Pain and Chronic Kidney Disease

Frank Brennan
Palliative Care Physician
Department of Nephrology, St George Hospital

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

Davison S, Koncicki H, Brennan F. Pain in Chronic Kidney Disease : A Scoping Review. *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.

Murtagh FEM et al. A Cross-sectional Survey of Symptom Prevalence in Stage 5 CKD managed without Dialysis. *J Pall Med* (2007) 10;6:1266-1276.

Brennan FP. Et al. Symptoms in patients with CKD managed without dialysis. *Progress in Palliative Care* 2015 (in Press)

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

Davison S, Jhangri GS. *J Pain Symptom Management* 2005; 30(5): 465-473

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.

Barakovsky AS et al. *J Am Soc Nephrol* 2006; 3198-3203

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

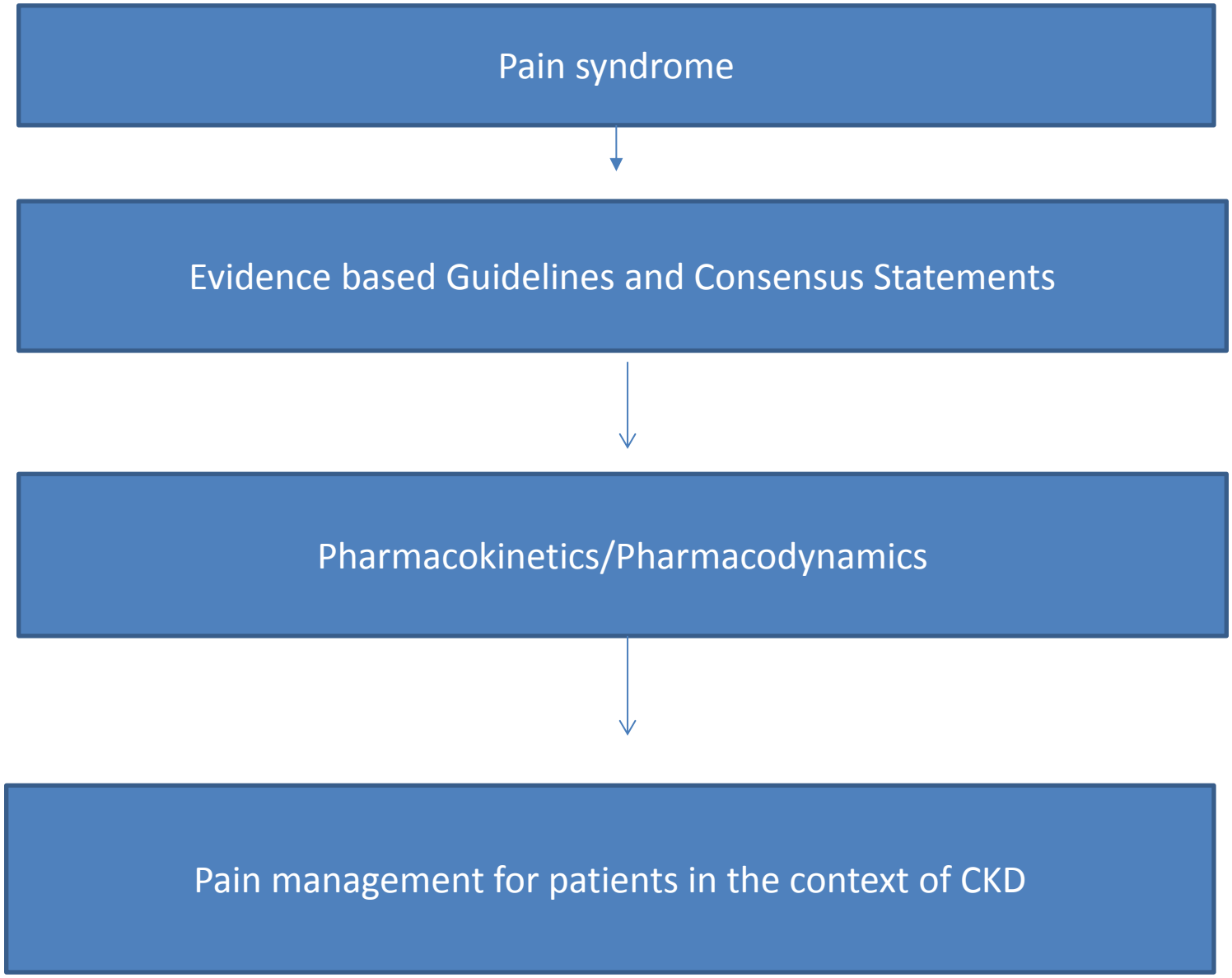
2. There are international evidence based guidelines and consensus statements on pain management of specific pain syndromes for the whole population.

