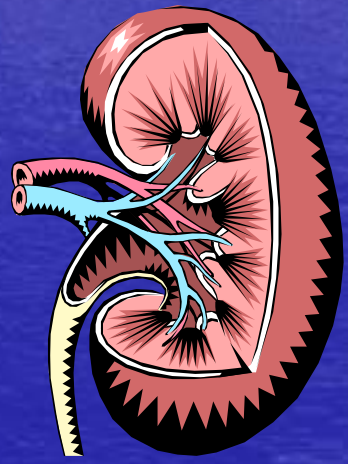
Pain Assessment and Management in the Renal Patient



Dr. Doris Barwich
Bruce Kennedy
Fraser Health
Hospice Palliative Care

Goals

- Review issues regarding pain management in renal patients
- Review analgesics available
- Review strategies for assessment and management
  - Basic Approaches
  - Neuropathic Pain

PAIN IN ESRD: Common

- Dialysis patients have significantly higher bodily pain than the general US population adjusted for age and sex.
- 50 % reported pain, yet
- 32% received no analgesics and
- 75% reported inadequate pain relief
- Then even when they did get a opioid, 16% of them were still suffering with moderate to extreme pain

Kidney Int 2004 205 Hemodialysis Patients[1]

Incidence of Pain in Renal Patients

- Outpatients receiving dialysis in Edmonton N=531
- Severe pain (>6 /10) reported by 26.5%
- Pain > 4/10 by 42.5 %
- 37 % had no pain
- Other common symptoms
  - Decreased activity in 63.4%
  - Pruritis 41.1%

Palliative Medicine 2003 Fainsinger et al[2]

Etiology of Pain in Renal Patients: Dr S Davison. Edmonton Data

Etiology	Percentage (%)
Musculoskeletal	63.1
Osteoarthritis	19.4
Musculoskeletal: Not yet diagnosed	18.4
Osteoporosis (resulting in spinal fractures)	9.7
Inflammatory Arthritis	6.8
Renal Osteodystrophy	4.9
Discitis/Osteomyelitis	1.9
Related to Dialysis Procedure	13.6
Peripheral Polyneuropathy	12.6
Peripheral Vascular Disease	9.7
Other (including trauma, PCKD, malignancy, calciphylaxis)	20.3

Untreated Chronic Pain

Impacts on Outcomes

- Function
- Sleep
- Impaired cognitive function
- Quality of life
- Depression
- Decreased socialization
- Increased health care utilization
- Increased costs

Professional Barriers to Effective Pain Management

- Lack of knowledge about pain management
- Physician reluctance to prescribe. Concerns re: legal issues
- Belief that patients exaggerate pain intensity
- Fear of iatrogenic addiction
- Inadequate pain assessment

Barriers to Effective Pain Management

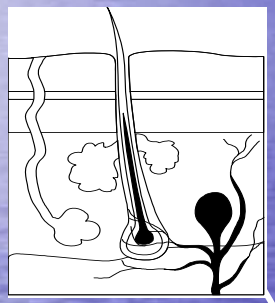
- Treatment algorithms used in patients with cancer may not apply to hemodialysis patients.
- Objective data lacking for the appropriate management of pain in long-term hemodialysis patients/chronic kidney disease
- Uremic symptoms may mimic adverse effects of opioids, resulting in inappropriate withdrawal of analgesics.
- Patients reluctance to report pain
- Lack of staff time and training in the basic principles of pain assessment and management

American Journal of Kidney Diseases 2003 Davison SN[3]

"If we know that pain and suffering can be alleviated and we do nothing about it, we, ourselves, are tormentors"

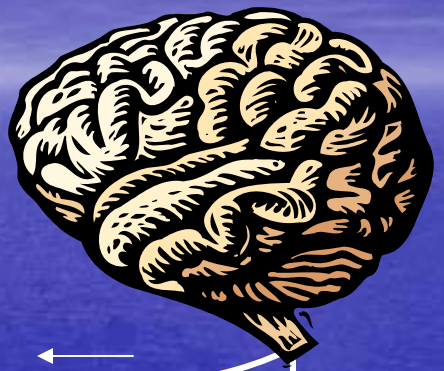
Primo Levi

Pain Pathways and Chemical Modulation



Nociceptors
- A-delta
- C
- Silent - skin
  - viscera
  - Joints
  - muscle

Peripheral
- Bradykinin
- Substance P
- Prostanoids
- Serotonin
- Cytokines



Dynorphin A

Central
- Prostanoids
- EAA – NMDA
- Substance P
- NO / CCK
- NGF / CGRP
- 5HT / NK
- GABA / CGRP

Dorsal horn of the Spinal Cord : **"Gate"**

Gate Control Theory of Pain
Wall and Melzack[4]

- "Transmission of pain from the peripheral nervous system through the spinal cord is subject to modulation by both intrinsic neurons and controls emanating from the brain"
- Three options for an incoming pain signal:
  - To suppress the pain signal (stress-induced analgesia)
  - To allow the pain signal to pass through to the brain unchanged
  - To augment the intensity of the pain signal sent to the brain (central sensitization)

