


New Treatment Options for Pain Management



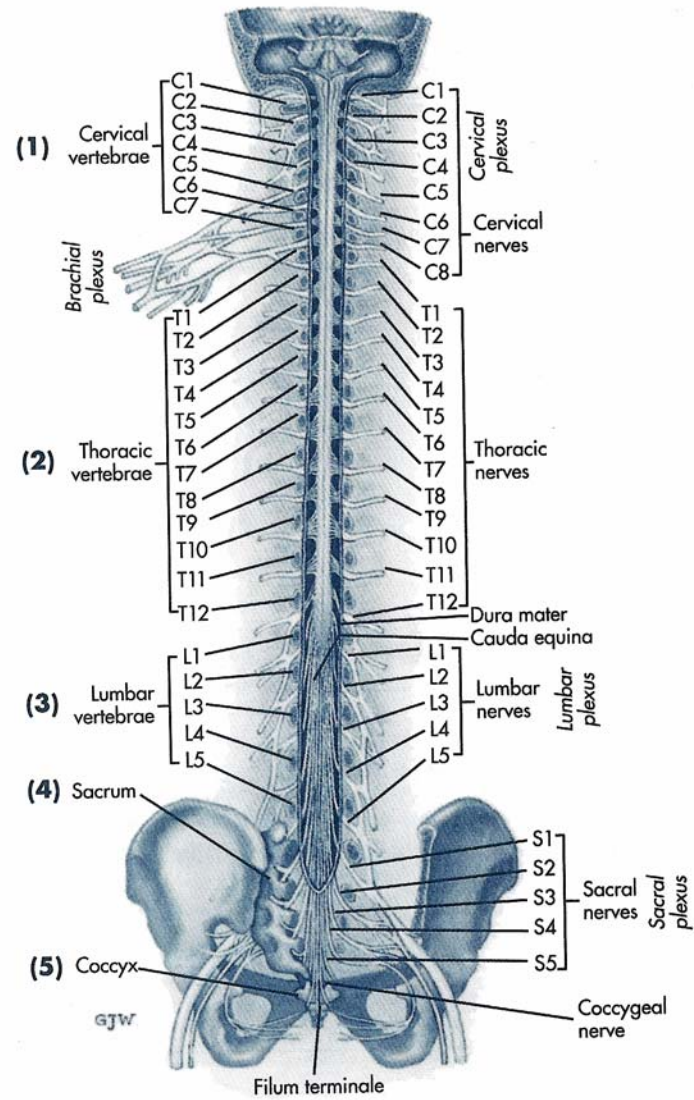
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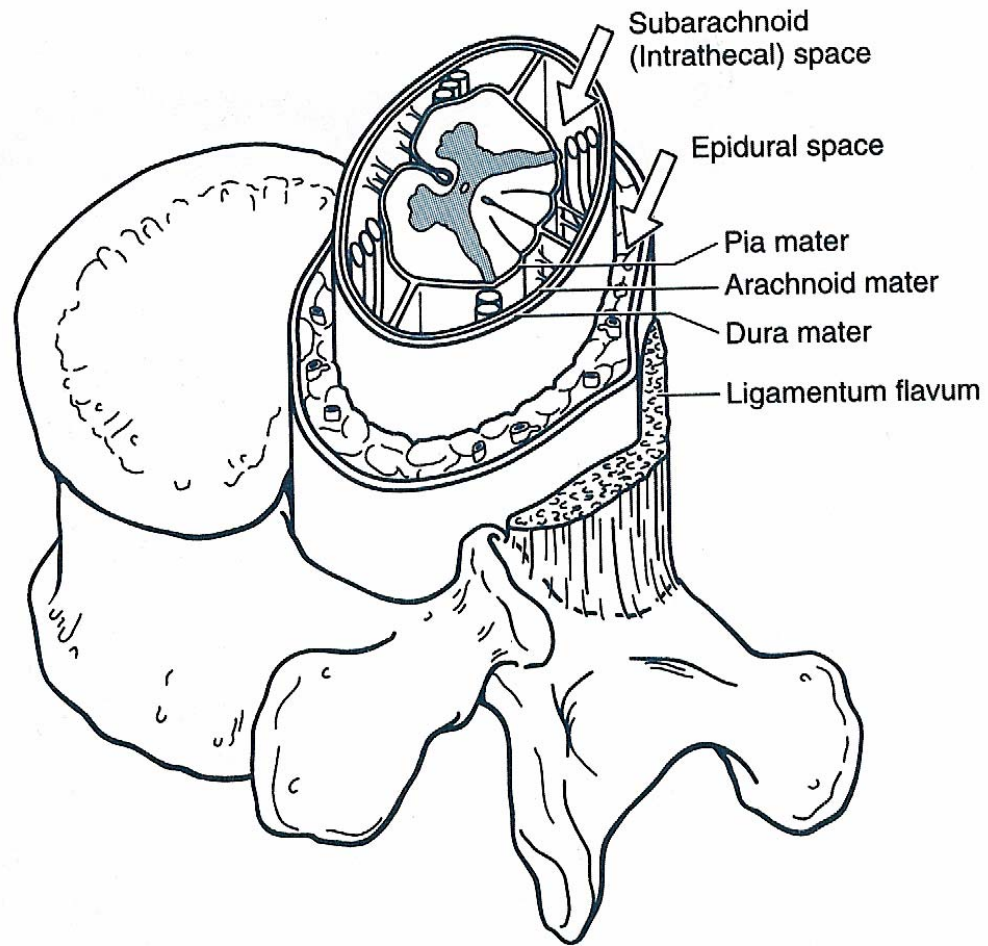
Prialt



