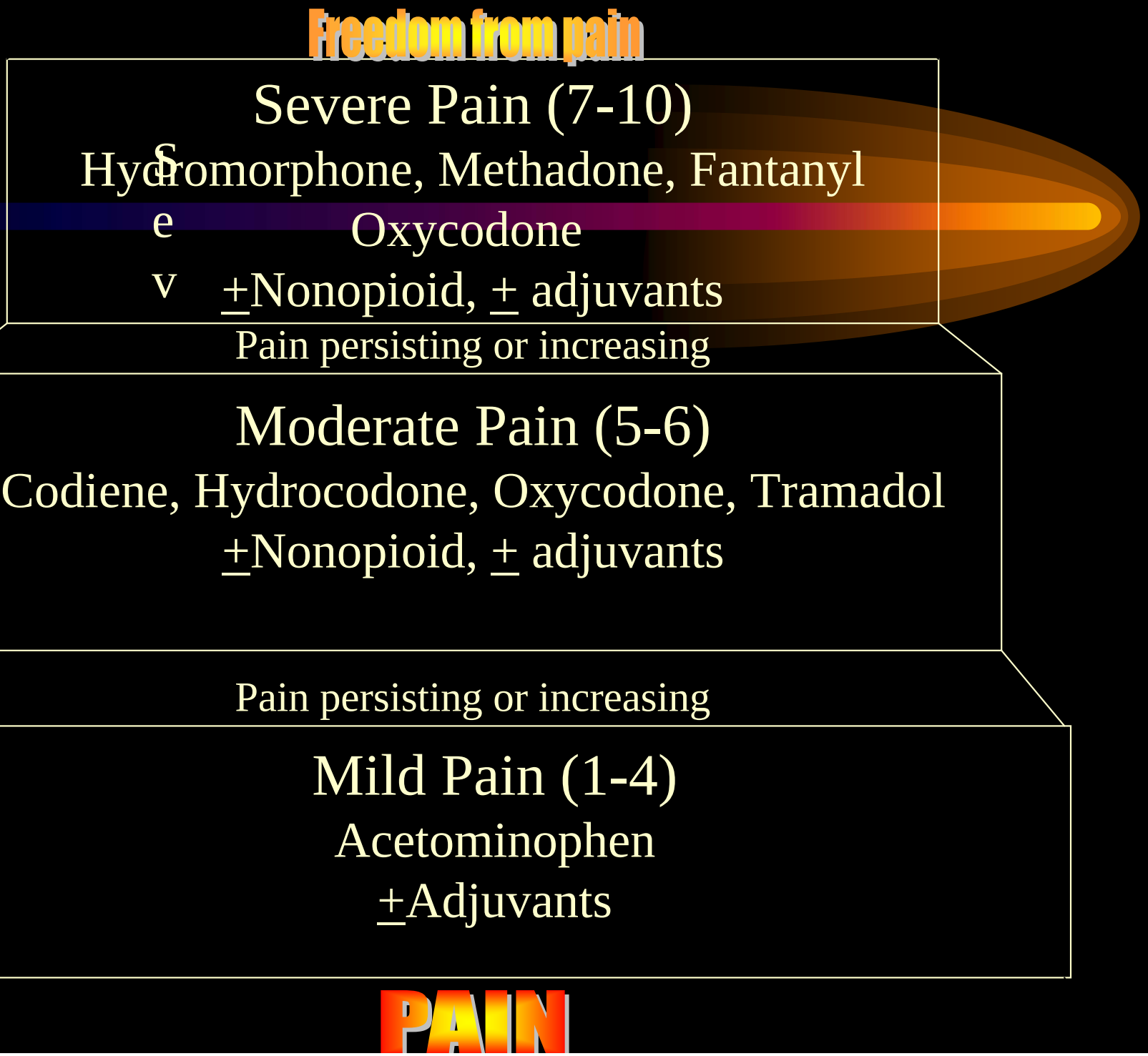
Pain

Should not and does not have to be a way of life in Chronic Kidney disease

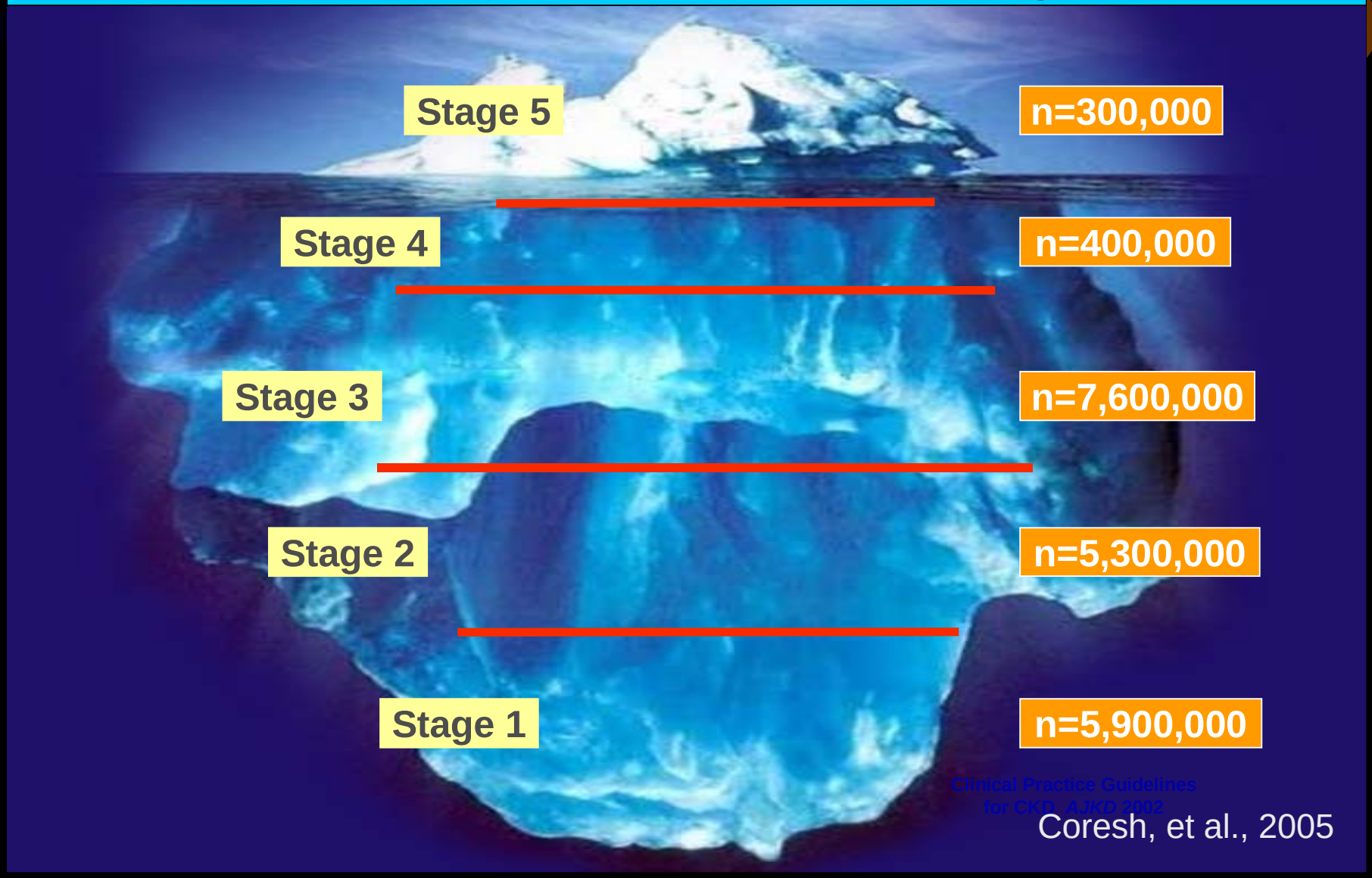
“To leave a person in avoidable pain and suffering should be regarded as a serious breach of fundamental human rights and can be regarded not only as unethical, but also as negligence. It also should be regarded as unprofessional conduct; that is , it should constitute a basis for disciplinary action by the relevant professional licensing body.”

Margaret Somerville
Professor of Law
Founding Director, The McGill Centere for Medicine, Ethics and Law

WHO PAIN RELIEF LADDER



At risk population: NHANES III 1988-1994: National Kidney Foundation CKD guidelines



Clinical Practice Guidelines for CKD. *AJKD* 2002

Coresh, et al., 2005

Altered pharmaco-kinetics and Drug Metabolism among CKD patients

Increased risk of side effects and toxicity

Obstacles preventing effective pain control

- Fear of narcotic addiction and loss of mental capacity
- Fear of loss of renal function
- Long waiting time for appropriate subspecialty care
- Fear of persecution
- Inadequate training in appropriate assessment and treatment of various pain syndrome

Burden of Symptoms in HD Patients

%	0	1-3	4-5	6-10
Pain	37.5	20.5	16.0	26.5
Nausea	61.4	24.0	7.0	7.6
Depression	50.6	22.6	14.0	12.8
Anxiety	44.8	26.4	13.7	15.1
Drowsiness	32.1	28.3	21.0	18.6
Appetite	28.1	28.4	20.8	22.7
Wellbeing	18.4	30.5	27.3	23.8
SOB	43.9	25.0	15.7	15.4
Pruritis	31.5	27.4	15.7	25.4
Activity	12.7	23.5	27.6	36.2

