Palliative Management for Patients with End Stage Kidney Disease

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• University of Alberta
• Director, Kidney Supportive Care Research Group

CHPCA Learning Institute
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Objectives

After this session, participants will be able to:

1. Define Conservative Kidney Management (CKM)

2. Use the CKM Patient Decision Aid in practice to facilitate shared decision-making - “Is Dialysis the Right treatment for Me”

3. Understand an integrated approach to conservative kidney management

4. Describe evidenced-based management of 3 common symptoms in ESKD
   - Restless legs syndrome
   - Pruritus
   - Pain
Caring For Fred

- 77 year retired farmer with long standing hypertension.
- Recent MI with 3V CABG
- Still lives independently on his farm in rural AB
- eGFR ~ 12 ml/min/1.73m² (currently stable)
Caring For Fred

Questions

1. What is his risk for progression to needing dialysis?

2. What is his anticipated prognosis on dialysis v. CKM?

3. What is the right care for Fred?
What is Fred’s Predicted Probability Needing Dialysis Over 2 & 5 Years?

<table>
<thead>
<tr>
<th>Risk of Progression to ESKD (dialysis)</th>
<th>Fred: 77 years eGFR 12 ml UACR 70 mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 2 years</td>
<td>21%</td>
</tr>
<tr>
<td>Over 5 years</td>
<td>52%</td>
</tr>
</tbody>
</table>

Smart phone app: [http://www.qxmd.com/kidney-failure-risk-equation](http://www.qxmd.com/kidney-failure-risk-equation) (model is based on age, gender, GFR and UACR)

C statistic 0.91
Clinical Context for Kidney Supportive Care

Patients ≥ 75 YRS: fastest-growing group of dialysis patients

Extremely high morbidity & mortality rates

Annual unadjusted mortality rate ~20%

Withdrawal from dialysis ~ 20% of deaths
### Unadjusted Survival Probabilities (%) for Patients Starting Dialysis

<table>
<thead>
<tr>
<th>Age</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 49</td>
<td>89.6</td>
<td>81.6</td>
<td>73.5</td>
<td>61.9</td>
<td>37.7</td>
</tr>
<tr>
<td>50 - 59</td>
<td>86.2</td>
<td>75.9</td>
<td>65.4</td>
<td>49.5</td>
<td>21.8</td>
</tr>
<tr>
<td>60 - 64</td>
<td>83.0</td>
<td>69.6</td>
<td>58.3</td>
<td>38.1</td>
<td>12.3</td>
</tr>
<tr>
<td>65 - 69</td>
<td>79.1</td>
<td>63.1</td>
<td>50.8</td>
<td>30.7</td>
<td>6.4</td>
</tr>
<tr>
<td>70 - 79</td>
<td>71.2</td>
<td>53.5</td>
<td>39.0</td>
<td>20.2</td>
<td>2.7</td>
</tr>
<tr>
<td>80+</td>
<td>60.5</td>
<td>40.8</td>
<td>25.7</td>
<td>9.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Survival for ESKD Patients v. General Population

Expected remaining life-years

- Europe
- US Whites
- General population

Dialysis

- No dialysis

Age (years)

Similar life expectancy
Age alone is not consistently an independent predictor of outcomes on dialysis

**LIFE EXPECTANCY**

- **Conservative Kidney Management**
  - Time in hospital: ½ month
  - Time at home: 13 ½ months
  - Total Life Expectancy: 14 months

- **Hemodialysis**
  - Time in hospital: 2 months
  - Time at dialysis clinic: 14 months
  - Time at home: 18 months
  - Total Life Expectancy: 34 months

*This does not take into account other health problems you may have*

Twice as likely to die in hospital v. home or hospice
The elderly are a heterogeneous group and rigorous evidence has not been synthesized to understand fully the benefits of dialysis in these “older” patients.

Symptom burden

- Similar between CKM and dialysis
- Can be treated successfully with supportive care
- Often deteriorates only in last 1-3 months of life
Functional Status of Elderly Adults before and after Initiation of Dialysis

Manjula Kurella Tamura, M.D., M.P.H., Kenneth E. Covinsky, M.D., M.P.H.,
Glenn M. Chertow, M.D., M.P.H., Kristine Yaffe, M.D., C. Seth Landefeld, M.D.,
and Charles E. McCulloch, Ph.D.

