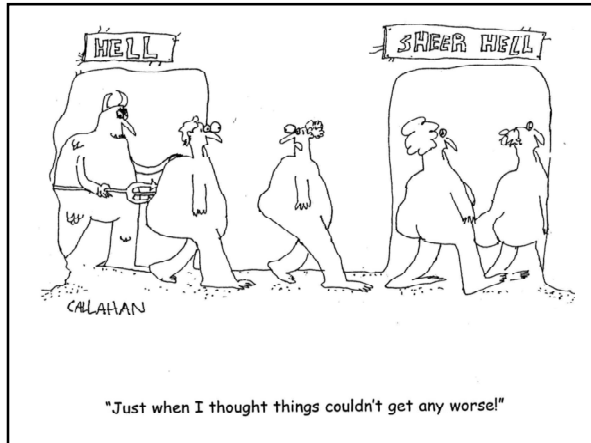


Pain Prevalence and Treatment in Patients with Renal Disease

**Michael Germain
Professor Medicine Tufts University**



Objectives

- **Highlight the magnitude and impact of chronic pain in ESRD**
 - Prevalence, severity, etiology
 - Impact of chronic pain on health-related quality of life
- **Discuss the management of chronic pain in ESRD**
 - Outline potential barriers
 - Outline potential strategies to enhance pain management

ESRD Population



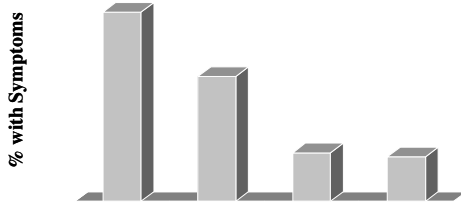
- 50% patients starting dialysis > 65 years old
- 75+ are the fastest growing group of dialysis patients
- Significant co-morbidity

Burden of Symptoms in Hemodialysis Patients

%	0	1-3	4-5	6-10
Pain	37.5	20.5	16.0	26.5
Nausea	61.4	24.0	7.0	7.6
Depression	50.6	22.6	14.0	12.8
Anxiety	44.8	26.4	13.7	15.1
Drowsiness	32.1	28.3	21.0	18.6
Appetite	28.1	28.4	20.8	22.7
Wellbeing	18.4	30.5	27.3	23.8
SOB	43.9	25.0	15.7	15.4
Pruritis	31.5	27.4	15.7	25.4
Activity	12.7	23.5	27.6	36.2

Fainsinger, 2002

Most Common Symptoms Reported by Symptomatic Dialysis Patients



Symptoms

Kimmel PL, AJKD 2003

Pain in Hemodialysis Patients

- Although dialysis sustains life, underlying systemic disease persist
 - Ischemic limbs, peripheral neuropathies
- Numerous painful syndromes unique to chronic kidney disease
 - Calciphylaxis, renal bone disease, NSF (nephrogenic sclerosing fibrosis), and dialysis-related amyloidosis
- Prospective cohort study of 205 HD patients (UAH)
 - 103 (50%) reported a current problem with pain
 - 55% of these patients reported their pain as severe
 - 18% had multiple causes for their pain

Davison, AJKD 2003

Etiology of Pain	Percentage (%)
Musculoskeletal	63.1
Osteoarthritis	19.4
Musculoskeletal: Not yet diagnosed	18.4
Osteoporosis (resulting in spinal fractures)	9.7
Inflammatory Arthritis	6.8
Renal Osteodystrophy	4.9
Discitis/Osteomyelitis	1.9
Related to Dialysis Procedure	13.6
Peripheral Polyneuropathy	12.6
Peripheral Vascular Disease	9.7
Other (including trauma, PCKD, malignancy, calciphylaxis)	20.3

Davison, AJKD 2003

Calciphylaxis (calcific uremic arteriopathy)





Osteitis Fibrosa

Adynamic Bone disease: bone and joint pain (at rest and with exertion), fractures, skeletal deformities

Bone and joint pain on exertion in skeletal sites that are subject to biomechanical stress. Frequently associated with calcium phosphate deposition in arteries, joints, soft tissues, and the viscera; may be associated with proximal myopathy, ruptured tendons, pseudogout, and calciphylaxis.

