



Chronic Pain in CKD

Sara N. Davison
Frank Brennan
Holly Koncicki

Scoping Review: Pain in CKD

Total number records identified for title and abstract review	N = 997
Pain assessment and screening	13
Epidemiology: prevalence, severity, etiology, and associations	55
Patterns of analgesic use	31
Specific pain syndromes	
Arthritides	6
Peripheral neuropathies: diabetic neuropathy, carpal tunnel synd	70
ADPKD	29
Pharmacokinetic/pharmacodynamic studies	143
Pain management: general approaches and guidelines	83

Prevalence of Pain in CKD

Studies	Patient Pop ⁿ	# Patients	Prevalence
36	Prevalent HD	5244	58.6% (21%-81%)
6	Moderate/ severe pain	1701	48.8% (41%-68.6%)
Studies	Patient Pop ⁿ	# Patients	Impact
11	Prevalent HD	3215	No clinically significant association with gender, age, race, biochemical parameters
9		2086	Decreased QOL

Pain: predominantly MSK but neuropathic component in > 50%

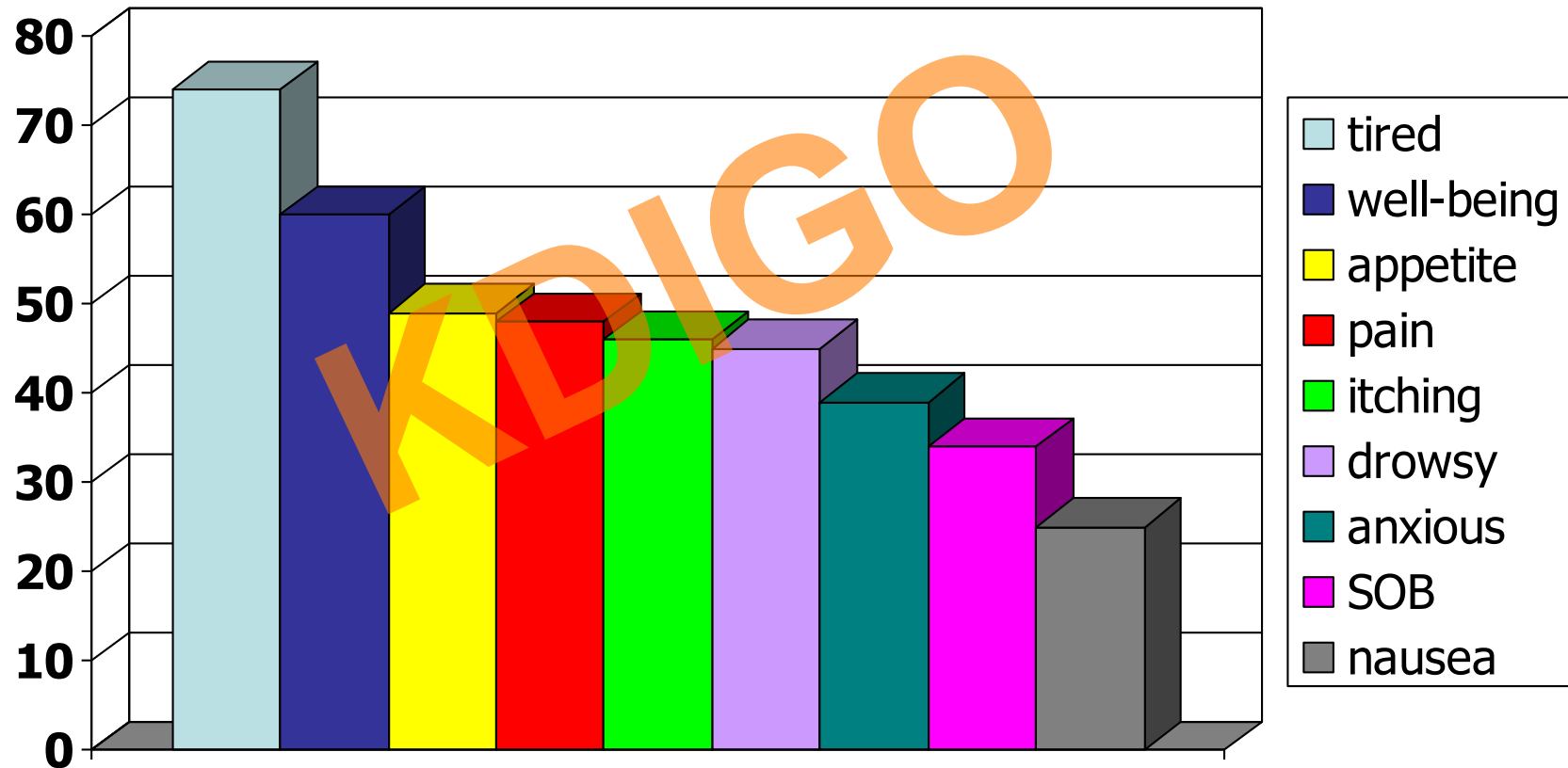
Data on exact causes/diagnoses of pain are lacking

Limited data in PD & conservatively cared for pts: prev & severity appear similar



Symptom Burden in Dialysis Patients

n = 507



Davison, et al KI 2006;69:1621



Prevalence of Analgesic Use in CKD

Analgesic	Prevalence of Prevalent HD Patients	
	All Patients (n = 25725) 13	Patient with Pain (n = 755) 7
Any analgesic	27% (n=6025) (18%-30.2%)	55.8% (n=240) (30%-65%)
Any narcotic	15.2% (n=25680) (0%-18%)	22.0% (n=340) (0%-35.9%)
Any NSAID	4.9% (n=6000) (1%-15.8%)	19.0% (n=231) (2.9%-42%)
Any acetaminophen	8.9% (n=6000) (0%-13.8%)	18.2% (n=231) (0%-44%)

Symptom (Pain) Screening Tools

Global symptom screening tools

Modified Edmonton Symptom Assessment System (mESAS)

- 11 x VAS, 0-10 scale anchored by the words no and severe at 0 and 10 respectively

Palliative Care Outcome Scale- Renal (POS-renal)

- 17 symptoms, rated in terms of their impact on patient over the last week from 0 (not at all) to 4 (overwhelmingly).

Physical Symptom Distress Scale (PSDS)

- 16 symptoms, rated on a 4 point Likert scale 0 = not bothered at all, 4 = extremely bothered.

