Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol

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Wie es begann
How it all started


In the mid-1990s, Grüenthal 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”.
EUROPIESE PATENTSCHRIFT

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

Anmeldenummer: 95110864.6
Anmeldetag: 12.07.1995

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

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

Priorität: 23.07.1994 DE 4426245
Veröffentlichungstag der Anmeldung:
24.01.1996 Patentblatt 1996/04

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Entgegenhaltungen:

• 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 chemotherapeutical 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.
Tapentadol - From Morphine and Tramadol to the Discovery of 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-Relationship
  - *In vitro* Profile
  - *In vivo* Pharmacology
  - Metabolism
  - Synthesis
  - Clinical Development
Pain Transduction

Pain

Le Mal de Tete
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.
Overview of the Different Types of Pain

- Physiological or nociceptive pain
- Neuropathic pain
- Inflammatory pain
- Diabetic neuropathy
- Phantom limb pain
- Post-herpetic neuralgia
- Perioperative pain
- Postoperative pain
- Non-surgical trauma
- Menstrual pain
- Bone pain
- Rheumatic pain
- Dental pain
- Visceral pain
- Cancer pain
- AIDS pain
- Back pain
- Acute pain
- Chronic pain
- Disease-related pain

Pain Transduction
**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

**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

**UNMET NEED FOR TREATMENT**

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

**Focus on Neuropathic Pain**

Neuropathic pain encompasses a wide range of pain syndromes

**Pain Transduction**
The Evolution in Pain Research

Descartes (1644)

Mayer et al. (1999)
Many Targets for one Disease

Multiple Mode of Actions for Analgesics

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
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 Transduction

**Pain Fibres**

*Aδ- and C-Fibres*

A-delta-Faser

C-Faser
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    - Synthesis
Pain markets based on drugs
Markets for pain according to therapies 2006-2015

Analgesic Market

Billion $
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Most analgesics are based on two principles:

**Salicylates**
- Inhibit prostaglandin synthesis
- COX2- inhibitors (Celebrex or Vioxx)

**Opioids**
- Activate inhibitory systems
- 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
Current Analgesic Treatment Options

Different Structures of Current Analgesic Drugs
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 management**
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\textsubscript{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
Therapeutic effects and side effects of NSAIDs are closely related to their biochemical mechanism of action. The side effects associated with the classical 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 hospitalized. Because of this problem, a major target of drug research is the development of NSAIDs with anti-inflammatory and analgesic activity but without side-effects.
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).

Opioids in History

Notretete

Babylonian God
Opioid Receptors
Historical Overview

- since 3000 BC use of the *pain relieving* and *euphoric effect* of opium in Egypt, 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.

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

Current Analgesic Treatment Options: Opioids
Current Analgesic Treatment Options: Opioids

Opioids
Historical Overview

- 1874 discovery of heroin
- 1898 introducing of heroin as a sure and non addicting antitussivum
"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 opioid receptor family is a G-protein-coupled receptor (GPCR) superfamily, characterized by a heptahelical structural motif.
- Opioid receptors were designated as \( \mu \), \( \kappa \), and \( \delta \) 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:
  - \( \mu \)-receptor: \( \mu_1, \mu_2 \)
  - Delta receptor: \( \delta_1, \delta_2 \)
  - Kappa receptor: \( \kappa_1, \kappa_2, \kappa_3 \)
  - 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 \( \mu \)-receptor.
  - It is the standard against which all other analgesics are compared.
Current Analgesic Treatment Options: Opioids

Wirkung der Opioider auf intrazelluläre Prozesse

Opioid

Binding affinity?

Opioid-Receptor

Signal cascade
(intracellular processes)
Current Analgesic Treatment Options: Opioids

Action of Opioids on Intracellular Processes

Opioid

Opioid-Rezeptor

G-Protein

Ca++

Calcium-Kanal

Phospho-lipasen

ATP

cAMP

Adenylat-Cyclase

Neurotransmitter
Current Analgesic Treatment Options: Opioids

Side effects associated with clinical use of opioids

Analgesic Profile

Side Effect Profile
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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“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.”