- 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.

Report of the American Academy of Neurology et al.

Bril V et al *Neurology* 2011; 76: 1758-1765.

In painful diabetic neuropathy there is :

- Level A evidence – Pregabalin

- Level B evidence for Gabapentin, Duloxetine, Amitriptline, 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 2nd 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."

Davison S, Ferro CJ. Management of Pain in CKD. *Progress in Palliative Care* 2009; 17: 186-195.

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)

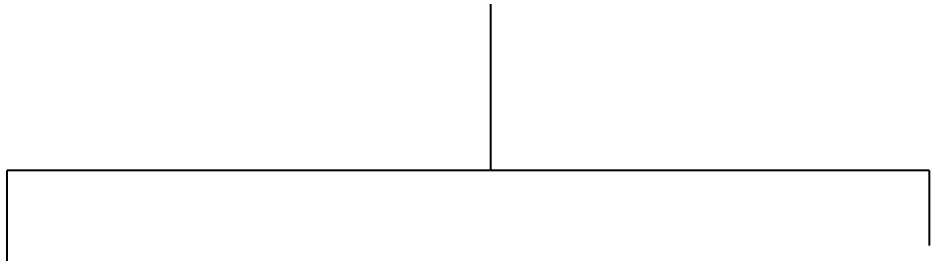
HD significantly removes Tramadol

so dose best given post-dialysis

Codeine

Metabolised in Liver

Codeine



Morphine

Norcodeine

Reports of :

profound hypotension

CNS and

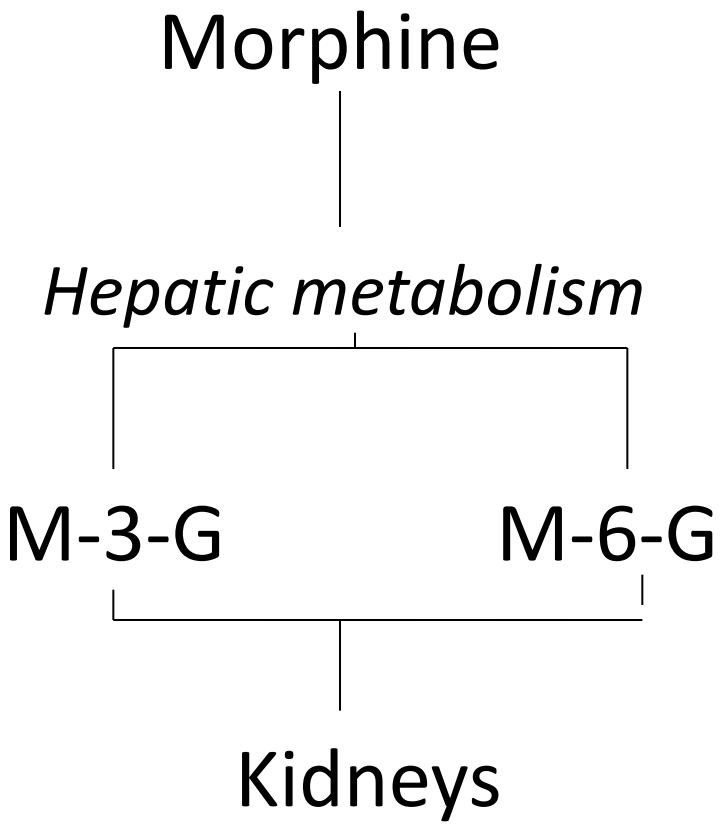
Respiratory depression

“Not recommended in CKD.”

Davison S et al. S*eminars 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. S*eminars 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.

Davison S, Chambers EJ, Ferro CJ. Management of pain in Renal Failure. In Chambers EJ et al (eds) *Supportive Care for the Renal Patient* 2010, 2nd ed, OUP.