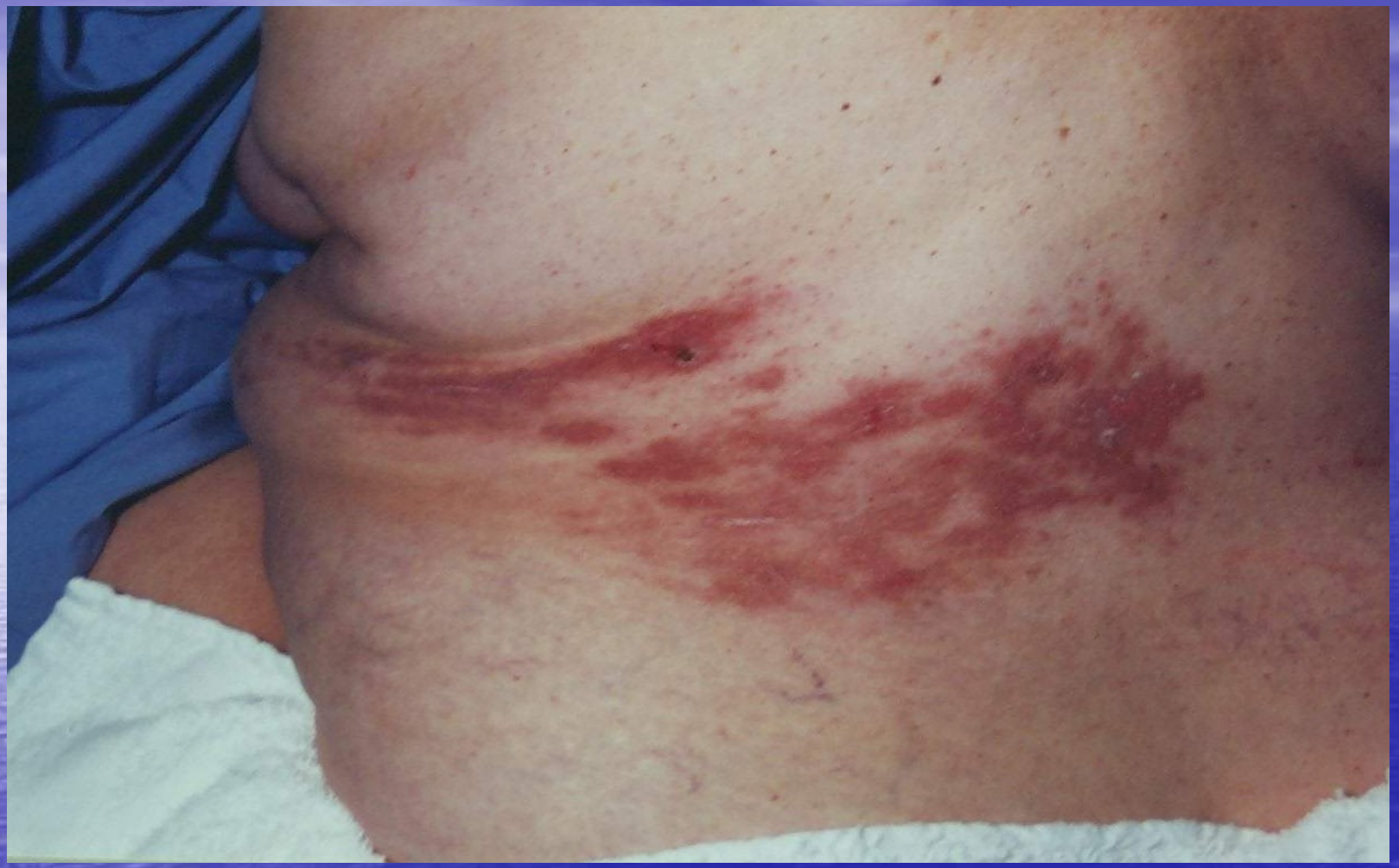
Nociceptive Pain

- Direct stimulation of intact peripheral pain receptors. Usually associated with tissue damage
- Severity of pain roughly proportional to the amount of nociception
- Often inflammatory process
- Two types: Visceral and Somatic

Neuropathic Pain

Pain that arises from injury, disease or dysfunction in the peripheral or central nervous system.

	CHRONIC	ACUTE
Cause	Neuronal or CNS abnormality (plasticity/sensitization)	Tissue Damage; Neuropathic
Duration	>3 months	Days to weeks
Course	Expected to persist	Expected to resolve
Emotional Response	Quiet, depressed	Anxiety Restlessness
Biological Function	No	Yes



74 year-old female with a 7 day history of a painful unilateral rash on the left chest

Pain Management: Treat Pain Early. Treat the cause

- Untreated pain means more pain signals enter the spinal cord
- More pain signals mean more pain
- The solution?
  - Block as many pain signals as possible
  - Treat pain as early and as aggressively as possible
- Results: Less pain, Less analgesics over time

Pain Assessment Tools

OLD CARTS

O: **Onset** – acute vs gradual
L: **Location** (+ radiation)
D: **Duration** (recent/chronic)

C: **Characteristics** (quality of pain)
A: **Aggravating** factors
R: **Relieving** factors
T: **Treatments** – previously tried – response; dose/duration; Why discontinued?
S: **Severity**: Pain Scales: 0 - 10

Pain Assessment

- What is your Pain at it's
  Best / Worst/ Present/ Average
  (Brief Pain Inventory: Cleeland[6])
- Pain and activity diaries
- Body Map: Many patients have more than one location of pain
- "Red Flags": History of substance abuse, addiction.
  - "Chemical coping" .

Opioid Addict vs. Pain Patient: Data suggests risk of addiction ~6%

Opioid Addict

- Can't control meds
- Meds decrease QoL
- Wants meds despite S/E
- Denies possibility of having a problem
- Doesn't follow treatment plan
- Seldom has meds left over
- Excuses for lost meds

Pain Patient

- Controls meds
- Meds improve QoL
- Complains of side effects
- Concerned re: medical problems
- Follows agreed upon treatment plan
- Left over meds
- Does not run out of or lose meds

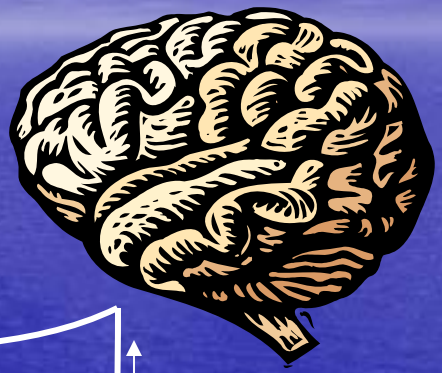
Pain Management: Non-pharmacological Treatments

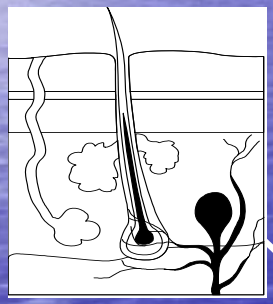
- Heat and ice therapy
- Transcutaneous electrical nerve stimulation (TENS)
- Massage
- Cognitive behavioural pain management techniques such as relaxation and biofeedback;
- Physical and occupational therapy
- Meditation; guided imagery
- Acupuncture

American Journal of Kidney Diseases 2003 Davison SN[3]

Pain Pathways and Chemical Modulation

- **Brain**
- NSAIDs
- Opioids
- a_2-agonists
- Anti-convulsants
- Anti-depressants





Peripheral
- NSAIDs
- Capsaicin
- Opioids
- Local Anesthetics

Spinal Cord
- Opioids
- NSAIDs
- a_2-agonists
- Blockers:
  - NMDA

Pain Management

- Right Drug
- Right Dose
- Monitor and evaluate response and adjust until pain control with minimal side effects

WHO Guidelines : ANALGESIC THERAPY:

1. Give right medication
2. Give medication orally.
3. Give medication regularly.

- Constant pain = Regular medication
- Breakthrough/Periodic pain = PRN medication as needed

85 % of cancer pain easily treated.

Stats for other diseases ??

Opioids and Renal Function

- Opioids implicated in modulation of renal water handling
  Oliguria has occurred from morphine and congeners
  - but actions may differ from drug to drug

- MECHANSIM:

  Morphine produces peripheral indirect blockade of bladder function and central inhibition of micturition reflex
  Other mechanisms involved including effect on atrial natriuretic peptide

  - can reduce the volume of urine voided

The Journal of Pain 2004 Mercandante S, Arcuri E[7]

Opioids and Renal Function

- Low doses - transient increase in urine output & GFR
- High doses - marked but transient reduction in urinary flow rate and GFR during first hour, followed by a delayed diuretic effect.

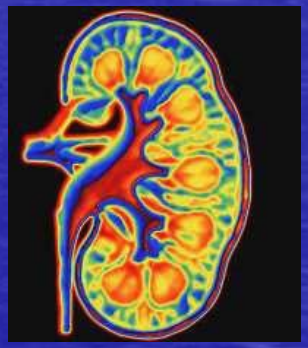
The Journal of Pain 2004 Mercandante S, Arcuri E[7]

Opioids and Renal Function

Are Side Effects Worse with these Drugs in Dialysis Patients?