Dialysis symptom index (DSI)

- Assesses 30 symptoms, rating them from 1 (not at all bothered) to 5 (very much bothered).

Pain Assessment Tools

Brief Pain Inventory (BPI)

- Assesses location, type (nociceptive v. neuropathic) and intensity of pain. It evaluates impact of pain on general activity, mood, walking ability, work, relationships, sleep, and enjoyment of life. Condensed to a 9 question SF.
- Used successfully in clinical and research settings internationally. Seriously ill patients have been successful in completing

Short-Form McGill Pain Questionnaire (SF-MPQ)

- Describes quality and intensity of pain; rated from 0-78; higher = worse pain.
- Not simple; does not assess other symptoms, hence decreasing it's clinical utility as a routine symptom-screening tool.
- Incomplete as a pain assessment tool as it does not explore impact of pain on function and QOL.

Health-Related Quality of Life Tools

CHOICE Health Experience Questionnaire (CHEQ) + SF-36

Kidney Dialysis Quality of Life-Short Form/ SF-36 (KDQOL-SF)

- Takes approximately 30 minutes to complete in healthier individuals
- Typically requires interviewer assistance and more time in elderly, frail patients.
- Provides comprehensive HRQL information but is more suited to a research environment where dedicated staff can help with the administration and complex scoring.
- Not suitable for patients who are pre-terminal.

Pharmacokinetic/Pharmacodynamic Studies of Analgesics in CKD (n=143)

- Data in CKD remain limited
- Suggested analgesics and dose reductions are based on both clinical experience and available data.
- Most pharmacokinetic studies are small or are case reports of subjects with varying degrees of renal function, medications, and doses.
- They are typically single dose studies or studies over very short periods of time which have not been designed to evaluate efficacy and safety.
- Only a few studies have provided information regarding clinically relevant outcomes such as analgesic effect or adverse effects.
- With respect to studies of NSAIDs, a few showed depressed thromboxane B2 levels suggesting there may be increased bleeding risk; however this was not described clinically.
- **With the advent of new opioid analogues and other classes of analgesic medications, this remains an emerging and important area of study**

Overall Approach to Chronic Pain Management (Adults) CKD (n=83)

- Data on the effects of treatment on clinically important outcomes (efficacy, overall symptom burden & QOL) are ~ nonexistent.
- Numerous review articles and recommendations for the treatment of chronic pain in CKD.
- Recommendations are based on international evidence-based guidelines & systematic reviews for non-malignant chronic pain
 - Appropriate use of analgesic (and opioid) therapy for nociceptive and neuropathic pain
 - Chronic pain management and opioid use in the geriatric population.
 - However, even these clinical guidelines are limited by the level of evidence and have been supplemented by expert consensus statements based on clinical experience.
- These approaches have been adapted for use in CKD based on the limited pharmacokinetic data.

Approach to the Pharmacological Tx of Chronic Nociceptive Pain for Adults in the Gen Population

1. **Step-wise approach** (WHO) Analgesic Ladder, making special consideration for analgesic selection as outlined below

KDIGO



Freedom from pain

3

OPIOID FOR SEVERE PAIN
± NON-OPIOID
± ADJUVANT

Pain persisting or Increasing

2

WEAK OPIOID FOR
MODERATE PAIN
± NON-OPIOID
± ADJUVANT

Pain persisting or Increasing

1

NON-OPIOID
± ADJUVANT

Approach to the Pharmacological Tx of Chronic Nociceptive Pain for Adults in the Gen Population

1. **Step-wise approach** (WHO) Analgesic Ladder, making special consideration for analgesic selection as outlined below
2. **Acetaminophen**: initial & ongoing pharmacotherapy (Step 1). Effective & safe (high quality evidence; strong recommendation)
3. **NSAIDs** should be considered **rarely & with extreme caution** for chronic use in the elderly (high quality evidence, strong recommendation). Older patients taking NSAIDs should be prescribed a proton pump inhibitor or misoprostol for GI protection (high quality evidence; strong recommendation).
4. **Tramadol** may be a reasonable choice (step 2 analgesic). Effective for non-cancer pain; lower risk of misuse, overdose or addiction compared v. opioids.
5. **Consider a trial of chronic opioid therapy** if pain is moderate to severe, having an adverse impact on function or QOL, & potential therapeutic benefits outweigh or are likely to outweigh potential harm (strong recommendation; low quality evid)

Opioid Use for Chronic Pain for Adults in the Gen Population

1. **Assess risks of substance abuse**, misuse or addiction (strong recommendation; low quality evidence)
2. **Informed consent** should be obtained. A continuing discussion with the patient re: goals, expectations, potential risks & alternatives (strong recommendation; low-quality evidence).
3. **Opioid selection**, initial dosing and titration should be individualised according to the patient's health, previous exposure to opioids, attainment of therapeutic goals and predicted or observed harms. The optimal dose of opioids is one that either reduces pain by 30% in pain ratings scale or improved functional status (strong recommendation; low-quality evidence)

Opioid Use for Chronic Pain for Adults in the Gen Population

- 4. Wean opioid therapy** when patients experience no progress towards therapeutic goals, experience intolerable adverse-effects or who engage in repeated aberrant drug-related behaviours or drug abuse/diversion (strong recommendation; low-quality evidence).
- 5. The evidence of the effectiveness of long-term strong opioid use (6 months and greater)** in chronic non-cancer pain is variable. Overall conclusion is a weak recommendation with high quality evidence where benefits closely balanced burdens.
- 6. Pursue consultation**, including interdisciplinary pain management, when patients may benefit from additional skills or resources that they cannot provide (strong recommendation; moderate quality evidence).

Systematic Review of Guidelines for Opioid Use in Chronic Pain: Adults

13 Guidelines between 2007 – 2013

Agree on several opioid risk mitigation strategies

- 1. Upper dose thresholds:** 90-200 mg morphine equivalents daily
- 2. Caution with certain medications:** fentanyl patches; additional knowledge to prescribe methadone; titrate cautiously, reduce dose by 25%-50% when switching opioids
- 3. Attention to drug-drug & drug-disease interactions**
- 4. Use of risk assessment tools**
- 5. Treatment agreements**
- 6. Urine drug testing**

Most recommendations are supported by observational data and expert opinion



Preferred Analgesic Medication and Dosing in CKD IV and V

Recommended

Acetaminophen: Maximum daily dose of 3.2 g/day. In high risk patients limit the maximal dose to 2.6 g/day (chronic stable liver disease, alcoholics, and malnourished patients).