Severity of Pain: Brief Pain Inventory Scores

Severity (n=103)	Mild (0-3)	Moderate (4-5)	Severe (6-10)	Mean BPI Score
Worst	17.5%	82.5%		7.03
Least	74.8%	16.5%	8.7%	3.07
Average	41.7%	58.3%		5.61
Now	44.7%	28.2%	27.2%	4.99

Cause of pain is NOT predictive for severity of pain

Davison, AJKD 2003

The Impact of Pain on Quality of Life, Depression and Insomnia

	No – Mild pain	Mod – Severe pain	Odds Ratio	P
Depression	18%	34%	2.31	0.01
Insomnia	53%	75%	2.32	0.02

Davison JPSM 2005

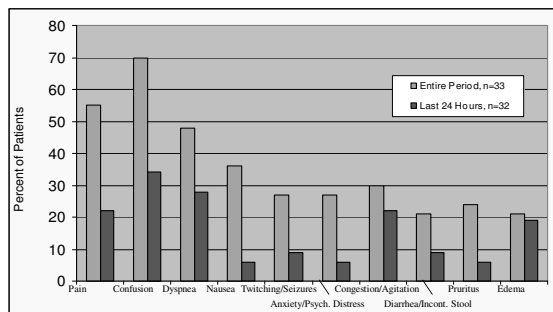
• Symptom burden accounted for 29% of the impairment in physical HRQL and 39% of the impairment in mental HRQL

Davison JPSM 2005

• Change in symptom burden accounted for 34% of the change in physical HRQL and 46% of the change in mental HRQL.

Davison JPSM 2005

Symptoms Experienced After the Withdrawal of Dialysis



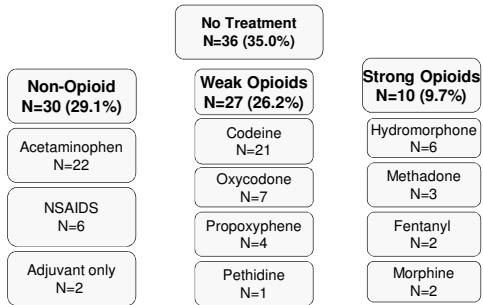
Symptoms Chater S, 2006

Point Prevalence of Analgesic Use: DOPPS

Analgesic	Number of Patients	
	1997 N = 2988	2000 N = 2476
Any analgesic	30.2%	24.3%
Any narcotic	18.0%	14.9%
Any NSAID	6.4%	2.3%
Any acetaminophen	11.1%	6.3%

¾ of patients reporting moderate to severe pain were not prescribed analgesics

Pain Management



Davison AJKD 2003

Barriers to Effective Pain Management

- Patient reluctance to report pain
- Lack of staff time and training in the basic principles of pain management

Barriers to Effective Pain Management



- ELDERLY**
- More sensitive to the effects of many analgesics
 - More susceptible to adverse effects
 - Polypharmacy
 - High number of comorbid conditions
 - Pharmacokinetic and pharmacodynamic changes occur with aging
 - Analgesics associated with falls in the elderly

Barriers to Effective Pain Management

ESRD Specific

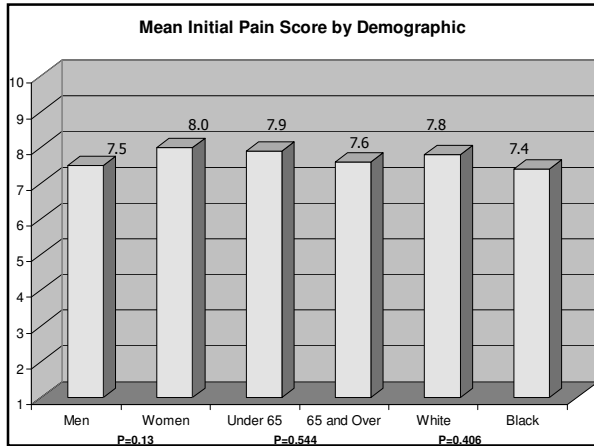
- **Lack of recognition of the problem: therefore not a clinical or research focus**
- **Complicated pharmacokinetics and pharmacodynamics**
- **Uremic symptoms may mimic opioid toxicity**
- **Limb preservation, defer high risk surgery**