⌘ Ziconotide intrathecal injection

⌘ Manufacturer: Elan Pharmaceuticals





FDA indication:

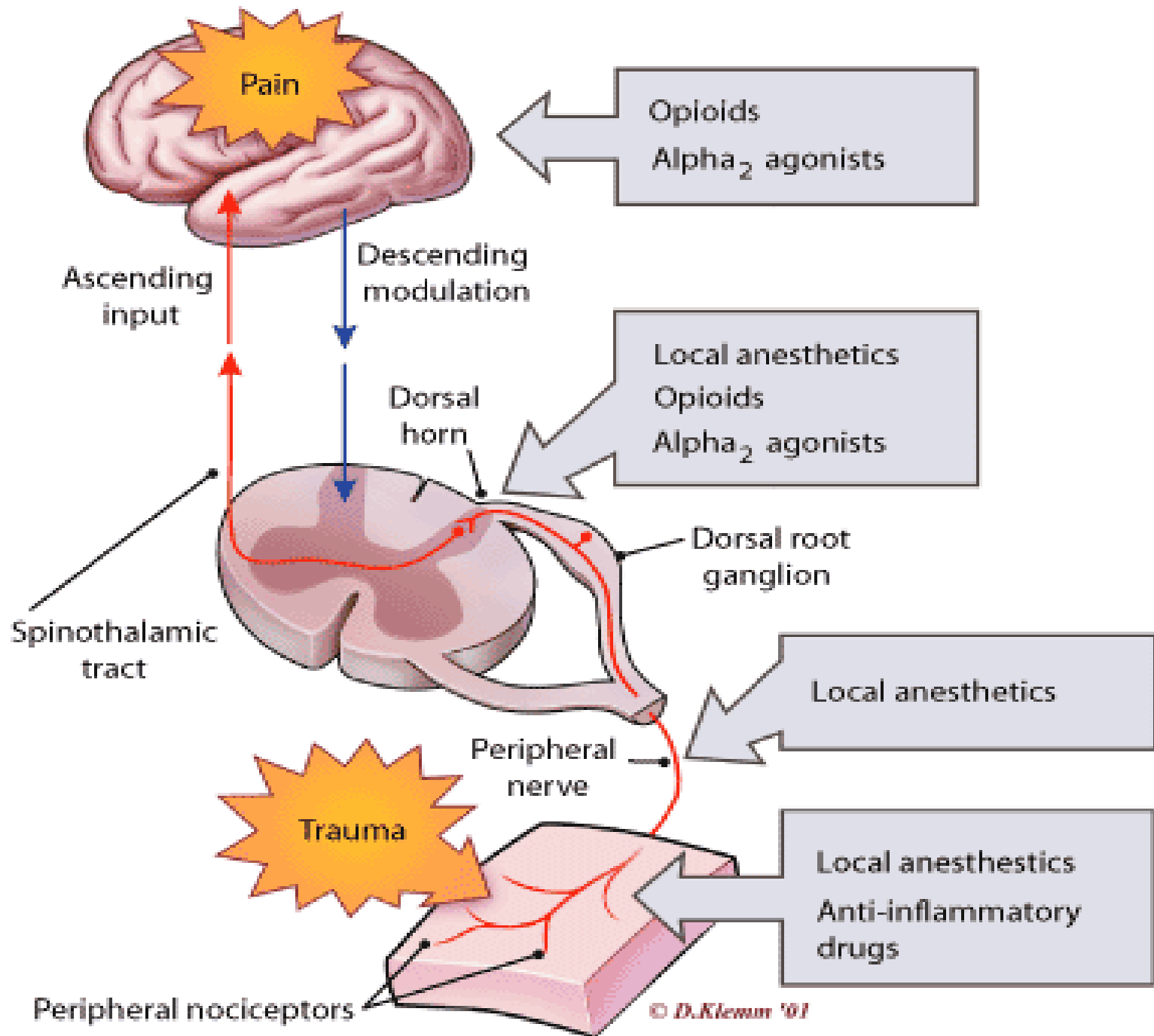


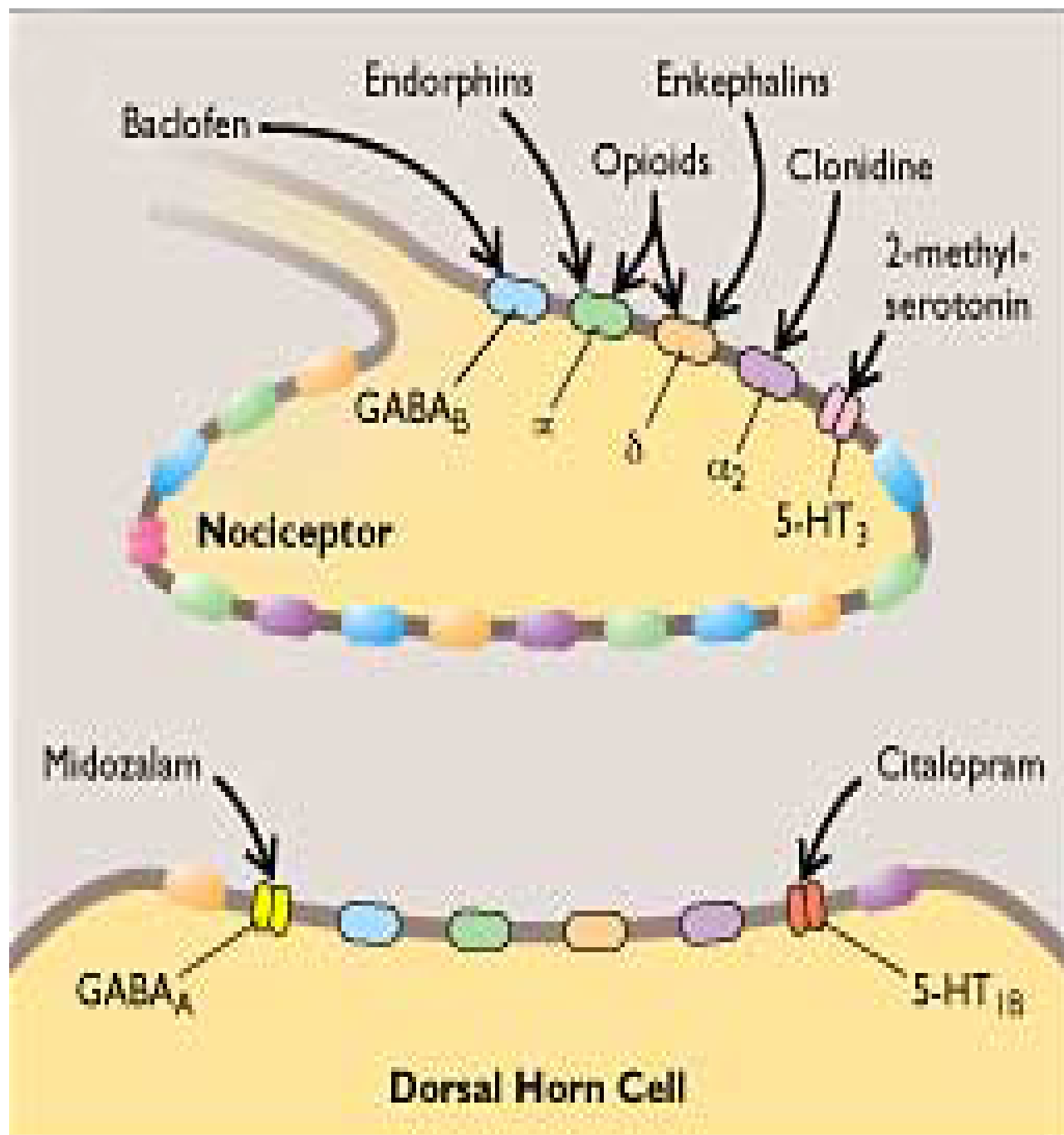
- ⌘ Management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant of or refractory to other treatment such as systemic analgesics, adjunctive therapies or intrathecal morphine.