Hydromorphone: Hydromorphone-3-glucuronide (a toxic metabolite) accumulates without dialysis therefore this may not be an appropriate analgesic for patients with stage 5 CKD NOT on dialysis.

Fentanyl Patch: Should not be started in opioid naïve patients

Methadone: Specific education and licensing (by CPSA) is required to prescribe. Monitor QT by ECG.

Gabapentin: Titrate slowly; doses up to 600 mg/day are generally safe but monitor for side effects with doses above 300 mg/day (nystagmus, ataxia, tremor, somnolence, and reduced level of consciousness).

Use With Caution

Oxycodone: Limited evidence of pharmacokinetic safety in CKD. Literature reports suggest no major concerns.

Tramadol: Sustained release tablets NOT recommended in dialysis patients. Regular release tramadol is only available as combination product with acetaminophen. Seizure with higher doses in GFR < 30 a concern.

Nortriptyline/desipramine: TCA antidepressants are alternatives to gabapentin with more adverse effects.

DO NOT USE Codeine, morphine, meperidine, propoxyphene

Morphine, codeine, meperidine, propoxyphene have neurotoxic metabolites that are renally excreted, and that accumulate in chronic kidney disease, and may cause toxicity.

Approach to the Pharmacological Tx of Chronic Neuropathic Pain for Adults in the Gen Population

1. A step-wise approach

2. Initiate treatment with one of the following
 - Secondary-amine tricyclic anti-depressant (**TCA**)
 - Selective Serotonin Norepinephrine Reuptake Inhibitor (**SSNRI**)
 - Calcium channel alpha-2-delta ligand (**gabapentin, pregabalin**)
3. Consider **topical lidocaine**, used alone or in combination with one of the first-line therapies for localized peripheral neuropathic pain.
4. For patients with acute neuropathic pain, neuropathic cancer pain or episodic exacerbations of severe pain and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, **opioid analgesics** or tramadol may be used alone or in combination with one of the first line therapies.
5. If no or inadequate pain relief at target dosage after an adequate trial, switch to an alternative first-line medication. No one medication is universally effective. Moreover, in most cases first-line medications provide only partial pain relief... hence, in clinical practice, two or more medications are often used in combination
6. If trials of first-line medications alone or in combination fail, consider referral to a pain specialist or multidisciplinary pain center.

Extrapolation of the guidelines to CKD

Many of the recommendations for the general population can be extrapolated to the CKD population

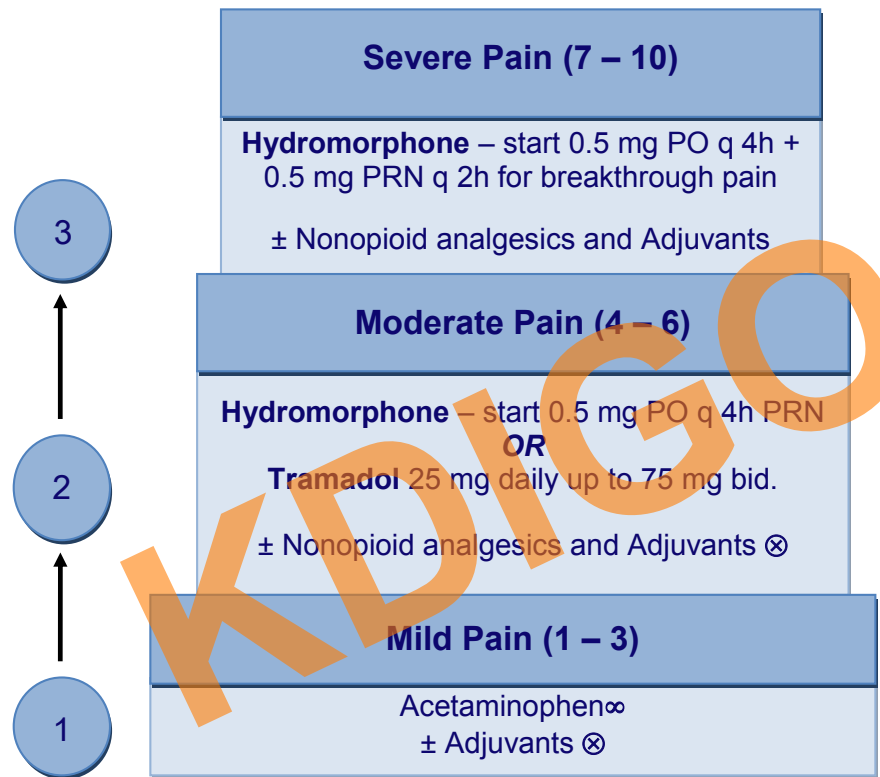
- Pharmacokinetic evidence
- Expert opinion

Key issue will be the careful selection and dosing of analgesics (not just opioids)

KIDIGO

Initial Approach to Chronic Pain Management in patient with Chronic Kidney Disease stages 4-5 and ESRD

(Adapted from the WHO 3 Step Analgesic Ladder)



[∞] **Acetaminophen.** Do not exceed 3.2 g/day of acetaminophen to avoid hepatotoxicity as per FDA recommendations. In high risk patients (malnourished, alcoholic) limit to 2.6 g/day.

