Symptom management in ESRD

Renal Supportive Care Symposium
Sydney
August 11 2017.

Frank Brennan
Palliative Care Consultant
Department of Nephrology
St George Hospital Sydney

A 53 year old woman

- Type 2 Diabetes Mellitus
- Hypertension
- OA – mild
- ESKD – Diabetic Nephropathy
- HD 3/week for 5 years

- Shuffled into the clinic room
- Head down
- No eye contact

"My legs move all through the night" –
Severe RLS - 2 years

"I itch all the time… often it becomes ferocious"
Severe uraemic pruritus – 3 years

"My feet and calves burn and get pins and needles – it is awful"
Severe diabetic peripheral neuropathy – 18 months

And sleep ?

"I don't sleep… I doze in 5 minute lots...

"I sit on a chair and put my elbows on my knees to hold them still…

and I pray to die."

Why is symptom management an important aspect of patient care ?

- Symptoms are prevalent
- Symptoms are multiple
- Symptoms are burdensome

"Patients with CKD, particularly those with ESRD are among the most symptomatic of any chronic disease group."

Murtagh F, Weisbord S. Symptoms in renal disease. In Chambers EJ et al (eds) *Supportive Care for the Renal Patient* 2010, 2nd ed, OUP.

What are the common symptoms associated with ESRD ?

The Prevalence of Symptoms in End-stage Renal Disease : A systematic Review

Murtagh FE et al. *Advances in Chronic Kidney Disease* Vol 14, No 1 (January) 2007; pp 82-99

A Cross-sectional Survey of Symptom Prevalence in Stage 5 CKD managed without Dialysis

Murtagh FEM et al. *J Pall Med* 2007; 10(6) :1266-1276

The symptoms of patients with CKD stage 5 managed without dialysis.

Brennan FP et al. *Progress in Palliative Care* 2015; 23 (5): 267-273.

SYMPTOM PREVALENCE

	Dialysis	Conservative
FATIGUE/TIREDNESS	71%	75%
PRURITUS	55%	74%
CONSTIPATION	53%	
ANOREXIA	49%	47%
PAIN	47%	53%
SLEEP DISTURBANCE	44%	42%
ANXIETY	38 %	
DYSPNEA	35 %	61%
NAUSEA	33 %	
RESTLESS LEGS	30 %	48 %
DEPRESSION	27 %	

Symptom control is challenging

Symptoms interact and compound each other

U.Pruritus
RLS → Insomnia → Fatigue
Pain

Symptoms may derive from the co-morbidities

ESRD constrains the use of medication

Pharmacology in the context of CKD is complex

Gaps in knowledge

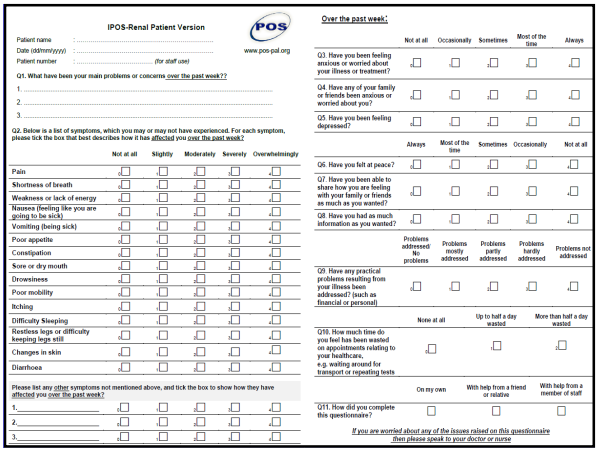
Recommendations in published data occasionally conflict on the specific doses of medications to be used.

Principles of symptom management

1. Think of the cause(s).
2. Be meticulous
3. Principle of non-abandonment

Symptom measurement instruments

I-POS –S (Renal)



IPOS-Renal Patient Version

www.pos-pal.org

Patient name : .....

Date (dd/mm/yyyy) : .....

Patient number : ..... (for staff use)

Q1. What have been your main problems or concerns over the past week??

1. .....

2. .....

3. .....

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick the box that best describes how it has affected you over the past week?

	Not at all	Slightly	Moderately	Severely	Overwhelmingly
Pain	0	1	2	3	4
Shortness of breath	0	1	2	3	4
Weakness or lack of energy	0	1	2	3	4
Nausea (feeling like you are going to be sick)	0	1	2	3	4
Vomiting (being sick)	0	1	2	3	4
Poor appetite	0	1	2	3	4
Constipation	0	1	2	3	4
Sore or dry mouth	0	1	2	3	4
Drowsiness	0	1	2	3	4
Poor mobility	0	1	2	3	4
Itching	0	1	2	3	4
Difficulty Sleeping	0	1	2	3	4
Restless legs or difficulty keeping legs still	0	1	2	3	4
Changes in skin	0	1	2	3	4
Diarrhoea	0	1	2	3	4

Please list any other symptoms not mentioned above, and tick the box to show how they have affected you over the past week?