42.5

26.8

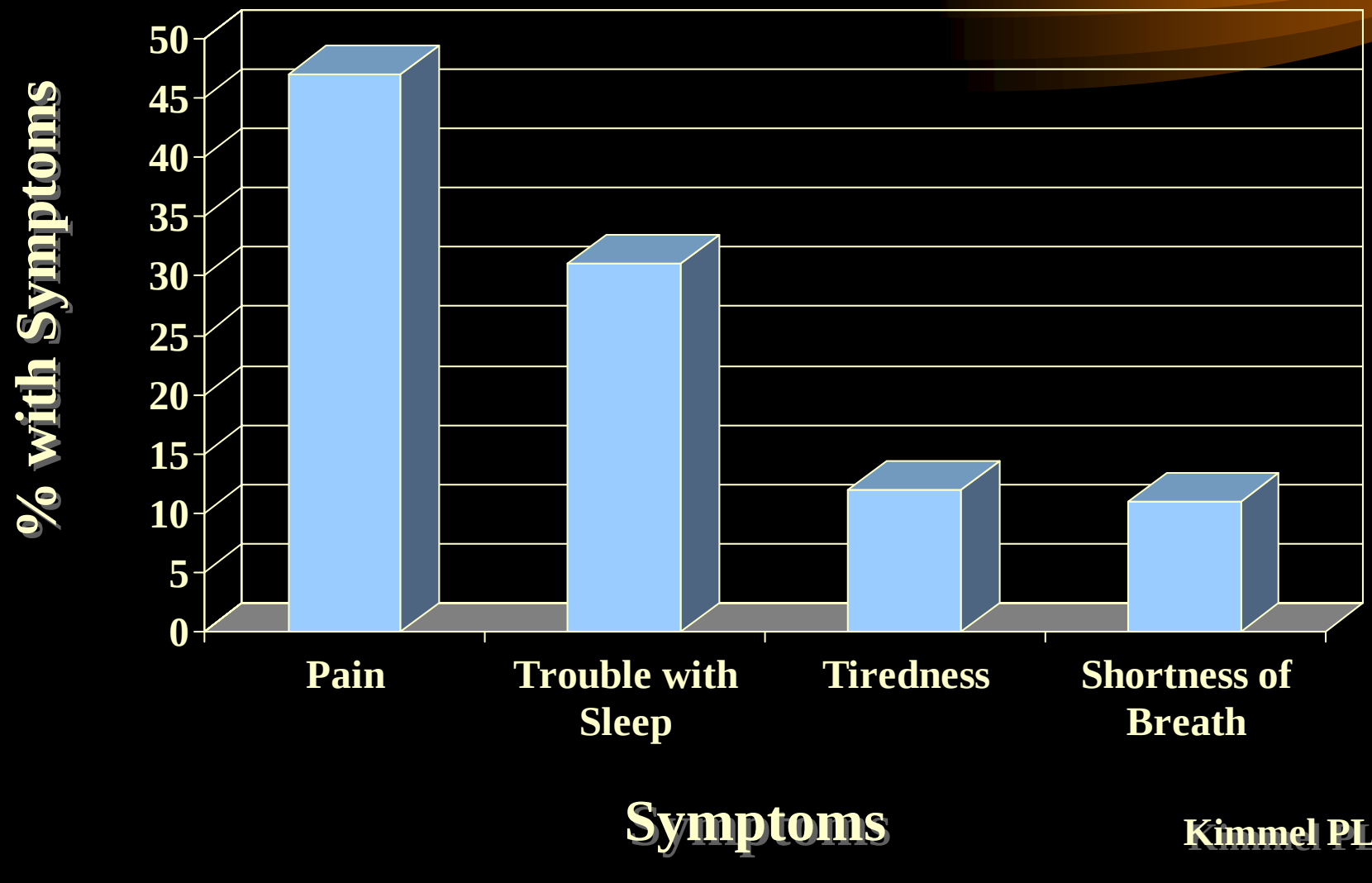
28.8

51.1

63.8

Davison, 2002

Most Common Symptoms Reported by Symptomatic HD Patients



Kimmel PL, AJKD 2003

Point Prevalence of Analgesic Use: DOPPS

Analgesic	Number of Patients	
	1997 N = 2988	2000 N = 2476
Any analgesic	30.2%	24.3%
Any narcotic	18.0%	14.9%
Any NSAID	6.4%	2.3%
Any acetaminophen	11.1%	6.3%

¾ of patients reporting moderate to severe pain were not prescribed analgesics

The Impact of Pain

- Symptoms, especially pain, are important determinants of HRQOL of patients with ESRD
- Pain is a multidimensional phenomenon with physical, psychological and social components
- Failure to treat pain adequately could be expected to lead to disruption in many aspects of life such as functional status, mood, sleep, and global HRQOL

Considerations for pain in CKD

Type of Pain

- Neuropathic
- MSS
- Viseral

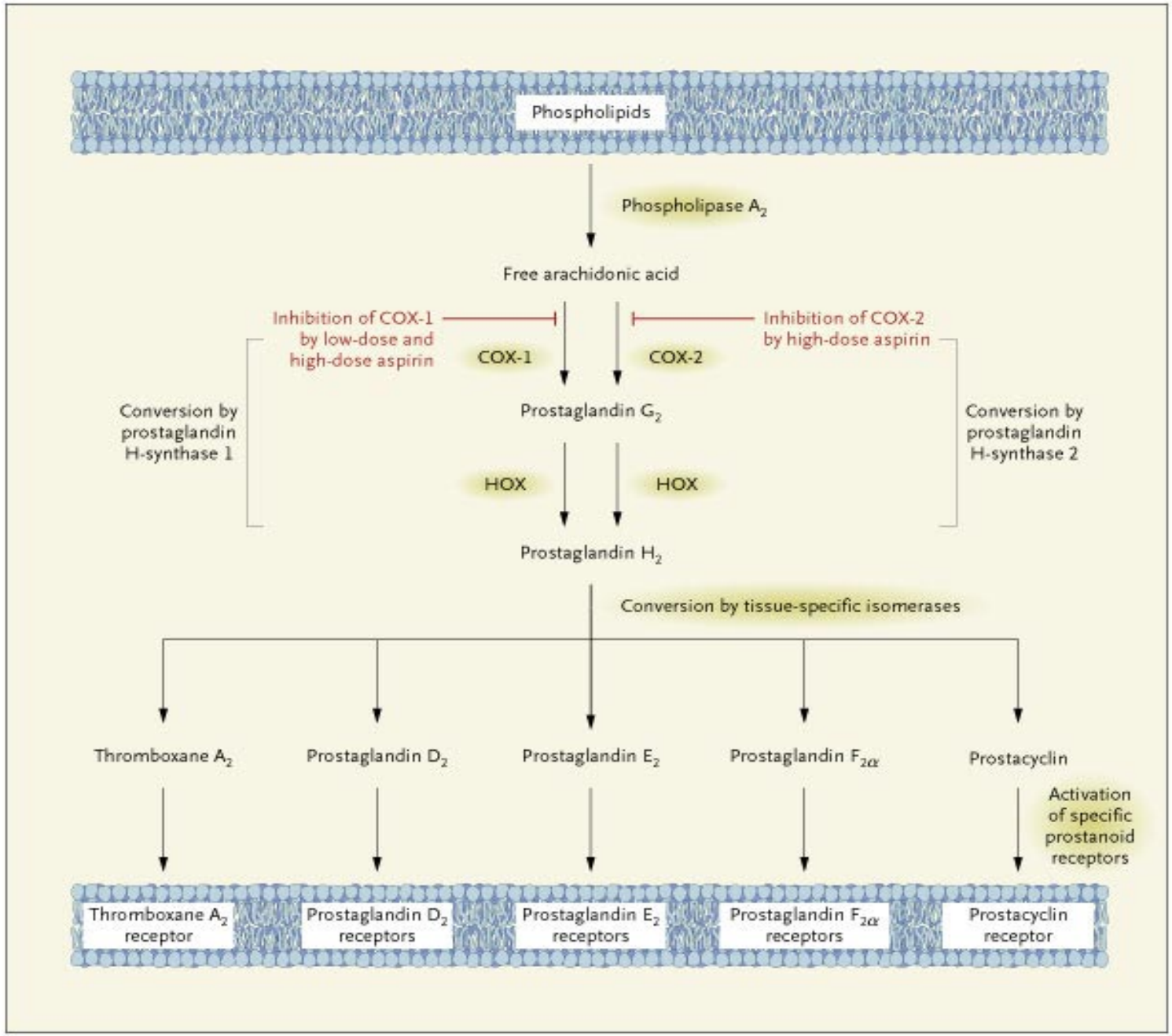
Stage of CKD (ml/min/1.73m2)

