Symptom management in dialysis: Novel interventions and the emerging role of cannabinoids

Nephrology Rounds

University of British Columbia

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HEALTH THROUGH KNOWLEDGE

Objectives

- Review the following symptoms in dialysis including the diagnosis, measurement and treatment of:
  - restless legs syndrome
  - pruritus
  - depression
  - chronic pain
- Describe the role of cannabinoids for uremic symptoms in dialysis
  - patient and physician surveys
  - PK study
  - DISCO-POT
  - other future trials

Symptoms on dialysis

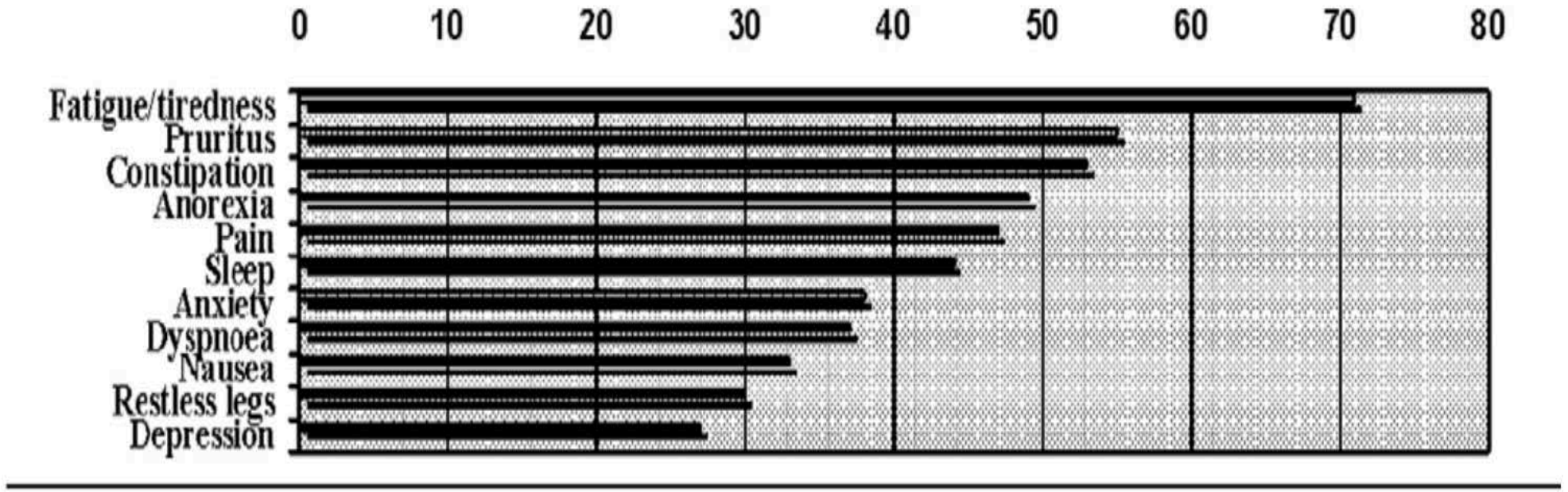


Figure 1. Weighted mean prevalence of symptoms (%) in ESRD (weighted by size of study).

Murtagh FE et al. ACKD 2007 14(1):82-89

Illness trajectory

Grubbs et al.
CJASN 2014;
9:2203-2209

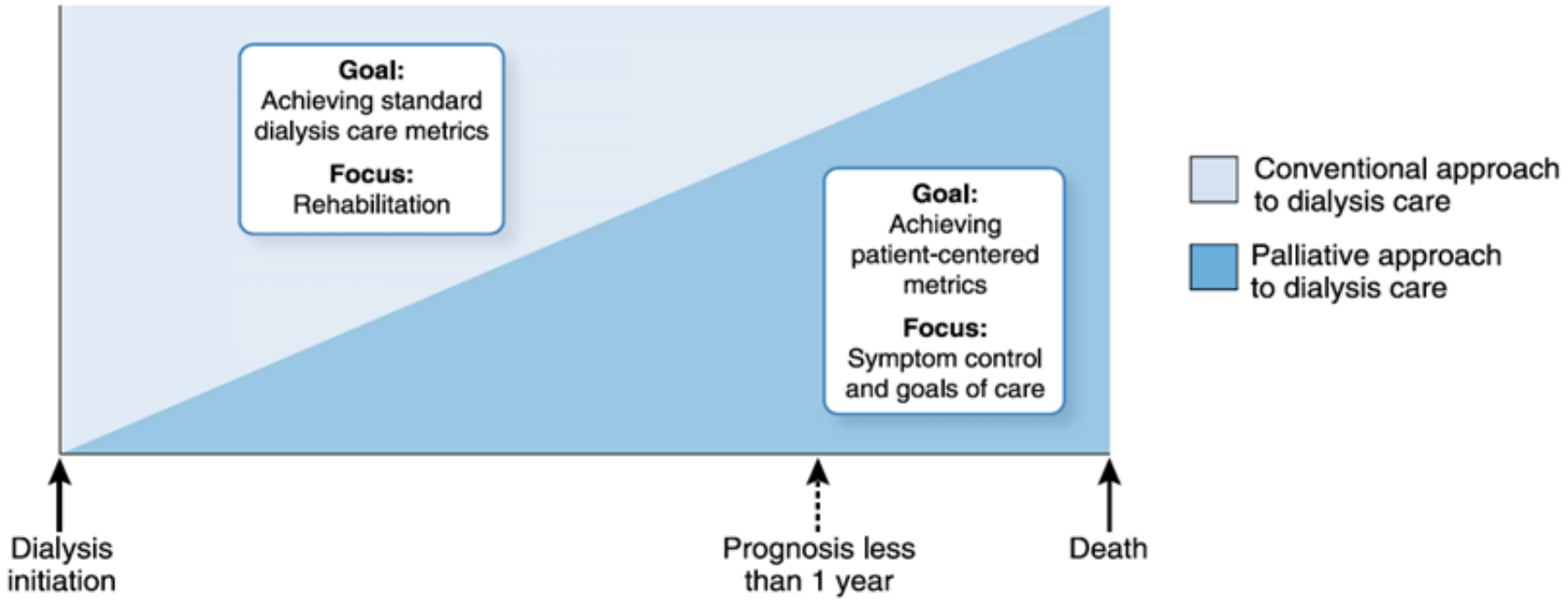
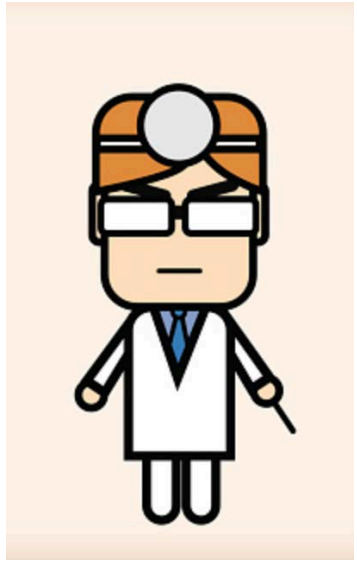


Figure 1. | As the patient nears the end of life (dashed arrow), there is an increasing focus on symptom control and patient goals of care and a shift in the approach to dialysis care from conventional to palliative. Adapted from Institute of Medicine (59).

Research priorities



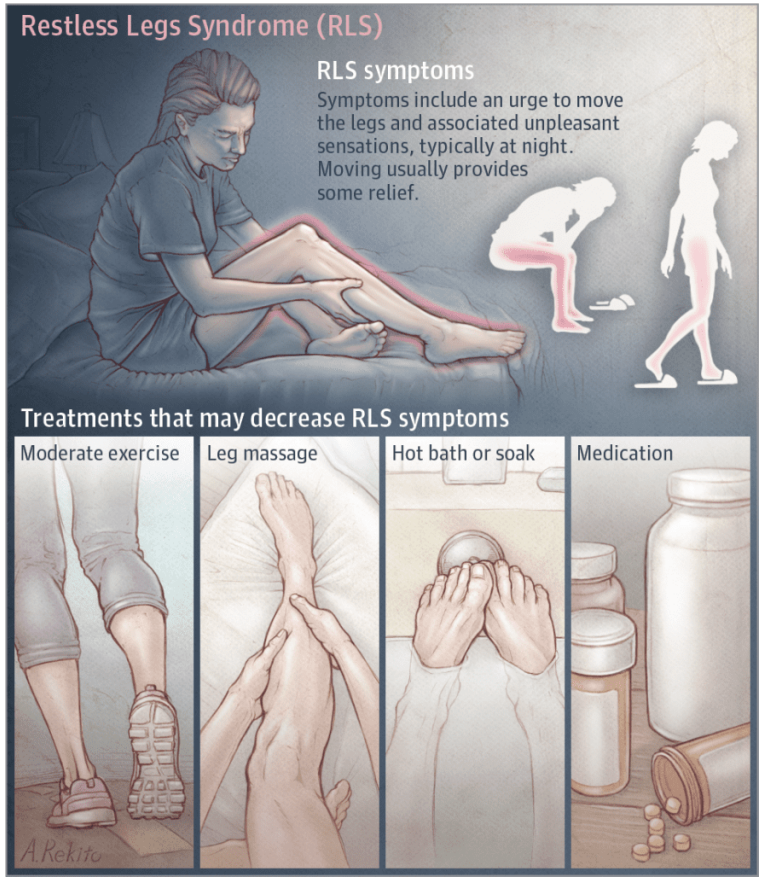
vascular access
MBD
modality
pruritus
timing of initiation of RRT
QOL
adequacy
phosphate restriction
cramping
drugs

"How much dialysis do I need?"
"I'm itchy"
"I'm tired"
"I want to go on vacation"
"I can't sleep"
"I'm depressed"
"Should I be exercising?"
How do I prevent my kidney disease from getting any worse?"
"My legs are cramping"
"I can't stop moving my legs"

Manns et al. CJASN 2014 9(10):1813-1821

Restless legs syndrome

- 5-10% of population, 2-3% clinically significant symptoms
- pathophysiology
  - central nervous system = iron deficiency, dopaminergic pathways
  - peripheral nervous system = neuropathy
- primary = genetic
- secondary = iron deficiency, CKD/ESRD, neuropathy, spinal cord pathology, pregnancy, MS, PD, essential tremor
- association with periodic limb movement syndrome, CV disease, sleep disturbance, poor HRQOL
- screening questions
- disease specific rating scales = IRLS, RLS-6, RLS-QOL
- clinically = patient global impression



Muth et al.
JAMA. 2017;317(7):780

2012 revised IRLSSG diagnostic criteria

- (1) An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
- (2) The urge to move the legs **and** any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
- (3) The urge to move the legs **and** any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
- (4) The urge to move the legs and any unaccompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night during the day
- **(5) The occurrences of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)**

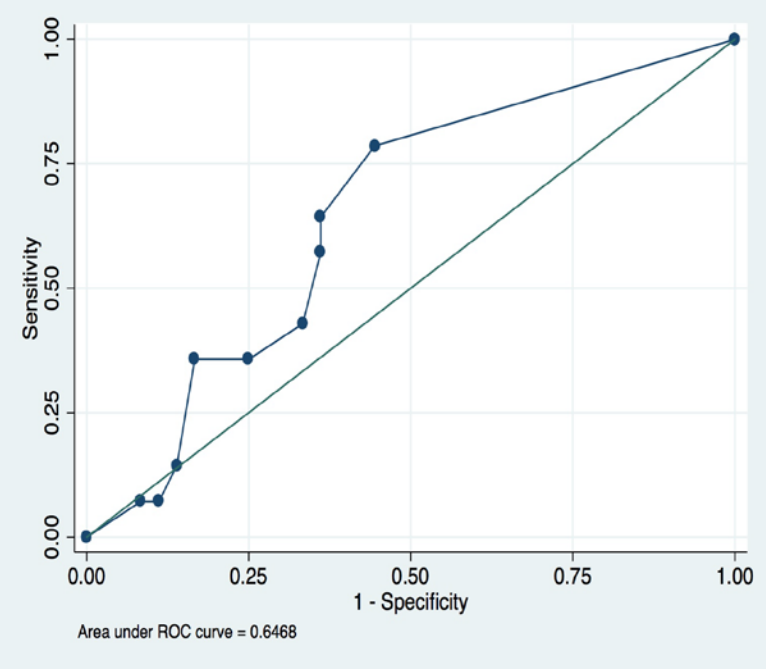
Allen et al. Sleep Medicine 15 (2014) 860–873

http://irlssg.org/diagnostic-criteria/

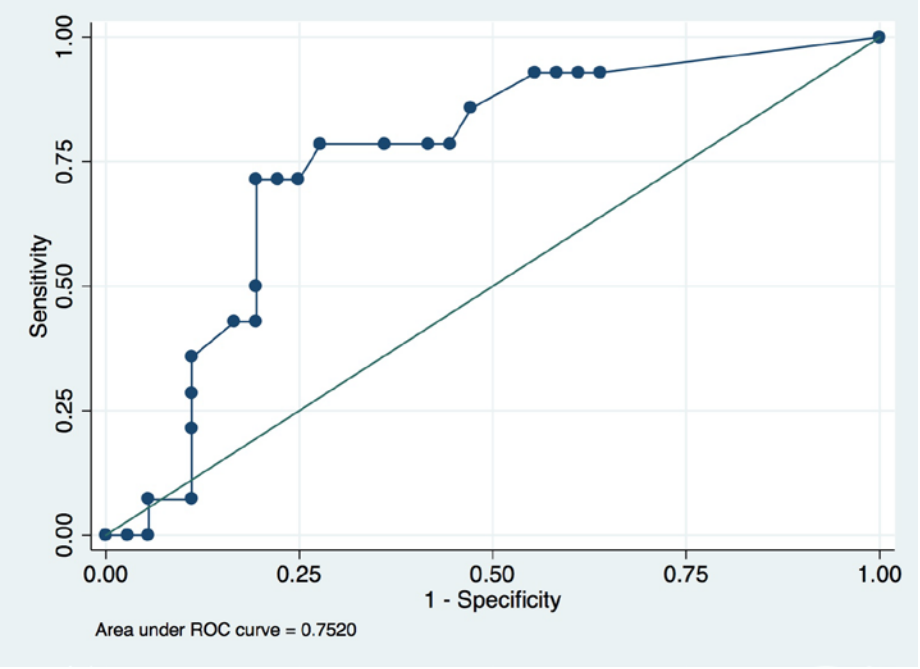
Screening questions for RLS

Collister et al.
Clin Kidney J. 2018
Dec 24;12(4):559-56

1) Single question SN: 0.86, SP: 0.58 with AUROC 0.72
"When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?"