- Unknown. Yet they are at greater risk.
  3 fold greater than patients with normal RF[8]
- Adverse effect risk increases in these patients with[9]

  a) the number of medications used – dialysis patients average 7 to 8
  b) the number of comorbid conditions
  c) the age of the patient
  d) the degree of renal impairment



Principles & Practice of Dialysis 2nd Edition 1999 Henrich WL Editor Lippincott, Williams and Wilkins[8]

2 Canadian Medical Association Journal 2002 Kappel, J Calissi, P[9]

Opioids and Renal Function

Problems providing answers

- Few studies with long term use of opioids in patients with renal impairment.
- Reluctance of physicians to prescribe
- Signs and symptoms of opioid overdose in CRF not compared with normal RF in the literature
- Many side effects of opioids are frequently observed symptoms of ESRD or dialysis treatment

American Journal of Kidney Diseases 2003 Kurella M[10]

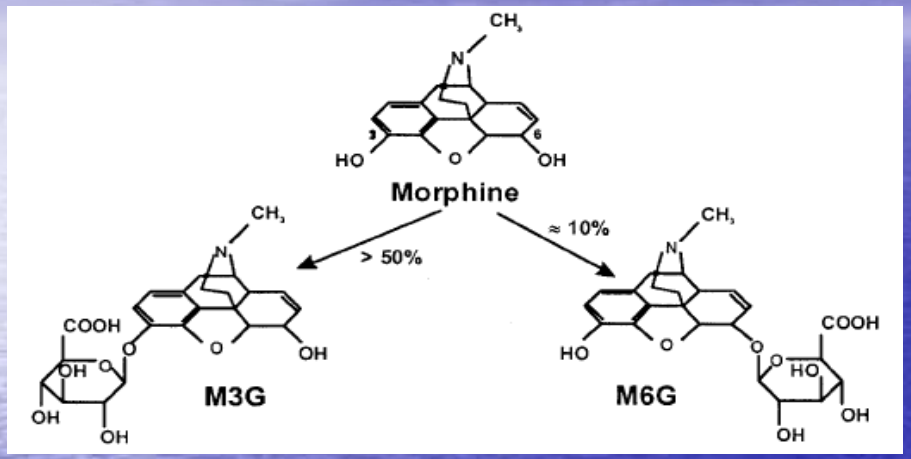
Opioid Side Effects

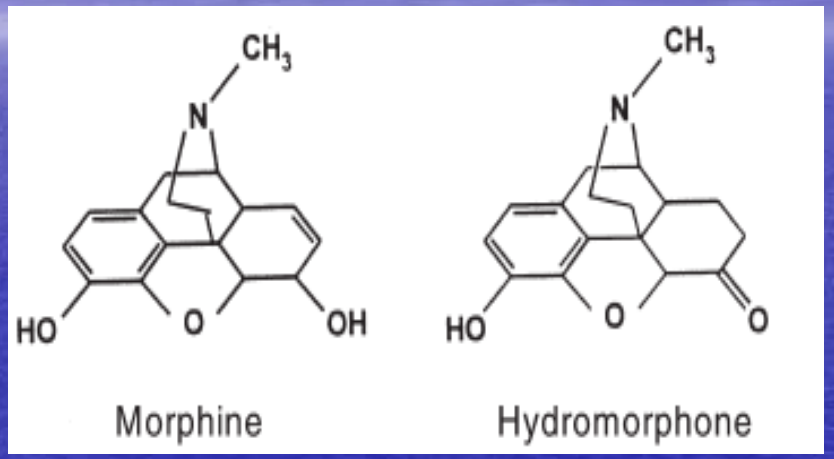
Respiratory Depression

- Seldom occurs.
- The respiratory centre becomes relatively resistant to the depressant effects of the opiates over time.
- Do *not* see unexpected deaths in palliative care patients on large doses of morphine and is why euthanasia is not performed using opioids… these drugs simply do not work for this purpose when patients have been on them for some time

Clinical and Experimental Pharmacology and Physiology 2000 Ravenscroft P, Schnider J[11]

Morphine and Hydromorphone





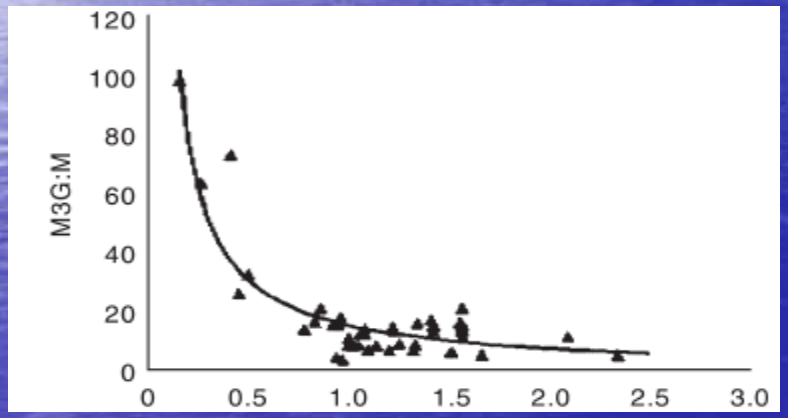
You get 55 % of the M3G metabolite from morphine

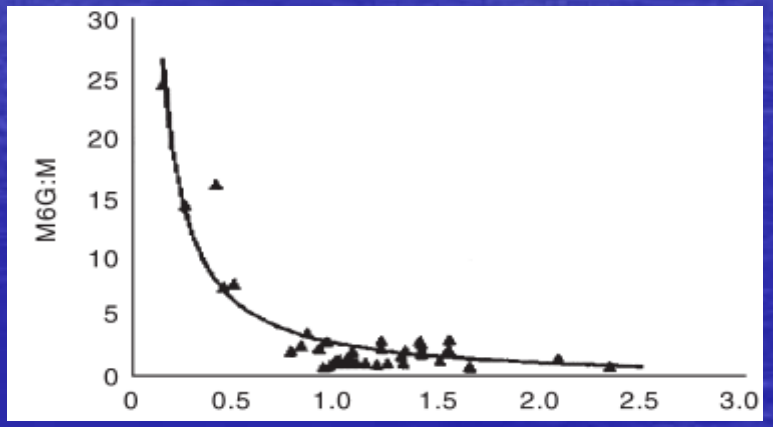
And 37% of the H3G metabolite from hydromorphone

Effect of Cr Cl on metabolites

18 patients studied over 4 to 26 weeks

As the creatinine clearance decreases, then ratios of the metabolites rise exponentially





Estimated creatinine clearance (mL/min per kg)

Clinical and Experimental Pharmacology and Physiology 2000 Ravenscroft P, Schnider J[11]

Morphine and Hydromorphone metabolites

- A 10 to 50 fold increase in elimination half lives of M3G and M6G for morphine

VERSUS

- A 4 fold increase in the H3G in chronic renal failure.

