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Pain Management
Khonkaen 2016

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Overview

- Concepts in pain management
- Case study
- Pharmacological management
  - Opioids
  - Adjuvants
- Neuropathic pain
- Non pharmacological management
- What is the evidence

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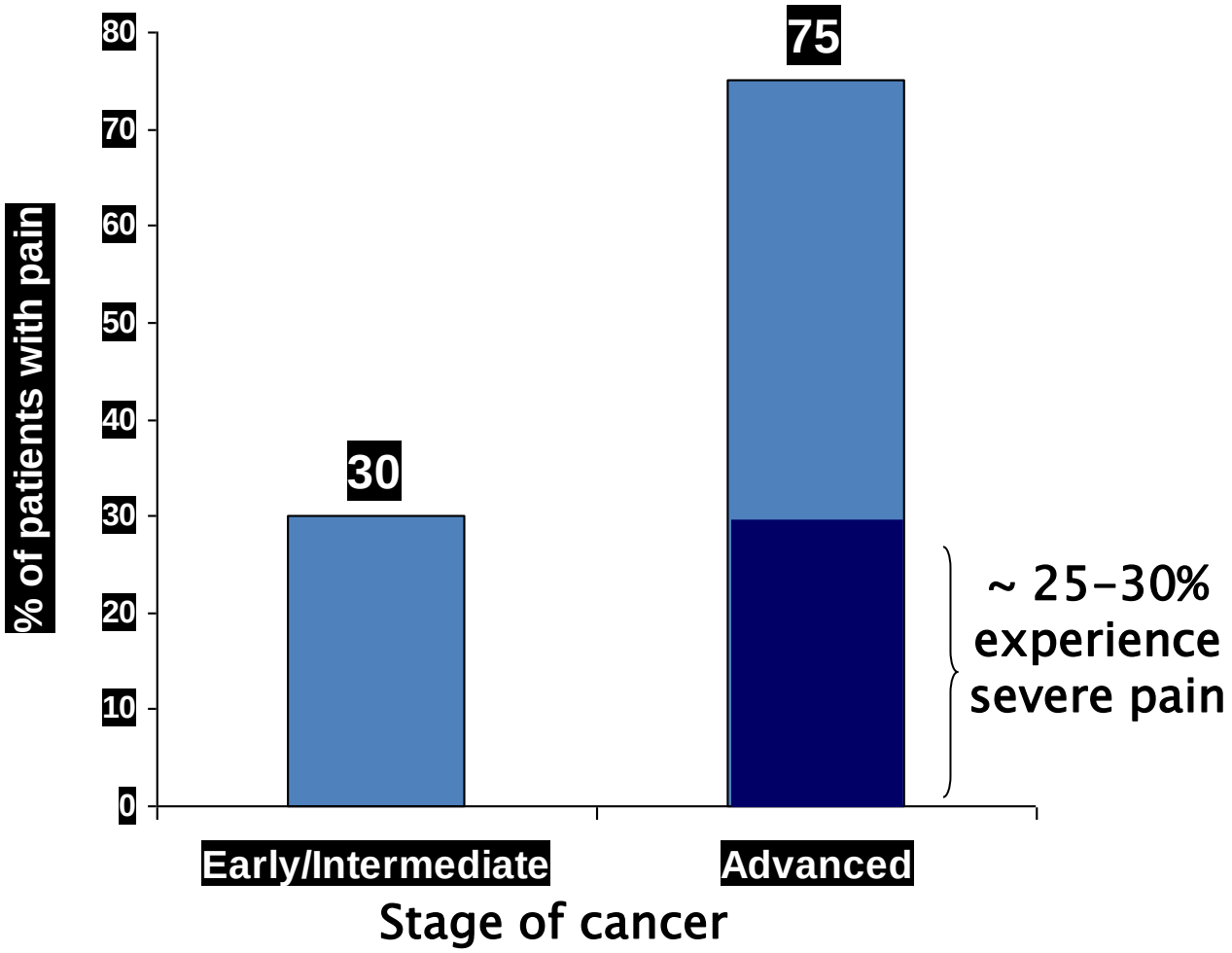
Current evidence based concepts:

- Pain is a frequent complication of cancer, and is common in many other life-limiting illnesses

Pain is the Most Common Treatable Symptom of Cancer



Pargeon et al. *Pain Symptom Manage* 1999;**18**:358–368.