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.

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

Pain Treatment Today…

Datamonitor: Pipeline Insight: Neuropathic Pain (Publication Date: 09/2007)
Significant Unmet Needs in Inflammatory/Nociceptive Pain Treatments

Pain Severity

- Severe
- Moderate
- Mild

Safety and Tolerability

- Poor
- Acceptable
- Good

Strong Opioids
- Morphine
- Oxicodone

Weak Opioids
- Tramadol

COX-2

NSAIDs

Acetaminophen

Unmet Need
Significant Unmet Needs in Neuropathic Pain Treatments

Level of Efficacy

Safety and Tolerability

Unmet Need

Duloxetine

AEDs Tricyclics

Gabapentin Pregabalin
Key Needs in Pain Treatments

- Greater Efficacy
- Faster Onset of Action

- New Drugs with Efficacy of Opioids but Greater Tolerability/Safety

Neuropathic Pain

Inflammatory & Nociceptive Pain
Unfulfilled Needs In The Treatment For Chronic Pain

Pain Research Today - The Unmet Needs

Current Treatment Options

Unfulfilled Needs

Diabetic Neuropathy
Complex Regional Pain
Cancer Pain
Migraine
Arthritic Pain

Efficacy and Tolerability of Pain Management

Efficacy
- Low Dosage
- High Dosage

Insufficient Efficacy
Acceptable Tolerability
- Low Dosage
- High Dosage

Sufficient Efficacy
Non Acceptable Tolerability
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  - Synthesis
Tramadol

The Search for a New Morphine Without Side Effects
**Synthesis of L 201**

K. Flick (1962)

**Characterization of Tramadol**

E. Frankus (1963)

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Characterization of Tramadol
Tramadol is a racemate

(-) tramadol

(+) tramadol
Metabolites of Tramadol

Metabolites are generated by O- or N-demethylation.
Metabolites of Tramadol

- **Tramadol**
  - **M1**: [Chemical structure]
  - **M2**: [Chemical structure]
  - **M3**: [Chemical structure]
  - **M4**: [Chemical structure]
  - **M5**: [Chemical structure]
Metabolites of Tramadol

Tramadol – Pharmacological Profile
Tramadol’s mode of action - biochemical profile

- µ-Opioid
- Norepinephrine Uptake Inhibition
- Serotonin Uptake Inhibition
Tramadol’s mode of action - biochemical profile

- µ-Opioid
- Norepinephrine Uptake Inhibition
- Serotonin Uptake Inhibition

Tramadol – Pharmacological Profile
Tramadol – Pharmacological Profile

µ-Opioid binding of tramadol and tramadol-M1

- Morphine
- (+) Tramadol
- (-) Tramadol
- (+)-M1
- (-)-M1

μ Ki (μM)

- Morphine: 0.002
- (+) Tramadol: 4.4
- (-) Tramadol: 100
- (+)-M1: 0.02
- (-)-M1: 1.8
Comparison of molecular structures

(+) Tramadol and Morphine

(+)-tramadol

(-)-tramadol

morphine
Tramadol's mode of action - biochemical profile

- μ-Opioid
- Norepinephrine Uptake Inhibition
- Serotonin Uptake Inhibition
Norepinephrine-Uptake inhibition of tramadol and tramadol-M1

**NE-Uptake Inhibition Ki (µM)**

- Desipramin: 0.002
- Venlafaxine: 0.14
- (+) Tramadol: 6.9
- (-) Tramadol: 0.6
- (+)-M1: 42
- (-)-M1: 1.8

Tramadol – Pharmacological Profile
Comparison of molecular structures

(+)-tramadol

(-)-tramadol

norepinephrine
Tramadol’s mode of action - biochemical profile

- Norepinephrine Uptake Inhibition
- Serotonin Uptake Inhibition

µ-Opioid

Tramadol – Pharmacological Profile
**5HT-Uptake inhibition of tramadol and tramadol-M1**

