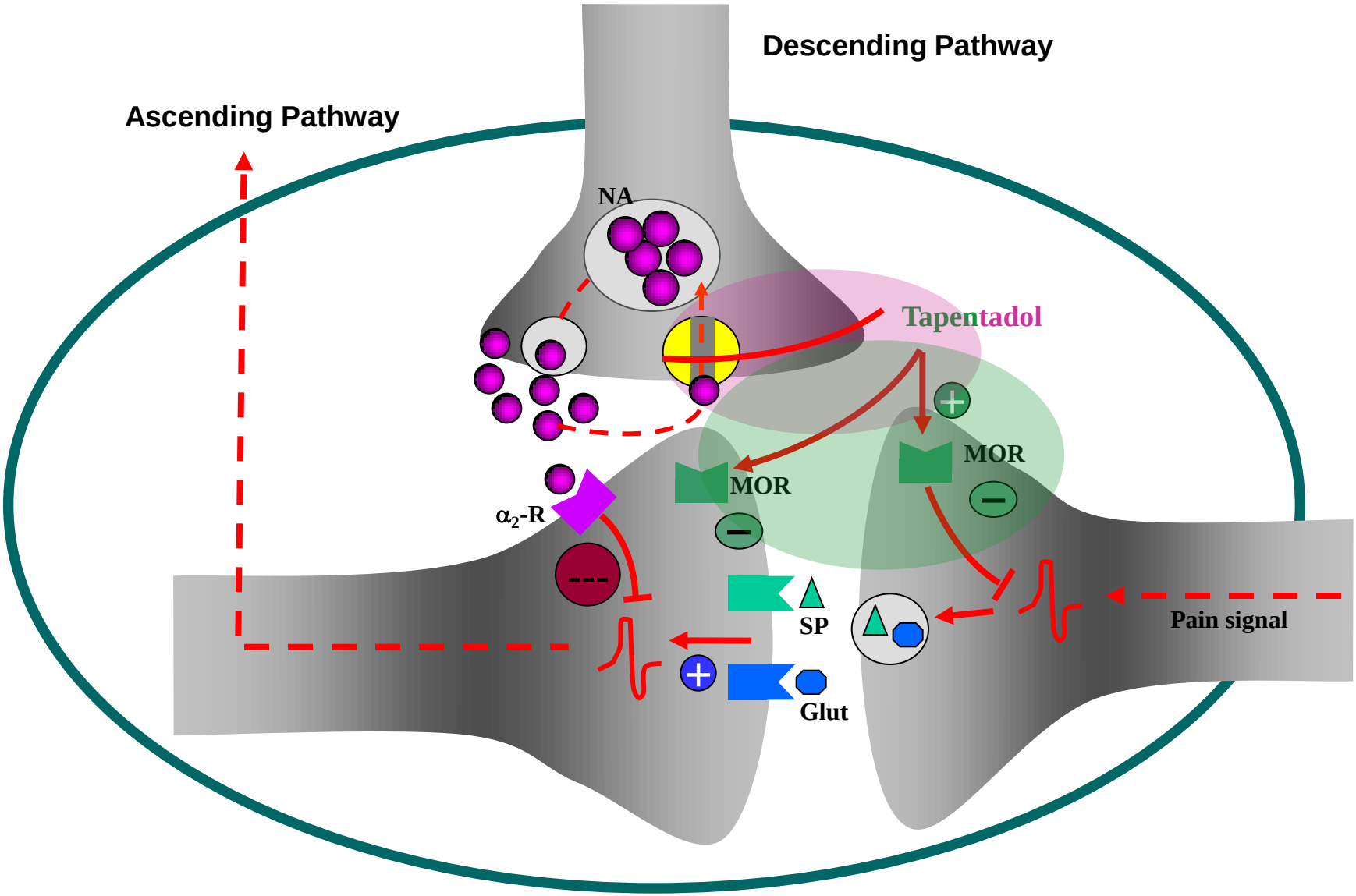
Spinal Mechanism of Action: MOR-NRI



Spinal Mechanism of Action: MOR-NRI

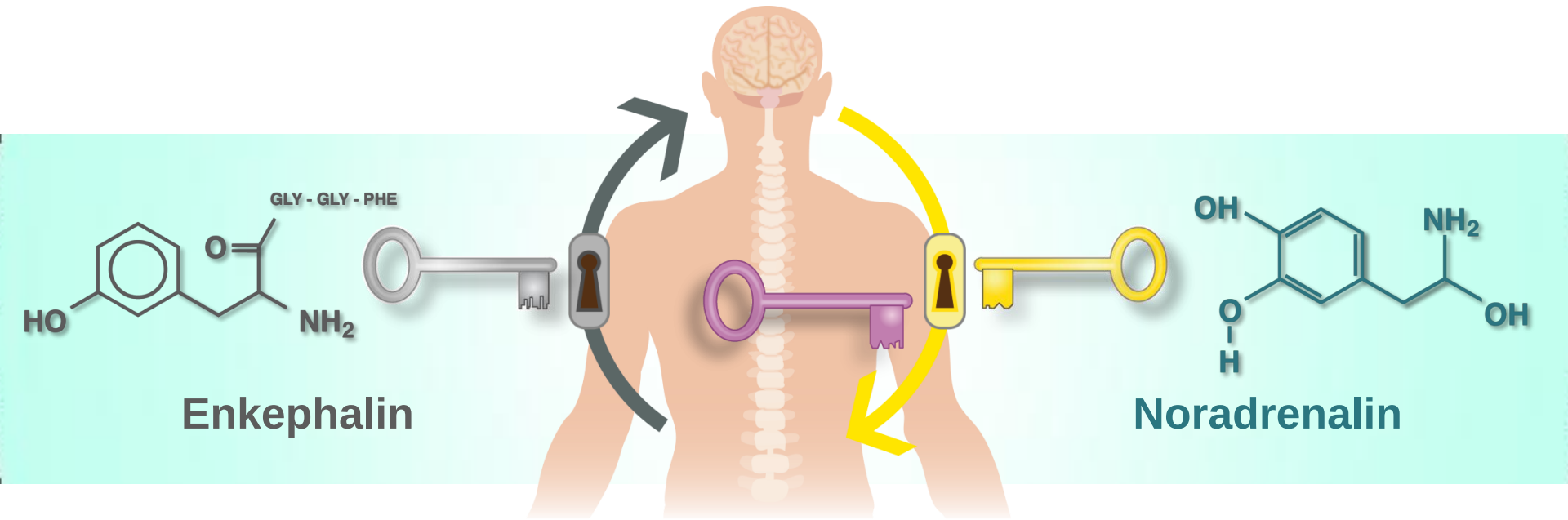


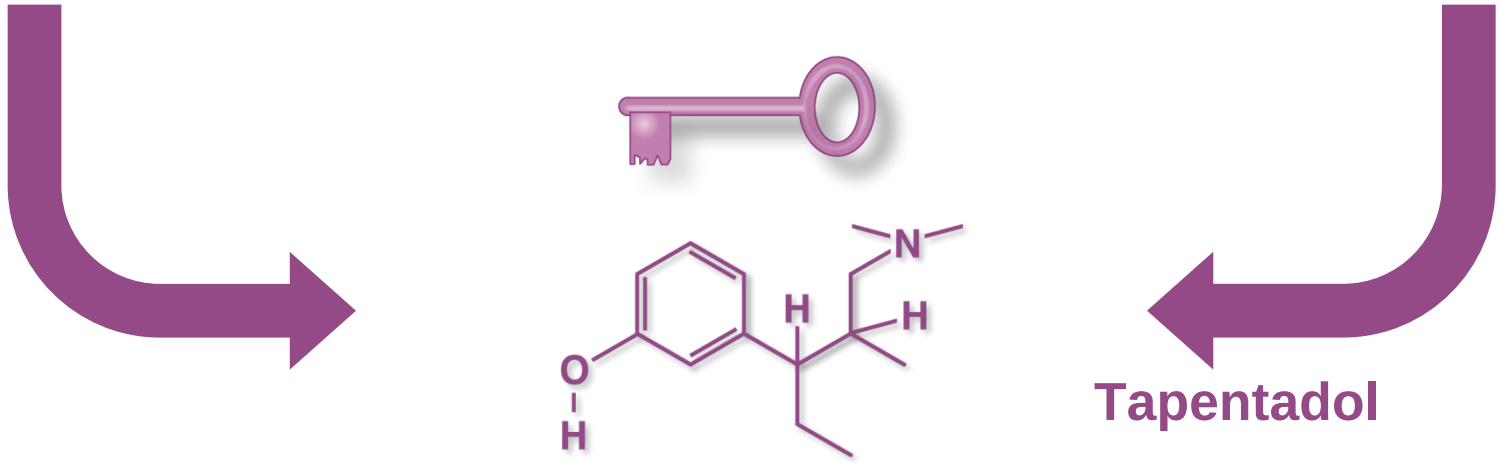
Spinal Mechanism of Action: MOR-NRI



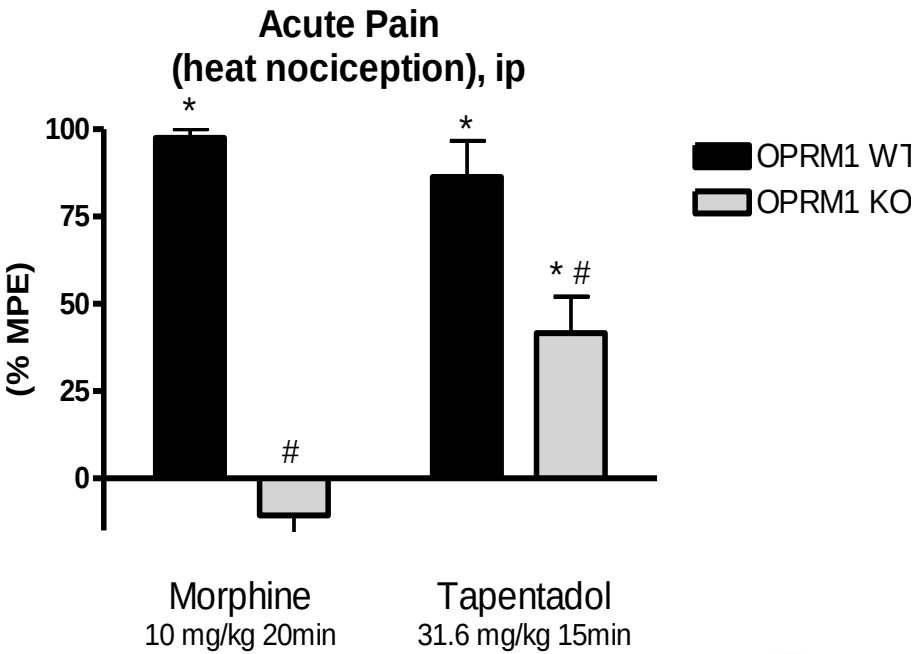
Tapentadol – A New Analgesic with a Dual Mode of Action

Neue Substanzklasse MOR-NRI

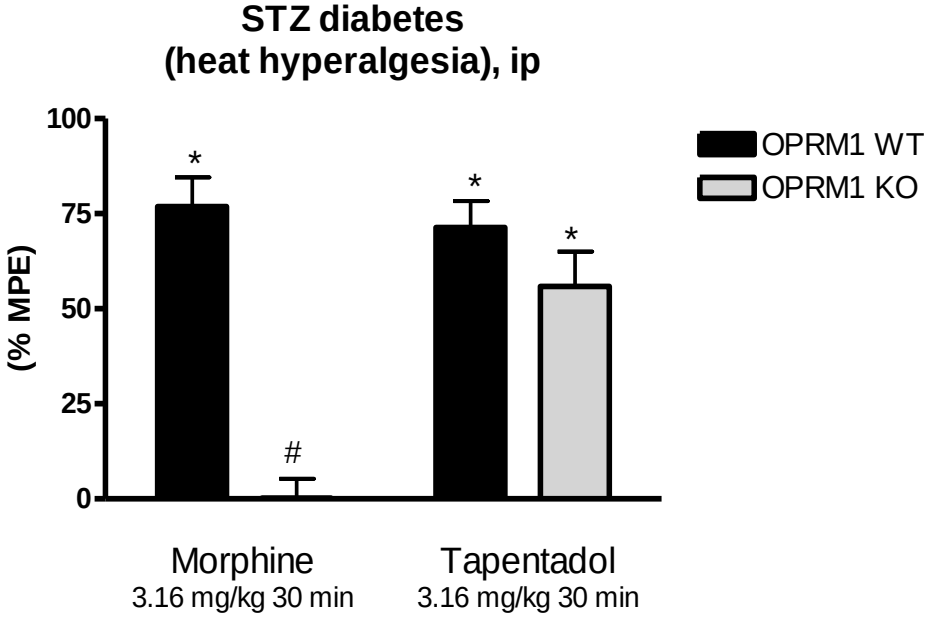




Tapentadol: Activityt in MOR knock-out- und Wildtype-Mice



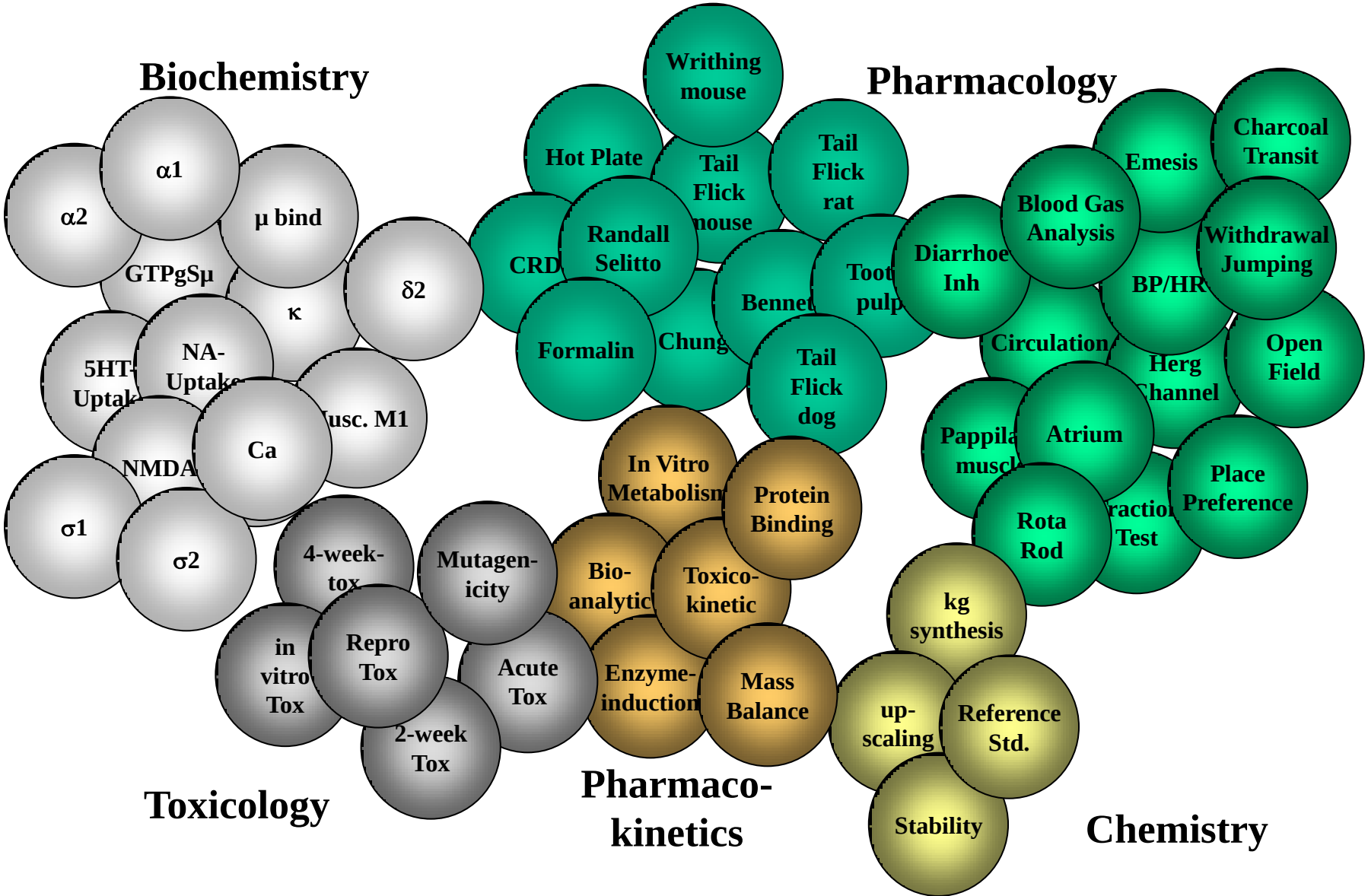
* p<0.05 treatment vs vehicle
# p<0.05 KO vs WT



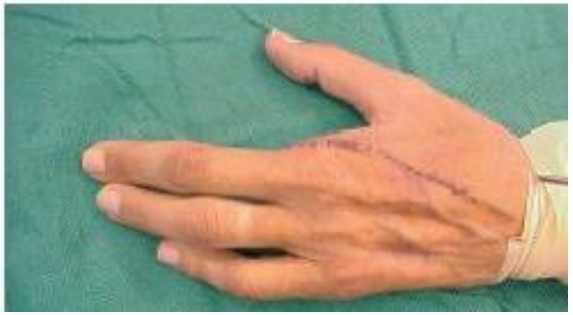
* p<0.05 treatment vs vehicle
# p<0.05 KO vs WT

Tapentadol remains partially active in MOR-Knock-out Mice

Characterization of Compounds

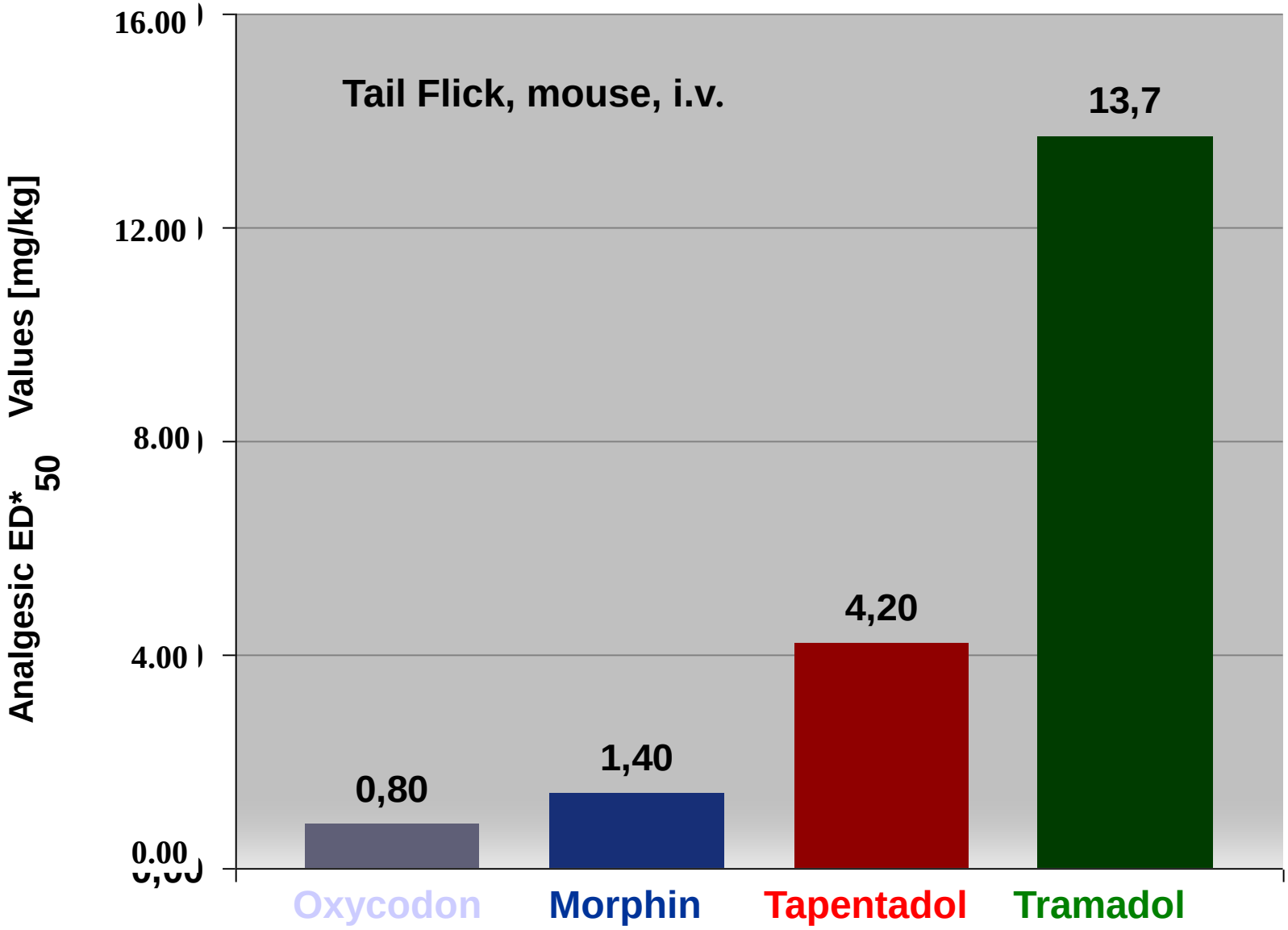


Pharmacology: Pain Models

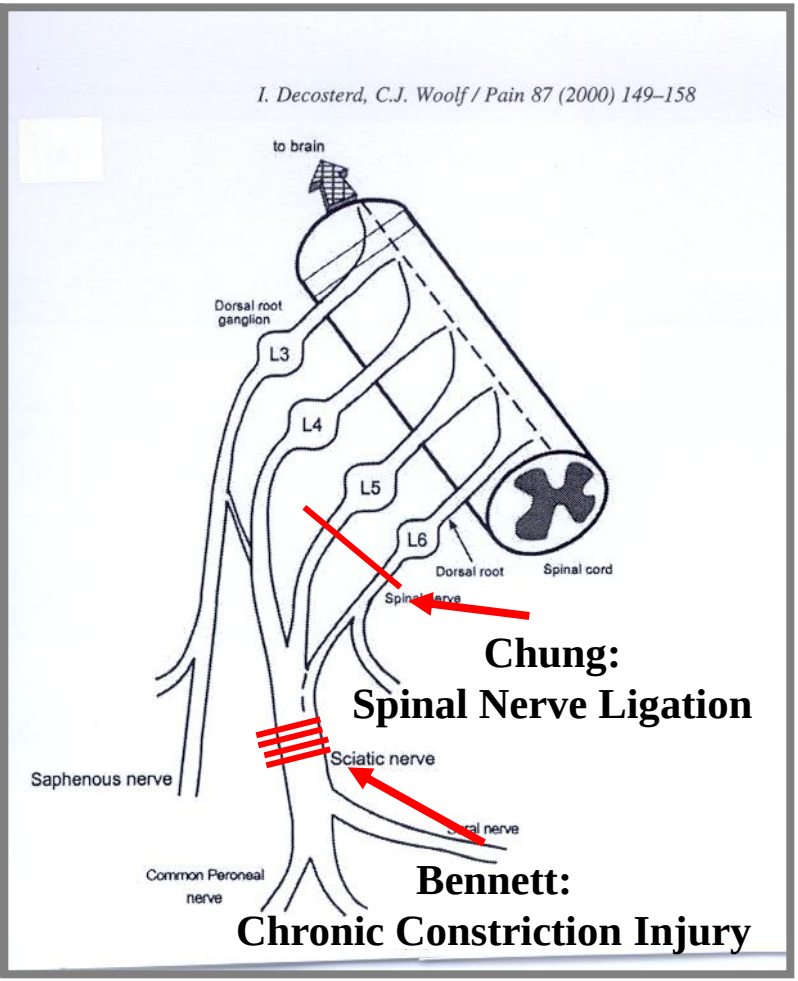
Acute	Chronic inflammatory	Chronic neuropathic
		
		

Tapentadol – *in vivo* Pharmacology

Analgesic Potency in Acute Pain

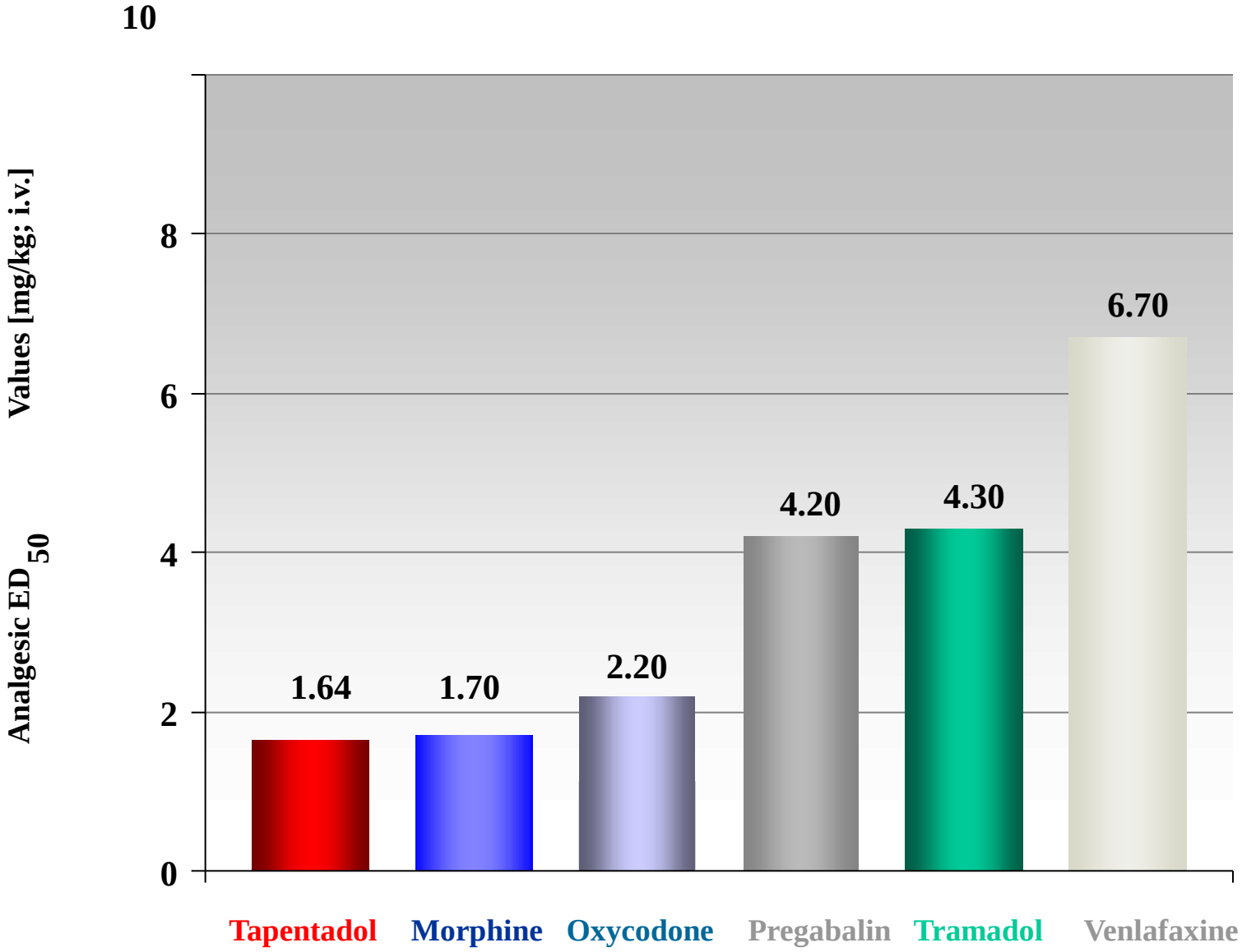


Neuropathic pain model: Peripheral Mononeuropathy (Chung model)