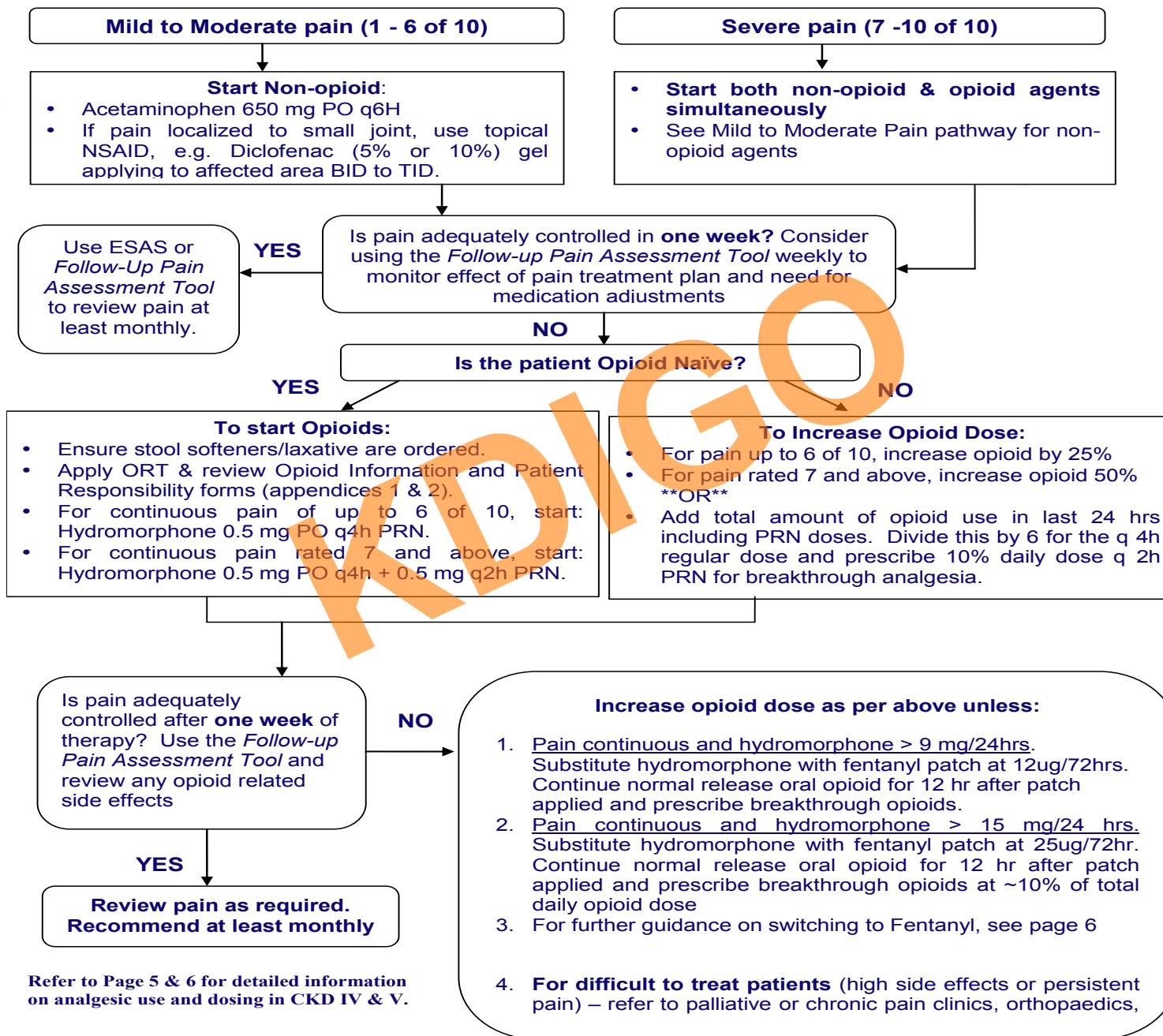
⊗ **Adjuvants** include medications such as anticonvulsants for neuropathic pain. It also refers to agents administered to manage adverse effects of an opioid.

PRN dosing for breakthrough pain: ~10% of the 24 hour dose of opioid prescribed every 1 to 2 hours as needed.

Long acting Hydromorphone (Dilaudid) is relatively contraindicated in advanced kidney disease based on expert opinion, due to the narrow therapeutic index for opioid analgesic effect relative to its side effects and toxicity.

Algorithm for Chronic Nociceptive or Musculoskeletal Pain

Nociceptive pain is described by patients as aching, dull, throbbing, cramping pressure.



Refer to Page 5 & 6 for detailed information on analgesic use and dosing in CKD IV & V.

RCT of 145 HD patients identified with pain ≥ 4 for 3 months (prevalence $< 50\%$)

- Algorithmic approach to chronic pain v. standard care (natural experiment)
- Patients within treatment arm (n=73)
- Management of pain
 - Nephrologist: 52.1%
 - Nephrology CNE: 8.2%
 - GP: 31.5%
 - Other specialist: 8.2%
- Patient goals = 3/10
- Type of pain:
 - Nociceptive pain: 40%
 - Neuropathic pain: 11%
 - Both: 60%
- Management
 - No change: 37%
 - Changed management but did not follow algorithm: 11%