Current evidence based concepts:

- Pain is a frequent complication of cancer, and is common in many other life-limiting illnesses
- Pain that is not well controlled
  - significant distress and disability
  - despite the availability of best practice approaches to pain management
  - wide variability in how pain is treated in practice
- Increasing complexity of cancer treatment (longer survival of patients)

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Current evidence based concepts:

- Cancer pain approach
  - Holistic
  - Multimodal
  - Mechanism-based
  - Starts at diagnosis

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Mechanistic Approach to cancer pain Management:

The four step approach *Lickiss 2001*

Based on adequate assessment and diagnosis of the mechanism of pain

1. To identify and reduce the noxious stimulus
2. Psychosocial assessment of the patient
3. Optimise opioids
4. Co-analgesics, including neuropathic pain

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APPROACH TO PAIN MANAGEMENT

IN PATIENTS WITH CANCER RELATED PAIN

4 STEP APPROACH

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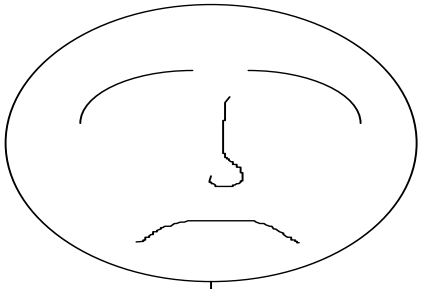
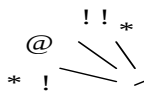


STEP 1

↓NOXIOUS STIMULUS

DIAGNOSIS
PRECISE TREATMENT (local)
- XRT
- SURGERY
- ANTIBIOTICS
- NSAIDS
- PARACETAMOL
- ANTISPASMODICS
- PHYSIOTHERAPY



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APPROACH TO PAIN MANAGEMENT

IN PATIENTS WITH CANCER RELATED PAIN

4 STEP APPROACH

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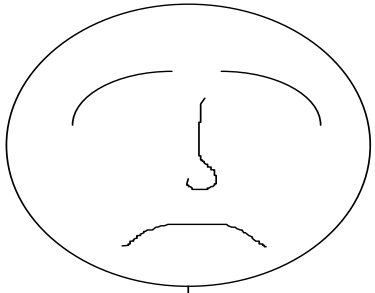
STEP 2

↑ THRESHOLD
- COMFORT
- CARE
- CONCERN

ANXIOLYTICS
ANTIDEPRESSANT
- if pathological depression



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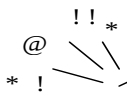

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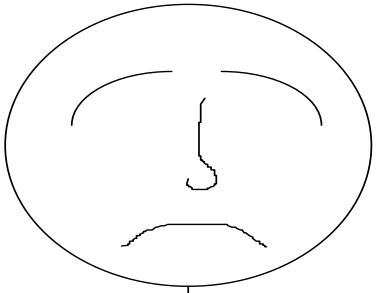

STEP 3

CONSIDER OPIOIDS
- exploiting opioid receptor system, use precisely

MORPHINE
OXYCODONE
FENTANYL
HYDROMORPHONE
CODEINE
(METHADONE)

STEP 1

↓NOXIOUS STIMULUS

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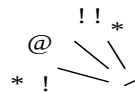

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APPROACH TO PAIN MANAGEMENT

IN PATIENTS WITH CANCER RELATED PAIN

4 STEP APPROACH

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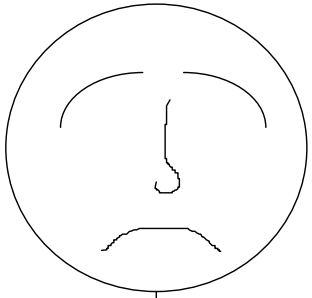

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STEP 4

CONSIDER NEUROPATHIC PAIN

ANTICONVULSANT
ANTIDEPRESSANT
CORTICOSTEROID
- lowest possible doses

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CASE 1:How would you manage his pain?

- Opioid titration with Morphine (equiv)
  - Constipation: route of opioids and bowel care
- Regular laxatives
- Paracetamol
- NSAID with gastro protective agent (PPI)
- Bisphosphonates: monthly for 3-6 months
- Radiotherapy if isolated area
- Psychosocial status?
- Education (analgesics/ opioid fears / side effects)

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Pharmacology of Cancer Pain

- Never opioids alone!