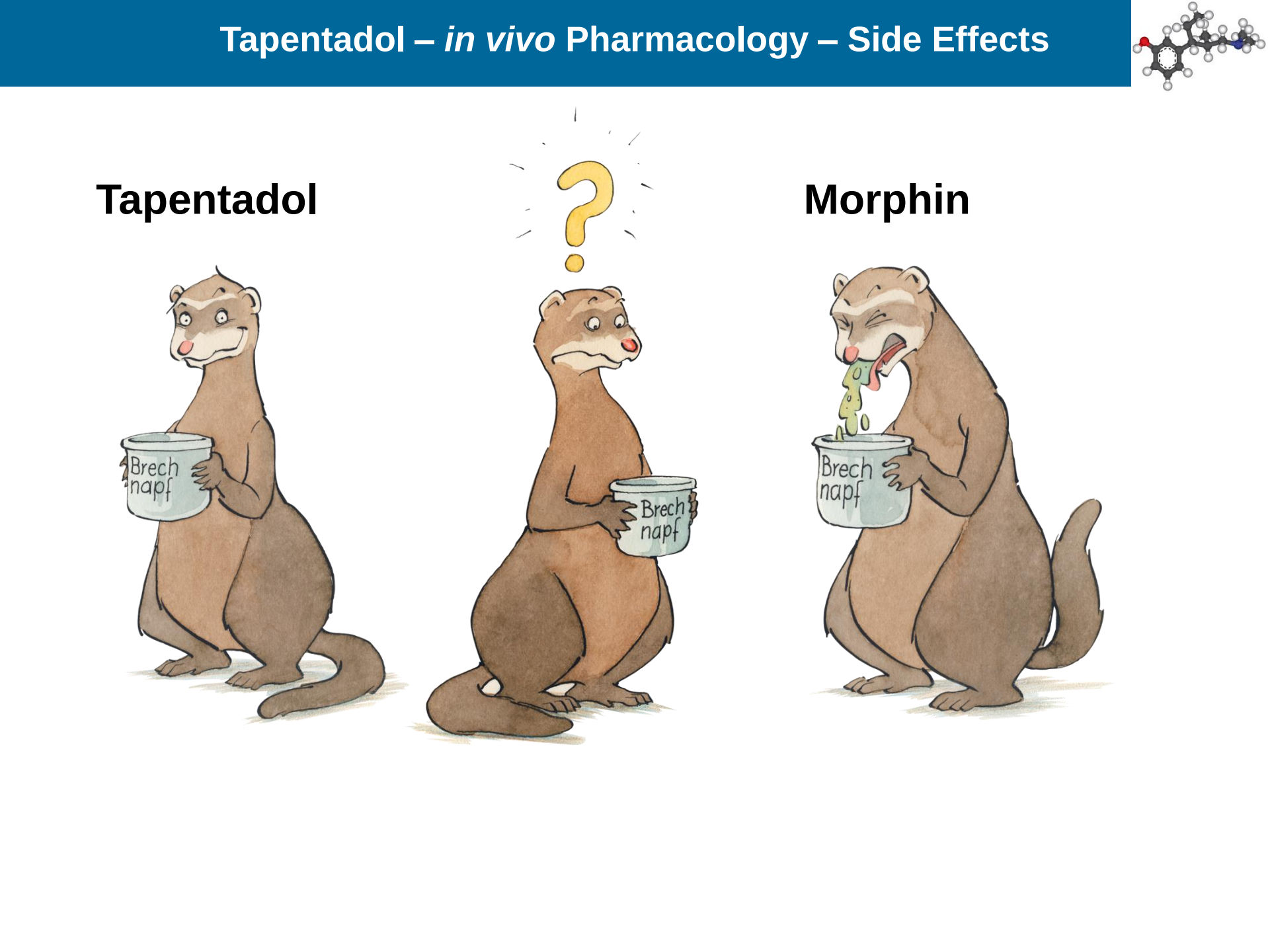


Investigation of tactile allodynia after tight ligation of the dorsal root of spinal nerves (L5, L6)

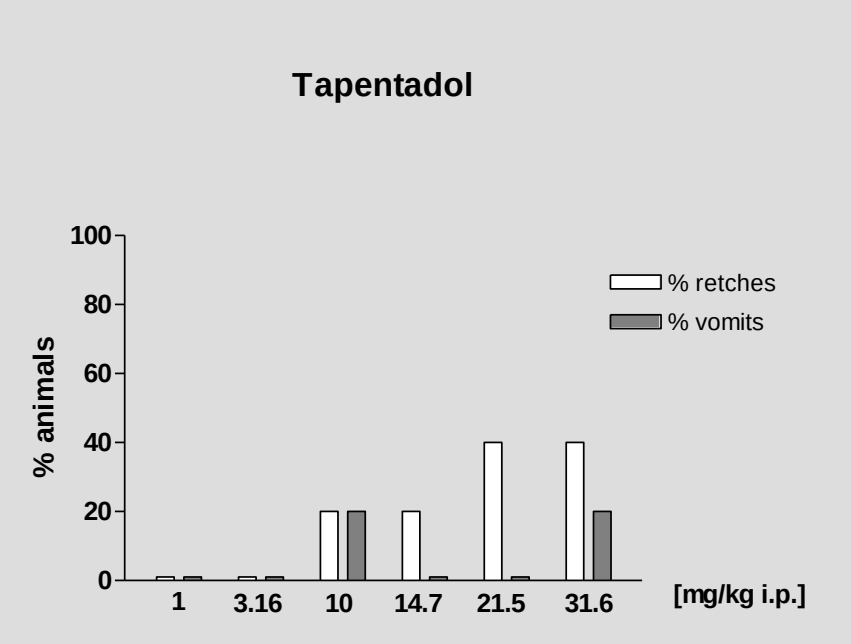
High potency and efficacy in neuropathic pain (Chung)

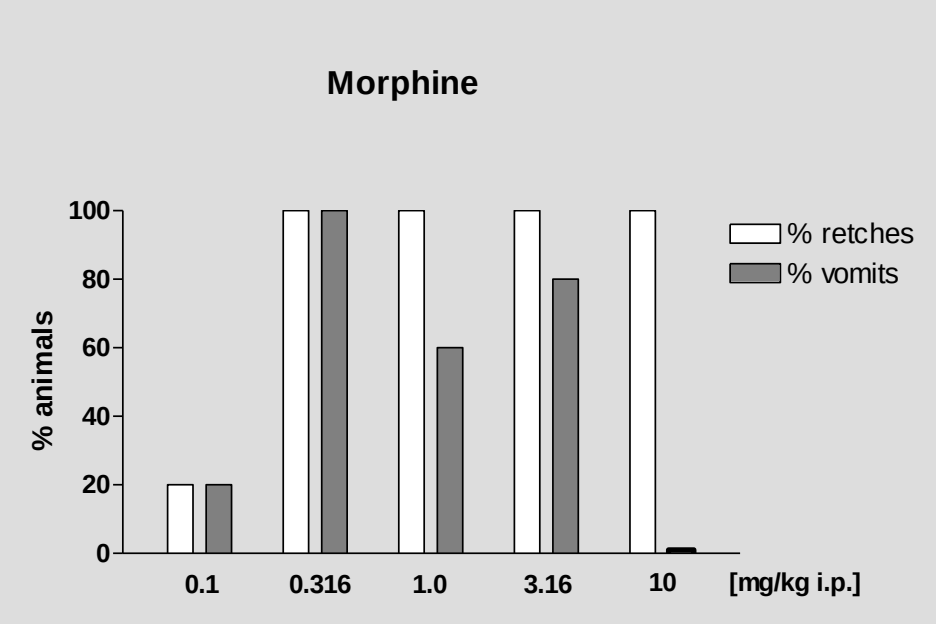


Tapentadol – *in vivo* Pharmacology – Side Effects



Opioid Induced Side Effects: Emesis





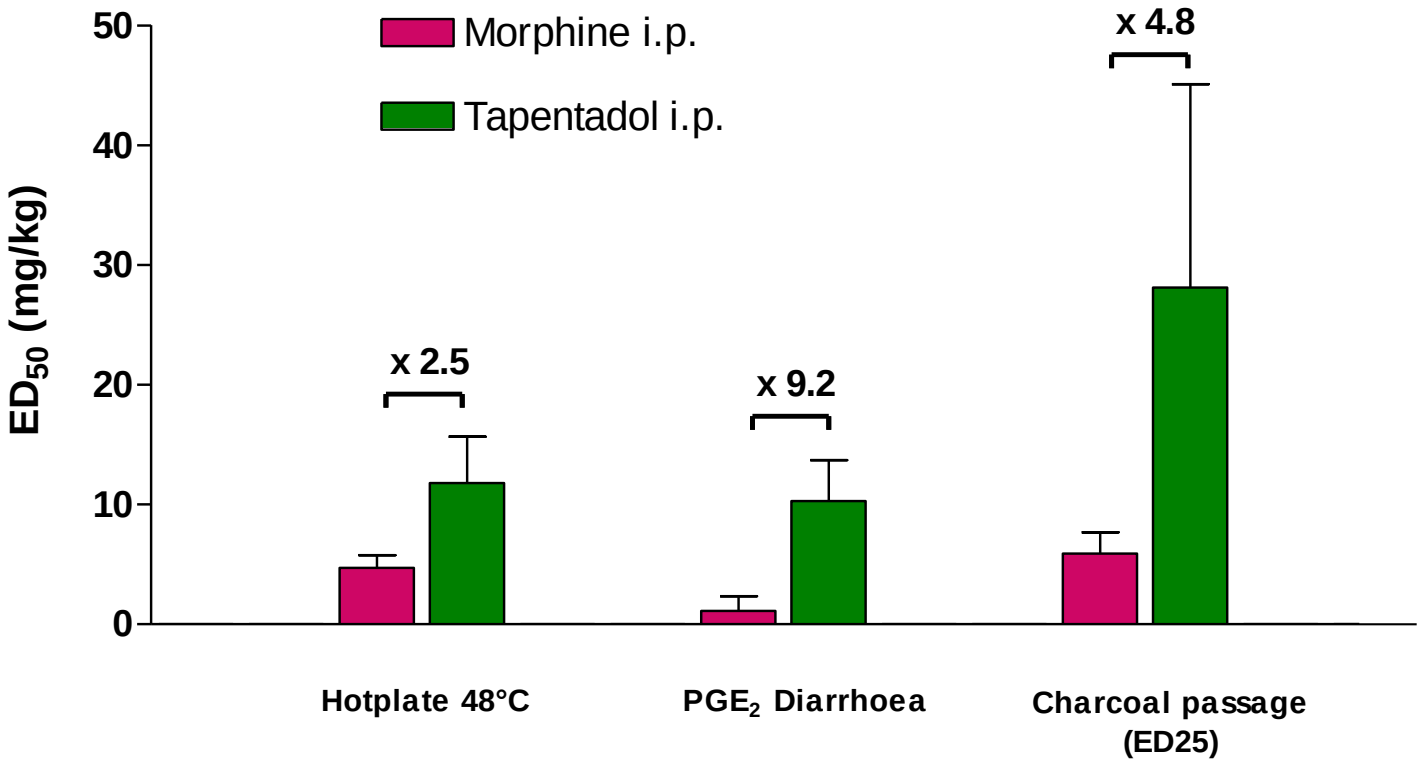
Tzschentke et al (2006) Drugs Fut 31:1053ff

Tapentadol shows a reduced emetic potential in comparison to Morphine

Opioid Induced Side Effects: Obstipation

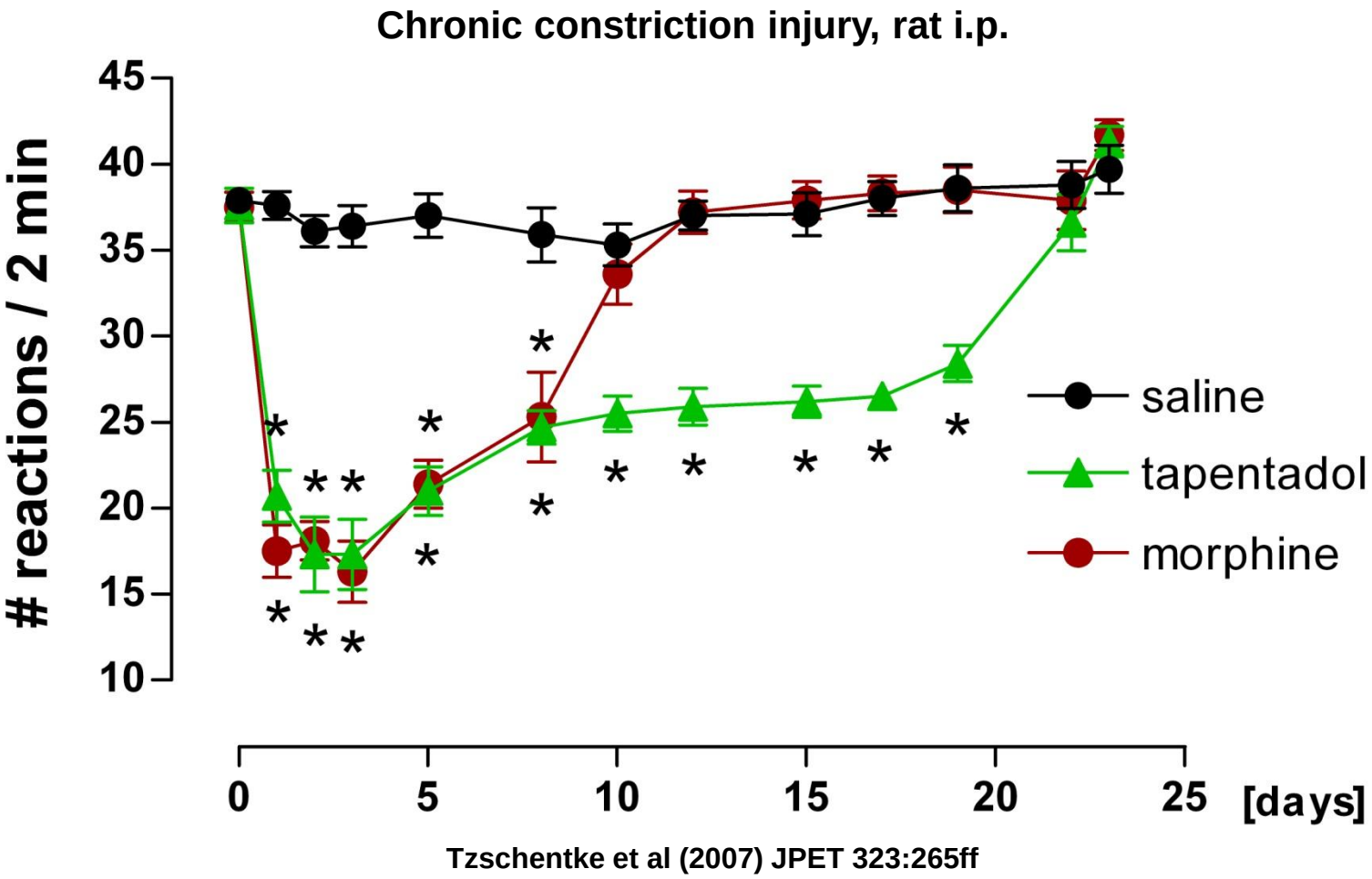
- **Increase of the intestinal charcoal passage**
- **Reduction of the PGE2 induced diarrhoe**

Opioid Induced Side Effects: Obstipation



Tapentadol shows a reduced gastrointestinal inhibitory potential in comparison to Morphine

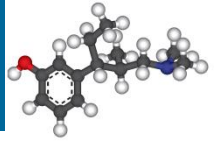
Opioid Induced Side Effects: Tolerance Development



Tzschentke et al (2007) JPET 323:265ff

Significant reduced tolerance development

Tapentadol – *in vivo* Pharmacology – Side Effects



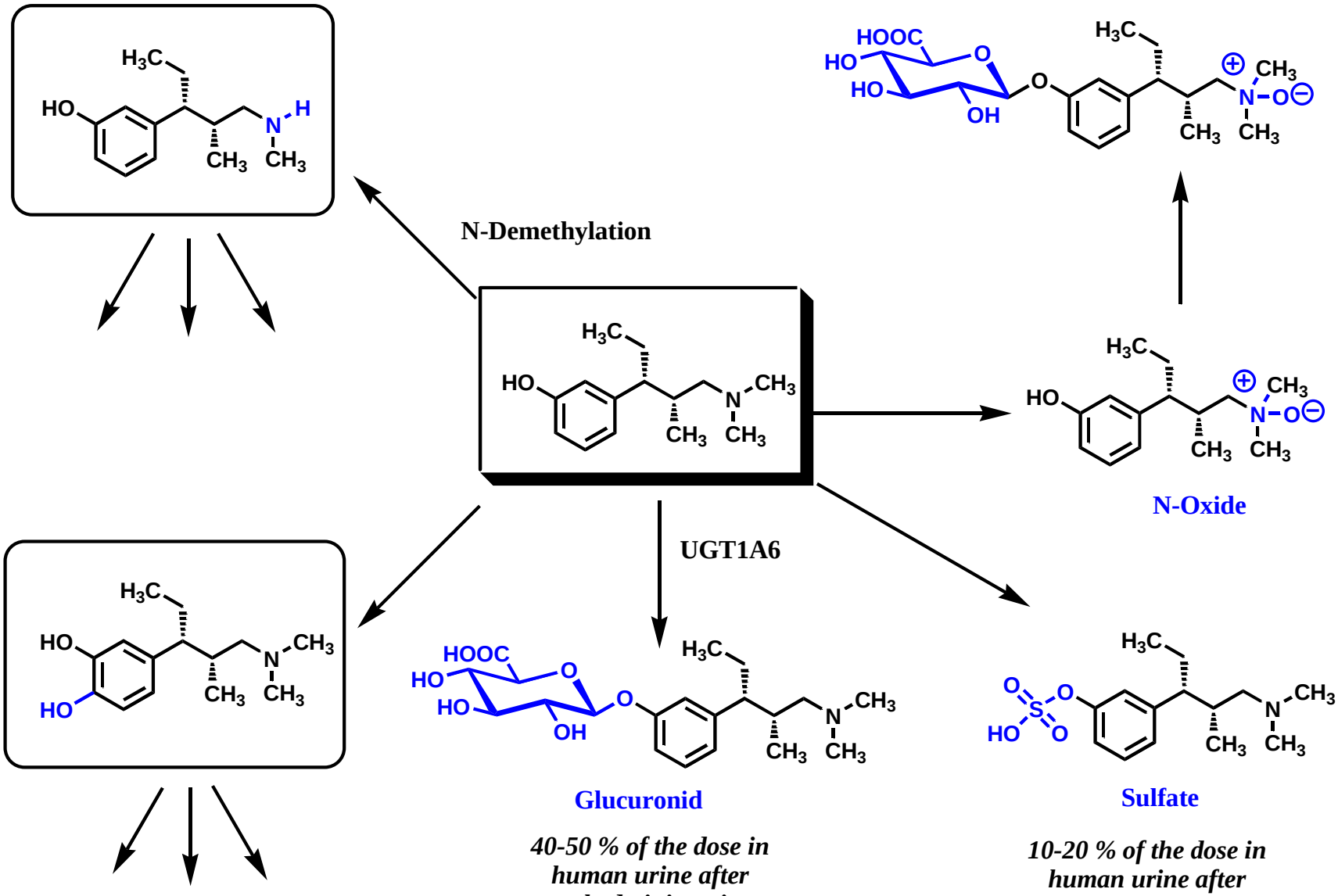
Overview of the analgesic activity of tapentadol and morphine in various animal models of acute and chronic pain

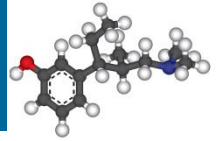
Pain model	Route of application	ED_{50} value (mg/kg)	
		Tapentadol	Morphine
Tail-flick (mouse)	i.v.	4.2	1.4
	p.o.	53.4	18.9
	i.c.v.*	65.0	0.4
Tail-flick (rat)	i.v.	2.2	1.1
	i.p.	10.0	5.8
	p.o.	121	55.7
Tail-flick (dog)	i.v.	4.3	0.7
Hot-plate 48° C (mouse)	i.v.	3.3	1.3
Hot-plate 58° C (mouse)	i.p.	27.7	8.5
Phenylquinone-induced writhing (mouse)	i.v.	0.7	0.4
	p.o.	31.3	4.7
	i.c.v.*	18.4	0.08
Tooth pulp stimulation (rabbit)	i.v.	3.1	2.3
Formalin (phase II) (rat)	i.p.	3.8	0.8
Yeast model (rat)	i.v.	2.0	0.9
	i.p.	10.1	5.6
	i.t.*	56.8	1.9
Colorectal distension-induced visceral pain (rat)	i.v.	5.5	3.5
Mustard oil-induced visceral pain (rat)	i.v.	1.5	1.0
Spinal nerve injury neuropathy (rat)	i.p.	8.3	2.9
Chronic constriction injury neuropathy (rat)	i.p.	13.0	13.8
Vincristine polyneuropathy (rat)	i.p.	5.1	3.4
Diabetic polyneuropathy (rat)	i.p.	8.9	3.0

*Dose in µg/animal. [1]All drug doses for preclinical and clinical testing are for the hydrochloride salt.

Tapentadol – *in vivo* Pharmacology – Metabolism

Metabolic Pathway





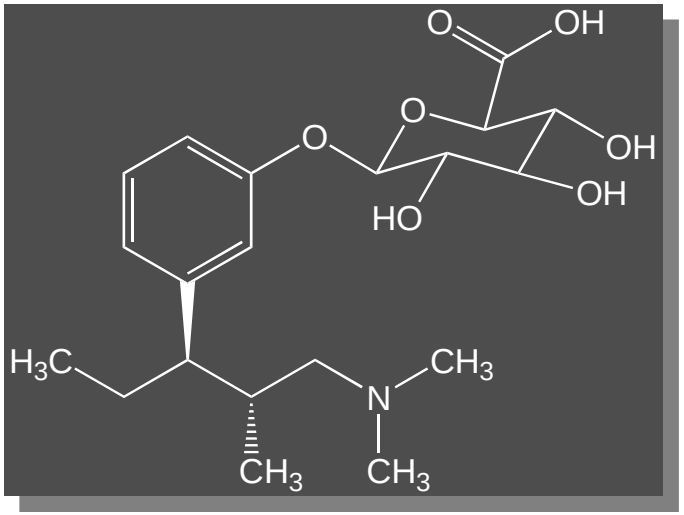
Tapentadol – Pharmakokinetik

Mittlere pharmakokinetische Parameter nach einer Einzeldosis PALEXIA® retard, Dosis normiert auf 200 mg Tapentadol

Parameter	N	Mittelwert +/- SA
AUC_{last} ng.h/ml	294	789 +/- 219
AUC_{inf}, ng.h/ml	292	805 +/- 220
$t_{1/2}$, h	292	5,9 +/- 2,0
CL_F, ml/min	292	4449 +/- 1199

Metabolic Pathway

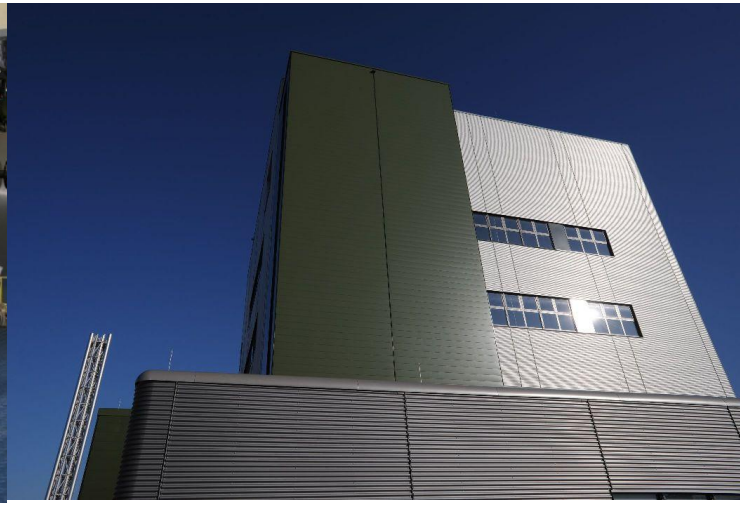
- Major Hepatic metabolism
- Phase 2 Metabolism:
- *O*-Glucuronidierung via UGTs
- 1A6, 1A9, 2B7, no CYP450
- No P-gp Substrate
- No Prodrug
- No analgesic active metabolites
- Low drug-drug interaction potential



Terlinden et al (2007) Eur J Metab Pharmacokinet 32:163ff
Kneip et al (2008) Drug Metab Letters 2:67ff

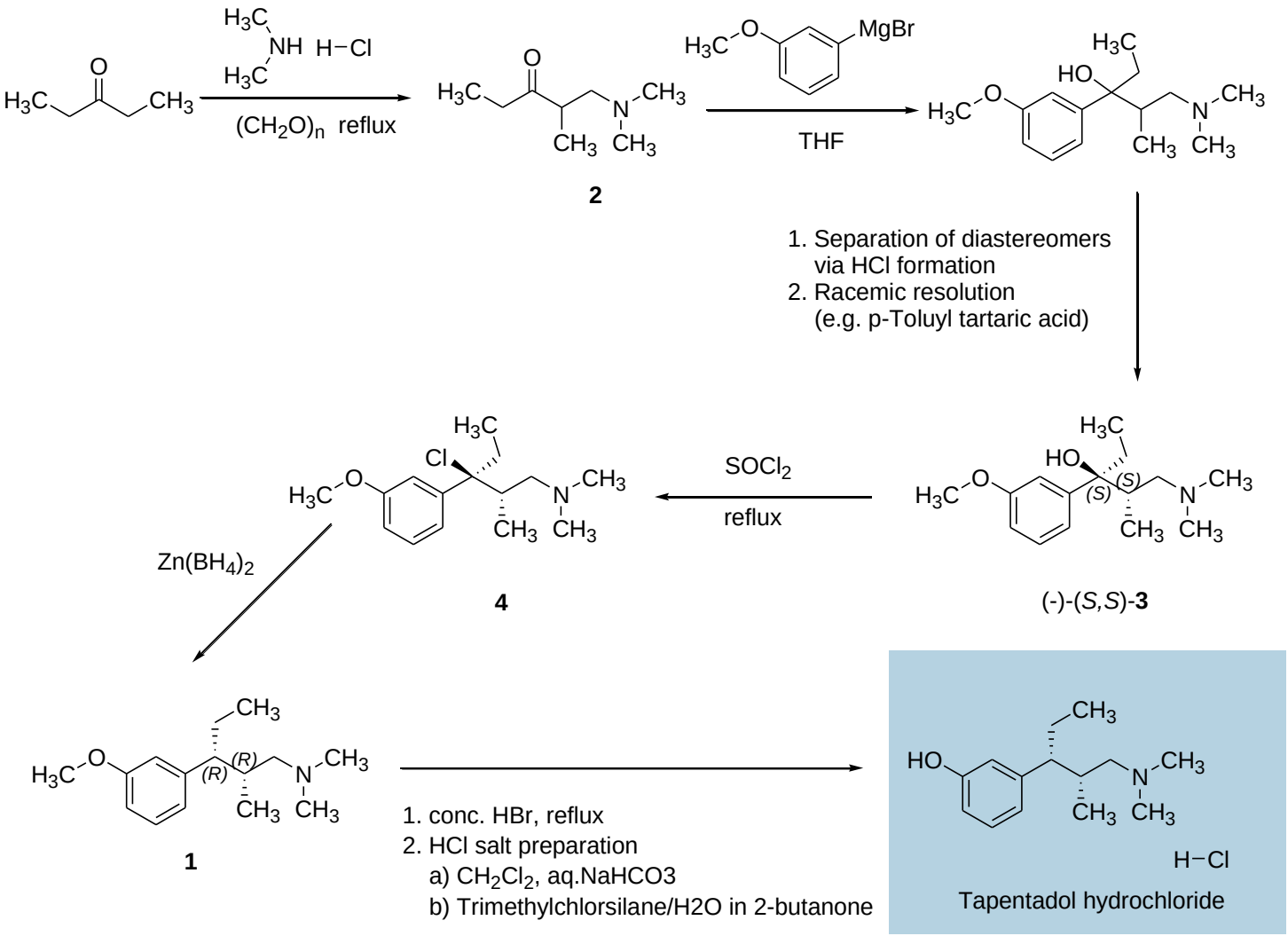
Tapentadol - Synthesis and Manufacture

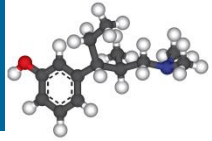


Lab Scale	Kilo-Lab	Pilot Plant	Production
0,1 – 100 g	0,5 – 5 kg	10 – 100 kg	> 50 kg