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Tramadol – Pharmacological Profile
Comparison of acute pain (Tail Flick) and chronic inflammatory pain (Randall Selitto)
Comparison of acute pain (Tail Flick) and neuropathic pain (Bennett)

Tailflick mouse i.v. (4,64 mg/kg)  Bennett CP i.p. (21,5 mg/kg)
Tramadol – Pharmacological Profile

Antinociceptive Potency Profile
Comparison Morphin - Tramadol

ED50 (mg/kg)
Side Effects of Tramadol

Central:
- Hallucinations
- Dizziness
- Drowsiness
- Insomnia
- Headache
- Nervousness
- Agitation

Nose:
- Sores

Mouth:
- Swollen tongue or lips
- Sores
- Dryness

Skin:
- Hives
- Rash
- Itching
- Sweating
- Chills

Respiratory:
- Difficulty breathing

Intestinal:
- Diarrhea
- Constipation

Hands, feet, ankles, or lower legs:
- Swelling

Systemic:
- Flu-like symptoms

Eyes:
- Sores
- Swelling

Face:
- Swelling

Throat:
- Sores
- Difficulty swallowing
- Swelling
- Hoarseness

Muscular:
- Seizures
- Tremor
- Tightness
- Weakness

Gastric:
- Heartburn or indigestion
- Nausea
- Vomiting

Red color - more serious effect
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*
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 \(\delta H = 6.77\) (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.
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What have we learned from the Tramadol story?

Can both principles be combined in one molecule (one enantiomer)?
Gold standard for the relief of moderate to severe pain
But: side effects

Noradrenalin Uptake Inhibition
Antidepressants and co-medication for chronic pain

Serotonin Uptake Inhibition

Synergistic pain relief and less opioid side effects

μ-Opioid

Noradrenalin Uptake Inhibition

Serotonin Uptake Inhibition
Several compounds with different biological profiles have been characterized.

- **µ-Opioid**
- **Noradrenalin Uptake Inhibition**
- **Serotonin Uptake Inhibition**

**Tramadol – The Research Strategy**

**Faxeladol**  
*03.12.1991*

**Axomadol**  
*08.02.1994*

**Tapentadol**  
*16.07.1993*
- You have to be novel
- You should have no active metabolite
- You shouldn’t be a racemate
- You should be more potent than Tramadol
- You should have less side-effects (e.g. emesis)
- You should have no abuse liability
- Your manufacturing should be cheap

Prof. Werner Winter (1980s – 1990s)
Tapentadol – A New Analgesic with a Dual Mode of Action
Tapentadol – A New Analgesic with a Dual Mode of Action

N\text{CH}_3
CH_3
OH_3C
HO
N\text{CH}_3
CH_3
HO\text{H}_O
N
H\text{CH}_3

\text{HO=}[H\text{CH}_3\text{O}]
\text{CH}_{3}\text{N}\text{CH}_3
\text{HO}\text{CH}_{3}\text{N}\text{CH}_3
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 hydroxyl group 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

- Methylen group substitution

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

- 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

Racemate with relative stereochemistry cis

Selecting of one enantiomer

Replacement of tert. OH group
CH₃ as replacement for C₂H₅

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<th>Enantiomer</th>
<th>↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)</td>
<td></td>
<td>Enantiomer</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5HT:</th>
<th>(+)</th>
<th>Enantiomer</th>
<th>↑</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)</td>
<td></td>
<td>Enantiomer</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NA:</th>
<th>(+)</th>
<th>Enantiomer</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)</td>
<td></td>
<td>Enantiomer</td>
<td></td>
</tr>
</tbody>
</table>

For the (+)-enantiomer µ-binding decreased, 5-HT-binding increased
### Tapentadol – A New Analgesic with a Dual Mode of Action