- Opioids
- Paracetamol
- NSAID'S
- Steroids
- Adjuvants
  - TCA / Anticonvulsants / NMDA antag / anti-tumour therapies
- Novel therapies
- Anti-cancer therapies (chemo, RT, hormonal, targeted)

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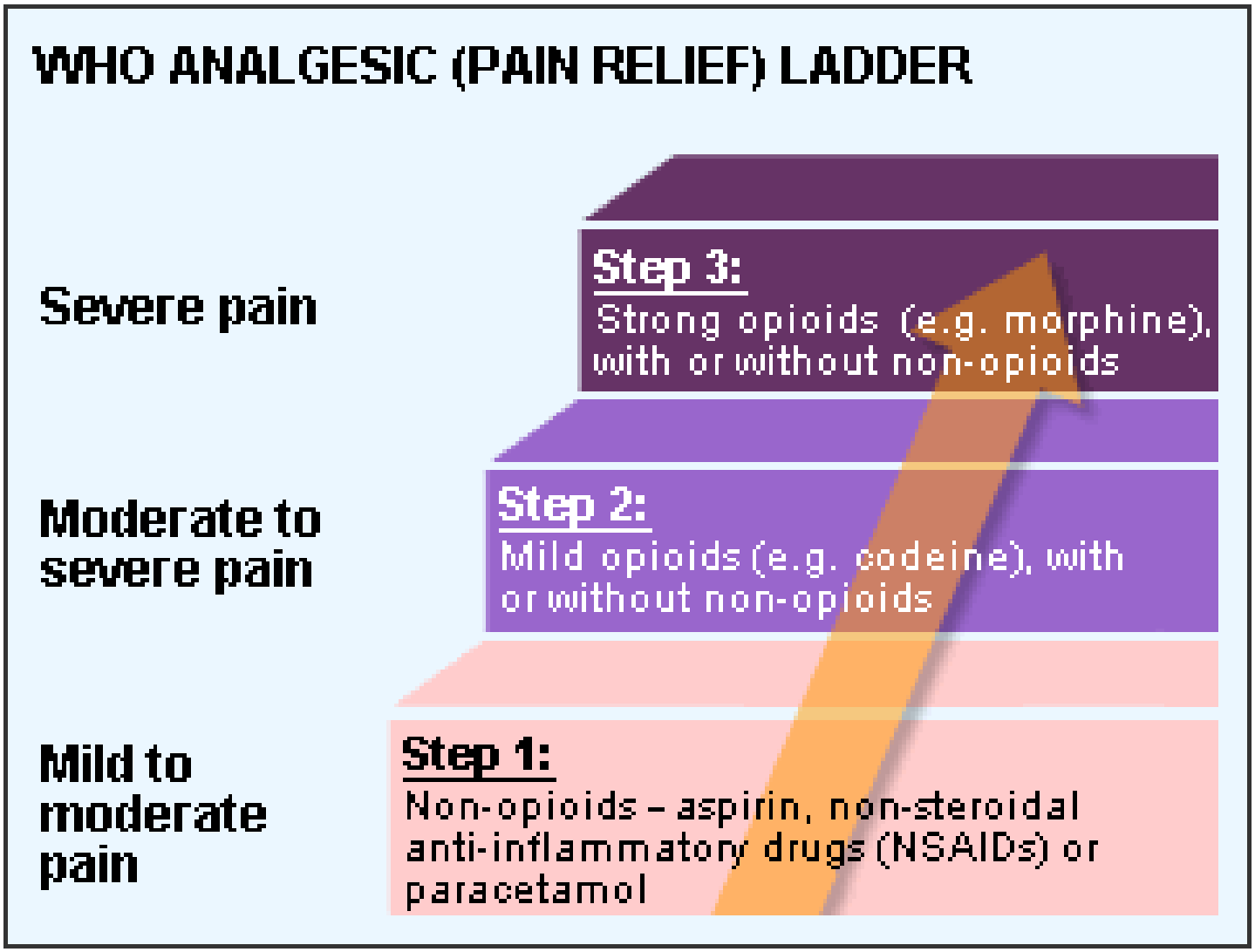
WHO ANALGESIC (PAIN RELIEF) LADDER
Severe pain
Step 3:
Strong opioids (e.g. morphine), with or without non-opioids
Moderate to severe pain
Step 2:
Mild opioids (e.g. codeine), with or without non-opioids
Mild to moderate pain
Step 1:
Non-opioids – aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol

Cancer pain: straight to strong opioids?