Oxycodone

Oxycodone

Short-acting	Long-acting
Endone	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. S*eminars in Dialysis* 2014; 27(2): 188-204

Fentanyl

- Metabolised in Liver
- Inactive metabolites
- 5-10 % excreted unchanged renally
- Fentanyl is not dialysed (HD/PD)

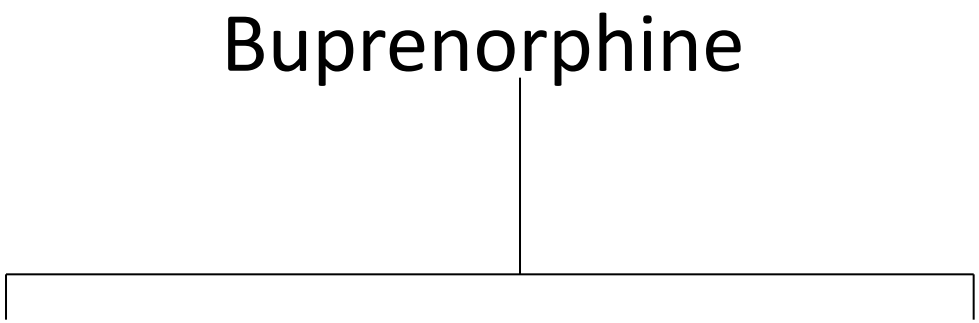
Fentanyl is safe to use at standard doses

- should monitor carefully.

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

Buprenorphine

= Norspan



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. S*eminars 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.**

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

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.

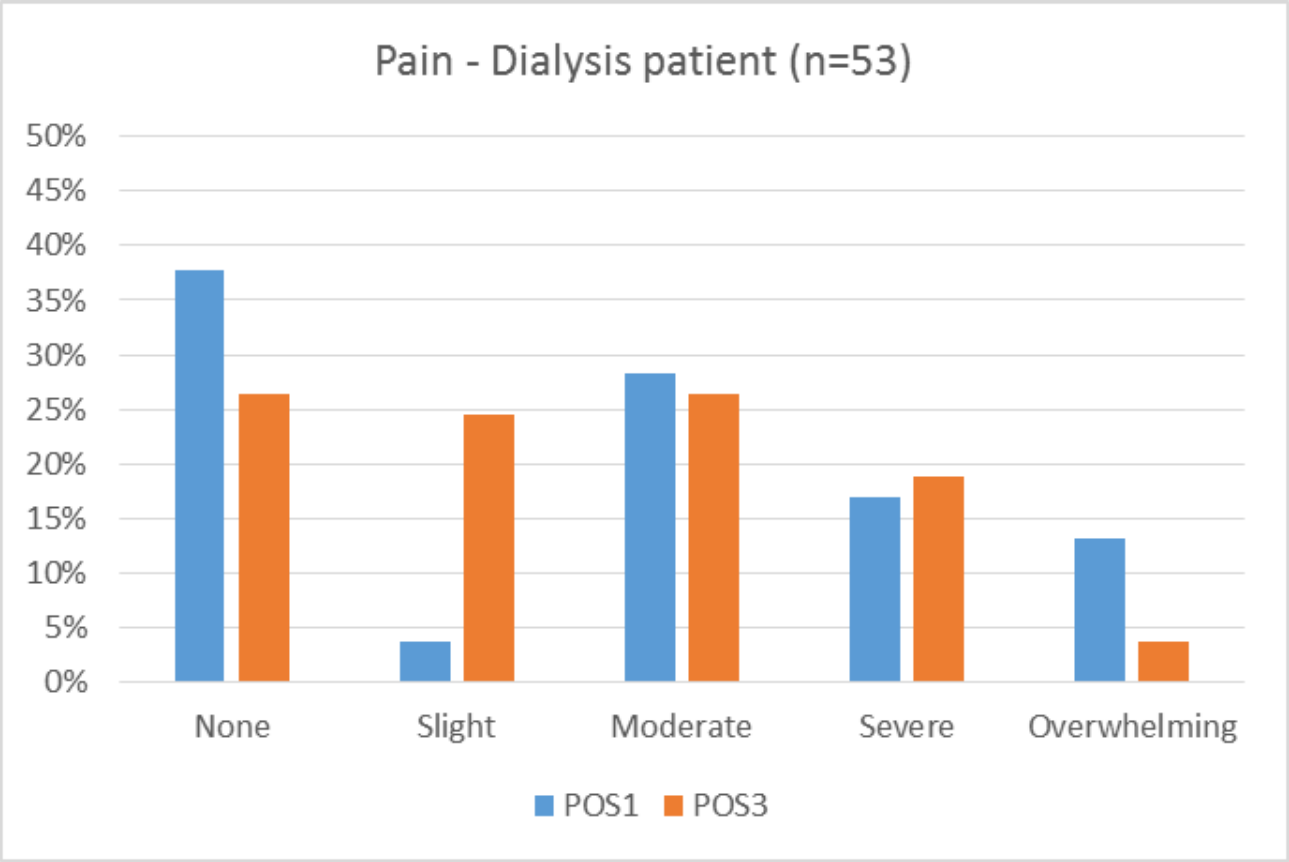
Between March 2009 and July 2015, 278 patients have completed a POS-S (Renal) at their first Renal Supportive Care clinic visit.