Mechanism of Action



- ⌘ Selectively binds to N-type voltage-sensitive calcium channels on primary nociceptive afferent nerves in the superficial layers of the dorsal horn in the spinal cord.
- ⌘ It is thought that this leads to blockade of excitatory neurotransmitter release in the primary afferent nerve terminals and antinociception.





Pharmacology



- ⌘ 10-100x more potent relative to morphine
- ⌘ Synthetic equivalent of a naturally occurring conopeptide (ω -conotoxin MVIIA)
- ⌘ Neurotoxin found in the marine snail *Conus magus*
- ⌘ No evidence of tolerance
- ⌘ No evidence of addiction

Pharmacokinetics



⌘ Intrathecal

☒ CL: 0.38 mL/min

☒ Vd: 140 mL

☒ Elimination half-life: 4.6 hours

☒ Protein binding: 50 %

☒ Metabolism: Cleaved by multi-tissue endo and exopeptidases

☒ Elimination: minimal amounts recovered in the urine (<1 %)

Adverse reactions (n=1254)



- ⌘ Dizziness 47 %
- ⌘ Confusion 33 %
- ⌘ Memory impairment 22 %
- ⌘ Speech disorder 14 %
- ⌘ Aphasia 12 %
- ⌘ Hallucination 12 %
- ⌘ Paranoia 3 %
- ⌘ Hostility 2 %
- ⌘ Delirium 2 %
- ⌘ Stupor 2 %
(unresponsiveness)
- ⌘ Amnesia 1 %
- ⌘ Mania 0.4 %

CNS side effects (cont)



- ⌘ Cognitive impairment may develop over several weeks
- ⌘ Need to rule other reasons for cognitive impairment
- ⌘ Cognitive side effects are generally reversible within 2 weeks of drug discontinuation
- ⌘ Elderly (> 65 years old) are at higher risk for confusion

Intrathecal complications



- ⌘ Headache
- ⌘ Spinal cord injury
- ⌘ Infection
- ⌘ Bleeding
- ⌘ Paralysis

Black box warning



Severe psychiatric symptoms and neurological impairment may occur during treatment with PRIALT. Patients with a pre-existing history of psychosis should not be treated with PRIALT. All patients should be monitored frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness.

Black box warning (cont)




⌘ PRIALT therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in the event of serious neurological or psychiatric signs or symptoms.

Monitoring



- ⌘ Frequent assessment for evidence of cognitive impairment, hallucinations, or changes in mood
- ⌘ Serum creatine kinase
 - ☑ 11 % had levels > 3 X ULN
 - ☑ One case of myopathy
 - ☑ Two cases of ARF associated with rhabdomyolysis (CK 17,000-27,000 IUnits/L)



⌘ Monitor CK “periodically such as every other week for first month and monthly as appropriate” and if patient reports neuromuscular symptoms such as myalgias, myasthenia, muscle cramps, or asthenia.

