Pain and Chronic Kidney Disease

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Renal Supportive Care Symposium
St George Hospital
August 21 2015
- Epidemiology
- Effect on function and QOL
- Causes
- Management
Epidemiology of pain in CKD

Dialysis patients – 58%

Mean weighted prevalence over 36 studies

Seminars in Dialysis 2014; 27(2): 188-204.
49% reported the pain as moderate to severe
Data on conservatively managed patients is more limited but shows similar prevalence and severity figures.


Impact on function and QOL
Data from 9 studies representing approximately 2100 HD patients found that pain was associated with lower HR-QOL.

Table 2 in Davison S, Koncicki H, Brennan F. Pain in Chronic Kidney Disease: A Scoping Review. *Seminars in Dialysis* 2014; 27(2): 188-204.
Impact on QOL

Davison (2002)
69 dialysis patients

62% stated that pain interfered with their ability to participate and enjoy recreational activities.
51% stated that pain caused them “extreme suffering”
41% stated that pain caused them to consider ceasing Dialysis
Positive correlation with depression

Causes of Pain

ESRD and its treatment

Co-morbidities
1. Pain related to the disease:

- Polycystic Kidney Disease
- Renal Bone Disease
- Amyloid — including Carpal Tunnel Syndrome
- Calciphylaxis
2. Pain secondary to treatment:

- PD pts with recurrent abdominal pain
- AV Fistulae > ‘Steal syndrome’
- Cramps
- Intradialytic headaches
3. Pain related to co-morbidities:

- OA
- Diabetic peripheral neuropathy
- PVD / IHD
Barriers to good pain management

Patient related:

• Stoicism
• Not wanting to “trouble the doctor”
• Fatalism
• Fear of analgesic medications.
Clinician related:

- Inadequate education in pain management
- Lack of standardised management regimens across multiple pain syndromes
- Fatalism that pain is an unavoidable aspect of ageing and being on dialysis
- Seeing pain and symptoms generally are secondary priorities.
Opiophobia and opioignorance
Pain etiquette

• ENQUIRE REGULARLY

• RESPOND COMPASSIONATELY

• TREAT COMPETENTLY

• REFER WISELY
Principles of pain management

1. Always enquire about pain.
2. Treat the underlying cause of the pain.
3. Treat the pain meticulously.
4. Treat the pain proportionately.
5. Constantly reassess.
Pain management in patients with CKD
The traditional approach to the pharmacological management of pain has been to use the WHO Analgesic Ladder.
Certainly, the WHO Ladder has been validated in the context of ESKD and it remains a useful construct.

Could the WHO Analgesic Ladder be used as part of a broader perspective in pain management in the specific context of CKD?
Towards a strategic approach to pain management in patients with CKD
1. There are few studies examining pain management in the specific context of CKD
2. There are international evidence based guidelines and consensus statements on pain management of specific pain syndromes for the whole population.
• Osteoarthritis

• Painful diabetic peripheral neuropathy

• Cancer pain
3. There is an increasing, although not complete, understanding of the pharmacology of analgesic medications in the context of CKD and their dialysability
These recommendations could be filtered through the known pharmacology of medications in the context CKD and their dialysability
Pain syndrome

Evidence based Guidelines and Consensus Statements

Pharmacokinetics/Pharmacodynamics

Pain management for patients in the context of CKD
• A 69 y. o. man with Type II DM, diabetic nephropathy.

• ESKD – HD for 4 years.

• Progressively more painful diabetic peripheral neuropathy
Evidence-based guideline: treatment of painful diabetic neuropathy.


In painful diabetic neuropathy there is:

- Level A evidence – Pregabalin

- Level B evidence for Gabapentin, Duloxetine, Amitriptiline, Sodium Valproate, Morphine, Tramadol, Capsaicin, Isosorbide trinitrate spray and TENS
Gabapentinoids

Gabapentin approx. 100 % renally excreted.

