ATTUALITA' TERAPEUTICHE NEL CONTROLLO DEL DOLORE

MICHELE MONTRONE
ONCOLOGIA MEDICA
OSPEDALE "SAN GIUSEPPE MOSCATI"
TARANTO

THERE HAS BEEN PROGRESS IN PAIN MANAGEMENT ?

OPIUM IS THE OLDEST PAIN-KILLER

DRUG – USE	YEAR - HISTORY
Opium	"bringer of sleep and forgetfulness" Homer, 900 BC.
Multiherbal source of some 200 forms of pain relief	Hippocratic Corpus, 800-400 BC
Willow Bark	Reverend E. Stone began using willow bark, 1763
Aspirin	Hoffman developed commercial aspirin, 1893
Paracetamol	1893
Morphine	1917
"Optimum dose of morphine should be 10mg, 6 hourly intramuscularly post-op"	Henry Knowles Beecher, 1946 (JAMA)

- Morphine
- Buprenorphine
- Dextromoramide
- Dipipanone
- Hydromorphone
- Methadone
- Nalbuphine
- Oxycodone (IR, SR)
- Fentanyl

Oxicodone/naloxone

Tapentadol

British Journal of Anaesthesia **107** (1): 19–24 (2011)
Advance Access publication 30 May 2011 · doi:10.1093/bja/aer126

BJA

CME

An update on analgesics

I. Power*

Royal Infirmary, University of Edinburgh—Anaesthesia, Critical Care and Pain Medicine, 51 Little France Crescent, Edinburgh EH16 4SA, UK

* E-mail: ian.power@ed.ac.uk

"progress in terms of the introduction of new drugs has been incredibly slow"

Power I. Br J Anaesth 2011; 107: 19–24.

Pain 3

Treatment of cancer pain

Russell K Portenoy

Conclusion

Although several decades of experience and research have not changed the consensus that opioid-based pharmacotherapy is the mainstay approach for the long-term treatment of chronic pain in populations with active cancer, there have been striking changes in the clinical approach to this problem. With analgesic strategies integrated into a palliative plan of care, there is increasing hope that patients can experience cancer with a minimum of suffering. Nonetheless, the treatments used have very little supporting evidence and there continues to be a pressing need for more research to provide comparative and long-term data pertinent to current treatments and novel treatment strategies for refractory conditions. Efforts to bring cost-effective strategies to resource-poor areas of the world should have equal priority.

Portenoy RK. Lancet 2011; 377: 2236-47

CANCER PAIN:
DIMENSION OF THE PROBLEM

DIMENSION OF THE PROBLEM

Support Care Cancer (2010) 18:801–810
DOI 10.1007/s00520-009-0712-5

ORIGINAL ARTICLE

Anxiety, depression, and pain: differences by primary cancer

Dena J. Fischer · Dana Villines · Young Ok Kim ·
Joel B. Epstein · Diana J. Wilkie

"Pain is a presenting symptom in 20 to 50 % of cancer patients"

Pain and symptom management

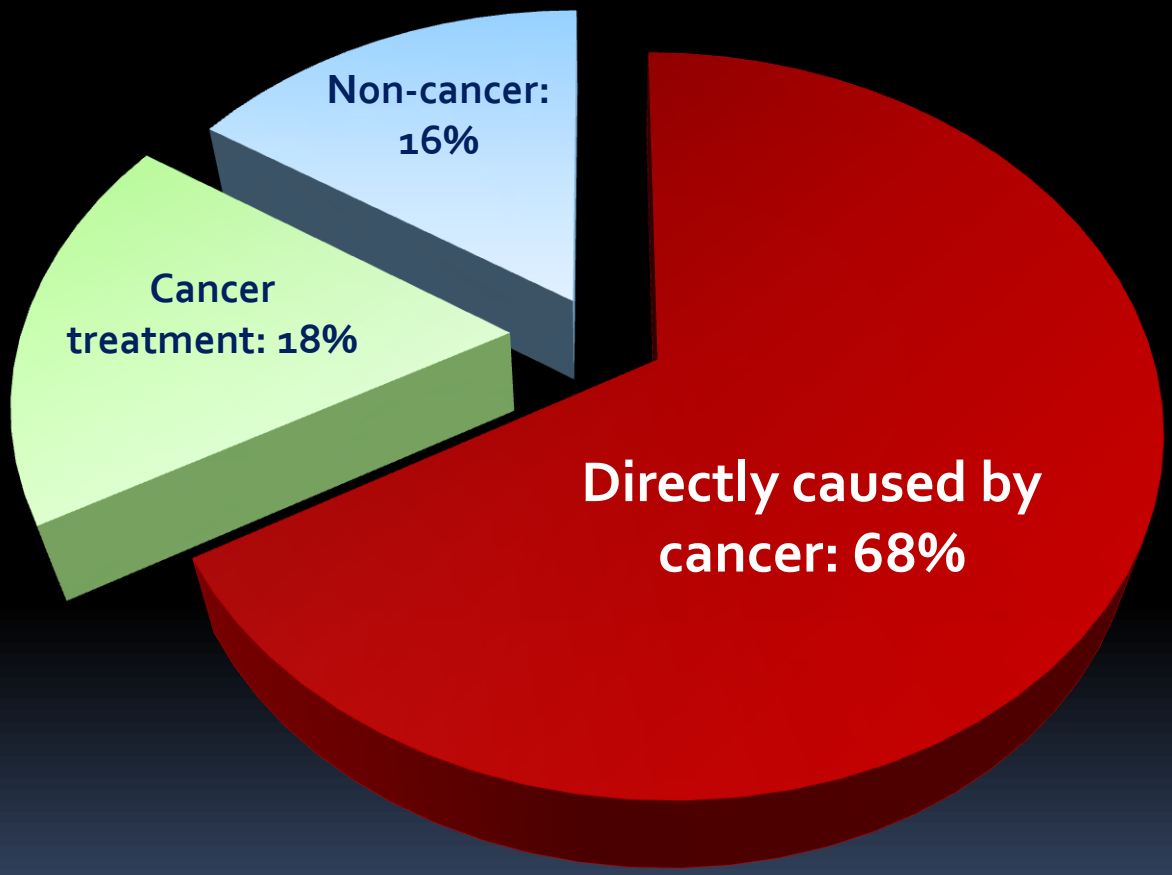
A prospective study of the pathophysiology and clinical characteristics of pain in a palliative medicine population

Terence Gutgsell, MD
Declan Walsh, MSc, FACP, FRCP (Edin)
Donna S. Zhukovsky, MD, FACP
Francisco Gonzales, MD
Ruth Lagman, MD

American Journal of Hospice & Palliative Care
Volume 20, Number 2, March/April 2003

100 cancer patients with pain reported

DIMENSION OF THE PROBLEM
CAUSE OF CANCER PAIN



Gutgsell T Eet al. Am J Hosp Palliat Care. 2003; 20: 140–8.

DIMENSION OF THE PROBLEM

ANATOMIC SITE	%
Chest	20
Abdomen	20
Extremity	20

- Usual pain intensity: moderate to severe 53%
- Intermittent pain: 53%
- Continuous pain: 47%

Gutgsell T Eet al. Am J Hosp Palliat Care. 2003; 20: 140–8.

review

Annals of Oncology 18: 1437–1449, 2007
doi:10.1093/annonc/mdm056
Published online 12 March 2007

Prevalence of pain in patients with cancer: a systematic review of the past 40 years

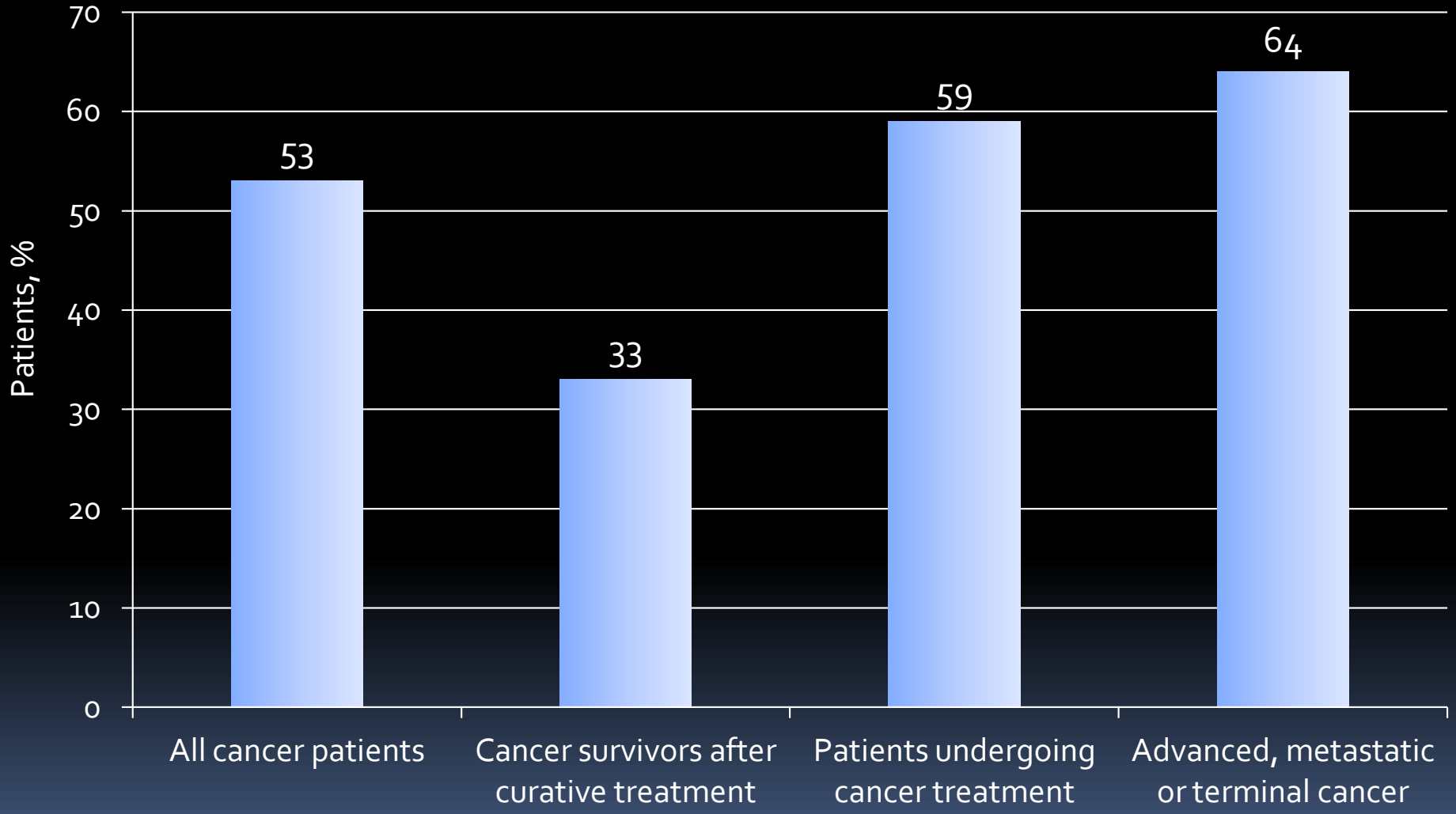
M. H. J. van den Beuken-van Everdingen[1]*, J. M. de Rijke[1], A. G. Kessels[2], H. C. Schouten[3], M. van Kleef[4] & J. Patijn[1]