Figure 3. Smoothed Trajectory of Functional Status before and after the Initiation of Dialysis and Cumulative Mortality Rate.
The dashed vertical line indicates the initiation of dialysis in a hypothetical 75-year-old nursing home resident. MDS–ADL denotes Minimum Data Set–Activities of Daily Living. The numbers on the MDS–ADL axis run from highest to lowest.

Figure 2. Change in Functional Status after Initiation of Dialysis.
Data were missing for 549 nursing home residents at 3 months, 696 residents at 6 months, 823 residents at 9 months, and 787 residents at 12 months from the full analytic cohort of 3702 residents.
Survival advantage for dialyzed elderly patients is lost in patients with high comorbidity scores
The burden of dialysis for some outweighs the benefits and there are those that may do particularly poorly on dialysis.

Cognitive dysfunction: >55 yrs (neuropsychiatric testing)
- 36% moderate impairment
- 37% severe impairment

Poor functional status:
- 11% dialysis patients require assistance with basic ADLs
- > 50% of patients > 75 yrs
Choosing CKM does **NOT** mean imminent death. This is usually a decision about how they wish to live their life rather than “life v. death”

Patients > 75 years, eGFR < 15 ml/min
CKM patients were older: 83.0 v. 79.6 years

<table>
<thead>
<tr>
<th></th>
<th>Dialysis (n = 52)</th>
<th>CKM (n = 77)</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year survival</td>
<td>84%</td>
<td>68%</td>
<td>74%</td>
</tr>
<tr>
<td>2 year survival</td>
<td>76%</td>
<td>47%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Conservative Kidney Management (CKM) is an alternative treatment option to dialysis or transplant.

“Comprehensive conservative care” is planned holistic patient-centered care for patients with G5 CKD - includes:

- Shared decision-making
- Delay progression of kidney disease & minimize complications
- Detailed communication including advance care planning
- Symptom management
- Psychological support
- Social and family support
- Cultural and spiritual domains of care

**Does not include dialysis**
“You tell me and I forget, you teach me and I may remember, you involve me and I learn.”

Benjamin Franklin

“Nothing about me without me.”

Valerie Billingham, Through the Patient's Eyes, Salzburg Seminar Session 356, 1998
Caring for Bob
The Conservative Kidney Management Pathway was co-designed with patients and families.
The guiding principle is that all investigations and management are aligned with the patient’s preferences, goals, & disease trajectory.
The pathway empowers patients and their families through increased knowledge and enhanced self care
Choosing CKM
If your patient requires support, consider using the Patient Decision Aid

Step 2
Initiate Care Planning
- Care Plan
- Engage Primary Care

Step 1
Plan

Step 3
Manage
CKM Care

Clinical Assessments
- Symptom Management
- CKD Management

Advance Care Plan

Establish Community Support & Referrals

Crisis Management Plan

End of Life Plan

Update CKM Care Plan

Step 4
Support
Grief & Loss

 ALERT
This patient has advanced chronic kidney disease and has chosen NOT to start dialysis and is following the Conservative Kidney Management (CKM) pathway
www.CKMcare.com

Date
Signature / Site

CONSERVATIVE KIDNEY PROFESSIONALS PATHWAY
### CKD Guidelines & Guiding Principles for a Palliative Approach to Care

<table>
<thead>
<tr>
<th>CKD Guideline</th>
<th>Guiding Principle</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids</td>
<td>Reduce risk of cardiovascular related mortality and morbidity.</td>
<td>Patients will not likely receive benefit from statins in the last few years of life; some research even suggests an improvement in QOL from stopping statins. …… Recommended that care providers, in discussion with the patient, discontinue statins for CKM patients.</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Avoid very high readings while optimizing cognition and physical function (minimize risk of falls).</td>
<td>≤160/90 mmHg GFR &lt; 5: No longer necessary to monitor BP. BP medications can be stopped. Diuretics are a unique consideration……</td>
</tr>
<tr>
<td>Sodium statement</td>
<td>Assist with volume control (SOB and peripheral edema)</td>
<td>Sodium intake &lt; 2 g sodium/day. Influence palatability (impacts nutrition, well-being and overall QOL).</td>
</tr>
</tbody>
</table>
# CKD Guidelines & Guiding Principles for a Palliative Approach to Care