Pregabalin – 92-99 % renally excreted.
H/Dialysis:

• Gabapentin dialysed
• Pregabalin dialysed (50% in 4 hours)
PD

Gabapentin possibly dialysed
Pregabalin – dialysed.
On Dialysis

Pregabalin 25 mg after each Dialysis

Titrate to effect
On conservative management

eGFR < 15

Pregabalin 25 mg every 2\textsuperscript{nd} night

Titrate to effect
On conservative management

eGFR > 15

Pregabalin 25 mg nocte

Titrate to effect
Davison S, Koncicki H, Brennan F.

Pain in Chronic Kidney Disease: A Scoping Review.

Seminars in Dialysis 2014; 27(2): 188-204.
Koncicki H, Brennan F, Vinen K, Davison SN.

An approach to pain management in End Stage Renal Disease – Considerations for General Management.

Seminars in Dialysis. April 11 2015
The challenge of multiple pain aetiologies
A 73 year old woman

Multiple co-morbidities including Type II DM, Diabetic Nephropathy on HD.
At first consultation:

- Osteoarthritis in lower back and knees bilaterally.
- Gouty arthropathy
- Carpal Tunnel syndrome
- Painful diabetic peripheral neuropathy (severe)
- Cramps on dialysis
- Post-operative pain
Role of Pain Services
Pharmacokinetics
Step 1

Paracetamol
- Metabolised in liver
- 2-5% excreted unchanged renally
- Inactive metabolites
• HD – dialysed

• PD – not dialysed
No dose adjustment = 1g qid
“It is considered the non-narcotic analgesic of choice for mild-moderate pain in CKD patients.”

Step 2

Tramadol
86% Metabolised in Liver

Tramadol

O- Desmethyl Tramadol (M1) (Active)

N- Desmethyl Tramadol (Inactive)
90 % of Tramadol and its metabolites are renally excreted

= 30 % unchanged; 60 % as metabolites.
Tramadol

- HD – dialysed

- PD – not known
Need for dose adjustment
Step 2

Tramadol “is the least problematic of the Step 2 Analgesics for ESRD patients”

Nevertheless use with caution – use a bd dose.
If on Conservative pathway eGFR 15-30

Commence 50mg bd

Maximum 100mg bd
If on a Conservative pathway

eGFR < 15

or Dialysis

Tramadol 50mg bd (maximum)
HD significantly removes Tramadol so dose best given post-dialysis
Codeine
Metabolised in Liver

Codeine

Morphine
Norcodeine
Reports of:
profound hypotension
CNS and
Respiratory depression
“Not recommended in CKD.”

Davison S et al. *Seminars in Dialysis* 2014; 27(2): 188-204
Step 3

Morphine
Morphine

Hepatic metabolism

M-3-G  M-6-G

Kidneys
Morphine is not recommended in CKD
Step 3

Hydromorphone
Metabolised in Liver

Hydromorphone

Hydromorphone -3- Glucuronide
Hydromorphone

- HD – H-3 G is dialysed

- PD – not known
“Much better tolerated than morphine with less toxic metabolites. Pharmacodynamic data shows less neuroexcitation compared to morphine...no clinically significant opioid toxicity if given in low doses and monitored carefully.”

Davison S et al. Seminars in Dialysis 2014; 27(2): 188-204
• Commence low (0.25-0.5mg) and qid.

• If tolerated – q4hours

• Titrate up dose carefully – once pain well controlled aim to convert to a safe long acting opioid.

Oxycodone
Oxycodone

Short-acting
Endone
Oxynorm

Long-acting
Oxycontin
Oxynorm
• Metabolised by liver

• Active metabolites are eliminated mainly by hepatic metabolism. Less than 10% excrete renally.

• Single dose study showed prolongation of oxycodone and its metabolites
Oxycodone

- HD – dialysed

- PD – not known
“Overall consensus is that Oxycodone is reasonably safe to use in CKD if monitored carefully.”