Dosage



⌘ Initial titration

☒ 2.4 mcg/day at maximum increases 2-3 times per week

⌘ Maximum dose

☒ 19.2 mcg/day

⌘ Supplied as a 25 mcg/mL solution

☒ 1 mL, 2 mL, 5 mL vials

Drug Interactions



⌘ Pharmacokinetic

- ☑ No known interactions


⌘ Pharmacodynamic


- ☑ Additive CNS effects

Efficacy



- ⌘ Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS. JAMA 2003;291:63-70
- ⌘ Double-blind, placebo-controlled, randomized, multicenter study

- 
- ⌘ N = 111 individuals 24-85 years old
 - ⌘ Visual Analog Scale of Pain Intensity (VASPI) of 50 mm or greater
 - ⌘ Main Outcome Measure: mean percentage change in VASPI score from baseline to the end of titration period



⌘ Titrated over 5-6 days followed by a 5 day maintenance phase for responders and cross over for nonresponders to the opposite treatment group

Results





Outcome	Ziconotide	Placebo	p
VASPI improvement	53.1 %	18.1 %	<0.001
Pain relief moderate to complete	52.9 %	17.5 %	<0.001
Complete pain relief	5	0	
Response to therapy	50.0 %	17.5 %	0.001

Avinza



- ⌘ Manufactured by Ligand Pharmaceuticals for Elan Holdings
- ⌘ Marketed by Organon
- ⌘ Morphine sulfate extended release tablets
- ⌘ Contain both immediate release and extended release beads
- ⌘ Once daily dosing

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- ⌘ May be swallowed whole or sprinkled on applesauce
 - ⌘ Do not chew, crush, or dissolve
 - ⌘ Dosages
 - ☑ 30 mg, 60 mg, 90 mg, 120 mg
 - ⌘ Spherical Oral Drug Absorption System or SODAS™

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- ⌘ The amount of morphine following oral administration is similar to that absorbed from other oral morphine products.
 - ⌘ Oral bioavailability shows large inter-individual variability due to extensive pre-systemic metabolism (< 40%)
 - ⌘ Oral to IV conversions range from 3-6:1
 - ⌘ Steady-state: 2-3 days