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<th>CKD Guideline</th>
<th>Guiding Principle</th>
<th>Recommendation</th>
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</thead>
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<tr>
<td>Metabolic Acidosis</td>
<td>Can lead to <strong>bone loss</strong>, <strong>muscle wasting</strong>, and <strong>fatigue</strong>. Treatment of acidosis is also associated with <strong>slower progression of CKD</strong>.</td>
<td>Reasonable to treat for as long as patient feels that it is not burdensome and is obtaining benefit. Monitor CO2 every 3 months. GFR &lt; 5, unable to swallow pills, or bed bound ... stop treatment and related blood work.</td>
</tr>
<tr>
<td>Anemia</td>
<td>Goal is to decrease <strong>fatigue</strong> and <strong>breathlessness</strong> rather than reduce cardiac mortality or morbidity.</td>
<td>Interventions continued only if they are of symptomatic benefit. GFR &lt; 5: it is no longer appropriate to manage fatigue and dyspnea via these interventions.</td>
</tr>
<tr>
<td>High K</td>
<td>Decrease risk of cardiac arrhythmias and sudden death.</td>
<td>In general, routine monitoring and acute treatment. For patients who wish to liberalize their intake, explain risks. GFR &lt; 5: appropriate to stop monitoring. The patient can eat as desired.</td>
</tr>
<tr>
<td>CKD Guideline</td>
<td>Guiding Principle</td>
<td>Recommendation</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Ca / PO4</td>
<td>Hyperphosphatemia can contribute to <strong>pruritus</strong> and <strong>RLS</strong>. Ca &amp; Po4 depositions can lead to <strong>myalgias</strong>, <strong>arthralgias</strong>, and <strong>pseudogout</strong>.</td>
<td>Patients can liberalize their diet if they so desire; they should be made aware of the link with symptoms. Interventions only if high PO4 is thought to be contributing to symptoms. If the patient desires treatment – monitor levels every 3 months. GFR &lt; 5: stop interventions and monitoring.</td>
</tr>
<tr>
<td>Vit D statement</td>
<td>May recommend active vitamin D to address the potential role of active vit D deficiency in <strong>fatigue</strong>, <strong>weakness</strong>, and <strong>muscle loss</strong>.</td>
<td><strong>Vitamin D3</strong>: there is lack of consensus to support routine supplementation in patients with CKD. <strong>Calcitriol</strong> (active form of vitamin D). Suggested starting dose: calcitriol 0.25mcg PO 3 times a week</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>PTH monitoring is not required</strong></td>
</tr>
</tbody>
</table>
Early results of the conservative kidney management pathway (n=254)

**Patient Preferences**

**Uptake of CKM**

- Pre: 8%
- Post: 18%

**Modality Changes**

Patients not changing their mind after choosing CKM

- Pre: 60%
- Post: 91%

**Advance Care Planning**

Completing GCD & recalling ACP conversation

- Pre: 14%
- Post: 75%

**Patient Outcomes**

**No Severe Symptoms**

- Pre: 51%
- Post: 72%

**Care at Preferred Place before death**

- Pre: 80%
- Post: 96%

**Stabilized Quality of Life**

Acceptable quality-of-life

- Pre: 51%
- Post: 57%
Framework for Palliative Dialysis

**TRADITIONAL DIALYSIS CARE**
Maximize survival and long-term health outcomes

**Patient-Centered Dialysis**
- Align treatment with patient preferences.
- Survival & long-term health outcomes are balanced with maximizing QOL and symptom control
  - Requires integration of supportive care

**Palliative Dialysis**
- Align treatment with patient preferences
- Maximizing QOL, symptom control, and ACP for end of life care become of paramount importance