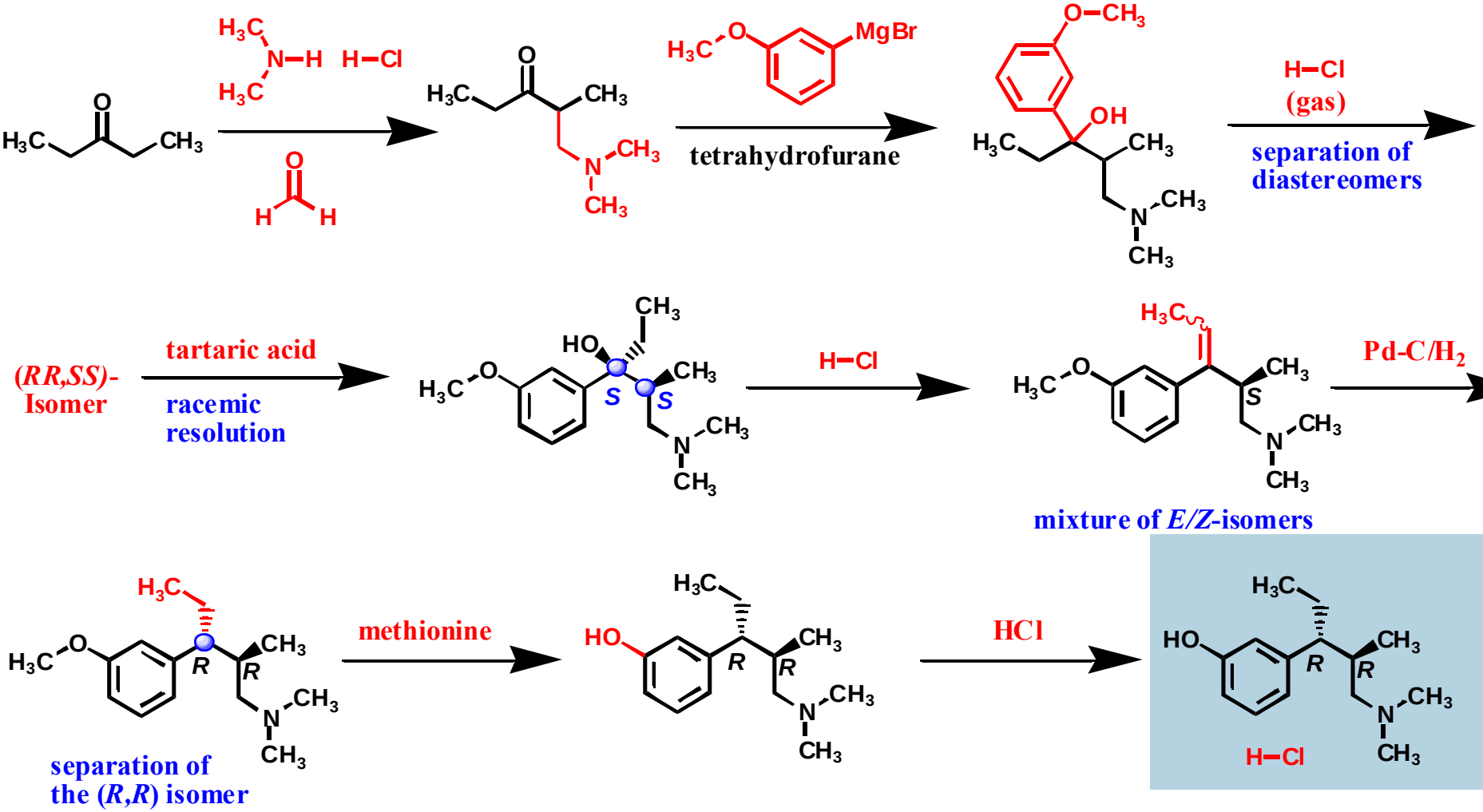
The synthesis of tapentadol hydrochloride as described in the first patent

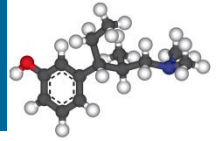




Synthesis of Tapentadol

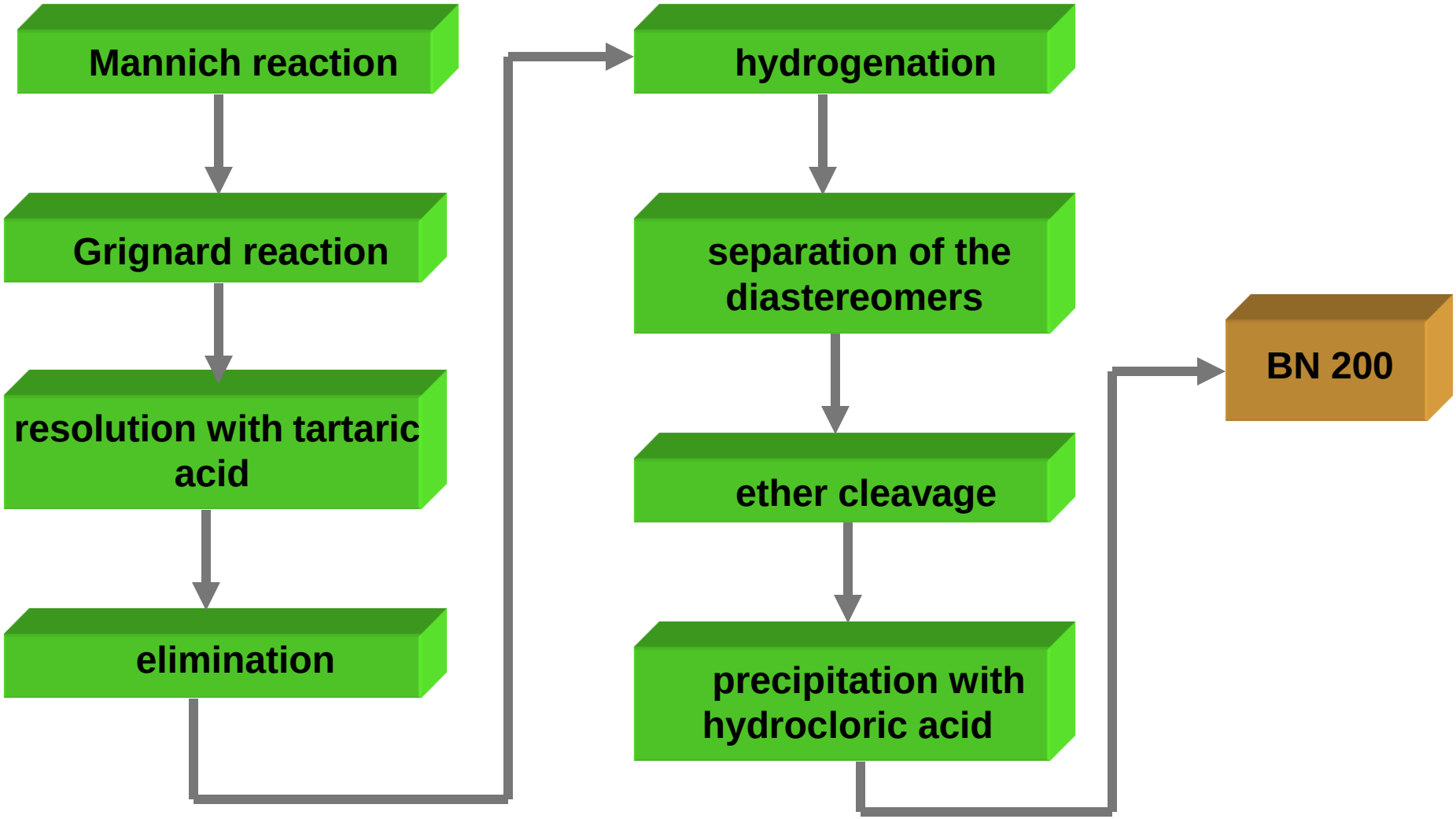
"Historical Route"

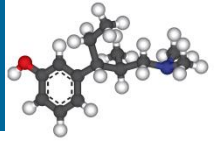




Synthesis of Tapentadol

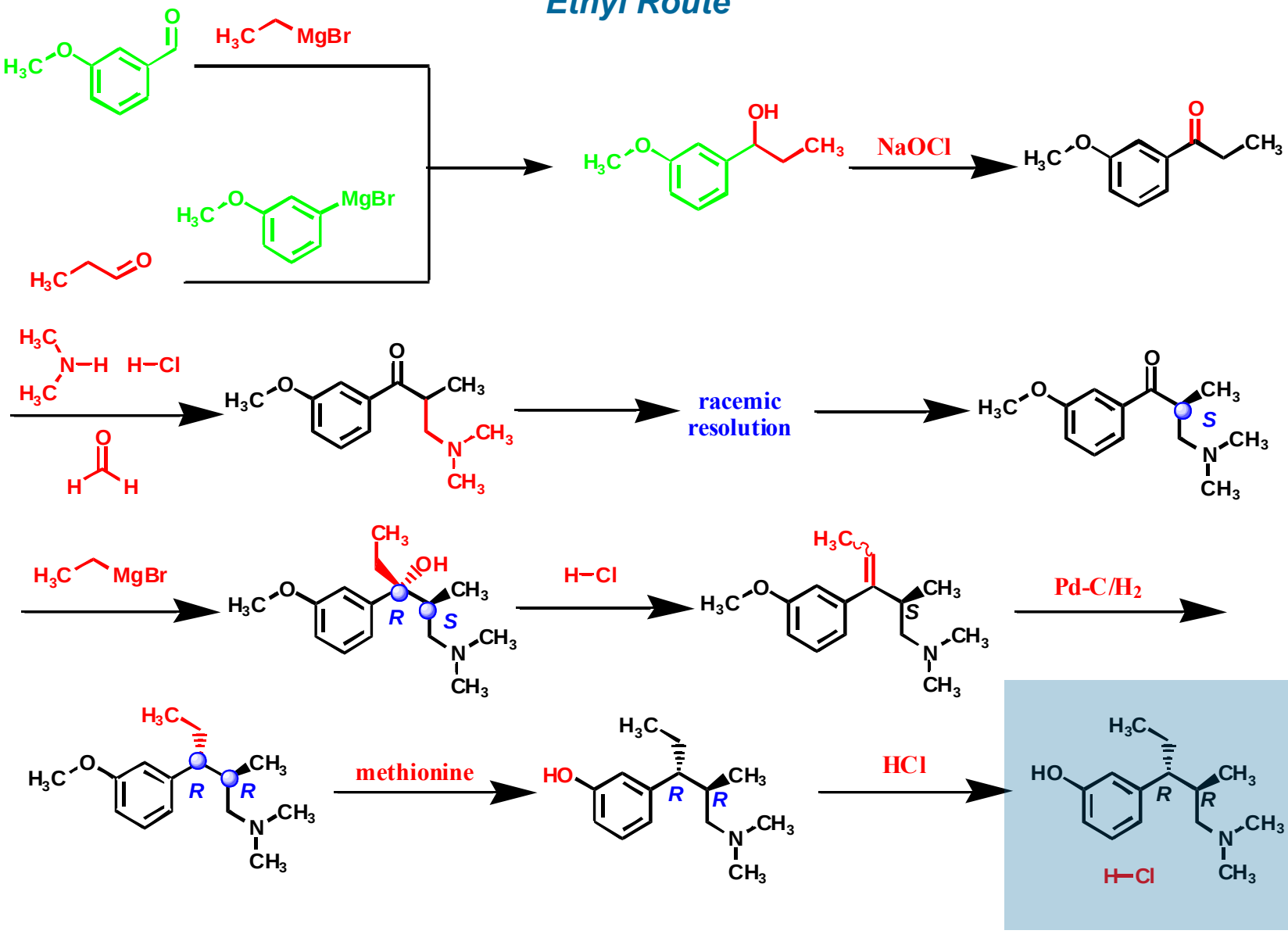
"Historical Route"



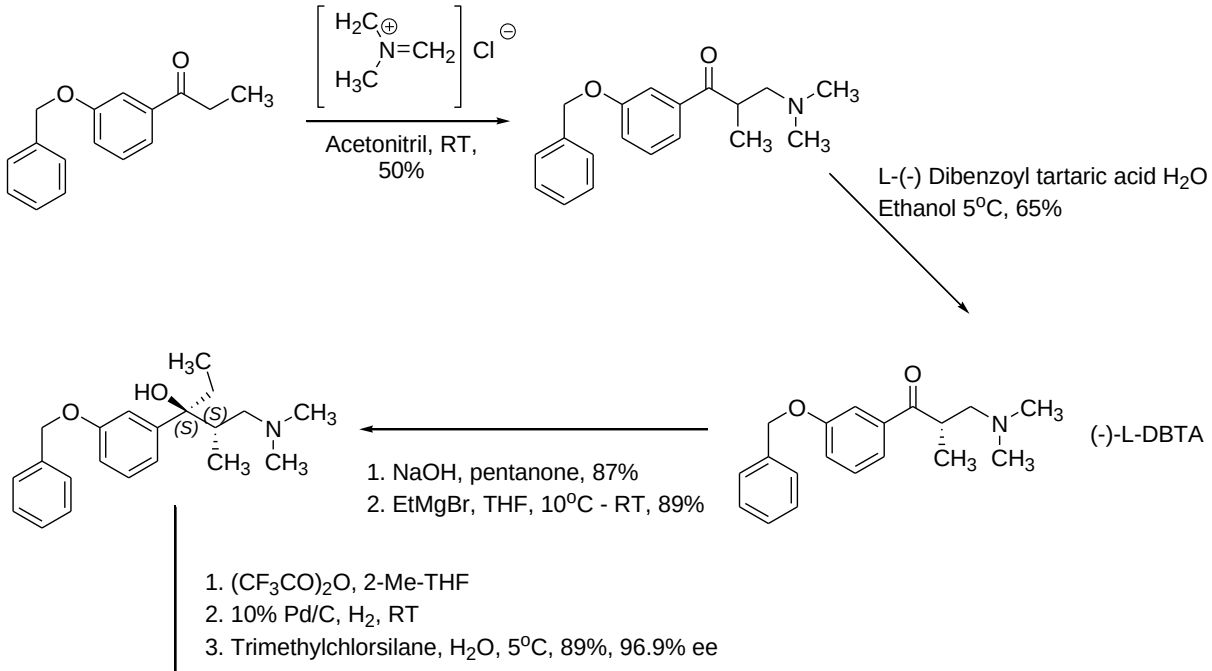


Synthesis of Tapentadol

"Ethyl Route"

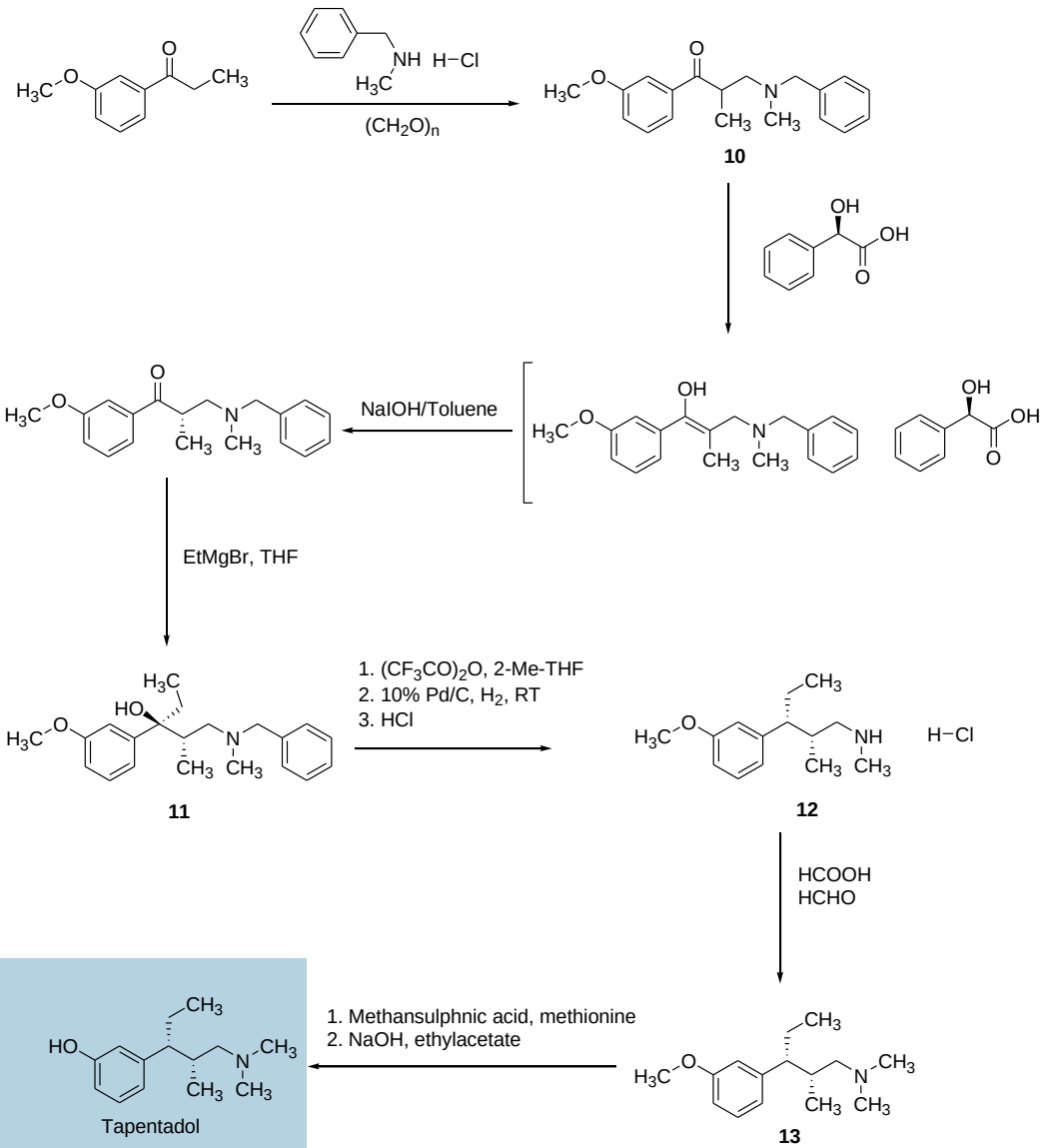


The synthesis of tapentadol hydrochloride according to WO 2008012047A1



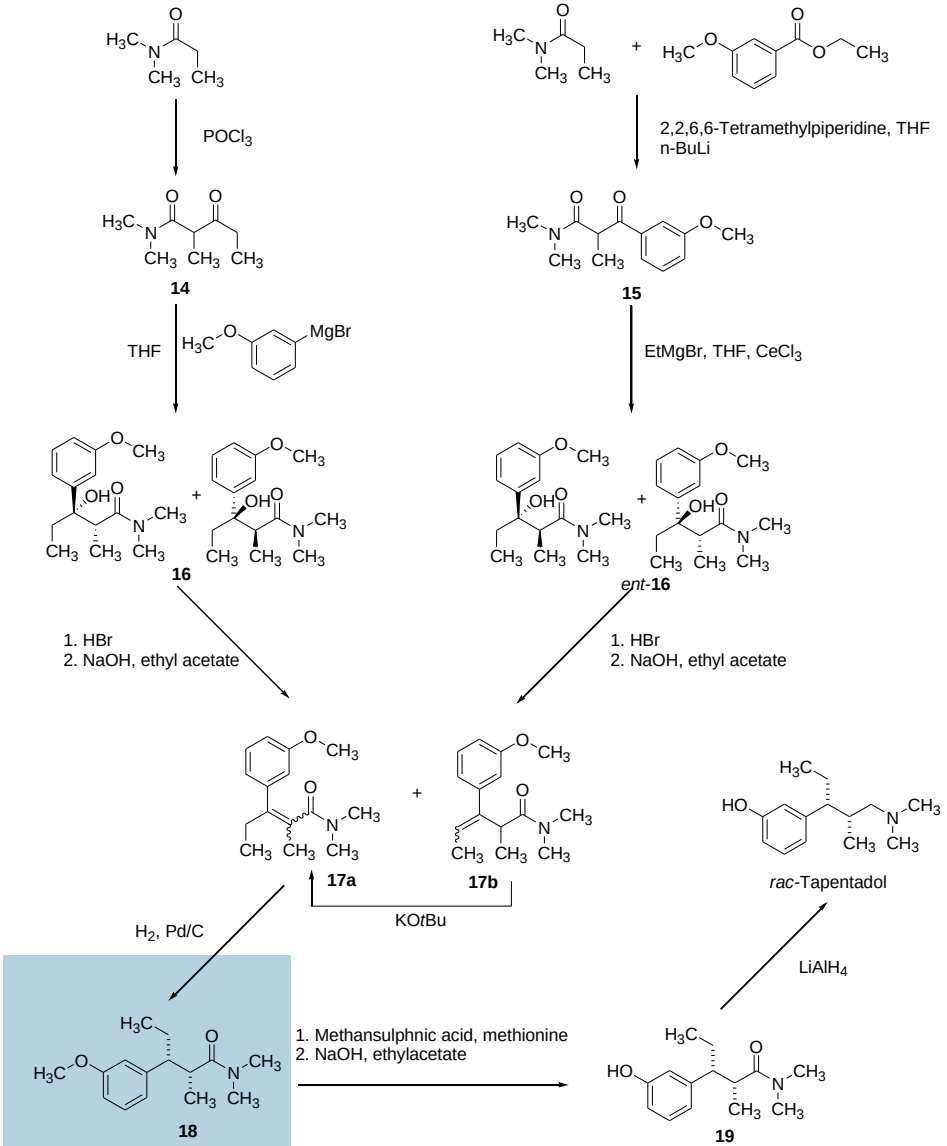
- **Hell W, WO 2008012046 A1, 2008.**
- **Hell W; Zimmer O; Buschmann, HH; Holenz J; Gladow S, WO 2008012047A1, 2008.**
- **Liu KKC; Subas Sakya M; O'Donnell CJ; Flick AC; Li J, Synthetic approaches to the 2009 new drugs Bioorg. Med. Chem. 2011, 19, 1136–1154.**

The synthesis of tapentadol hydrochloride according to WO 2012/001571 A1



Tapentadol - Synthesis and Manufacture

The synthesis of tapentadol hydrochloride according to WO2011/157390 A2

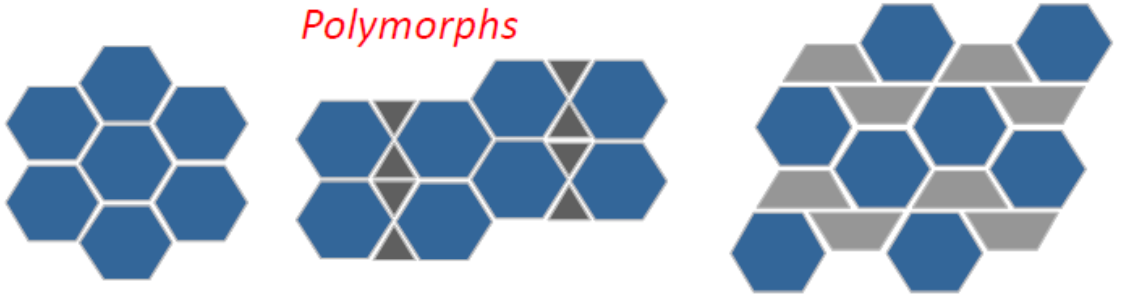


Solid Forms in Pharmaceutical Industry

Classes of Multicomponent Molecular Crystals

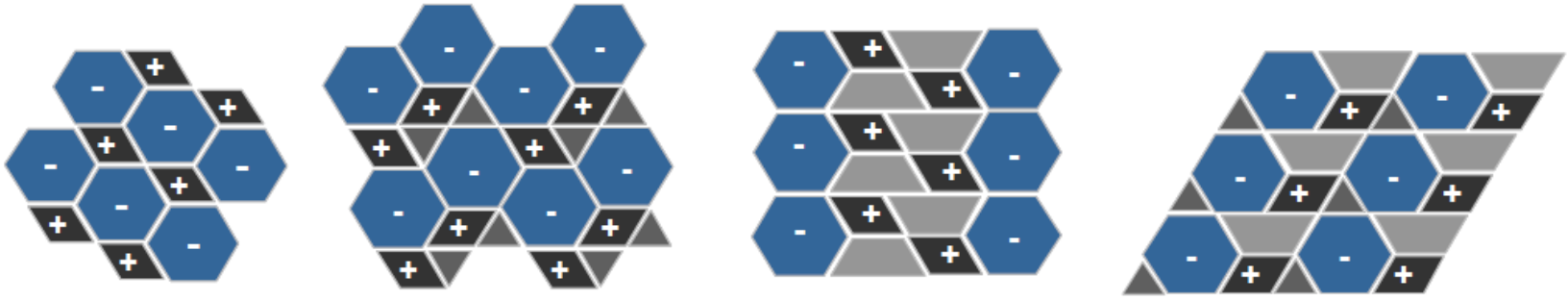
Neutral

Polymorphs



1. Homomeric
2. Hydrate/solvate
3. Cocrystal
4. Cocrystal hydrate

Charged



5. Salt
6. Salt hydrate/solvate
7. Salt cocrystal
8. Salt hydrate cocrystal

Relationship between the Structure and Properties of Pharmaceutical Crystals

Packing Properties

- Molar volume and density
- Refractive index
- Conductivity, electrical and thermal
- Hygroscopicity

Thermodynamic Properties

- Melting and sublimation temperatures
- Internal energy (i.e. structural energy)
- Enthalpy (i.e. heat content)
- Heat capacity
- Entropy
- Free energy and chemical potential
- Thermodynamic activity
- Vapor pressure
- Solubility

Kinetic Properties

- Dissolution rate
- Rates of solid state reactions
- Stability

A.R. Sheth, D.J.W. Grant, Relationship between the Structure and Properties of Pharmaceutical Crystals, KONA 2005, *23*,

Relationship between the Structure and Properties of Pharmaceutical Crystals

Spectroscopic Properties

- Electronic transitions (i.e. ultraviolet-visible absorption spectra)
- Vibrational transitions (i.e. infrared absorption spectra and Raman spectra)
- Rotational transitions (i.e. far infrared or microwave absorption spectra)
- Nuclear spin transitions (i.e. nuclear magnetic resonance spectra)

Surface Properties

- Surface free energy
- Interfacial tensions
- Habit (i.e. shape)

Mechanical Properties

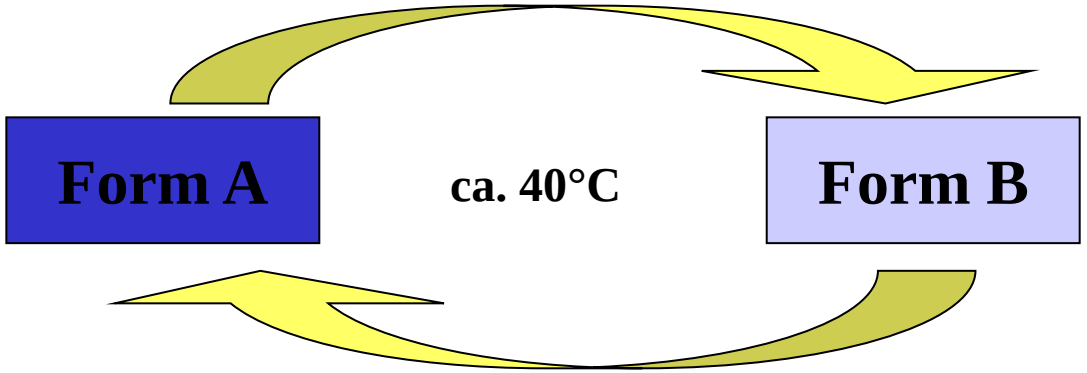
- Hardness
- Tensile strength
- Compactibility, tableting
- Handling, flow, and blending

A.R. Sheth, D.J.W. Grant, Relationship between the Structure and Properties of Pharmaceutical Crystals, KONA 2005, *23*, 36-47.