Palliative Medicine 2001 Lee, Leng, MEF, Tiernan, Ejj [12]

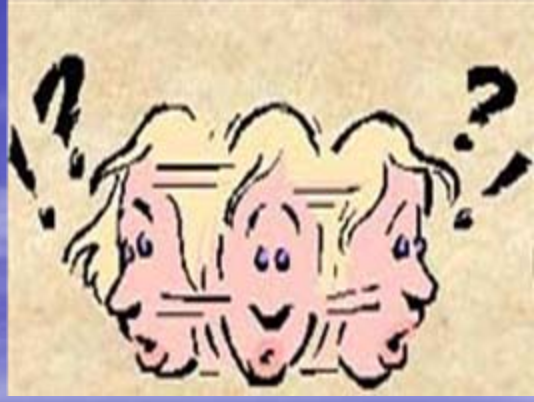
Journal of Pain and Symptom Management 1995 Babul , Darke, Hagen[13]

Neuroexcitatory Effects of Morphine and Hydromorphone

- The Cerebrospinal fluid concentrations of M3G exceed those of morphine and M6G by approximately 2 and 5 fold respectively
- These findings suggest that when the M3G concentration (or H3G by analogy) exceeds the neuroexcitatory threshold, excitatory behaviors will be evoked in patients
- M3G and H3G have *no pain relieving effects, but are potent neuroexcitants* and are at least TEN FOLD more potent neuroexcitants than the respective parent opioids

Clinical and Experimental Pharmacology and Physiology 2000 Smith, MT[14]

Opioid Neurotoxicity



- Occurs more commonly in renal failure[15]
- Myoclonus: Jerks are usually generalized when due to drugs or toxins[1] ; May be provoked by a stimulus or voluntary movement[16]
- Hyperalgesia
- Delirium with hallucinations and eventually
- Grand mal seizures may develop

www.palliative.org Palliative Care Tips March 2004 #18 Myoclonus-Seizures-Hyperalgesia Dr. Robin Fainsinger Royal Alexandra Hospital[15]

www.eperec.mcw.edu Fast Fact # 114 Myoclonus DeMonaco N, Arnold R [16]

Opioid Neurotoxicity

Several strategies

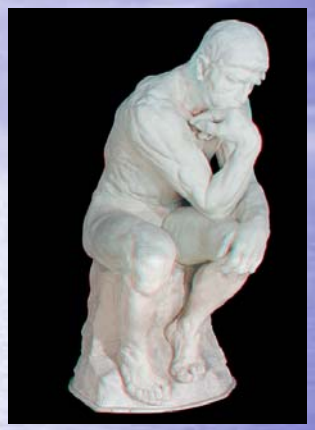
- Reduction in opioid dose by 25 to 50%
- Symptomatic treatment:
  - Hydration; correct renal failure
  - +/- haloperidol, methotrimeprazine, lorazepam, clonazepam, midazolam, phenobarb
- Opioid rotation

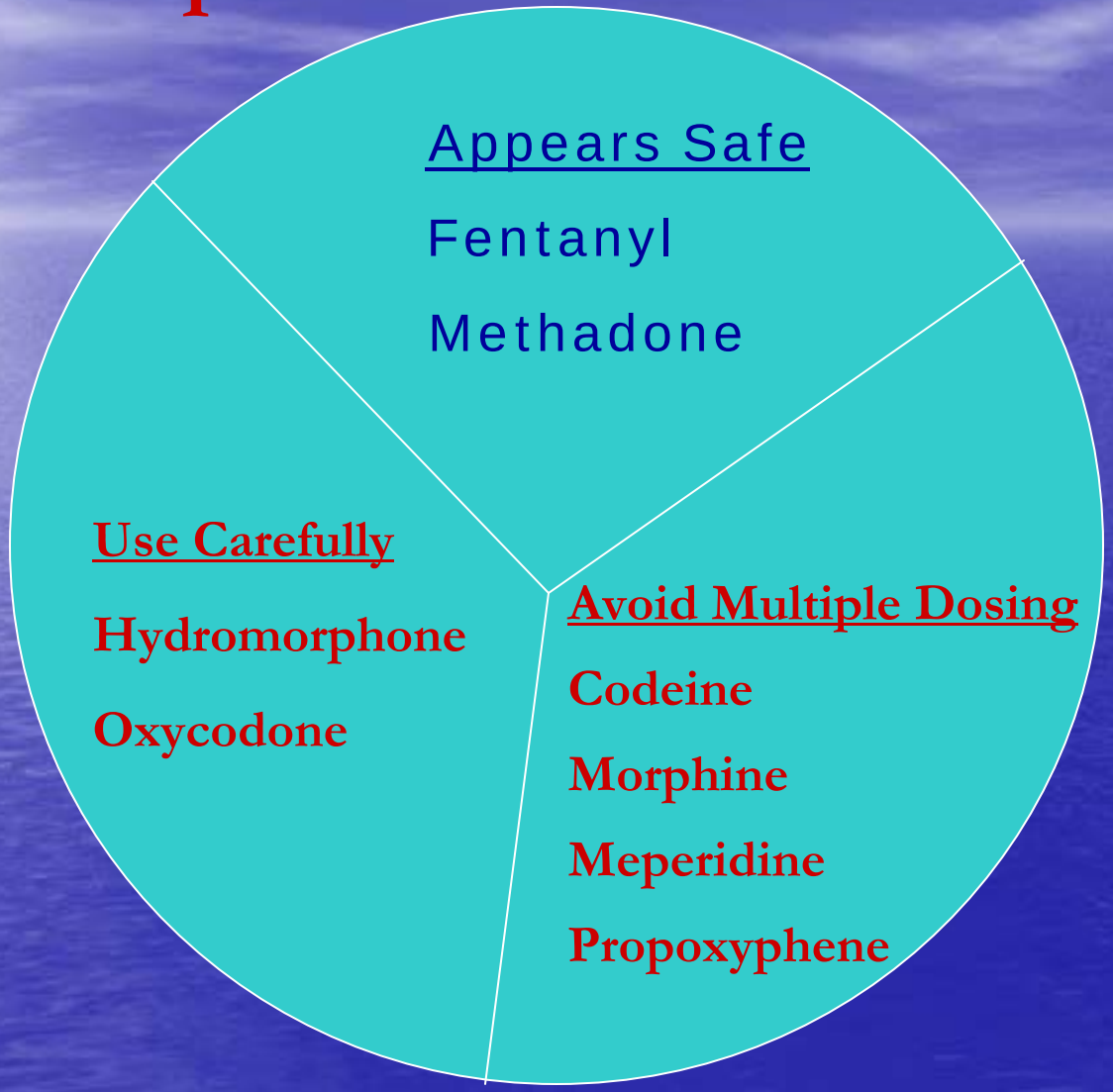
Opioid rotation

Switch (= rotate) to a different opioid to better balance analgesia and side effects

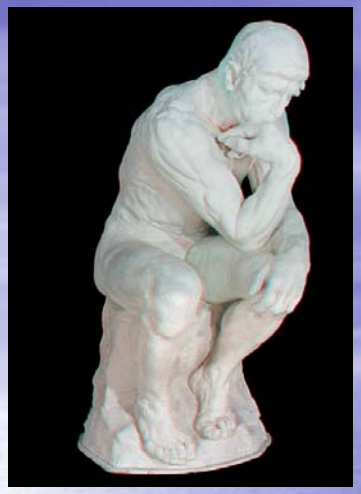
- Different receptors
- Tolerance to a specific opioid
- Variability in analgesia due to incomplete cross-tolerance
- Prospective studies:
  Delirium relieved ! 61% Maddocks
  72% Ashby
  34% Gagnon
  When opioid rotated from morphine to oxycodone or other agents