[1]Pain Management and Research Centre, University Hospital Maastricht; [2]Department of Clinical Epidemiology and Medical Technology Assessment, University Hospital Maastricht; [3]Department of Internal Medicine, University Hospital Maastricht; [4]Department of Anaesthesiology, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands

Received 18 December 2006; revised 11 January 2007; accepted 12 January 2007

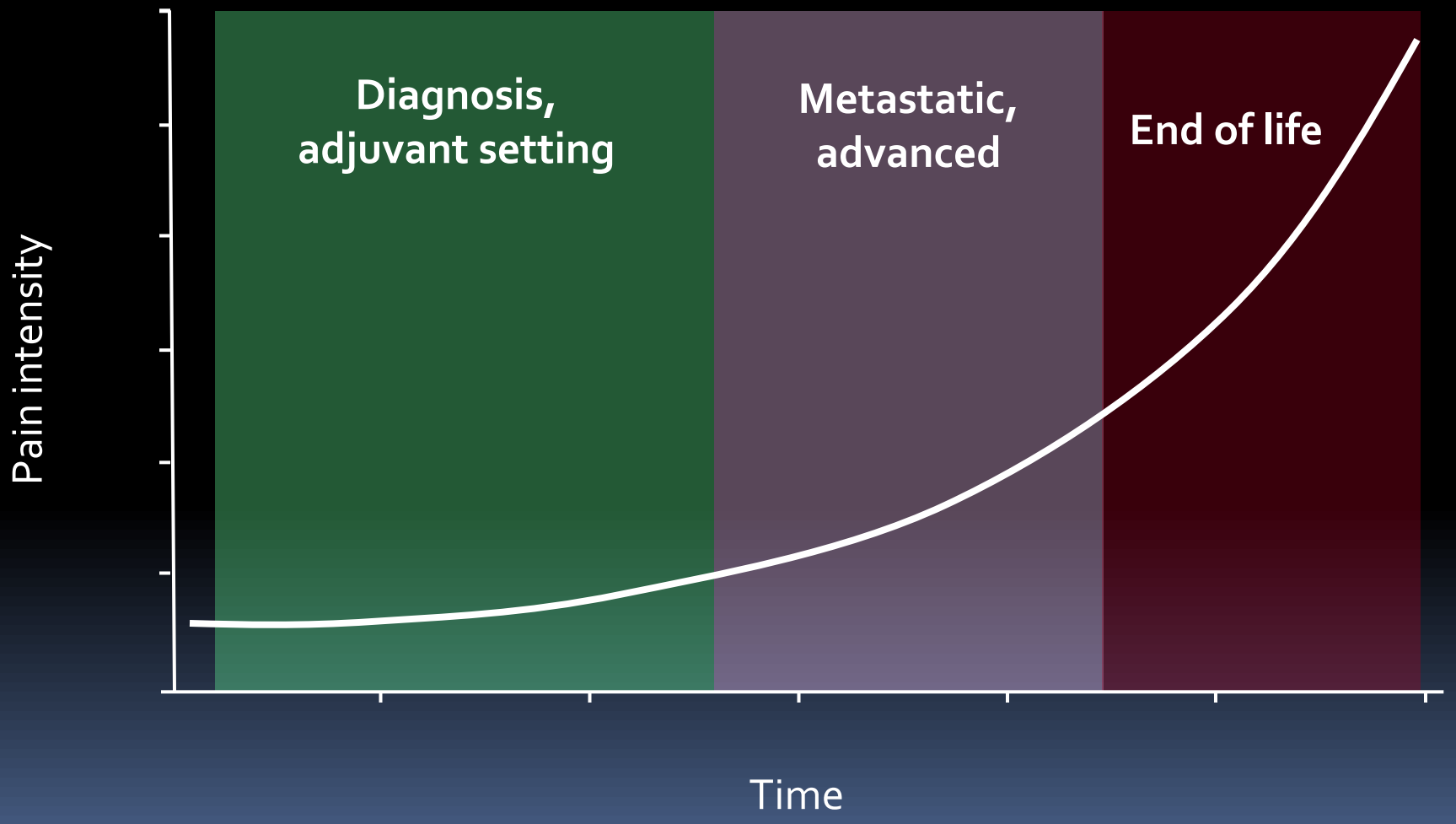
52 studies

PREVALENCE OF CANCER PAIN



van den Beuken-van Everdingen MH et al. Ann Oncol. 2007;18:1437–49

PREVALENCE OF CANCER PAIN



EPIDEMIOLOGY – PREVALENCE OF CANCER PAIN

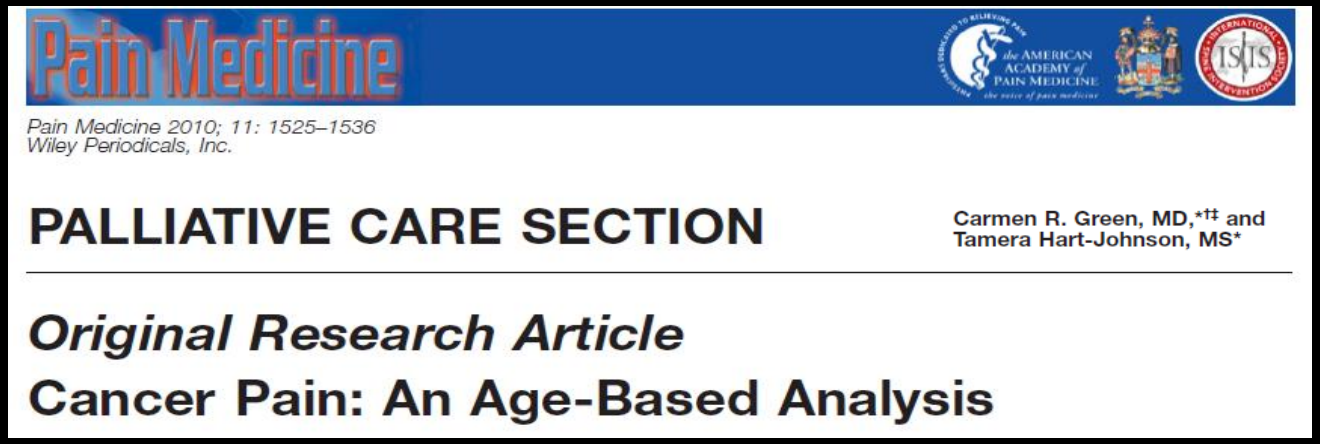
POOLED CANCER PAIN PREVALENCE BY CANCER TYPE

Cancer location	Average pain prevalence, %
Head/neck	70
Gynecological	60
Gastrointestinal	59
Lung/bronchus	55
Breast	54
Urogenital	52

"…although pain was reported by over half of patients with all type of cancer"

van den Beuken-van Everdingen MH et al. Ann Oncol. 2007;18:1437–49

EPIDEMIOLOGY – PREVALENCE OF CANCER PAIN



Pain Medicine

Pain Medicine 2010; 11: 1525–1536
Wiley Periodicals, Inc.

PALLIATIVE CARE SECTION

Carmen R. Green, MD,*†‡ and
Tamera Hart-Johnson, MS*

Original Research Article

Cancer Pain: An Age-Based Analysis

179 pts

- Pain is seen in at least half of patients actively involved in cancer treatment.
- Cancer pain in 65% of patients.
- Patients younger than 65 years were significantly more likely to experience pain compared with older patients.
- More pain flares in younger patients with cancer pain.

Green CR et al. Pain Med 2010; 11: 1525–36.

EPIDEMIOLOGY – CANCER SURVIVORS

BREAST

TIME AFTER TREATMENT	%
First 6 months	26-47
6-12 months	20-23
1-2 years	21-41
2-5 years	19-41

- **54% of prostate cancer survivors up to 5 years after tretament**
- **27% of colorectal cancer survivors more than 5 years after diagnosis**
- **Slightly pain decrease 6 months after treatment among gynecological cacner patients, stable up to 24 months after treatment**

Harrington CB et al. Int J Psychiatry Med 2010; 40: 163–81.

THERE AS BEEN PROGRESS IN PAIN MANAGEMENT ?

review

Annals of Oncology 19: 1985–1991, 2008
doi:10.1093/annonc/mdn419
Published online 15 July 2008

Prevalence of undertreatment in cancer pain. A review of published literature

S. Deandrea[1,2*], M. Montanari[3,4], L. Moja[5] & G. Apolone[3,4]

[1]*Laboratory of Epidemiological Methods, Department of Epidemiology, Mario Negri Institute for Pharmacological Research, Milano;* [2]*Department of Epidemiology, Institute of Medical Statistics and Biometry, University of Milano, Milano;* [3]*Center for the Evaluation and Research on Pain, Department of Oncology, Mario Negri Institute for Pharmacological Research, Milano;* [4]*Laboratory of Translational and Outcome Research, Department of Oncology, Mario Negri Institute for Pharmacological Research, Milano;* [5]*Department of Oncology, Italian Cochrane Centre, Mario Negri Institute for Pharmacological Research, Milano*

An average of 43% of cancer patients receive inappropriate care for cancer

BARRIERS TO CANCER PAIN MANAGEMENT

PATIENT FACTORS

- Reluctance to report pain
- Poor treatment adherence
- Cognitive issues and affective distress may limit reporting
- Fear of addiction or developing tolerance
- Fear of side effects
- Effort to be a "good patient" by tolerating pain
- Belief that doctor should focus on cancer cure rather than pain relief
- Concerns about negative views of family, friends, coworkers if patient uses pain medications

Jacobsen R et al. Medicina. 2009;45:427–33.

BARRIERS TO CANCER PAIN MANAGEMENT

PROVIDER FACTORS

- Poor communication about pain experience
- Preference for weaker analgesics
- Failure to assess pain or use pain-measuring instruments routinely
- Inadequate knowledge about pain management and opioid dosing

Jacobsen R et al. Medicina. 2009;45:427–33.

- PAIN ASSESSMENT
- MANAGEMENT OF CANCER PAIN
- MOLECULES – NEUROBIOLOGY
- OPIOIDS
- “NEW MOLECULES”
- ROUTES OF ADMINISTRATION
- DOSAGE
- MANAGEMENT OF SIDE EFFECTS
- OTHER TREATMENTS FOR CANCER PAIN

- PAIN ASSESSMENT
- MANAGEMENT OF CANCER P
- MOLECULES
- OPIOIDS
- "NEW MOL
- ROUT RATION
- MENT OF SIDE EFFECTS
- OTHER TREATMENTS FOR CANCER PAIN

CACNER PAIN SPECIALISTS
PHARMACOLOGISTS
ANESTESIA SPECIALISTS

21st CENTURY

43 % OF PATIENTS DO NOT RECEIVE ADEQUATE PAIN RELIEF

Deandrea S et al. Ann Oncol 2008; 19: 1985–91.