Pain Severity & Characteristics

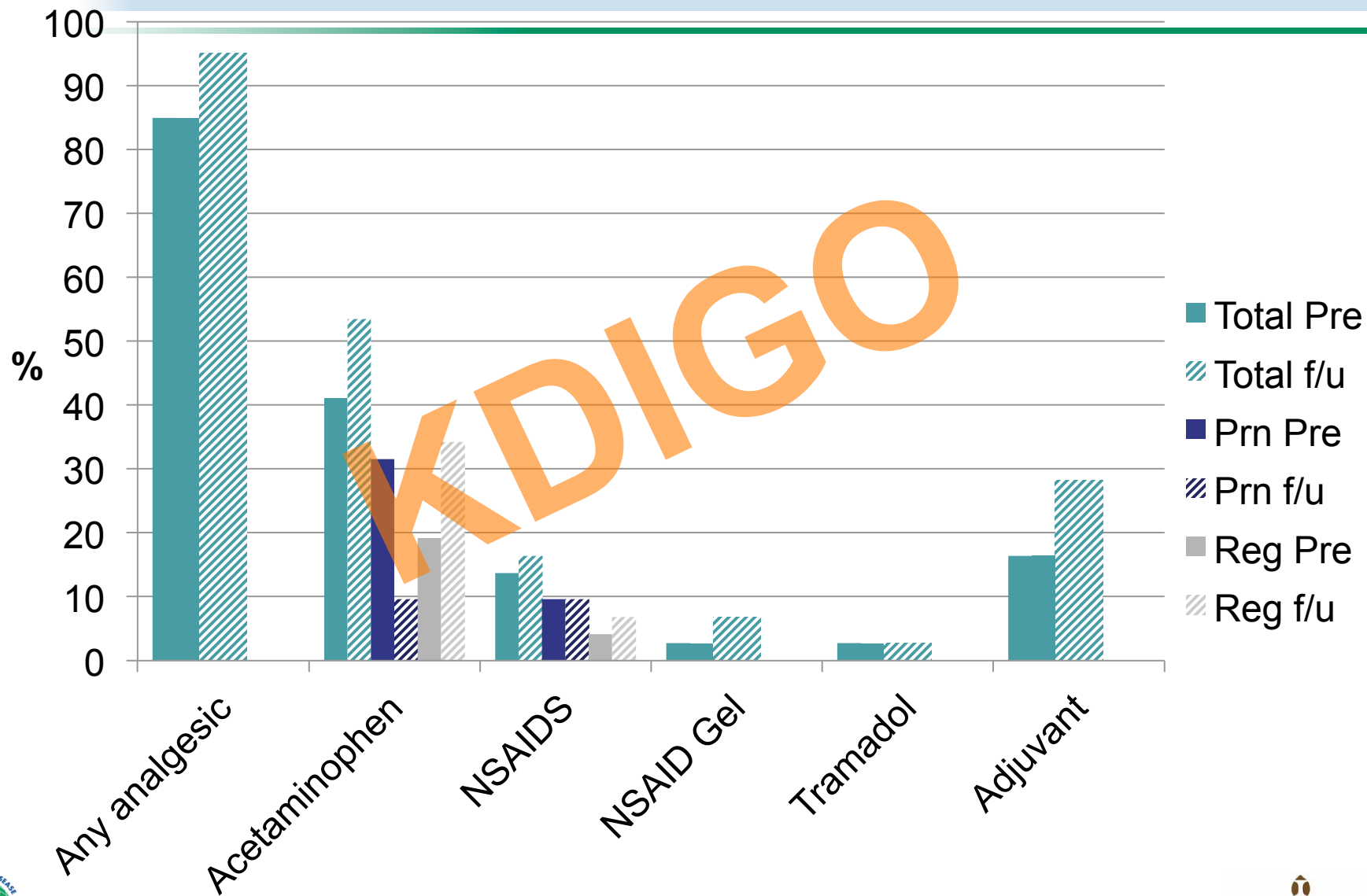
Pain Severity N = 73	Baseline Mean (SD); median	At follow-up Mean (SD); median
Pain now	4.9 (3.1); 5	3.2 (2.8); 2
Worst pain	8.3 (1.8); 9	6.4 (2.6); 6
Least pain	2.9 (2.6); 3	1.8 (2.5); 0
Average pain	5.8 (1.7); 5	3.6 (2.4); 3

- No change in management: 37%
- Changed management but did not follow algorithm: 11%
- Followed algorithm: 52%

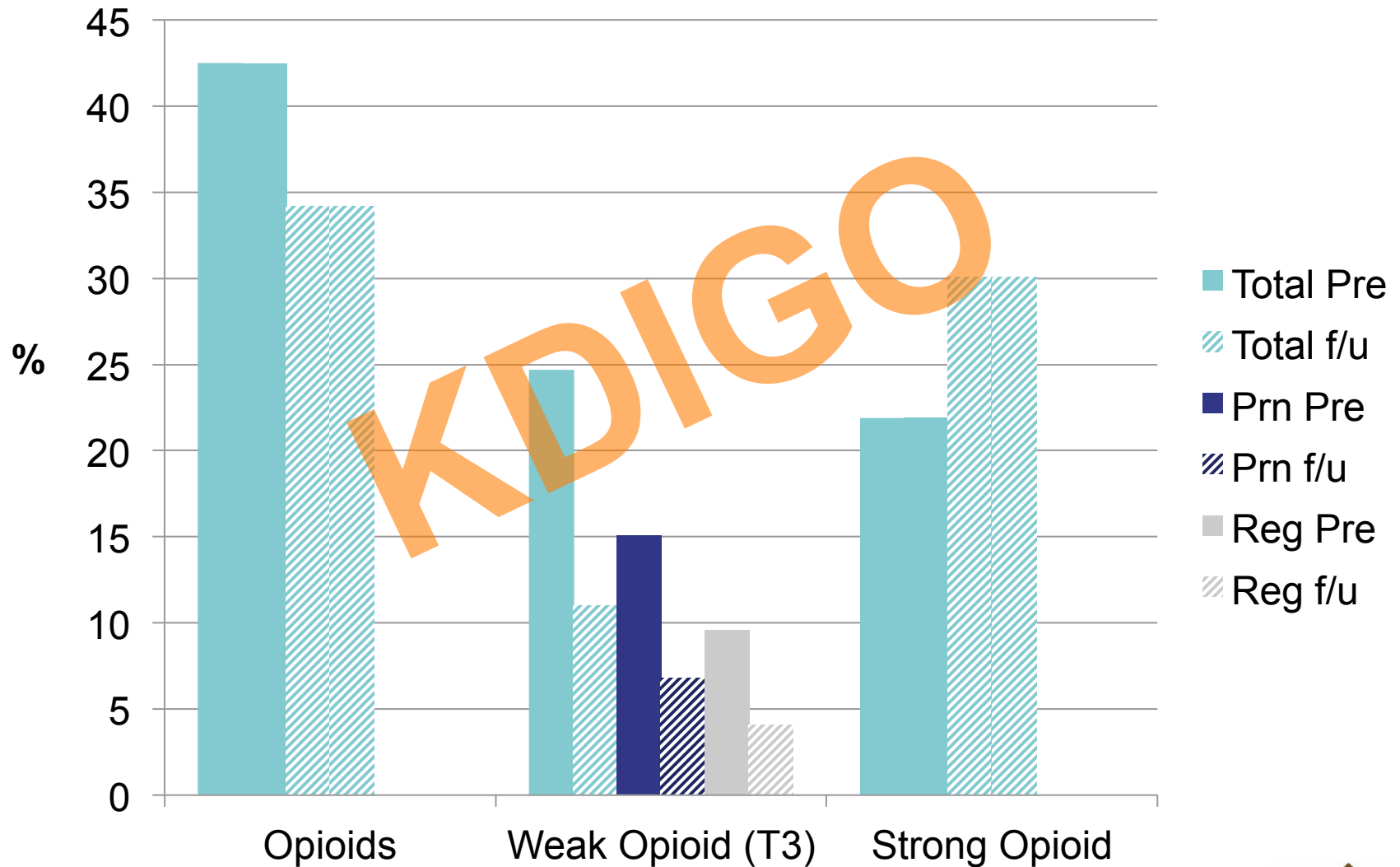
Impact of Pain

Impact of Pain N = 73	Baseline Mean (SD); median	At follow-up Mean (SD); median
General Activity	6.3 (2.7); 6	4.5 (3.3); 4
Mood	5.4 (3.1); 5	3.6 (3.0); 3
Walking	6.1 (3.3); 7	4.1 (3.3); 3
Normal work	5.5 (3.6); 6	3.9 (3.5); 3
Relationships	3.6 (3.4); 3	2.4 (2.8); 0
Sleep	5.4 (3.5); 5	3.7 (3.2); 2
Enjoyment	5.7 (2.9); 6	3.9 (2.8); 3