- Should the second step be removed?
- World wide barriers to opioid access
  - Opioid availability
  - Drug regulation
  - Phobias and misconceptions
- Where opioids are readily available, strong opioids should be utilised for cancer pain

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MORPHINE: prototype?

- The optimal route of administration of opioid is by mouth.
  - Immediate release - for dose titration
  - Controlled release - for maintenance treatment
- Dose titration is with immediate release opioid given every 4 hours
- Steady state reached within 4-5 half lives (i.e.. Within 24 hours)

COMMENCING MORPHINE

- No standard dose of morphine
- No ceiling dose, but restricted by side effects
- The starting dose is determined by previous analgesic treatment
  - Codeine 60mg: 8 - 10mg q4h morphine
  - Tramadol 50mg : 10 mg morphine
  - (Buprenorphine 5mcg / hr : 2mg q4h morphine)

Oxycodone (not available in Thailand, ?coming)

- Endone / Oxynorm / Oxycontin *(slow release)*
- Synthetic derivative of morphine
- Dosing interval fourth hourly
- 1.5 times the potency of oral morphine
- Similar side effect profile as morphine
- ~ Same rules in renal and hepatic impairment
- Helpful with ‘morphine’ phobia

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MORPHINE VERSUS PETHIDINE

Pethidine: No role in cancer pain Mx

MORPHINE	PETHIDINE
Fourth hourly dosing	2-3 hourly dosing
Oral, Subcutaneous, rectal routes	IM
Regular analgesia optimal	Because of side effect profile PRN dosing is often chosen
Phamacodynamics and kinetics better understood	Less well understood in normal patients and patients with renal and hepatic failure
Defined and short lived cognitive impairment	Neurotoxicity Seizures, especially if > 1g / day
Less psychological addiction	High incidence of addiction

Tramadol

- weak μ-opioid agonist activity
- NA/5HT reuptake inhibition
  - Some anti-neuropathic effect
- May have less side effects but they still do occur
- Constipation is significant
- Limits use of other adjuvants
- Minimal use in cancer pain management

FENTANYL

- Potent synthetic opioid agonist
- Transdermal route
- Continuous controlled release for 72 hours
- New Matrix system
- 12mcg/hr
- Amount released proportional to surface area of the patch
- Less SE profile (constipation, CNS)
- Difficult titration / conversion factor
- Patient preference
- Breakthrough analgesia is difficult
  - Fentanyl citrate, lozenge on a stick

Methadone

- Opioid with following properties
  - analgesia
  - NMDA antagonist
- Limitation by long and unpredictable half life, dosing schedule and available preparations
- Adjuvant role in cancer pain for resistant neuropathic and wind-up pain
  - Add small doses of methadone
- Can be used as background opioid
  - Renal impairment
  - Low dose ≤ 200mg morphine use 2:1 conversion
  - Higher doses > 200mg morphine use 10:1

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UNFOUNDED FEARS OF MORPHINE

- Abuse of morphine linked with its therapeutic use
- Addiction (physical dependence / psychological addiction)
- Too early in the course of the disease
  - Morphine can be continued for many months
  - When pain subsides morphine can be weaned down and discontinued
  - Continues to be effective in the terminal stage
- Excessive sedation
- Respiratory depression