1._____	0	1	2	3	4
2._____	0	1	2	3	4
3._____	0	1	2	3	4

Over the past week:

	Not at all	Occasionally	Sometimes	Most of the time	Always
Q3. Have you been feeling anxious or worried about your illness or treatment?	0	1	2	3	4
Q4. Have any of your family or friends been anxious or worried about you?	0	1	2	3	4
Q5. Have you been feeling depressed?	0	1	2	3	4

	Always	Most of the time	Sometimes	Occasionally	Not at all
Q6. Have you felt at peace?	0	1	2	3	4
Q7. Have you been able to share how you are feeling with your family or friends as much as you wanted?	0	1	2	3	4
Q8. Have you had as much information as you wanted?	0	1	2	3	4

	Problems addressed/ No problems	Problems mostly addressed	Problems partly addressed	Problems hardly addressed	Problems not addressed
Q9. Have any practical problems resulting from your illness been addressed? (such as financial or personal)	0	1	2	3	4

	None at all	Up to half a day wasted	More than half a day wasted
Q10. How much time do you feel has been wasted on appointments relating to your healthcare, e.g. waiting around for transport or repeating tests	0	1	2

	On my own	With help from a friend or relative	With help from a member of staff
Q11. How did you complete this questionnaire?			

If you are worried about any of the issues raised on this questionnaire then please speak to your doctor or nurse

FATIGUE

Complex and multifactorial

Anaemia - Hb best kept at 11-12

Electrolyte imbalance :

Hyper K	Hypo K
Hyper Ca	Hypo Ca
	Hypo Mg
	Hypo Na
	Hypo PO4

- Nutritional deficiency
- Depression
- Insomnia > Daytime somnolence
- Pain > deconditioning

Fatigue will have an effect on multiple other aspects for the patient :

- QOL
- ADLs
- Need for transport assistance
- Frustration

Management

- Optimise Dialysis
- Correct reversible causes
- Physiotherapy
- Sleep Hygiene
- Social Supports

URAEMIC PRURITUS

Not every patient with ESKD reporting itch
has uraemic pruritus.

At the point of assessment always consider a differential diagnosis of the pruritus.

Associations

- Poor sleep quality
- Depression
- QOL
- Mortality

Pisoni RL, Wikstrom B et al. *Neprol Dial Transplant* 2006; 21: 3495-3505.

The pathogenesis of pruritus remains elusive.

There are a plethora of suggested treatments

Pathogenesis Management

Too often the literature concentrates on one or the other but rarely both

The pathogenesis of pruritus

C Fibres

5- 10 % of the C fibres
are dedicated to itch

For many years the assumption was :

Histamine → C Fibres → Spinal Cord

Of the C Fibres that are itch-sensitive :

10 % are Histamine-dependent

90 % are Histamine-independent

Davidson S. *J Neuroscience* 2007;27: 10007-14
Nainer B. *J Neurophysiology* 2008;100: 2062-9.

Myth 1

That all itch is histamine mediated

Myth 2

That the best first line medication for pruritus of whatever cause are Anti-Histamines

Pathogenesis of UP

Multiple theories, conflicting findings

Adequacy of dialysis

Dialysis adequacy (as measured by Kt/V) did not correlate with the frequency of UP in large epidemiological studies

Pisoni RL, Wikstrom B et al. *Neprol Dial Transplant* 2006; 21: 3495-3505.
Narita et al. *Kidney Int* 2006;69; 1626-32.
Duque et al. *Clin Nephrology* 2006; 66: 184-191.

Xerosis

Dry skin is an association
and exacerbating factor
but not a primary cause

Szepietowski JC. *Nephrol Dial Transplant* 2004; 19: 2709-2712.

HyperParathyroidism

- There is no correlation between PTH levels and UP
- PTH itself is not pruritogenic

Calcium

Inconsistent findings on s.Calcium and UP

One study found increased extracellular Calcium ions in the deepest layer of the Epidermis in patients on HD with UP

Momose A et al. Neprol Dial Transplant (2004) ; 19; 2061-2066

Phosphate

Inconsistent findings on Phosphate and UP

s. Calcium x s.Phosphate

In the DOPPS II study
only at a very high Calcium-Phosphate product (ie. > 80 mg2/dL2)
was there a correlation with UP frequency

Pisoni RL, Wikstrom B et al. Neprol Dial Transplant 2006; 21: 3495-3505.

"Despite this vast array of possible explanations, none consistently have been demonstrated to be the underlying cause of pruritus associated with CKD. Large epidemiological studies ultimately may facilitate our understanding of the elusive pathophysiological process of this distressing symptom."

Patel TS et al. *Am J Kidney* 2007; 50(1): 11-20.

What therapies have the strongest foundation in evidence – based practice ?

- Topical preparations
- Oral medications
- UV- B Therapy

Topical preparations

Moisturisers

Capsaicin cream (0.025 %)

Side effect – transient “burning” feeling on the skin

Systemic therapies

Gabapentin

Gabapentin for uremic pruritus in hemodialysis patients : a qualitative systematic review.

Lau T et al. *Canadian J Kidney Health and Disease* 2016; 3: 14.

"Our review supports a trial of Gabapentin for the management of UP in hemodialysis patients refractory to antihistamines and/or emollients. The results should be interpreted cautiously doe to the lower quality of included studies. We recommend a starting dose of 100mg after hemodialysis to minimize adverse events…"

Treatment of Uremic Pruritus :
A Systematic Review.

Simonsen E et al. *Am J Kid Dis* 2017. Article in Press.