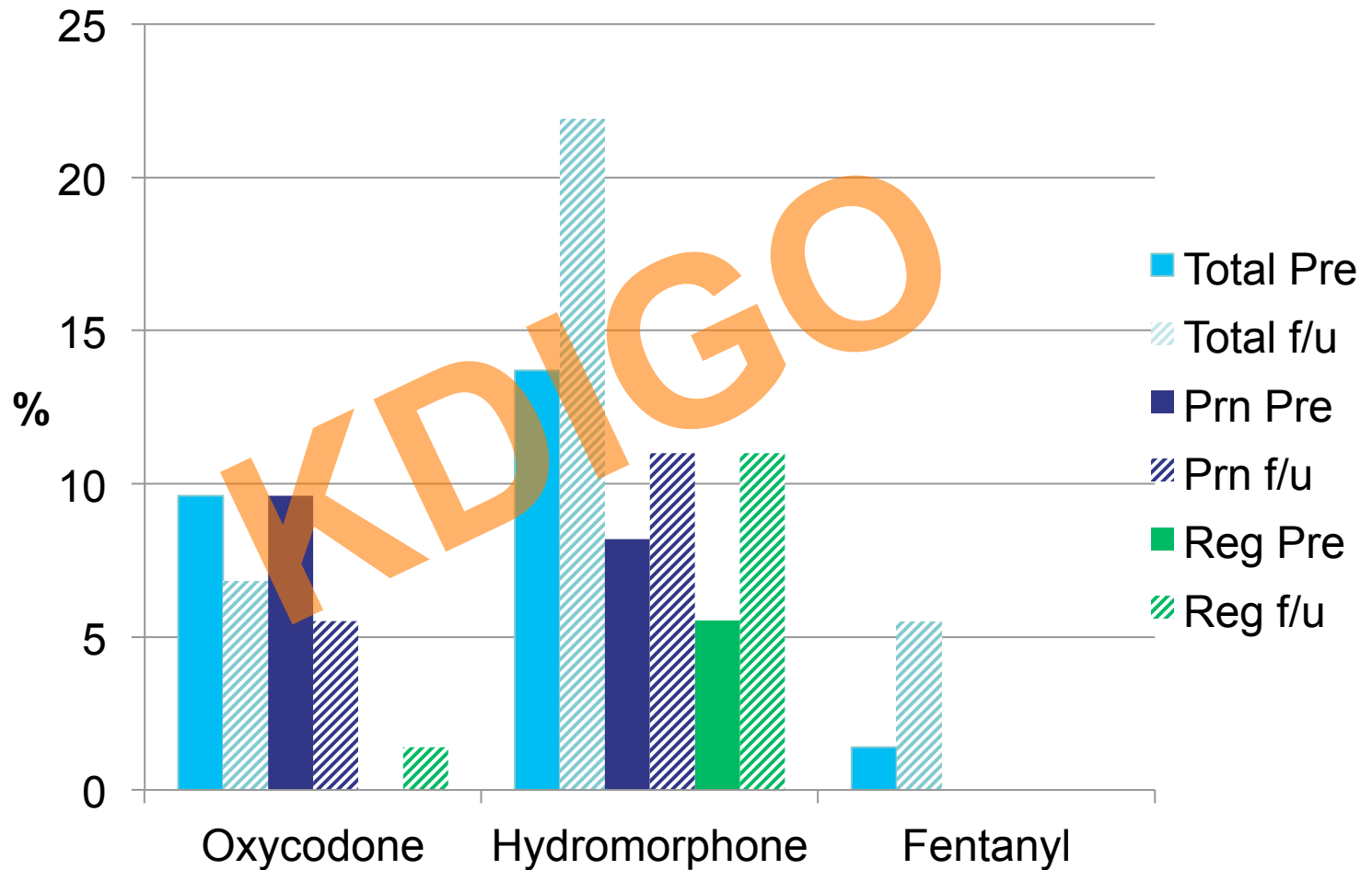
Total Analgesic Use (n = 73)



Total Opioid Use (n = 73)