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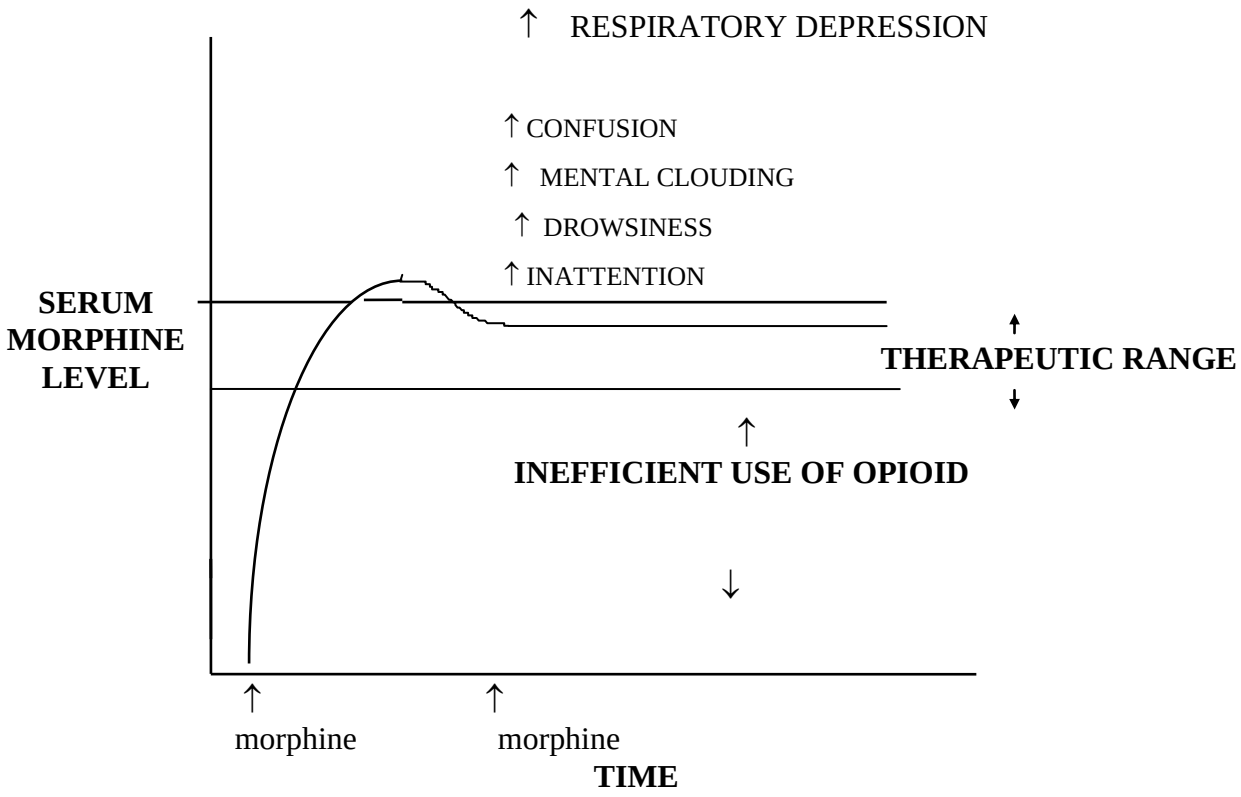
OPIOID PRECISION



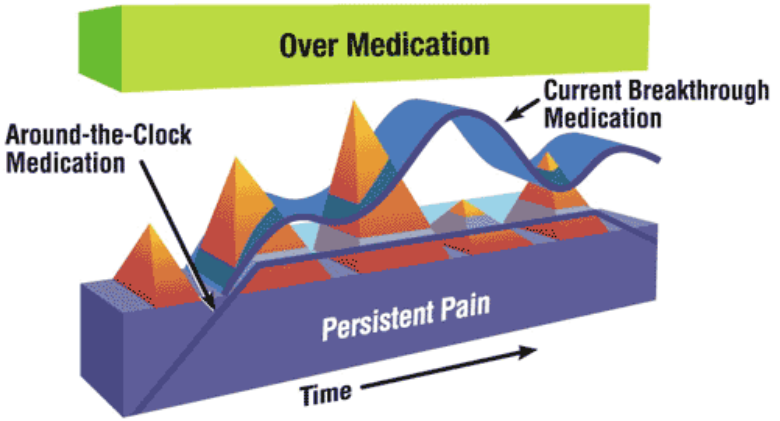
Opioids on respiration

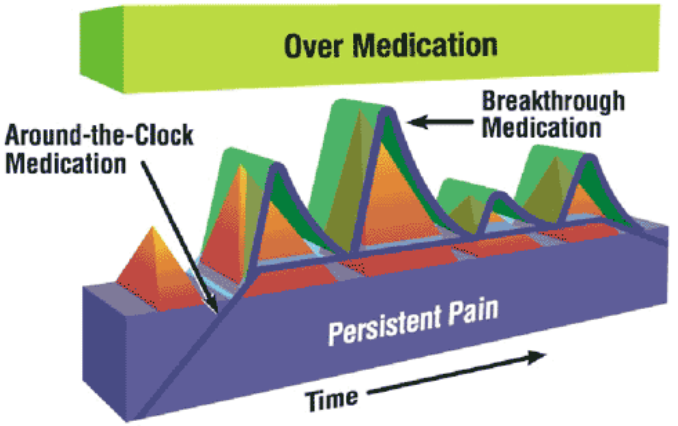
- Mechanism for effect on dyspnoea: not reduction of ventilatory rate, overall ventilation or sedation
- Can depress respiration but an effect of rate of rise of the opioid dose (titration rate)
- Steady state level of opioid
  - Negligible effect on respiratory drive
  - And on sedative effects
  - *Hallenbeck, JPM, 2012*