Opioids in Renal Failure





Journal of Pain and Symptom management 2004 Dean, M



Opioids in Dialysis

Journal of Pain and Symptom management 2004 Dean, M

Conclusion: Opioids and Renal Function

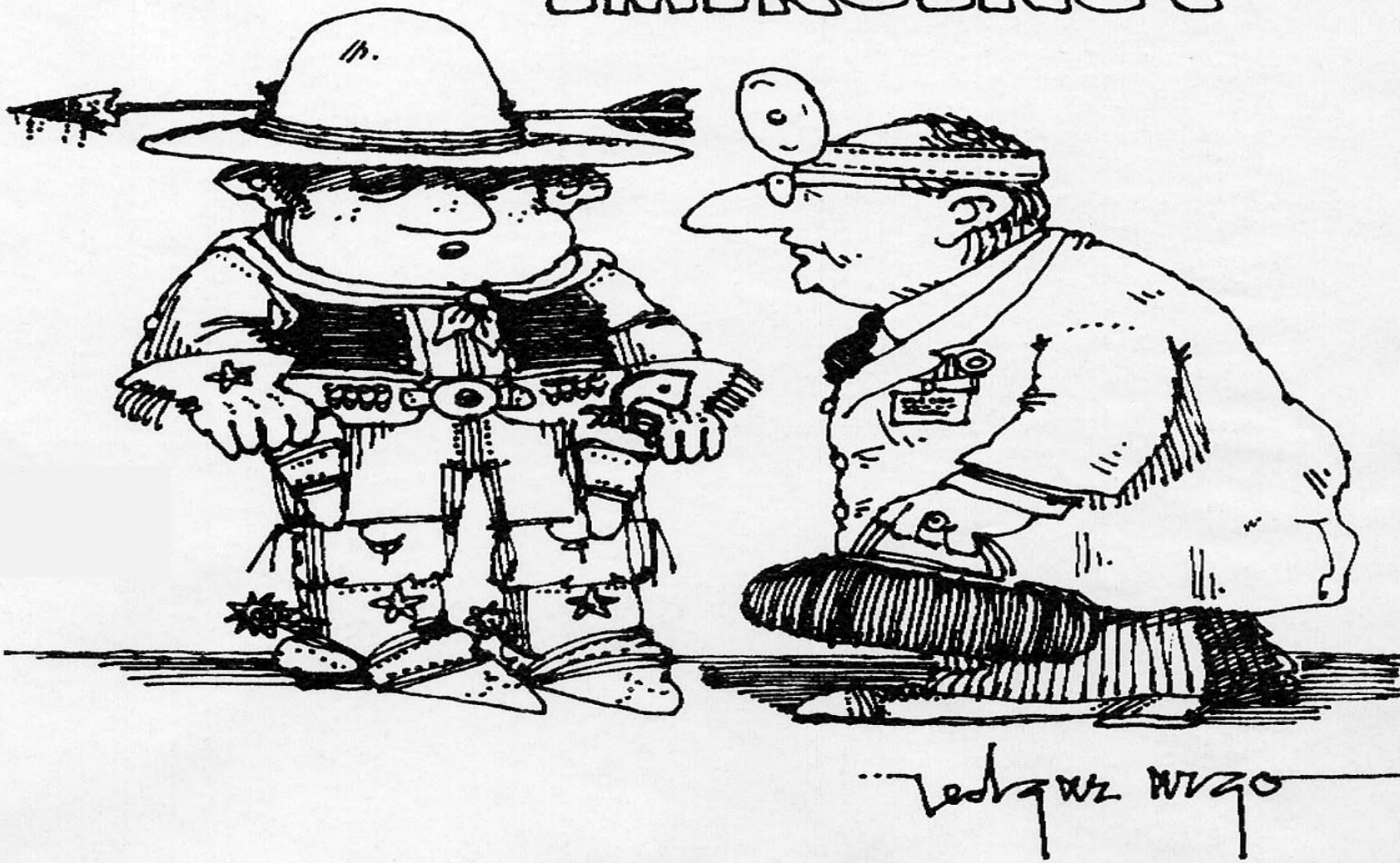
- Find therapeutic options in specific conditions
- Pay attention to titrating doses
- Choose opioids with a more favorable renal profile, like methadone and fentanyl
- Prolonged use of opioids in older, dehydrated patients *might* enhance the risk of compromising renal function

The Journal of Pain 2004 Mercandante S, Arcuri E[7]

George

- 83 year old widower: Lives alone
- Ca Prostate with Bony metastases: R Humerus/ Compression #'s thoracic spine
- Hx ESRD/ISHD/ Depression
- Brought in by daughter: Pain ++ .
- Creatinine 250

EMERGENCY



"The pain isn't too bad, but I can't take my hat off!"

Pain History: George

- O(nset): Several months, ↑ 2 weeks
- L(ocation): R shoulder, R chest wall pain.
- D (uration): Constant. ↑ with movement.
- C(haracteristics): Steady aching pain
- A(ggravating): Any movement; breathing; coughing
- R (elieving): Sitting still;
- T(reatments): T#3 helps for about 2 to 3 hours
  Takes about 10 T#3 a day
  - "Not going on any morphine; I'm not dead yet." No recent RXT
- S (everity): 6/10. 10/10 with movement

Examination

- No evidence of fractures but clearly limited ROM in the shoulder due to pain; R chest wall tenderness with some numbness
- No vertebral tenderness and no neurological signs consistent with Spinal Cord Compression (SCC)
- Xrays show bony metastasis in shoulder and thoracic spine

- *What is your assessment of George's pain?*

Pain management: Assessment

Important first step

Once complete:

- Type of pain:
  - Mixed: Malignant Bone pain; Neuropathic Pain; Incident Pain
- Severity
- Functional Impairment
- Probable cause of pain
- Patient Goals and level of understanding

Pain Management

- Treat the cause: Consider RXT, etc
- Right Drug ?
- (Currently 10 T#3 per day)
- What are our options?

Codeine

- 5 to 10% is metabolized to morphine
- Some individuals metabolize codeine poorly ➲ drug may not be effective
- Often used in combination with ASA or acetaminophen
- Analgesic ceiling with doses > 600 mg/day
- Constipation is a major complaint
- 1:10 (morphine:codeine)

Morphine

- Standard for comparison of all opioids
  - ➲ 'Gold Standard'
- Very versatile: variety of dosing forms and routes of administration
- Concern re: accumulation of active metabolites in ↓ renal function
- Caution in the elderly
- 2:1 (oral:parenteral)

Hydromorphone

- Approximately 5x more potent than morphine
- More soluble than morphine
- Fewer metabolites
- Often preferred for use in ↓ renal function and the elderly

Oxycodone

- Metabolized by liver, but metabolite is not a glucuronide ➲ thus safer in ↓ renal function
- Less constipating than codeine
- Used in combination with acetaminophen or ASA, or as single agent IR and SR
- No ceiling effect BUT no parenteral form available
- 1:1 (morphine:oxycodone) single dose studies
- 1.5:1 (morphine:oxycodone) chronic dosing

Fentanyl

- Approximately 100x more potent than morphine
- Appears to cause less constipation, nausea
- Less histamine release
- Useful in opioid allergy

Fentanyl Transdermal Patch

- Useful for: stable pain
  compliance issues
  difficulty with PO route
  intractable side effects
- Forms depot under skin
- Takes 12 to 48 hours to reach steady state
- Patch lasts 72 hours in most patients

Methadone

- Multiple studies showing good response
- Advantage:
  - Lack of neuroactive metabolites
  - Clearance independent of renal function
  - Racemic mixture with activity at both opioid OP3 (mμ) and OP1 (delta) receptors and NMDA receptors

Methadone

- Disadvantage:
  - Long, unpredictable half-life
    - ➲ potential for serious, even life threatening toxicity
  - Can be difficult drug to titrate
  - Currently no parenteral form readily available
  - Requires special license