Specifics of Strong Opioid Use

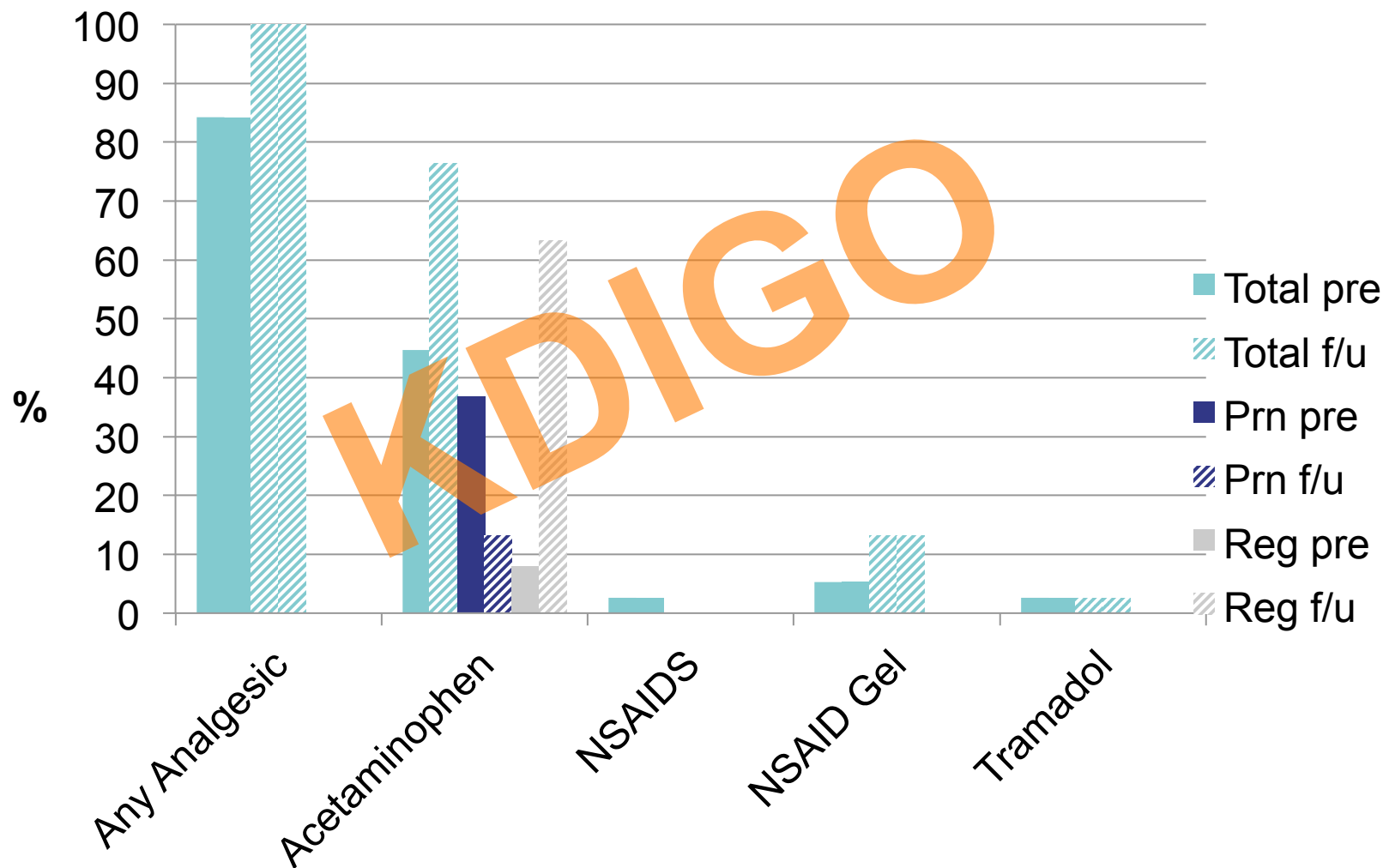


prn: 4.2mg v. 5.6mg
reg: 35 mg v. 11.6 mg

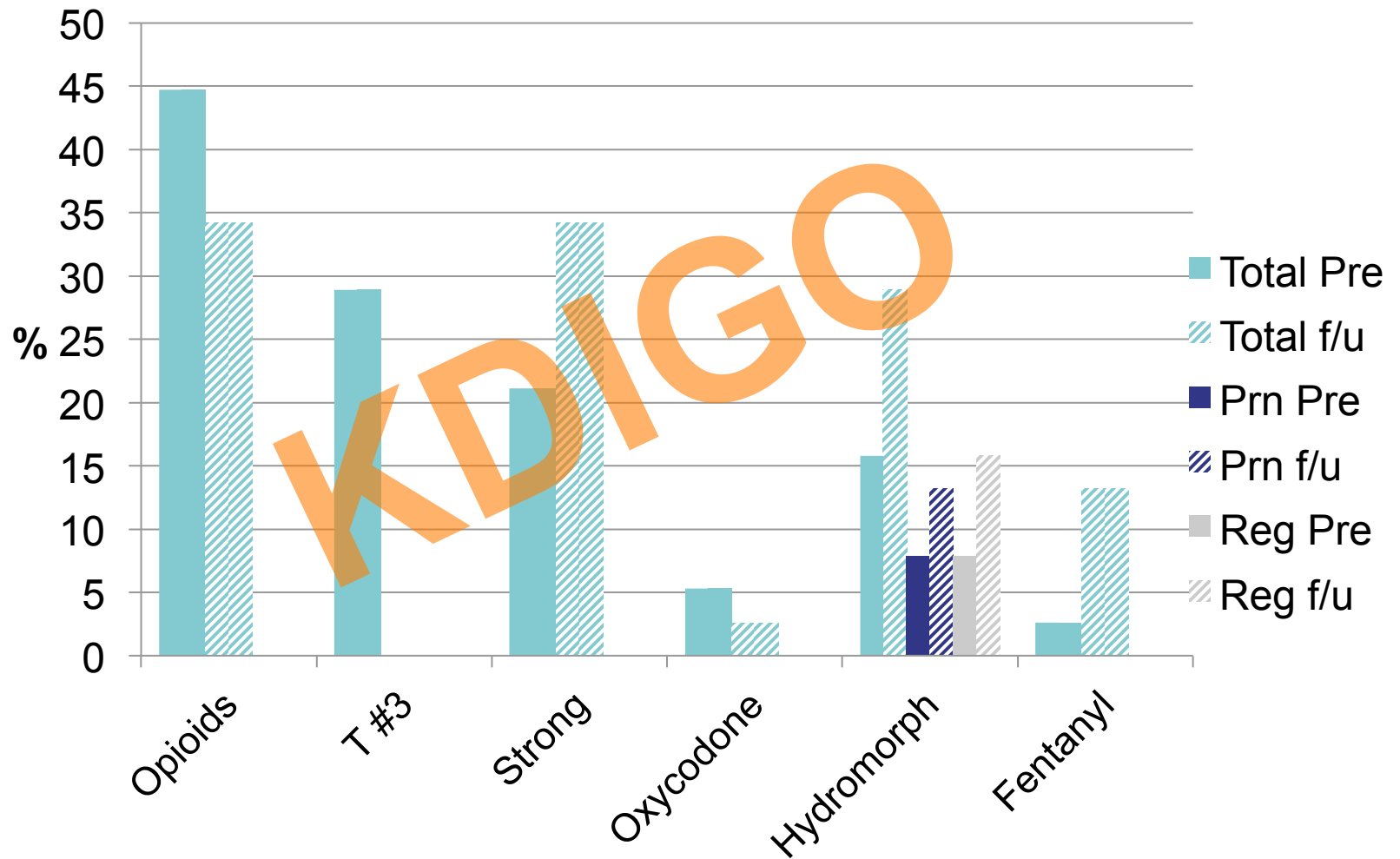
50ug v. 37ug/72hrs



Analgesic Use in Patients Managed by Algorithm (n = 38)