Randomized Clinical Trial of an Implantable Drug Delivery System Compared With Comprehensive Medical Management for Refractory Cancer Pain: Impact on Pain, Drug-Related Toxicity, and Survival

By Thomas J. Smith, Peter S. Staats, Timothy Deer, Lisa J. Stearns, Richard L. Rauck, Richard L. Boortz-Marx, Eric Buchser, Elena Català, David A. Bryce, Patrick J. Coyne, and George E. Pool for the Implantable Drug Delivery Systems Study Group

Journal of Clinical Oncology, Vol 20, No 19 (October 1), 2002: pp 4040-4049
DOI: 10.1200/JCO.2002.02.118

- **PAIN REDUCTION (VAS)**
  - ↓ 39.1 % for CMM
  - ↓ 51.5 % for IDDS
- **COMPOSITE TOXICITY (CTC)**
  - ↓ 17.1 % for CMM
  - ↓ 50.3 % for IDDS

(P: 0.004)

TRICKS IN PAIN MANAGEMENT

ONCOLOGIC PAIN

A MECHANICISTIC APPROACH

- SOMATIC?
- VISCERAL?
- NEUROPATHIC?

- HISTORY
- PHISICAL EXAMINATION
- DEDICATED TESTING

ONCOLOGIC PAIN

CURRENT TRENDS:

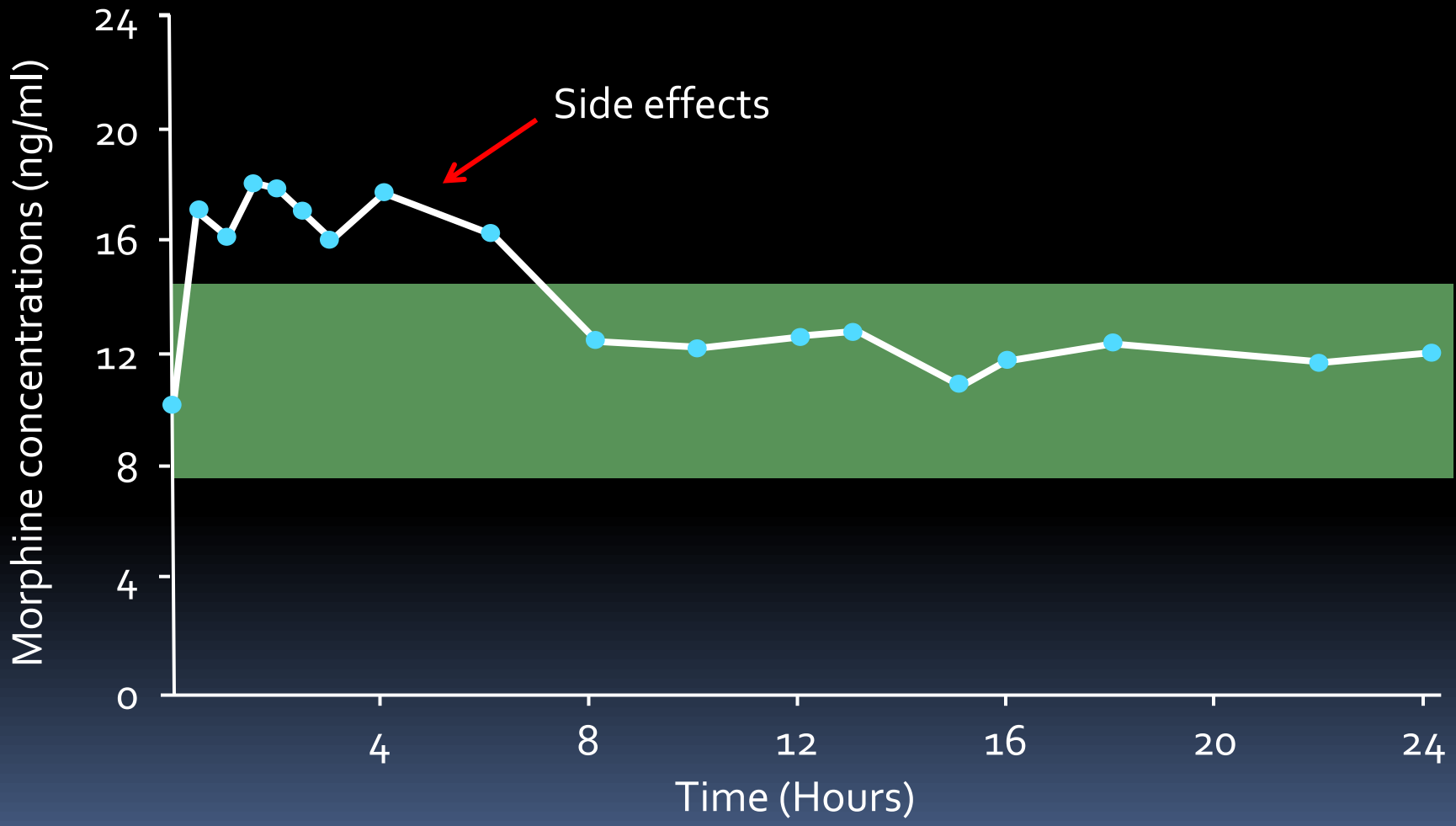
OPIOD THERAPY

STARTING THERAPY

"If you look at all the studies, doesn't matter – cancer patient, osteoarthritis low back pain – 37% dropout rates during the first 2 weeks of therapy regardless of the drug – oxycodone, morphine-controlled release, oxymorphone-controlled release. And that is because there is a high incidence of side effects".

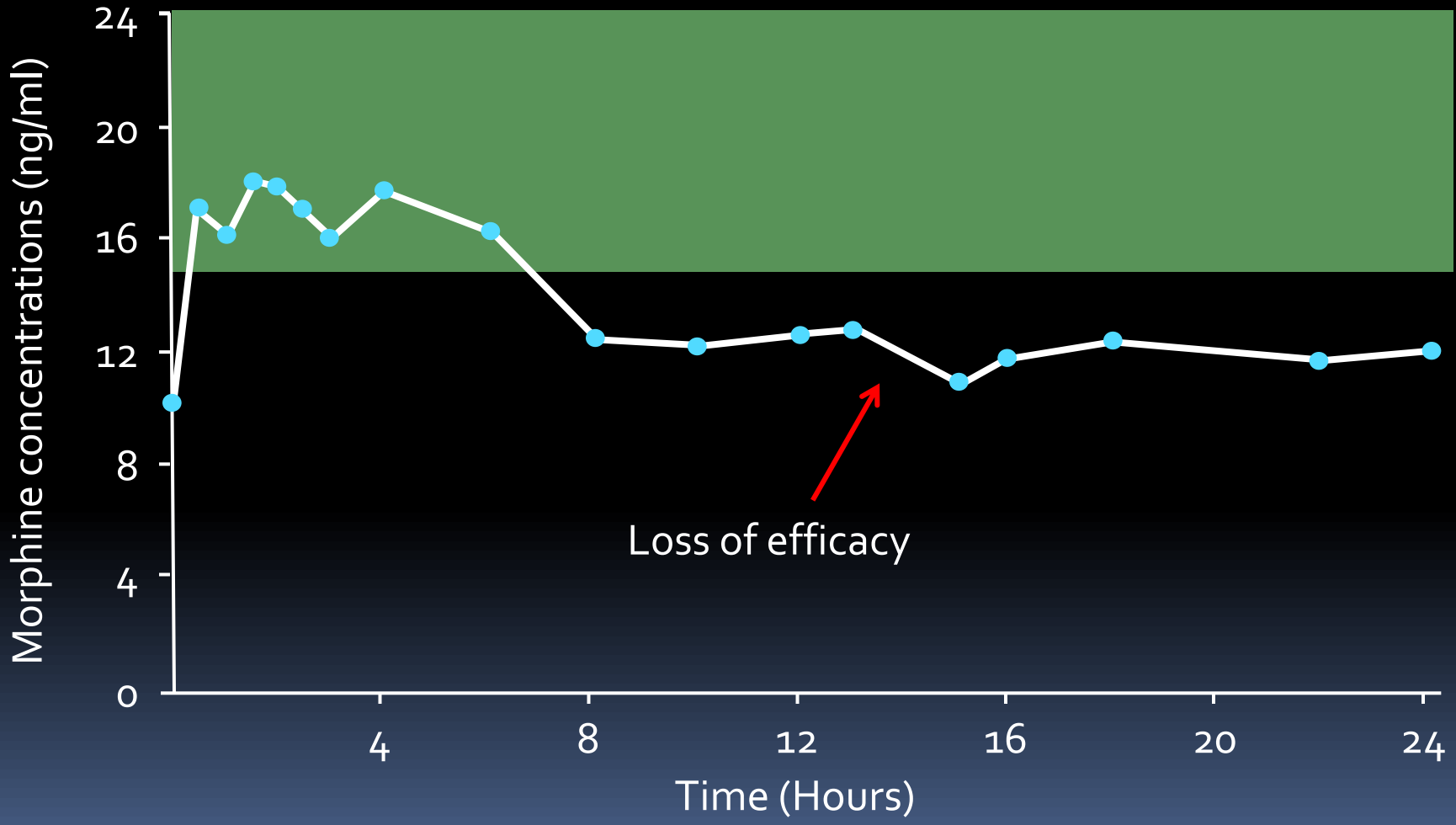
Oscar de Leon Cassola, Roswell Park Cancer Institute, NY

PHARMACOKINETIC AND PHARMACODYNAMIC RELATIONSHIP



De Leon-Cassola O. Oncol Nurs Forum 2008; 35 (s): 7-12.