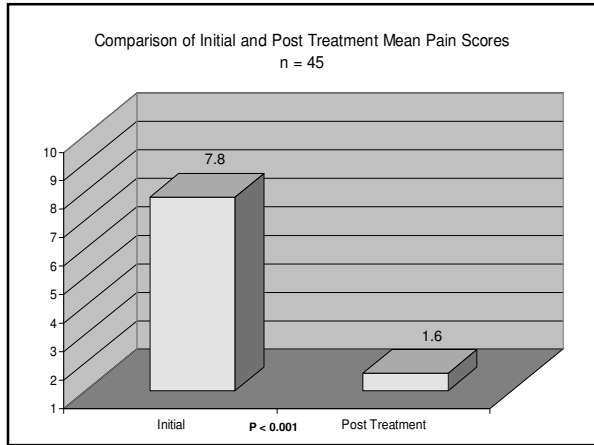
Barriers to Effective Pain Management

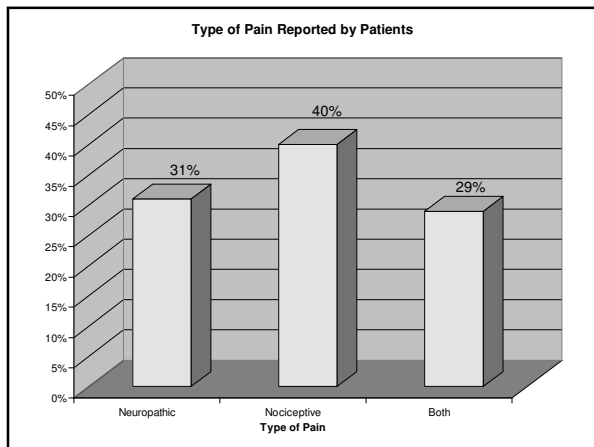
- **Treatment algorithms for cancer patients may not apply to ESRD patients**
 - **Objective data on appropriate and effective management strategies for ESRD patients are still required**
 - **Many patients will require analgesic therapy for several years**
- **Pain is often experienced in the context of multiple, complex symptoms and end-of-life issues which may interfere markedly with psychological, social and physical coping skills**

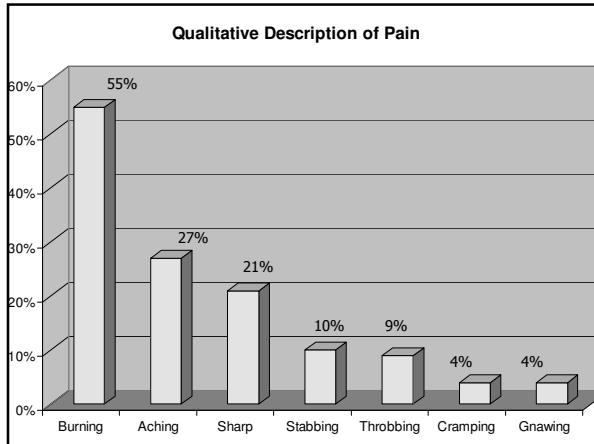
Barriers to Pain Assessment in ESRD

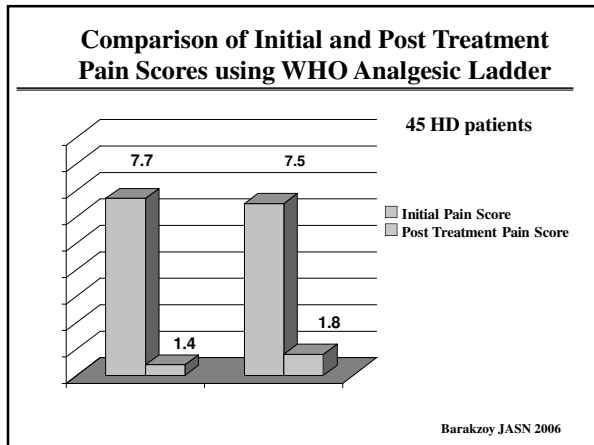
- **Cognitive impairment – dementia**
- **Language / cultural barriers**
- **Family members rarely accompany patients to dialysis**
- **Family doctors often not involved in the care of (urban) dialysis patients (at least in Canada)**
- **Nephrology multidisciplinary team not educated to adequately assess pain.**
- **Technology and biochemical focus during dialysis rounds**