173 patients attended at least 3 visits (3 transplant patients were excluded from analysis)

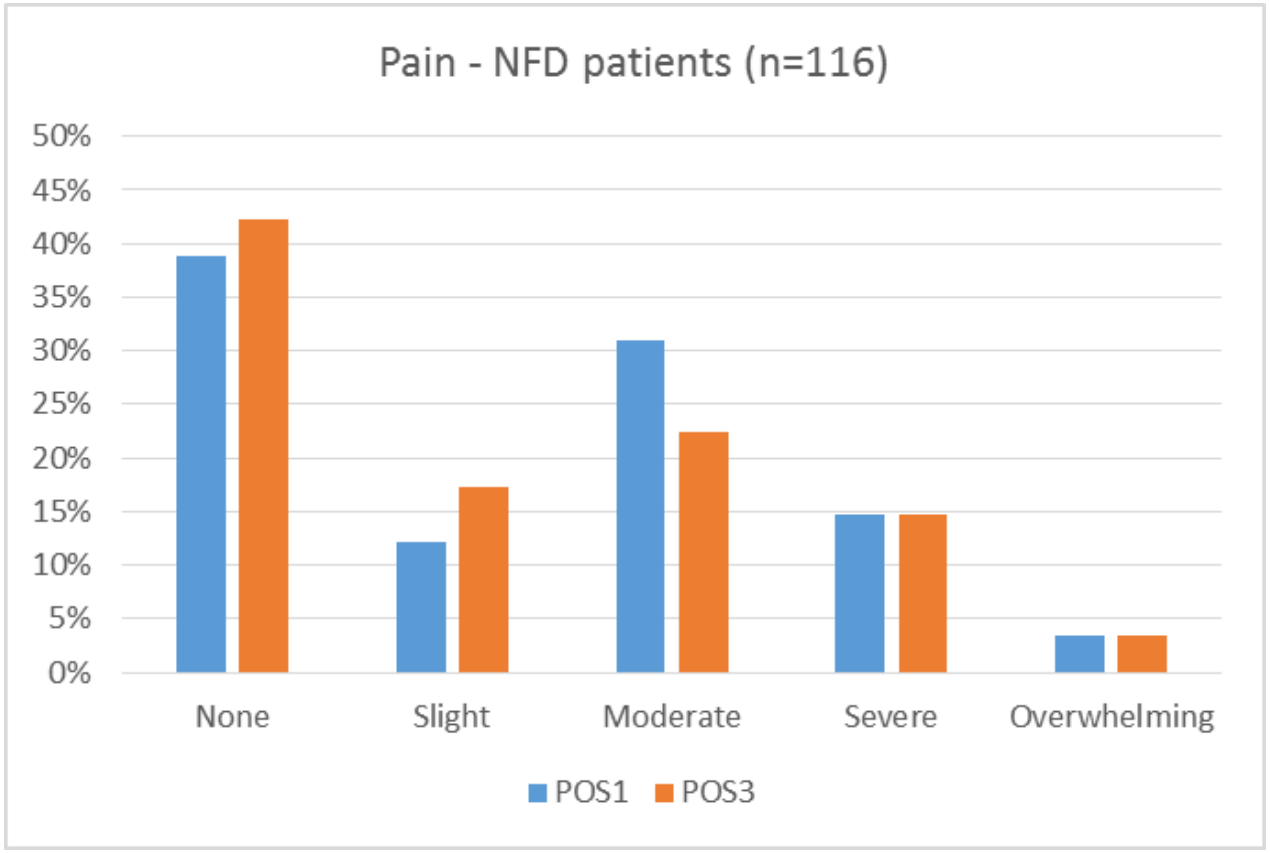
	Total n=173	NFD n=116	RRT n=53	CKD/ Undecided n= 4
Age, years				
Mean ± SD	77 ± 11	82 ± 8	69 ± 13	80 ± 5
Median	81	83	72	80
Range	37 - 99	50 - 99	37 - 89	75 - 85
Male, n (%)	98 (56)	58 (50)	36 (64)	1 (25)
eGFR				
Mean ± SD	17 ± 12	17 ± 10	12 ± 9	28 ± 11
Median	13	14	9	26
Range	3 - 90	5 - 52	3 - 60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