"The main finding…is that with exception of the evidence for gabapentin, there remains considerable uncertainty about effective treatments for this important and burdensome symptom…"

On Dialysis

Gabapentin 100 mg after each Dialysis

Titrate to effect

On conservative management

eGFR < 15

Gabapentin 100mg every 2nd night

Titrate to effect

On conservative management

eGFR > 15

Gabapentin 100mg nocte

Titrate to effect

Pregabalin

Several prospective cohort studies showed efficacy.

Aperis. *J Renal Care* 2010; 36(4): 180-185; Shavit L. *J Pain Symptom Management* 2013; 45(4): 776-781.

Side effects of Gabapentinoids :

- Drowsiness
- Confusion
- Ataxia
- Blurred vision

Evening Primrose Oil

Chen YC et al. *Am J Kid Dis* 2006; 48: 69-76

Gabba Linolenic Acid (GLA)

Essential Fatty Acids (EFA)
in the epidermis

n- 6 EFA

Linolenic Acid (LA)
↓
Gabba –Linolenic Acid (GLA)
↓
DGLA
↓
Arachidonic Acid
↓
Adrenic Acid
↓
Docosapentaenoic Acid

n-EFA

Linolenic Acid (LA)
↓
Gabba –Linolenic Acid (GLA)
↓
DGLA
↓
PGE2 ← Arachidonic Acid (AA)
Leukotriene B4 ←
↓
Adrenic Acid
↓
Docosapentaenoic Acid

Supplementing the Gabba-Linolenic Acid (GLA) has an anti-inflammatory/ anti-itch effect

n-EFA

Linolenic Acid (LA)
↓
Gabba –Linolenic Acid (GLA)
↓
PGE1 ← DGLA
15 OH DGLA ←
↓
Arachidonic Acid (AA)
↓
Adrenic Acid
↓
Docosapentaenoic Acid

100mg bd

= Blackmores Evening Primrose Oil contains 100mg GLA per capsule

Sertraline
(SSRI)

Shakiba M et al. *Int J Nephrology* 2012; Article ID 363901; 1-5

- Before and after trial of 19 HD patients.
- 50mg daily for 4 months.
- The difference in the grade of pruritus before and after sertraline was significant.

Thalidomide 100mg nocte

Silva SR. *Nephron* 1994; 67(3): 270-273

Kappa – receptor agonists

Wikstrom B et al. *J Am So Nephrol* 2005; 16: 3742-3747;
Kumagai H et al. *Nephrol Dial Transplant* 2010; 25: 1251-1257.

Other oral medications

- Anti-Histamines – evidence does not support use.
- Ondansetron – conflicting results. Not recommended.
- Cimetidine – not recommended
- Naltrexone – conflicting results. Not recommended.

Murtagh FEM, Weisbord D . Symptom management in Renal Failure. In : Chambers EJ et al (eds). *Supportive Care for the Renal Patient.* 2nd ed. 2010. OUP. p. 120. To THM et al. *J Pain Symptom Management* 2012;44: 725-730.

UV B Therapy

Acupuncture

Che-yi et al. *Nephrol Dial Transplant* 2005; 20: 912-915

Uraemic pruritus summary

Moisturisers plus

1. Gabapentin/Pregabalin

2. Evening Primrose Oil

3. UV – B therapy

4. Others.
Note - Anti-histamines do not help

PAIN

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

Pain etiquette

- ENQUIRE REGULARLY
- RESPOND COMPASSIONATELY
- TREAT COMPETENTLY
- REFER WISELY

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 very useful construct.

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

Is an approach based on the WHO Analgesic Ladder the most appropriate approach in the specific context of CKD ?

Towards a strategic approach to pain management in patients with CKD

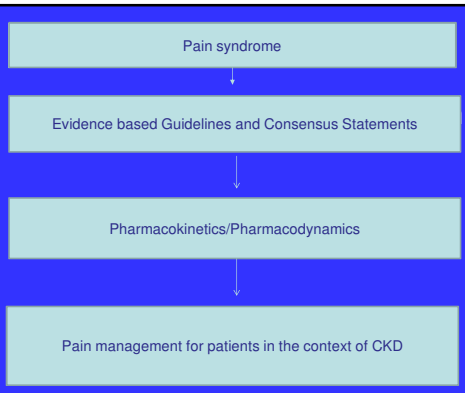
1. There are few studies examining pain management in the specific context of CKD

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
- Post herpetic neuralgia
- 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



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 2015; 28(4): 384-391.

Painful diabetic peripheral neuropathy

1. Currently there are no evidence-based or consensus guidelines on the management of painful DPN in patients with CKD.

"Clinical evidence regarding the effects of [analgesic agents] to treat DPN in patients on dialysis therapy and those with CKD Stage 4-5 is virtually non-existent."

Pop- Busui R et al. The Management of Diabetic Neuropathy in CKD. *Am J Kid Dis* 2010; 55(2): 365-385.

2. There is a significant body of literature on the management of painful DPN.

That literature includes several international evidence based guidelines.

Evidence-based guideline : Treatment of painful diabetic neuropathy. Report of the American Association of Neurology et al.