Tapentadol Hydrochloride – Polymorphic Forms

Solid Phase Characteristics

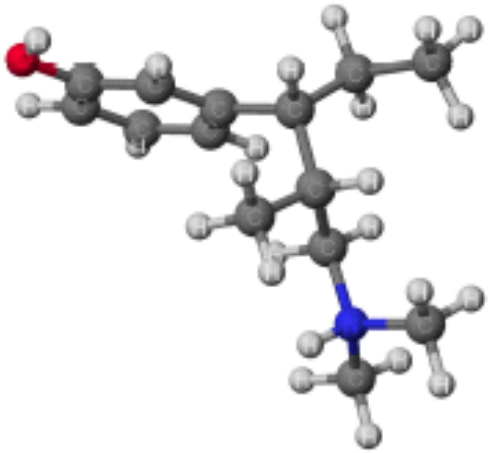
Hydrochloride Salt

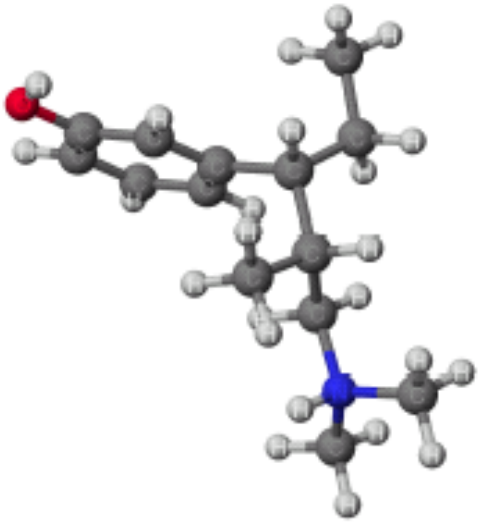


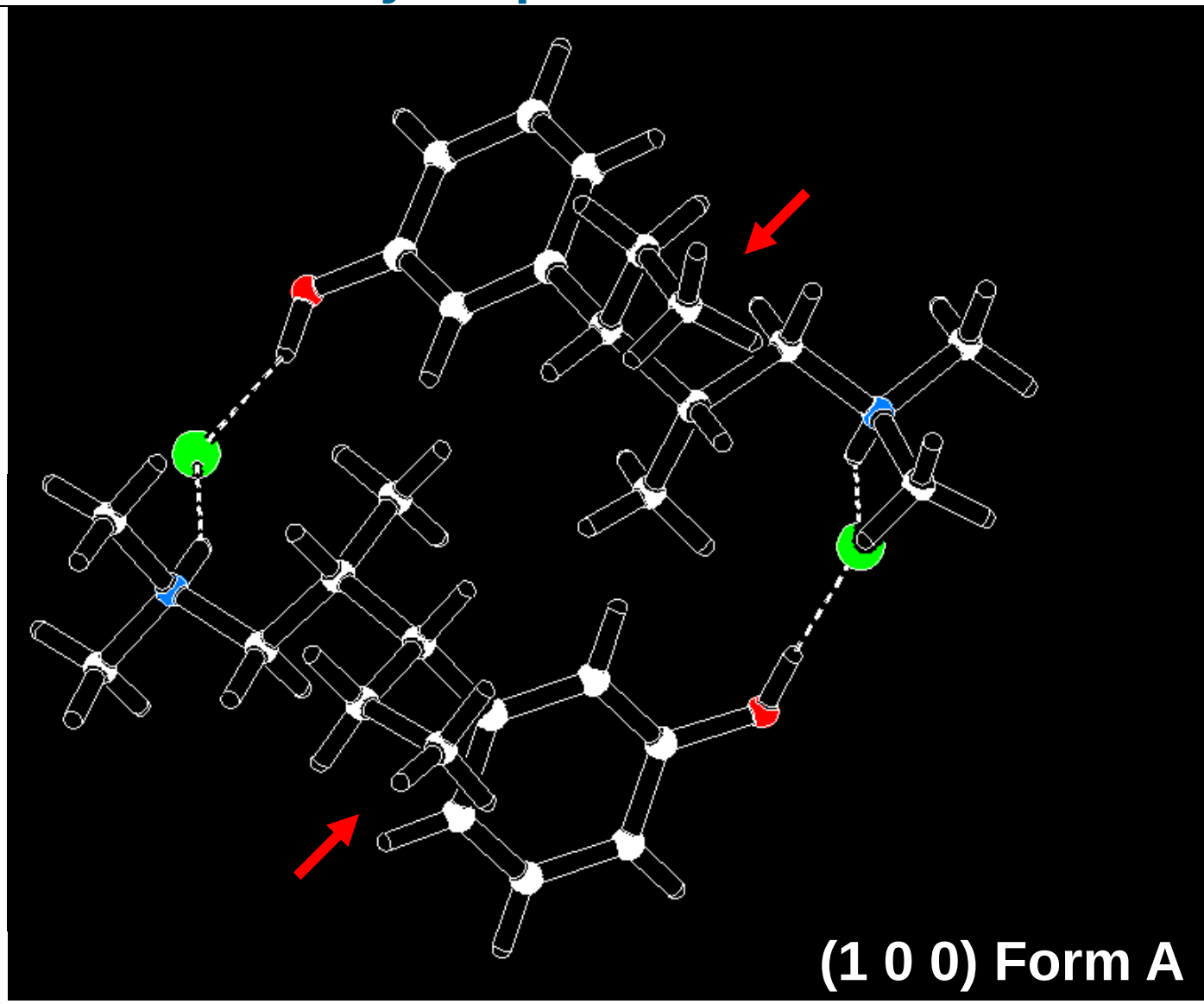
	Form A (monoklin)	Form B (orthorhombic)
Formula	C14 H24 Cl N O	C14 H24 Cl N O
M.W. / g/mol	257,79	257,79
Space group	No. 4, $P2_1$	No. 19, $P2_12_12_1$
Z (No. of Units)	4	4
a/Å	7,110(3)	7,0882(3)
b/Å	11,615(4)	11,8444(6)
c/Å	17,425(6)	17,6708(11)
α/°	90	90
β/°	95,00(3)	90
γ/°	90	90
Volume of elementary cel/Å^3	1434	1484
Density (calc.) / g/cm	1.20	1.15

Tapentadol Hydrochloride – Polymorphic Forms

GRT1: Polymorph A

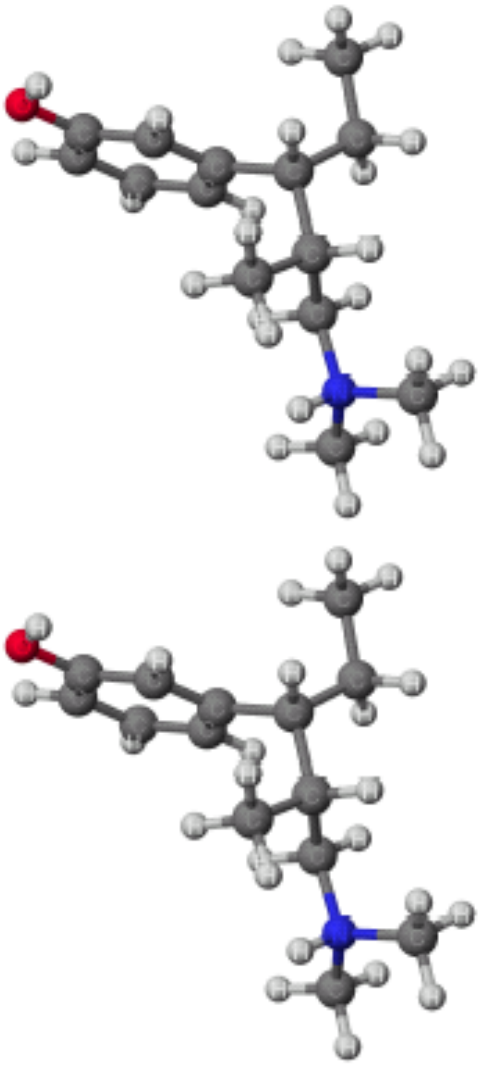


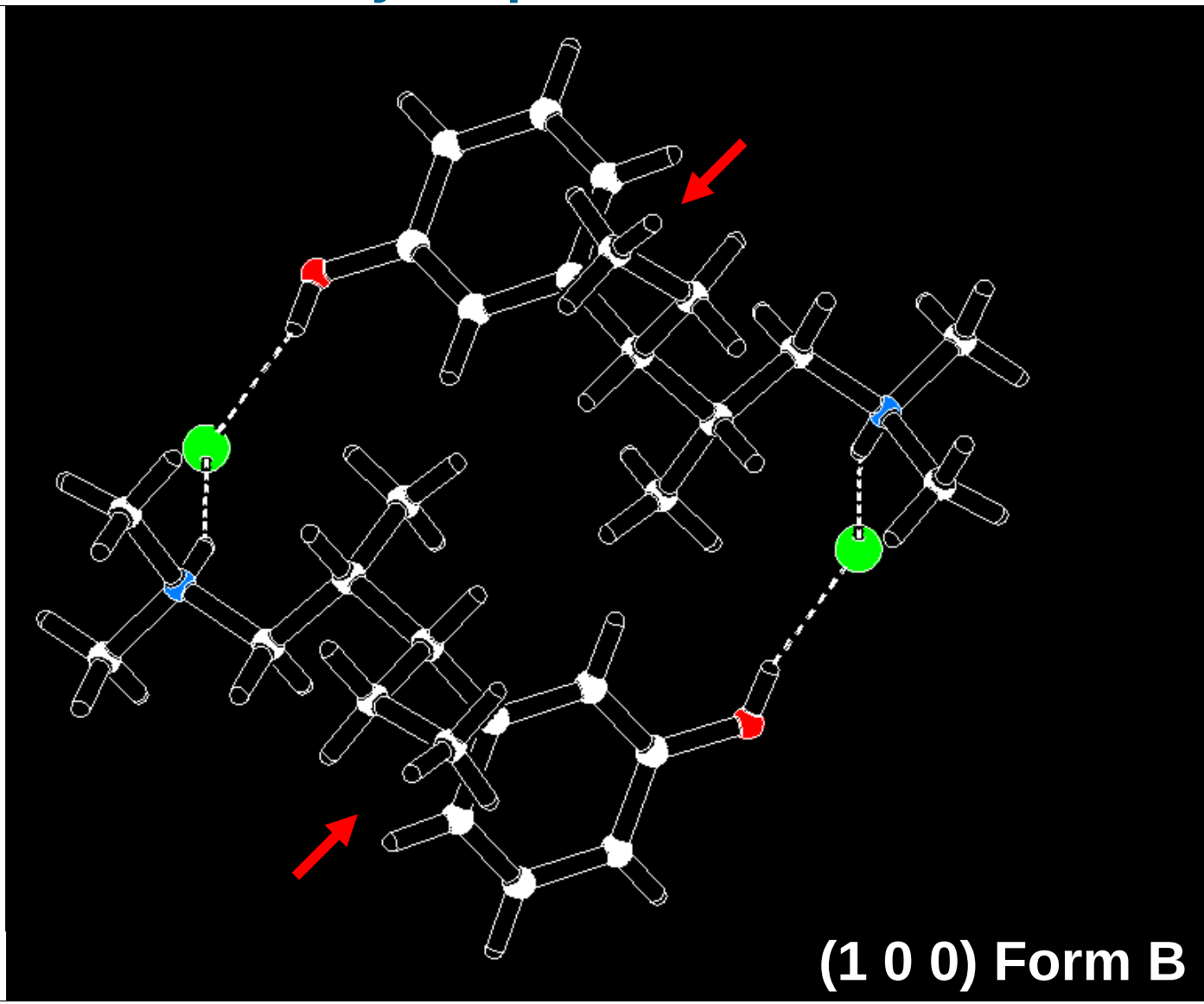




Tapentadol Hydrochloride – Polymorphic Forms

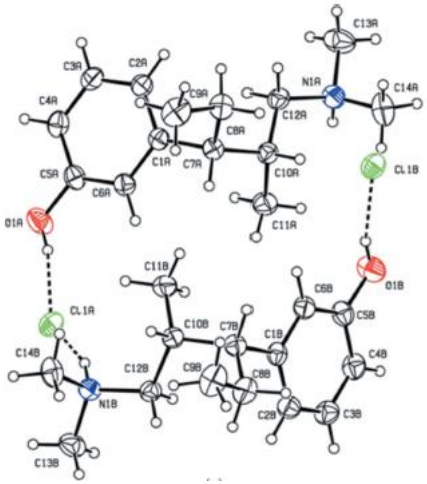
GRT1: Polymorph B



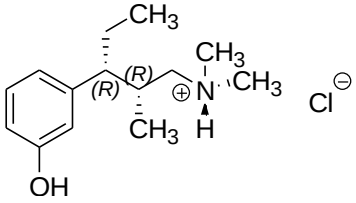


(1 0 0) Form B

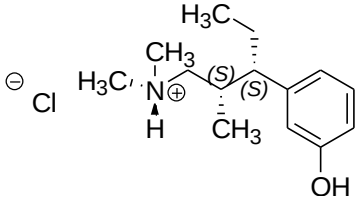
Four stereoisomers of the novel μ-opioid receptor agonist tapentadol hydrochloride

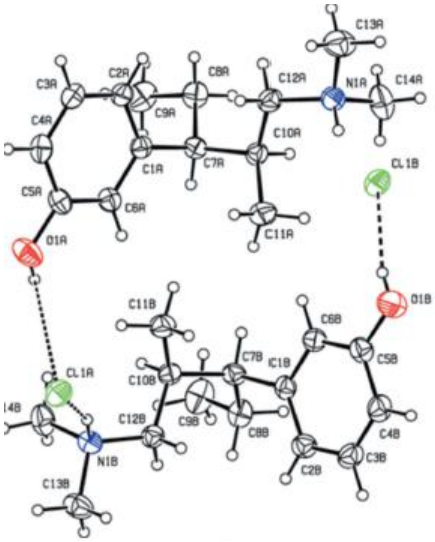


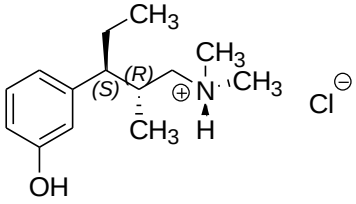
Monoclinic, $P2_1$
a = 7.1600 (15) Å
b = 11.688 (3) Å
c = 17.514 (4) Å
β = 94.535 (3)°

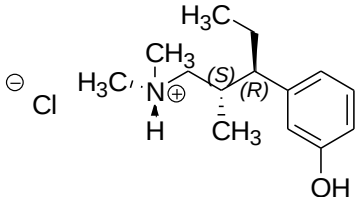


Monoclinic, $P2_1$
a = 7.160 (3) Å
b = 11.688 (5) Å
c = 17.526 (8) Å
β = 94.570 (7)°



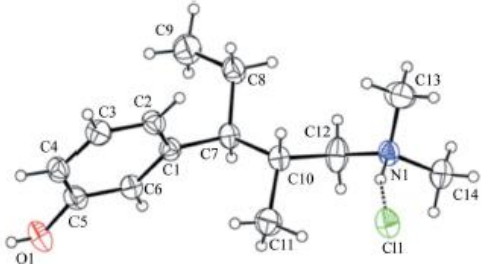


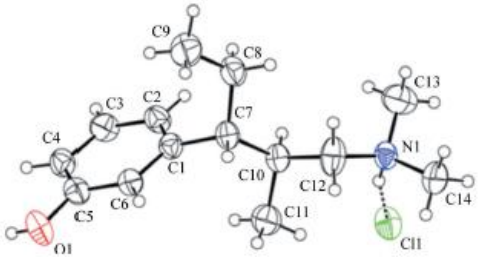




Orthorhombic, $P2_12_12_1$
a = 8.8218 (6) Å
b = 12.1304 (8) Å
c = 14.0031 (9) Å

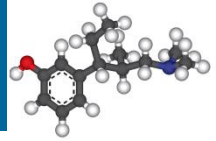
Orthorhombic, $P2_12_12_1$
a = 8.8101 (6) Å
b = 12.1094 (8) Å
c = 13.9784 (9) Å





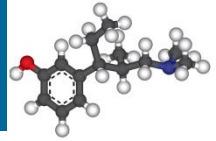
Krishnan Ravikumar, Balasubramanian Sridhar, Nitin, Pradhan and Mayur Khunt, Four stereoisomers of the novel μ-opioid receptor agonist tapentadol hydrochloride, Acta Cryst. (2011). C67, o71–o76

Tapentadol - Tramadol



- Tapentadol is a single molecule (pure enantiomer); tramadol is a racemate.
- Tapentadol has no active metabolites that contribute to its analgesic effects; tramadol has a major active metabolite.
- Tapentadol acts at MOR and NET with minimal activity at SERT; tramadol acts at MOR, NET, and SERT in a time- and patient-variable manner. Thus tapentadol has less potential to produce serotonin-related adverse effects or serotonin syndrome than does tramadol.
- The mechanisms of action of tapentadol reside in a single molecule, thus the relative ratio of mechanisms does not change over time which provides constant analgesic synergism; the mechanisms of action of tramadol reside in different molecules (enantiomers of the parent and a metabolite), thus the relative ratio of mechanisms changes as tramadol is metabolized.

Tapentadol - Tramadol



- Tapentadol is 2 to 5 times more potent than tramadol across a range of animal pain models. Likewise, clinically, tramadol is effective for treating moderate to moderately-severe pain (WHO step 2); tapentadol is effective in treating moderate to severe pain (WHO step 3).

- Tapentadol is a schedule II drug in the US and scheduling is anticipated for all countries where it is marketed; tramadol is not scheduled in most countries.

- In clinical trials, tapentadol has been shown to be equiefficacious to oxycodone with fewer gastrointestinal adverse effects

- The main pathway of tapentadol metabolism is glucuronidation; tramadol is metabolized mainly via the CYP450 enzyme complex. Therefore, there is greater chance for phenotype variability in response to tramadol.

- Fewer drugs are metabolized via UGT than CYP enzymes, so there is less chance of drug-drug interactions with tapentadol than with tramadol.

Synthetische Chemie

Buschmann, Dr. H.
Akyildiz, Frau K.
Finkam, Dr. M.
Gerlach, Dr. M.
Holenz, Dr. J.
Maul, Frau Dr. C.
Przewosny, Dr. M.
Pütz, Frau Dr. C.
Sattlegger, Dr. M.
Sundermann, Dr. B.
Uragg, Dr. H.
Zimmer, Dr. O.
Bergrath, Frau E.
Bünte, R.
Döteberg, H.
Drunk, Frau U.
Freude, K.
Freymann, Frau H.
Frings, V.
Fuhr, M.
Gussmann, C.
Henn, Frau G.
Honne, Frau G.
Horbach, Frau S.
Jagusch, Dipl.-Ing. U.
Jung, Frau H.
Kaldenbach, W.
Kaulartz, Frau D.
Kerwer-Thomas, F
Koth, Frau S.
Krebber, U.
Kreutzer, Frau M.
Maus, Frau A.
Mueller, Frau M
Ohligschläger,
Reinardy, Frau
Schäfer, M.
Schilling, Frau
Schmitz, Frau I
Schock, G.
Scholz, Frau A.
Schweikart, Fra
Stoffels, Frau H
Weber, Frau M
Wetzig, A.
Wildschütze, F

Pharmakolog

Friderichs, D
Loeser, Frau
Kögel, Frau
Antoine, Fra
Basten-Büttg
Behrendt, Fr
Butz, F.
Dadun-Dego
Haase, Frau
Haase, G.
Jansen, Frau
Jaschinski, F
Kujawski, Fr
Leunissen, T
Liebenhoff, E
Linnhoff, Fra
Mülfarth, Fra
Püttgen, Frau
Reinartz, Fra
Reißmüller,
Schwartz, Fr
Thevis, P.
Tzschentke,

Toxikologie

Matthiesen, Dr. T.
Schulte, Frau M.
Chanier, Frau A.
Gerhards, Frau M.
Hogen, Frau K.
Kaminski, Frau M.
Leipelt, H.
Ossig, Frau S.
Will, Dr. O.
Zimmermann, Frau B.

Pharmakokinetik

Kerdar, Dr. R.
Frentzen, Frau S.
Beier, Dr. H.
Kurth, Dr. B.
Ossig, Dr. J.
Saunders, Dr. D.
Terlinden, Dr. R.
Becker, Frau R.
Gülpen, Frau A.
Hentschel, Frau C.
Kaiser, Frau K.
Keubgen, S.
Kremer, E.
Krüger, Frau H.
Kruse, C.
Langhans, M.
Langhans, M.
Malmendier, K.
Malmendier, K.
Niechwiejczyk, Frau J.
Niechwiejczyk, Frau J.
Poensgen, Frau H.
Rogge-Toehgiono, Frau A
Rosenbaum, Frau N.
Schmitt, Frau B.
Schmitt, Frau B.
Sluijsmans, I.
Sluijsmans, I.
Sluijsmans, I.
Steinberger, G.
Wacker, Frau P.

Theoretische Chemie

Strassburger, Prof.Dr. W.
Kless, Dr. A.
Dahlke, Frau E.
Friedenberger, Frau S.
Melake,Frau T.

Pharmakologie 2

Jahnel, Dr. U.
Loeser, Frau I.
Schneider, Dr. J.
Tchij, Dr. B.
Bloms-Funke, Frau Dr. P.
Bruckmann, W.
Christoph, Dr. T.
Dichant, Frau A.
Fischer, Frau H.
Gross, Frau S.
Haben, Frau I.
Hauser, Frau R.
Heeren, Frau J.
Isemann, Frau N.
Krug, M.
Läufer, J.
Lerch, R.
Morr, Frau A.
Nienierza, Frau J.
Scheede, Frau M.
Schlütz, H.
Schumacher, Frau E.
Valdor, M.
Vanderbrück, T.
Weber, H.
Werner, Frau A.
Wolf, Frau M.
Antiphlogistik II

Molekulare Pharmakologie

Wnendt, Dr. S.
Britz, Frau J.
Englberger, Dr. W.
Gillen, Dr. C.
Haurand, Dr. M.
Hennies, Dr. H.
Biermann, Frau S.
Brandt, Frau P.
Charlier, Frau W.
Cosler, Frau D.
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Ewers, Frau S.
Frings, Frau S.
Habekost, F.
Hees, Frau S.
Hildebrandt, R.
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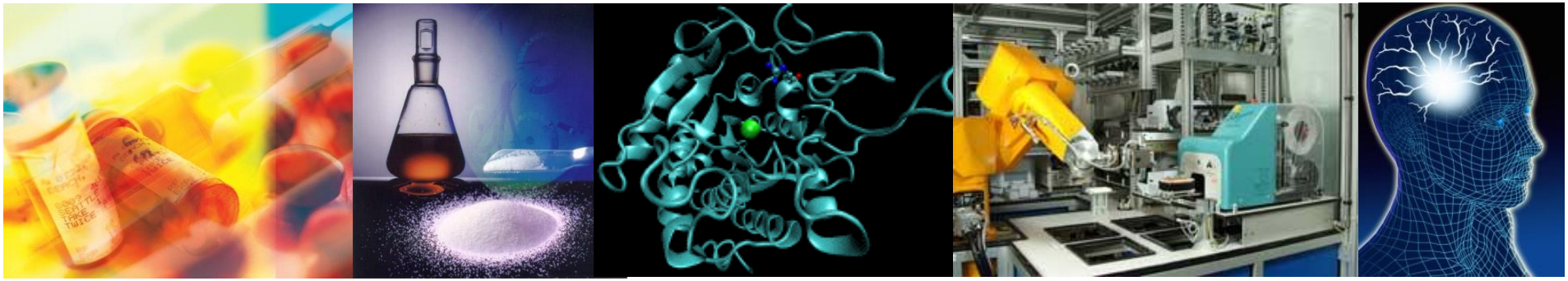


Medicinal Chemistry, Quo Vadis?
The changing climate of Pharmaceutical R&D

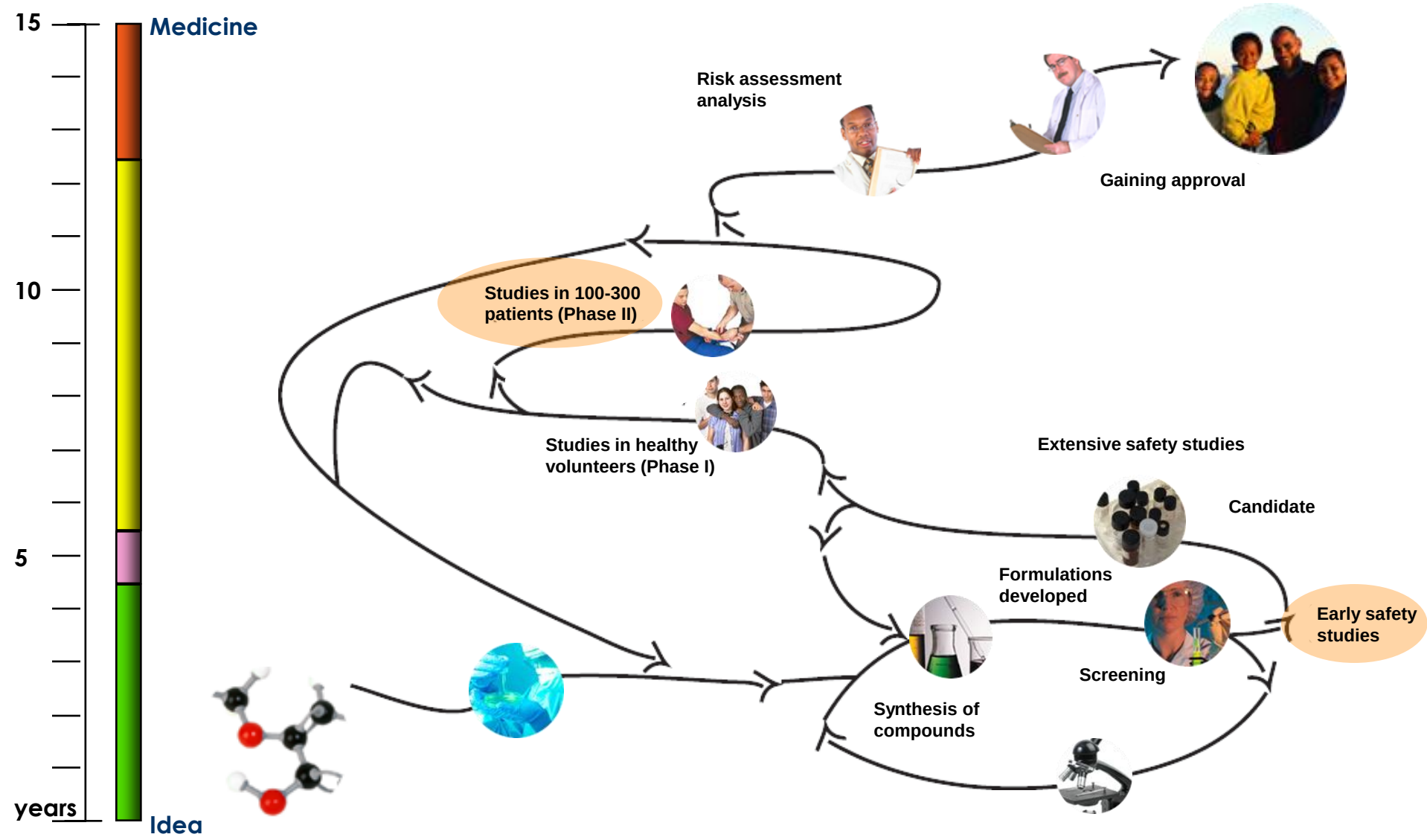
New Drug Development: Some Facts

- **Global situation:**
  - Word population: 7 Billion with Growth rate of 1.1%
  - Word GDP: 70 Trillion Dollars with Growth rate of 5.2%
  - Word Pharma Market: 950 Billion Dollars with Growth rate of 6%

- **Drug discovery and development:**
  - To develop a new drug takes 10-15 years
  - The average cost of a new drug is in the range of $ 1.3 billion, this being a big financial risk
  - 20-30 new drugs are approved annually by the US-FDA: on average; 24 between 2000 and 2009;
  - Similar numbers by EMA
  - >3000 potential new drugs are under clinical development (Phase I, II, and III), however, the attrition rate has become very high

Pharmaceutical Industry – The R & D Process

Creating New Medicines is a High Risk Journey

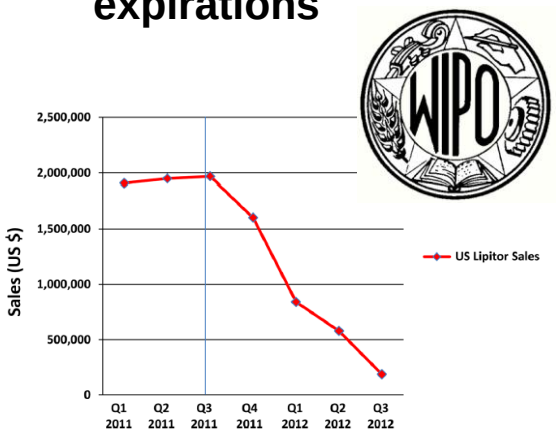


Commonly Perceived Criticisms of the Pharmaceutical Industry

Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 1. Criticisms Faced by the Pharmaceutical Industry, J. Med. Chem 56, 5659-5672 (2013)

Trends driving the evolution of the global healthcare environment

Blockbuster patent expirations



Pressure to control health care spending

R&D productivity crisis

Rise of Emerging markets

Source: *Global Intelligence Alliance, Business Perspectives on Emerging Markets 2012-2017 Survey, Qn: Which are the top 5 Emerging Markets for your industry over the next 5 years? N=38*

Metamorphosis of the Pharmaceutical Industry

- The recent years has brought considerable sales and erosions for most of the leading multinational pharmaceutical companies

- There is not a single reason for this development, many different causes happened at nearly the same time:

  – Patent expiries of big blockbuster drugs and lack of innovative new drugs due to a decline in R&D productivityand efficiency;
  – Wordwide economy crisis;
  – Health care reforms in many countries with cost and price pressures and shift to cheap generics.