**H, F as replacement for OH**

![Chemical structure of Tapentadol](image)

<table>
<thead>
<tr>
<th>Code</th>
<th>R₁</th>
<th>R₂</th>
<th>µ Ki</th>
<th>5-HT Ki</th>
<th>NA Ki</th>
<th>TF mouse ED50</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRT6 (+)</td>
<td>OH</td>
<td>C₂H₅</td>
<td>0,009</td>
<td>75</td>
<td>4,4</td>
<td>0,32</td>
</tr>
<tr>
<td>GRT5 (-)</td>
<td>OH</td>
<td>C₂H₅</td>
<td>1,4</td>
<td>84</td>
<td>0,7</td>
<td>56,1</td>
</tr>
<tr>
<td>GRT2 (+)</td>
<td>H</td>
<td>C₂H₅</td>
<td>0,007</td>
<td>7,3</td>
<td>1,9</td>
<td>0,85</td>
</tr>
<tr>
<td>GRT1 (-)</td>
<td>H</td>
<td>C₂H₅</td>
<td>0,1</td>
<td>2,3</td>
<td>0,6</td>
<td>3</td>
</tr>
<tr>
<td>GRT4 (+)</td>
<td>F</td>
<td>C₂H₅</td>
<td>0,007</td>
<td>27,8</td>
<td>1,7</td>
<td>0,32</td>
</tr>
<tr>
<td>GRT3 (-)</td>
<td>F</td>
<td>C₂H₅</td>
<td>0,04</td>
<td>4,1</td>
<td>0,3</td>
<td>1,44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>µ-binding:</th>
<th>(+) Enantiomer</th>
<th>(-) Enantiomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT:</td>
<td>(+) Enantiomer</td>
<td>(-) Enantiomer</td>
</tr>
</tbody>
</table>

| NA:        | (+) Enantiomer | (-) Enantiomer |

The (-)-enantiomers have µ-binding and NA-reuptake inhibition in a similar range.
Phenol as replacement for naphtol

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
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)

<table>
<thead>
<tr>
<th>Substanz</th>
<th>MOR</th>
<th>KOR</th>
<th>DOR</th>
<th>NOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapentadol</td>
<td>0,1</td>
<td>0,9</td>
<td>1,0</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Morphin</td>
<td>0,002</td>
<td>0,17</td>
<td>0,002</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Tapentadol</th>
<th>Desipramin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenalin</td>
<td>0,5</td>
<td>0,001</td>
</tr>
<tr>
<td>5-HT</td>
<td>2,4</td>
<td>1,4</td>
</tr>
<tr>
<td>Dopamin</td>
<td>KE</td>
<td>KA</td>
</tr>
<tr>
<td>Cholin</td>
<td>39</td>
<td>KA</td>
</tr>
</tbody>
</table>

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

Vergleich zwischen Tapentadol und Morphin-Bindung an den humanen μ-Opioidrezeptor (Tzschentke et al. 2007)

Vergleich der Hemmung durch Tapentadol-synaptosomale NA- und 5-HT-Wiederaufnahme (Tzschentke et al. 2007)

- **Morphin**
  - EC₅₀: 22 ± 3 nM · Rel. Wirksamkeit: 100 %
- **Tapentadol**
  - EC₅₀: 0.67 ± 0.15 nM · Rel. Wirksamkeit: 88 ± 8 %

- **5-HT**
  - Kᵣ: 2.37 ± 0.23 μmol/l
- **NA**
  - Kᵣ: 0.48 ± 0.07 μmol/l
Tapentadol – A New Analgesic with a Dual Mode of Action

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

μ-Rezeptor Binding (Rat brain-Membrane)

Tapentadol

0,002

Morphine

0,001

0,01

0,1

1

Tapentadol – A New Analgesic with a Dual Mode of Action

Functional NA-Transporter-Inhibition (Rat-Synaptosome)