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

Level A Evidence - Pregabalin

Level B Evidence :

- Gabapentin
- Duloxetine
- Amitriptyline
- Sodium Valproate
- Morphine
- Tramadol
- Oxycodone
- Capsaicin
- Isosorbide Dinitrate spray
- TENS

Step 1

Paracetamol

- Metabolised in liver
- 2-5 % excreted unchanged renally
- Inactive metabolites

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

90 % of Tramadol and its metabolites are renally excreted

= 30 % unchanged; 60 % as metabolites.

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

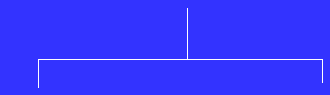
If on a Conservative pathway
eGFR < 15
or Dialysis

Tramadol 50mg bd (maximum)

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

"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 (0.25mg-0.5mg) 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

"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

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

Norbuprenorphine (NorB)

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

"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

Role of Pain Services

Pain management in patients with ESKD

A one day Symposium - 2016

St George Hospital

RESTLESS LEGS SYNDROME

Definition

1. An urge to move the limbs, usually associated with parasthesia/dyaesthesia
2. Motor Restlessness
3. Symptoms exclusively while at rest, with relief (completely or partially) with movement.
4. Symptoms worse at night.
5. Cannot be solely attributed to another cause.

International RLS Study Group – Definition of RLS (2012)

Incidence in the general population :
2-15 %

Incidence in ESRD : 20-30 %

Not all ESKD patients
with a disturbance of their legs
have Restless Legs Syndrome.

Differential diagnosis

- Leg cramps
- Peripheral neuropathy
- Osteoarthritis
- Pruritus
- Akathisia

Associations

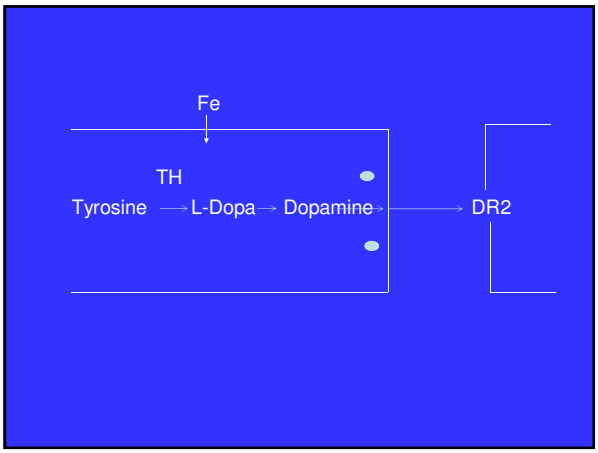
Sleep disturbance

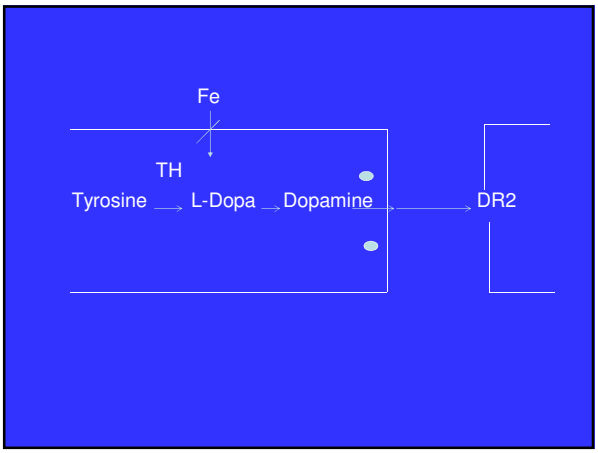
Daytime somnolence

Premature cessation of dialysis sessions

- Sleep disturbance
- Daytime somnolence
- Premature cessation of dialysis sessions
- Reduced QOL
- Hypertension
- New CVS events
- Mortality

Mechanism is not completely understood





Management

Dopamine agonists

Non-Ergot Dopamine Agonists
(Pramipexole, Ropinirole, Rotigotine)

Ergot-Dopamine Agonists (Pergolide, Cabergoline) – not recommended

- Augmentation
- Rebound

Gabapentinoids

Two RCTs have shown efficacy for Gabapentin in the treatment of RLS in Dialysis patients

1. Placebo controlled – Thorp et al (2001)

2. Gabapentin compared to Levo-dopa – Micozkadioglu et al (2004)

Three RCT comparing Pregabalin, Pramipexole and placebo.

Heuber et al. *Neurology* 2013; 80: 738-742
Allen RP et al. *N Eng J Med* 2014; 370; 621-632
Garcia-Borroguero MD. *Sleep* 2014; 37(4): 635-643.

Two found that Pregabalin was significantly more efficacious than Pramipexole and placebo in treating uraemic RLS.

Heuber et al. *Neurology* 2013; 80: 738-742
Garcia-Borroguero MD. *Sleep* 2014; 37(4): 635-643.

One found Pregabalin provided significantly improved treatment over placebo but not Pramipexole. Also Pregabalin caused statistically less augmentation.

Allen RP et al. *N Eng J Med* 2014; 370; 621-632

Dose of Gabapentin/Pregabalin – identical to above.