2) ROC curve of **ESAS-r RLS** and
the revised 2012 IRLSSG diagnostic criteria
Note: SN 0.79, SP 0.56
AUROC 0.65 for ESAS-r RLS≥1



3) ROC curve of **IRLS** and
the revised 2012 IRLSSG diagnostic criteria
Note: SN 0.71, SP 0.81,
AUROC 0.75 for IRLS≥20

CCO Ontario Renal Network

Measuring RLS: IRLS, RLS-6, RLS-QOL

1. Overall, how would you rate the RLS discomfort in you legs or arms?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

2. Overall, how would you rate the need to move around because of your RLS symptoms?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

3. Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?

   (4) No relief
   (3) Slight relief
   (2) Moderate relief
   (1) Either complete or almost complete relief
   (0) No RLS symptoms and therefore question does not apply

4. Overall, how severe is your sleep disturbance from your RLS symptoms?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

5. How severe is your tiredness or sleepiness from your RLS symptoms?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

6. Overall, how severe is your RLS as a whole?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

7. How often do you get RLS symptoms?

   (4) Very severe (This means 6 to 7 days a week.)
   (3) Severe (This means 4 to 5 days a week.)
   (2) Moderate (This means 2 to 3 days a week.)
   (1) Mild (This means 1 day a week or less.)
   (0) None

8. When you have RLS symptoms, how severe are they on an average day?

   (4) Very severe (This means 8 hours per 24 hour day or more.)
   (3) Severe (This means 3 to 8 hours per 24 hour day.)
   (2) Moderate (This means 1 to 3 hours per 24 hour day.)
   (1) Mild (This means less than 1 hour per 24 hour day.)
   (0) None

9. Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school, or work life?

   (4) Very severe
   (3) Severe
   (2) Moderate
   (1) Mild
   (0) None

10. How severe is your mood disturbance from your RLS symptoms–for example angry, depressed, sad, anxious, or irritable?

    (4) Very severe
    (3) Severe
    (2) Moderate
    (1) Mild
    (0) None

RLS-6 rating scales.

Please, evaluate the following questions for the last 7 days or nights respectively:

How satisfied are you with your sleep during the last 7 nights?

completely satisfied — completely dissatisfied

0 1 2 3 4 5 6 7 8 9 10

How severe were your RLS symptoms during the last 7 nights or days respectively in the following situations?

At falling asleep

none — very mild — very severe

0 1 2 3 4 5 6 7 8 9 10

During the night

none — very mild — very severe

0 1 2 3 4 5 6 7 8 9 10

During the day when you were at rest (sitting, lying)

none — very mild — very severe

0 1 2 3 4 5 6 7 8 9 10

During the day when you were not at rest but engaged in activities (walking, activities in your job, homework, leisure activities)

none — very mild — very severe

0 1 2 S 4 5 6 7 8 9 10

How tired or sleepy were you during the day (between getting up in the morning and bedtime in the evening) within the last 7 days?

not at all — very mild — very severe

0 1 2 3 4 5 6 7 8 9 10

Appendix: RLS Quality of Life Questionnaire*

The following are some questions on how your Restless Legs Syndrome might affect your quality of life. Answer each of the items below in relation to your life experience in the past 4 weeks. Please mark only one answer for each question.

In the past four weeks:

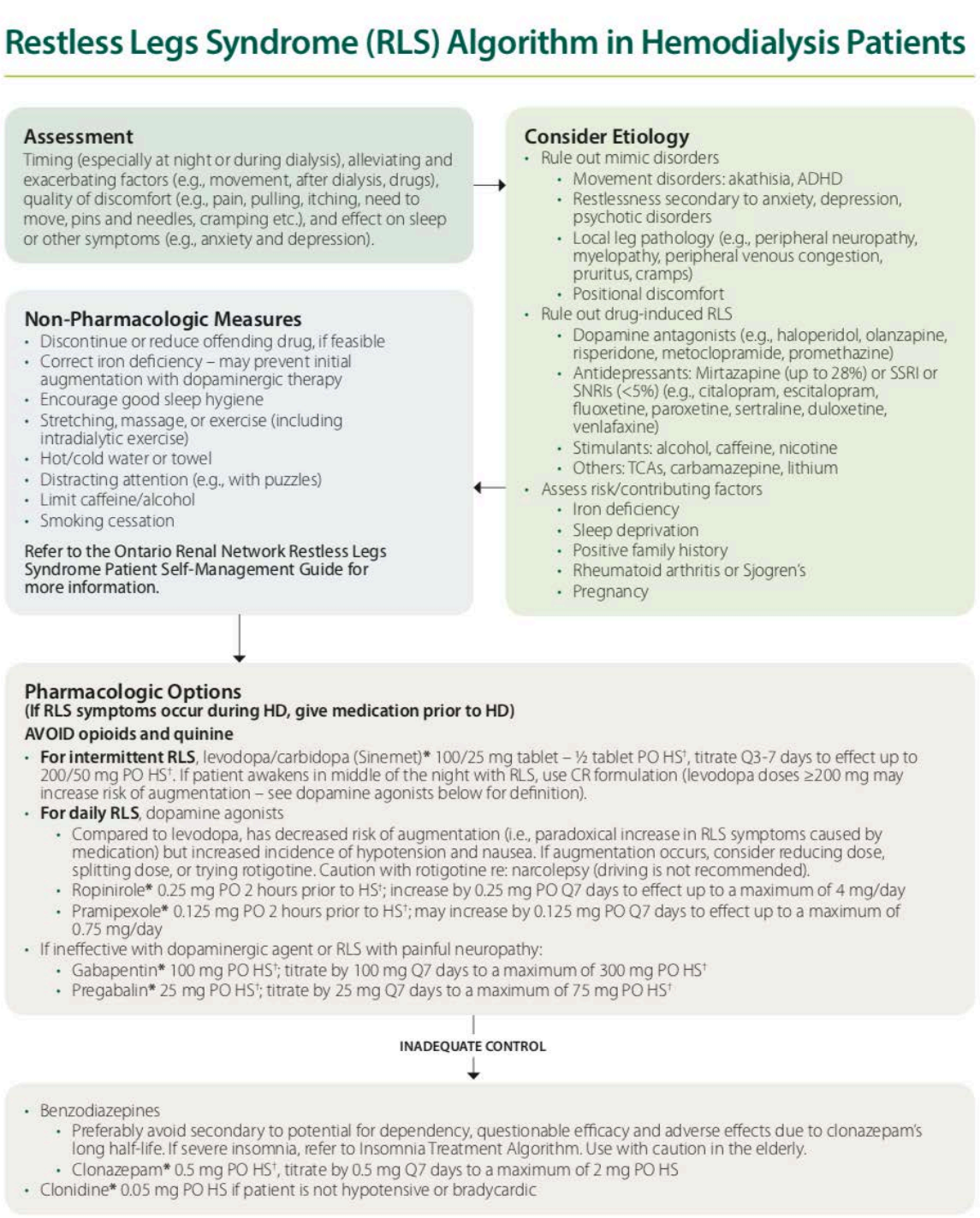
1. How distressing to you were your restless legs?
☐ Not at all ☐ A little ☐ Some ☐ Quite a bit ☐ A lot
2. How often in the past 4 weeks did your restless legs disrupt your routine evening activities?
☐ Never ☐ A few times ☐ Sometimes ☐ Most of the time ☐ All the time
3. How often in the past 4 weeks did restless legs keep you from attending your evening social activities?
☐ Never ☐ A few times ☐ Sometimes ☐ Most of the time ☐ All the time
4. In the past 4 weeks how much trouble did you have getting up in the morning due to restless legs?
☐ None ☐ A little ☐ Some ☐ Quite a bit ☐ A lot
5. In the past 4 weeks how often were you late for work or your first appointments of the day due to restless legs?
☐ Never ☐ A few times ☐ Sometimes ☐ Most of the time ☐ All the time
6. How many days in the past 4 weeks were you late for work or your first appointments of the day due to restless legs?
Write in number of days: ☐☐
7. How often in the past 4 weeks did you have trouble concentrating in the afternoon?
☐ Never ☐ A few times ☐ Sometimes ☐ Most of the time ☐ All the time
8. How often in the past 4 weeks did you have trouble concentrating in the evening?
☐ Never ☐ A few times ☐ Sometimes ☐ Most of the time ☐ All the time
9. In the past 4 weeks how much was your ability to make good decisions affected by sleep problems?
☐ None ☐ A little ☐ Some ☐ Quite a bit ☐ A lot
10. How often in the past 4 weeks would you have avoided traveling when the trip would have lasted more than two hours?
☐ Never ☐ A few times ☐ Sometimes ☐ Most of the time ☐ All the time
11. In the past 4 weeks how much interest did you have in sexual activity?
☐ None ☐ A little ☐ Some ☐ Quite a bit ☐ A lot
☐ Prefer not to answer
12. How much did restless legs disturb or reduce your sexual activities?
☐ None ☐ A little ☐ Some ☐ Quite a bit ☐ A lot
☐ Prefer not to answer
13. In the past 4 weeks how much did your restless legs disturb your ability to carry out your daily activities, for example carrying out a satisfactory family, home, social, school or work life?
☐ Not at all ☐ A little ☐ Some ☐ Quite a bit ☐ A lot
14. Do you currently work full or part time (paid work, unpaid or volunteer)?
(mark one box)
☐ YES If Yes please answer questions #15 through #18
☐ NO, because of my RLS – Please go to the next page
☐ NO, due to other reasons – Please go to the next page
15. How often did restless legs make it difficult for you to work a full day in the past 4 weeks?
☐ Never ☐ A few times ☐ Sometimes ☐ Most of the time ☐ All the time
16. How many days in the past 4 weeks did you work less than you would like due to restless legs?
Write in number of days: ☐☐
17. On the average, how many hours did you work in the past 4 weeks?
Write in number of hours per day: ☐☐
18. On days you worked less than you would like, on average about how many hours less did you work due to your restless legs.
Write in number of hours per day: ☐☐

ORN symptom management guide for RLS

Ontario Renal Network

https://www.ontariorenalnetwork.ca/en/kidney-care-resources/clinical-tools/symptom-management

Gopaluni et al. Cochrane 2016, 11, CD010690



The risks of alpha 2 delta ligands in hemodialysis

	Gabapentin N=26916 %	Pregabalin N=5829, %
Neuropathic pain	65	69
Anxiety	14	15
Insomnia	8	8
Fibromyalgia	6	8
Pruritus	5	5
RLS	4	4
Bipolar	2	2
Migraine	0.5	0.4
Ssizures	0.4	0.5
PLMS	0.3	0.4
No diagnosis	29	26

Dose Category	LOC	falls	fractures
	Adjusted HR (95% CI)	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**
Gabapentin, mg			
None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>0–100	1.10 (0.97 to 1.24)	**1.26 (1.07 to 1.48)**	1.04 (0.82 to 1.32)
>100–200	**1.31 (1.17 to 1.46)**	**1.35 (1.15 to 1.57)**	1.20 (0.96 to 1.49)
>200–300	**1.41 (1.30 to 1.54)**	**1.30 (1.14 to 1.48)**	1.08 (0.89 to 1.31)
>300	**1.50 (1.39 to 1.63)**	**1.55 (1.39 to 1.72)**	**1.38 (1.18 to 1.61)**
Pregabalin, mg			
None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>0–100	**1.51 (1.32 to 1.74)**	1.24 (1.00 to 1.54)	1.20 (0.87 to 1.66)
>100	**1.46 (1.24 to 1.71)**	**1.68 (1.36 to 2.08)**	1.38 (1.00 to 1.92)