Davison, Jassel. CJASN 2016
Mrs MW

- 76 year-old woman
- She has been on HD for 6 months
- ESKD due to hypertension
  Stroke 2 years ago, no apparent residual deficits
  Known CAD (stable angina), no prior MI
- Still lives in her own home with her husband
- Very knowledgeable re: politics and loves to engage in philosophical discussions
Online calculator to estimate prognosis for prevalent HD patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Predicted Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Surprise Question</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1=not surprised, 0=surprised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>76</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93%</td>
</tr>
<tr>
<td>Dementia ( 1 = yes, 0 = no)</td>
<td>0</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84%</td>
</tr>
<tr>
<td>Peripheral vascular disease ( 1 = yes, 0 = no)</td>
<td>0</td>
<td>18 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74%</td>
</tr>
</tbody>
</table>

[http://touchcalc.com/calculators/sq](http://touchcalc.com/calculators/sq)
Mrs MW

- Upon closer questioning of Mrs MW her husband……..
- She had become forgetful - short-term memory
- Unable to recall what she ate the day before
- Occasional odd behaviour – found missing socks in her fridge!
- Geriatric assessment: multi-infarct dementia
Online calculator to estimate prognosis for prevalent HD patients

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<tr>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>1=not surprised, 0=surprised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>76</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66% (93%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
<td>12 months</td>
</tr>
<tr>
<td>1 = yes, 0 = no</td>
<td></td>
<td>35% (84%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0</td>
<td>18 months</td>
</tr>
<tr>
<td>1 = yes, 0 = no</td>
<td></td>
<td>16% (74%)</td>
</tr>
</tbody>
</table>

http://touchcalc.com/calculators/sq
I get up in the morning ... I worry. Even though I’m laughing, it’s only on the inside.

Health care providers are reluctant to talk about end of life issues. I think they are afraid of how you are going to react.

I don’t think they know what to say. No, I want to talk about it, but nobody will talk to me. At least that’s how I feel ... inside I am hurting like mad, but I can’t get that out.

"Yikes! Okay, I’m going to pretend I didn’t see that."
Symptom burden accounts for 30% - 46% of the reduction in dialysis patients quality of life

Davison et al. KI 2006, JPSM 2010
Symptom Assessment: ESAS-r: Renal

http://www.palliative.org

- Itching
- Sleep
- Restless legs

---

**Edmonton Symptom Assessment System Revised: Renal (ESAS-r:Renal)**

Please circle the number that best describes how you feel NOW:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Tiredness (Tiredness = lack of energy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Drowsiness (Drowsiness = feeling sleepy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Nausea (Nausea = feeling sick)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Lack of Appetite (Lack of appetite)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Shortness of Breath (Shortness of breath)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Depression (Depression = feeling sad)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Anxiety (Anxiety = feeling nervous)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best Wellbeing (Wellbeing = how you feel overall)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Itching</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Problem Sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Restless Legs</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

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Patient's Name: 

Completed by (check one):

- Patient
- Family caregiver
- Health care professional caregiver
- Caregiver-assisted

Developed by the Edmonton Zone Palliative Care Program and Northern Alberta Renal Program
The aim of treatment is to ameliorate pain that is adversely impacting the patient’s QOL . . . it is not always necessary or possible to resolve it completely.

1. Medication should not be the sole focus of treatment!
2. Assess & treat contributing reversible factors
3. Non-pharmacologic treatment
4. Pharmacologic treatment

- Topical treatment
- Physical therapies
- Behavioral therapies
- Cognitive behavioral therapy
- Interventions
  - Nerve blocks
  - Trigger point injections.
The etiologies of **pain** in patients with ESKD reflect multi co-morbidity as well as syndromes more specific to kidney disease.
Pain is common in dialysis patients, is often moderate or severe in intensity, and is linked to reduced QOL.

- **Overall Pain (HD)**: 19 studies, n = 4873
  - Moderate-Severe: 16 studies, n = 4365
  - Prevalence: 68.9%