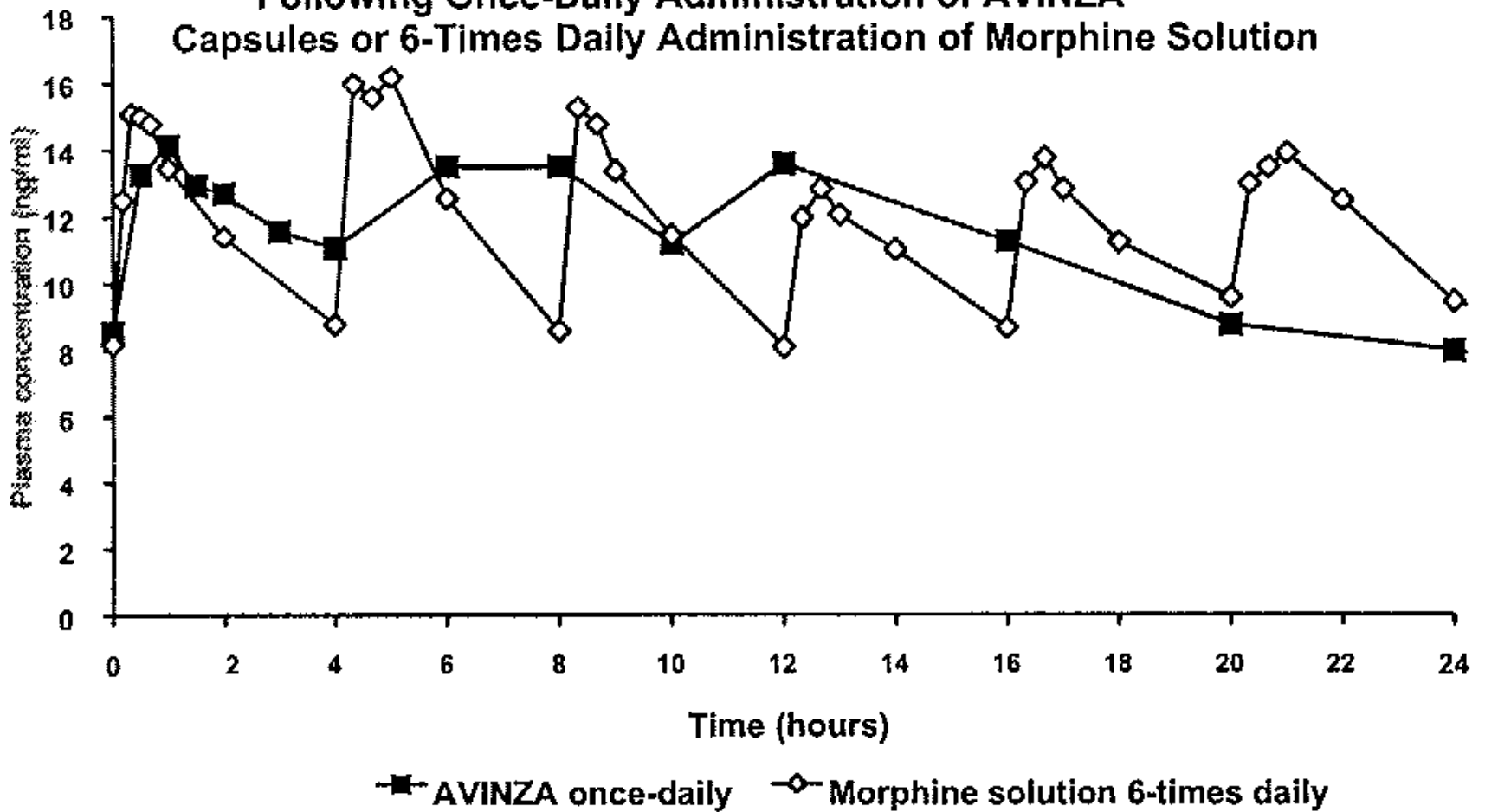
SODAS™



⌘ In the GI tract, fluid enters the beads and solubilizes the drug. This is mediated by fumaric acid which acts as an osmotic agent and a local pH modifier. The resultant solution then diffuses out in a predetermined manner which prolongs the *in vivo* dissolution and absorption phases.

⌘ AVINZA® SODAS Mechanism of Action

Graph 1
Mean Steady-State Plasma Morphine Concentrations
Following Once-Daily Administration of AVINZA
Capsules or 6-Times Daily Administration of Morphine Solution



Metabolites- review



⌘ Renally excreted metabolize

☑ Morphine-6-glucuronide

- ☒ More potent than morphine
- ☒ Longer T_{1/2} than morphine
- ☒ Accounts for most of the analgesia in chronic use