Pain reported at third clinic visit

Pain Scores for Dialysis patients at first and third visits



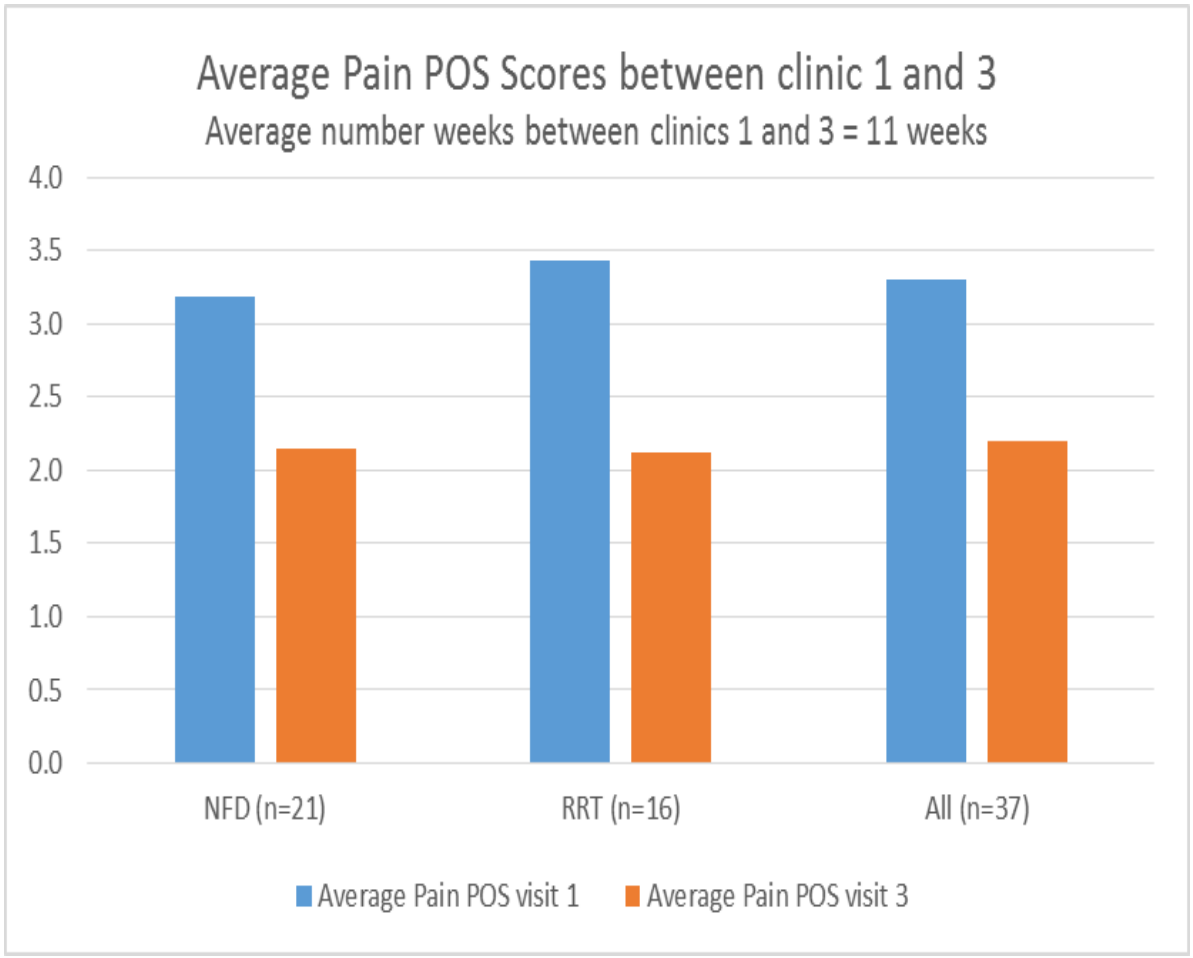
Pain Scores for Conservative patients at first and third visits