- I $\geq$ 90
- II 60 -89
- III 30 – 59
- IV 15-29
- V <15 or dialysis

Acetaminophen

- Metabolized by liver
- Non-narcotic analgesic of choice by NFK
- Suggested to cause papillary necrosis with prolonged use and high dose
- Weak association between acetaminophen use and CKD in case controlled studies
- In many combined OTC analgesics

Mechanism of Action of NSAID



Patrono C et al. N Engl J Med 2005;353:2373-2383

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NSAID

- COX-2 inhibition
  - Decrease prostaglandin mediating pain and inflammatory responses
- Cox-1 inhibition
  - Gastric mucosal damage and platelet inhibition

NSAID

- Used as primary or adjuvant at all steps of WHO pain relief ladder
- Renal toxicity <1% in healthy population
- Use carefully in stage IV (<30ml/min) or higher
- If used in CKD, precise indication and time course are keys; lowest dose and close monitoring

NSAID related ARF is associated with

- Decreased effective perfusion of kidneys (CHF, Cirrhosis, Nephrotic syndrome, renal vascular disease, shock)
- Chronic renal failure
- Medications (ACEI, ARB, Aldosterone antagonist, diuretics, Calcineuriums)

NSAID

- AIN

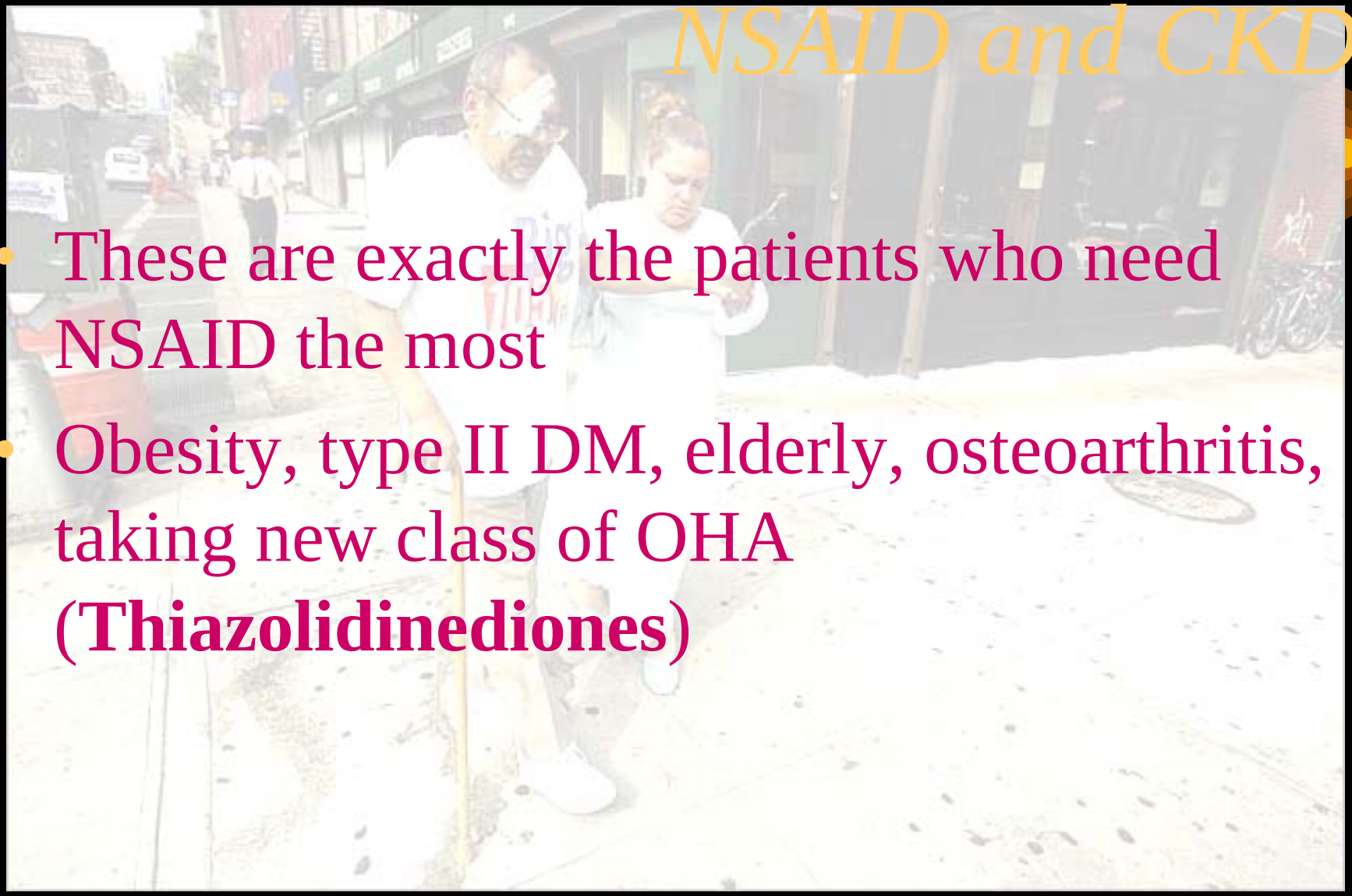
  Atypical menifestation

  More common with proprionic acids derivatives (ibuprofen, fenoprofen and naproxen)
- Proteinuria and Nephrotic syndrome
- Chronic consumption leads to classic analgesic nephropathy