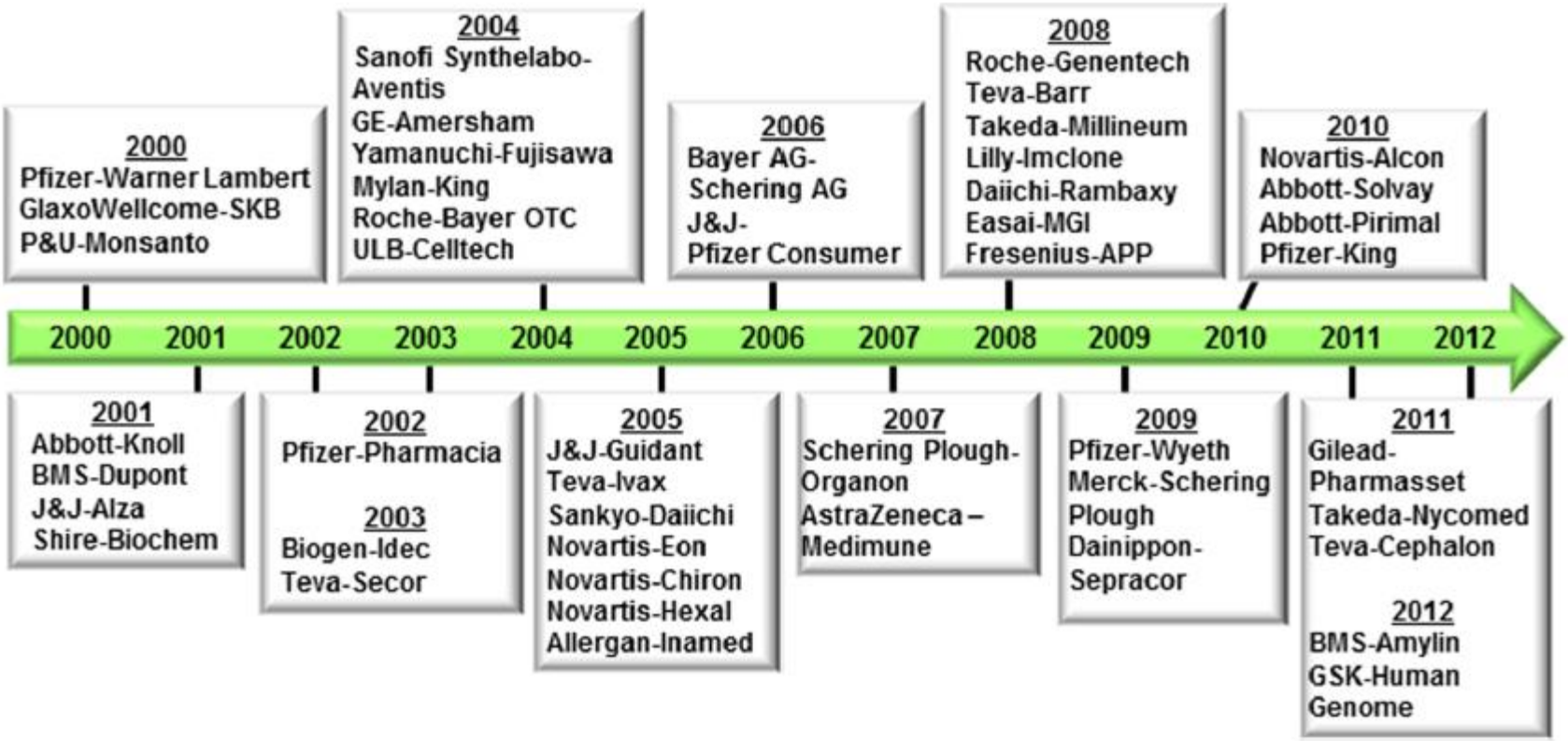
- The traditional blockbuster model is more or less outdated;

- Megamergers and acquisitions in this industry will surely continue, but will not be the solutions of the problems.

- Also outsourcing of (newly-defined) non-core activities like manufacturing and parts of R&D will only give temporary cost relief.

A. Kleemann, Metamorphosis of the Pharmaceutical Industry; Pharm. Ind. 75(4), 562-574 (2013)

Timeline of mergers and acquisitions with values ≥$2 billion that occurred from 2000 to 2012



Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

Pharma Industry Layoffs (2000-2011)

Year	Number of jobs cut
2000	2,453
2001	4,736
2002	11,488
2003	28,519
2004	15,640
2005	26,300
2006	15,638
2007	31,732
2008	43,014
2009	61,109
2010	53,636
2011	ca. 21,000
Total:	315,265

2009 *Total layoffs: 61,109*
thereof Pfizer (19,500), Merck & Co. (16,000), J&J (8,900), AstraZeneca (7,400), GSK (6,000), Eli Lilly (5,500)

2010 *Total layoffs: 53,636*
thereof AstraZeneca (8,550), Pfizer (8,480), GSK (5,201), Roche (4,800), Bayer (4,500), Abbott (3,000), Sanofi-Aventis (2,500), Takeda (1,400), Novartis (1,400), Genzyme (1,280)

A. Kleemann, Metamorphosis of the Pharmaceutical Industry; Pharm. Ind. 75(4), 562-574 (2013)

Blockbuster Drug Patent Expirations between 2011and 2016

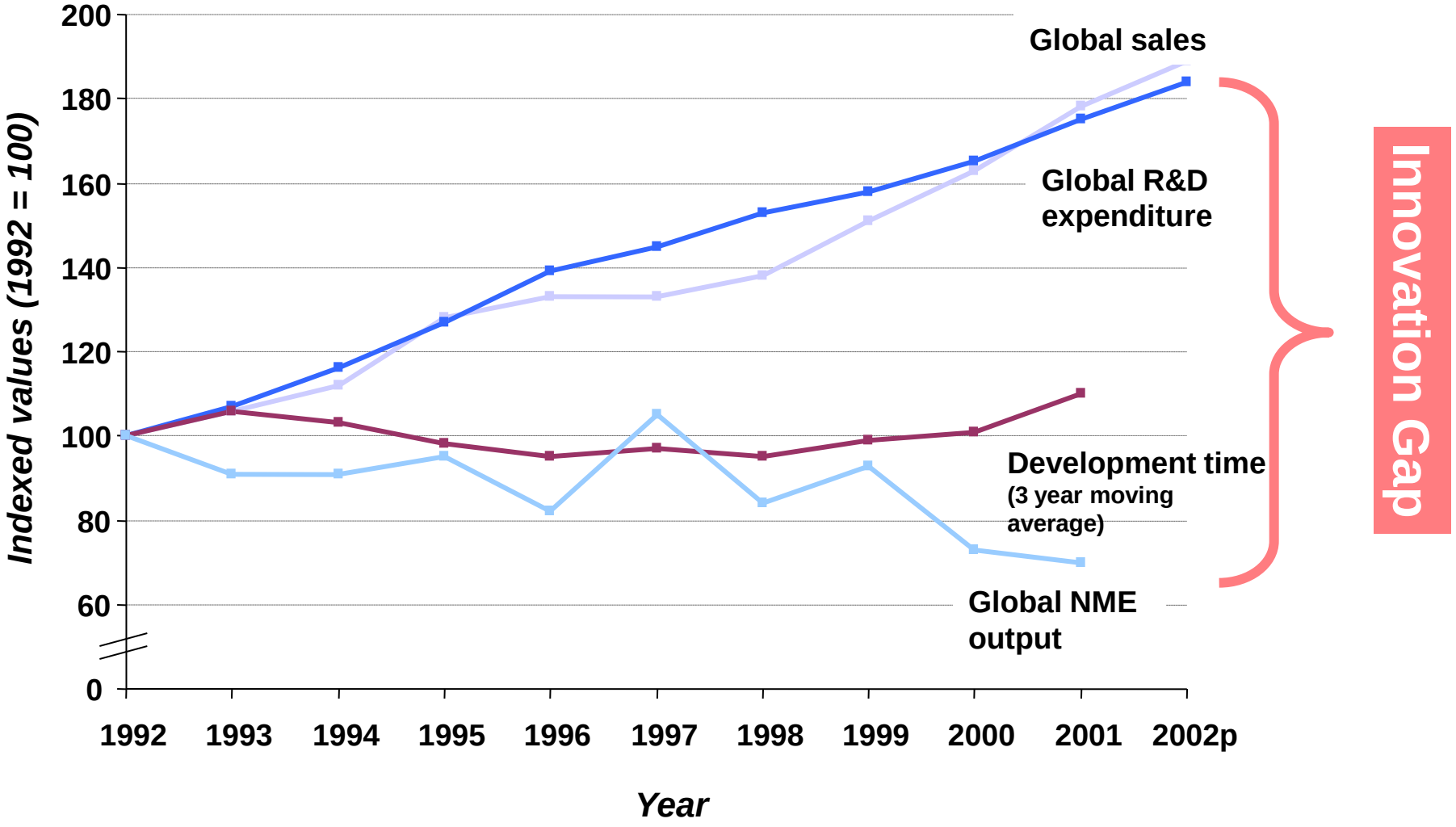
year	brand name	2010 sales (billions of dollars)[b]	company
2011	Actos®	4.6	Takeda
2011	Zyprexa®	5.0	Eli Lilly
2011	Lipitor®	12	Pfizer
2012	Levaquin®	1.4	Janssen
2012	Lexapro®	3.5	Forest
2012	Seroquel®	5.6	AstraZeneca
2012	Plavix®	9.1	BMS[c]/ Sanofi
2012	Singulair®	5.4	Merck
2012	Diovan®	6.1	Novartis
2013	Cymbalta®	3.5	Eli Lilly
2013	OxyContin®	2.4	Purdue
2013	Zometa®	1.5	Novartis
2014	Nexium®	5.0	AstraZeneca
2014	Celebrex®	2.7	Prizer
2014	Sandostatin®	1.3	Novartis
2015	Abilify®	4.6	BMS[c]
2015	Gleevec®	4.3	Novartis
2016	Crestor®	6.1	AstraZeneca

[a]Source: ref 49. [b]World-wide sales. [c]BMS, Bristol-Myers Squibb.

Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

Pharmaceutical Industry – Productivity

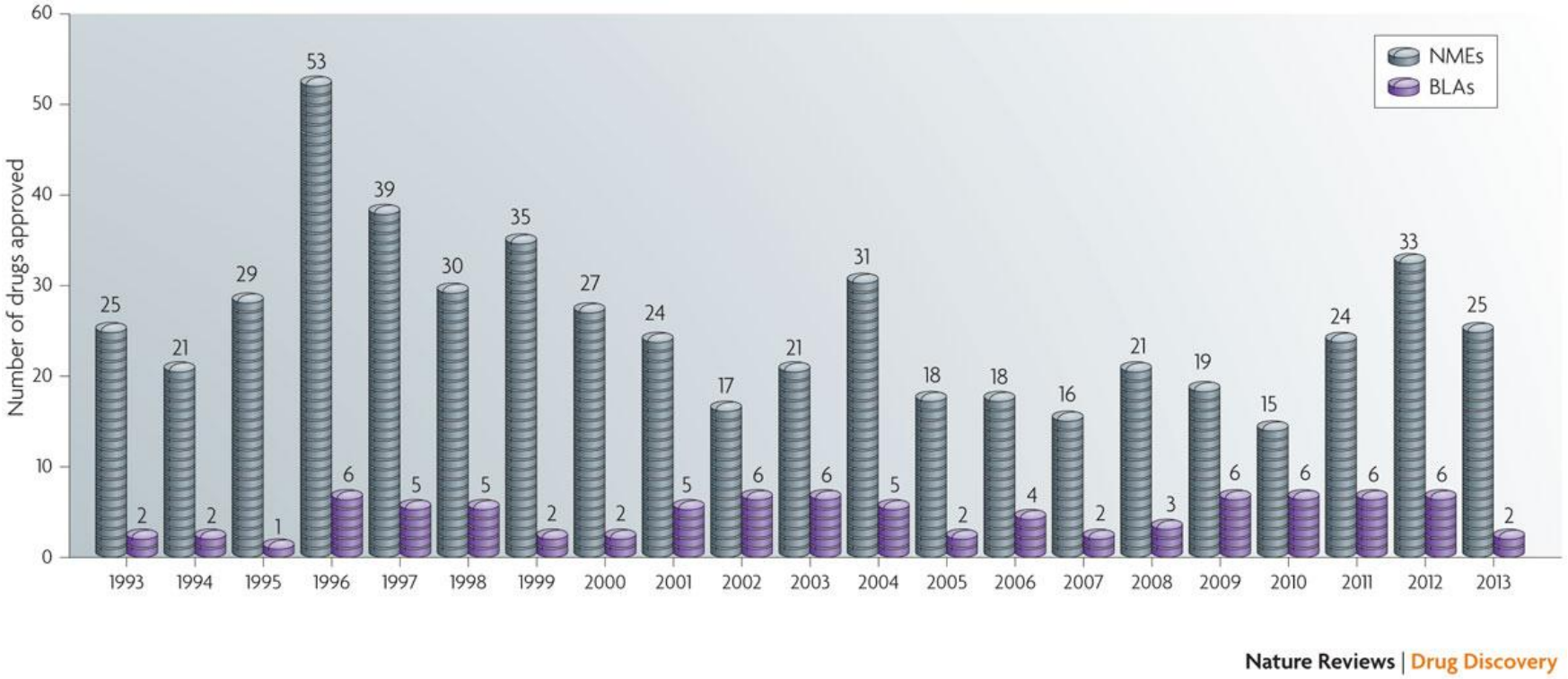
Global pharmaceutical R&D expenditure, development time, NME output and sales 1992-2002p



Pharmaceutical Industry – Productivity

FDA drug approvals since 1993.

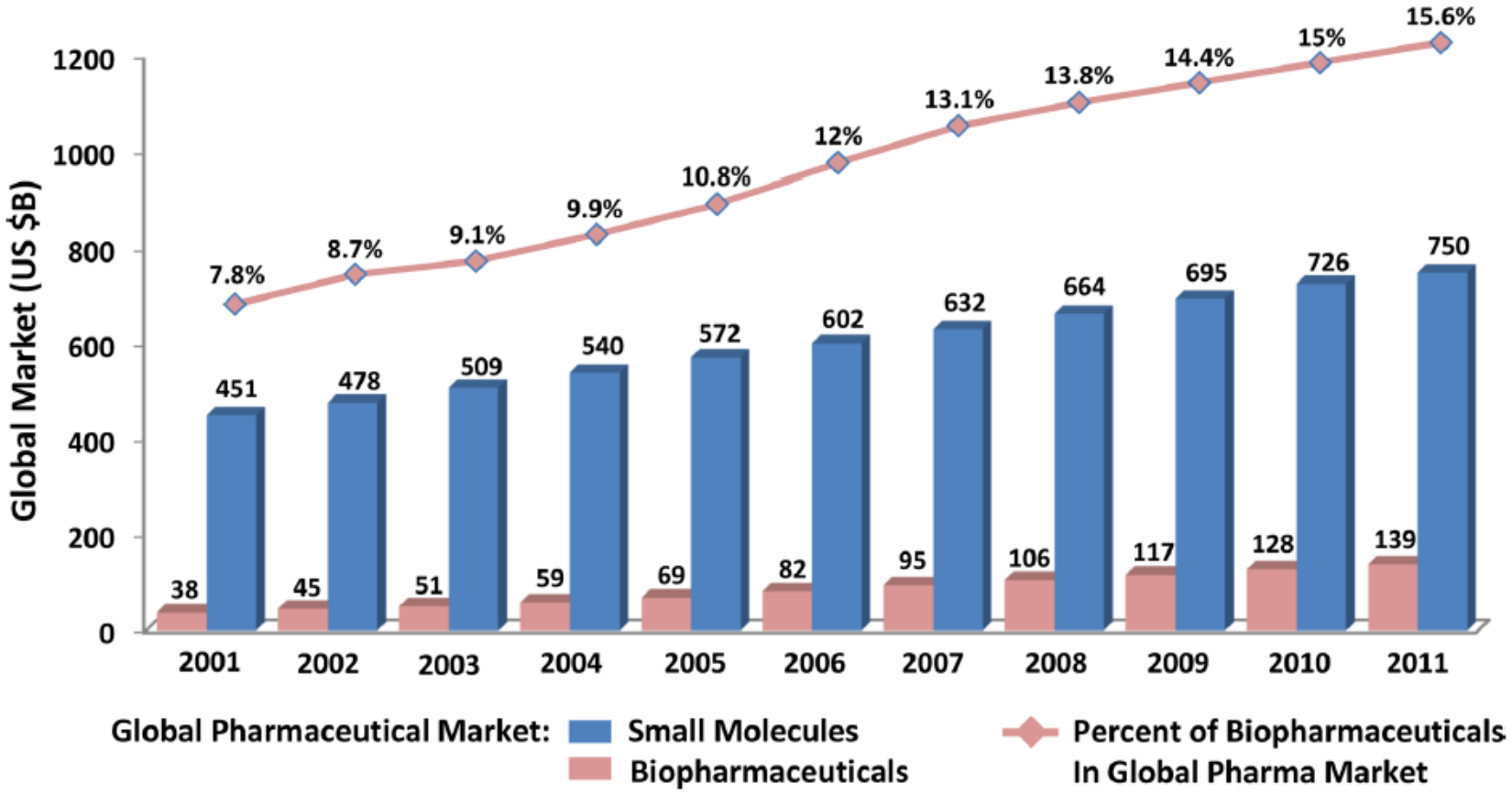
New molecular entities and biologics license applications approved by the US Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research, by year.



Nature Reviews Drug Discovery13, 85–89 (2014)

Pharmaceutical Industry – Productivity

Percentage of biopharmaceuticals in the pharmaceutical market, 2001–2011

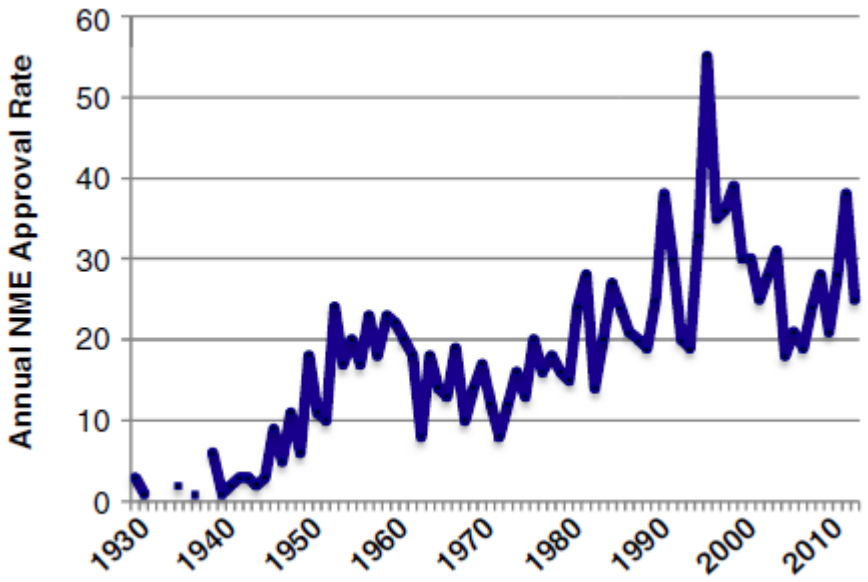


Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

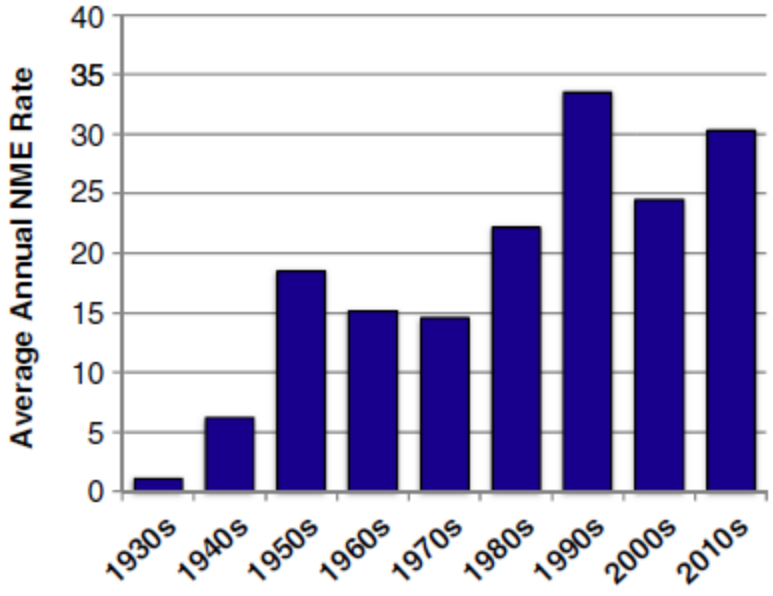
Pharmaceutical Industry – Productivity

R&D Productivity – FDA-approved New Molecular Entities

The number of annual approvals since 1930



The average annual rates of approval by decade since 1930

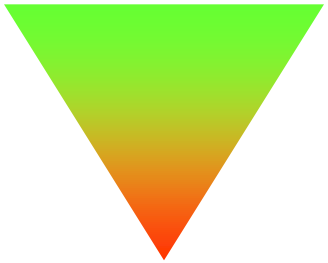


M.S. Kinch, S. L. Kinch, D. Hoyer, An overview of FDA-approved new molecular entities: 1827–2013
Drug Discovery Today 19, 1033-1039 (2014)

Pharmaceutical Industry - Innovation

Ranking System for New Drug Approvals Using FDA Characterizations as Criteria*)

New Drug Approval (NDA) Type	Level of Innovation
Priority NMEs	Most Innovative
Standard NMEs	
Priority IMDs	
Standard IMDs	
Other Drugs	Least Innovative



*) www.nihcm.org; Changing Patters of Pharmaceutical Innovation, May 2002.

The Pharmaceutical Marketplace

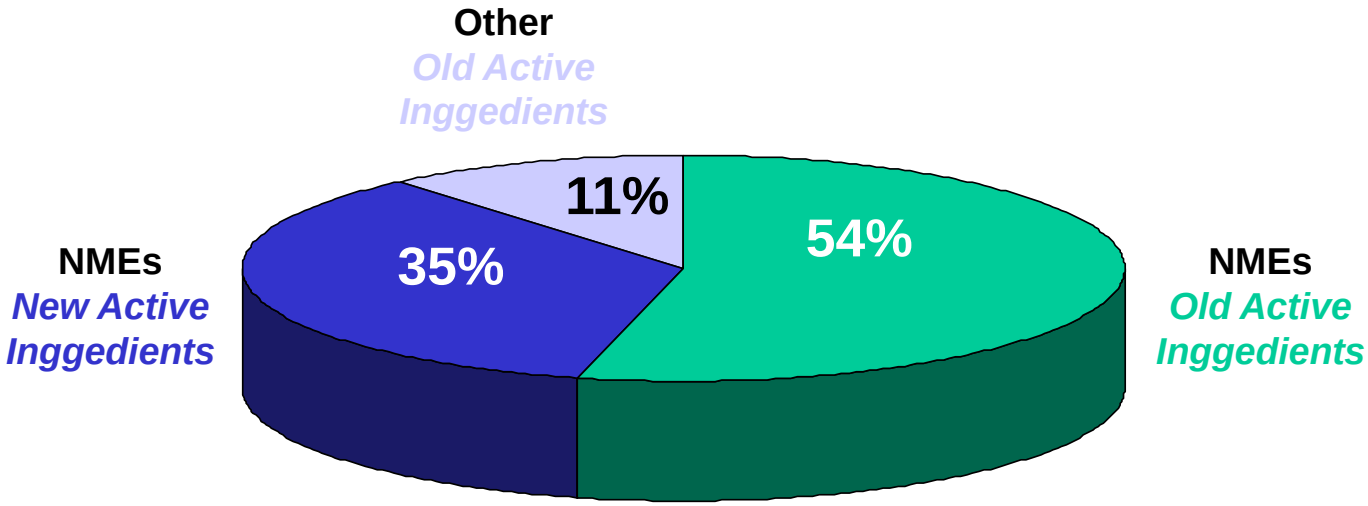
“New drugs to treat and cure sick patients are coming into the market in the United States at the slowest rate in a decade, despite billions invested by pharmaceutical companies on research and a costly expansion by the federal agency that”

“The decline in the number of new drugs is most pronounced in the category considered by the Food and Drug Administration to have the greatest promise for patients -- those listed as breakthrough "priority" drugs and "new molecular entities" that are different from any others on the market.”