Ishida et al.
J Am Soc Nephrol 29: 1970–1978, 2018

DISCO-RLS

Eligibility Assessment

Key inclusion criteria: adult age≥18 years on in-center hemodialysis at least three times weekly for >90 days with restless leg syndrome defined by 2012 Revised IRLSSG Diagnostic Criteria with IRLS≥10 with symptoms more than 2 days per week, able to provide informed consent without language barrier or cognitive impairment

Key exclusion criteria: anemia defined by hemoglobin≤80g/L, hospitalization within previous 4 weeks, previous intolerance to study drugs, change in baseline RLS therapy in previous 4 weeks, pregnancy, planned kidney transplantation, travel or relocation in the next 6 months

Informed Consent

Placebo Run-in Period

Single blind placebos for 1 weeks

Final Eligibility Assessment

Adherence>5/7 days by pill counts
IRLS≥10
No worsening symptoms

Randomization

1) gabapentin + ropinirole 2) gabapentin + placebo 3) placebo + ropinirole 4) placebo + placebo	→	1) gabapentin + ropinirole 2) gabapentin + placebo 3) placebo + ropinirole 4) placebo + placebo	→	1) gabapentin + ropinirole 2) gabapentin + placebo 3) placebo + ropinirole 4) placebo + placebo	→	1) gabapentin + ropinirole 2) gabapentin + placebo 3) placebo + ropinirole 4) placebo + placebo
4 weeks		4 weeks		4 weeks		4 weeks

Follow-up

1,3,4,5,7,8,9,11,12,13,15,16 weeks

placebo controlled crossover RCT
interventions = ropinirole, gabapentin
sample size = 72
10 sites across Canada
1 outcome = IRLS
2 outcomes = RLS-6, PGI, EQ-5D5L, safety

DISCO-RLS patient engagement

= ropinirole

= gabapentin

P = placebo

P = placebo

Screening and single blind run-in period

Randomization

Treatment

Cross-over

Cross-over

Cross-over

End of study

Period 1

Period 2

Period 3

Period 4

1 week

4 weeks

4 weeks

4 weeks

4 weeks

1 week

P P

Total study duration = 18 weeks

Uremic pruritus

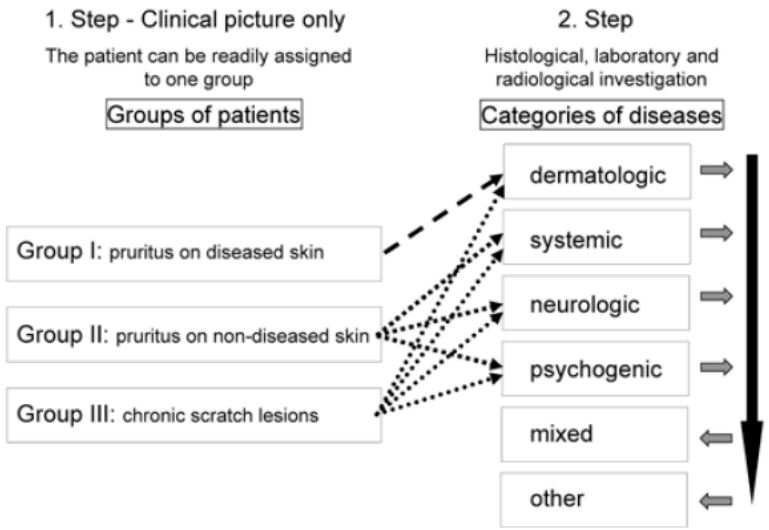


Fig. 1. Clinical classification in the management of chronic pruritus patients. As a first step, patients are grouped according to their clinical picture and history. Although group I and II may already suggest a category, the classification of the patient is performed in a second step based on histological, laboratory and radiological investigation. If no category fits or several diseases are found (small arrows), the patients are classified into "mixed" or "others" (*arrow on the right*).

Ständer et al.
Acta Derm Venereol 2007; 87: 291–294

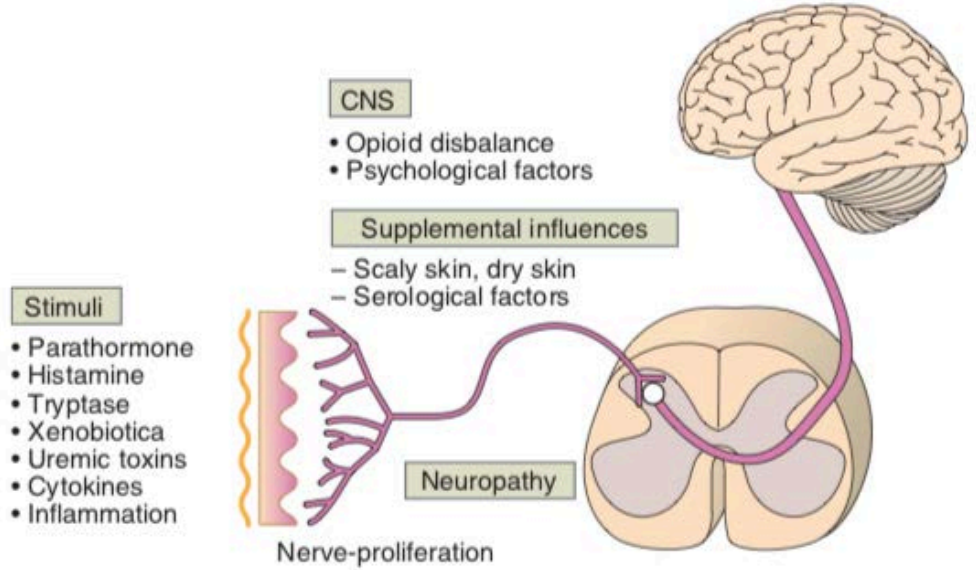


Figure 4 | Schematic synopsis of potential pathogenic factors in chronic kidney disease-associated pruritus (CKD-aP). CNS, central nervous system.

Mettang et al.
KI(2015) 87, 685–691

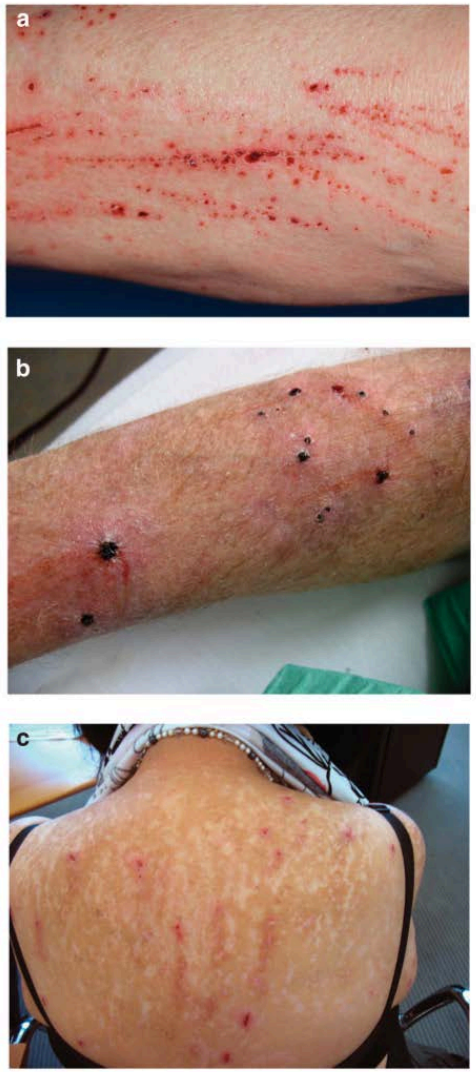


Figure 1 | Typical skin changes observed in patients suffering from chronic kidney disease-associated pruritus (CKD-aP). (**a**) Scratch marks with excoriations at the lower leg. (**b**) Typical hyperkeratotic partly excoriated nodules (prurigo nodularis) located on the forearm. (**c**) Deep scars and prurigo nodules at the shoulders and back of a female patient.

DOPPS 1-5

Murtagh et al.
ACKD 2007
Jan;14(1):82-99
prevalence = 55%
range 10-77%

"During the past 4 weeks, to what extent were you bothered by itchy skin?"

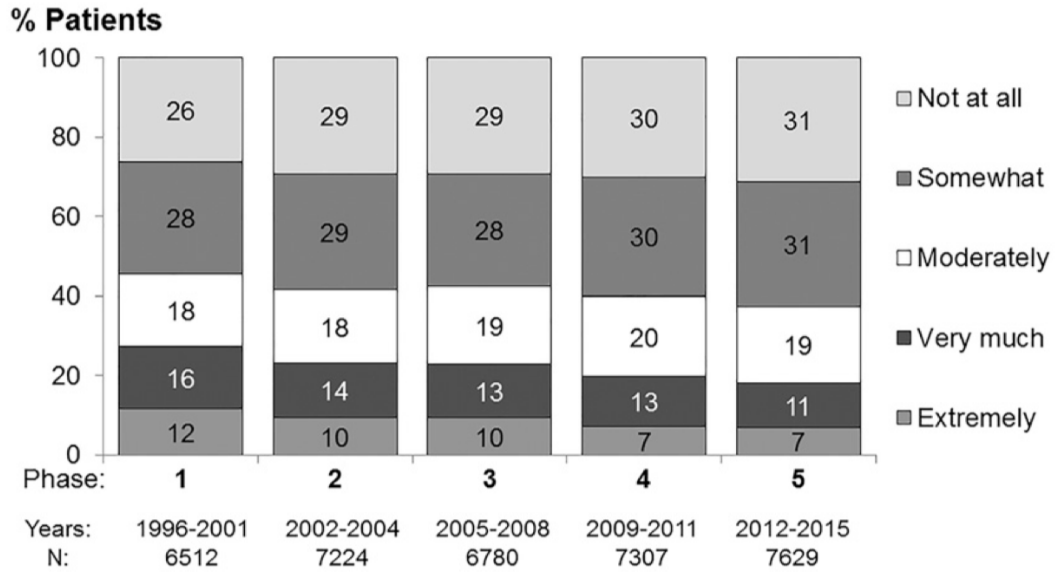


Figure 1. | The percentage of patients very much or extremely bothered by itchy skin declined between 1996 and 2015 from 28% to 18%. Question wording: "To what extent were you bothered by itchy skin during the past 4 weeks?" Australia, Belgium, Canada, China, France, the six Gulf Cooperation Council (GCC) countries (Bahrain, Qatar, Kuwait, Oman, Saudi Arabia, and United Arab Emirates), Germany, Italy, Japan, New Zealand, Russia, Spain, Sweden, Turkey, the United Kingdom, and the United States were analyzed. The DOPPS phase 1 collected data from 1996 to 2001, the DOPPS phase 2 collected data from 2002 to 2004, the DOPPS phase 3 collected data from 2005 to 2008, the DOPPS phase 4 collected data from 2009 to 2011, and the DOPPS phase 5 collected data from 2012 to 2015. Data collection in Australia, Belgium, Canada, New Zealand, and Sweden did not begin until phase 2; data collection in China began in phase 4 and started in the GCC countries, Russia, and Turkey in phase 5. Australia, China, France, and New Zealand were excluded in phase 5.