NSAID AND CKD

- Worsen hypertension control
- Increase edema and decrease diuretic effectiveness
- Mild to moderate hyponatremia with inhibited water excretion in CKD
- Hyperkalemia in susceptible patients (prostaglandins mediates renin release from JG cells)

NSAID and CKD



- These are exactly the patients who need NSAID the most
- Obesity, type II DM, elderly, osteoarthritis, taking new class of OHA (**Thiazolidinediones**)

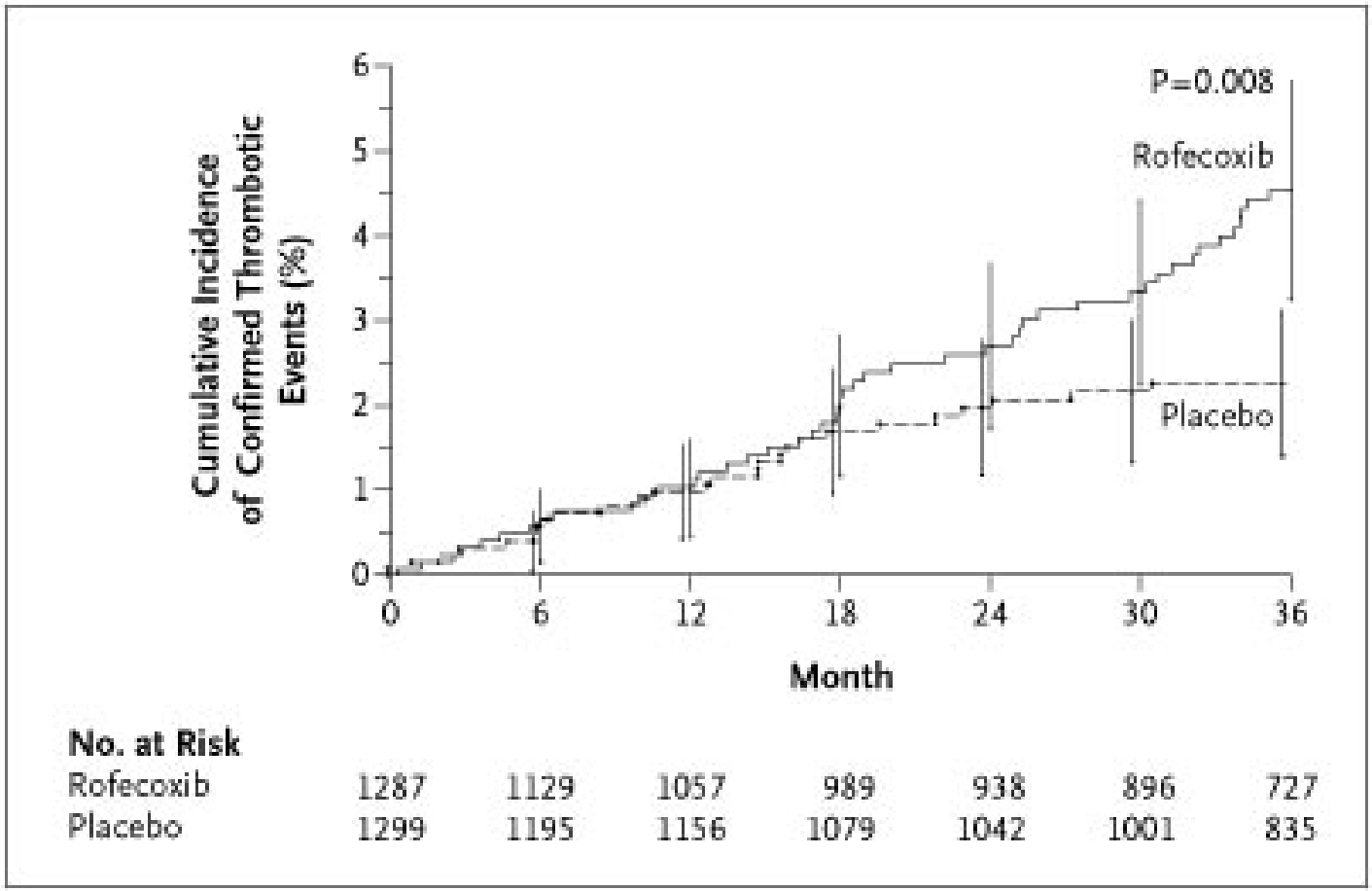
Aspirin and CKD

- Aspirin is primarily a COX-1 inhibitor
- Transient reduction of GFR with dose > 325 mg/d in CKD
- Does not influence hypertension or increase risk of CKD when given in dose recommended for cardiovascular prophylaxis

COX-2 inhibition and CKD

- CKD patients were excluded from initial clinical trials of gastric protection
- Higher incidence of cardiovascular events
- Induces more hypertension
- Can induce same renal side effects as non-selective NSAIDs

Kaplan-Meier Estimates of the Cumulative Incidence of Confirmed Serious Thrombotic Events