Opioids Not Recommended for Use in Chronic Pain

- Meperidine
  - short half-life requiring q2h to q3h dosing
  - toxic metabolites may accumulate with chronic dosing
    - ➲ CNS excitation/seizures at analgesic doses
- Pentazocine
  - mixed agonist/antagonist
  - adverse effects: hallucinations
    vivid dreams
    psychomimetic effects
  - dose ceiling effect

Approximate Opioid Equivalencies

Drug	Oral (mg)	Parenteral (mg)
Morphine	20	10
Codeine	200	120
Hydromorphone	4	2
Oxycodone	13.3	-

Pain Management

- Consider regular medication for continual pain
- PRN medication for breakthrough pain
- Titrate to effect: calculate using Total Daily Dose (TDD) to adjust

George

- Right Drug ?
- Right Dose ?
- Use TDD (Total Daily Dose) of current medication to convert to more appropriate opioid

- Start with and Titrate with short acting:
- Give dose regularly at half life (3 to 4 hours)
- Give breakthrough as needed
- Ask patient to DOCUMENT and adjust as needed

George: 2 days later

Oxycodone 5 mg Q4H = 30 mg

PLUS 6 BT of 2.5 mg = 15 mg

TDD : = 45 mg

45/6 = 7.5 mg IR q 4h

45/2 = 20 mg SR q12 h (Oxycontin)

- BT: 10% of TDD = 4 to 5 mg Oxycodone

George: Cannot swallow

- Right Drug?
- Oxycodone not available parenterally
- Use TDD (Total Daily Dose):
- 45 mg Oxycodone ~ 68 mg PO Morphine ~14 mg PO Hydromorphone
- May consider Fentanyl Patch (25 mcg) or Subcutaneous route

Right Dose ?

- Parenteral is usually HALF the oral dose (TDD/2)
- For switch to Hydromorphone PO= 12 mg = 6mg parenteral dose (Subcutaneous or IV)
- Divide by 6 for Q4H dose (6/6)
- New order

  = 1mg SC Q4H and 0.5 mg Q1H prn

Fentanyl Patch

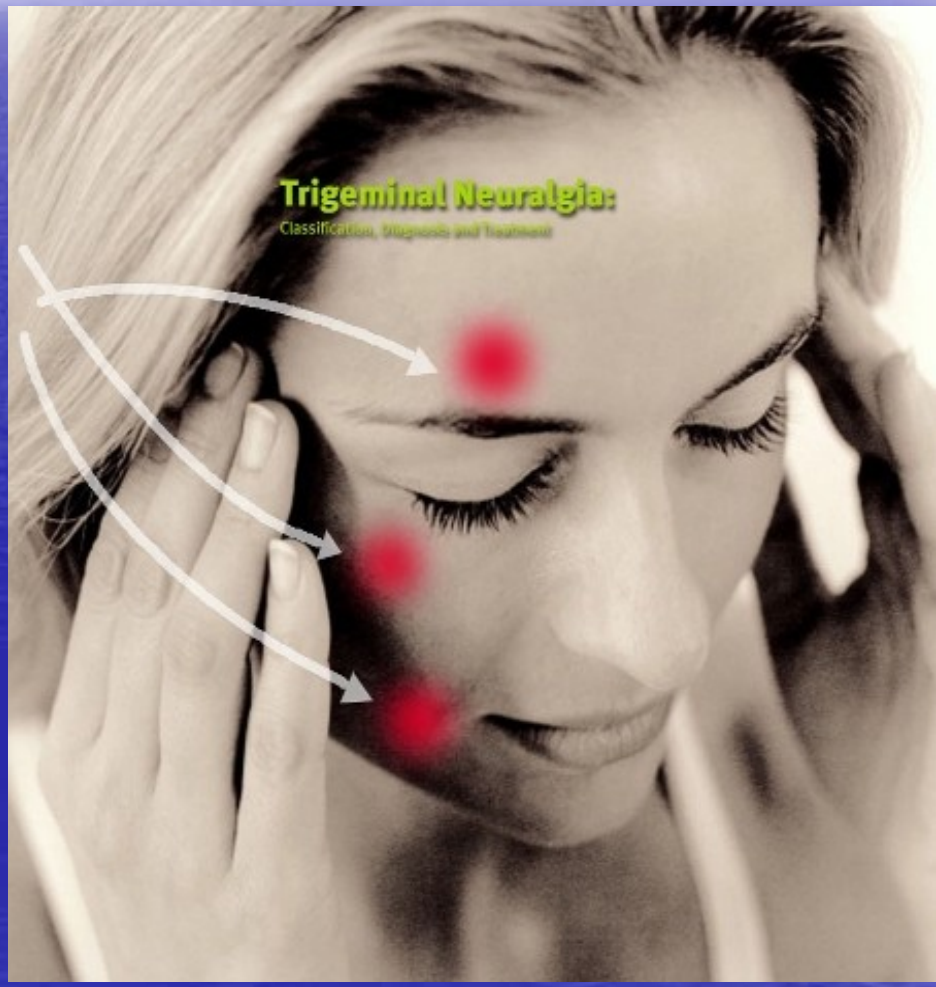
- Would apply patch and continue previous analgesic for another 12 hours or give with SR dose and then discontinue
- Will still need breakthrough dose of short acting medication
- TITRATE to effect: If BT > 10 mg of hydromorphone per day (~ 100 mg PO morphine) consider increasing the patch

Fentanyl Patch Conversion Chart

Oral Morphine (mg/day)	Fentanyl Patch (mcg/hr)
45-134	25
135-224	50
225-314	75
315-404	100
Each further 100	+ 25

Neuropathic Pain

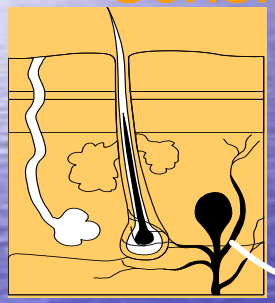
Initiated or caused by primary lesion or dysfunction in the peripheral or central nervous system