- **Muscle Pain (HD)**: 10 studies, n = 2102
  - Prevalence: 59.4%

- **Muscle Pain (PD)**: 1 study, n = 573
  - Prevalence: 64.0%
US adult nephrology trainees are poorly prepared to deal with patient’s pain and other palliative care-related issues.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having end-of-life discussions</td>
<td>6.3</td>
<td>20</td>
<td>32.6</td>
<td>27.4</td>
<td>13.7</td>
</tr>
<tr>
<td>with patients on dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treating depression in dialysis</td>
<td>14.6</td>
<td>34.4</td>
<td>31.3</td>
<td>14.6</td>
<td>5.1</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Managing pain with medications</td>
<td>11.3</td>
<td>21.6</td>
<td>34</td>
<td>23.7</td>
<td>9.4</td>
</tr>
<tr>
<td>with advanced renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not offering dialysis</td>
<td>9.3</td>
<td>35.1</td>
<td>29.9</td>
<td>20.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Withdrawing dialysis</td>
<td>20.6</td>
<td>28.9</td>
<td>25.8</td>
<td>19.6</td>
<td>5.1</td>
</tr>
</tbody>
</table>

1 = least comfortable ...............5 = most comfortable

Pain is not being effectively managed in CKD

The literature suggests this is partially due to **BOTH under and over prescription** of analgesics

- **Any Analgesic**: 11 studies (n = 4,719) - 47%
- **Any Opioid**: 12 studies (n=188,823) - 22% (95% CI 0.07-0.41)
- **Any NSAID**: 17 studies (n=93,568) - 16%
- **Acetaminophen**: 7 studies (n=11,556) - 26%

Davison, SR Analgesics in CKD (under review), Nagar VR Pain Medicine 2017
The forest plot of random effects model on opioid prevalence with pooled estimate and 95% confidence interval. There is very large between-study heterogeneity and highly influential samples are present.
Unlike most of the world, inappropriate opioid prescribing in the United States appears to extend to dialysis patients.

- 64% of patients have at least one opioid prescription in 1 year.
- 23.4% have a ≥ 90 day supply in 1 year (chronic).

Increased:
- Mortality
- Dialysis withdrawal
- Hospitalizations

- 51.4% Opioid Only
- 11.0% Opioid & Analgesic
- 3.2% Analgesic Only

Chronic opioid prescription rates ranged from 9.5% of dialysis patients in Hawaii to 40.6% of patients in West Virginia. A total of 8 states had prescription rates > 30%.

Kimmel P JASN 28:3658-3670, 2017
The opioids being prescribed for \( \geq 90 \text{ days} \) for dialysis patients in the United States are not those that are recommended for ESRD patients.

<table>
<thead>
<tr>
<th>Opioid</th>
<th>% (2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>11.7</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5.4</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>1.4</td>
</tr>
<tr>
<td>Tramadol</td>
<td>2.5</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.6</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.7</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.3</td>
</tr>
</tbody>
</table>


Kimmel P JASN 28:3658 -3670, 2017
# The Five Principles of Pain Management

<table>
<thead>
<tr>
<th>General principle</th>
<th>Description</th>
<th>Specific considerations in advanced CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>“By mouth”</td>
<td><strong>Oral</strong> administration</td>
<td>HD patients - easy <strong>IV access</strong>. This is to be <strong>avoided</strong></td>
</tr>
<tr>
<td>“By the clock”</td>
<td>For continuous or predictable pain</td>
<td>Start with <strong>low</strong> doses and titrate <strong>slowly</strong>. Some with mild pain may achieve pain relief with analgesic dosing post-HD only.</td>
</tr>
<tr>
<td>“By the ladder”</td>
<td>WHO analgesic ladder... step wise approach</td>
<td><strong>Careful selection of analgesics</strong>&lt;br&gt;Avoid sustained-release</td>
</tr>
<tr>
<td>&quot;For the individual&quot;</td>
<td>“<strong>Correct</strong>” dose = dose needed for pain relief with no intolerable side effects.</td>
<td><strong>Numerous other symptoms, often within the context of end-of-life issues</strong></td>
</tr>
<tr>
<td>&quot;Attention to detail&quot;</td>
<td>Regular <strong>reassessment</strong>.&lt;br&gt;<strong>Side effects:</strong> explained &amp; managed actively</td>
<td><strong>No chronic studies therefore attention must be paid to efficacy &amp; safety, including the impact on function &amp; QOL</strong></td>
</tr>
</tbody>
</table>
Patients with ESKD are chemically sensitive with **small therapeutic windows** - careful dosing with close follow-up is essential.