Bresalier R et al. N Engl J Med 2005;352:1092-1102

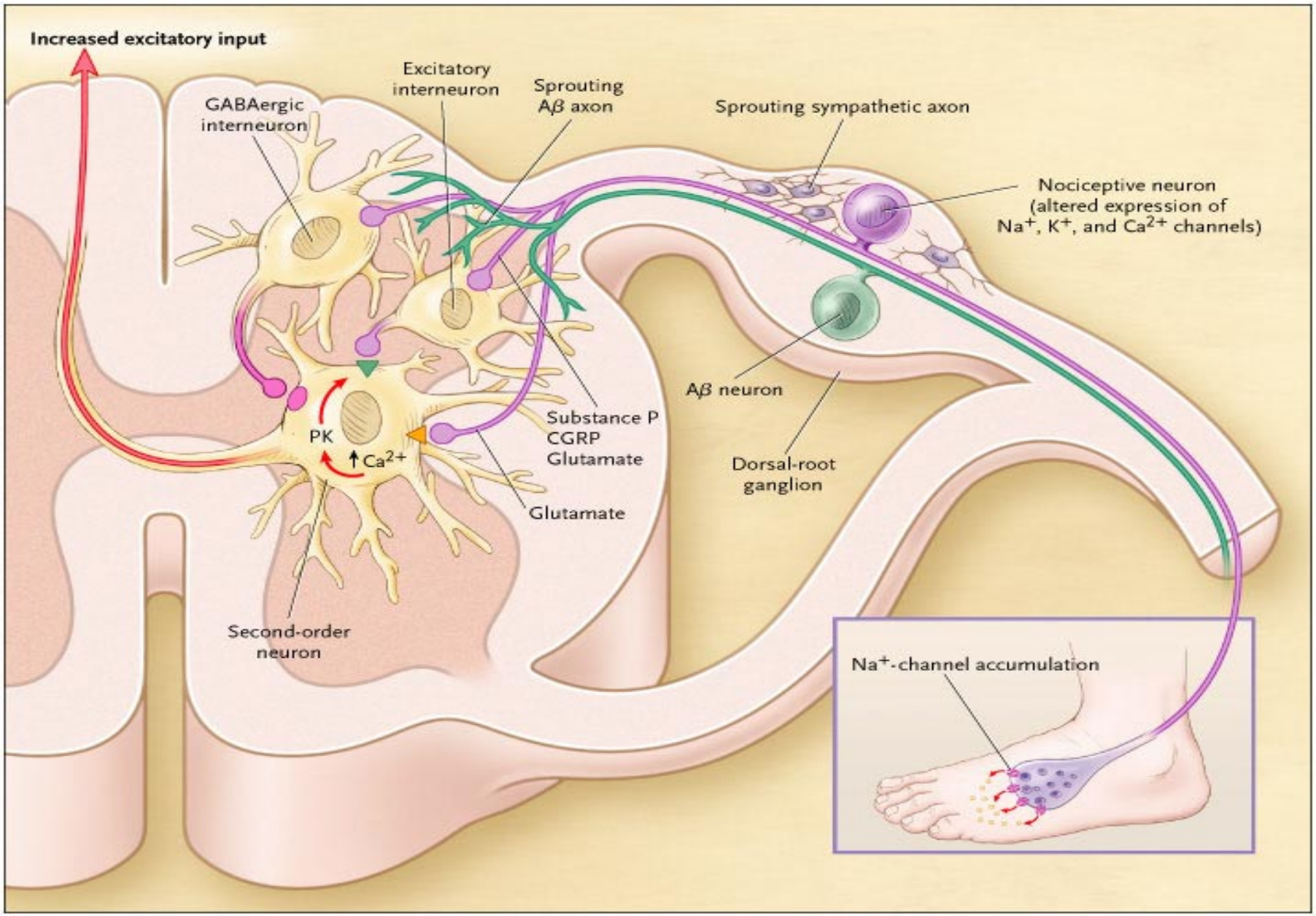
Use of NSAID in patients on peritoneal dialysis

- Residual renal function affects survival of PD patients
- Use of NSAID should be fine if PD patient is anuric
- Prolonged use of NSAID should be avoided if patients has residual renal function
- Indirectly, it may have implication on long term peritoneal function

Use of NSAID among patients on hemodialysis

- The effect of residual renal function in regards to survival of hemodialysis patients is less clear
- Use of NSAID can probably be more liberal for HD patients than PD patients

Pathways Leading to Pain in Peripheral Neuropathy and Potential Sites of Pharmacologic Interventions



Mendell J and Sahenk Z. N Engl J Med 2003;348:1243-1255

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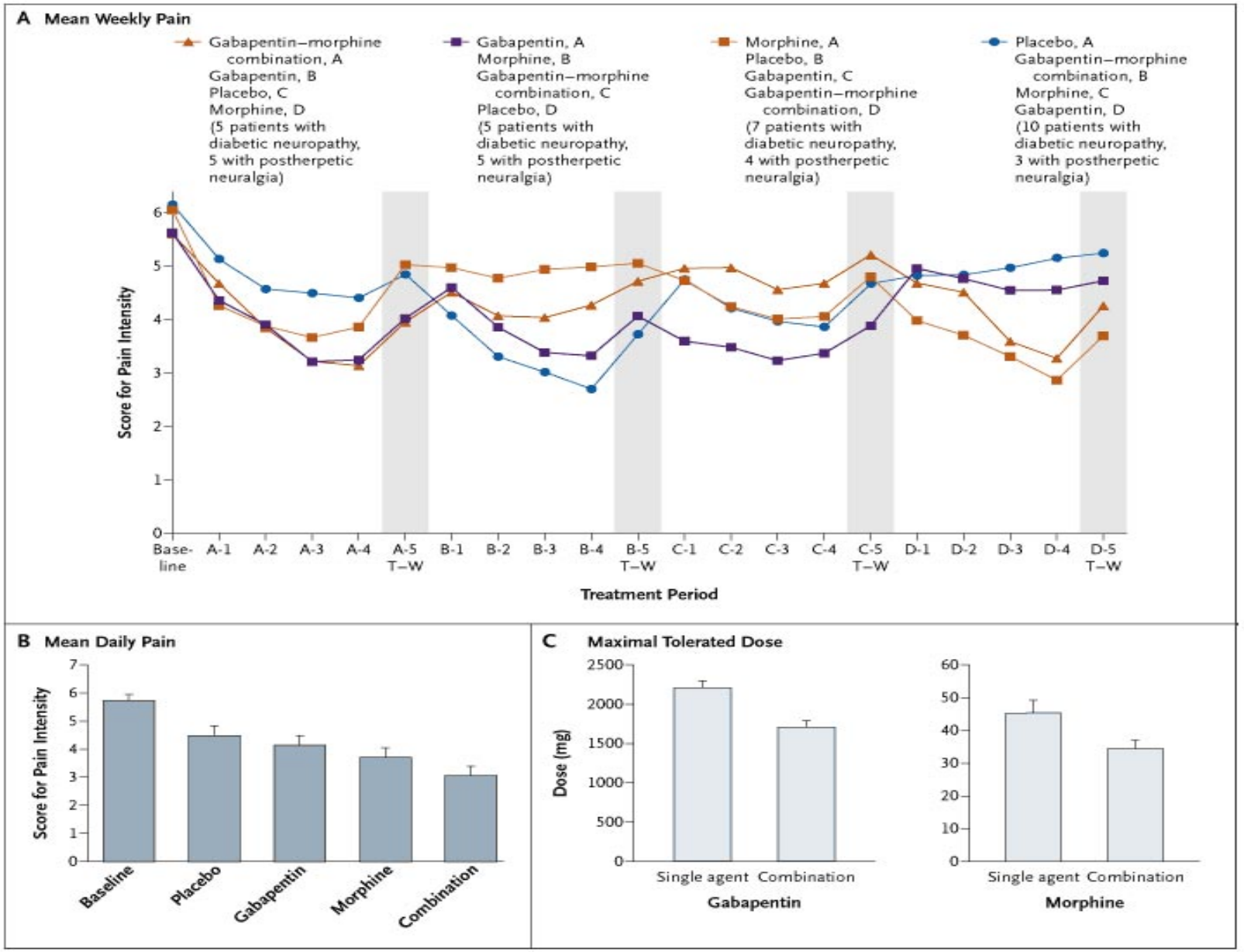
Gabapentin Neuropathic Pain