- Pain: stimulant to respiratory drive

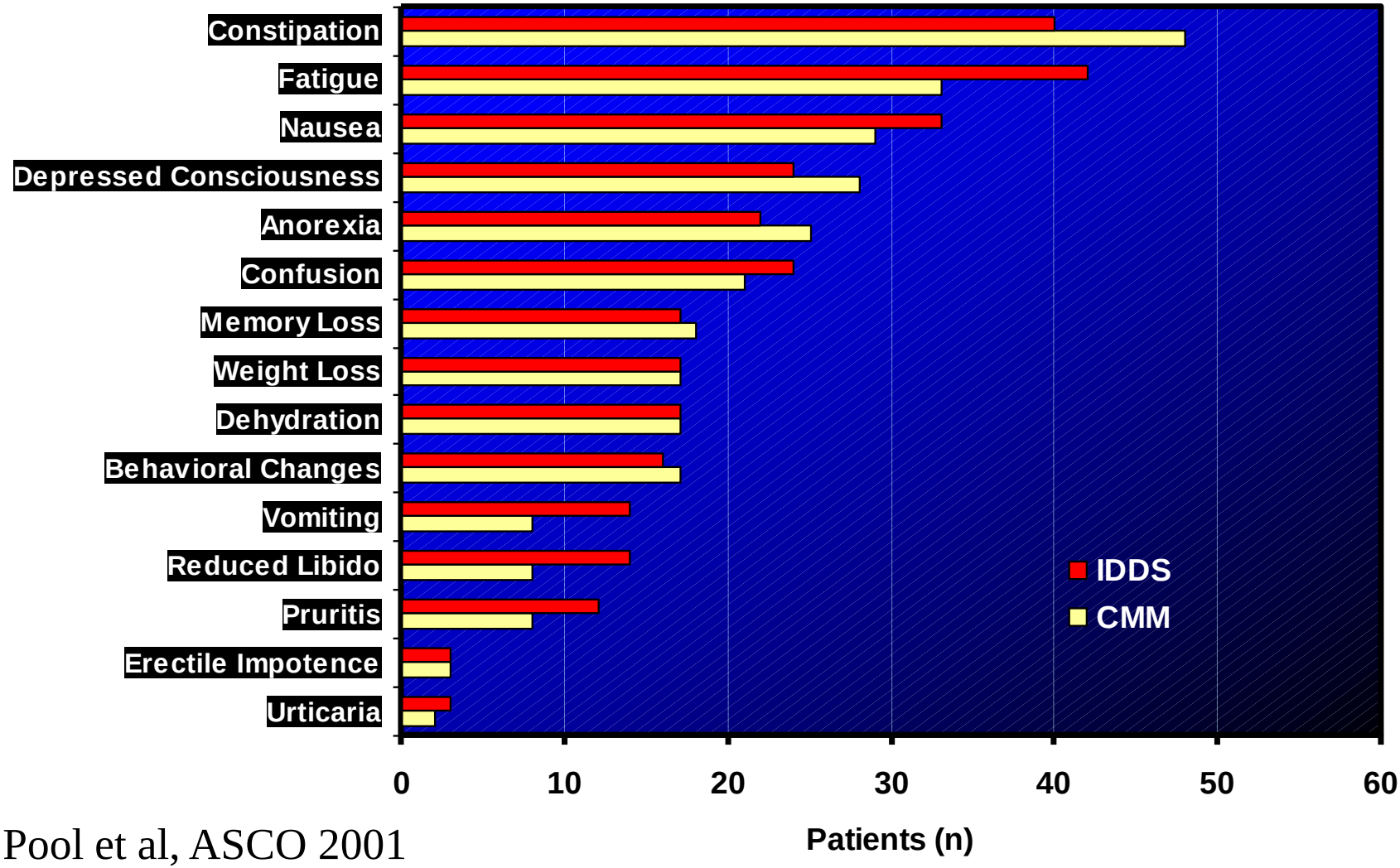
Breakthrough pain

- Important to allow for breakthrough pain
- Limited by type, duration and half life of opioids
- Adjuvants and cancer treatments important