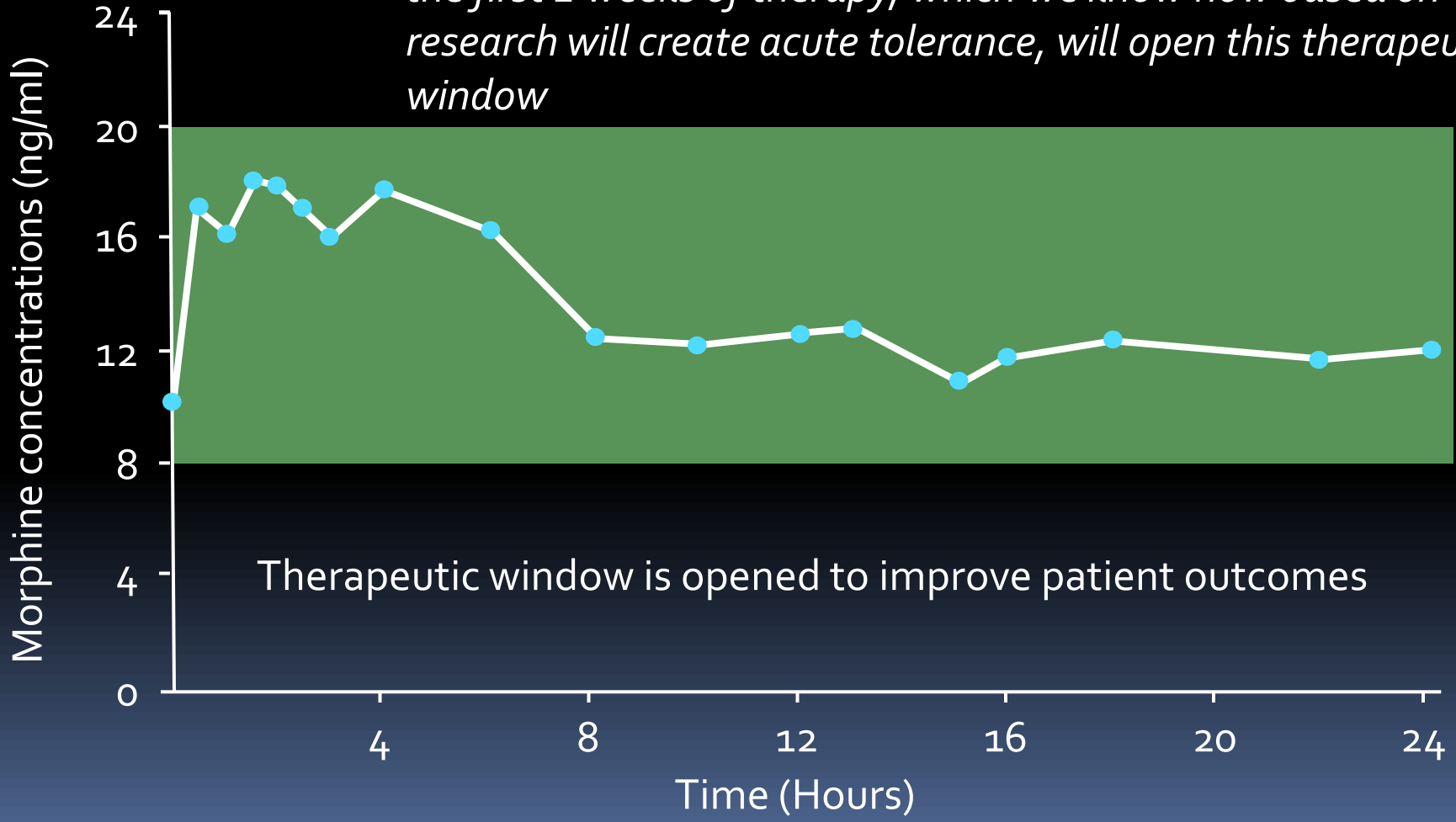
PHARMACOKINETIC AND PHARMACODYNAMIC RELATIONSHIP



De Leon-Cassola O. Oncol Nurs Forum 2008; 35 (s): 7-12.

PHARMACOKINETIC AND PHARMACODYNAMIC RELATIONSHIP

For instance, using short-acting medications, opioids, during the first 2 weeks of therapy, which we know now based on research will create acute tolerance, will open this therapeutic window



De Leon-Cassola O. Oncol Nurs Forum 2008; 35 (s): 7-12.

DOSE TITRATION

- **Monitor and document pain scores.**
- **Monitor and document use of rescue medications.**
- **Monitor and document psychosocial variables of functioning.**
  sleep
  activities of daily living
  (this will be the most important piece of information to make decisions regarding your titration of the drugs)
- **Monitor and document risk of drug abuse/diversion.**
- **Adjust dose of the long-acting opiate based on pain scores and amount of rescue medication used.**
- **Increase dose and rescue as needed**

PEARLS

- Morphine therapy over time
- Morphine therapy in patients with renal dysfunction
- Patients receiving multiple medications metabolized by the CYP450 system
- Implementing and stopping transdermal fentanyl therapy
- Methadone therapy

Oscar de Leon Cassola, Roswell Park Cancer Institute, NY

PEARLS

- Morphine therapy over time
- Morphine therapy in patients with renal dysfunction
- **PATIENTS RECEIVING MULTIPLE MEDICATIONS METABOLIZED BY THE CYP450 SYSTEM**
- Implementing and stopping transdermal fentanyl therapy
- Methadone therapy

Oscar de Leon Cassola, Roswell Park Cancer Institute, NY

OPIOD METABOLISM

Opioid	Phase 1 metabolism	Phase 2 metabolism	Comment
Morphine[12]	None	Glucuronidation via UGT2B7	
Codeine[13]	CYP2D6	None	
Hydrocodone[14]	CYP2D6	None	One of the metabolites of hydrocodone is hydromorphone, which undergoes phase 2 glucuronidation
Oxycodone[11]	CYP3A4 CYP2D6	None	Oxycodone produces a small amount of oxymorphone, which must undergo subsequent metabolism via glucuronidation
Methadone[15]	CYP3A4 CYP2B6 CYP2C8 CYP2C19 CYP2D6 CYP2C9	None	CYP3A4 and CYP2B6 are the primary enzymes involved in methadone metabolism; other enzymes play a relatively minor role
Tramadol[16]	CYP3A4 CYP2D6	None	
Fentanyl[10]	CYP3A4	None	
Hydromorphone[17]	None	Glucuronidation via UGT2B7	
Oxymorphone[18]	None	Glucuronidation via UGT2B7	

CYP = cytochrome P450; UGT2B7 = uridine diphosphate glucuronosyltransferase 2B7.

CYP2D6 and CYP34A4 CRITICALLY IMPORTANT

SUBSTRATES AND INHIBITORS: Increase opioid concentrations
INDUCERS: Hypermetabolize

Smith HS. Mayo Clin Proc 2009; 84: 613-24.

CYP3A4

SUBSTRATES

CCBs
Amlodipine
Diltiazem
Nicardipime
Nifedipime
Verapamil

Statins
Atorvastatin
Lovastatin
Simvastatin

Other Cardiov.
Amiodarone
Digoxine
Ivabradine
Quinidine
Warfarin

Phosphodiest.inh.
Sildenafil

Benzodiaz.
Alprazolam
Clonazepam
Midazolam
Triazolam

SSIRs
Citalopram
Fluoxetine

Other Psyc.
Bromocriptine
Carbamazepine
Haloperidol
Risperidone
Valproate
Venlafaxine
Zolpidem
Zopiclone

Retrovirals

Antibiotics
Azithromycin
Clarithromycin
Erythromycin

Antifungal
Itraconazole
Ketoconazole

Chemother.
Cyclophosphamide
Docetaxel
Doxorubicin
Etoposide
Gefitinib
Ifosfamide
Paclitaxel
Tamoxifen
Vinblastine
Vindesine

INHIBITORS

CCBs
Amlodipine
Diltiazem
Nicardipime
Nifedipime
Verapamil

Statins
Simvastatin

Antiarrythm.
Amiodarone
Quinidine

Psychiatr.
Bromocriptine
Comazepam
Fluoxetine
Haloperidol
Nortriptyline
Sertraline

Antibiotics
Ciprofloxacin
Clarithromycin
Erythromycin

Antifungal
Nifedipime

Retrovirals

Chemother.
Imatinib
Irinotecn
Tamoxifen

Hormon
Etinilestradiol
Levonogestrel
Raloxifene

Other
Cimetidine

Foods
Bergamottin (grapefruit)

INDUCERS

Statins

Antiretroviral

Hypnotics

Anticonvusant
Carbamazepine
Oxcarbazepine
Phenobarbital
Phenitoin
Valproic ac.

Foods
Caffeine

Adapted from Zhou SF et al. Ther Drug Monit 2007; 29: 687-710.

CYP3A4

Drug	Relative tumor activity	P450 Inactivation	P450 Activation
Etoposide	Testicular, lung, lymphoma, osteosarcoma	CYP34A4	
Paclitaxel	Ovary, Breast, Lung, Kaposi's	CYP34A4	
Docetaxel	Breast, lung, prostate, stomach, H&N	CYP34A4	
Tamoxifen	Breast	CYP34A4	
Vinblastine	Breast, bladdder, lung, lymphoma	CYP34A4	
Cyclophosphamide	Breast, sarcoma, ovarian		CYP34A4
Ifosfamide	Sarcoma		CYP34A4 and CYP2B6
Doxorubicin	Breast, sarcoma, ovarian		CYP34A4

CYP2D6

SUBSTRATES

Anti-arrhythmics
Encaidine
Flecainide
Lidocaine
Mexiletine
Propafenone
Sparteine

Beta Blockers
Alprenolol
Carvedilol
Metoprolol
Propranolol
Timolol

Antipsychotics
Aripiprazole
Haloperidol
Perphenazine
Risperidone

Antipsychotics
Thioridazine
Zuclopenthixol

SSRIs
Duloxetine
Venlafaxine
Fluoxetine
Fluvoxamine
Paroxetine

Tricyclics
Amitriptyline
Amoxapine
Clomipramine
Desipramine
Doxepine
Imipramine
Nortriptyline

Others
Amphetamine
Clorphenamine
Dexomethorphan
Metoclopramide
Phenformin
Tamoxifen

INHIBITORS

Anti-arrhythmics
Amiodarone
Quinidine

Antipsychotics
Chlorpromazine
Reduced-Haloperidol
Levomepromazine

SSRIs
Citalopram
Escitalopram
Fluoxetine
Paroxetine
Sertraline

Tricyclics
Clomipramine

Other antidepressants
Bupropione

Others
Clorpheniramine
Cimetidine
Ranitidine
Celecoxib
Doxorubicin
Ritonavir
Ticlopidine

INDUCERS

Rifampicin
Dexamethasone

Adapted from Flockhart DA. Drug interactions: cytochromr P450 drug interaction table. Indiana University School of Medicine. http://medicine.iupui.edu/clinpharm/ddis/table.aspx

PEARLS

- Morphine therapy over time
- Morphine therapy in patients with renal dysfunction
- Patients receiving multiple medications metabolized by the cyp450 system
- Implementing and stopping transdermal fentanyl therapy
- **METHADONE THERAPY**

Negative chronotropic effects

QTc interval prolongation
(Polymorphic VT, torsade de pointes)