Source: Washington Post, 11/18/02

Pharmaceutical Industry - Innovation

New Drug Approvals by the FDA in 1989-2000*)

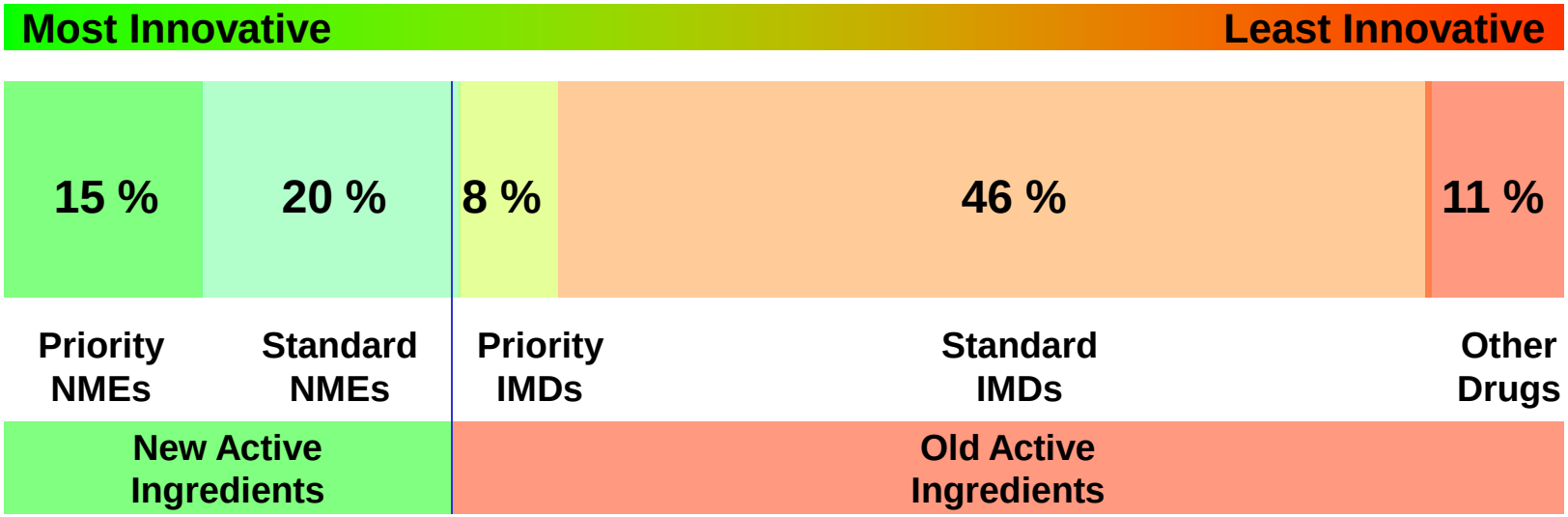


Two-third of new drugs approved in 1989-2000 used active ingredients already on the market
Source: FDA 2001

*) www.nihcm.org; Changing Patters of Pharmaceutical Innovation, May 2002.

Pharmaceutical Industry - Innovation

New Drug Approvals by the FDA in 1989-2000*)



Distribution of NDAs, 1989-2000: Total 1.035 New Drugs

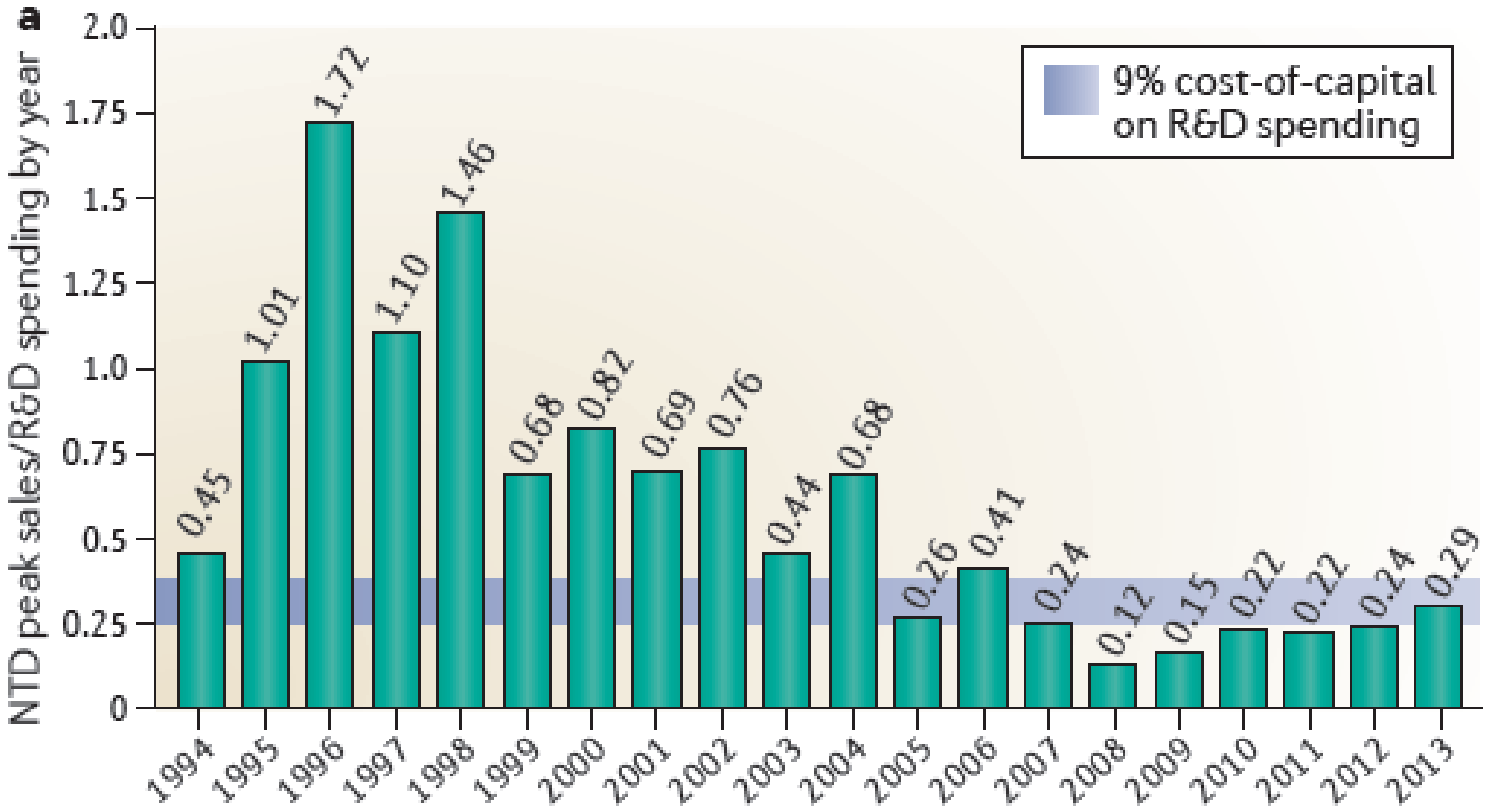
Only 15 % of new drugs approved in 1989-2010 were highly innovative priority NMEs
Source: FDA 2001

*) www.nihcm.org; Changing Patters of Pharmaceutical Innovation

Pharmaceutical Industry - Innovation

R&D Productivity

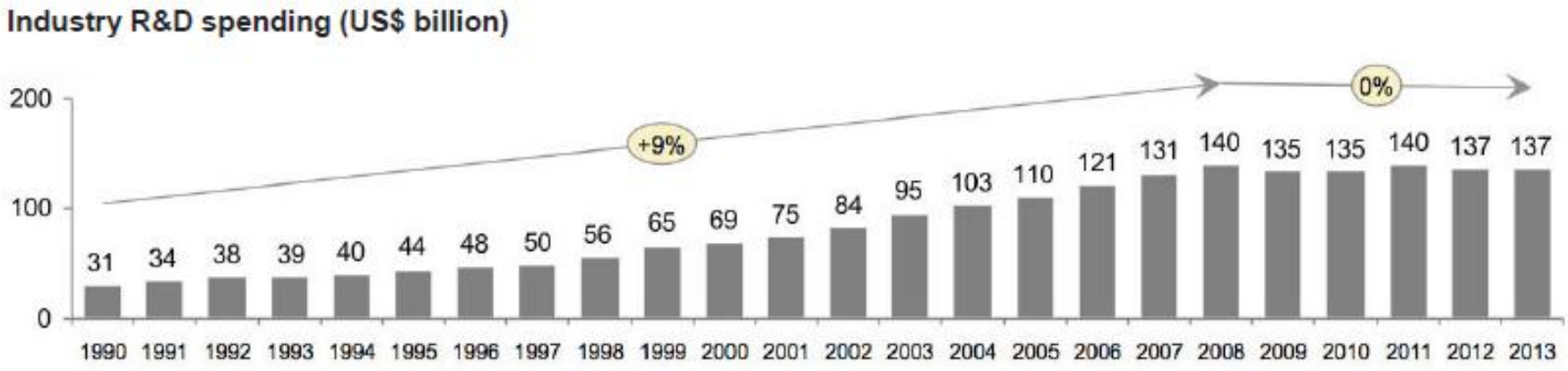
R&D Productivity Data



U. Schulze, M. Baedeker, Yen Ting Chen, D. Greber, R&D productivity: on the comeback trail, Nature Reviews Drug Discovery 13, 331–33, (2014)

R&D Productivity

Aggregate industry spending on research and development



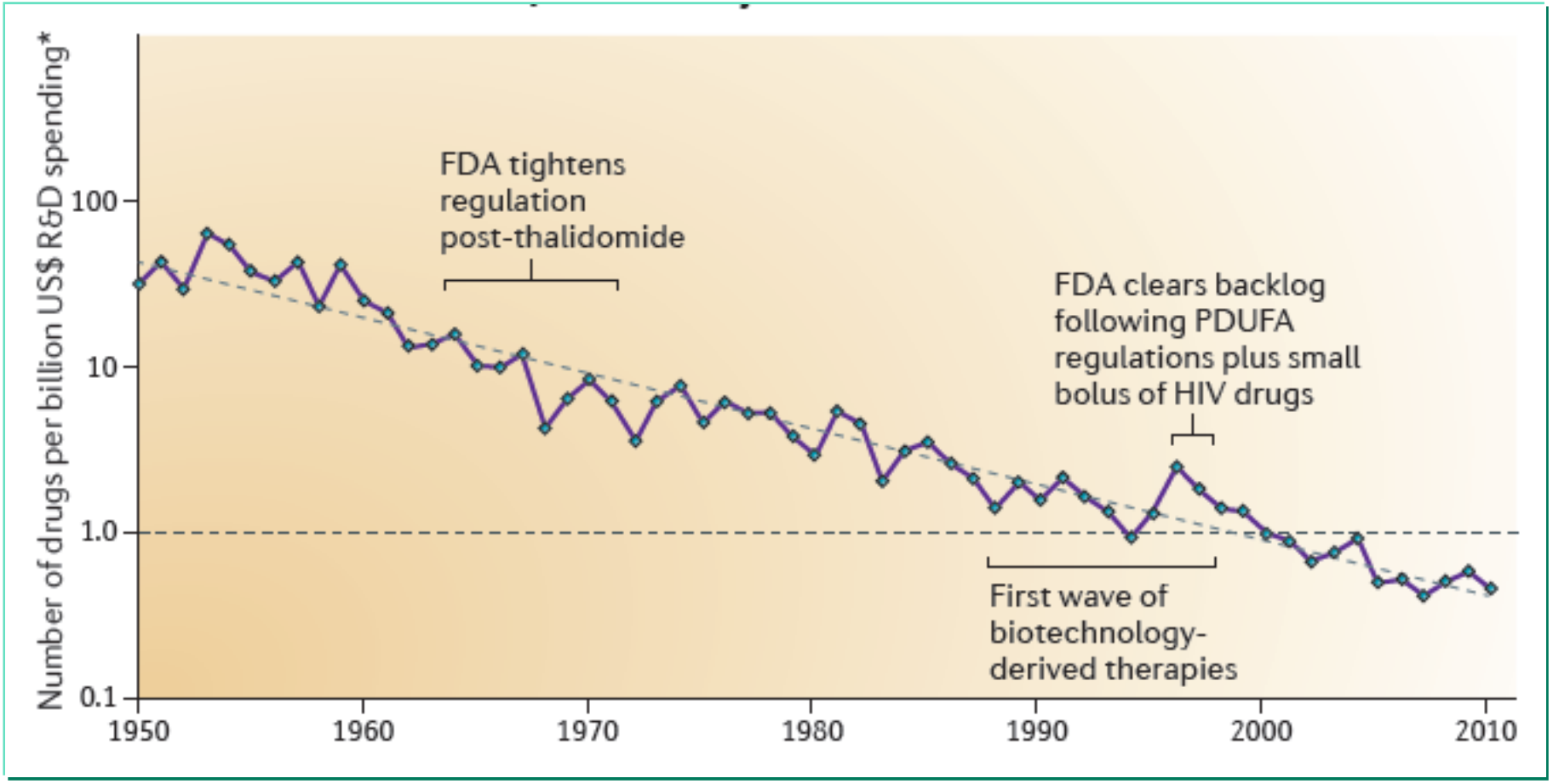
All values inflation adjusted to 2013.
Sources: EvaluatePharma; US Food and Drug Administration (FDA); Boston Consulting Group (BCG) analysis

U. Schulze, M. Baedeker, Yen Ting Chen, D. Greber, R&D productivity: on the comeback trail, Nature Reviews Drug Discovery 13, 331–33, (2014)

Pharmaceutical Industry – Changing Climate

Eroom's Law in pharmaceutical R&D.

Overall trend in R&D efficiency (inflation-adjusted)

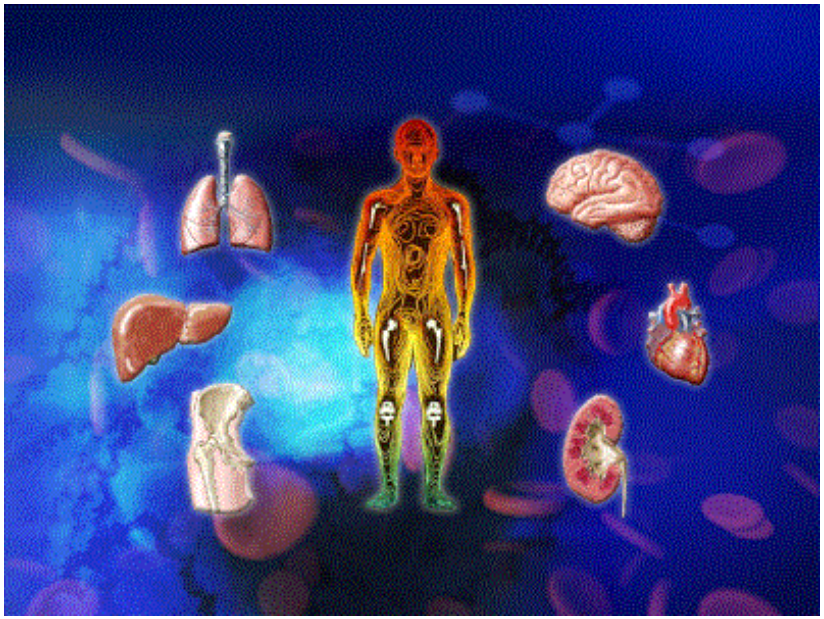


The number of new drugs approved by the US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years.

J.W. Scannel, A. Blanckley, H. Boldon, B. Warrington, Diagnosing the decline in pharmaceutical R&D efficiency, Nature Reviews Drug Discovery **2012**, 11, 191-200.

The Changing Climate in Pharmaceutical Research

The human body is complex



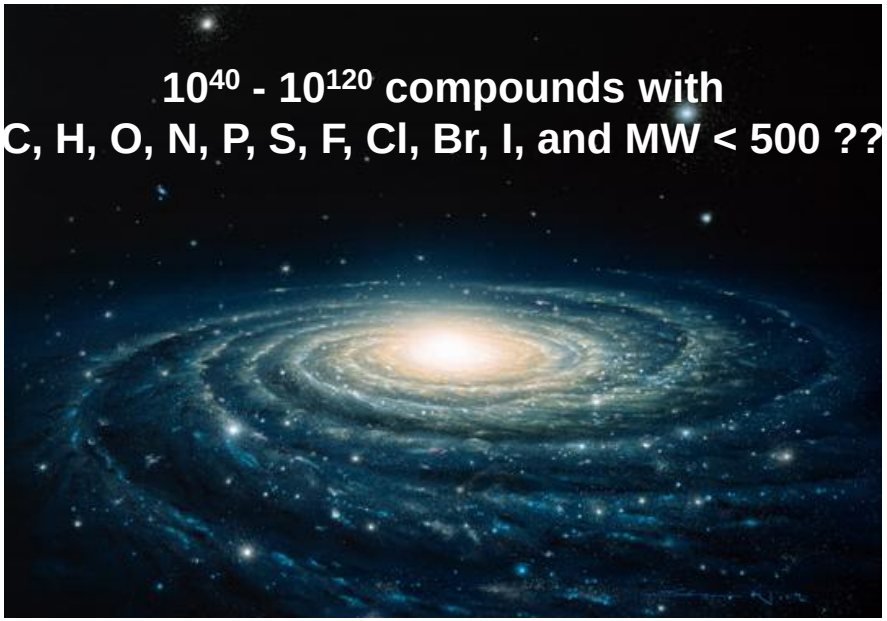
100	organs,
1500	different cell types,
10.000	diseases

- **Scientific Advances**
  - The Human Genome
  - Advances in Screening Technologies
  - Advances in Synthesis Technologies
- **Raising bar on drug-like characteristics**
  - Attrition rates too high
  - Increasing multi-parameter property optimization
- **Increasing Scale**
  - Data volumes and complexity soar
  - Global, multi-site, multi-cultural organizations
  - Rising costs of drug discovery and development

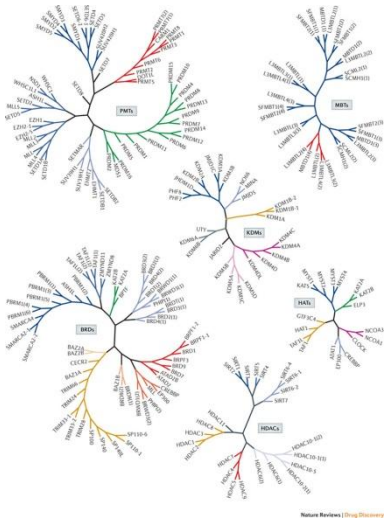
Pharmaceutical Industry – The R & D Process

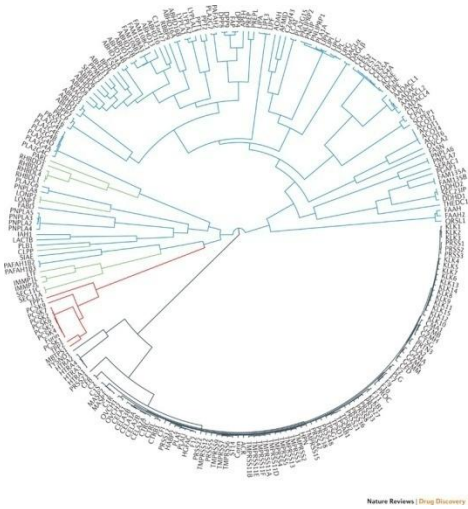
Chemogenomics

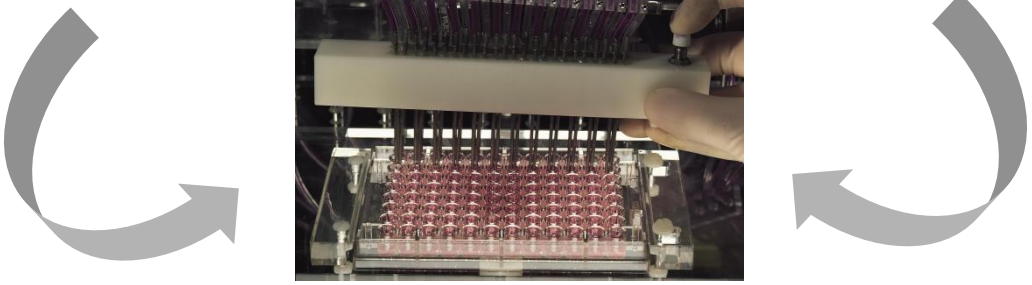
Cemical Universe



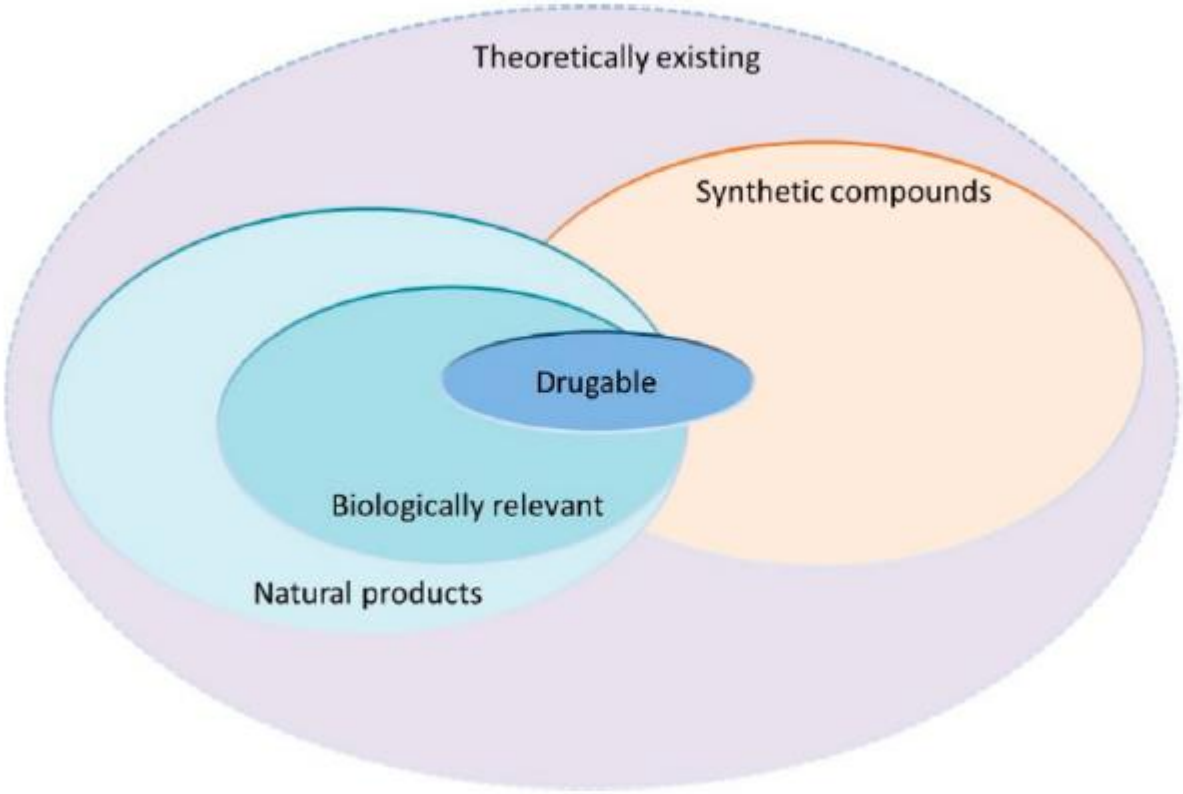
Target Universe







Venn diagram of the distribution of commonly used libraries in chemical space



Zhi-Luo Deng et al., Exploring the Biologically Relevant Chemical Space for Drug Discovery 53, 2820–2828 (2013)

Technological Inputs into Drug Research & Development

Number of drug like molecules that could be synthesized per chemist per year




1970s | 1980s | 1990s | 2000s | 2010s

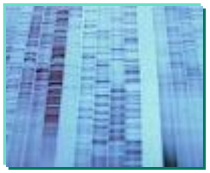
100 compounds per chemist per year

10.000 – 100.000 compounds per chemist per year

x 1.000

Technological Inputs into Drug Research & Development

DNA Sequencing

1970s | 1980s | 1990s | 2000s | 2010s

1st Genome Sequence

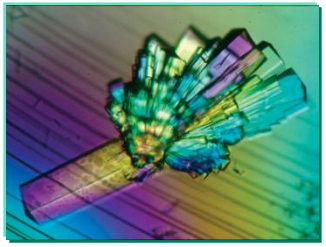
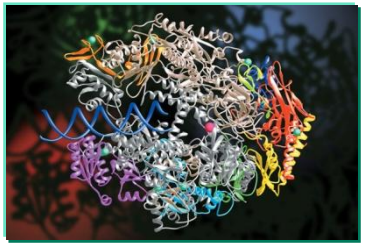
Genomics

x 1.000.000.000 faster

Technological Inputs into Drug Research & Development

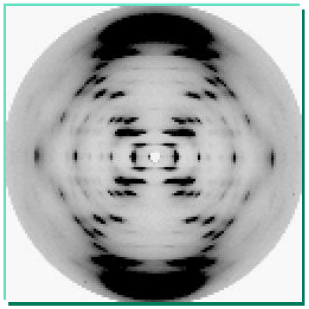
X-ray Crystallography



1970s | 1980s | 1990s | 2000s | 2010s

1st Protein X-ray Structures



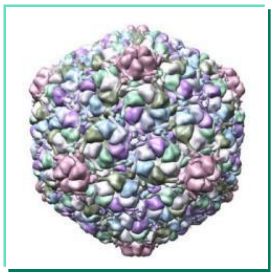
Structure-Based Design

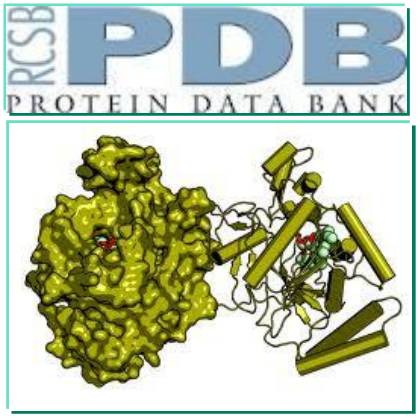
x 1.000 faster calculation

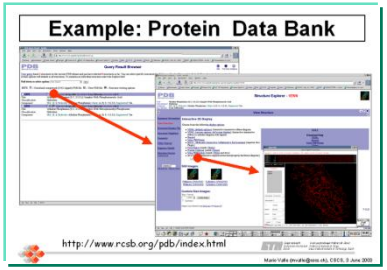
R & D Performance: Drug Discovery Technologies

Technological Inputs into Drug Research & Development

Three Dimensional Protein Structures



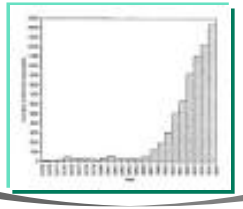




1970s | 1980s | 1990s | 2000s | 2010s

Some 100s Structures

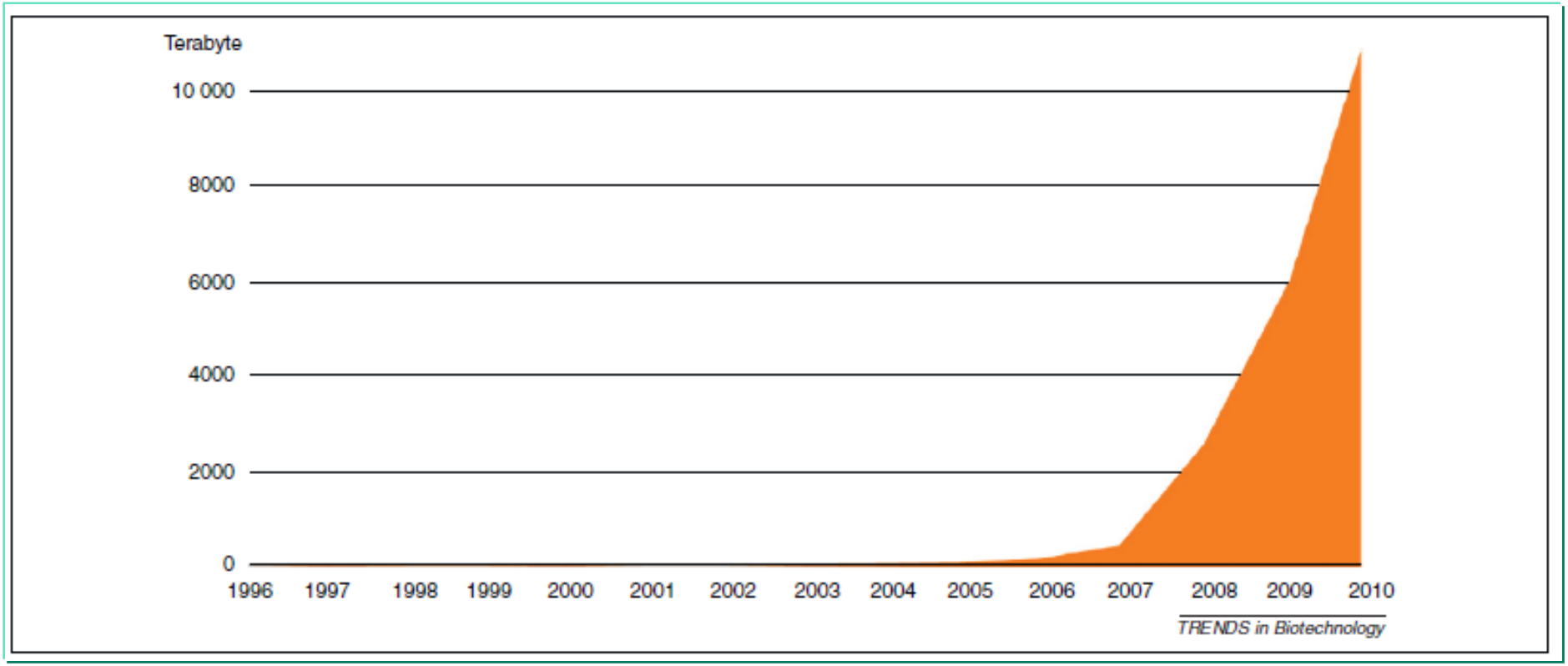
> 50.000 Structures



x 300 more entities in the last 25 years

Technological Inputs into Drug Research & Development

The scale of data growth



The chart shows the trend in storage capacity needed to store biological data at EMBL-EBI (a terabyte is a million million bytes).