0,5

50-fold weaker μ-receptor binding in comparison to Morphine
Tapentadol – A New Analgesic with a Dual Mode of Action

Binding Affinity of µ-Opioids

- Tapentadol
- Hydromorphone
- Buprenorphine
- Fentanyl
- Morphine
- Methadon
- Pentacocin
- Dextropropoxyphene
- Oxycodone
- Pethidin
- Propiram
- Codein
- Tildin
- Tramadol

The bar chart illustrates the binding affinity of µ-opioids, with Tapentadol having a significantly higher affinity compared to other opioids listed.
Analgetische Effekte von Opioiden

Tapentadol – A New Analgesic with a Dual Mode of Action
Effect on Noradrenalin- und Serotonin

Tapentadol – A New Analgesic with a Dual Mode of Action

extracellular noradrenaline (NA) levels

extracellular serotonin (5-HT) levels

Tzschentke, JPET 2007
Tapentadol – A New Analgesic with a Dual Mode of Action

Spinal Mechanism of Action: MOR-NRI

Ascending Pathway

Pain signal
Spinal Mechanism of Action: MOR-NRI

Ascending Pathway

Descending Pathway

α₂-R

NA

Glut

SP

Pain signal

Tapentadol – A New Analgesic with a Dual Mode of Action
Spinal Mechanism of Action: MOR-NRI

Ascending Pathway

Descending Pathway

Tapentadol

MOR

γ2-R

NA

SP

Glut
Spinal Mechanism of Action: MOR-NRI

Ascending Pathway

Descending Pathway

α₂-R

NA

MOR

Tapentadol

Pain signal

Glut

SP
Tapentadol – A New Analgesic with a Dual Mode of Action

Neue Substanzklasse MOR-NRI

Enkephalin

Noradrenalin

Tapentadol
Tapentadol remains partially active in MOR-Knock-out Mice
Characterization of Compounds

Biochemistry
- $\alpha_1$
- $\alpha_2$
- $\mu$ bind
- $\kappa$
- $\delta_2$
- 5HT-
- Uptake
- NA-
- Uptake
- Ca
- NMDA
- $\sigma_1$
- $\sigma_2$
- GTPgS$\mu$
- 4-week-tox
- Mutagen-
- icity
- Repro-
- Tox
- Acute Tox
- 2-week Tox

Toxicology
- 4-week-
- tox
- in vitro Tox

Pharmacology
- Hot Plate
- Tail Flick
- mouse
- CRD
- Randall
- Selitto
- Formalin
- Chung
- Bennett
- Tail Flick
- rat
- Tooth-
- pulp
- In Vitro
- Metabolism
- Protein Binding
- Bio-
- analytic
- Toxico-
- kinetic
- Mass Balance
- Enzyme-
- induction

Pharmacokinetics
- Bio-
- analytic
- Toxico-
- kinetic
- Mass Balance
- Enzyme-
- induction

Chemistry
- Reference Std.
- Stability
- up-scaling
- kg synthesis

Biochemistry
- $\alpha_1$
- $\alpha_2$
- $\mu$ bind
- $\kappa$
- $\delta_2$
- 5HT-
- Uptake
- NA-
- Uptake
- Ca
- NMDA
- $\sigma_1$
- $\sigma_2$
- GTPgS$\mu$
- 4-week-tox
- Mutagen-
- icity
- Repro-
- Tox
- Acute Tox
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- Bio-
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- Mass Balance
- Enzyme-
- induction

Chemistry
- Reference Std.
- Stability
- up-scaling
- kg synthesis
Tapentadol – *in vivo* Pharmacology

Pharmacology: Pain Models

**Acute**

**Chronic inflammatory**

**Chronic neuropathic**
Tapentadol – *in vivo* Pharmacology
Analgesic Potency in Acute Pain

Tail Flick, mouse, i.v.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Analgesic ED*&lt;sub&gt;50&lt;/sub&gt; [mg/kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodon</td>
<td>0.80</td>
</tr>
<tr>
<td>Morphin</td>
<td>1.40</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>4.20</td>
</tr>
<tr>
<td>Tramadol</td>
<td>13.7</td>
</tr>
</tbody>
</table>
Tapentadol – *in vivo* Pharmacology – Side Effects