☑ Morphine-3-glucuronide

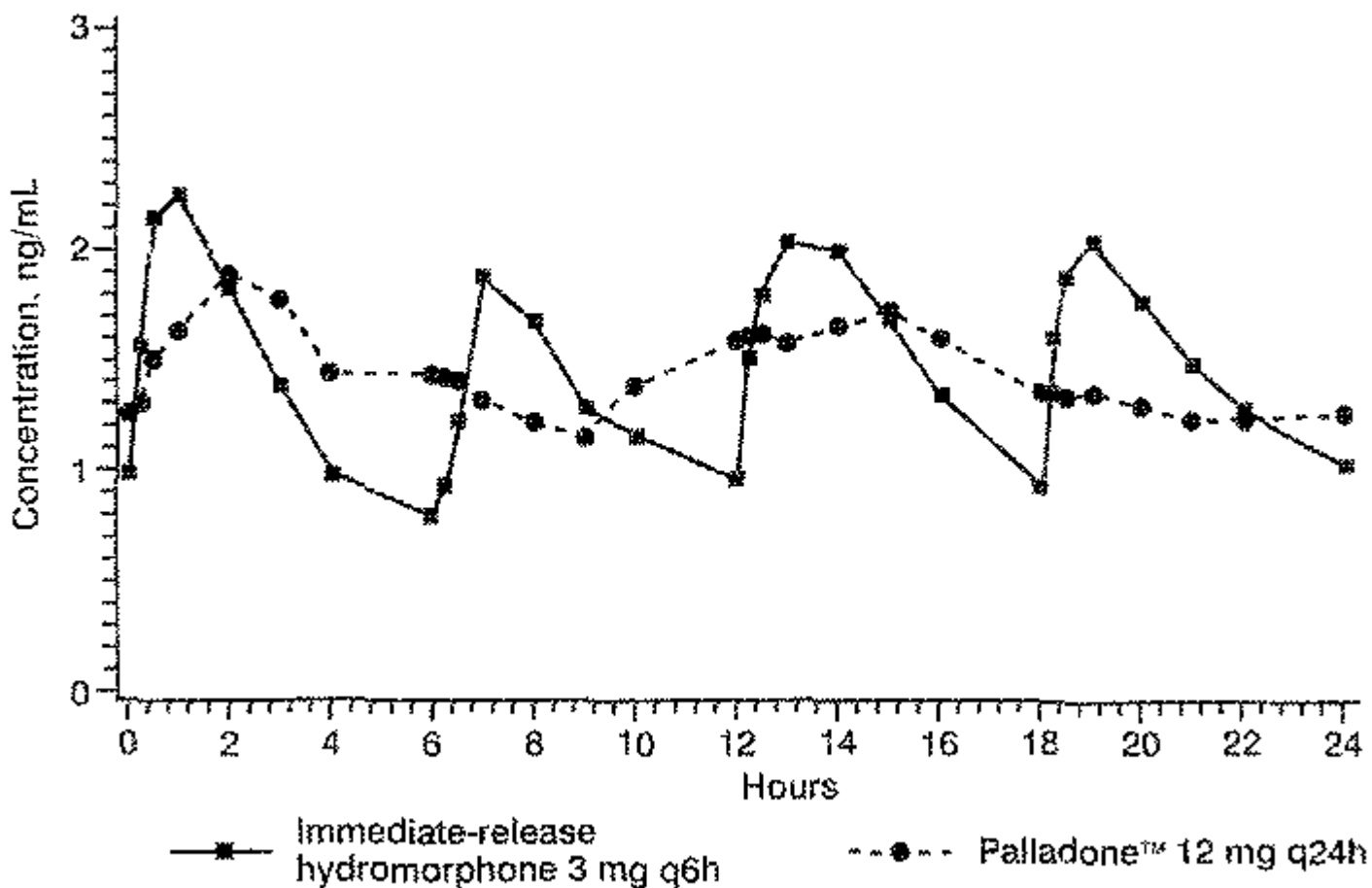
- ☒ No analgesia
- ☒ Longer T_{1/2} than morphine
- ☒ CNS excitation
- ☒ Can increase perception of pain