Prevalence of Opioid Side Effects in 150 patients with severe cancer pain



Pool et al, ASCO 2001

Expert Panel: 2009 Perry, Portenoy et.al

Journal of Pain and Sympt Management

- Step 1
  - Reduction of 25% to 50% of the calculated equianalgesic dose
  - Exceptions
    - Methadone: 75 – 90% reduction (?low dose)
    - Fentanyl: safety factor already incorporated
    - Fentanyl citrate: lowest available dose
- Genetic differences

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Expert Panel: 2009 Perry, Portenoy et.al

Journal of Pain and Sympt Management

- Step 2
  - Severity of pain at time of switching
  - Other medical factors
  - Psychosocial factors
  - additional change in dose required?
    - 15 – 30% further reduction
- Need for breakthrough or rescue analgesics

Is oral morphine still the first choice of opioid for moderate to server cancer pain: A systematic review with the EPCRC guidelines project 2010

- No further information to previous Cochrane review: limitation of efficacy and tolerability data
- Oral morphine, oxycodone and hydromorphone have similar efficacy and toxicity in this patient population

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SYDNEY SOUTH WEST
AREA HEALTH SERVICE
NSW HEALTH

OPIOID CONVERSATION CHART

FROM		TO codeine PO mg/day	morphine PO mg/day	morphine SC mg/day	hydromorphone PO mg/day	hydromorphone SC mg/day	oxycodone PO mg/day	fentanyl TD mcg/hr	tramadol PO mg/day
codeine	PO mg/day		6	12	30	60	8	24	1.2
morphine	PO mg/day	6		2	5	10	1.5	3	0.2
morphine	SC mg/day	12	2		2	5	0.6	1.2	0.1
hydromorphone	PO mg/day	30	5	2		2	0.3	0.6	0.04
hydromorphone	SC mg/day	60	10	5	2		0.1	0.2	0.02
oxycodone	PO mg/day	8	1.5	0.6	0.3	0.1		2	0.15
fentanyl	TD mcg/hr	24	3	1.2	0.6	0.2	2		-
tramadol	PO mg/day	1.2	0.2	0.1	0.04	0.02	0.15	-	

multiply divide


cure
Bells
Palsy

Adjuvants

- Paracetamol
  - Mixed evidence base for its efficacy in cancer pain
  - Should be used with opioids especially in the titration phase
- NSAID's
- Antidepressants
  - NNT 2-5 (non cancer studies)
- Anticonvulsants
  - NNT 3 (non cancer studies)
  - Gabapentin / Lyrica
- NMDA receptor antagonists
- Steroids
- Antispasmodic drugs

Antidepressants

- Analgesic efficacy in chronic pain / neuropathic pain
- Block reuptake of monoamines
- McQuay systematic review 1996
  - 30/100 will get >50% pain relief
  - NNT 3 in DN, adverse events 2.8
- Studies in non-malignant pain
  - Diabetic neuropathy / PHN
- Significant SE
- Dosing
- Response within 24-72 hours

Antidepressants

- Tricyclic antidepressants
  - Amitriptylline
  - Doxepin, imipramine, desipramine, nortriptylline
- Selective seretonin reuptake inhibitors
  - Paroxetine
  - citalopram
- Monoamine oxidase inhibitors
  - Phenelzine

Anticonvulsants

- Suppresses paroxysmal discharges of pain fibers
- Reduces neuronal hyperexcitability
- DN: NNT 2.5 for effectiveness, 3.1 Adv E, 20 serious adv e McQuay 1995
- Studied in Phenytoin, Carbamazepine, sodium valproate
- Mainly studied in CNMP, but also cancer

Anticonvulsants

- Sodium Valproate
  - 100 – 200 mg nocte to bd and then titrate to 800-1,000mg / day
  - RR cancer 55.6%
- Carbamazepine 100 mg nocte
- Clonazepan useful in the terminal setting
  - 1-2mg/day
- Response within a week
- SE: sedation, dizziness, nausea, unsteadiness, hepatic toxicity