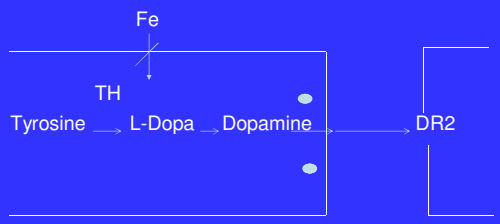
Clonazapem

0.5mg – 1mg nocte

Opioids

Opioids have a protective effect on dopamine cells that have been subject to Fe deficit.

Trenkwalder C et al. *Lancet Neurol* 2013; 12 : 1141-1150.



Fe infusions

IVI 1000mg Iron Dextran

Statistically improved RLS over placebo. Effect faded at 4 weeks.

Giannaki CD. *BMC Nephrol* 2013; 14: 194.

Intradialytic exercise

Giannaki CD et al. *BMC Nephrol* 2013; 14: 194.

International Guidelines

European Federation of Neurological Societies (2012)
International RLS Study Group (2013)

"The use of a dopamine-receptor agonist or a [Gabapentinoid] is recommended as the first line treatment of RLS…for most patients…"

Garcia-Borreguero D et al. International RLS Study Group. *Sleep Medicine* 2013; 14: 675-684.

INSOMNIA

This may be the product of multiple other symptoms

- Pain
- Uraemic Pruritus
- Cramps
- RLS
- Periodic Leg Movement Disorder
- Nocturia
- Sleep Apnea

In a study of 254 HD patients
there was a 57 % prevalence of moderate to severe OSA.

Nicholl DD et al. *Chest* 2012; 141: 1422-1430.

The 53 year old woman referred to clinic because of extreme :

1. Uraemic Pruritus
2. Restless Legs Syndrome
3. Diabetic peripheral neuropathy
3. Very poor sleep

U.Pruritus
RLS → Insomnia → Fatigue
Neuropathic pain

Gabapentin commenced
at 200mg at the completion of each dialysis

- Complete cessation of all symptoms and a markedly improved sleep
- Sleeping *"the best I have for a long time."*

Gastrointestinal symptoms

Taste disturbances

ANOREXIA

Multifactorial

- Nausea
- Dry mouth
- Altered taste
- Delayed gastric emptying
- Depression
- Uraemia
- Inadequate dialysis
- Abdominal discomfort and swelling from CAPD

- Patients on Dialysis require 2 x protein of the non-dialysis patient.
- Chronic Protein Energy Malnutrition is common

Management

- Attempt to reverse the reversible causes
- Renal Dietitian Review

NAUSEA

Look for the cause (s)

- Uraemia → CTZ zone
- Delayed Gastric emptying
- Concurrent medications
- Constipation

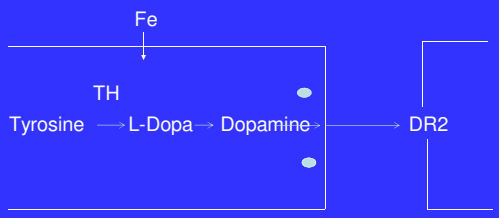
Treat the symptom :

Maxalon 5mg – 10mg tds

Haloperidol 0.5mg bd
Cyclizine 25- 50mg tds
Ondansetron – very constipating

A 72 y.o. man.

- ESKD – on Home HD
- Main symptom is nausea.
- Commenced on Metoclopramide 10mg tds.
- Two weeks later reports nausea well controlled.
- "By the way, doctor, my legs keep moving at night." - Restless Legs ++



Depression/Anxiety

Slides prepared, with acknowledgement, to Dr Kirsty Morris, Liaison Psychiatrist, Royal Prince Alfred Hospital, Sydney

Depression

Especially chronic kidney disease

20% of patients with CKD have depression

CKD 1 – 4	21.5%
Dialysis	22.8%

Palmer et al 2013

The diagnosis of depression in CKD

This is challenging given that several of the DSM criteria for depression are also experienced by patients with CKD

Fatigue, anorexia, insomnia

"It is recommended that the diagnosis of depression in a patient with CKD should rely more heavily on psychological features such as loss of enjoyment in life, guilt, loss of self-esteem, hopelessness and suicidal ideation."

Bautovich A et al. *Aust NZ J Psychiatry* 2014; 48(6): 530-541

Why is depression in ESKD important?

- Increased mortality rates from all causes[1]
- Reduced compliance[2,3,4]
- Withdrawal from treatment[5,6]
- More symptoms - fatigue, cognitive, pain, sleep, sexual[7,8]
- Reduced quality of life[9]
- More disability[10]

•1.Palmer et al 2013
•2.Kaveh and Kimmel 2001
•3.Kao et al 2003
•4.Leggat et al 2005
•5.Lacson et al 2012
•6.McDade-Montez et al 2006
•7.Katon et al 2011
•8.Soni et al 2010
•9.Pretjevic et al 2013
•10.Teng et al 2010

Suicide

Suicide, suicidal ideation and suicide attempts probably more frequent in dialysis patients[1]

- Risks[2,3]: older age, male, medical comorbidity, substance use disorder, depression/anxiety,? ↓QOL[4,5]

•Pompili et al 2013
•2.Bronisch T and Wittchen H 1994
•3.Kurella M et al 2005
•4.Haenel et al 1980
•5.Chen C et al 2010

"Unfortunately, despite these associations (between CKD and depression and depression and poor outcomes) and the increasingly available evidence, clinicians remain cautious when managing depression in those with CKD, and rates of detection and treatment remain very low."