Oscar de Leon Cassola, Roswell Park Cancer Institute, NY

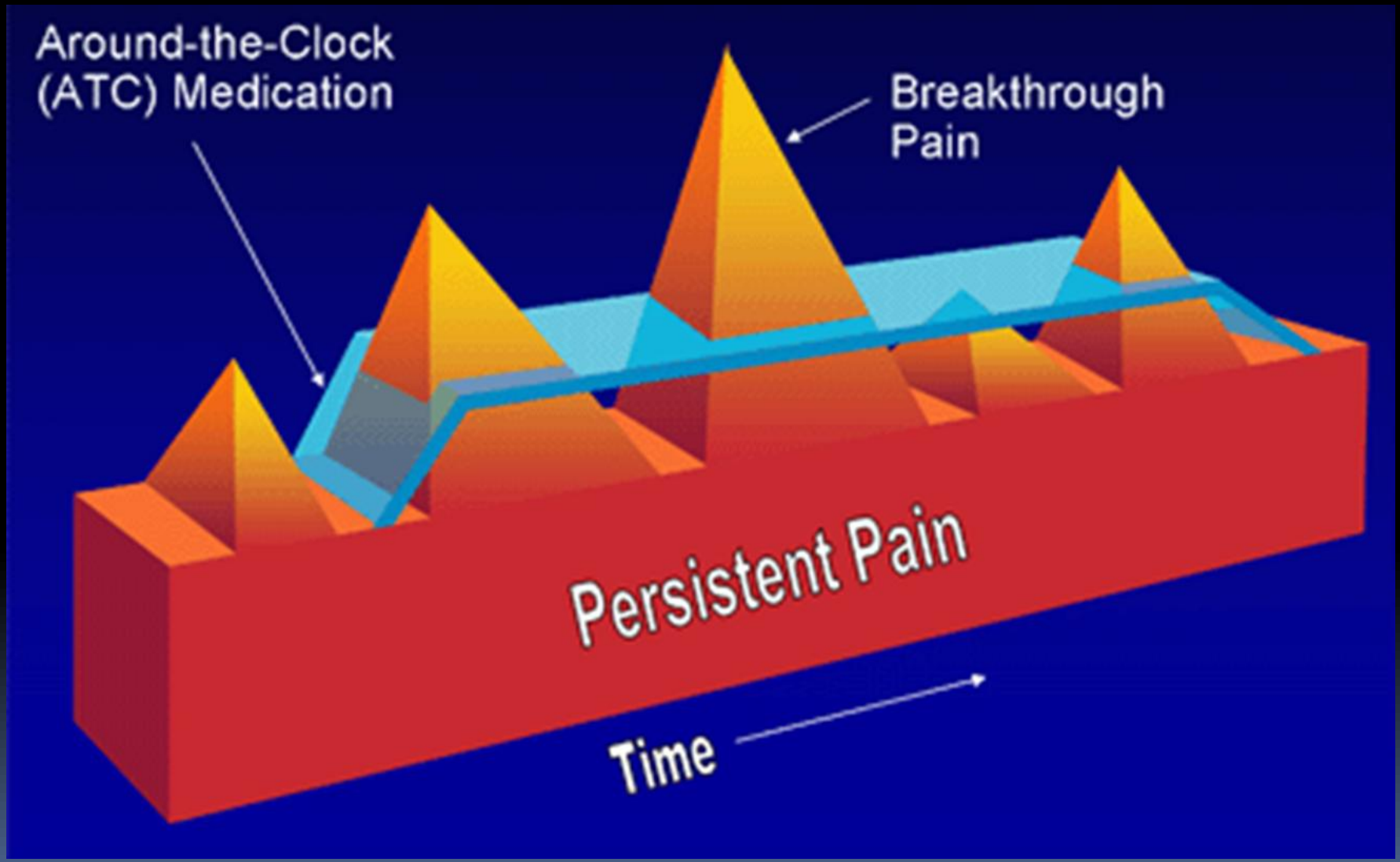
Table. Some Common Drugs That in Combination May Prolong the QT Interval.

Commonly Used Inhibitors of Cytochrome P-450 Enzymes	Cytochrome P-450 Enzymes Inhibited*
Amiodarone	1A2, 2C9, 2D6, 3A4
Antiretroviral agents	
Amprenavir	3A4
Indinavir	3A4
Nelfinavir	3A4
Ritonavir	2D6, 3A4
Saquinavir	3A4
Antifungal agents	
Fluconazole	2C9, 3A4
Itraconazole	3A4
Ketoconazole	3A4
Terbinafine	2D6
Calcium-channel antagonists	
Diltiazem	3A4
Verapamil	3A4
Macrolide antibiotics	
Erythromycin	3A4
Clarithromycin	3A4
Selective serotonin-reuptake–inhibitor antidepressants	
Fluoxetine	2C19, 2D6
Fluvoxamine	1A2, 2C19, 2C9, 3A4
Paroxetine	2D6
Sertraline	2C9, 2D6
Quinolone antibiotics	
Ciprofloxacin	1A2, 3A4

Cytochrome P-450 Enzymes Involved in Drug Metabolism	QT-Interval–Prolonging Drugs Metabolized by Major Cytochrome P-450 Enzymes
1A2	Amitriptyline, haloperidol, imipramine, clozapine
2C9	Amitriptyline, tamoxifen
2D6	Amitriptyline, desipramine, imipramine, haloperidol, thioridazine, tamoxifen
3A4	Cisapride, disopyramide, quinidine, pimozide, tamoxifen, erythromycin, clarithromycin

Liu b et al. N Engl J Med 2004; 351: 1053-56.

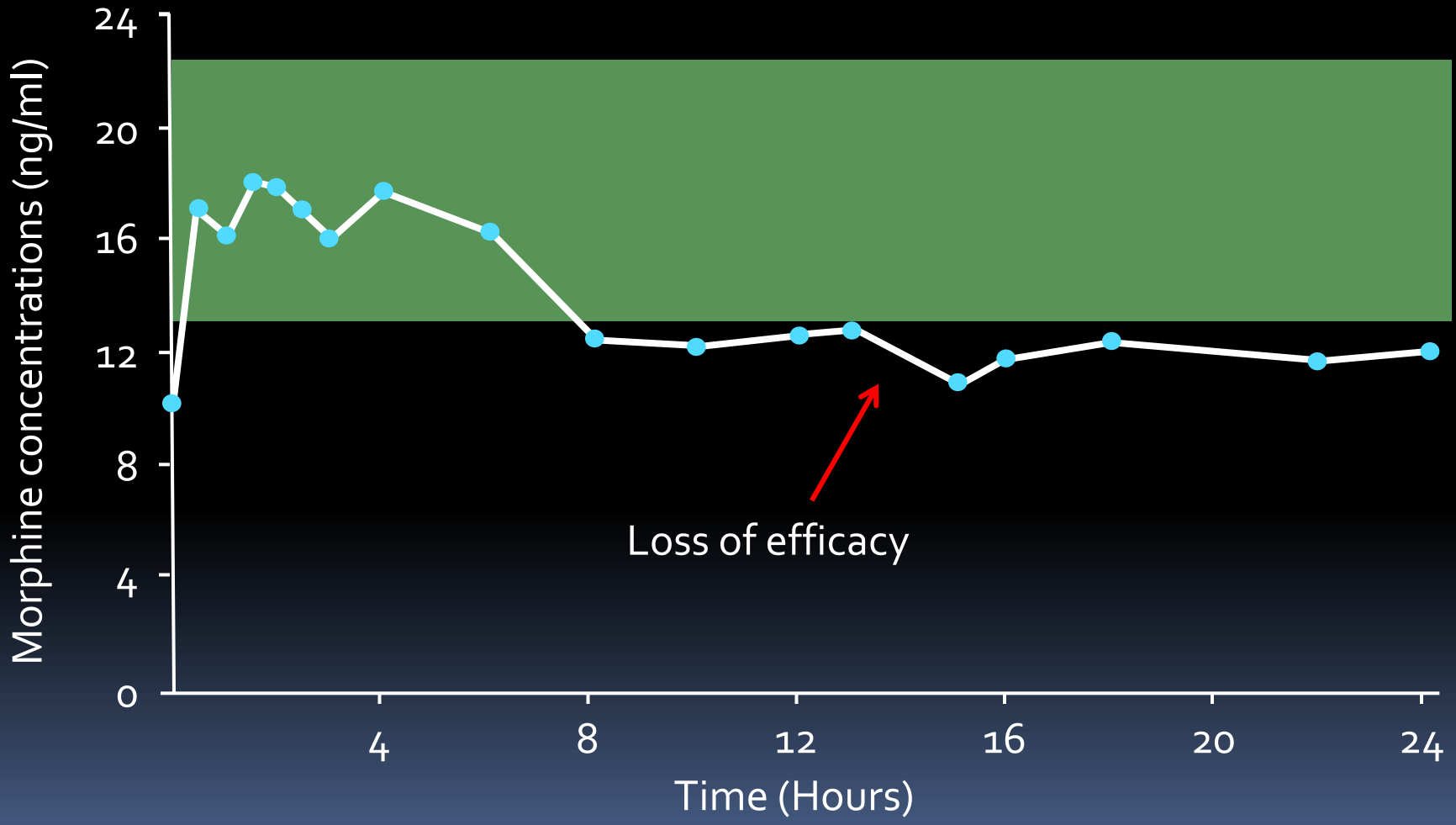
BREAKTHROUGH PAIN



BREAKTHROUGH PAIN

- END OF DOSE FAILURE
- INCIDENTAL PAIN
- BREAKTHROUGH PAIN

END OF DOSE FAILURE



De Leon-Cassola O. Oncol Nurs Forum 2008; 35 (s): 7-12.

CHARACTERISTICS OF TRUE BREAKTHROUGH PAIN

- MODERATE TO SEVERE INTENSITY
- RAPID ONSET (< 3 MINUTES IN 45% OF PATIENTS)
- RELATIVELY SHORT DURATION (< 30 min)
- FREQUENCY: 1-4 EPISODES PER DAY
- ASSOCIATED WITH MORE SEVERE PAIN CONDITIONS

ALL BREAKTHROUGH PAIN EVENTS ARE SOMATIC IN ORIGIN AND, THEREFORE, SHOULD BE TRETAED WITH OPIOIDS

Oscar de Leon Cassola, Roswell Park Cancer Institute, NY

CURRENT TRENDS

ADJUVANT THERAPY

ADJUVANT THERAPY

Triciclics antidepressants:
side effects profile dictates choice

RANDOMIZED CLINICAL TRIALS INVOLVING FIRST- AND SECOND-LINE MEDICATIONS FOR PATIENTS WITH NEUROPATHIC PAIN

	Antidepressants			Calcium Channel Ligands		Topical Lidocaine Patch 5%	Opioid Receptor Agonists	
	Tricyclic Antidepressants	Duloxetine	Venlafaxine	Gabapentin	Pregabalin		Opioid Analgesics	Tramadol
Peripheral NP								
Painful DPN	Positive	Positive	Positive	Both	Both	—	Positive	Positive
PHN	Positive	—	Negative	Positive	Both	Positive†	Positive	Positive
Painful polyneuropathy	Positive	—	Positive	Positive	—	Positive†	Positive	Positive
Phantom limb pain	Negative	—	—	Both	—	—	Positive	Positive
Postmastectomy pain	Positive	—	Negative	—	—	—	—	—
Guillain-Barré syndrome	—	—	—	Positive	—	—	—	—
Neuropathic cancer pain	Negative	—	—	Positive	—	—	—	—
Complex regional pain syndrome (type I)	—	—	—	Negative	—	—	—	—
Chronic lumbar root pain	Negative	—	—	—	—	—	Negative	—
Chemotherapy-induced neuropathy	Negative	—	—	Negative	—	—	—	—
HIV neuropathy	Negative	—	—	Negative	—	—	—	—
Central NP								
Central poststroke pain	Positive	—	—	—	Positive	—	—	—
Spinal cord injury pain	Negative	—	—	Positive	Positive	—	—	—

O'Connor AB et al. Am J Med 2009; 122 (10S): 22-32.

TRICYCLIC ANTIDEPRESSANTS

Drug	Sedation	Ach effect	Orthostatism	Cardiac
Amitriptyline	+++	++++	+++	+++
Nortriptyline	+++	+	+	++
Desipramine	+	+	++	++
Doxepin	+++	++	++	++

Alvarez W Jr et al. Pharmacotherapy 2003; 23: 754-771.