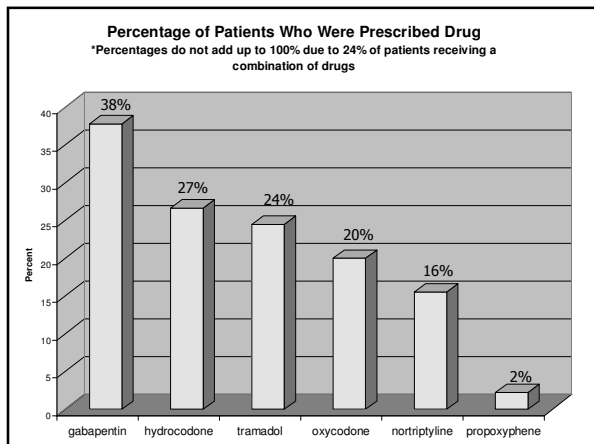








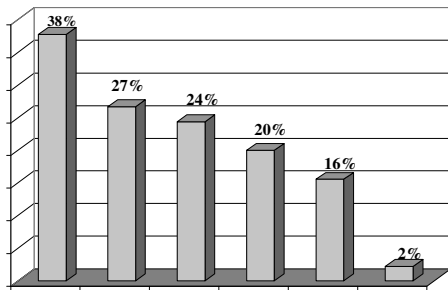




QOL Outcomes from Pain Management

- **Improved function**
 - “I am able to walk to my mailbox, something I could not do before because of hip and leg pain.”
- **Better ability to tolerate dialysis**
 - “I am able to tolerate 4 hours of dialysis without the severe back pain.”
- **More restful sleep**
 - “I have more energy because I am resting better at night.”

Percentage of Patients Who Were Prescribed Analgesics



Barakzoy JASN 2007

Non-Narcotic Analgesics

- Acetaminophen**
- Does not require dose adjustment in ESRD
 - Non-narcotic of choice for mild-moderate pain in CKD/ESRD
 - Numerous OTC meds contain acetaminophen: hepatotoxicity
 - Potential cause of CKD/loss of GFR
- NSAIDS**
- Can be used in conjunction with acetaminophen
 - Increased risk of bleeding with CKD/ESRD
 - Potential cardiovascular risks associated with COX-2 inhibitors
 - Renal side effects: hypertension, hyponatremia, hyperkalemia, and loss of RRF (CKD)

Tramadol

- Synthetic opioid with similar adverse effects to other opioids
- It inhibits norepinephrine and serotonin reuptake, therefore should not be given to patients on serotonin selective reuptake inhibitors (SSRIs).
 - Depression common in ESRD – these patients often on a SSRI
- Active metabolite (M1) and 30% of the parent drug is excreted via the kidneys: prolonged $\frac{1}{2}$ life and accumulation in ESRD.
- Epileptogenic in conditions with lowered seizure threshold such as uremia (most reported cases have been in association with SSRIs).
- Renal dosing is tentative : two Tramacet BID or one 150mg SR tablet po daily (i.e. max 150 mg/day)

Narcotics

- Can be used in combination with non-narcotics or alone for moderate-severe pain
- Active metabolites are renally excreted

Side Effects – more common, more difficult to discern in ESRD

- Constipation
- Nausea and vomiting, anorexia
- Gastroparesis, reflux symptoms
- Pruritus
- Dry mouth/urinary retention/antidiuretic
- Decreased libido
- Hypotension
- CNS and respiratory depression



Codeine

- Elimination $\frac{1}{2}$ life is significantly increased in dialysis patients
 - Reports of neurotoxicity
- Should be used with caution in ESRD

Oxycodone

- Elimination significantly decreased in ESRD
 - Fibrillary GN
 - Growing popularity as a drug of abuse and is now considered one of the most desirable of prescription drugs (in Canada)
 - No PK data in ESRD
- Should be used with caution in ESRD

Morphine

- Active metabolites M3G and M6G is renally excreted and accumulates in ESRD: increased side effects and toxicity
- No data regarding dose adjustments for sustained-release preparations of morphine
- Should not be used for chronic pain management

Hydromorphone

- Limited PK data, case reports of adverse effects – neuroexcitation and cognitive impairment
- Actives metabolites are renally excreted: primarily H3G (very small amounts of H6G). H3G accumulates in ESRD – removed by hemodialysis
- Published and clinical experience indicates that it may be administered safely in ESRD; may be particularly useful in patients who have intolerable side effects from other narcotics

Lee MA, Palliat Med 2001

Non-Compartmental Pharmacokinetics for Hydromorphone and H3G

Phase	t1/2 (h)	AUC(Tau) (ng.h/mL)	R
Hydromorphone			
Dialysis	3.2 ± 2.4	41.6 ± 20.3	1.8 ± 0.8
Multi-Dose	5.9 ± 4.4	33.9 ± 27.3	2.7 ± 1.6
Hydromorphone-3-Glucuronide			
Dialysis	3.3 ± 2.1	3243.9 ± 2768.0	1.8 ± 0.7
Multi-Dose	33.3 ± 41.8	4229.9 ± 2975.4	12.5 ± 15.1