Tapentadol

Morphin

![Image of ferrets with a question mark and bowls labeled "Brech napf".](image-url)
Opioid Induced Side Effects: Emesis

Tapentadol – in vivo Pharmacology – Side Effects

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
**Tapentadol – in vivo Pharmacology – Side Effects**

**Opioid Induced Side Effects: Obstipation**

Tapentadol shows a reduced gastrointestinal inhibitory potential in comparison to Morphine.
**Opioid Induced Side Effects: Tolerance Development**

Chronic constriction injury, rat i.p.

Significant reduced tolerance development

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

<table>
<thead>
<tr>
<th>Pain model</th>
<th>Route of application</th>
<th>ED$_{50}$ value (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tapentadol</td>
</tr>
<tr>
<td>Tail-flick (mouse)</td>
<td>i.v.</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>53.4</td>
</tr>
<tr>
<td></td>
<td>i.c.v.*</td>
<td>65.0</td>
</tr>
<tr>
<td>Tail-flick (rat)</td>
<td>i.v.</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>i.p.</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>121</td>
</tr>
<tr>
<td>Tail-flick (dog)</td>
<td>i.v.</td>
<td>4.3</td>
</tr>
<tr>
<td>Hot-plate 48° C (mouse)</td>
<td>i.v.</td>
<td>3.3</td>
</tr>
<tr>
<td>Hot-plate 58° C (mouse)</td>
<td>i.p.</td>
<td>27.7</td>
</tr>
<tr>
<td>Phenyquinone-induced writhing (mouse)</td>
<td>i.v.</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>31.3</td>
</tr>
<tr>
<td></td>
<td>i.c.v.*</td>
<td>18.4</td>
</tr>
<tr>
<td>Tooth pulp stimulation (rabbit)</td>
<td>i.v.</td>
<td>3.1</td>
</tr>
<tr>
<td>Formalin (phase II) (rat)</td>
<td>i.p.</td>
<td>3.8</td>
</tr>
<tr>
<td>Yeast model (rat)</td>
<td>i.v.</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>i.p.</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>i.t.*</td>
<td>56.8</td>
</tr>
<tr>
<td>Colorectal distension-induced visceral pain (rat)</td>
<td>i.v.</td>
<td>5.5</td>
</tr>
<tr>
<td>Mustard oil-induced visceral pain (rat)</td>
<td>i.v.</td>
<td>1.5</td>
</tr>
<tr>
<td>Spinal nerve injury neuropathy (rat)</td>
<td>i.p.</td>
<td>8.3</td>
</tr>
<tr>
<td>Chronic constriction injury neuropathy (rat)</td>
<td>i.p.</td>
<td>13.0</td>
</tr>
<tr>
<td>Vincristine polyneuropathy (rat)</td>
<td>i.p.</td>
<td>5.1</td>
</tr>
<tr>
<td>Diabetic polyneuropathy (rat)</td>
<td>i.p.</td>
<td>8.9</td>
</tr>
</tbody>
</table>

*Dose in µg/animal. *All drug doses for preclinical and clinical testing are for the hydrochloride salt.
Tapentadol – *in vivo* Pharmacology – Metabolism

**Metabolic Pathway**

- **N-Demethylation**

- **UGT1A6**

- **Glucuronid**
  - 40-50% of the dose in human urine after oral administration

- **Sulfate**
  - 10-20% of the dose in human urine after oral administration

40-50% of the dose in human urine after oral administration

10-20% of the dose in human urine after oral administration
Metabolic Pathway

Tapentadol – in vivo Pharmacology – Metabolism
Tapentadol – *in vivo* Pharmacology – Metabolism