- Little interaction with other drugs
- 3-alkylated analogue of gamma-amino butyric acid, which modulates calcium-channel subunits
- Totally excreted by kidneys
- Use minimal effective dose
- GFR<15ml/min, use 300 mg q2d

Mean Daily Pain and Maximal Tolerated Doses of the Study Drugs



Gilron I et al. N Engl J Med 2005;352:1324-1334

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Carbamazepine for Neuropathic Pain

- Little analgesia
- Metabolized in liver
- Modifies pain transmission
- No adjustment for CKD
- Monitor adverse effects (CBC, LFT, GFR, Lytes)
- Abrupt withdrawal may precipitate seizure

Lyrica (Pregabalin) Neuropathic Pain

- Antiepileptic
- Elimination is proportional to GFR

Adverse effects

- Dizziness, drowsiness, dry mouth, edema, blurred vision, weight gain, and difficulty concentrating, reduced blood platelet counts, and increased blood creatinine kinase levels (rhabdomyolyis)

Lyrica (pregabalin)
Dose Adjustment in CKD

Creatinine Clearance (CLcr) (mL/min)	**Total Pregabalin Daily Dose (mg/day)**			Dose regimen
>60	150	300	600	TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD

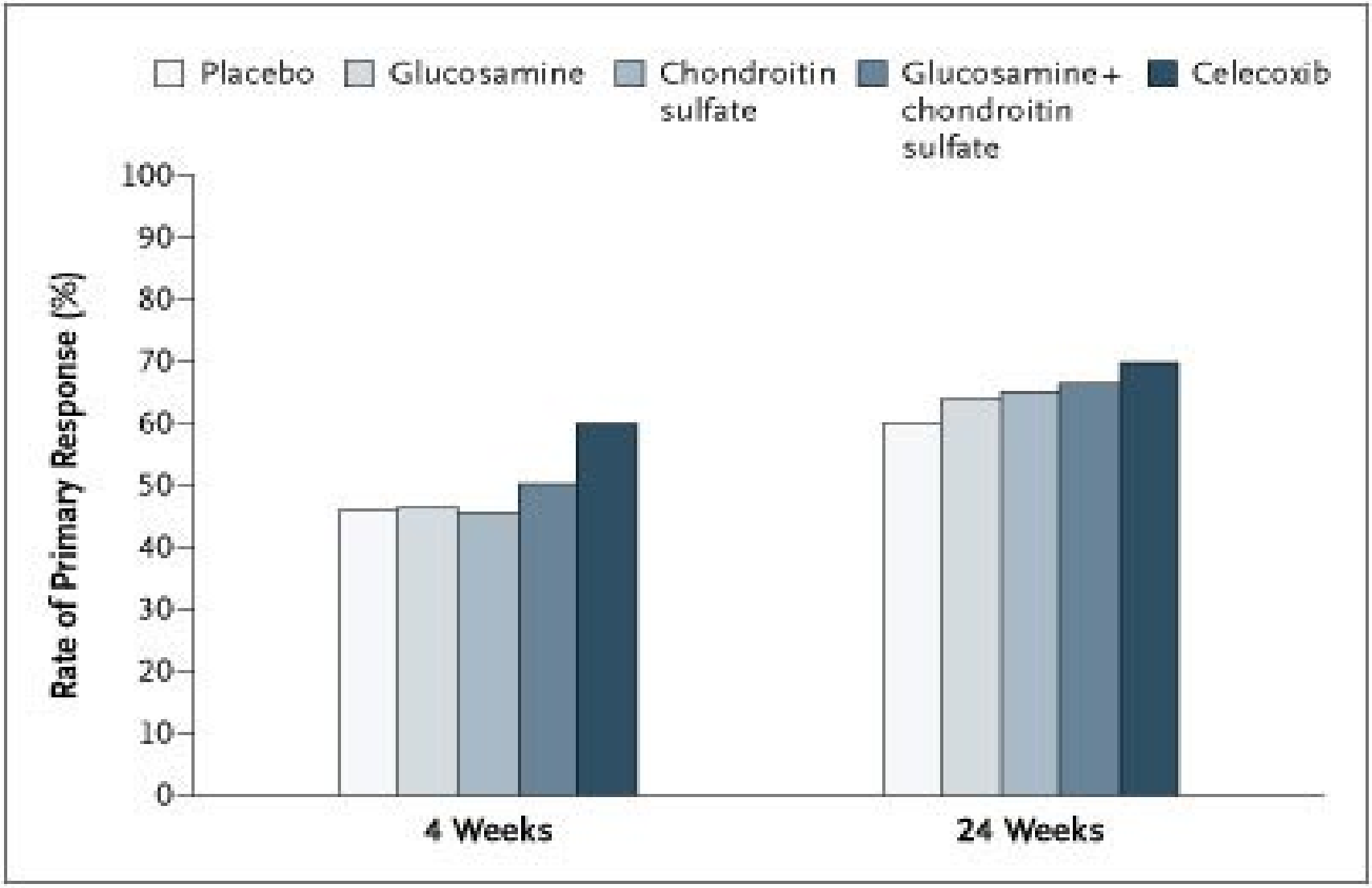
Supplementary dosage following hemodialysis (mg)