Davison, Mayo, submitted

Non-Compartmental Pharmacodynamics:

Phase	Time to Max Analgesia (hours ± SD)	Maximun Analgesia (% ± SD)	% time with analgesia (% ± SD)
Dialysis	1.8 (0.5 - 4.0)	-68.8 ± 37.5	66.3 ± 40.1
Multi-dose	3.0 (0.5 - 4.0)	-65.5 ± 43.3	40.2 ± 21.8

Methadone

- Opioid commonly used for treatment of severe pain or withdrawal in narcotic addicts
- High oral bioavailability and a long 1/2 life
- Not well cleared with hemodialysis
- Limited PK data in ESRD; single report suggesting normal levels in ESRD due to elimination via the bowel
- Anecdotal experience suggests a relatively good safety profile in ESRD if monitored carefully

Fentanyl

- Transdermal formulation
- Essentially no PK data for transdermal formulation in ESRD or effect of dialysis on levels (one report stated poor removal)
- Inactive metabolites, only 5-10% excreted unchanged in the urine
- Toxicity has been reported but anecdotal experience suggests a reasonable safety profile in ESRD if monitored carefully

Analgesics in Chronic Kidney Disease

Recommended	Use with caution	Do Not Use
Acetaminophen	Tramadol	Codeine
Hydromorphone	Hydrocodone	Morphine
Fentanyl	Oxycodone	Meperidine
Methadone		Propoxyphene

Exogenous cannabinoids?

Adjuvants

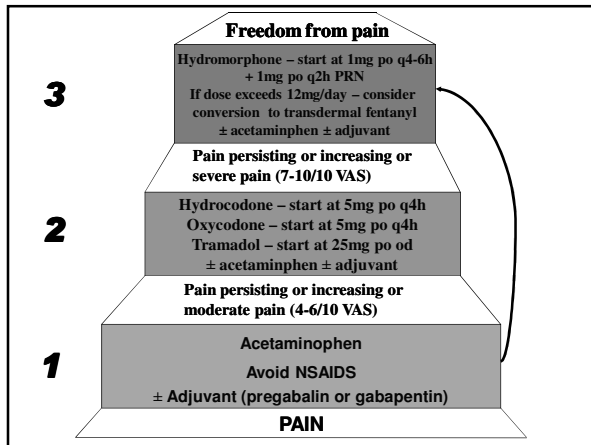
Anticonvulsants

- **Gabapentin:** effective for restless legs and neuropathic pain
 - Not appreciably metabolized, eliminated renally, removed by HD.
 - Accumulation with toxicity in ESRD has been documented
 - Start with 100mg qhs and increase weekly by 100mg –doses of 300mg/day are usually well tolerated; occ 600mg/day has been used
- **Pregabalin:** start at 25mg qhs and increase every few days to 100mg/day
- **Carbamazepine:** does not require dose adjustment in ESRD, only 2-3% is excreted unchanged in the urine, start @ 200mg BID

Adjuvants

Antidepressants

- **Tricyclic antidepressants:** metabolized in the liver, active metabolites renally excreted
 - Poorly tolerated in ESRD due to the anticholinergic, histaminergic, and adrenergic effects: dry mouth, sedation, weight gain, orthostatic hypotension; caution in patients with cardiac conduction abnormalities
 - CKD patients show greater unpredictability and interpatient variability in their response to TCAs
 - TCAs are also highly protein bound with a large apparent volume of distribution, therefore are not effectively removed by dialysis.
 - TCAs a distant second choice compared to pregabalin & gabapentin
 - Desipramine may have less side effects than amitriptyline



Management of Opioid Adverse Effects

Excessive sedation, compromised respiration with low O2 saturation.

- Small doses of naloxone 0.1 mg SC or IV every 1 or 2 minutes unless severe respiratory depression in which case 0.4 mg SC or IV should be used initially (along with other supportive measures)

Nausea &/or vomiting

- Prochlorperazine 2.5 to 10 mg PO, SC or PR QID prn,
- Haloperidol 0.5 to 1 mg PO, SL, SC BID-TID prn
- Metoclopramide 5 to 10 mg PO, SC, IV QID prn.
- Dimenhydrinate may be used 25 to 50 mg PO, SC, IV Although it may reduce opioid-induced pruritus, not effective for uremic pruritus
- Ondansetron 4-8 mg PO or IV Q8H prn.

Constipation

- Start docusate sodium and stimulant laxative (e.g., Senna, Bisacodyl) at same time as opioids as preventative therapy.