Neuropathic Pain

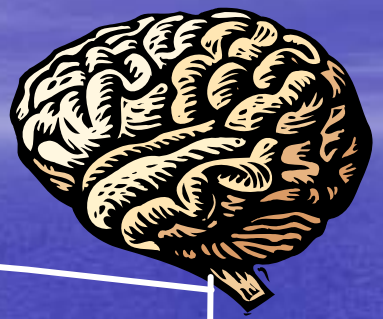
Tissue damage or Inflammation

Peripheral Sensitization



Inflammatory Reaction
Neuron Damage
Ion Channel changes
Ectopic discharges

Reorganization of cortex
Changes in inhibitory pathways



Central Cortex

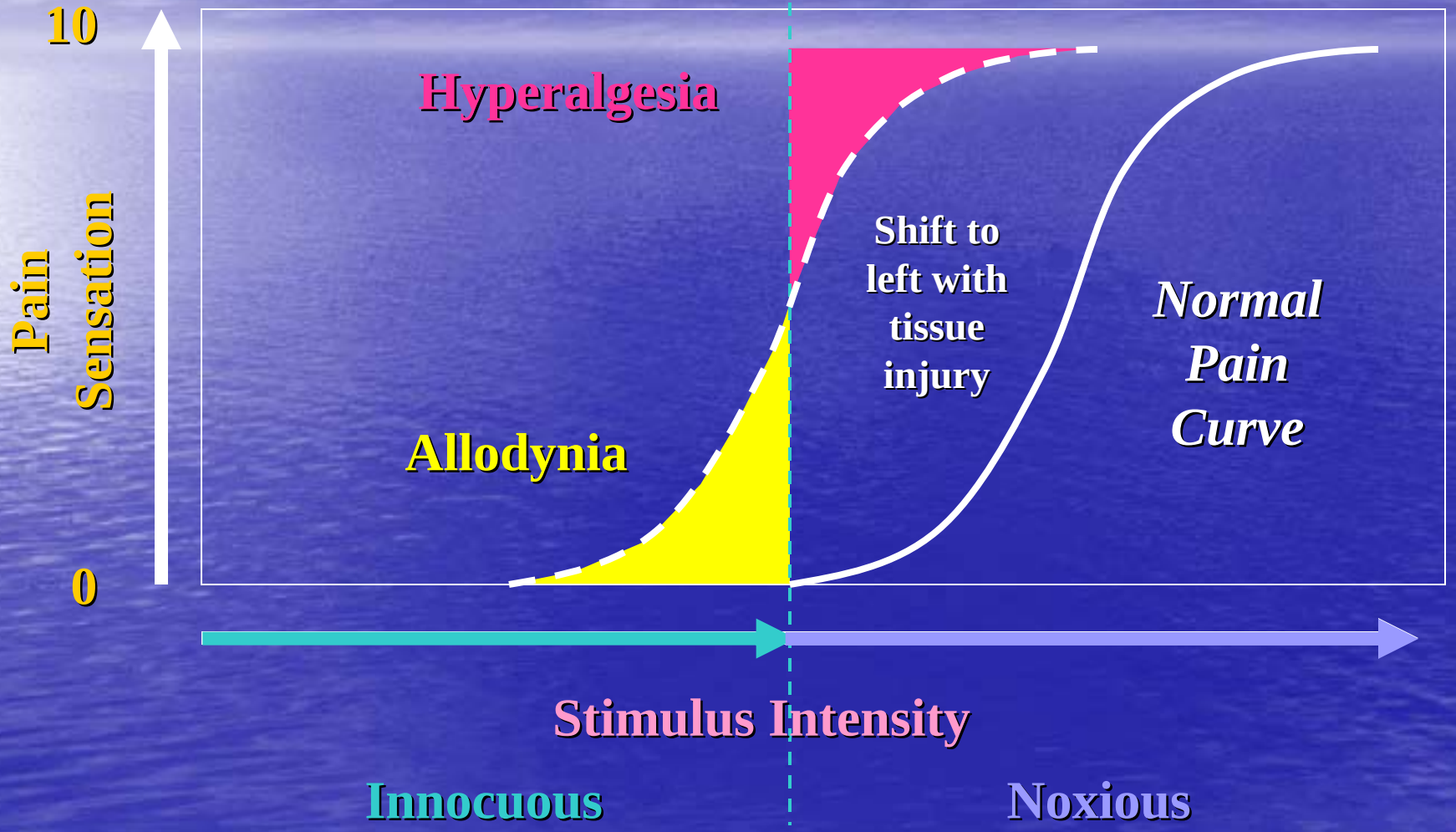
Descending Inhibitory Pathways

Dorsal Horn

NMDA

Afferent barrage provides constant input leading to dorsal horn and central reorganization

Development of Neuropathic Pain



M. Downing

Opioids and Neuropathic Pain: Definite Role

- Raja. Neurology 2002; 59: Cross-over of 76 pts with PHN between opioids, TCA and placebo
- Opioids and TCA reduced pain more than placebo ($p<0.001$)
- Patients completing all three treatments preferred opioids (54%) over TCA (30%)
- Higher doses needed for effect
  (NEJM 2003 Rowbotham et al[19])
- Methadone good results
- Emerging data re Tramadol

Tricyclic Antidepressants for Neuropathic pain

- Good evidence for their benefit in PHN and DN
  - Esp amitriptyline, nortriptyline, desipramine
- Improvements in pain, insomnia, anxiety, and depression
- Nortriptyline better tolerated than amitriptyline
  - < 5% incidence of anticholinergic side effects
- Start at 10 to 25 mg at bedtime
  - Increase as tolerated to target dose of 25 – 150 mg
- Antidepressant effect independent of analgesic effect

Non-TCA antidepressants and neuropathic pain

- Results with SSRI's discouraging
  - Paroxetine is only SSRI to be superior to placebo in controlled trials
  - Equal in most cases to imipramine
- SNRI venlafaxine has shown some promise
- Newer data supporting use of Bupropion:

  Start at 100 mg daily increase weekly to 150 mg b.i.d. (Neurology 2001 Semenchuk et al[18])

Anticonvulsants: Gabapentin

- Clinical evidence for efficacy in PHN and DN
- Targets the Na and Ca channels
  - Reducing central excitation
- 100 to 6000 mg/day (1200 to 3600 mg/day)
  - If elderly, start at 100 mg per day at bedtime
  - If younger, 100 mg t.i.d
  - Titrate weekly
- Reduced dose in renal failure
- Other options: Good initial results: Pregabalin and Oxcarbazepine. Lamotrigine for central pain

Treatment for Neuropathic Pain: Use of adjuvants

- Tricyclic antidepressants: Useful for multiple pain syndromes
- Anticonvulsants: Gabapentin; Pregabalin; Lamotrigine
- Opioids: Including Oxycodone; Methadone; Tramadol
- Local anesthetics: Lidocaine (5% patch); systemic
- Corticosteroids if inflammatory component
- Capsacin