Bautovich A et al. *Aust NZ J Psychiatry* 2014; 48(6): 530-541.

Vulnerable periods for developing depression in CKD

- First year of treatment
- Failing transplant
- Non-listing for transplant[1]

1. Hooper J and Cohen LM (in *Supportive Care for the Renal Patient*) 2004

Not everyone with CKD gets depressed

Treatment

There are very few studies

There is only one RCT of an antidepressant medication in CKD patients

Blumenfield et al 1997

Antidepressants

- Evidence is lacking
- Think about pharmacokinetics, potential interactions, and side effect profile
- Reasonable choices include citalopram, sertraline, venlafaxine, amitriptyline, mirtazapine

Other biological treatments

- ECT
  - Case reports of good response in patients with CKD[1,2]
- Exercise therapy[3,4]
- Changes in dialysis regimen[5,6] - insufficient evidence

1. Varghese et al 2006
2. Williams and Ostroff 2005
3. Ouzoni et al 2009
4. Kouidi et al 2010
5. Hedayati and Finkelstien 2009
6. Jaber et al 2010

Psychosocial treatments

- Evidence for CBT in chronic medical illness
  - Limited evidence in ESKD population[1,2]
  - Role of internet in treatment[3]
- Social support[4,5,6]
- Family/marital counselling[4,5]

•1. Cukor 2007
•2. Duarte et al 2009
•3. [illegible]
•4. Cohen et al 2007
•5. Hedayati et al 2012
•6. Patel 2005

Anxiety

What do we mean by "anxiety" ?

- Normal
  - -- adaptive response to a threat
  - - many threats when unwell
- Maladaptive
  - •- refusing needles
- Anxiety disorders

Chronic illness is anxiety-provoking

- Much less researched than in depression
- Strong association between anxiety and chronic medical illnesses
- Bidirectional relationship

1. Harter et al 2003
2. Sareen et al 2005

Chronic kidney disease is associated with anxiety

- Literature is limited
- 27 – 46% of patients with ESKD have anxiety[1]
- Less information on CKD before dialysis[2]
  - 28% patients with CKD 3-5 with high levels anxiety
- Often co-occurs with depression in HD[3]

1. Kring and Crane 2009
2. Lee 2013
3. Cukor et al 2008

Chronic kidney disease - anxiety

- Situation
  - diagnosis, crisis, conflict, anticipatory, awaiting results
- Disease-related
  - pain, hypoxia, hypoglycaemia
- Treatment-related
  - procedures, medications, withdrawal
- Exacerbation of pre-existing anxiety disorder

Consequences of anxiety

- Inattention, reduced ability to retain information
- Interference with investigation or treatment
- Risk factor for medical conditions - MI, angina, H/T[1-6]
- Functional impairment, reduced QOL[7]
- Increased mortality rates?[8]

1. Albert et al 2005
2. Eaker et al 1992
3. Jonas 1997
4. Kawachi et al 1994
5. Kubzansky et al 1997
6. Nicholson et al 2005
7. Cukor et al 2008
8. Prelijevic 2013

Treatment

Limited evidence

Psychosocial treatment

- General measures
  - preparation for unpleasant procedures, reassurance vs honesty, involve support system
- Psychological treatments
  - CBT, supportive therapy, mindfulness therapy

Medication

- Antidepressants - for persistent anxiety
- Benzodiazepines - for acute or anticipatory anxiety
- Antipsychotics – for acute or short-term use

The experience of the Renal Supportive Care Service, St George Hospital in symptom management.

Between March 2009 and June 2017

424 patients completed a Symptom Survey at their first

Renal Supportive Care service visit

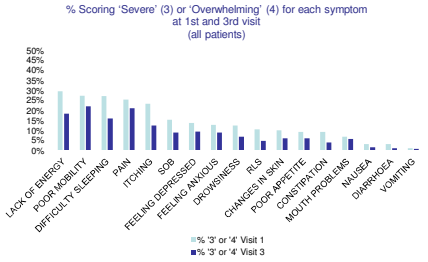
Of those 424 patients

- 35% dialysis patients
- 57% conservatively managed patients
- 2% transplant patients
- 5% Undecided

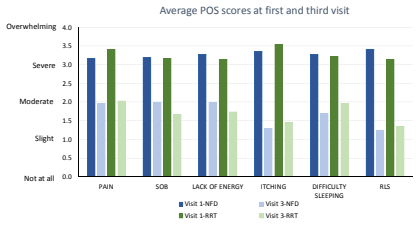
Following those patients
who had at least 3 clinic visits.