A. **Normal ‘window of comfort’**

B. **Small ‘window of comfort’** in CKD pts
<table>
<thead>
<tr>
<th>Neuropathic Pain</th>
<th>Nociceptive Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start with adjuvant therapy</strong></td>
<td><strong>N/A</strong></td>
</tr>
<tr>
<td>1. <strong>Gabapentin</strong> 50-300 mg PO nightly.</td>
<td></td>
</tr>
<tr>
<td>2. <strong>Carbamazepine</strong> starting at 100mg twice daily</td>
<td></td>
</tr>
<tr>
<td>3. <strong>TCA</strong>s e.g., amitriptyline starting at 10-25mg daily or doxepine starting at 10mg daily</td>
<td></td>
</tr>
<tr>
<td><strong>Acetaminophen</strong>, max 3g daily in addition to adjuvant therapy</td>
<td><strong>Acetaminophen</strong>, max 3g daily</td>
</tr>
<tr>
<td>(adjuvant can be stopped if of no benefit or not tolerated)</td>
<td>Consider a topical NSAID if pain is localized to a small joint.</td>
</tr>
<tr>
<td><strong>E.g., Hydromorphone</strong> starting at 0.5 mg PO q4-6 hrs in addition to adjuvant therapy and acetaminophen.</td>
<td><strong>E.g., Hydromorphone</strong> starting at 0.5 mg PO q 4-6 hrs</td>
</tr>
<tr>
<td>Also consider <strong>buprenorphine</strong>, <strong>fentanyl</strong> and <strong>methadone</strong>.</td>
<td>Also consider <strong>buprenorphine</strong>, <strong>fentanyl</strong> and <strong>methadone</strong>.</td>
</tr>
</tbody>
</table>

*If pain persists*:

- **Add a non-opioid +/- adjuvant therapy**
- **Add a strong opioid**
- **Titrate slowly as tolerated to adequate pain relief**
This algorithmic approach to pain management was highly effective in improving analgesia and other patient outcomes in patients on HD.

**Opioid Use**

- Total Pre
- Total f/u

**Patient-Centered Outcome**

- Pain now
- Worse pain
- Least pain
- Average pain
- General activity
- Mood
- Walking
- Normal work
- Relationships
- Sleep
- Enjoyment of life

prn: 4.0 v 4.4mg/day
reg: 37.7 v 6.3 mg/day 50ug v. 37ug/72 hrs

Davison 2018 .......
Restless Legs Syndrome

“Leaping and contractions of the tendons...that the diseased are no more able to sleep, than if they were in a place of the greatest torture”
Thomas Willis, Instructions for Curing the Watching Evil, 1685

“I cannot stay in bed...so most nights I sit in a chair praying that it will subside long enough for me to get an hour of sleep.”

Novak et al, Seminars in Nephrology 2015
The essential criteria for diagnosing Restless Legs Syndrome (Willis-Ekbom disease)

1. Overwhelming urge to move the legs

2. Worsened by inactivity

3. Worse in the evenings or at night

4. Relieved with exercise

5. Not caused by other condition that can mimic RLS (myalgia, leg cramps)

Often associated with periodic leg movements (PLMs)
RLS is common but without routine screening it is poorly recognized

General Population: ~ 7%

ESKD Population: 15-30%

DeFerio, BMC Nephrology 2017; Kutner et al, QJM 2013
RLS can lead to poor health outcomes and quality of life for patients . . .

- Decreased QOL: mental and physical aspects
- More likely to leave dialysis early
- Increased mortality?

We can’t improve what we do not measure. However, measuring is insufficient to improve care – it requires action.

Edmonton Symptom Assessment System Revised: Renal (ESAS-r:Renal)

Please circle the number that best describes how you feel NOW:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worst Possible Pain</td>
</tr>
<tr>
<td>No Tiredness (Tiredness = lack of energy)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Drowsiness (Drowsiness = feeling sleepy)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Lack of Appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Shortness of Breath</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Depression (Depression = feeling sad)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Anxiety (Anxiety = feeling nervous)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Best Wellbeing (Wellbeing = how you feel overall)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Itching</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Problem Sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>No Restless Legs</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

- Restless Legs Syndrome Rating Scale (RLSRS)
  10 questions: 0-4 scale
  Moderate: 11-20/40
  Severe: 31-40/40

- Johns Hopkins Restless legs Severity Scale (JHRLSS)
  A single-item scale
  Based on the time of day the symptoms begin to appear

ESAS-revised:Renal

IRLSSG: Sleep Medicine 2003
Allen R et al  Sleep Medicine 2001
Brain iron deficiency

- Decreased iron transport

Decreased dopamine activity

- Decreased D₂ receptor binding
- Increased brain dopamine
Brain iron deficiency  

- Decreased iron transport

Decreased dopamine activity

- Decreased D$_2$ receptor binding
- Increased brain dopamine

Other neurotransmitter systems . . .