Davison S et al. Seminars in Dialysis 2014; 27(2): 188-204
Fentanyl
• Metabolised in Liver

• Inactive metabolites

• 5-10 % excreted unchanged renally

• Fentanyl is not dialysed (HD/PD)
Fentanyl is safe to use at standard doses

- should monitor carefully.

Davison S et al. *Seminars in Dialysis* 2014; 27(2): 188-204
Buprenorphine

= Norspan
Buprenorphine

- Buprenorphine – 3 – Glucuronide (B-3-G)
- Norbuprenorphine (NorB)

Both accumulate in CKD
B-3-G is inactive; NorB has minor analgesic quality
Buprenorphine

- HD – dialysed
- PD – dialysed
“Buprenorphine may be given in standard doses to patients with CKD. Generally considered safe for use in CKD if monitored carefully.”

Davison S et al. *Seminars in Dialysis* 2014; 27(2): 188-204
Methadone
• Metabolised in liver

• Excreted mainly in the feces. Some renal excretion of Methadone and its metabolites

• Not dialysed

• Safe to use, but requires skill in dosing regimen – specialist use.
The hand that writes the opioid must also write the laxative
WHO Ladder ESRD summary

Step 1 --- Paracetamol 1g qid
Step 2 --- Tramadol (adjusted dose)
Step 3

Hydromorphone

Oxycodone

Fentanyl

Buprenorphine

Methadone
The experience of the Renal Supportive Care Service, St George Hospital
Between March 2009 and July 2015, 278 patients completed a POS (S) – Renal at their first Renal Supportive Care clinic visit.
### Questionnaire POS-S (renal) – staff version

Below is a list of symptoms which the patient may or may not have experienced. Please record how these symptoms have affected the patient in the table below. Put a tick in the box to show how you think they have affected how they have been feeling **over the last week.**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Not at all, no effect</th>
<th>Slightly — but not bothered to be rid of it</th>
<th>Moderately — limits some activity or concentration</th>
<th>Severely — activities or concentration markedly affected</th>
<th>Overwhelmingly — unable to think of anything else</th>
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<tbody>
<tr>
<td>Pain</td>
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<tr>
<td>Shortness of breath</td>
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<td>Weakness or lack of energy</td>
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<td>Nausea (feeling like you are going to be sick)</td>
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<td>Vomiting (being sick)</td>
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<td>Poor appetite</td>
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<td>Constipation</td>
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<td>Mouth problems</td>
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<td>Drowsiness</td>
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<td>Poor mobility</td>
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<td>Itching</td>
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<td>Difficulty sleeping</td>
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<td>Restless legs or difficulty keeping legs still</td>
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<td>Feeling anxious</td>
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<td>Feeling depressed</td>
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<td>Changes in skin</td>
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<tr>
<td>Diarrhoea</td>
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<tr>
<td><strong>Any other symptoms?</strong></td>
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</table>

Which symptom has affected the patient the most? ...........................................................

Which symptom, if any, has improved the most? ............................................................
Of those 278 patients:

38% were dialysis patients

59% were conservatively managed patients

(3% transplant and undecided)
Pain reported at first clinic visit

- 62% of dialysis patients reported pain (51% moderate / overwhelming)

- 56% of conservatively managed patients reported pain (51% moderate/ overwhelming)
Following those patients who had at least 3 clinic visits.
Between March 2009 and July 2015, 278 patients have completed a POS-S (Renal) at their first Renal Supportive Care clinic visit. 173 patients attended at least 3 visits (3 transplant patients were excluded from analysis).