George: 1 week later

Much more comfortable at rest and sleeping well

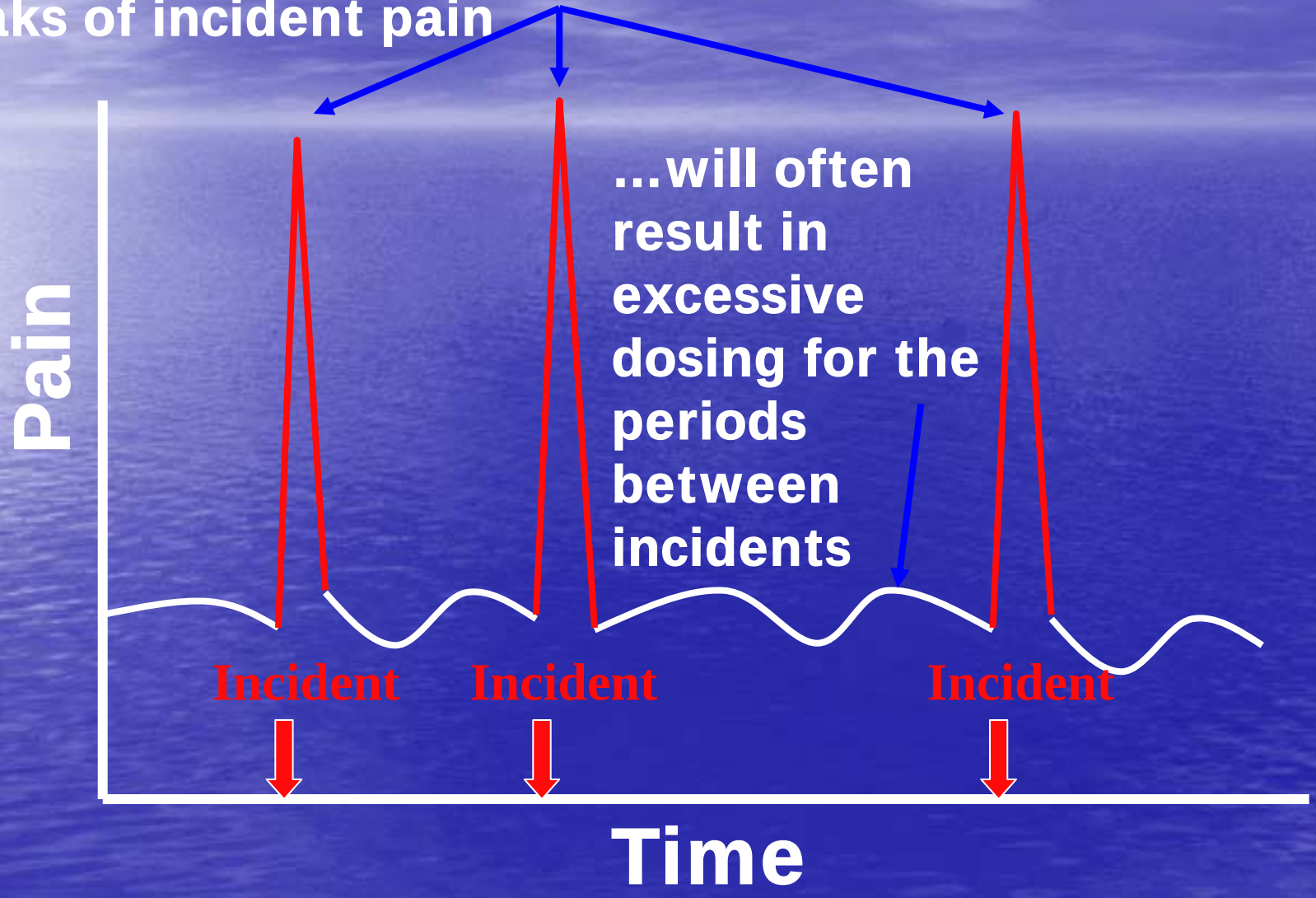
but still pain ++ with morning bath

INCIDENT PAIN

- Common; short lived
- Movement of the patient, either active or passive (Sitting up in bed; Transfer to commode or stretcher; Turns)
- Procedures

INCIDENT PAIN: Duration usually brief

- Having a steady level of enough opioid to treat the peaks of incident pain



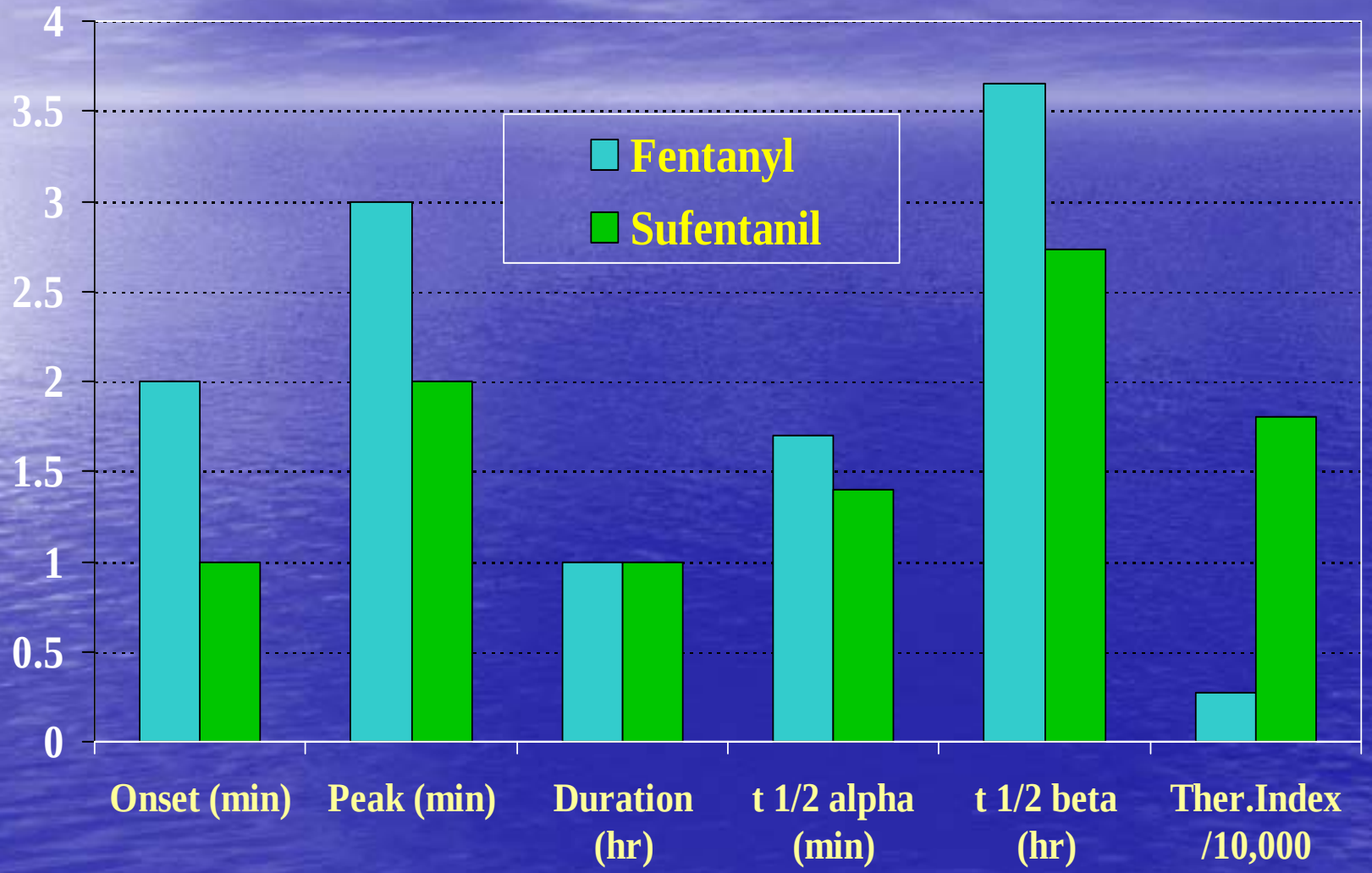
Addition of Fentanyl and Sufentanil

- Highly lipid soluble Synthetic OP3 agonist opioids
  - Transmucosal absorption
- Used for procedural pain since early 1980's
- Useful sublingually, intranasally, parenteral routes
- Safe & effective in initial studies
- Side effects similar to other opioids
- **10 mg morphine**

  ≈ 100 mcg fentanyl (100X)

  ≈ 10 mcg sufentanil (1000X)

Comparison of Fentanyl and Sufentanil



Dosage

Fentanyl: 0.5 to 1.0 mL of parenteral drug (50 mcg/ml) given under the tongue or intranasally (spray bottle: Stable ~ 2 weeks).

- Equivalent to approx 2.5 to 5 mg of Morphine

Sufentanil: IF TDD >100 mg Morphine

- Incremental titration: Begin at 0.2 mL (~ 10 mg of Morphine). Usual dose 0.4 mL or 0.5 mL
  - Can repeat q5min until relief. Use effective dose
- Last ~45 to 60 minutes
- Instruct patient NOT to swallow for 2 minutes.

Pain

- "Pain is a more terrible lord of mankind than even death itself" *Albert Schweitzer*
- Addressing pain and suffering at the heart of every other approach and treatment
  - Quality of life
  - Quality of care

Thank you

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