Between March 2009 and June 2017,
424 patients have completed a POS at their first Renal Supportive Care clinic visit.
247 patients attended at least 3 visits

	Total * (n=247)	NFD (n=147)	RRT (n=90)	Undec (n=10)
Age (yrs)	77	82	68	78
Males (%)	55	51	63	30
Diabetes (%)	49	45	58	20
IHD (%)	46	48	46	20
Dementia (%)	10	12	7	0

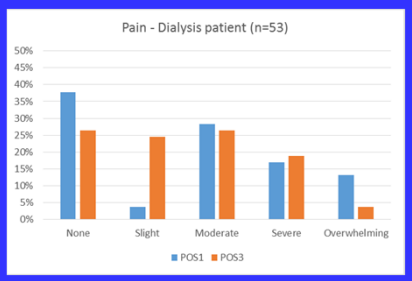


Of those who presented at first clinic visit with a symptom that was reported as at least “severe”…

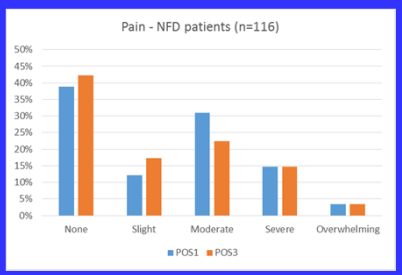


Pain

Pain Scores for Dialysis patients at first and third visits



Pain Scores for Conservative patients at first and third visits

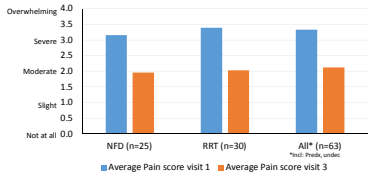


Isolating those patients that reported severe to overwhelming pain at the first clinic visit….

What happened to them by the 3rd clinic visit ?

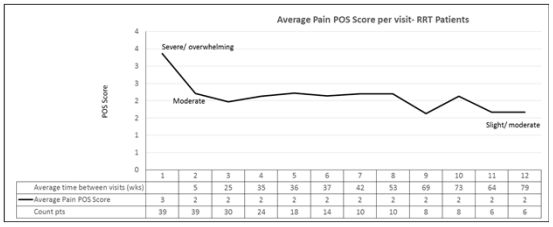
Average **Pain** Scores reported at first and third Clinic
For patients that reported Severe or Overwhelming pain at the first clinic

Average number of weeks between clinic 1 and 3 = 14 weeks



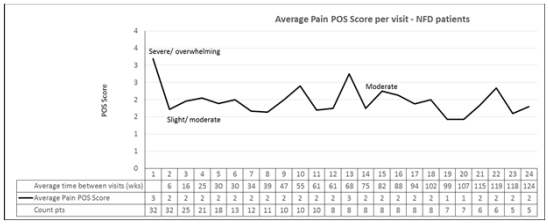
What happened over time ?

Pain Score- patterns - Dialysis (RRT) 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
Average time between visits (wks)		5	25	35	36	37	42	53	69	73	64	79
Average Pain POS Score	3	2	2	2	2	2	2	2	2	2	2	2
Count pts	39	39	30	24	18	14	10	10	8	8	6	6

Pain Score- patterns - Conservative (NFD)
- 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
Average time between visits (wks)		6	16	25	30	30	34	39	47	55	61	61	68	75	82	88	94	102	99	107	115	119	118	124
Average Pain POS Score	3	2	2	2	2	2	2	2	2	2	2	3	2	2	2	2	2	2	1	1	2	2	2	2
Count pts	32	32	25	21	18	13	12	11	10	10	10	8	8	8	8	8	8	8	7	7	6	6	5	5

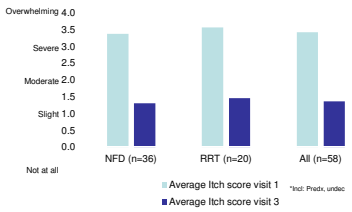
Pruritus

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

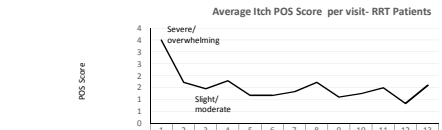
What happened to them by the 3rd clinic visit ?

Average **Itch** Scores reported at first and third Clinic
For patients that reported Severe or Overwhelming itch at the first clinic

Average number of weeks between clinic 1 and 3 = 14 weeks

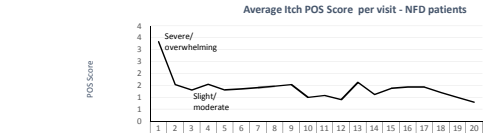


Itch Score- patterns - (RRT) patients
- for patients with more than one visit
- for patients that scored 3-4 for itch on their first visit (**Severe to overwhelming**)
- for clinic visits where there were 5 or more patients



Average time between visits (wks)		6	14	16	19	25	39	41	65	71	59	64	82
Average Itch POS Score	4	2	1	2	1	1	2	1	1	2	1	2	
Count pts	22	22	20	14	12	12	12	11	9	8	6	6	5

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

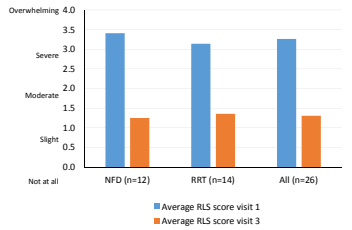


Average time between visits (wks)		6	12	16	20	26	30	32	38	44	50	56	63	63	70	74	79	88	94	98
Average Itch POS Score	3	2	1	2	1	1	1	1	2	1	1	1	2	1	1	1	1	1	1	1
Count pts	41	41	36	29	26	23	20	17	15	15	12	11	11	8	8	7	7	5	5	5