Rayner et al.
CJASN 2017
12: 2000–2007

Measurement of itch

VAS, VRS, NRS

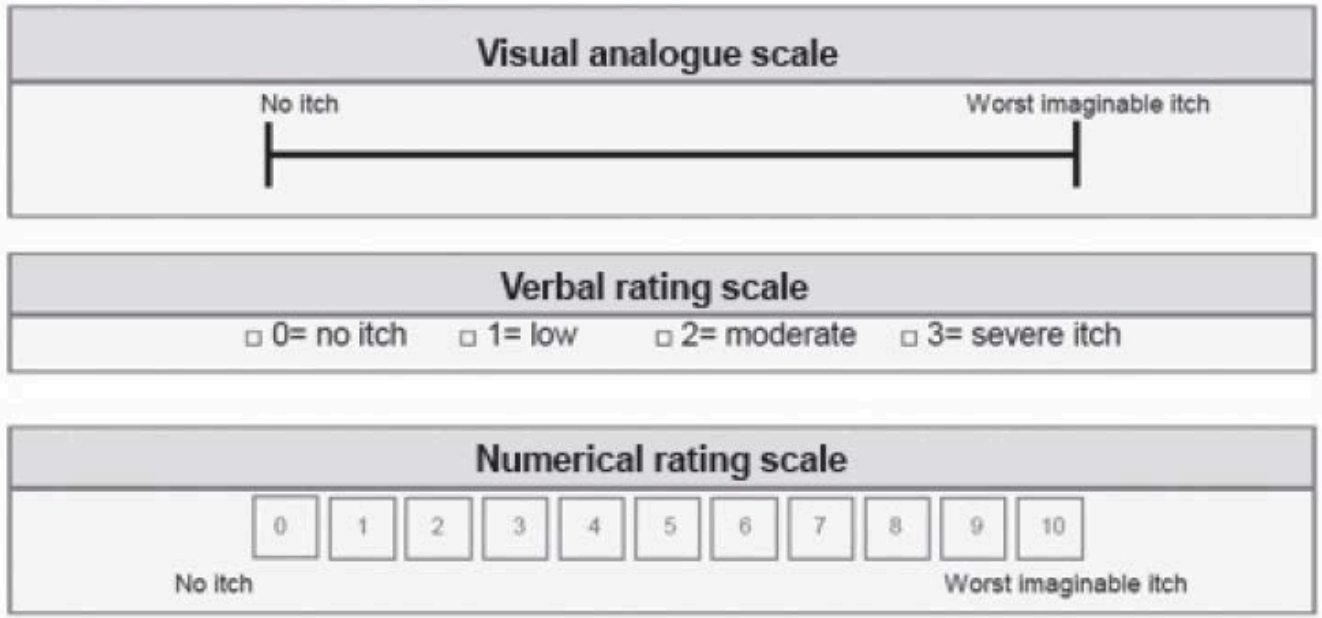


Fig. 1. Assessment scales: visual analogue scale (VAS), numerical rating scale (NRS) and verbal rating scale (VRS).

Phan et al.
Acta Derm Venereol 2012;
92: 502–507

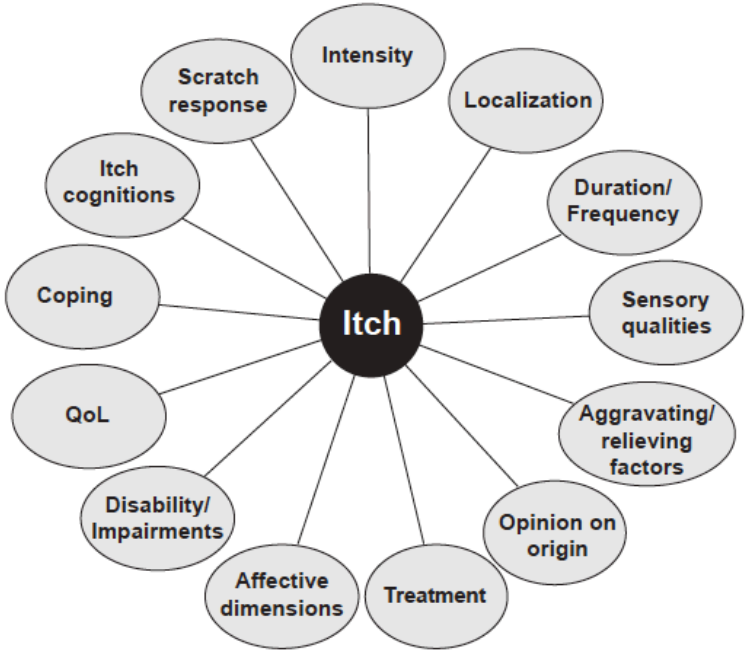
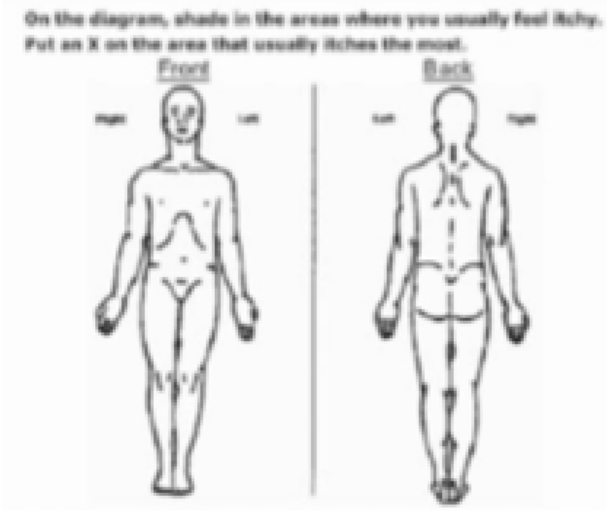


Fig. 1. Summarizes important factors that an itch questionnaire needs to address. QoL: quality of life.



DOPPS 1-5:Treatments

	Overall bothered by itchy skin	Nearly always or always bothered by itchy skin	
	All	All	Canada
Non-Rx topical	29%	30%	51%
Rx topical	38%	44%	31%
Non-Rx oral	7%	7%	4%
Rx oral	19%	22%	24%
UV light	1%	1%	0%
None	25%	18%	21%
Responders	N=2434	N=971	N=45

Rayner et al.
CJASN 2017
12: 2000–2007

	1st line	2nd line	3rd line	Never	N
Topical antihistamines	23%	9%	7%	36%	249
Oral antihistamines (OTC)	32%	13%	3%	31%	238
Oral antihistamines (prescription)	46%	24%	5%	7%	259
IV antihistamines	2%	6%	9%	48%	254
Topical corticosteroids	9%	11%	12%	29%	256
Oral corticosteroids	2%	2%	4%	66%	253
IV corticosteroids	1%	1%	1%	79%	249
Gabapentin	5%	19%	21%	52%	198
Antidepressants	2%	8%	21%	60%	252
Anxiolytics/sedatives	2%	6%	20%	53%	251
Opioids	1%	5%	9%	79%	249

Table 1. Characteristics of the 44 Included Studies Categorized by Intervention

Study	Country	Design	Population	N	Pruritus Measurement Tool[a]	Treatment	Comparator
Gabapentin/Pregabalin							
Foroutan[60] (2017)	IR	Parallel arm	HD	90	0-10 VAS	Pregabalin	Doxepin
Amirkhanlou[21] (2016)	IR	Parallel arm	HD	52	5-point VRS	Gabapentin	Ketotifen
Nofal[41] (2016)	EG	Parallel arm	HD	54	10-cm VAS and 5-D pruritus scale	Gabapentin	Placebo
Yue[56] (2015)	CN	Parallel arm	HD	188	10-cm VAS + questionnaire	Pregabalin	Ondansetron or placebo
Solak[47] (2012)	TR	Crossover	HD	29[b]	10-cm VAS	Gabapentin	Pregabalin
Tol[50] (2010)	TR	Crossover	HD	14	10-cm VAS	Gabapentin	Placebo
Wu[59] (2010)	CN	Parallel arm	HD	41	0-10 VAS	Gabapentin	Standard treatment
Naini[38] (2007)	IR	Parallel arm	HD	34	10-cm VAS	Gabapentin	Placebo
Gunal[33] (2004)	TR	Crossover	HD	25	10-cm VAS	Gabapentin	Placebo
Mast Cell Stabilizers							
Nakhaee[40] (2015)	IR	Crossover	HD	25	10-cm VAS + questionnaire	*Avena sativa*	Diluted vinegar or hydroxyzine
Omidian[42] (2013)	IR	Parallel arm	HD	50	0-5 VAS	Nicotinamide	Placebo
Feily[30] (2012)	IR	Parallel arm	HD	60	0-5 VAS	Topical cromolyn sodium 4%	Placebo
Najafabadi[39] (2012)	IR	Parallel arm	HD	40	0-10 VAS	Zinc sulfate	Placebo
Vessal[51] (2010)	IR	Parallel arm	HD	62	0-10 VAS	Cromolyn sodium	Placebo
Phototherapy							
Ko[35] (2011)	TW	Parallel arm	CKD stages 3-5, HD, and PD	21	0-10 VAS + questionnaire	Narrow band UV-B (narrow-band UV-B)	Long-wave UV-A
Hsu[34] (2009)	CN	Parallel arm	HD	49	10-cm VAS + questionnaire	Thermal therapy using far-infrared rays	Placebo
Gilchrest[31] (1979)	US	Parallel arm	HD, CKD	18	4-point VRS	UV-B	UV-A
Gilchrest[32] (1977)	US	Parallel arm	HD	24	4-point VRS	UV-B	UV-A
Dialysis Prescription Modification							
Jiang[61] (2016)	CN	Parallel arm	HD	51	0-10 VAS	High-flux HD	HD filtration
Zhang[64] (2016)	CN	Parallel arm	HD	40	0-10 VAS	HD with hemoperfusion	Hemodiafiltration with hemoperfusion
Hui[57] (2011)	CN	Parallel arm	HD	38	10-cm VAS	High-flux HD	Low-flux HD
Chen[27] (2009)	CN	Parallel arm	HD	166	100-mm VAS	High-permeability HD	Conventional HD
Carmichael[24] (1988)	UK	Crossover	HD	17	VAS	Magnesium-free dialysis	Standard dialysis fluid
Other Systemic Treatments							
Mahmudpour[62] (2017)	IR	Parallel arm	HD	80	0-10 VAS	Montelukast	Placebo
Kumagai[36] (2010)	JP	Parallel arm	HD	339	100-mm VAS	Nalfurafine HCl 5 μg	Nalfurafine HCl 2.5 μg or placebo
Wikström[52] (2005)	SE/DK/NO/FI/PL	Parallel arm	HD	79	100-mm VAS	Nalfurafine 5 μg IV	Placebo
Murphy[37] (2003)	UK	Crossover	HD	24	10-cm VAS	Ondansetron	Placebo
Ashmore[22] (2000)	UK	Crossover	HD	19	0-10 VAS	Ondansetron	Placebo
Pauli-Magnus[43] (2000)	DE	Crossover	HD and PD	23	0-10 VAS + questionnaire	Naltrexone	Placebo
Yoshimoto-Furuie[54] (1999)	JP	Parallel arm	HD	16	5-point VRS	GLA-enriched evening primrose oil	Linoleic acid
Peer[44] (1996)	IR	Crossover	HD	15	10-cm VAS	Naltrexone	Placebo
Silva[45] (1994)	BR	Crossover	HD	29	4-point VRS	Thalidomide	Placebo
Silverberg[46] (1977)	IL	Parallel arm	HD	10	4-point VRS	Cholestyramine	Placebo
Other Topical Treatments							
Boaz[23] (2009)	IR	Parallel arm	HD	78	5-point NRS	Dead Sea mineral lotion	Lotion with no Dead Sea mineral, or lotion with no active ingredient
Young[55] (2009)	US	Parallel arm	HD	28	10-cm VAS	Topical 1% pramoxine HCl	Bland emollient
Chen[26] (2006)	TW	Crossover	HD and PD	17	100-mm VAS + questionnaire	GLA	Placebo
Duque[29] (2005)	US	Parallel arm	HD	22	10-cm VAS	Tacrolimus 0.1% ointment	Placebo
Bai[58] (2002)	CN	Parallel arm	HD	80	5-point VRS	Chinese herb–based cream	Control cream
Cho[28] (1997)	TW	Crossover	HD	22	4-point VRS	Capsaicin 0.025% cream	Placebo
Tarng[49] (1996)	TW	Crossover	HD	19	4-point VRS	Capsaicin 0.025% cream	Placebo
Tan[48] (1990)	SG	Crossover	HD	31	4-point VRS + 100-mm VAS	Sarna lotion (0.5% of each camphor, menthol, and phenol)	Eurax lotion (10% crotamiton)
Alternative Treatments							
Kılıç Akça[63] (2016)	TR	Parallel arm	HD	75	0-10 VAS	Acupressure	Transcutaneous electrical acupoint stimulation or control
Yan[53] (2015)	CN	Parallel arm	HD	71	0-10 VAS	Vaccaria seed auricular acupressure	Sham acupressure
Cavalcanti[25] (2003)	BR	Parallel arm	HD	28	4-point VRS 3×/d (9 total scores) converted to % of max score	Verum medication	Placebo

Abbreviations: BR, Brazil; CKD, chronic kidney disease; CN, China; DE, Germany; DK, Denmark; EG, Egypt; FI, Finland; GLA, gamma-linolenic acid; HCl, hydrochloride; HD, hemodialysis; IL, Israel; IR, Iran; IV, intravenous; JP, Japan; NO, Norway; NRS, numerical rating scale; PD, peritoneal dialysis; PL, Poland; SE, Sweden; SG, Singapore; TR, Turkey; TW, Taiwan; UK, United Kingdom; US, United States; VAS, visual analogue scale; VRS, verbal rating scale.

[a]Questionnaire refers to pruritus questionnaire.

[b]Population was taken from pruritus cohort.