ADJUVANT THERAPY

ANTICONVULSANTS

- TITRATE TO MAXIMUM DOSE
- SIDE EFFECTS MAY BE A PROBLEM
- HOWEVER, THEY SUBSIDE

RANDOMIZED CLINICAL TRIALS INVOLVING FIRST- AND SECOND-LINE MEDICATIONS FOR PATIENTS WITH NEUROPATHIC PAIN

	Antidepressants			Calcium Channel Ligands		Topical Lidocaine Patch 5%	Opioid Receptor Agonists	
	Tricyclic Antidepressants	Duloxetine	Venlafaxine	Gabapentin	Pregabalin		Opioid Analgesics	Tramadol
Peripheral NP								
Painful DPN	Positive	Positive	Positive	Both	Both	—	Positive	Positive
PHN	Positive	—	Negative	Positive	Both	Positive†	Positive	Positive
Painful polyneuropathy	Positive	—	Positive	Positive	—	Positive†	Positive	Positive
Phantom limb pain	Negative	—	—	Both	—	—	Positive	Positive
Postmastectomy pain	Positive	—	Negative	—	—	—	—	—
Guillain-Barré syndrome	—	—	—	Positive	—	—	—	—
Neuropathic cancer pain	Negative	—	—	Positive	—	—	—	—
Complex regional pain syndrome (type I)	—	—	—	Negative	—	—	—	—
Chronic lumbar root pain	Negative	—	—	—	—	—	Negative	—
Chemotherapy-induced neuropathy	Negative	—	—	Negative	—	—	—	—
HIV neuropathy	Negative	—	—	Negative	—	—	—	—
Central NP								
Central poststroke pain	Positive	—	—	—	Positive	—	—	—
Spinal cord injury pain	Negative	—	—	Positive	Positive	—	—	—

O'Connor AB et al. Am J Med 2009; 122 (10S): 22-32.

CANCER PAIN MANAGEMENT

Drug	Starting dose	Target dose	Side effects*	Renal exccretion	Hepatic pathways
Gabapentin	100-300	3600	Weight gain, twitching	> 95%	No
Oxcarbazepine	300	2400	Hypo Na+, SJS, EM	30%	Yes, ~ 50%
Pregabalin	50-100	900	Visula defects, weight gain	> 95%	No

* Dizziness, sedation, ataxia and diplopia

Mc Greeney BEet al. J Pain Symptom Mamnage 2009; 38 (2s): 15-27.

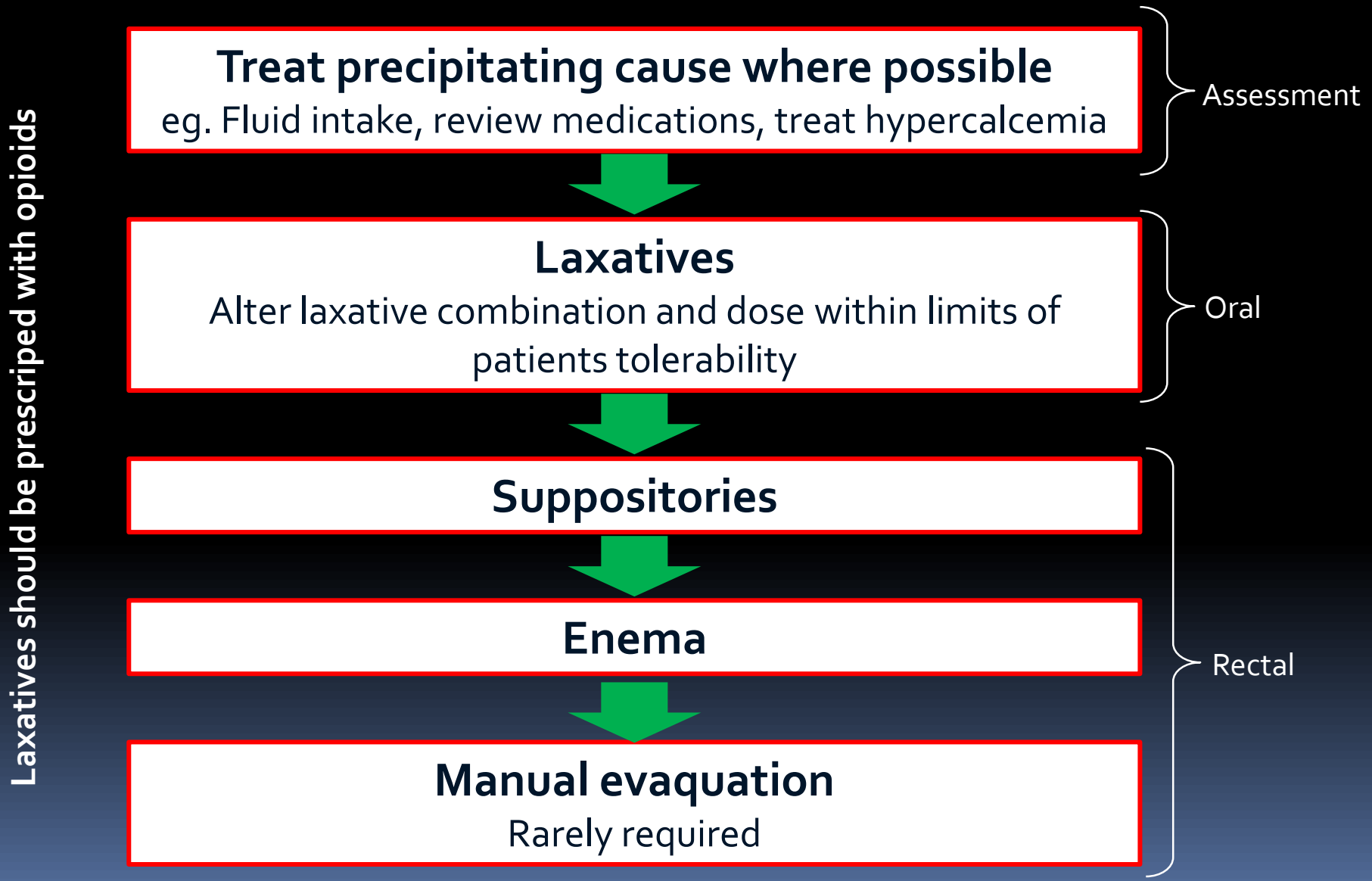
ADJUVANT THERAPY

STEROIDS

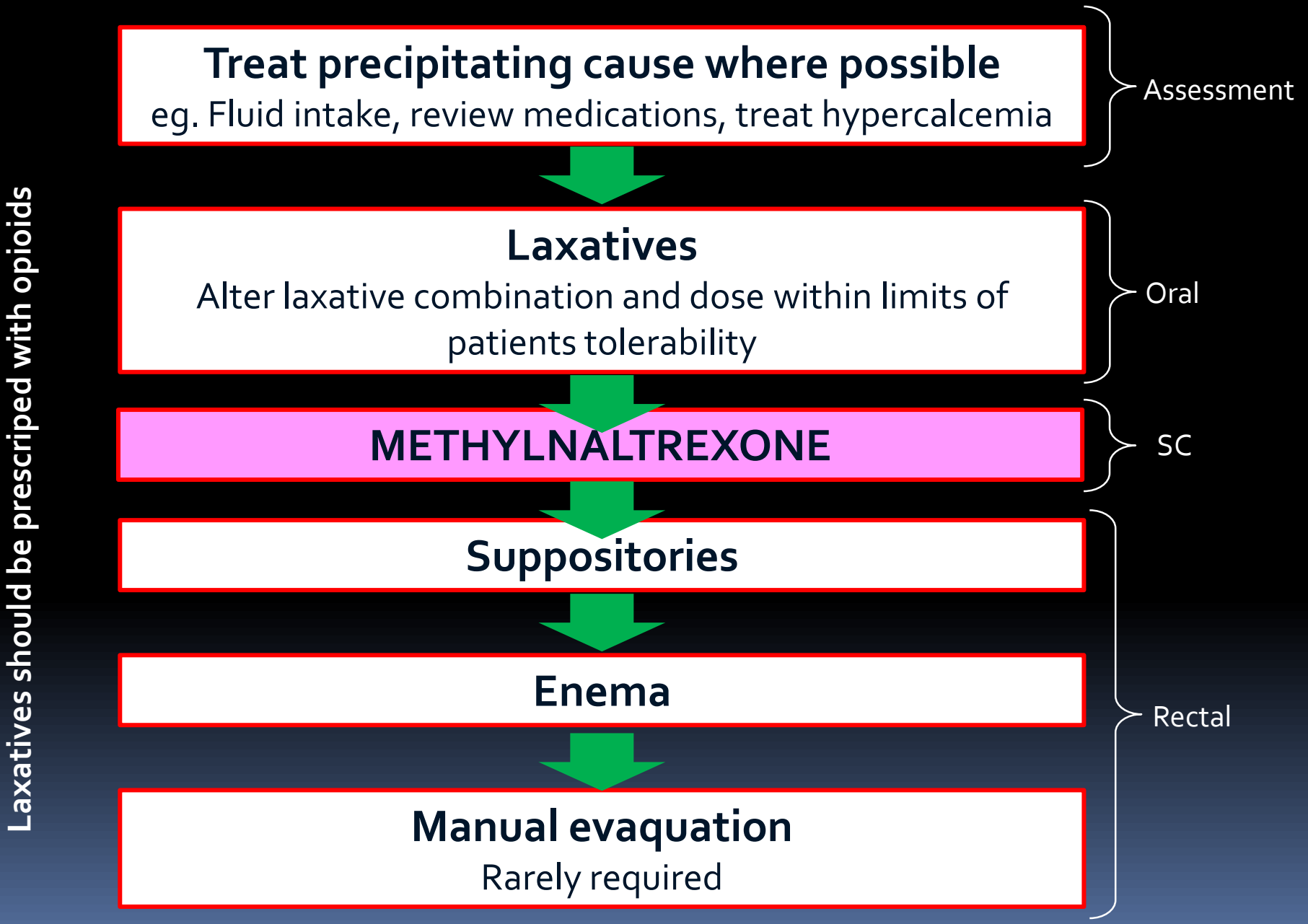
PATIENT FOLLOW-UP: THE FOUR A's

- **A**NALGESIA
  (pain relief)
- **A**CTIVITIES OF DAILY LIVING
  (psycosocial functioning)
- **A**DVERSE EFFECT
  (side effects)
- **A**BERRANT DRUG TAKING
  (addiction-related outcomes)

TREATMENT OPTIONS FOR OIC IN CANCER PAIN



TREATMENT OPTIONS FOR OIC IN CANCER PAIN



METHYLNALTREXONE DOSING SCHEDULE

The recommended dose is:

- 8 mg (for pts weighting 38-61 Kg)
- 12 mg (for pts weighting 62-114 Kg)
- Pts whose weight falls outside of the range should be dosed at 0,15 mg/kg