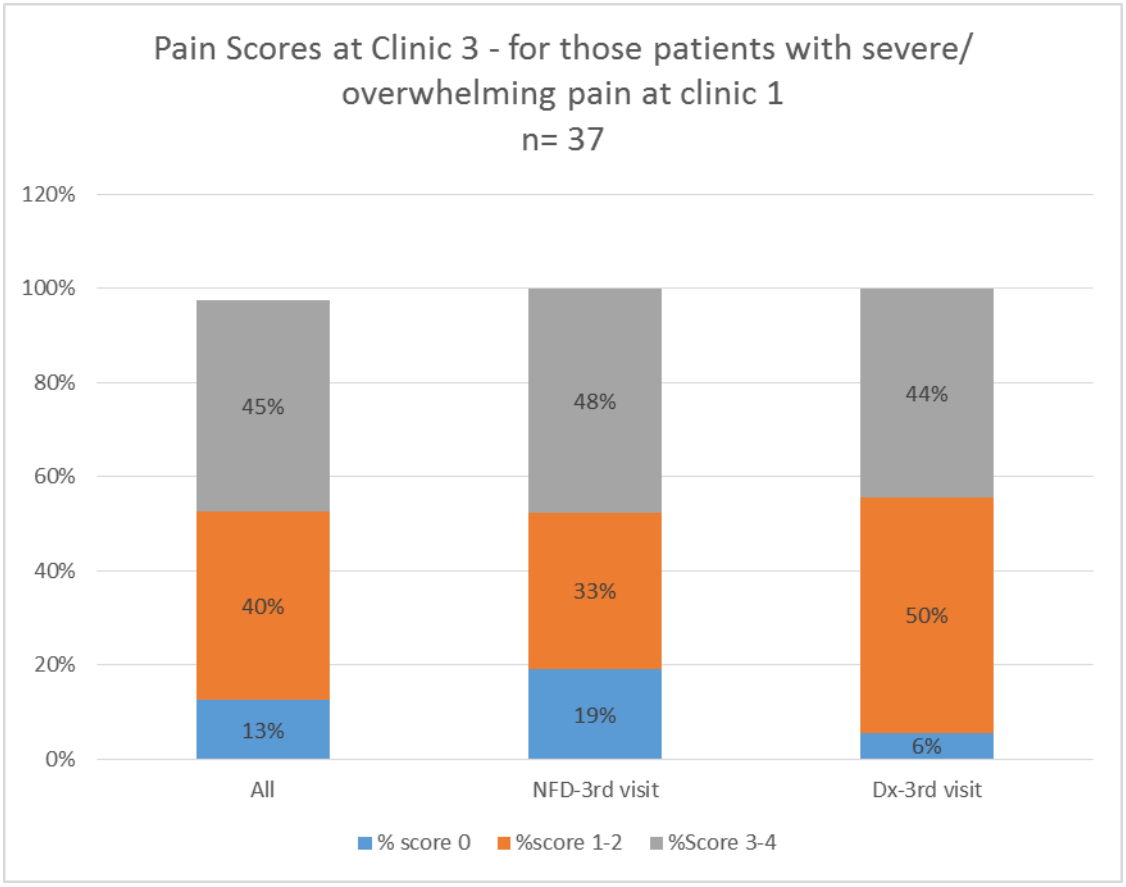


Isolating those patients that reported severe to overwhelming pain at the first clinic visit….

What happened to them by the 3rd clinic visit ?

Average Pain POS Scores
for patients that scored Pain as severe or overwhelming at their first visit