Simonsen et al.
AJKD 2017;
70(5):638-655

SR, MA of RCT's

Emollient

glycerol 15%
paraffin 10%
oil-in-water emulsion

Table 2. Comparison of uremic xerosis severity on the lower legs between the two treatment groups after 7 days (Period I) in the study population (intent-to-treat analysis)

Study Parameters	Test Product (n = 99)	Comparator (n = 99)	P
Treatment response (n, %)			
yes	72 (73%)	44 (44%)	<0.0001
no	27 (27%)	55 (56%)	
Instrumental severity of xerosis (arbitrary units, mean ± SEM)			
SURFT			
baseline	11.37 ± 0.64	10.25 ± 0.55	
day 7	3.19 ± 0.42	5.35 ± 0.57	<0.0001
MOD			
baseline	19.20 ± 0.98	18.02 ± 0.76	
day 7	7.83 ± 0.60	11.56 ± 0.93	<0.0001
Test side preference			
clearly better	60	13	<0.0001
comparable	26	26	

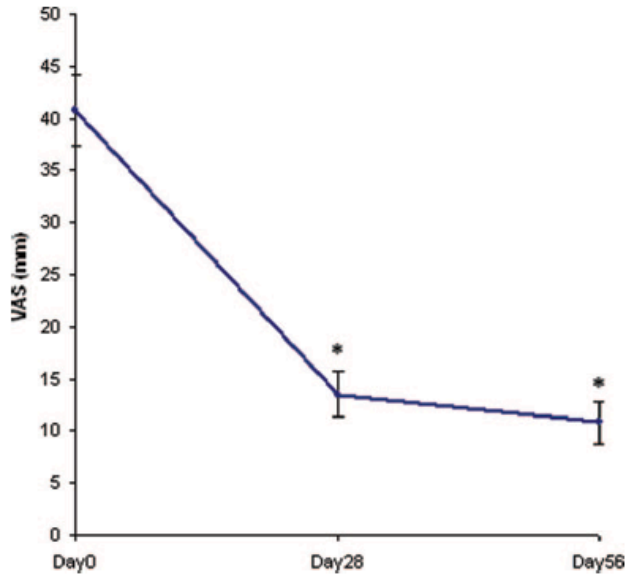


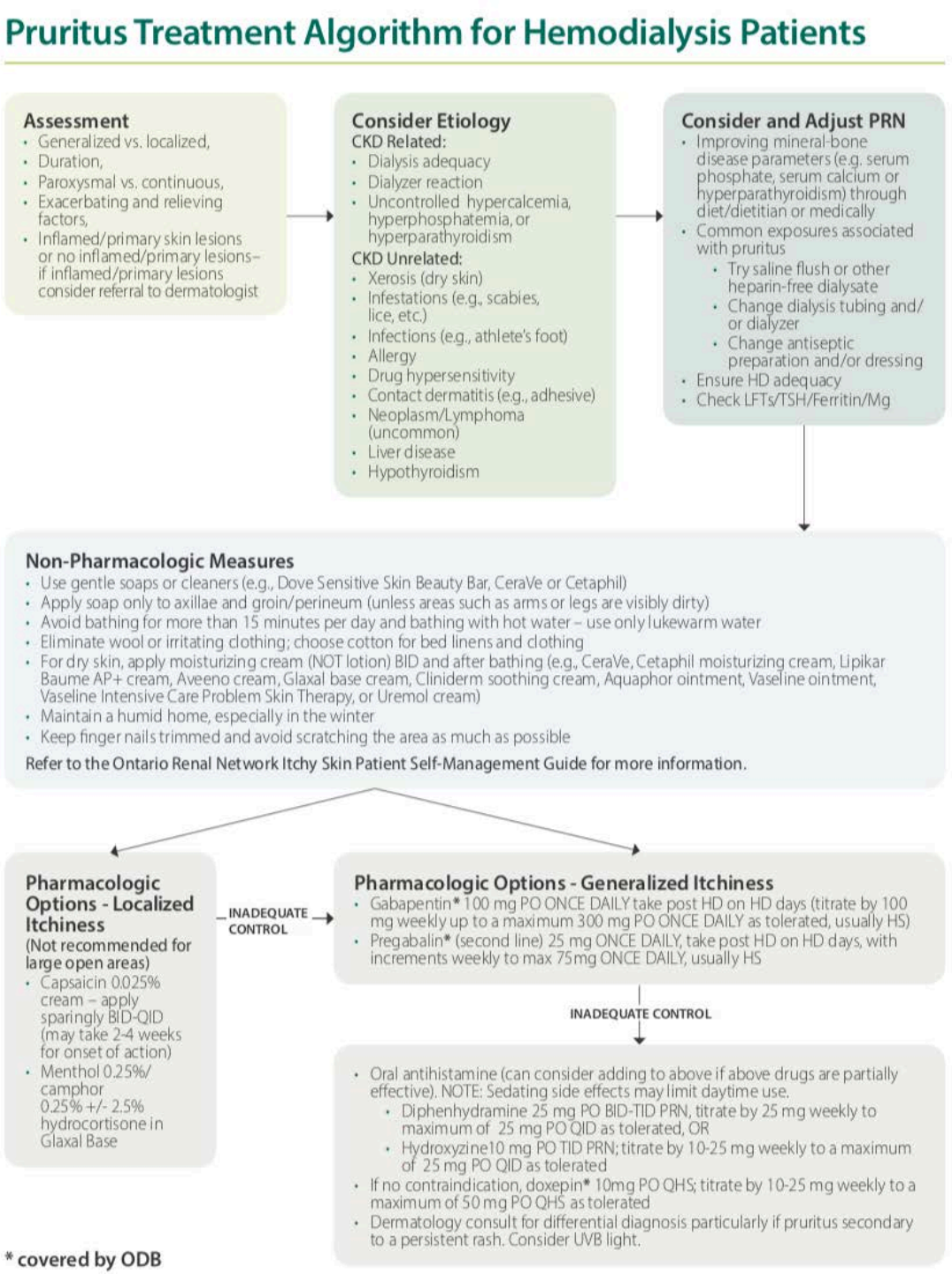
Figure 2. | Evolution of the severity of uremic pruritus under treatment in the study population (n = 99). *P < 0.0001 (intragroup analysis).

Balaskas et al.
CJASN 2011;
6: 748–752

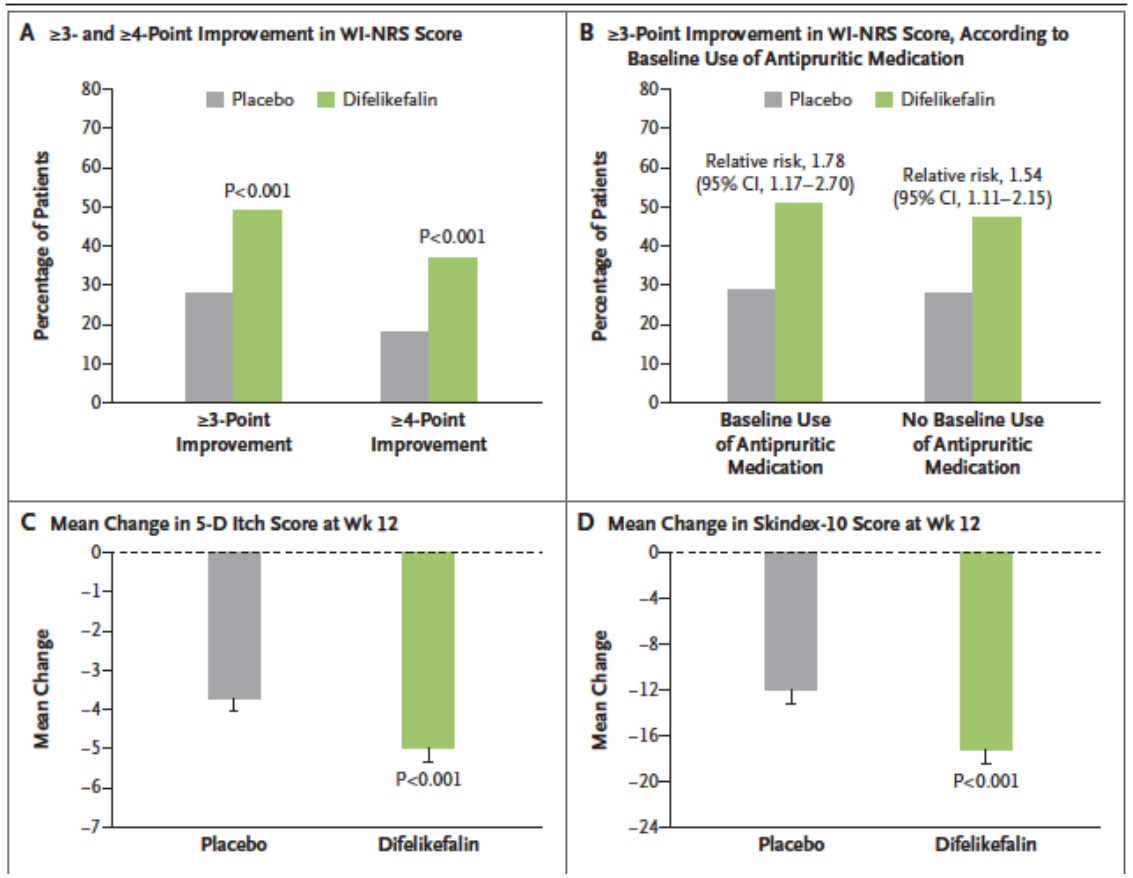
ORN symptom management guide for pruritus

Ontario Renal Network

https://www.ontariorenalnetwork.ca/en/kidney-care-resources/clinical-tools/symptom-management



KALM-1 = difelikefalin



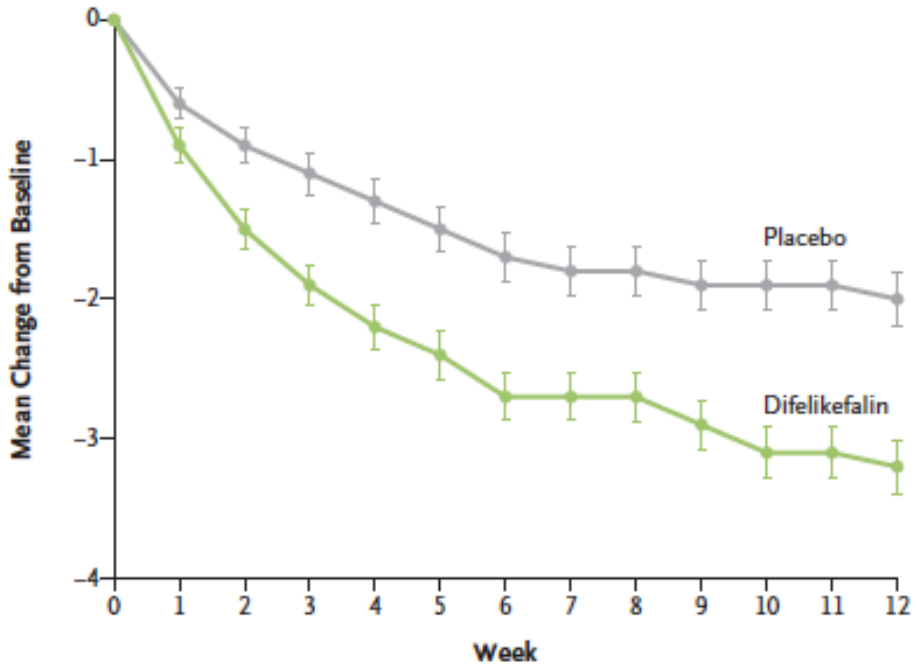
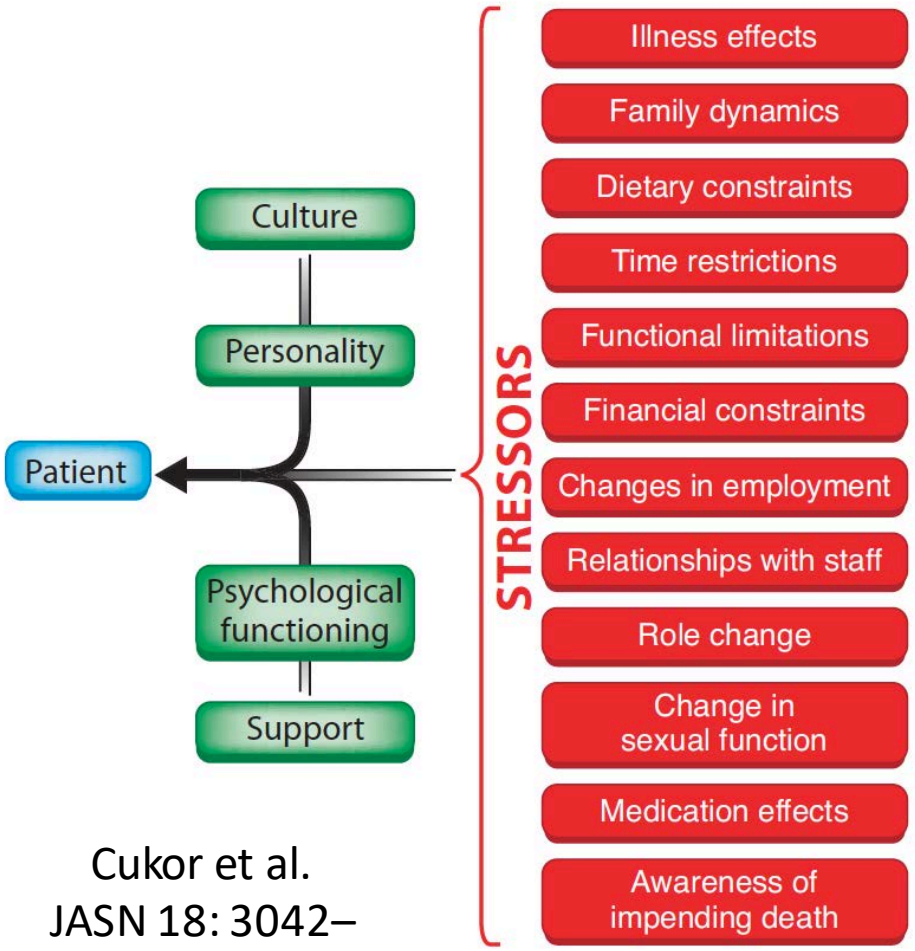


Figure 2. Mean Change in Worst Itching Intensity Numerical Rating Scale (WI-NRS) Score.