- Methylnaltrexone should be added to induce prompt bowel movement when response to laxative therapy has been insufficient
- The usual administration schedule is one single dose every other day. Doses may also be given with longer intervals , as per clinical need
- Patients may receive two consecutive doses 24 hours apart, when there as been no response (bowel movement) to the dose on the preceding day
- Local clinical guidelines may be taken into consideration

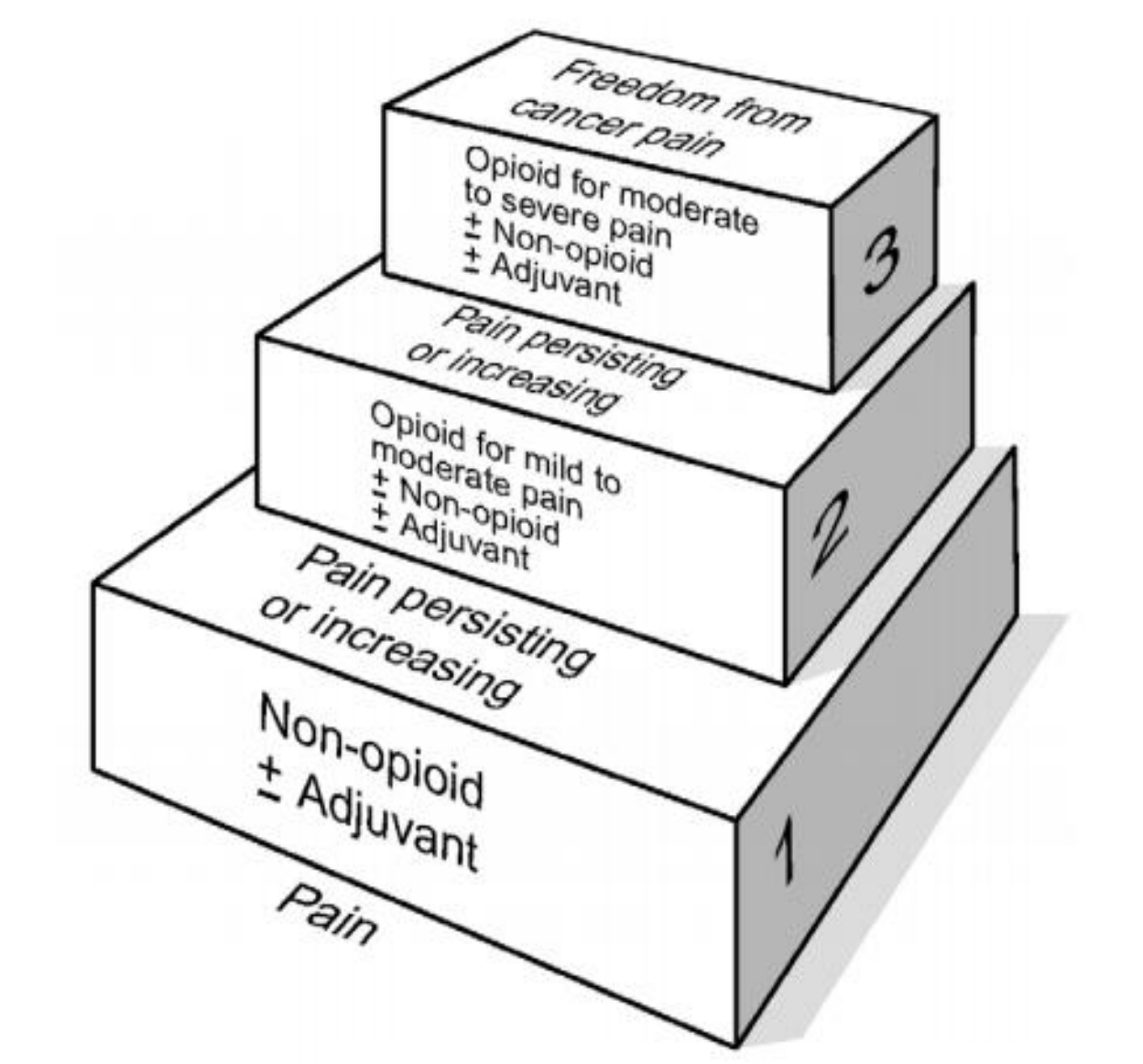
Miles CL et al. Cochrane Database Syst Rev 2006; 4: CD003448.

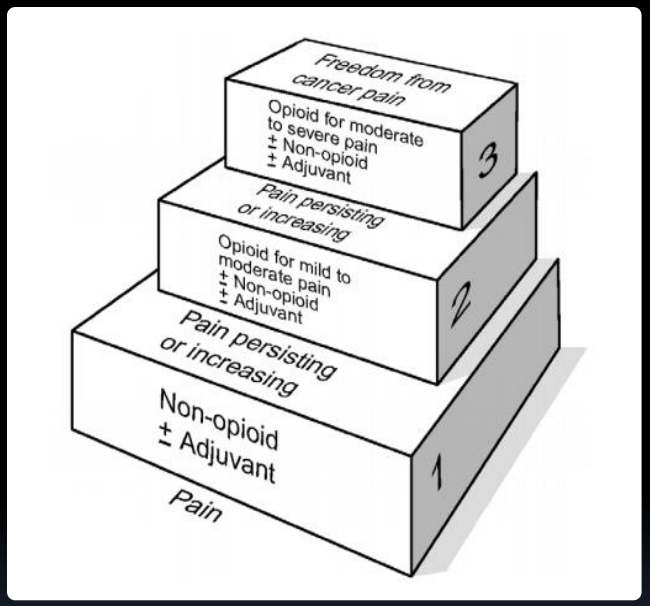
Thomas J et al. N Engl J Med 2008; 358: 2332-42

CANCER PAIN MANAGEMENT CONCLUSIONS

- CURRENT PHARMACOLOGIC THERAPEUTHIC REGIMENS MAY BE IMPLEMENTED IN PATIENTS WITH PAIN-RELATED TO CANCER WITH A HIGH SUCCESS RATE – 90-95%
- THUS, 5-10% WILL NEED AN INVASIVE PROCEDURE
- THE KNOWLEDGE IS CONTINUOSLY EVOLVING, RESULTING IN BETTER PAIN CONTROL

WHO ANALGESIC LADDER




Freedom from cancer pain
Opioid for moderate to severe pain
± Non-opioid
± Adjuvant
3
Pain persisting or increasing
Opioid for mild to moderate pain
± Non-opioid
± Adjuvant
2
Pain persisting or increasing
Non-opioid
± Adjuvant
1
Pain

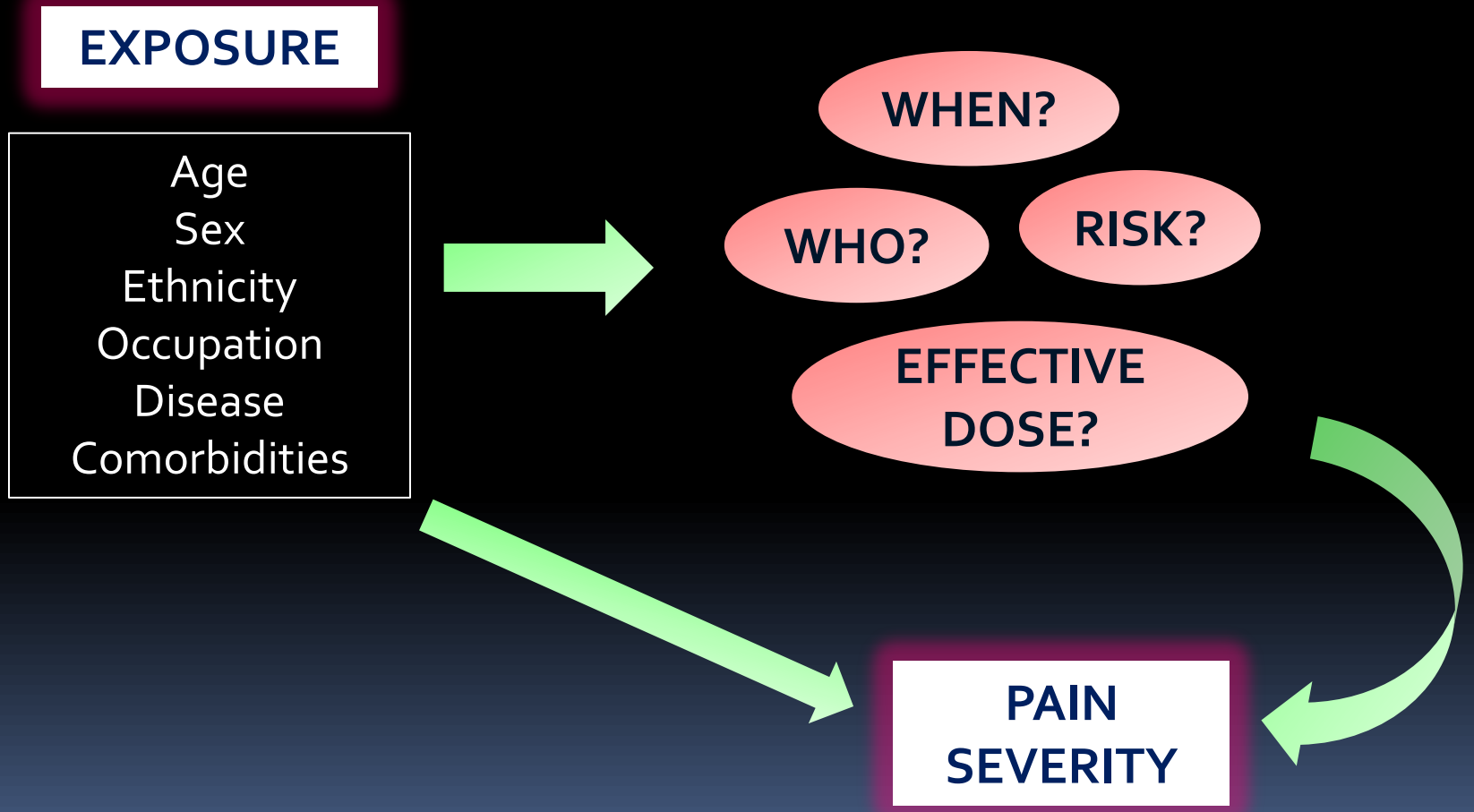
GENETIC AND NONGENETIC DETERMINANTS OF CANCER PAIN MANAGEMENT

APPROACH TO EPIDEMIOLOGY OF PAIN

1990S → 2000S

TRADITIONAL → MOLECULAR → INTEGRATIVE

TRADITIONAL EPIDEMIOLOGY OF PAIN



Human Genome Project

COMPLETION OF HUMAN GENOME PROJECT

IDENTIFY THE ENTIRE SET OF GENES IN DNA

ANALYZE GENETIC VARIATIONS AMONG HUMANS

DISSEMINATE GENOME INFORMATION

EXAMINE ETHYCAL, SOCIAL AND LEGAL ISSUES

EACH PERSON'S GENOME IS SLIGHTLY DIFFERENT

- WHICH DIFFERENCES ALTER FUNCTION?
- WHICH DIFFERENCES MATTER?