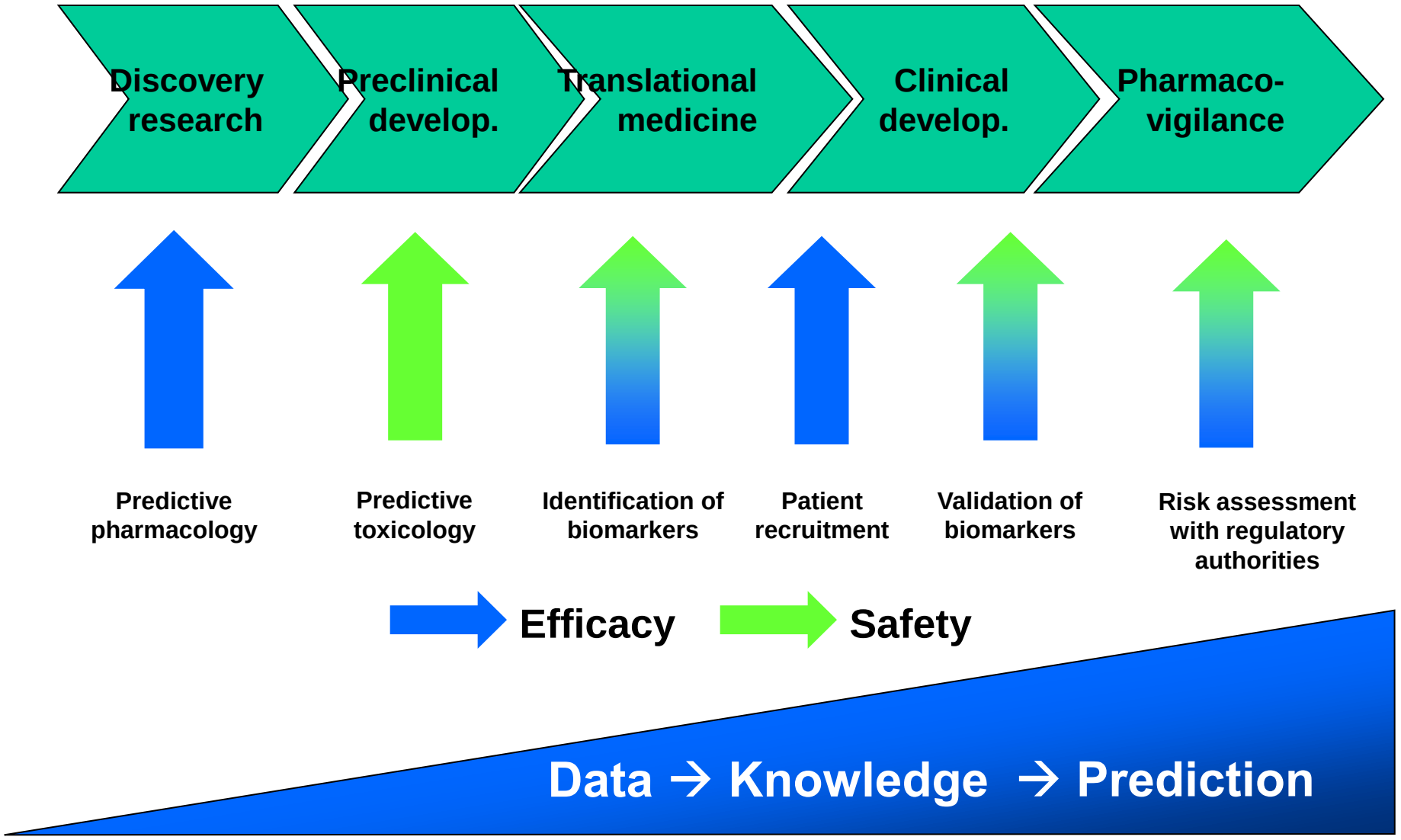
Potential outcome of new technologies

- Proteomics
- Genomics
- Genetics
- Imaging
- Tissue banks
- Disease definition
- Nanosciences
- Knowledge management

- Molecular definition of disease
- New Drug targets
- Prediction of Efficacy
- Prediction of Toxicity
- Better clinical trials design
- Reduced side-effects
- Diagnostic tools
- Personalised Treatments

Pharmaceutical Industry – The R & D Process

Key R&D bottlenecks to overcome



EFFICACY in Pharmacology

TRANSLATIONAL MEDICINE

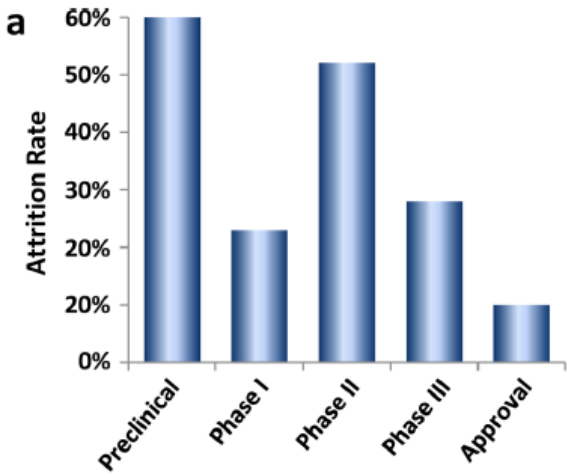
Preclinical models that are more predictive of clinical efficacy and safety

Drug Discovery Strategies Today – *What Has Pharmaceutical Industry Learned From The Past?*

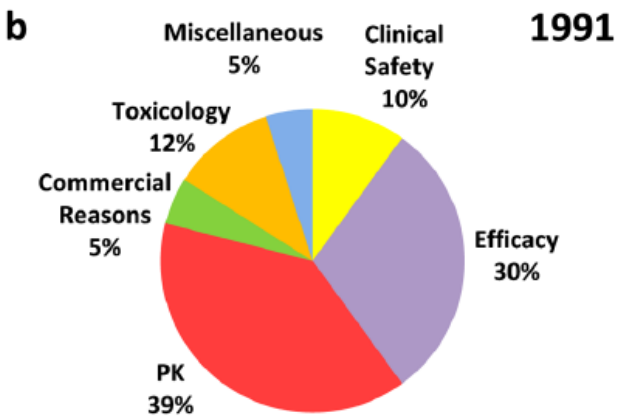
Nothing

Clinical attrition statistics

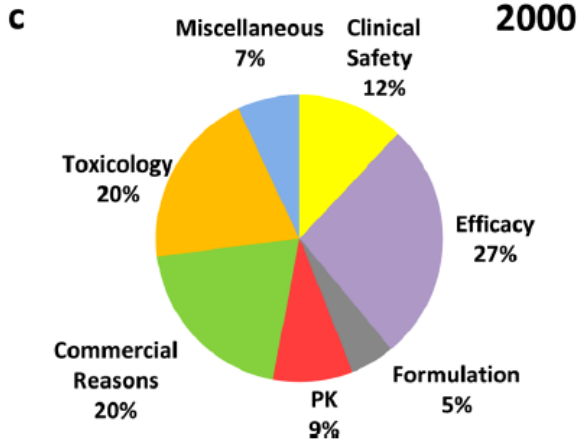
Attrition rate by stage of development



Reasons for clinical failure in 1991



Reasons for clinical failure in 2000



Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

Pharmaceutical Industry – The R & D Process

Drug Research was and is…

…the Search for a Needle in a Haystack

Pharmaceutical Industry – The R & D Process

Success in Drug Research

An compound with an interesting structure has not nessecarily a biological activity

Á compound with biological activity is not a hit

A hit is not a lead

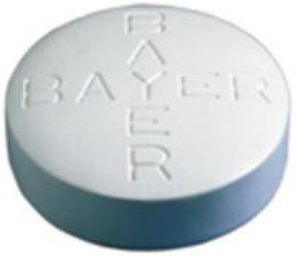
An optimized lead is no candidate

A candidate is not a drug

A drug is not a success

A successful drug is luck!

10^{100} Chemical Space of Organic Molecules



1.000.000s

100.000s

10.000s

100s - 1000

10s

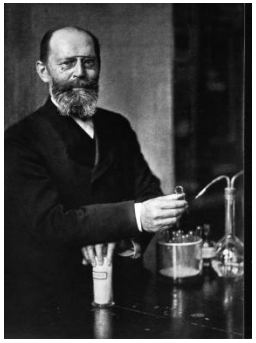
1

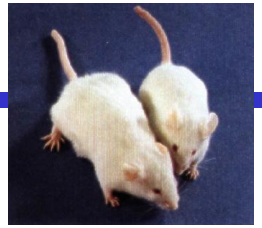
0 -1

Pharmaceutical Industry – The R & D Process

The Evolution of Drug Discovery Strategies

„blind fisching“ → rational design → high throughput screening → „blind screening“ → ?





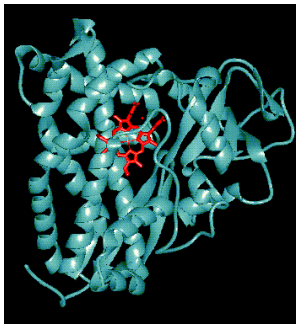
1900

- *in vivo* screening of any available chemical compound: industrial chemicals, dyestuffs, natural compounds, copies of existing drugs, mimics of endogenous molecules
- Pharmacological tests on whole animals or isolated organs
- Objective: detection of the therapeutic effect
- Knowledge of mechanism of action was not not considered as mandatory

1960

- Progress in biochmistry and
- Structural biology

- use of *in vitro* screening based on a mechanism of action hypothesis



1985

- Development of miniturized and automated bioasssays
- Progress in molecular biology
- Receptor identification
- Cloning techniques
- Automatized combinatorial chemistry

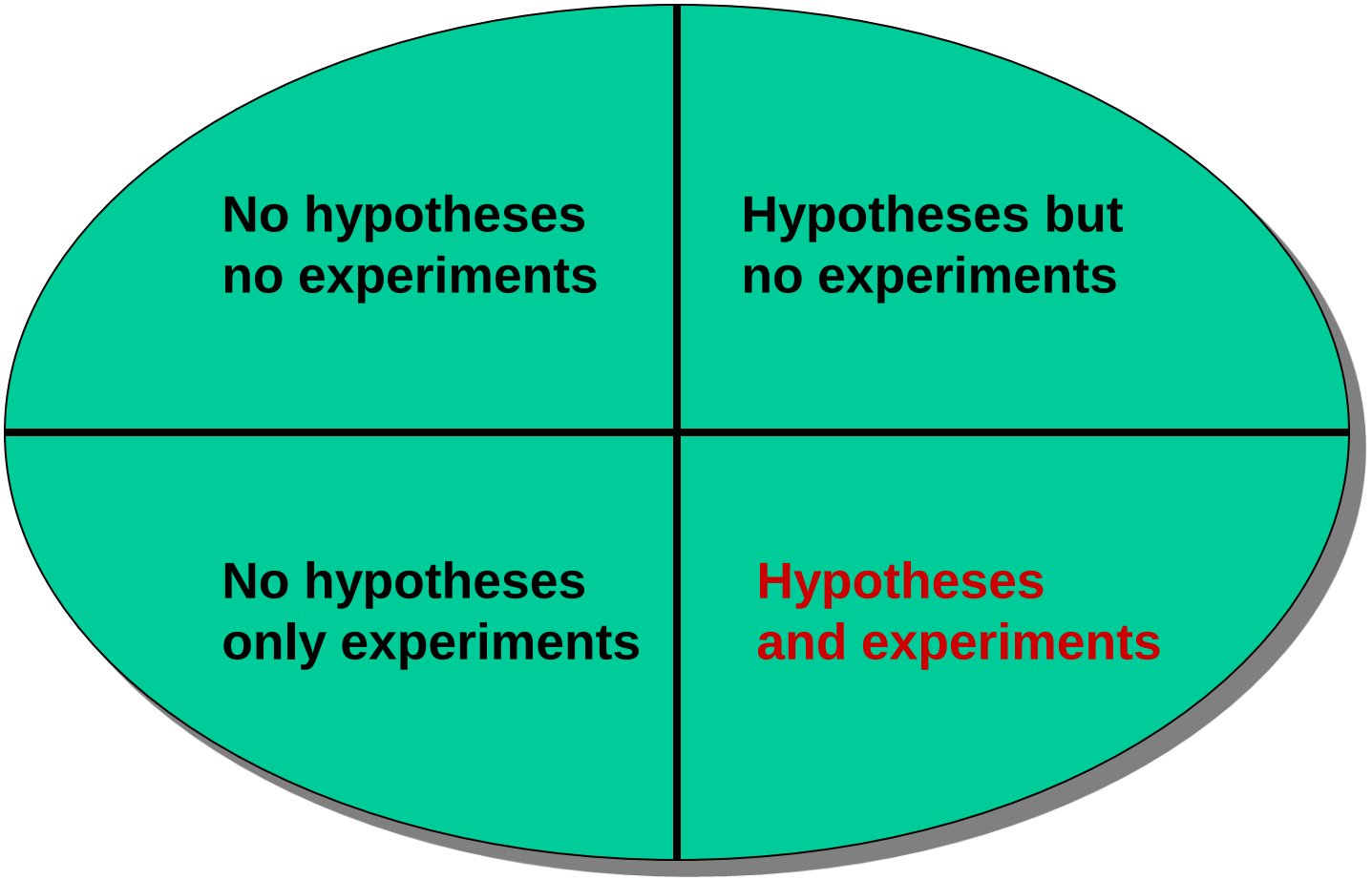
- High throughput screening programs

1995

- Development of in silico technology
- Virtual screening
- Computational assessment of „drug likeness“

- screening of > 100.000 compounds/day
- timeconsuming and expensive process
- Many hits and too few leads
- low diversity of many libraries: large series of similar in house cpds, chemical catalog series,...
- low drug likeness

Four Possible Strategies in Research



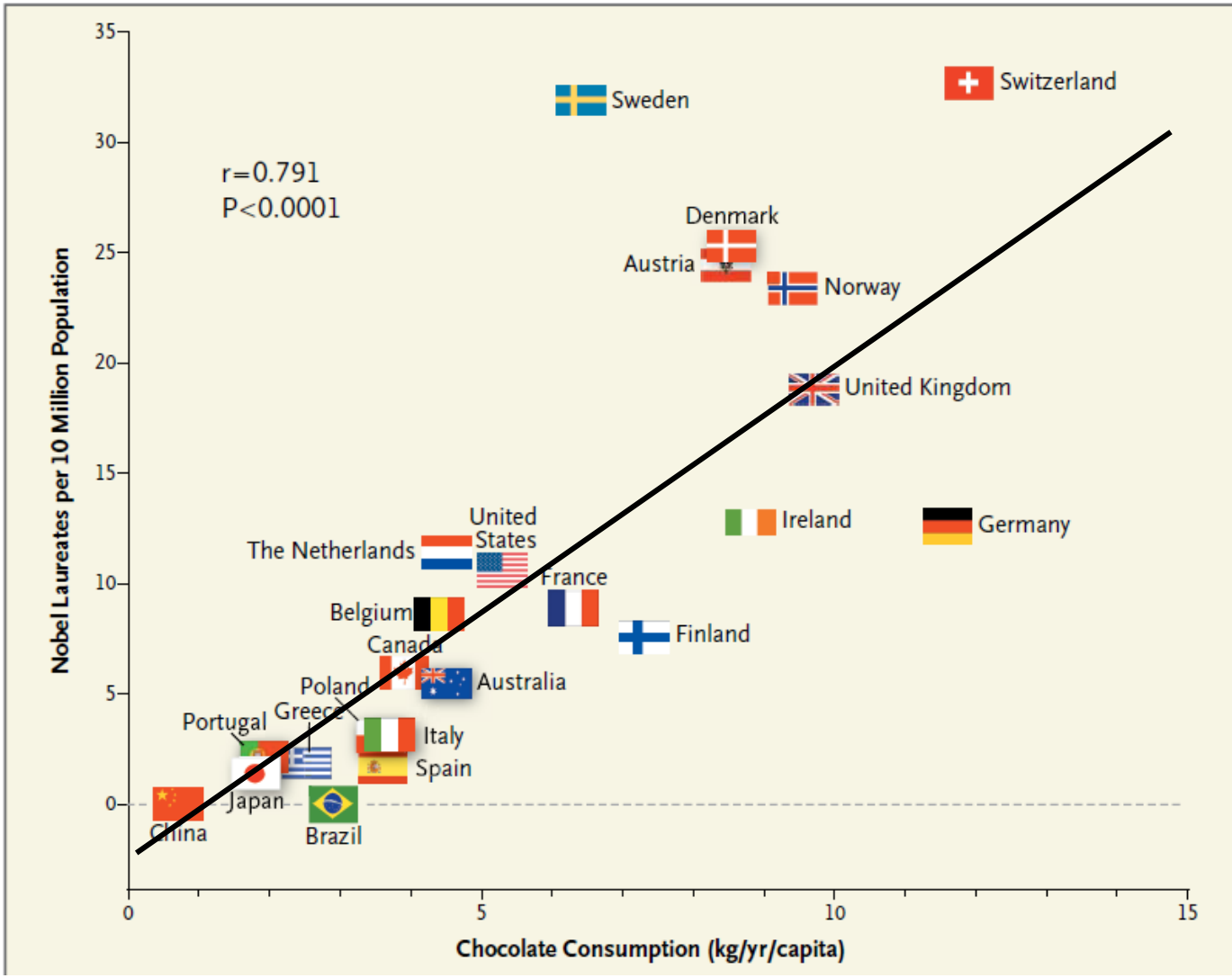
Rolf Zinkernagel (Nobel prize in Medicine 1996)

Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

Chocolate consumption enhances cognitive function,

which is a sine qua non for winning the Nobel Prize,

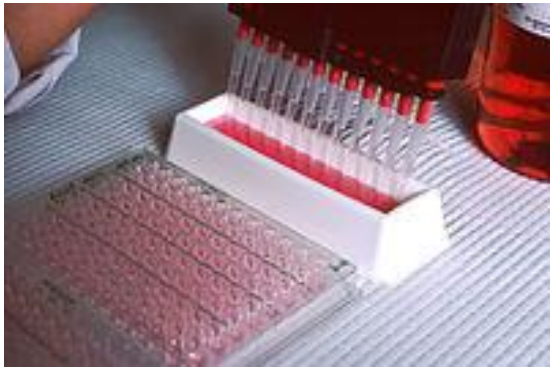
and it closely correlates with the number of Nobel laureates in each country.



Franz H. Messerli, Chocolate Consumption, Cognitive Function, and Nobel Laureates, The New England Journal of Medicine 367 (16), 2012 , 1562-1564.

The early days of drug discovery at Grünenthal (1990)

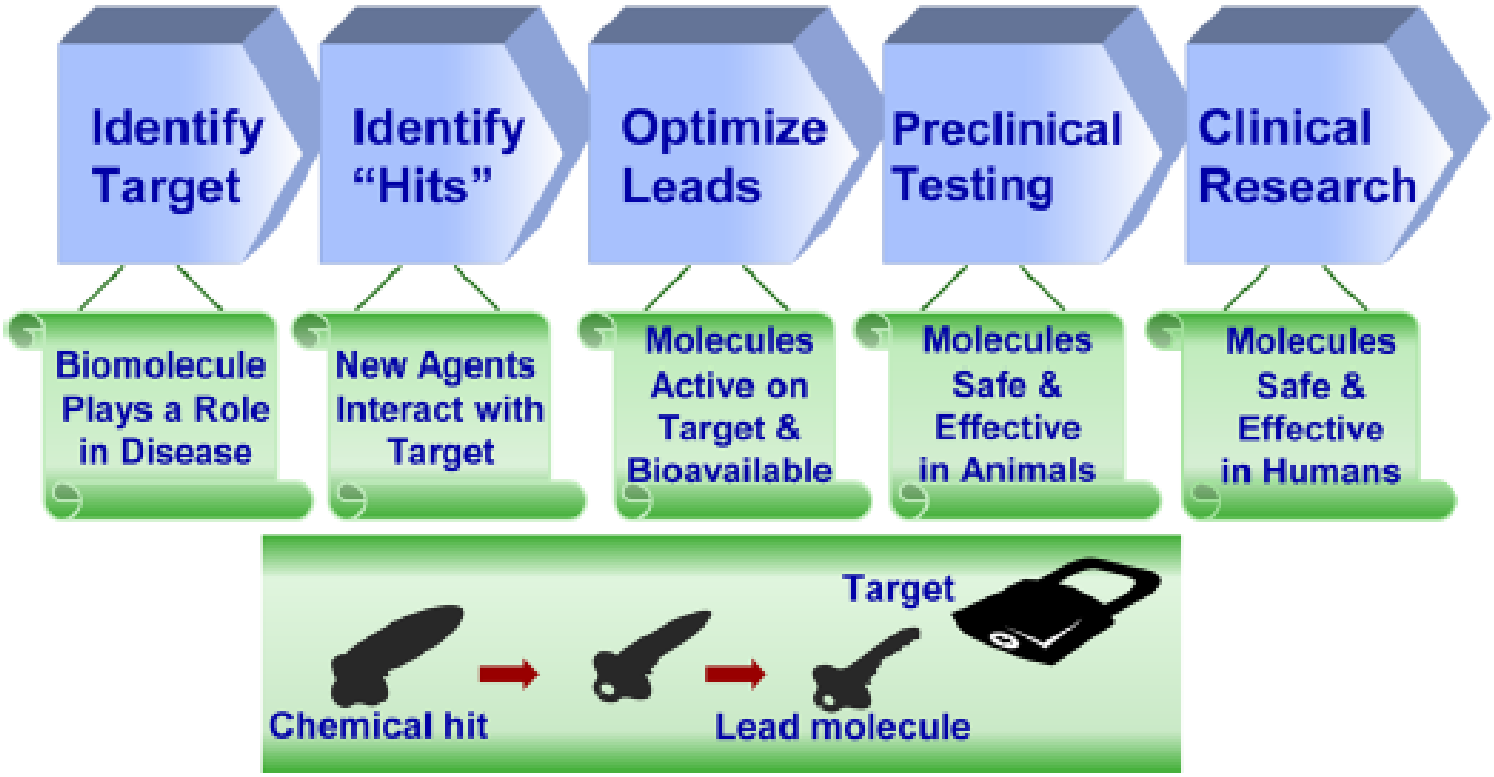
***in vivo* activity**
Writhing Mouse
ED_{50}, oral



***in vitro* Profile**
μ-Opioid receptor affinity
Naloxon binding (K_I)

Pharmaceutical Industry – The R & D Process

Drug discovery process



Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation, J. Med. Chem 57, 5525–5553 (2014)

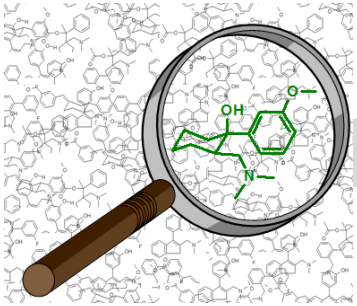
Advantages of early *in vivo* testing

Onset of Action

CNS Side Effects

Oral Bioavailability

Duration of Action



SAR based
Lead Opzimization

***in vivo* activity**
Writhing Mouse
ED_{50}, oral

***in vitro* Profile**
μ-Opioid receptor affinity
Naloxon binding (K_i)

Early Clinical
Proof of Concept

1000 Compounds (14 scaffolds)
280 open chain lead series

The Future of Medicinal Chemistry & Medicinal Chemists

drugs research

”Drug research needs a paradigm shift”

[By Kalle Lötberg]

According to earlier leading researchers, a paradigm shift is necessary that sees pharmaceutical research returning to animal testing in its primary stages.

Per Lindberg

- …Top executives of global ”Big Pharma” companies have to realise that pharmaceutical research needs a paradigm shift, moving away from the current practice of early stages protein target testing.
- A new paradigm is needed in which research returns to experiments based on animal testing models (phenotypic research)….

- …People are very biased today. But medicinal chemists neither can nor have to know exactly how a substance acts.
- This has always been the case, since organisms are very much more complex than the sum of their receptors, enzymes and ion channels….