<table>
<thead>
<tr>
<th></th>
<th>Total n=173</th>
<th>NFD n=116</th>
<th>RRT n=53</th>
<th>CKD/ Undecided n= 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
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<tr>
<td>Mean ± SD</td>
<td>77 ± 11</td>
<td>82 ± 8</td>
<td>69 ± 13</td>
<td>80 ± 5</td>
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<tr>
<td>Median</td>
<td>81</td>
<td>83</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>Range</td>
<td>37 - 99</td>
<td>50 - 99</td>
<td>37 - 89</td>
<td>75 - 85</td>
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<tr>
<td><strong>Male, n (%)</strong></td>
<td>98 (56)</td>
<td>58 (50)</td>
<td>36 (64)</td>
<td>1 (25)</td>
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<tr>
<td><strong>eGFR</strong></td>
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<tr>
<td>Mean ± SD</td>
<td>17 ± 12</td>
<td>17 ± 10</td>
<td>12 ± 9</td>
<td>28 ± 11</td>
</tr>
<tr>
<td>Median</td>
<td>13</td>
<td>14</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>Range</td>
<td>3 - 90</td>
<td>5 - 52</td>
<td>3 - 60</td>
<td>16 - 43</td>
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<tr>
<td><strong>Co-morbidities</strong></td>
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<tr>
<td>Diabetes, n (%)</td>
<td>87 (49)</td>
<td>52 (45)</td>
<td>33 (59)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>IHD, n (%)</td>
<td>75 (43)</td>
<td>52 (45)</td>
<td>22 (39)</td>
<td>1 (25)</td>
</tr>
<tr>
<td><strong>Average POS Severity score- 1st visit</strong></td>
<td>1.9</td>
<td>1.9</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Average POS Severity score- 3rd visit</strong></td>
<td>1.7</td>
<td>1.7</td>
<td>1.6</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Pain reported at third clinic visit
Pain Scores for Dialysis patients at first and third visits

Pain - Dialysis patient (n=53)

- None: POS1 (35%) POS3 (25%)
- Slight: POS1 (5%) POS3 (20%)
- Moderate: POS1 (40%) POS3 (25%)
- Severe: POS1 (15%) POS3 (15%)
- Overwhelming: POS1 (0%) POS3 (5%)

Legend:
- POS1
- POS3
Pain Scores for Conservative patients at first and third visits

Pain - NFD patients (n=116)

None: POS1 40%, POS3 45%
Slight: POS1 15%, POS3 12%
Moderate: POS1 30%, POS3 25%
Severe: POS1 10%, POS3 12%
Overwhelming: POS1 5%, POS3 3%
Isolating those patients that reported severe to overwhelming pain at the first clinic visit....

What happened to them by the 3\textsuperscript{rd} clinic visit?
Average Pain POS Scores for patients that scored Pain as severe or overwhelming at their first visit

Average Pain POS Scores between clinic 1 and 3
Average number weeks between clinics 1 and 3 = 11 weeks

- NFD (n=21)
- RRT (n=16)
- All (n=37)

[Graph showing average pain POS scores for different groups]
Pain Scores at Clinic 3 - for those patients with severe/overwhelming pain at clinic 1

n = 37
What happened over time?
Pain Score - patterns - Dialysis patients
- for patients with more than one visit
- for patients that scored 3-4 for pain on their first visit (Severe to overwhelming)
- for clinic visits where there were 5 or more patients
Pain Score - patterns - Conservative patients
- for patients with more than one visit
- for patients that scored 3-4 for pain on their first visit (Severe to overwhelming)
- for clinic visits where there were 5 or more patients
Conclusion

Pain is a common symptom in patients with CKD
Pain may be secondary to:

• The underlying renal disease

• Management of ESKD

• Co-morbidities
Requires a careful and calibrated approach based on:

- Identifying the aetiology of the pain
- Best evidence for management generally
- Pharmacokinetics of specific medications
- Where appropriate consider a non-pharmacological approach.
Role of Pain Services
Acknowledgements:

- Anna Hoffman for her preparation of the graphs.

- Elizabeth Josland, Alison Smyth, Gemma Collet, Mark Brown.