GENETIC BACKGROUND CAN BE USED IN:

- **ASSOCIATION STUDIES**
  Variant and risk of disease

- **OUTCOME STUDIES**
  Predict clinical outcomes
  Determine drug response
  Assist in the clinical decision making
  Tailor therapeutics

- **CLINICAL GOALS OF PHARMACOGENETICS**
  Avoid adverse drug reactions
  Maximize drug efficacy
  Select responsive patients

GENETIC VARIATION

- **PAIN TRAITS ARE MAINLY**
  - Polygenic (influenced by several genes, the effect may be additive or interactive)
  - Multifactorial (both genetic and environmental factors contribute)

- **SOME ARE (but rarely)**
  - Monogenic

DEVELOPING GENETICS AS CLINICAL TOOL

- **BEGIN WITH PHYSIOLOGY**
  - What are the critical genes to be examined?
- **CHOOSE THE RIGHT TARGET**
  - Functional polymorphisms/variants
  - Reasonable allelic frequency
- **THINK ABOUT STUDY DESIGN**
  - End points
  - Study number
  - Statistical analysis

CANCER PAIN

Population	Candidate Genes	Outcome	Results
Lung (n: 446 non-Hispanic) [1]	IL6, IL8; TNFα	Severe pain (≥ 7)	IL8-251 T/A OR 2.35 (95% CI, 1.1-5.0)
Pancreas (n: 156 non-Hispanic) [2]	7 cytokine genes; 13 SNPs	Severe pain (≥ 7)	IL8-251 T/A OR 2.43 (95% CI, 1.3-4.7)
Lung (n: 677 non-Hispanic) [3]	37 inflammation genes; 59 SNPs	Severe pain (≥ 7)	PTGS2 exon10+837 T>C OR: 0.33 (95% CI 0.11-0.97) TNFα – 308GA OR 1.67 (95% CI 1.08-2.58) NFKBIA Ex6 + 50C>T OR 0.64(95% CI 0.43-0.93)

[1]Reyes-Gibby CC et al. Cancer Epidemiol Biomarker Prev 2007;16: 2745-51.

[2]Reyes-Gibby CC et al. J Pain Symptom Manage 2009; 894-902.

[3]Reyes-Gibby CC et al. Cancer Epidemiol Biomarker Prev 2009;18: 2636-42.

NONGENETIC FACTORS

Variable	Pain severity	OR (95% CI)	*P*
	Severe/ nonsevere		
Stage of disease			
Early stage	34/291	1.0	
Advanced stage	69/252	2.34 (1.50-3.65)	0.001
Age (y)			
>50	71/462	1.0	
≤50	35/109	2.10 (1.32-3.30)	0.002
Sex			
Male	47/304	1.0	
Female	59/267	1.43 (0.99-2.16)	0.06
Comorbidities			
Heart disease			
No	65/371	1.0	
Yes	27/115	1.34 (0.82-2.19)	0.15
Diabetes			
No	87/447	1.0	
Yes	57/39	0.66 (0.25-1.72)	0.39
Hypertension			
No	61/301	1.0	
Yes	31/185	0.83 (0.51-1.32)	0.42
Stroke			
No	88/461	1.0	
Yes	4/25	0.84 (0.28-2.46)	0.54
Lung disease			
No	68/340	1.0	
Yes	24/146	0.82 (0.49-1.36)	0.44
Symptoms			
Depressed mood*			
None to mild	84/499	1.0	
Moderate to severe	18/29	3.68 (1.96-6.93)	0.001
Fatigue†			
None to mild	32/327	1.0	
Moderate to severe	70/192	3.72 (2.36-5.87)	0.001
Opioid dose, range	0-1,000		
MEDD, mean (SD)	6.05 (47.25)	1.02 (1.01-1.03)	0.001

Reyes-Gibby CC et al. Cancer Epidemiol Biomarker Prev 2009;18: 2636-42.

CANCER PAIN AND ANALGESIA

- **Opioids are the cornerstone of treatment of cancer-related pain**
- **Huge interindividual variability in opioid dose**
- **Active metabolites of morphine can accumulate and result in opioid-induced neurotoxicity**
- **Repeated administration leads to:**
  - Opioid dose escalation
  - Reduced analgesia
  - Need for a change in opioid analgesic

MORPHINE CONSUMPTION

Population	Candidate Genes	Outcome	Results
Cancer patients in pain tx (n. 207)[1]	OPRM1-118 A/G 172 G/T IVS2+31+IVS2+691	Morphine consumption and serum concentration	GC subjects show higher morphine dose with higher serum concentration
Cancer patients in pain tx (n. 207)[2]	COMT Val 158 Met	Morphine consumption	Val allele needs more morphine
Cancer patients in pain tx (n. 207)[3]	COMT and OPRM1	Morphine consumption	Val allele needs more morphine COMT Met and OPRM1 A combinantion requires lowest morphine for achieving pain relief

[1]Klepstad P et al. Acta Anaesthesiol Scand 2004; 1232-9.

[2]Rakvag TT et al. Pain 2005; 116: 73-8.

[3]Reyes-Gibby CC et al. Cancer Epidemiol Biomarker Prev 2007; 16: 2745-51.

ANALGESIA

Population	Candidate Genes	Outcome	Results
137 cancer patients 77 with metastases[1]	ATP-binding cassette B1 (ABCB1)/ multiple drug resistance 1 (MDR1)	Verbal Rating Scale (5 point Likert scale) and Numeric Rating Scale (0-10)	Pain relief significantly associated with ABCB1/MDR1. Combination of C/C of ABCB1/MDR1 and g/G of OPRM1 show lower response to morphine
140 lung cancer patients[2]	TNF-α 308 G/A; IL6-174G/C; IL8-251T/A	Morphine equivalent daily dose	IL6-174C/C genotypes required 4.7 times higher dose of opioids for pain relief [OR: 4.7 (95% CI, 1.2-15.0)] relative to GG and GC genotypes

[1]*Campa D et al. Clin Pharmacol Ther 2008; 83: 559-66.*

[2]*Reyes-Gibby CC et al. Lancet Oncol. 2008; 9: 777-85.*

ANALGESIA

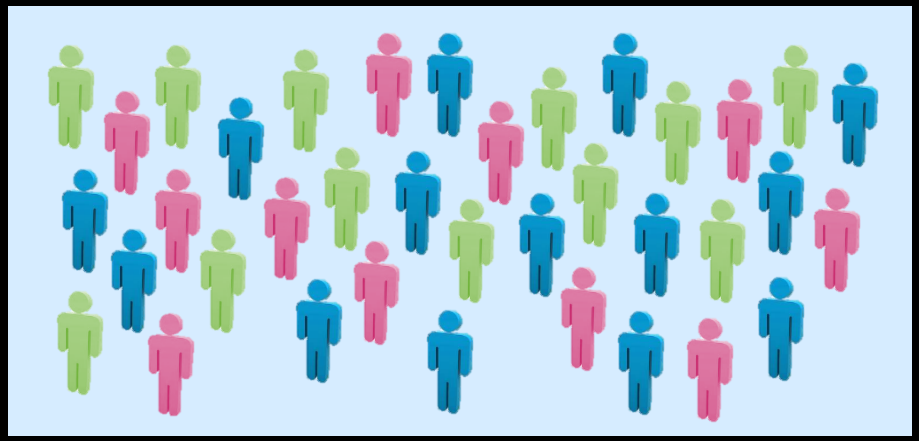
Population	Candidate Genes	Outcome	Results
70 patients with gastric cancer admitted for gastrectomy[1]	Cytocrome P450 2D6 (CYP2D6)	Tramadol consumption (2, 4, 24 and 48 h), pain VAS	Consumption of tramadol in group without CYP2D6*10 allele is higher than other groups at 4, 24, and 48 h post-surgery. No difference in pain intensity
251 cancer patients[2]	GTP cyclohydrolase 1	Interval between cancer diagnosis and opioid therapy initiation	Homozigotes had longer interval (78 ± 65,2 mo) than in hetrozygotes (37 ± 46.5 mo)

[1] *Wang et al 2004.*

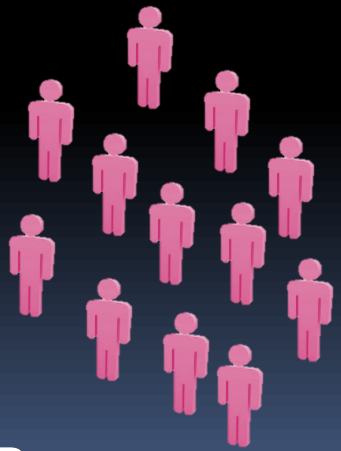
[2] *Lotsch J et al. Pain. 2010 ; 148: 103-6.*

GERM-LINE (INHERITED) GENETIC VARIATIONS

PATIENTS WITH SAME DIAGNOSIS



Good response to tested drug



Poor or non response
Use different drug

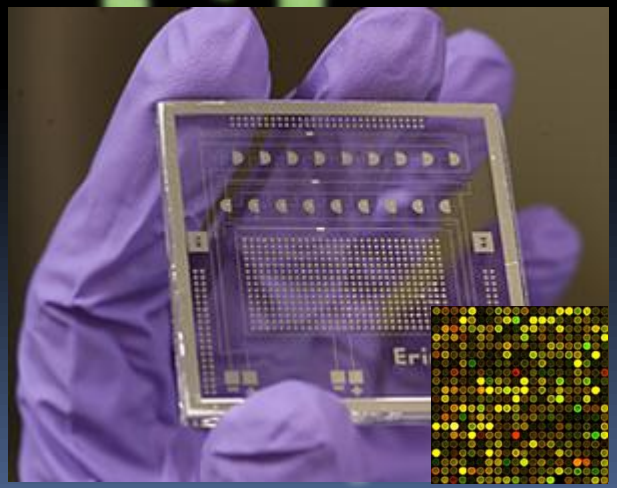
Increased toxicity risk
Decrease dose or use different drug

GERM-LINE (INHERITED) GENETIC VARIATIONS

PATIENTS WITH SAME DIAGNOSIS

PHARMACOGENETICS

THE ASSOCIATION BETWEEN HERITABLE FUNCTIONAL VARIANTS (GENOTYPE) WITH OUTCOME OF THERAPY (PHENOTYPE)



NONIVASIVE
STABLE
HIGHTHROUGHPUT

Poor or non response
Use different drug

THIS DRUG'S FOR YOU!

Conclusion

Although several decades of experience and research have not changed the consensus that opioid-based pharmacotherapy is the mainstay approach for the long-term treatment of chronic pain in populations with active cancer, there have been striking changes in the clinical approach to this problem. With analgesic strategies integrated into a palliative plan of care, there is increasing hope that patients can experience cancer with a minimum of suffering. Nonetheless, the treatments used have very little supporting evidence and there continues to be a pressing need for more research to provide comparative and long-term data pertinent to current treatments and novel treatment strategies for refractory conditions. Efforts to bring cost-effective strategies to resource-poor areas of the world should have equal priority.

Portenoy RK. Lancet 2011; 377: 2236-47

Conclusion

Advances in therapy of pain have been slow, but better trial design will address this producing, it is hoped, safer, and more effective drugs in the near future.

Power I. Br J Anaesth 2011; 107: 19–24.