- Avoid fleet enemas (PO, overload)

Monitor cognitive function

Opioid Abuse & Addiction in ESRD

- **Addiction (psychological dependence): primary, chronic, neurobiologic disease with genetic, psychological, and environmental factors.....characterized by behaviors that include 1 or more of the following:**
 - Impaired control over drug use
 - Compulsive use
 - Continued use despite harmful consequences
 - Craving
- **Prevalence in ESRD or similar chronically ill populations is unknown**
- **Unknown which aberrant drug-taking behaviors best predict drug abuse or addiction in ESRD**
- **Screening for addiction: consider for everyone**
 - **ORT, SOAPP, DIRE (not validated in ESRD)**



Historical Use of Marijuana (Cannabis)



- Oldest known Neolithic culture in China
- An 1848 commentary in the British Pharmacopoeia outlined psychotropic, antispasmodic and analgesic effects of Cannabis



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Cannabinoid Receptors

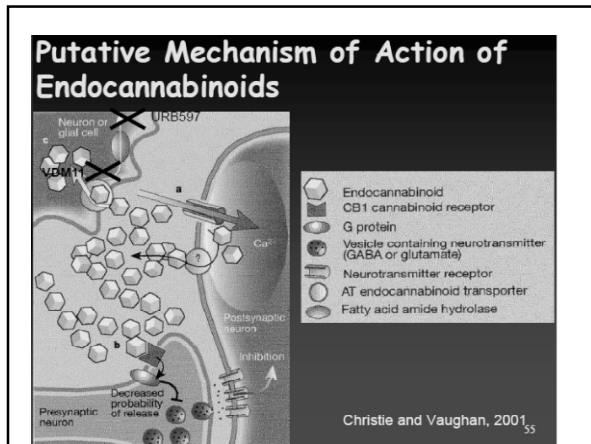
CB₁ receptor

- Found in the brain, spinal cord and peripheral nervous system.
 - ◆ Also present in various peripheral tissues such as heart and vasculature

CB₂ receptor

- Found on immune cells in peripheral tissues
 - ◆ More recently, found in the CNS

(Davison JS et.al. Science 2006) 51



Cannabinoids v. Opioids

	Opioids	Cannabinoids
Nausea & Vomiting	Increases	Decreases
Appetite	Decreases	Increases
Agitation	Increases	Decreases
Sleep	Disturbs	Improves
Pruritus	Increases	Decreases
Hypotension	++	+
Constipation	++	+/-
Sense of well-being	+/-	Increases
Psychosis/abuse	+	++

- ### Cannabinoid Drugs Approved by FDA and Health Canada
- **Dronabinol:** synthetic THC (Marinol)
 - ◆ Anorexia/wasting in patients with HIV
 - ◆ Emesis due to cancer chemotherapy
 - **Nabilone:** synthetic cannabinoid similar to THC (Cesamet)
 - **THC:CBD Cannabis extract (Sativex)**
 - ◆ Adjunctive tx for neuropathic pain (MS)
 - ◆ Adjunctive tx for cancer pain
- 56

Cannabidiol (CBD)

- Anti-inflammatory
- Antioxidant
- Anti-seizure
- Anxiolytic
- Antipsychotic properties.
- Inflammatory and neuropathic pain

Resources

- RPA-ASN Guidelines “Shared Decision Making: Withdrawal and Withholding Dialysis. www.renalmd.org
- Updated edition 2010
- Supportive Care for the Renal Patient Ed. J Chambers. E Brown, M Germain Oxfprd Press 2004 (2nd Ed 2010)
- Renal EOL coalition (pain algorithm on web site) www.kidneyeol.org

KIDNEY END-OF-LIFE COALITION



For additional information, including resources for patients and families, visit www.kidneyeol.org.

- Advance care planning information
- Do not resuscitate orders in the dialysis unit
- Access to hospice
- Clinician educational resources

Contact the Kidney End of Life Coalition at kidneyeol@nw5.esrd.net

**Shared Decision-Making
in the Appropriate Initiation of
and Withdrawal from Dialysis**



rpa@renalmd.org
301.468.3515

Take Home Message

- **Because of the high symptom burden and shortened life expectancy, palliative care, including aggressive pain and symptom management, needs to be incorporated into dialysis unit practices to provide ESRD patients with quality care throughout the continuum of treatment.**

Woody Allen

- **I am not afraid of death, I just don't want to be there when it happens.**