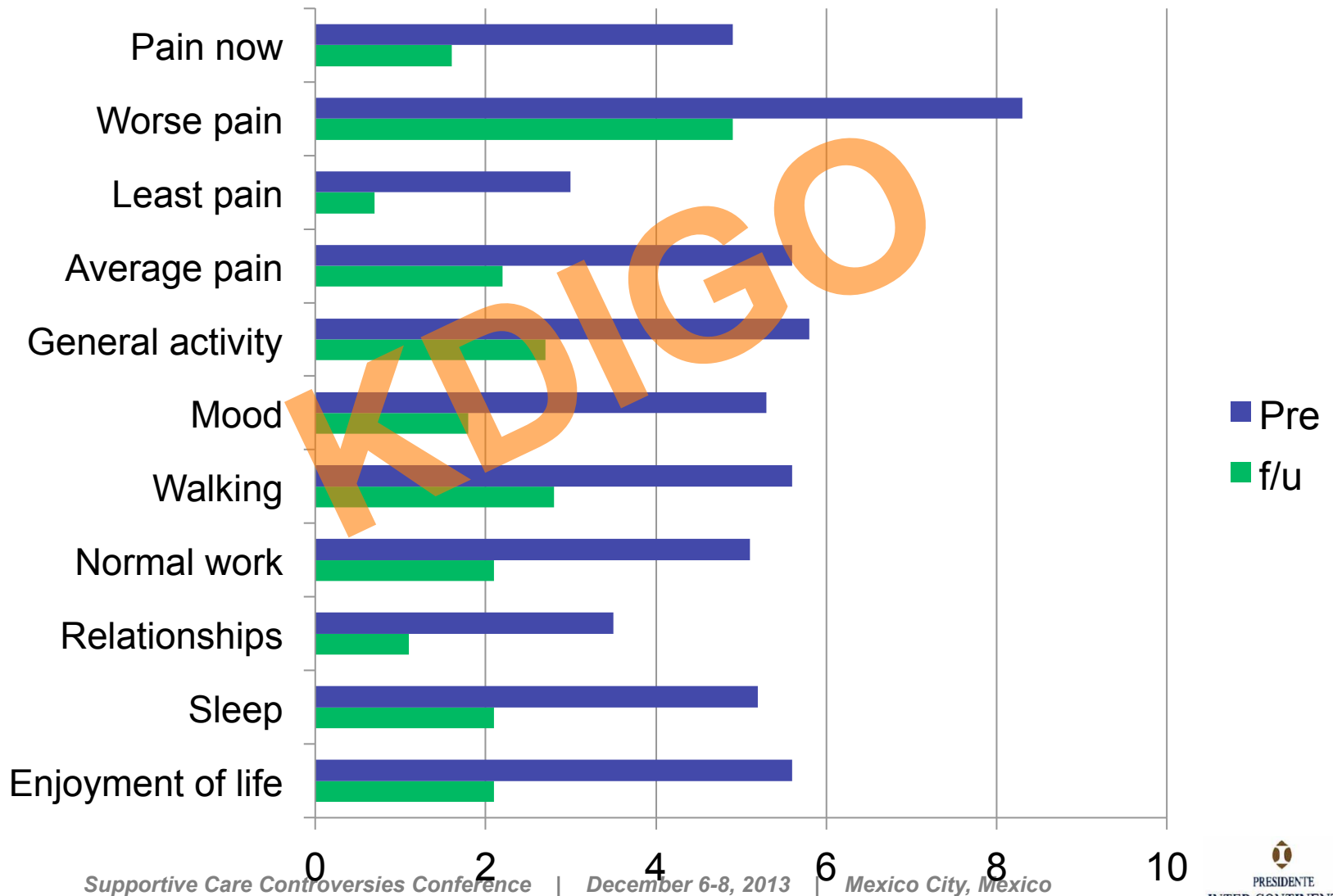


Opioid Use in Patients Managed by Algorithm (n=38)



prn: 4.0 v 5.4mg/day 50ug v. 37ug/72 hrs
 reg: 37.7 v 6.3 mg/day

Patients Managed with the Algorithm (n=38)



Pain Management RCT Summary

- Adverse effects of analgesics were minimal: constipation, somnolence
- 27/73 (37%) had no change in management
 - 12 of these patients (16%) refused suggested changes
- Addiction risk ?
 - ORT scores done on 47/73 pts (64%)
 - Only 3/47 patients were high risk (6%)
- Overall use of opioids decreased
 - Very little increase in the number of patients taking strong opioids
 - Those that did, doses were small
- Overall substantial benefit to the majority of patients
- Gabapentin use increased:
 - Additional benefits of pruritus, decreased restless legs and sleep?
 - Dosing was much higher than appropriate (did not adhere to guideline)

Pain Management in Developing Nations

- Access to opioids is limited or non-existent in many nations. The International Narcotics Control Board (INCB) which monitors both the licit and illicit use of opioids reports that over 80 % of the world's population has limited or no access to opioids for medical purposes.¹
- Inadequate education in medical schools on the safe use of opioids.
- Domestic opioid laws, which concentrate on the restriction of opioid use with little if any regard for the use of opioids in a medical context. Other factors also play a role.
- A majority of governments reported that fears of addiction among patients and health professionals and insufficient training for health-care professionals were critical issues.
- Issues of costs – not just for the medications themselves but for the infrastructure and processes required for safe and effective use of those medications.
- Most nations have no national policy on pain management (or the provision of Palliative Care).

Pain Management in Developing Nations

- National and International Pain and Palliative Care Associations (e.g. International Association for the Study of Pain (IASP)) have been advocating to national governments and the United Nations through a series of declarations that pain relief should be seen as a basic human right within the international right to health.
- The most recent declaration to emerge from the IASP of pain management as a human right was The Montreal Declaration that emerged from the inaugural International Pain Summit held in Montreal in 2011. That document expressly referred to chronic pain in the context of chronic illnesses which includes CKD

Chronic Pain in CKD

Recommendations

Evidence is sufficient to proceed with guideline development

Research Priorities

1. Symptom (pain) epidemiology and burden in LMIC.
2. Symptom (pain) epidemiology and burden in conservatively cared for patients (with comparisons made to those on dialysis).
3. Symptom (pain) trajectories at the end-of-life.
4. Analgesic prescribing in CKD patients with pain.
5. Analgesic use & availability for CKD patients in LMIC.
6. **Barriers in managing chronic pain in CKD: healthcare provider & healthcare system perspectives; high and LMIC perspectives**
7. Efficacy & safety of chronic pain management strategies. These strategies would need to evaluate various analgesics (and adjuvants) at all levels of the WHO analgesic ladder.....outcome includes global symptom burden