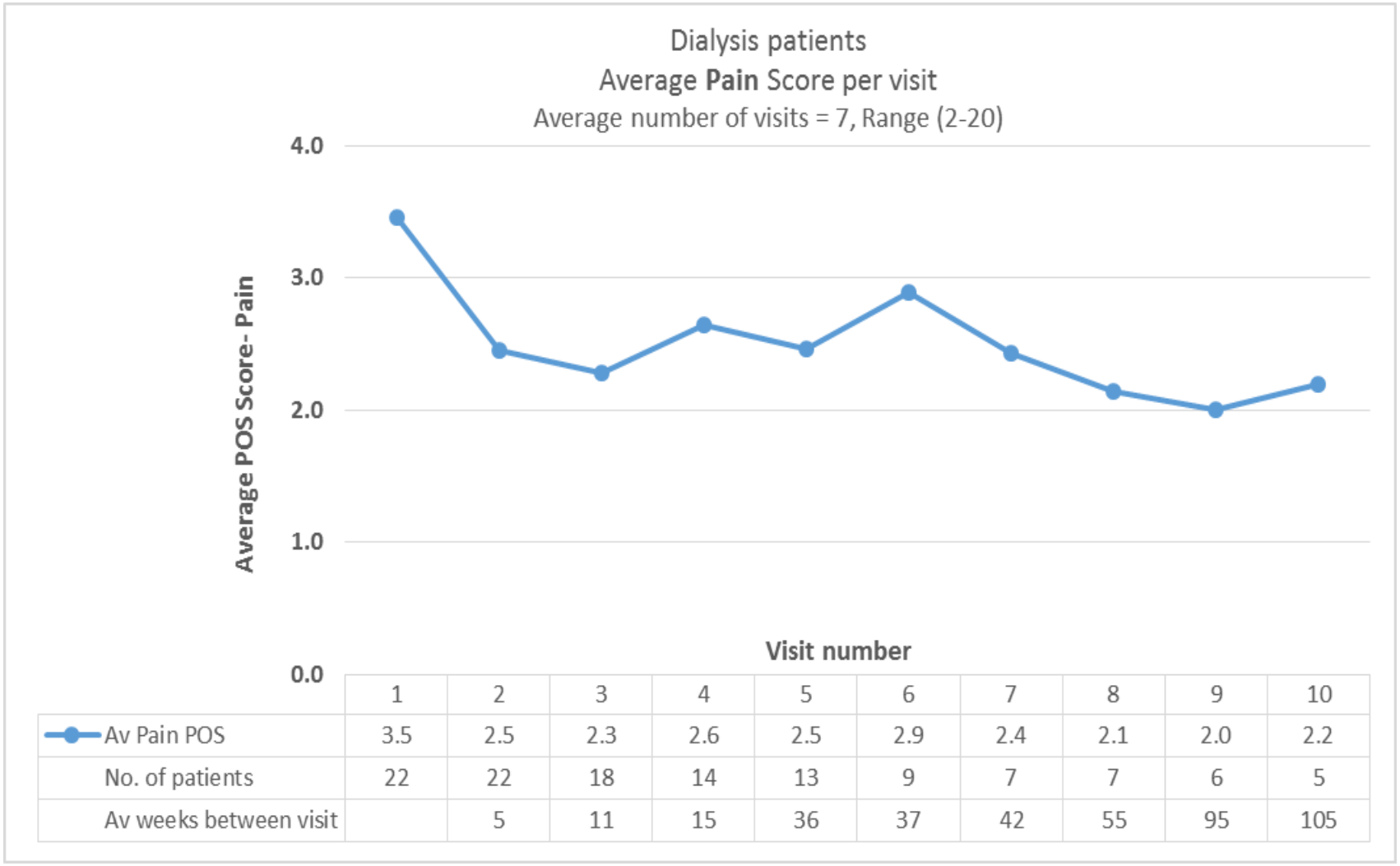



Pain Scores at Clinic 3 - for those patients with severe/ overwhelming pain at clinic 1
n= 37
120%
100%
80%
60%
40%
20%
0%
45%
40%
13%
48%
33%
19%
44%
50%
6%
All
NFD-3rd visit
Dx-3rd visit
% score 0
%score 1-2
%Score 3-4

What happened over time ?