- Increased brain glutamate . . . gabapentinoids
- Decreased opioid function (receptors) . . . opioids

- Genetics

Faulkner CNS Drugs, 2018; Venkateshiah Crit Care Clinics, 2015; Allen Sleep Med Clin 2015
The aim of symptom management is to ameliorate symptoms that cause significant distress - it is not always necessary or possible to resolve the symptom completely.

1. Assess & treat contributing reversible factors

2. Non-pharmacologic treatment
   - Iron, Vit D
   - X Olanzapine & Quetiapine
   - X SSRIs & ?mirtazapine
   - X Topiramate

3. Pharmacologic treatment

4. Reassess for impact: QOL, sleep, social functioning
Patients can be empowered to manage some of their symptoms conservatively

- Stop or reduce stimulants
- Exercise
- Activities that use the brain (cross word puzzles)
- Gentle leg massage
- Good sleep hygiene
- Provide information

www. CKMcare.com
1. Shorter and more frequent HD sessions? (FREEDOM study, no control)

- 35% Patients reporting RLS, 26% Moderate to severe RLS

2. Cold dialysis?

- 36°C v. 37°C
  - 36% Motor symptoms
  - 10% Sensory symptoms

3. Move HD to earlier in the day?

- 34% Before 2pm (OR 1.35)

A systematic review and meta-analysis of exercise included 15 RCTs (683 HD patients) and showed improved RLS, depression, and fatigue although sleep quality does not appear to improve.
Pharmacologic management involves 2 main options . . . and a 3\textsuperscript{rd} for intractable symptoms

1. **Dopamine agonists**
   - Levodopa – **Augmentation \( \sim 80\% \) of patients**
     - Ropinirole
     - Pramipexole
     - Rotigotine transdermal system

2. **Gabapentinoids (\( \alpha_2\delta \) ligands)**
   - Gabapentin
   - Pregabalin
   - Gabapentin enacarbil

3. **Opioids:** methadone, oxycodone/naloxone

Patatanian E et al Annals of Pharmacotherapy, 2018; Faulkner MA CNS Drugs, 2018
Studies in patients with ESKD are limited with very small number of patients.

<table>
<thead>
<tr>
<th>Drug</th>
<th># Studies</th>
<th>N</th>
<th>Results</th>
<th>Dose (~2 hrs before bed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>3</td>
<td>16-87</td>
<td>Improved IRLS score, sleep parameter, social fct and QOL vs. L-dopa/placebo</td>
<td>50-300mg qhs</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>1</td>
<td>11</td>
<td>Superior to levodopa SR in reducing IRLS scores and in increasing sleep time</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>1</td>
<td>10</td>
<td>Improved IRLS score</td>
<td>0.125 mg</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>2</td>
<td>30</td>
<td>Improved IRLS score v. placebo</td>
<td>1 -3 mg TD</td>
</tr>
</tbody>
</table>
Recommendations for RLS – a stepped approach starting with screening, evaluate severity and discuss treatment options...

1. Review Fe status, medications, smoking, alcohol, caffeine
   - Modify dialysis prescription

2. Non-pharmacologic treatment
   - Exercise, activities that use the brain, gentle leg massage, good sleep hygiene

3. Pharmacologic treatment
   - Gabapentin
     - Consider non-ergot dopaminergic agents

4. Reassess for impact: QOL, sleep, social functioning; adverse effects
   - Start low
   - Go slow
   - Consider polypharmacy
**Pruritus.** “unrestricted and uncomfortable sensation that elicits the desire to scratch

- ~50% of patients experience pruritus
- Experienced as daily or near daily
- No associated skin lesions
- Not dermatomal
- Localized or generalized
- Symptoms tend to increase at night...
- Associated with poor sleep, anxiety and depression