Gabapentin

- Gabapentin
  - designed as an analogue of GABA
  - site unknown, mechanism unknown (Ca channel)
  - PHN, complex regional pain syndrome, peripheral neuropathies
  - Prevent allodynia and hyperalgesia
  - Acts also on NMDA receptors
- ???opioid sparing effect
- Improved pain and sleep
- Dose 1.5g to 3g to have efficacy
- Drowsiness, dizziness, ataxia, peripheral oedema
- Lomotigine (not promising)

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Pregabalin (Lyrica)

- Analogue of GABA
- Analgesic and anticonvulsant activity
- PHN main studies showing efficacy
- Indication: Rx of neuropthic pain in adults
- SE: dizziness, somnolence
- Dose adjustment in renal impairment
- Dose: 150 to 600mg / day in 2 divided doses

METHADONE

- Methadone can be used in this situation

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Side effects

- Ineffective assessment and treatment of side effects
  - Reduces compliance
- Adjuvants: interactions
- NSAID's GIT / renal side effects

- If SE's well controlled, can titrate opioids
- Titrate adjuvants separately

- Education about SE's to patients and family

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Australian Pain Society evidence-based recommendations for the pharmacologic management of neuropathic pain..

- Noradrenergic antidepressants: Nortryptiline, desipramine, amitryptiline,venlafaxine, duloxetine
- Calcium channel alpha 2-delta ligands Gabapentin, pregabalin
- Sodium channel antagonists Topical (and intravenous) lignocaine
- Opioid agonist Morphine, oxycodone, methadone
- Partial opioid agonist Tramadol

Pain interventions

- TENS
- Massage, acupuncture
- Regional blocks and neurolytic blocks
  - Coeliac plexus, intercostal, trigger points
- Spinal analgesia (opioids and anaesthetics)
  - Epidural catheter, Intra-thecal
- Surgical procedures
  - Decompression
  - Vertebro-plasty

Psychological Assessment and Support

- The relationship of pain experience and the whole person
- The psychological status of a person impacts on their pain perception and pain behaviour
- Effect on the emotional and psychological well being
- Effect on relationships, social responses
- Impact on work, financial security, recreation

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Threshold Issues

- Assessment of their psychological and psychosocial dimensions
- Assess level of anxiety or depression
- Prior coping mechanisms
- Enquire about support structure
- The impact of: breaking bad news, progression of disease
- Treat pathological anxiety and/or depression
- Ongoing support (psychosocial, spiritual)
- Education: pain, meaning, significance of pain, side effects, myths

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Cancer Pain Summary

- The majority of cancer pain can be effectively treated with available drugs and best practice management strategies
  - which includes regular assessment of pain
- Comprehensive approach begins at diagnosis
- Mechanism-based
- Multimodal management that is patient centred and individualised

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Cancer Pain Summary

- Strong evidence supports treating cancer pain with non-steroidals, opioids, radionuclides and radiotherapy (Lorenz KA 2008)
- Bisphosphonates are effective in the treatment of malignant bone pain (Qaseem 2008)
- Oral morphine, oxycodone and hydromorphone all have similar efficacy and toxicity in opioid naïve cancer patients. (Caraceni 2011)
- According to updated recommendations from the European Association of Palliative Care, any of these opioids can be used as first line strong opioids. (Caraceni 2012)

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Cancer Pain Summary: cont'd

- For moderate to severe cancer pain
  - "around the clock" coverage by long-acting strong opioids
  - availability of "as needed" doses of immediate release opioids continues to be recommended as best practice.

    (Dy SM 2010)
  - pre-emptive doses of immediate release opioids for predictable episodes of breakthrough pain. (Caraceni 2012)

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Cancer Pain Summary: cont'd

- Recent evidence-based guidelines for neuropathic pain
  - first line adjuvant treatment
    - antidepressants, either tricyclics, or duloxetine or venlafaxine,
    - anticonvulsants, either gabapentin or pregabalin
    - amitriptyline and gabapentin are the two agents recommended for neuropathic pain in recent guidelines from the European Association of Palliative Care
  - Opioids are also effective in neuropathic pain, and may be co-administered as first line treatments, alongside adjuvants
- *(Care search)*

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