Shown is the least-squares mean change from baseline (point estimates) in the weekly mean WI-NRS score, as analyzed with the use of a mixed-effects model with repeated measures. Scores range from 0 to 10, with higher scores indicating greater intensity. The I bars indicate the standard error. Missing data were imputed with the use of multiple imputation under a missing-at-random assumption. There were 189 patients in each trial group.

Fishbane et al. NEJM 2019
November 8, 2019

Transition to dialysis: Stressors and mood disorders



Cukor et al. JASN 18: 3042–3055, 2007

DSM V MDE criteria

- 5 or more of the following symptoms: SIGECAPS present most of the day nearly ever day for a minimum of 2 consecutive weeks.
- at least 1 symptom is ether depressed mood or loss of interest or pleasure
- the symptoms cause substantial distress or impair psychosocial functioning
- not the direct result of the physiological effect of a substance or general medical disorder
- symptoms cannot be explained by response to significant loss

- depressed mood
- loss of interest or pleasure in most or all activities
- insomnia or hypersomnia
- change in appetite or weight
- psychomotor retardation or agitation
- low energy
- poor concentration
- thoughts of worthlessness or guilt
- recurrent thoughts about death or suicide

Depression in CKD, dialysis

Table 1 | Summary of prevalence and heterogeneity findings for depressive symptoms in adults with CKD

	No. of study populations	No. with symptoms/ no. at risk	Prevalence of clinical depression Random effects (95% CI)	Heterogeneity I^2	*P*-value for subgroup difference
Patient- or clinician-administered questionnaire					
Stage 5D	170	15,085/43,650	39.3% (36.8–42.0)	95.6%	
Stages 1–5	12	521/2121	26.5% (18.5–36.5)	94.9%	<0.001
Transplant	22	1195/4640	26.6% (20.9–33.1)	93.6%	
Interview-based assessment					
Stage 5D	28	609/2855	22.8% (18.6–27.6)	79.8%	
Stages 1–5	4	259/1388	21.4% (11.1–37.2)	74.1%	0.82
Transplant	3	33/122	25.7% (12.8–44.9)	55.2%	

Abbreviations: CI, confidence interval; CKD, chronic kidney disease.
Heterogeneity interpretation: I^2 >80% = moderate; I^2 >90% = high.
CKD stage 5D = estimated glomerular filtration rate <15 and treated with dialysis.

Palmer et al.
KI 2013;84(1):
179–91

1 Abdel-Kader CJASN 2009
2 Preljevic GHP 2013
3 Peng NDT 2007
4 Theofilou HI 2010
5 Balayev HI 2015
6 Kimmel KI 1998
7 Afsar KI 2009
8 Cukor KI 2009
9 Weisbord CJASN 2014
10 Kop CJASN 2011
11 Hedayati JAMA 2010
12 Tsai AJKD 2012
13 Chiang JPS 2015
14 Lopes KI 2002
15 Hedayati AJKD 2005
16 Hedayati KI 2008
17 Hedayati JAMA 2010
18 Lacson CJASN 2014
19 Kutner CJASN 2010
20 Weisbord CJASN 2014
21 Troidle AJKD 2003
22Griva IUN 2016
23 Boulare CJASN 2006
24 Saglimbene NDT 2016
25 Chen Psychosomatics 2010
26 Lacson 2012 NDT
27 Farrokhi AJKD 2014

- HRQOL[1,2]
- sexual dysfunction[3,4]
- pain[5]
- non-adherence[6,7,8,9]
- progression of CKD[10,11,12,13]
- hospitalizations[14,15,16,17,18]
- employment[19]
- health resource utilization[20]
- peritonitis[21]
- technique survival[22]
- CV events, mortality[23,24]
- suicide[25]
- dialysis withdrawal[26]
- mortality[27]

Association of depression with mortality SR, MA

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Diefenthaeler 2008	1.8718	1.0792	0.3%	6.50 [0.78, 53.89]
Riezebos 2010	1.6094	0.688	0.7%	5.00 [1.30, 19.26]
Drayer 2006	1.4109	0.623	0.8%	4.10 [1.21, 13.90]
Kojima 2010	0.859	0.398	1.9%	2.36 [1.08, 5.15]
Balogun 2011	0.647	0.304	3.1%	1.91 [1.05, 3.47]
Griva 2010	0.536	0.297	3.2%	1.71 [0.95, 3.06]
Boulware 2006	0.7975	0.248	4.4%	2.22 [1.37, 3.61]
van den Beukel 2010	0.604	0.15	9.6%	1.83 [1.36, 2.45]
Lacson 2012	0.278	0.136	11.0%	1.32 [1.01, 1.72]
Kimmel 2000	0.278	0.081	18.6%	1.32 [1.13, 1.55]
Lopes 2002	0.329	0.062	22.1%	1.39 [1.23, 1.57]
Lopes 2004	0.3506	0.0501	24.4%	1.42 [1.29, 1.57]
Total (95% CI)			**100.0%**	**1.51 [1.35, 1.69]**

Heterogeneity: Tau² = 0.01; Chi² = 18.33, df = 11 (P = 0.07); I² = 40%

Test for overall effect: Z = 7.34 (P < 0.00001)

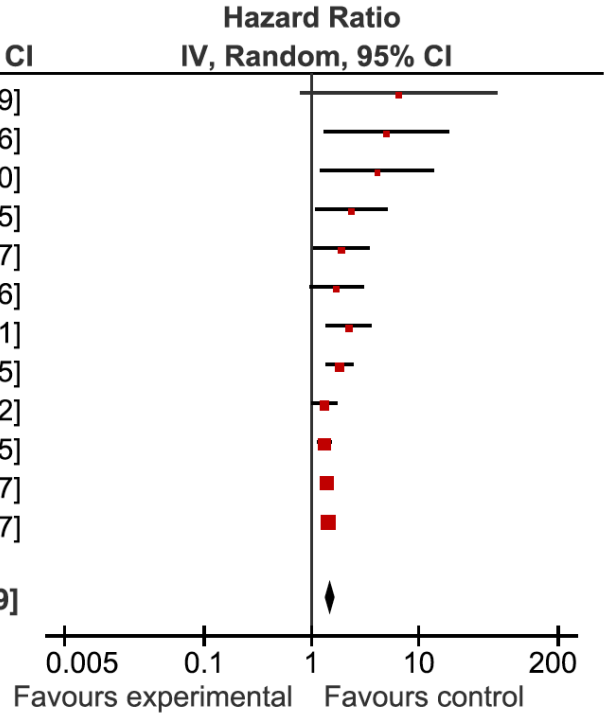
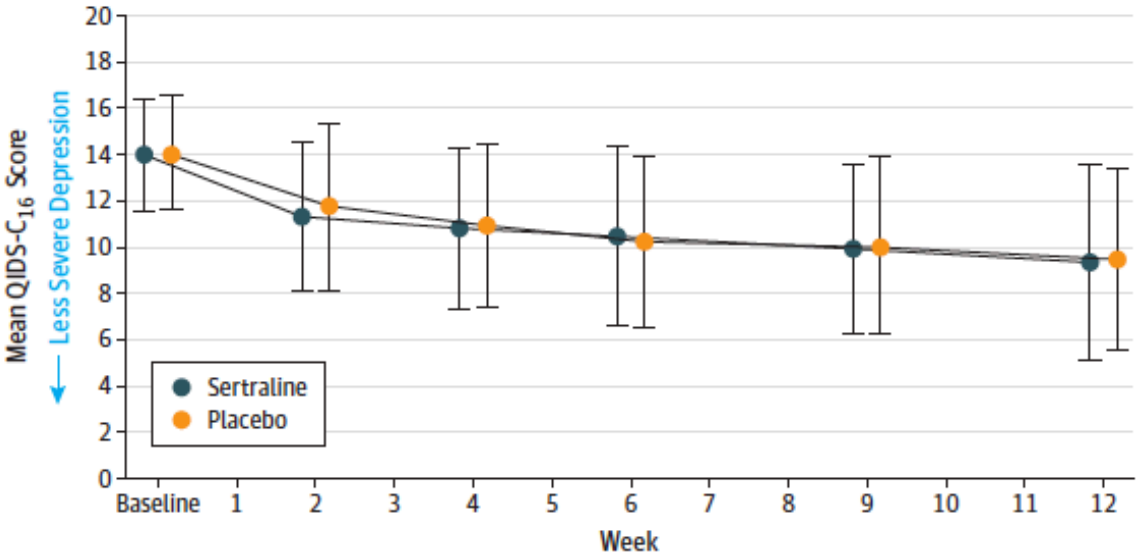


Figure 2. The association between the presence of depressive symptoms and mortality (adjusted risk estimates using hazard ratios). Abbreviations: CI, confidence interval; SE, standard error.

Farrokhi et al.
AJKD 2014;
63(4):623-635

CAST = sertraline vs placebo in CKD

Figure 2. Serial Changes in the 16-Item Quick Inventory of Depressive Symptomatology–Clinician Rated ($QIDS\text{-}C_{16}$) Scores



No. of participants						
Sertraline	97	95	87	83	81	81
Placebo	96	94	91	88	81	81

Participants completed at least 1 assessment after randomization and were included in the primary analysis. Error bars indicate SDs, which were calculated separately for each time point. Each of the 16 $QIDS\text{-}C_{16}$ items can yield a score of 0 to 3 on a Likert scale. The score range is 0 to 27; higher scores indicate more severe depression; a score of 0 to 5 corresponds to a normal affect; 6 to 10 to a mild affect; 11 to 15 to a moderate affect; 16 to 20 to a severe affect; and 21 or greater to very severe depression.

Hedayati et al.
JAMA
November 2017

Annals of Internal Medicine

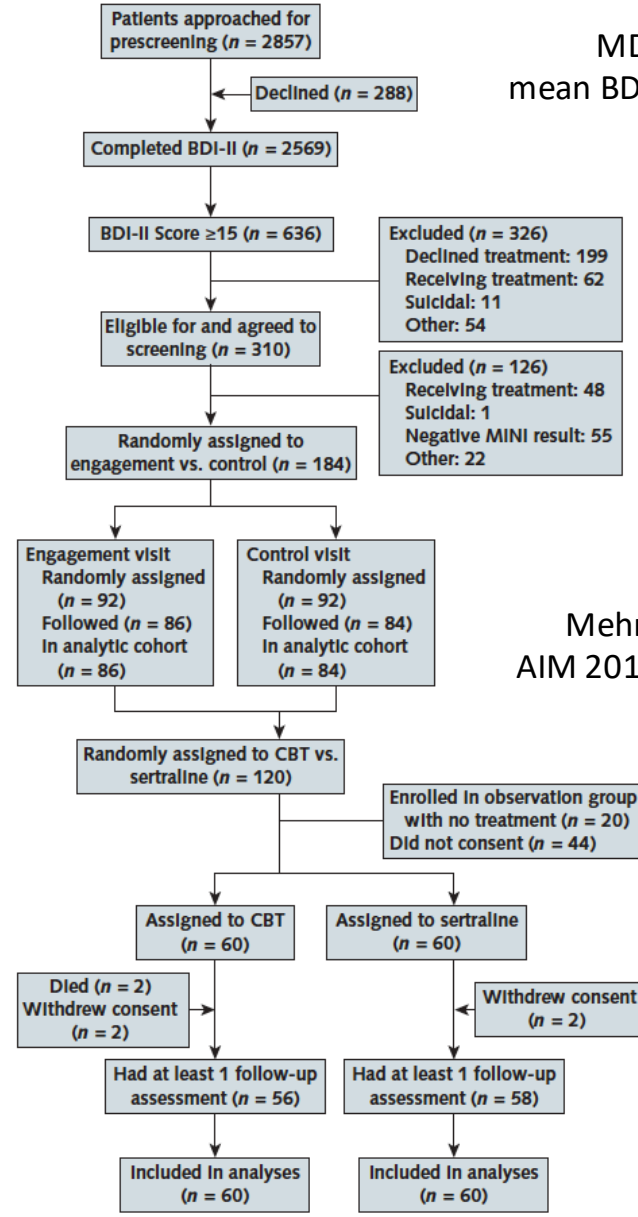
Comparative Efficacy of Therapies for Treatment of Depression for Patients Undergoing Maintenance Hemodialysis

A Randomized Clinical Trial

Duarte et al. KI 2009 Aug;76(4):414-21
Cukor et al. JASN 2014 25 (1) 196-206

- CBT vs sertraline
- n=120 from 3 states in the U.S.
- age≥21, ICHD≥3 months with MDD/dysthymia by BDI-II>15 confirmed by MINI
- CBT = face to face 10 60 minute sessions over 12 week during IHD with education, behavioral + cognitive interventions, modification guided by QIDS-SR
- sertraline = titrated to 200mg po daily guided by side effects
- 1=QIDS-C at 12 weeks
- 2=BDI-II, GAD-7, disability, energy/vitality of SF-36, Global QOL scale, SWLS, social support, PSQI, physical activity, adherence, AE's

Figure 1. Enrollment, randomization, and follow-up.