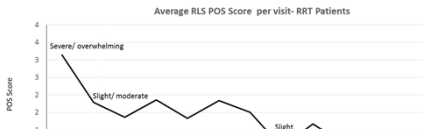
Restless Legs Syndrome

Average **RLS** Scores reported at first and third Clinic
For patients that reported Severe or Overwhelming itch at the first clinic

Average number of weeks between clinic 1 and 3 = 14 weeks

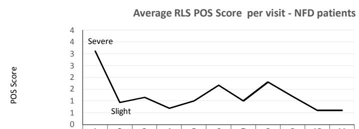


RLS Score- patterns - (RRT) patients
- for patients with more than one visit
- for patients that scored 3-4 for RLS on their first visit (**Severe to overwhelming**)
- for clinic visits where there were 5 or more patients



Average time between visits (wks)		1	9	15	12	32	51	55	59	69	79	96
Average RLS POS Score	3	2	1	2	1	2	2	1	1	1	0	0
Count pts	14	14	14	7	6	6	6	6	6	5	5	5

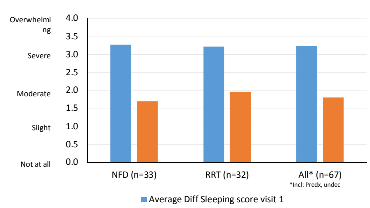
RLS Score- patterns - Conservative (NFD)
- for patients with more than one visit
- for patients that scored 3-4 for RLS on their first visit (**Severe to overwhelming**)
- for clinic visits where there were 5 or more patients



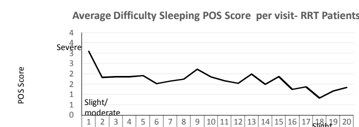
	1	2	3	4	5	6	7	8	9	10	11
Average time between visits (wks)		5	16	20	24	30	26	30	35	44	50
Average RLS POS Score	3	1	1	1	1	2	1	2	1	1	1
Count pts	16	16	13	10	8	6	5	5	5	5	5

Difficulty sleeping

Average **Difficulty Sleeping** Scores reported at first and third Clinic
For patients that reported Severe or Overwhelming itch at the first clinic
Average number of weeks between clinic 1 and 3 = 14 weeks

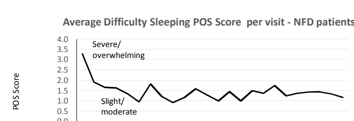


Difficulty Sleeping Score- patterns - (RRT) patients
- for patients with more than one visit
- for patients that scored 3-4 for RLS on their first visit (**Severe to overwhelming**)
- for clinic visits where there were 5 or more patients



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Average time between visits (wks)		4	12	19	21	32	44	53	66	70	67	79	72	83	89	95	107	98	103	112
Average Difficulty Sleeping POS Score	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1
Count pts	38	38	33	26	22	21	17	16	13	14	12	11	9	8	8	8	8	6	6	6

Difficulty Sleeping Score- patterns - Conservative (NFD)
- for patients with more than one visit
- for patients that scored 3-4 for RLS 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
Average time between visits (wks)		6	13	15	19	25	28	33	41	45	51	53	61	63	70	74	79	85	90	95	100	105	111	115
Average Difficulty Sleeping POS Score	3	2	2	2	1	1	2	1	1	1	2	1	1	1	1	2	1	2	1	1	1	1	1	1
Count pts	36	36	34	29	24	19	17	14	13	12	12	10	10	9	9	8	8	8	8	8	7	7	6	6

Case 1

A 69 year old woman. Type II Diabetes Mellitus. ESKD on Haemodialysis. Main symptom is profound nausea.

What is/are the mechanisms of the nausea ?

What management is possible ?

Case 2

A 72 year old woman with ESKD on dialysis has uraemic pruritus. Gabapentin is commenced at 100mg directly after dialysis. Her itch improves but it still remains moderate in intensity. Her Gabapentin dose is increased to 200mg after dialysis. She complains of sleepiness and clumsiness.

Case 3

An 83 year old man.
ESKD secondary to ischaemic nephrosclerosis.

Consensus decision made to have conservative, non-dialysis management.

Current eGFR is 11.

Main symptoms are fatigue and Restless Legs that commence predictably between 7pm and 8pm every night. When asked "How long have you had the Restless Legs ? " he replies : "Since I was 13 years old."

- *What other questions would you like to ask him ?*
- *Why has he had Restless Legs since he was a child ?*
- *He states he has been prescribed Sinemet for "a long time."*
- *What is your management approach ?*

Case 4

A 69 year old man with ESKD on haemodialysis is prescribed Pregabalin for Restless Legs Syndrome. The dose is 25 mg after each dialysis. He then describes a surge of Restless Legs *during* the dialysis ?

- *Why might this be occurring ?*
- *What will you do ?*

Case 5

A 62 year old man has ESRD secondary to diabetic nephropathy, on PD. He is troubled by pruritus, nausea, recurrent vomiting and Restless Legs.

What is your management ?

Conclusion

- Symptom management is an important arm of management.
- Symptoms are prevalent and multiple

Be curious and reactive
rather than passive and nihilistic

- Be meticulous
- Symptom relief may have a significant impact of patients' Hr QOL

Acknowledgements :

- Anna Hoffman for the preparation of the graphs.
- Elizabeth Josland, Alison Smyth, Dr Kelly Li, Professor Mark Brown.