**Metabolic Pathway**

- **Starting Compound**
- **Intermediate Products**
- **Final Products**

Phenolate Betaine
## Tapentadol – Pharmakokinetik

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Mittelwert +/- SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\text{last}, ng.h/ml</td>
<td>294</td>
<td>789 +/- 219</td>
</tr>
<tr>
<td>AUC\text{inf}, ng.h/ml</td>
<td>292</td>
<td>805 +/- 220</td>
</tr>
<tr>
<td>t\text{1/2}, h</td>
<td>292</td>
<td>5,9 +/- 2,0</td>
</tr>
<tr>
<td>CL\text{F}, ml/min</td>
<td>292</td>
<td>4449 +/- 1199</td>
</tr>
</tbody>
</table>
Tapentadol – *in vivo* Pharmacology – Metabolism

Tapentadol – Pharmakokinetik

Mittlere Serumkonzentration – Zeitprofile für CG5503-Base nach Einzeldosisgabe von CG5503-Base PR2 50, 100, 200 und 250 mg
Tapentadol – *in vivo* Pharmacology – Metabolism

**Tapentadol – Pharmakokinetik**

Durchschnittliche Konzentrations- versus Zeitprofile von Tapentadol-Konjugaten, Tapentadol und Radiokohlenstoff nach oraler Verabreichung von 100 mg 14C-markiertem Tapentadol-HCl (1,867 MBq Radiokohlenstoff) an 4 gesunden männlichen Probanden (Terlinden et al. 2006)

![Graph showing concentration versus time profile](image)

Werte entsprechen arithmetischen Mittelwerten, aufgeführt als semilogarithmische Koordinaten.
## Tapentadol – Pharmaokinetik

Ausscheidung von Tapentadol-HCl bei gesunden Probanden:
Ausscheidungsbilanz für Radiokohlenstoff (% der Dosis) (Terlinden et al. 2006)

<table>
<thead>
<tr>
<th>Ausscheidungswege</th>
<th>Subjekt 1</th>
<th>Subjekt 2</th>
<th>Subjekt 3</th>
<th>Subjekt 4</th>
<th>Mittelwert</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urin</td>
<td>98,7</td>
<td>98,5</td>
<td>99,0</td>
<td>98,3</td>
<td>98,6</td>
<td>0,3</td>
</tr>
<tr>
<td>Stuhl (Fäzes)</td>
<td>1,59</td>
<td>0,664</td>
<td>0,870</td>
<td>1,84</td>
<td>1,24</td>
<td>0,57</td>
</tr>
<tr>
<td>Ausgeatmetes CO₂</td>
<td>0,039</td>
<td>0,048</td>
<td>&lt; LLOQ</td>
<td>0,020</td>
<td>0,035</td>
<td>0,015</td>
</tr>
<tr>
<td>Gesamt</td>
<td>100</td>
<td>99,1</td>
<td>99,8</td>
<td>100</td>
<td>99,9</td>
<td>0,52</td>
</tr>
</tbody>
</table>

SA: Standardabweichung, LLOQ: Untere Quantifizierungsgrenze.
Tapentadol – *in vivo* Pharmacology – Metabolism

**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

Tapentadol - Synthesis and Manufacture

- **Lab Scale**: 0.1 – 100 g
- **Kilo-Lab**: 0.5 – 5 kg
- **Pilot Plant**: 10 – 100 kg
- **Production**: > 50 kg
The synthesis of tapentadol hydrochloride as described in the first patent

1. Separation of diastereomers via HCl formation
2. Racemic resolution (e.g. p-Toluyl tartaric acid)

1. conc. HBr, reflux
2. HCl salt preparation
   a) CH₂Cl₂, aq.NaHCO₃
   b) Trimethylchlorsilane/H₂O in 2-butanone

Tapentadol hydrochloride
Synthesis of Tapentadol

"Historical Route"