---

**Keratosis Papules**

**Lichen Simplex**

**Purigo Nodularis**
Pathogenesis remains poorly understood and is likely multifactorial - **skin/nerve inflammation** in the context of systemic inflammation or an **increase in activity of u-opioid receptors**

<table>
<thead>
<tr>
<th>Pathogen/Process</th>
<th>Mechanism</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xerosis</td>
<td>Impairment of sweat and sebaceous glands</td>
<td>Increased prevalence in patients w/dry skin, yet evidence is contradictory</td>
</tr>
<tr>
<td>Histamine</td>
<td>Release from skin mast cells triggers itching</td>
<td>Reports of elevated plasma histamines, yet no established correlation and a muted flare reaction to histamine</td>
</tr>
<tr>
<td>Elevated PTH</td>
<td>Stimulates mast cells to release histamine</td>
<td>Disappears after Tx→ not every patient gets symptoms</td>
</tr>
<tr>
<td>Divalent ions: Ca, Mg, Phos</td>
<td>Deposit in the skin</td>
<td>Initially data to support this, not consistent</td>
</tr>
<tr>
<td>Better adequacy</td>
<td>Improved Kt/V</td>
<td>No improvement even at 1.5</td>
</tr>
</tbody>
</table>
Opioid Hypothesis

- µ-opioid receptor is associated with pruritus through disinhibition of the central itch response via their antinociceptive properties.
- Dialysis patients have been shown to have an elevated level of β-endorphin, a µ-opioid receptor agonist.
Itch

Topical

• **Capsaicin** (Zostrix) ointment

• **Pramoxine**
  – OTC as Gold Bond
  – With hydrocortisone 1% each

• **Menthol, Camphor & Phenol** (0.3%)

• **Gamma-Linolenic acid (GLA)** cream (2.2%)

Systemic

• **Gabapentin** (pregabalin): low dose
  – 50-300mg qhs

• **Doxepin** (TCA): low dose
  – 10mg qhs
  – Gabapentin > doxepin

• High flux HD

• Phototherapy
  – UVB

• Acupuncture

Simonsen et al, AJKD 2017; Balaskas et al. CJASN 2011,
Treatment: Opioid Hypothesis

K-agonist Nalfurifine HCl 2.5 - 5 ug IV daily
• 2 randomized studies: only one showed benefit

µ-antagonist Naltrexone 50 mg po daily
• 2 randomized studies: only one showed benefit

µ-antagonist + K-agonist Nalbuphine
• 1 RCT – beneficial

Systematic Review of uremic Pruritus: Simonsen E et al. AJKD 2017
Nalbuphine ER

- Multi-center, randomized, double-blind placebo controlled trial of 373 patients with mod-severe itch
- 120 mg BID or 60 mg BID v. placebo - 8 weeks
Recommendations for Pruritus – a stepped approach .......

1. Assess & treat contributing reversible factors
2. Conservative measures
   - Glycerol/high water containing emollients
3. Non-pharmacologic treatment
   - Gabapentin
4. Pharmacologic treatment
   - Consider opioid modulator: Nalbuphine

Conservative measures:
- Glycerol/high water containing emollients

Pharmacologic treatment:
- Gabapentin

Start low
Go slow
Consider polypharmacy

Reassess for impact: QOL, sleep, social functioning; adverse effects

Review kt/v, Ca, albumin
Determine amount of Xerosis

Conservative measures
Glycerol/high water containing emollients

Non-pharmacologic treatment
Gabapentin
Consider opioid modulator: Nalbuphine

Start low
Go slow
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Conservative measures
Glycerol/high water containing emollients

Non-pharmacologic treatment
Gabapentin
Consider opioid modulator: Nalbuphine
Our vision is a single supportive care pathway for all Albertans with advanced chronic illness

Adapt
Implement
Evaluate
...Adapt
“The good physician treats the disease. The great physician treats the patient who has the disease.”
-Sir William Osler
Acknowledgements

Kidney Supportive Care Research Group (KSCRG)

www.ualberta.ca/~kscrg

CKM website for integrated care plans and symptom management CKMcare.com

My inspirations . . .