Pain Score- patterns - Dialysis patients

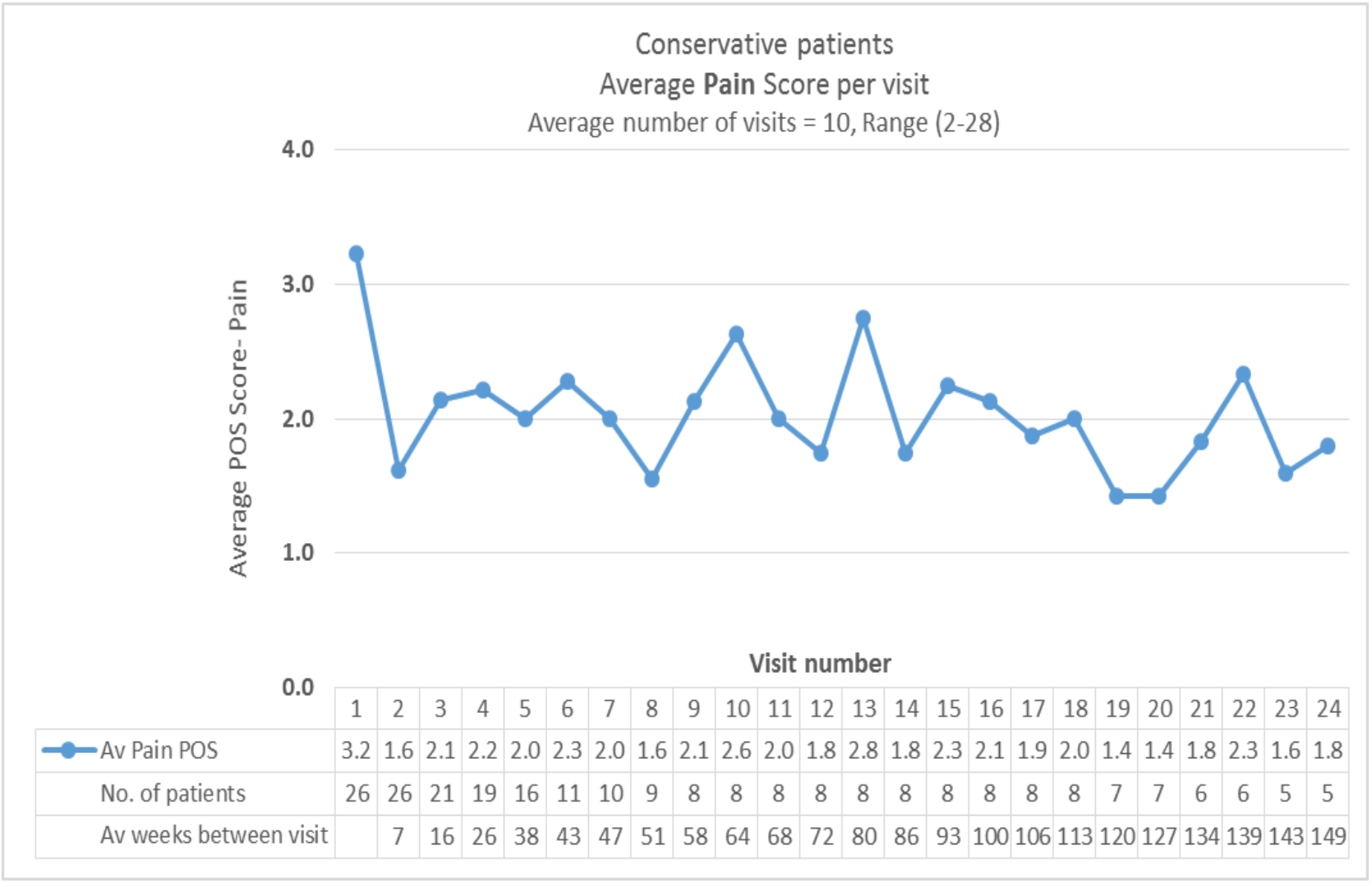
- for patients with more than one visit
- for patients that scored 3-4 for pain on their first visit (**Severe to overwhelming**)
- for clinic visits where there were 5 or more patients



	1	2	3	4	5	6	7	8	9	10
Av Pain POS	3.5	2.5	2.3	2.6	2.5	2.9	2.4	2.1	2.0	2.2
No. of patients	22	22	18	14	13	9	7	7	6	5
Av weeks between visit		5	11	15	36	37	42	55	95	105

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



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Av Pain POS	3.2	1.6	2.1	2.2	2.0	2.3	2.0	1.6	2.1	2.6	2.0	1.8	2.8	1.8	2.3	2.1	1.9	2.0	1.4	1.4	1.8	2.3	1.6	1.8
No. of patients	26	26	21	19	16	11	10	9	8	8	8	8	8	8	8	8	8	8	7	7	6	6	5	5
Av weeks between visit		7	16	26	38	43	47	51	58	64	68	72	80	86	93	100	106	113	120	127	134	139	143	149

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.