1. $\text{CH}_3\text{N-H-H-Cl}$
2. $\text{CH}_3\text{C-CH}_3\text{O}$
3. $\text{H}_2\text{Cl}$ (gas)
4. separation of diastereomers

(RR,SS)-Isomer

1. tartaric acid racemic resolution
2. $\text{H}_2\text{Cl}$
3. mixture of E/Z-isomers

(R,R)-Isomer

1. methionine
2. $\text{HCl}$
3. separation of the (R,R) isomer from the (S,R)-diastereomer
Synthesis of Tapentadol

"Historical Route"

- Mannich reaction
- Grignard reaction
- Resolution with tartaric acid
- Elimination
- Hydrogenation
- Separation of the diastereomers
- Ether cleavage
- Precipitation with hydrochloric acid
- BN 200
Synthesis of Tapentadol

“Ethyl Route”

Tapentadol - Synthesis and Manufacture

Synthesis of Tapentadol - “Ethyl Route”
The synthesis of tapentadol hydrochloride according to WO 2008012047A1

Tapentadol hydrochloride

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

Tapentadol - Synthesis and Manufacture
Solid Forms in Pharmaceutical Industry

Classes of Multicomponent Molecular Crystals

- = API
- = water/solvent
\( \square \) = neutral guest
+ = counterion

**Neutral**

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

**Charged**

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

_Polymorphs_
<table>
<thead>
<tr>
<th>Packing Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molar volume and density</td>
</tr>
<tr>
<td>Refractive index</td>
</tr>
<tr>
<td>Conductivity, electrical and thermal</td>
</tr>
<tr>
<td>Hygroscopicity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thermodynamic Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting and sublimation temperatures</td>
</tr>
<tr>
<td>Internal energy (i.e. structural energy)</td>
</tr>
<tr>
<td>Enthalpy (i.e. heat content)</td>
</tr>
<tr>
<td>Heat capacity</td>
</tr>
<tr>
<td>Entropy</td>
</tr>
<tr>
<td>Free energy and chemical potential</td>
</tr>
<tr>
<td>Thermodynamic activity</td>
</tr>
<tr>
<td>Vapor pressure</td>
</tr>
<tr>
<td>Solubility</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kinetic Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution rate</td>
</tr>
<tr>
<td>Rates of solid state reactions</td>
</tr>
<tr>
<td>Stability</td>
</tr>
</tbody>
</table>

Solid Forms in Pharmaceutical Industry

**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

Solid Phase Characteristics
*Hydrochloride Salt*

### Form A (monoklin) vs. Form B (orthorhombic)

<table>
<thead>
<tr>
<th>Property</th>
<th>Form A</th>
<th>Form B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C14 H24 Cl N O</td>
<td>C14 H24 Cl N O</td>
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<tr>
<td>M.W. / g/mol</td>
<td>257,79</td>
<td>257,79</td>
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<tr>
<td>Space group</td>
<td>No. 4, $P2_1$</td>
<td>No. 19, $P2_12_12_1$</td>
</tr>
<tr>
<td>Z (No. of Units)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>a/Å</td>
<td>7,110(3)</td>
<td>7,0882(3)</td>
</tr>
<tr>
<td>b/Å</td>
<td>11,615(4)</td>
<td>11,8444(6)</td>
</tr>
<tr>
<td>c/Å</td>
<td>17,425(6)</td>
<td>17,6708(11)</td>
</tr>
<tr>
<td>α/°</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>β/°</td>
<td>95,00(3)</td>
<td>90</td>
</tr>
<tr>
<td>γ/°</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Volume of elementary cel/Å³</td>
<td>1434</td>
<td>1484</td>
</tr>
<tr>
<td>Density (calc.) / g/cm</td>
<td>1.20</td>
<td>1.15</td>
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</table>
Tapentadol Hydrochloride – Polymorphic Forms

GRT1: Polymorph A

(1 0 0) Form A
Four stereoisomers of the novel \(\mu\)-opioid receptor agonist tapentadol hydrochloride

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 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.
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