BDI-II = Beck Depression Inventory-II; CBT = cognitive behavioral therapy; MINI = Mini International Neuropsychiatric Interview.

MDD 91%
mean BDI-II 23.8 (7.5)

Mehrotra R et al.
AIM 2019;170:369-379

Table 2. Primary and Secondary Outcomes for Patients Receiving Hemodialysis With Depression Randomly Assigned to CBT or Sertraline Treatment

Time Point	Participants, *n*	Mean Score or Proportion of Raw Data (95% CI)		Effect Estimate (95% CI)*	Sensitivity Analyses With Multiple Imputation†
		CBT	Sertraline		
Primary outcome measure					
QIDS-C (range, 0-27; higher scores indicate worse depression)					
Baseline	120	12.2 (11.0 to 13.5)	10.9 (9.6 to 12.1)	-	-
Week 6	109	8.4 (7.0 to 9.8)	7.1 (6.1 to 8.2)	-	-
Week 12	113	8.1 (6.7 to 9.4)	5.9 (4.8 to 7.1)	−1.84 (−3.54 to −0.13)	−1.85 (−3.55 to −0.16)
Secondary outcome measures					
BDI-II (range, 0-63; higher scores indicate worse depression)					
Baseline	115	26.2 (23.6 to 28.8)	25.8 (23.3 to 28.4)	-	-
Week 6	98	20.0 (16.8 to 23.1)	17.4 (14.4 to 20.5)	-	-
Week 12	99	18.7 (15.2 to 22.2)	14.1 (11.2 to 17.0)	−3.7 (−7.4 to −0.02)‡	−2.9 (−6.7 to 0.8)
Generalized Anxiety Disorder 7-Item Scale (range, 0-21; higher scores indicate worse anxiety)					
Baseline	116	11.8 (10.2 to 13.3)	11.9 (10.5 to 13.4)	-	-
Week 6	102	10.2 (8.4 to 12.0)	8.3 (6.6 to 9.9)	-	-
Week 12	99	7.5 (5.9 to 9.2)	6.5 (4.9 to 8.1)	−1.2 (−3.1 to 0.8)	−0.7 (−2.7 to 1.3)
Sheehan Disability Scale (range, 0-30; higher scores indicate worse disability)					
Baseline	112	18.3 (16.0 to 20.6)	16.1 (13.6 to 18.5)	-	-
Week 6	103	14.7 (12.4 to 17.1)	13.1 (10.6 to 15.6)	-	-
Week 12	102	15.2 (12.8 to 17.6)	11.0 (8.7 to 13.3)	−3.1 (−6.2 to −0.1)§	−2.1 (−5.3 to 1.1)
Energy/vitality subscale of the 36-Item Short Form Health Survey (range, 0-100; lower scores indicate worse energy/vitality)					
Baseline	116	28.4 (23.0 to 33.9)	36.0 (30.6 to 41.4)	-	-
Week 6	99	35.2 (30.2 to 40.2)	44.3 (37.2 to 51.3)	-	-
Week 12	100	39.2 (33.4 to 44.9)	53.0 (45.7 to 60.3)	10.2 (1.3 to 19.0)‖	8.2 (−1.0 to 17.5)
Global Quality of Life Scale (range, 0-10; lower scores indicate worse quality of life)					
Baseline	111	4.0 (3.4 to 4.7)	4.7 (4.1 to 5.3)	-	-
Week 6	102	4.7 (4.2 to 5.3)	5.9 (5.3 to 6.5)	-	-
Week 12	106	5.6 (5.0 to 6.2)	6.4 (5.8 to 7.0)	0.6 (−0.2 to 1.4)	0.4 (−0.4 to 1.3)
Satisfaction With Life Scale (range, 1-35; lower scores indicate worse satisfaction)					
Baseline	115	14.7 (12.9 to 16.6)	16.6 (14.3 to 18.9)	-	-
Week 6	102	17.0 (15.0 to 19.0)	18.1 (15.9 to 20.3)	-	-
Week 12	105	16.8 (14.9 to 18.6)	20.1 (17.9 to 22.3)	2.6 (0.1 to 5.1)¶	2.3 (−0.4 to 4.9)
Pittsburgh Sleep Quality Index (range, 0-21; higher scores indicate worse sleep quality)					
Baseline	109	12.3 (11.3 to 13.2)	11.1 (10.0 to 12.1)	-	-
Week 6	88	10.7 (9.3 to 12.0)	8.2 (7.0 to 9.4)	-	-
Week 12	82	9.5 (8.1 to 10.8)	6.8 (5.5 to 8.1)	−1.8 (−3.4 to −0.2)**	−1.2 (−2.7 to 0.4)

no difference in response (50% decrease in QIDS-C) or remission (QIDS-C<5) at 12 weeks
P>0.05

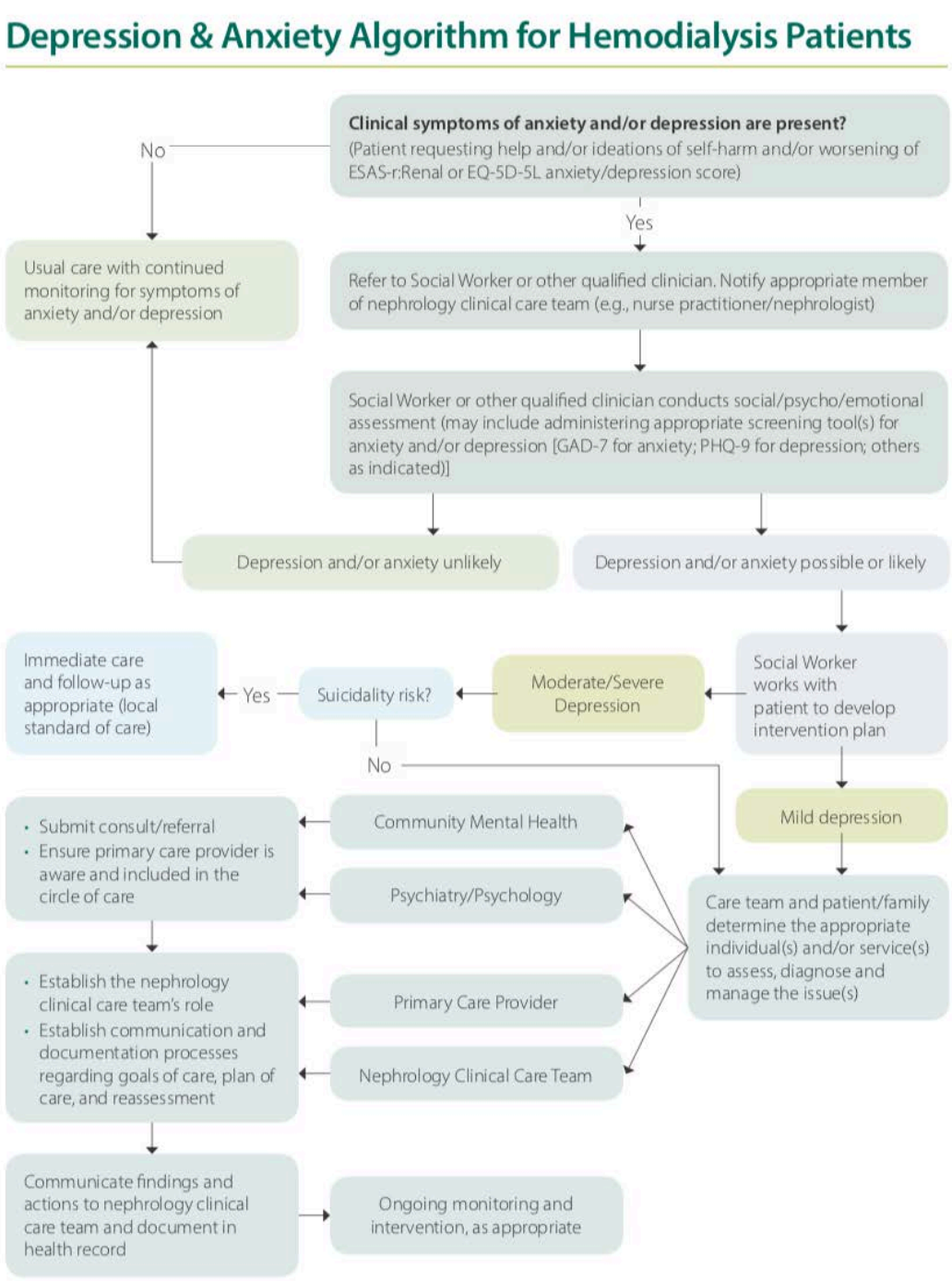
- missing data
- multiple imputation
- MID's
- no placebo comparison
- AE's

Mehrotra R et al. AIM 2019;170:369-379

ORN symptom management guide for depression

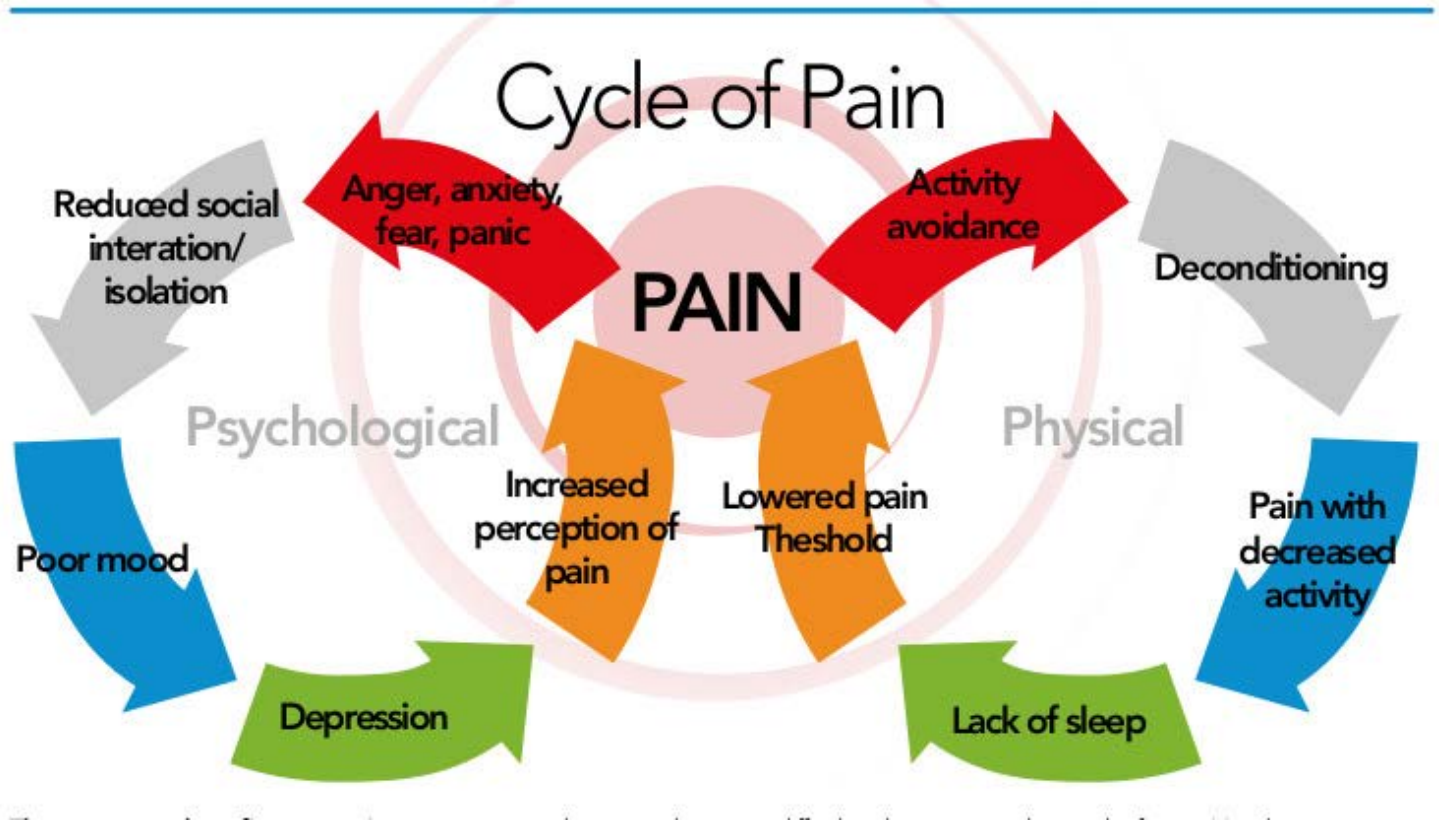
Ontario Renal Network

https://www.ontariorenalnetwork.ca/en/kidney-care-resources/clinical-tools/symptom-management