Palladone

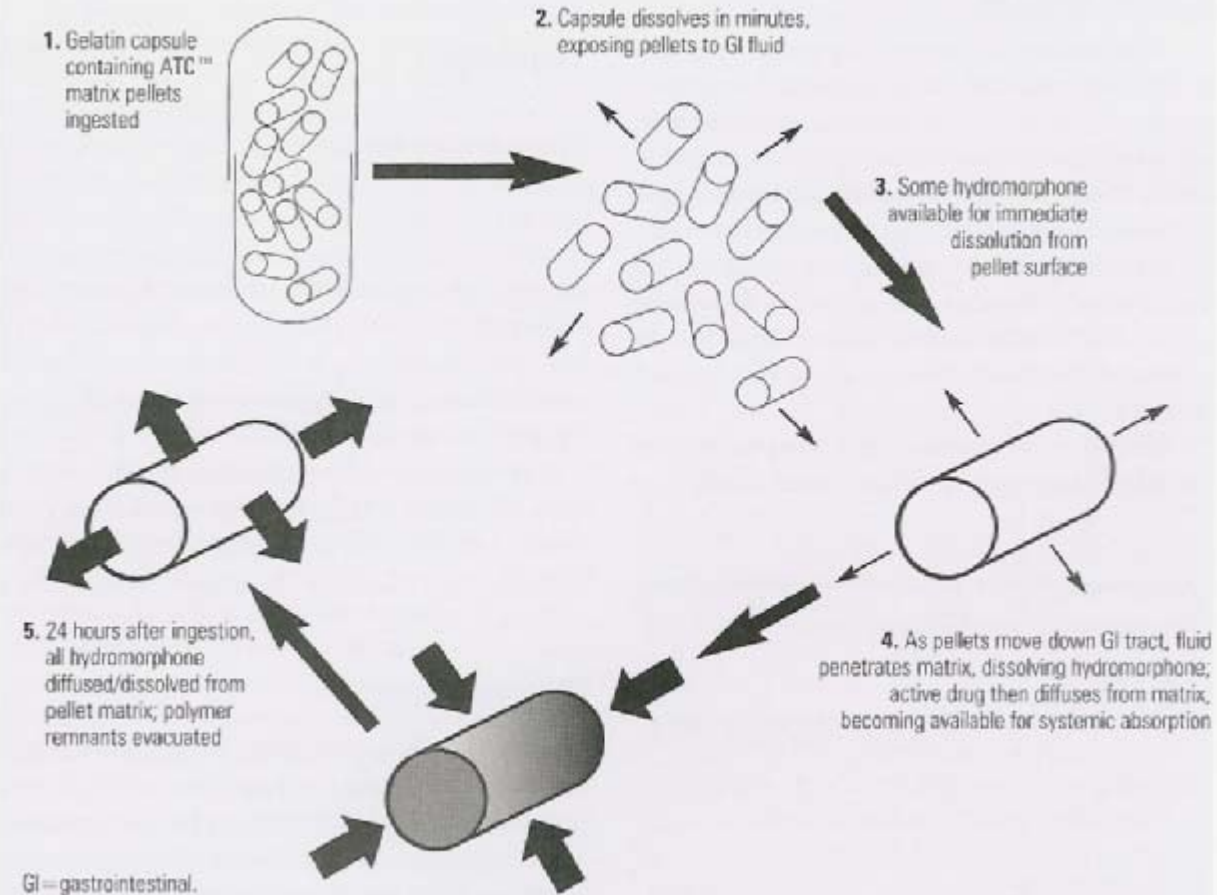


- ⌘ Manufactured by Purdue Pharma
- ⌘ Hydromorphone HCl extended-release capsules
- ⌘ Once daily administration
- ⌘ Dosages
 - ⊞ 12 mg, 16 mg, 24 mg, 32 mg

FIGURE 1. Steady-State Plasma Hydromorphone Concentration –Time Curves



ATC™ Delivery System for 24-Hour Pain Relief With Hydromorphone HCl Extended-Release Capsules



Carrig BA, Kwarcinski MA, Oshlack B. The ATC extended release delivery system. Poster presented at: Midyear Clinical Meeting of ASHP; 12/2/2001; New Orleans, LA.

Precautions



⌘ For use in opioid-tolerant patient only

☑ Morphine 60 mg/day

☑ Oxycodone 30 mg/day

☑ Hydromorphone 8 mg/day

⌘ Do not break, chew, dissolve, crush, or open capsules

⌘ Drinking alcohol while taking Palladone can release the full 24-hour dose at one time

Disadvantages of short-acting opioids for around-the-clock pain

- ⌘ Patient must make the pills last
- ⌘ Patient experiences recurring peaks & valleys of opioid concentration
 - ☒ Continues to experience pain that we are trying to control
 - ☒ Side effects more common
 - ☒ Withdrawal possible between doses
 - ☒ Conditions patient to euphoria (mood alteration)
 - ☒ Conditions patient that no mood alteration = no analgesia
- ⌘ Patient awakens several times during the night

Advantages of long-acting opioids



- ⌘ People who use drugs compulsively prefer short-acting opioids
- ⌘ Produce less euphoria (mood alteration)
- ⌘ Less drug craving & compulsive pill taking
- ⌘ Analgesia throughout dosing interval
- ⌘ Less frequent dosing = less focus on pill taking behavior (pain & disability)

Opportunity



- ⌘ Pharmacy Practice Act revised in 2001
- ⌘ Collaborative Drug Therapy Management
- ⌘ DEA number

- ⌘ Team approach to medication management