Kalle Lötberg, ”Drug research needs a paradigm shift”, Kemivärlden Biotech med Kemisk Tidskrift. Nr 3 March 2014

The Future of Medicinal Chemistry & Medicinal Chemists

”Drug research needs a paradigm shift”

1970s – 1990s

- *Disease models for animals were often developed in collaboration with hospital-based researchers.*
- *Newly synthesized compounds were tested in vivo directly on animals.*
- ***Effect in animals were the all im portant driving force.***

1990s - Today

- *The golden era of the genome had begun, receptors were linked to specific genes, and an in vitro technique for measuring a protein’s affinity to synthetic substances was developed.*
- *The process became rational, efficient, simple, elegant and super-fast – and therefore also attractive.*

The Future

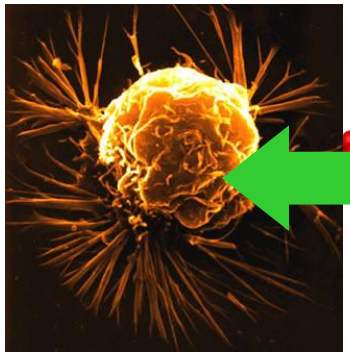
- *Focus on building disease models - for many years an area neglected in favour of for instance multi-chemistry.*
- *Use modern integrated screening directly on animals, including both behaviour and various analyte parameters.*
- ***Synthesize carefully selected substances and test them all on animals.***

The chemists were divided into those who worked at the early and the late testing stages respectively, and their previously acquired competence was often wasted.
It was taboo not to know the target and the mechanism already at the start of a new project.

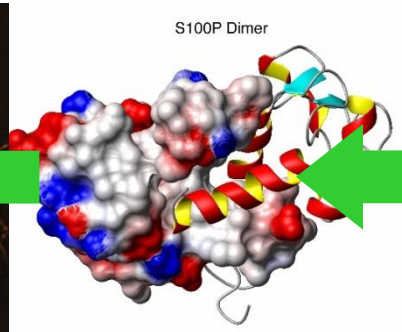
The Future of Medicinal Chemistry & Medicinal Chemists

in vivo Pharmacology

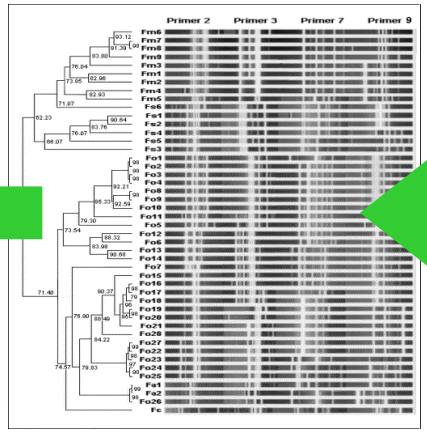
The Future of Medicinal Chemistry & Medicinal Chemists



Cell Structure and Function

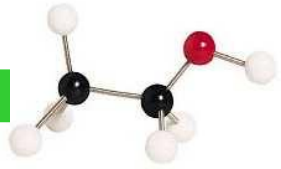


Proteine

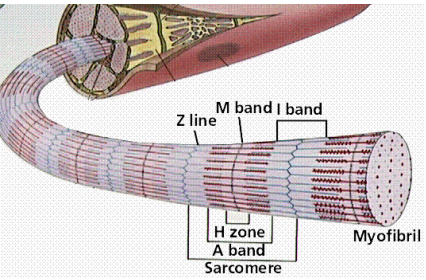


Genome

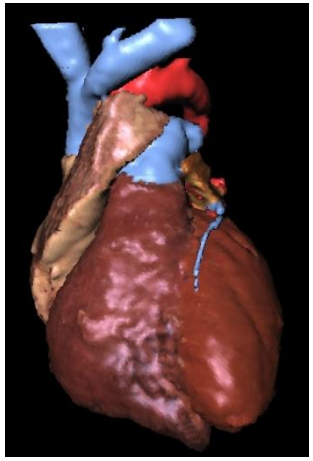
Gene



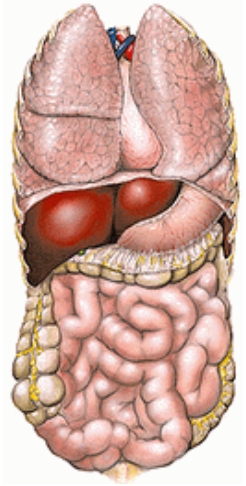
Molecule



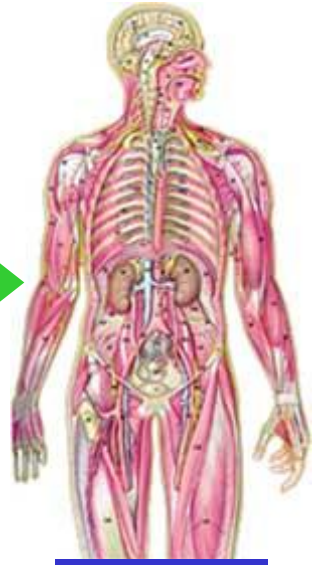
Tissue Structure and Function



Organ Structure and Function



Organ System



Organism

The Future of Medicinal Chemistry & Medicinal Chemists

ACS Medicinal Chemistry Letters

Viewpoint

pubs.acs.org/acsmedchemlett

Tough Times for Medicinal Chemists: Are We to Blame?

Takashi Tsukamoto*

Department of Neurology and Brain Science Institute, Johns Hopkins University, Baltimore, Maryland 21205, United States

ABSTRACT: In the United States, medicinal chemists continue to face job insecurity and high rates of unemployment. The situation is unlikely to improve in the near future. Is there a light at the end of the tunnel? Is there anything we can do to revitalize our community? The answer may be right in front of us.

- ….We have arguably the most talented and well-trained pool of synthetic chemists in the world, who could contribute innovative ideas to solve the most difficult challenges.
- **However, we have, instead, discouraged innovative and unconventional ideas in the practice of medicinal chemistry.**
- We have not raised the bar for our most capable and skilled chemists. **We failed to provide them with the opportunity to achieve their full potential and push the boundaries of medicinal chemistry**……

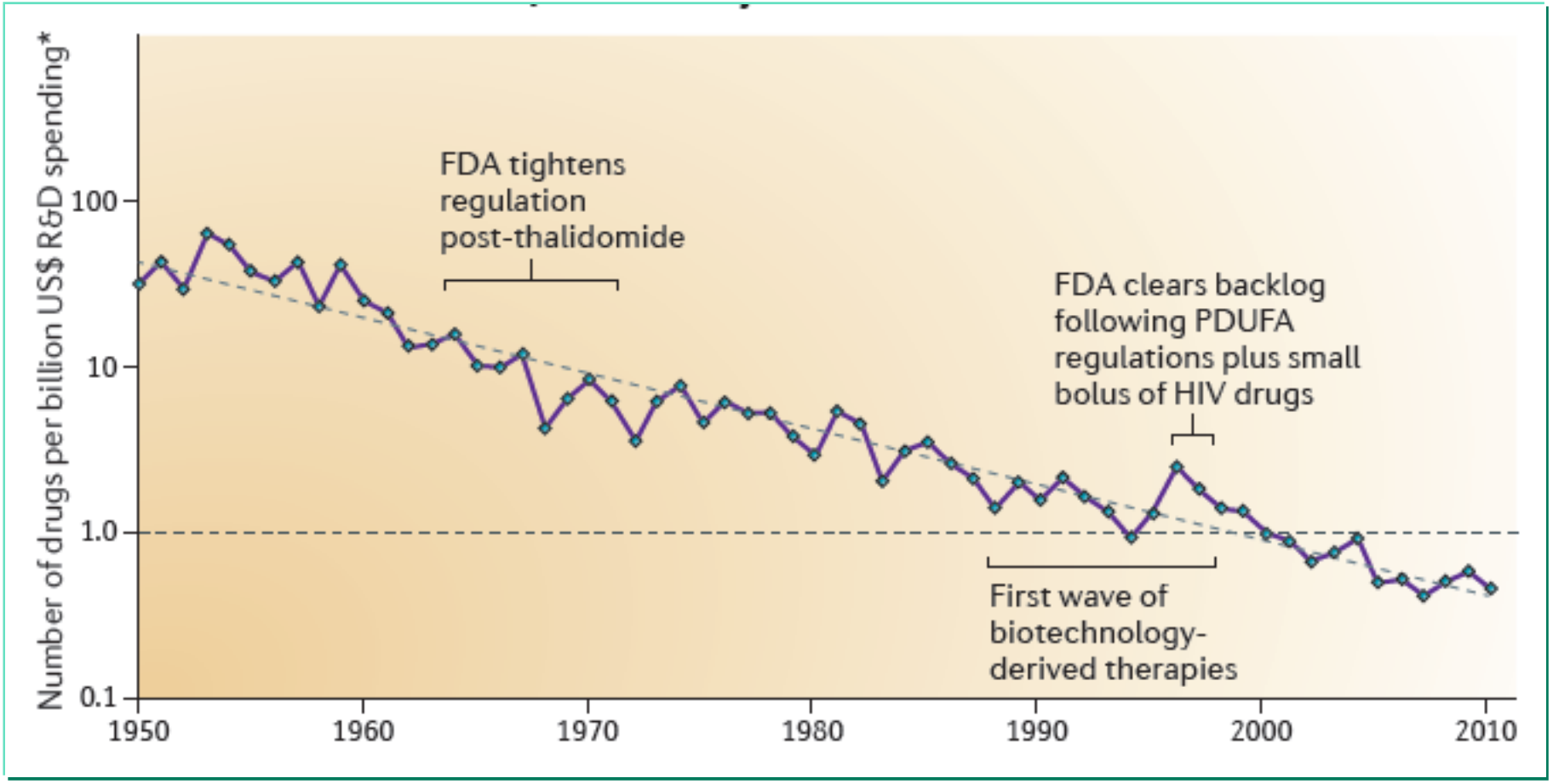
- …Steve Jobs once said, "*When you grow up, you tend to get told that the world is the way it is, and your life is just to live your life inside the world. Try not to bash into the walls too much. Try to have a nice family life. Have fun, save a little money*."
- Computers and drugs are not quite the same, but his statement captures the current mind-set of many medicinal chemists…

Takashi Tsukamoto, Tough Times for Medicinal Chemists: Are We to Blame?, ACS Med. Chem. Lett. 2013, 4, 369−370

R & D Performance

Eroom's Law in pharmaceutical R&D.

Overall trend in R&D efficiency (inflation-adjusted)

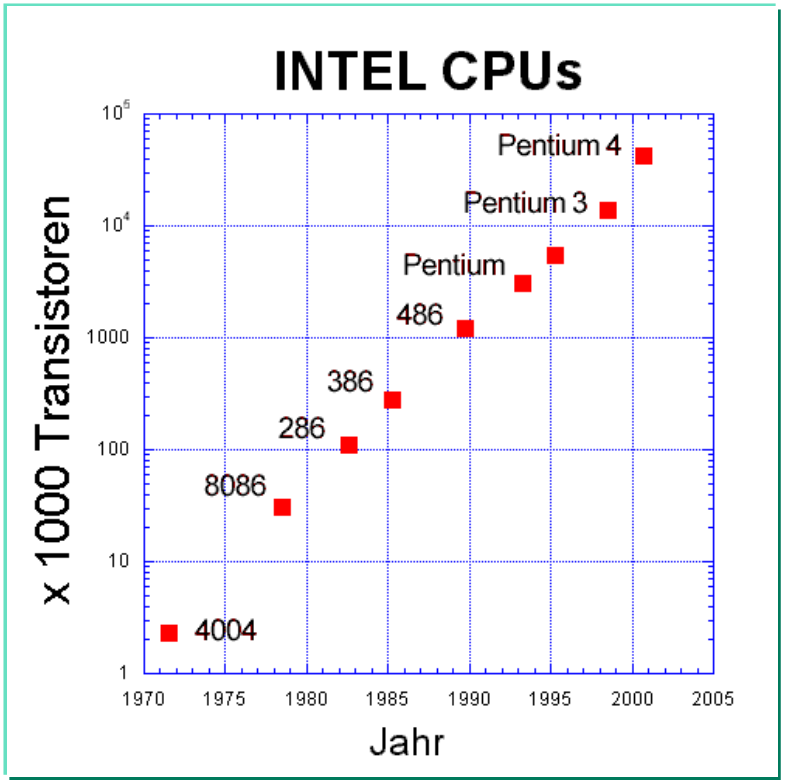


The number of new drugs approved by the US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years.

J.W. Scannel, A. Blanckley, H. Boldon, B. Warrington, Diagnosing the decline in pharmaceutical R&D efficiency, Nature Reviews Drug Discovery **2012**, 11, 191-200.

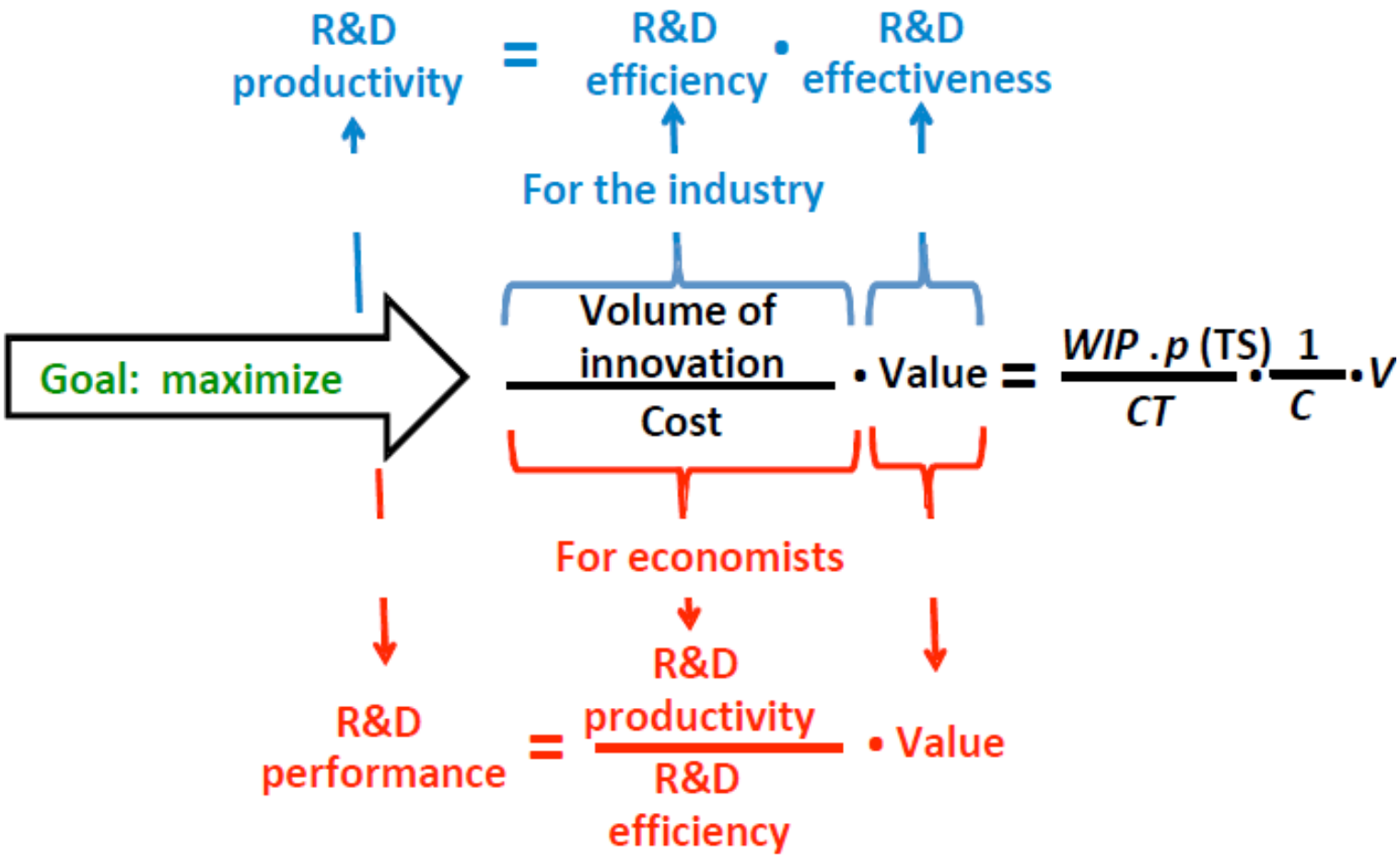
R & D Performance

Moore´s Law



Microprocessor	Year of Introduction	Transistors
4004	1971	2,300
8008	1972	2,500
8080	1974	4,500
8086	1978	29,000
Intel286	1982	134,000
Intel386™ processor	1985	275,000
Intel486™ processor	1989	1,200,000
Intel® Pentium® processor	1993	3,100,000
Intel® Pentium® II processor	1997	7,500,000
Intel® Pentium® III processor	1999	9,500,000
Intel® Pentium® 4 processor	2000	42,000,000
Intel® Itanium® processor	2001	25,000,000
Intel® Itanium® 2 processor	2003	220,000,000
Intel® Itanium® 2 processor (9MB cache)	2004	592,000,000

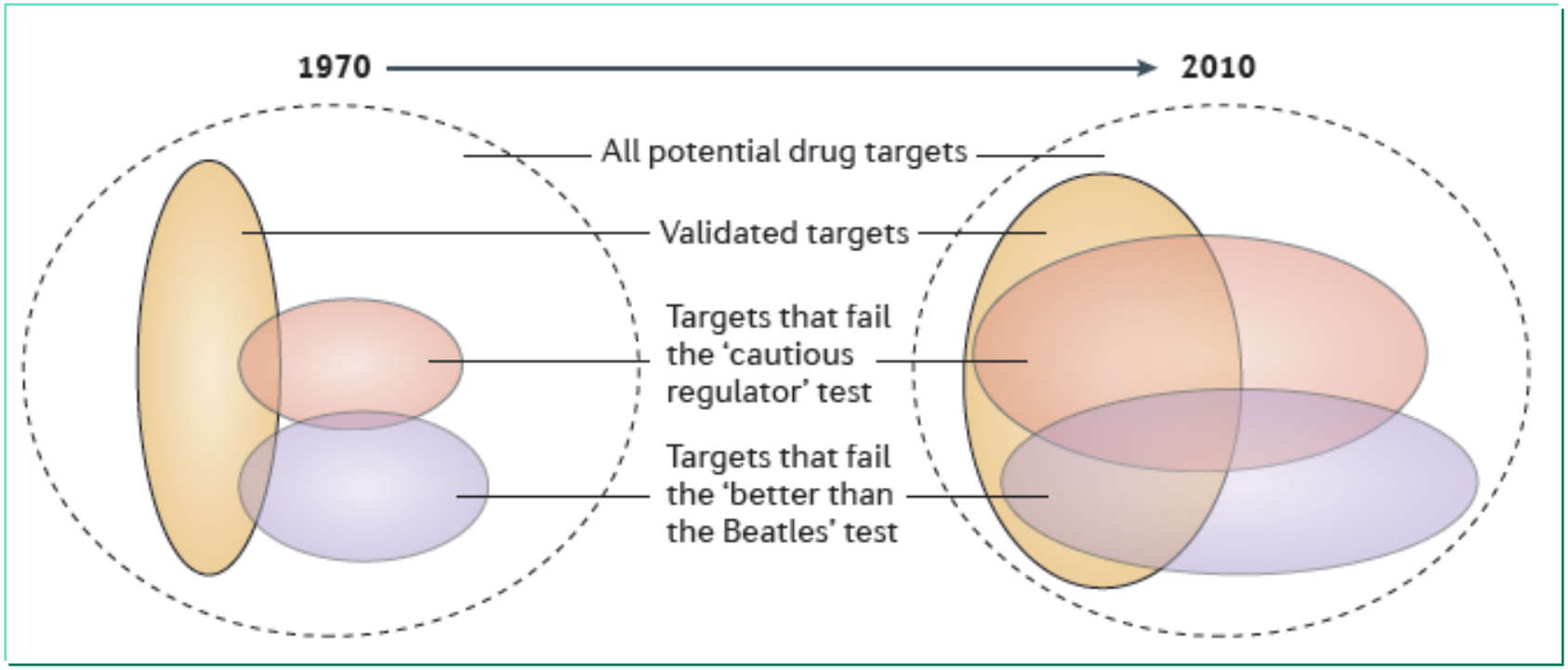
R&D Performance and Productivity



R & D Performance: The Target Space

Eroom's Law in pharmaceutical R&D.

Venn diagram illustrating hypothetical headwinds to R&D efficiency



- **Research and development (R&D) efficiency could decline if scientific, technical and managerial improvements are offset by other factors.**
- **For example, R&D efficiency could be limited by the supply of validated targets that could be drugged without failing the 'cautious regulator' test and/or the 'better than the Beatles' test.**
- **In this hypothetical illustration, the increase in the number of validated targets between 1970 and 2010 is outweighed by increasing regulatory caution and an improving catalogue of approved drugs.**

J.W. Scannel, A. Blanckley, H. Boldon, B. Warrington, Diagnosing the decline in pharmaceutical R&D efficiency, Nature Reviews Drug Discovery **2012**, 11, 191-200.

R & D Performance: Clinical Trials

Drug Discovery – The Ancient Times

Folk Medicine (mainly plants)

Public theriak preparation at a market.

- pro: Thousands years of human experience
- con: Lack of reproducibilit (varying doses)

Experiments in Humans

J. Lind, 1747, „Treatmant of Scurvy“

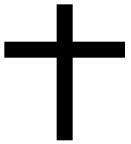
- pro: The „right“ object
- con: Toxicity

R & D Performance: Clinical Trials

Drug Discovery: „Clinical Studies“ in Ancient Times

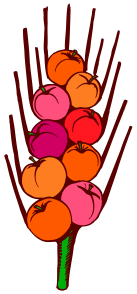
Feel sick

Eat plant



Feel worse

Feel better



Eat another plant

New Drug

R & D Performance: Clinical Trials

An Early Clinical study – Coffee or Tea?

- In late 18th century Gustav III, King of Sweden, performed a “clinical study” to confirm the negative effects of coffee drinking on health.
- One convicted murder had to drink only coffee, another one tea, instead.
- Two physicians supervised the study.
- First, one physician died.
- Then the other physician died.
- Then the king was murdered.
- The tea drinker died in the age of 83.
- The coffee drinker survived all others.

Nevertheless, in 1794 coffee drinking was forbidden in Sweden and later again, in 1822.

An early clinical trial, Ann. Int. Med. 117, 1, 30 (1992)

R & D Performance: Clinical Trials

The big clinical trial problem

900 → >4,000

Number of patients per pivotal trial for a new oral antidiabetic drug

Simvastatin (Merck)

4,400

Anacetrapib (Merck)

>30,000

1948 | 1987 | 1993 | 2001 | 2006 | 2010s

First randomized controlle trial:

- 109 patients were recruited
- 107 were randomized

1990s

Post marketing study long-lasting bronchodilator

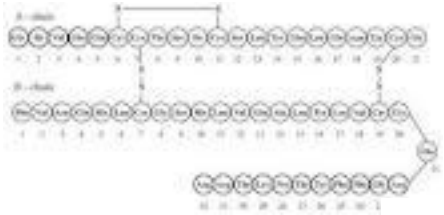
>53,000

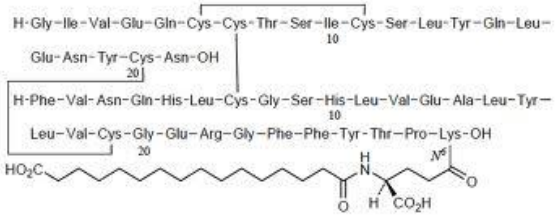
Number of patients per pivotal trial for an antihypertensive agent

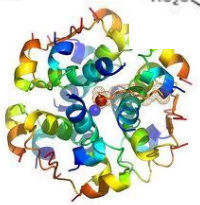
100 → 200 → 450

R & D Performance: Clinical Trials

The big clinical trial problem





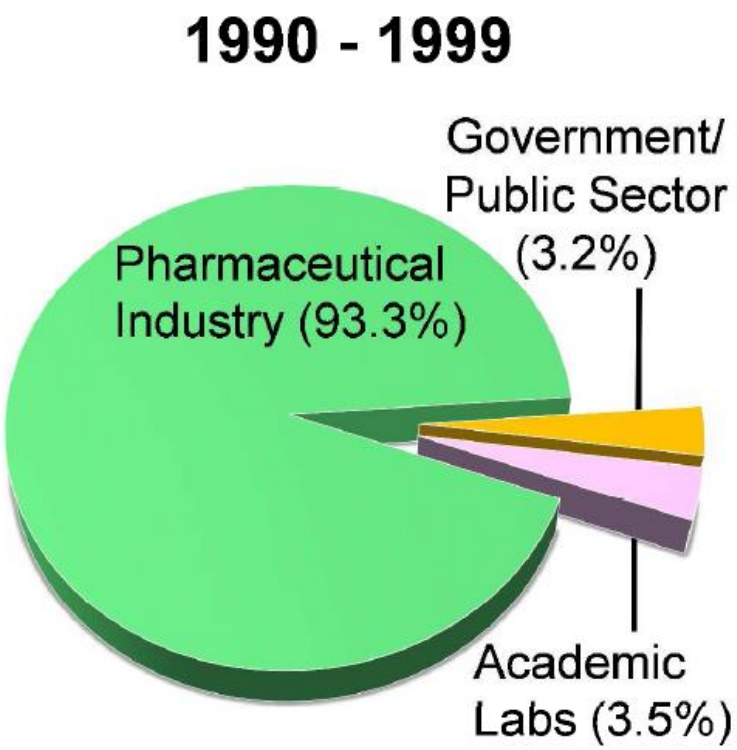


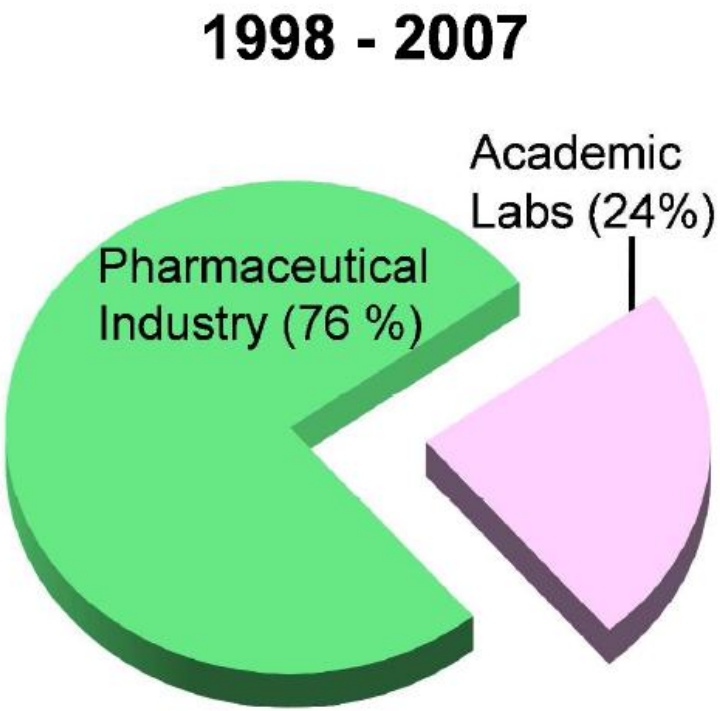
Glargine | **Degludec**

1999 — **2011**

3 pivotal Phase III trials → **12 pivotal Phase III trials**

Estimates of Where New Drugs Come From





Data taken from Kneller, 2010.

Data taken from DiMasi et al., 2003.

Magid Abou-Gharbia and Wayne E. Childers, Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 1. Criticisms Faced by the Pharmaceutical Industry, J. Med. Chem 56, 5659-5672 (2013)