Tricylics Antidepressants (Neuropathic Pain)

- More effective for burning pain
- Inhibits serotonin and norepinephrine reuptake in CNS
- Maximal analgesia in several weeks
- synergistic with opioids
- Anticholinergic effects: dry mouth; sedation, weight gain; cardiac conduction abnormalities
- Despiramine may have less side effects than amitriptyline
- Renal excretion, lower dose in CKD

Rates of a Primary Response in the Five Groups at 4 and 24 Weeks

20 percent decrease in the summed score for the pain subscale



Painful Osteoarthritis of the Knees

Clegg D et al. N Engl J Med 2006;354:795-808

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Opioids

- Opioid receptors (mu, kappa, delta)
- Receptors in CNS, dermis, joints
- Endogenous opioids and kidneys
  - Regulating ECFV via ANP
  - ? Mediators of uremic symptoms

Tramadol

- Centrally acting non-narcotic agent
- Acts on Mu-opioid receptor, similar therapeutic and side effect profile as opioid without the same abusive potential
- Inhibits reuptake of Monoamines and CNS pain sensing
- Metabolized by liver and excreted by kidneys ($T_{1/2}$*2 in CKD)
- < 200 mg/day for GFR<30ml/min

Codeine

- Elimination ½ life is significantly increased in dialysis patients
  - Reports of neurotoxicity
- Should be used with caution but tolerated relatively well if carefully monitored

Oxycodone

- Elimination significantly reduced in ESRD
  - Fibrillary GN
  - Growing popularity as a drug of abuse and is now considered one of the most desirable of prescription drugs
- Should be used with caution but tolerated relatively well if carefully monitored

Morphine

- Active metabolite M6G is renally excreted and accumulates in ESRD
- Increased side effects
- No data regarding dose adjustments for sustained-release preparations of morphine
- Dose interval 6-8 hrs and dosage reduce by 30-50% in CKD in chronic use

Lee MA, Palliat Med 2001

Hydromorphone

- 10 times more potent than morphine, shorter duration of action
- Case reports of adverse effects, essentially no PK data
- Published and clinical experience indicates that it may be administered safely in ESRD; may be particularly useful in patients who have intolerable side effects from other narcotics

Methadone

- Opioid commonly used for treatment of severe pain or withdrawal in narcotic addicts
- High oral bioavailability and a long ½ life
- Essentially no PK data in ESRD; single report suggesting normal levels in ESRD
- Anecdotal experience suggests a relatively good safety profile

Fentanyl

- Transdermal formulation
- Metabolized by liver
- Essentially no PK data of transdermal formulation or effect of dialysis on levels (one report stated poor removal)
- Toxicity has been reported but anecdotal experience suggests a reasonable safety profile if monitored carefully

Propoxyphene

- Related to Methadone
- Active metabolite, norpropoxyphene is renally excreted
- Local anesthetic properties similar to quinidine
  - Predispose patients to risk of cardiac conduction abnormalities
  - Neither propoxyphene or norpropoxyphene are removed with dialysis
  - Cardiotoxicity cannot be reversed by naloxone
- Use with extreme caution
- Never use

5As for Opioids Management

- Analgesia
- Activity (functional status)
- Adverse reactions
- Aberrant drug-related activities
- Accuracy

Dosing of Analgesics

"by mouth"

- When ever possible, drugs should be given orally (transdermal)

"by the clock"

- Drugs should be given regularly + PRN "breakthrough"

"by the ladder"

- Use the sequence of the WHO analgesic ladder

"for the individual"

- There is no standard (ceiling) dose for strong opioids. The "right" dose is the dose that relieves pain without unacceptable side effects
- Every patient is different

"attention to detail"

- Pain changes over time: assessment and reassessment
- Actively prevent adverse effects

Dosing

- Ineffective medications should be tapered and discontinued and REPLACED with another agent
- Clear communication: ensure patients understand the regimen, the goals of therapy, adverse effects and what to do if control inadequate.
- Dosing should be as simple as possible

Dosing to Effect for Pain

- Starting at low dose
- Increase dosage at regular intervals
- Till adequate pain relief or
- Unacceptable and persistent adverse effects
- Except acetaminophen or NSAIDs

- CKD patients have a high burden of symptoms throughout their illness
- Pain in ESRD is common, often severe and poorly managed
- Symptoms, especially pain, have a tremendous negative impact on all aspects of HRQOL
- Effective pain and symptom management is an integral component of quality CKD patient care
- For effective management of pain, psychological status, sleep, functional ability and HRQOL must be addressed

Conclusions

- Multidisciplinary nephrology teams must focus on pain and symptom management (clinical and research)
  - Enhanced training for residents, CME for staff, training for nursing staff and allied HCP
  - Culture of the dialysis unit must change to support this new focus on pain and symptom management
  - Infrastructure must reflect these new priorities: dedicated resources

Conclusions

- Concerns about analgesics (especially opioids) has lead to a more cautious use of analgesics in ESRD patients and has resulted in potential under prescription

- Must optimize BOTH pharmacological and non-pharmacological interventions for effective pain management