Pain

- “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”
- multidimensional
  - physical and psychosocial
- acute vs chronic
- nociceptive vs neuropathic
- psychological effects
- physical function
- experiences, goals, expectations



Turk DC et al.
Lancet 2011; 377:2226

Chronic pain

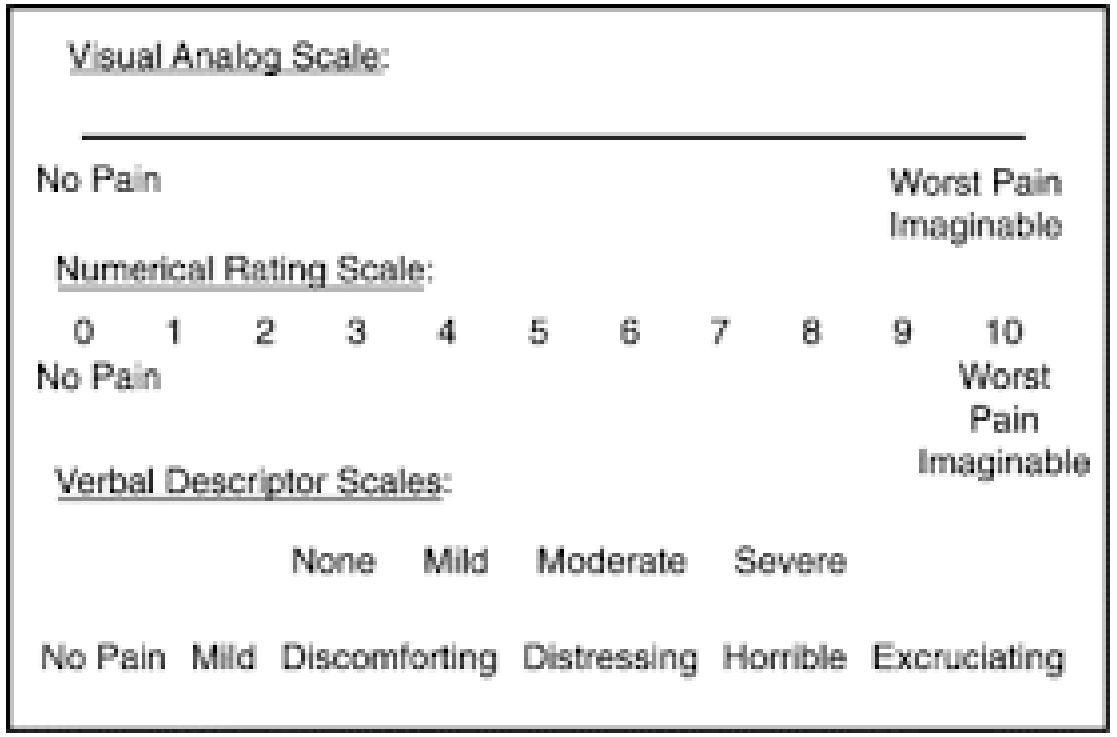
Turk DC et al.
Lancet 2011; 377:2226

International Association for the Study of Pain
IASP®
Working together for pain relief

- cancer vs non-cancer
- 4 categories = neuropathic, MSK, inflammatory, mechanical/compressive
- treatment
  - non-pharmacologic = physical medicine, behavioural medicine, neuromodulation, interventional and surgical approaches
  - pharmacologic = acetaminophen, NSAID, tramadol, opioids, A2DL, TCA/SSRI/SNRI, AED, muscle relaxants, NMDA receptor antagonists, topical agents
- nociceptive pain
  - 1st line = acetaminophen, NSAID, 2nd line = opioids
- neuropathic pain
  - 1st line = TCA/SNRI or A2DL, 2nd line = opioids
- opioids
  - controversial
  - insufficient evidence for long term efficacy
  - harms

Measuring pain

- severity = numeric, visual, or verbal scales
- mild pain = 0–3
- moderate pain = 4–6
- severe pain = 7–10
- MID = approximately >10mm on VAS
- physical function
- emotional function = anxiety, depression
- life participation = ADL's
- quality of life



Serlin et al.
Pain 1995;61: 277--284.

Farrar et al.
Pain 2001; 94:149

Pain

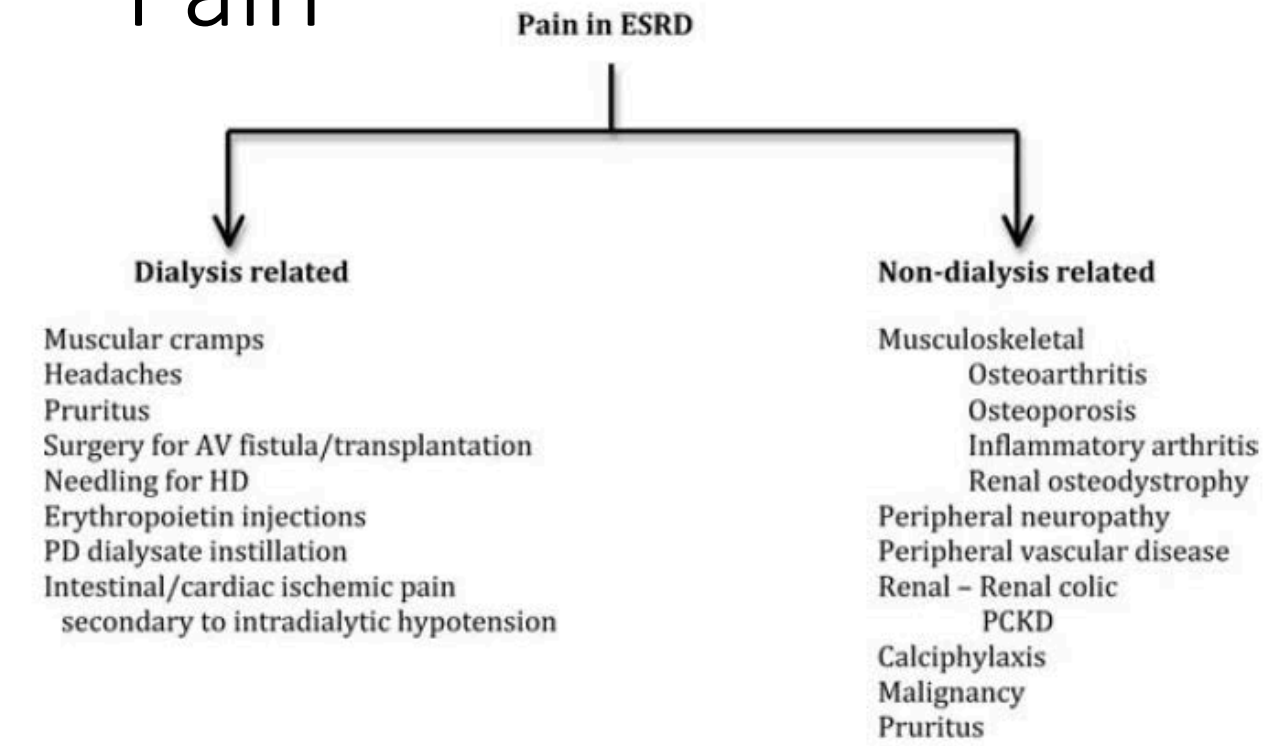


Figure 1 Etiology of pain in ESRD.[1,2]

Raina R et al.
HI 2018; 22:290–296

Table 2. Cause of Pain

Cause	No. of Patients*	Percent
Musculoskeletal	65	63.1
Osteoarthritis	20	19.4
Musculoskeletal, not yet diagnosed	19	18.4
Osteoporosis (resulting in spinal fractures)	12	9.7
Inflammatory arthritis	7	6.8
Renal osteodystrophy	5	4.9
Diskitis/osteomyelitis	2	1.9
Related to dialysis procedure	14	13.6
Peripheral polyneuropathy	13	12.6
Peripheral vascular disease	10	9.7
Carpal tunnel	2	1.9
Other (including trauma, polycystic kidney disease, malignancy, calciphylaxis)	19	18.4

*Numbers add to more than 103 (100%) because 19 patients had more than 1 cause for their pain.

Davison et al. AJKD
2003;42(6):1239-47

Analgesic use in CKD, dialysis

TABLE 3. Analgesic use in CKD

Patient population	Patient number	Any analgesic	NSAID	Acetaminophen	Opioids
CKD (3 studies)	2342	–	24% (range 6%-54%)	24%	–
CKD with pain (1 study)	130	–	15%	33%	–
Incident HD/PD (2 studies)	4826	11%	1.8%	–	7% (range 5–18%)
Prevalent HD (13 studies)	25725	27% (range 18–30%)	5% (range 1–16%)	9% (range 0–14%)	15% (range 0–18%)
Prevalent HD with pain (7 studies)	755	56% (range 30–65%)	19% (range 3–42%)	18% (range 0–44%)	22% (range 0–36%)
Withdrawn from dialysis (1 study)	79	87%	–	–	–
Withdrawn from dialysis and followed by palliative care (1 study)	35	–	–	–	97%

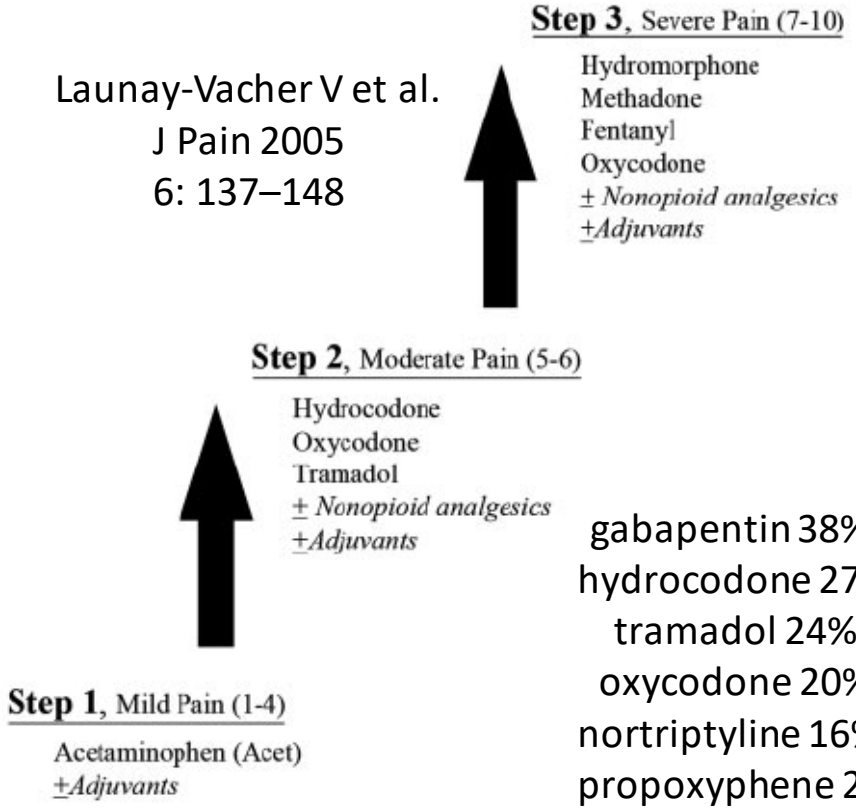
Davison SN et al. Semin Dial 27: 188–204, 2014

overall 47% (95% CI 0.35 to 0.59)
acetaminophen prevalence 26% (95% CI, 0.16 to 0.36)
NSAID prevalence 16% (95% CI, 0.11 to 0.21)
opioid prevalence 22% (95% CI, 0.07 to 0.41)
???A2DL
???TCA
???cannabinoids

SN Davison et al. submitted article

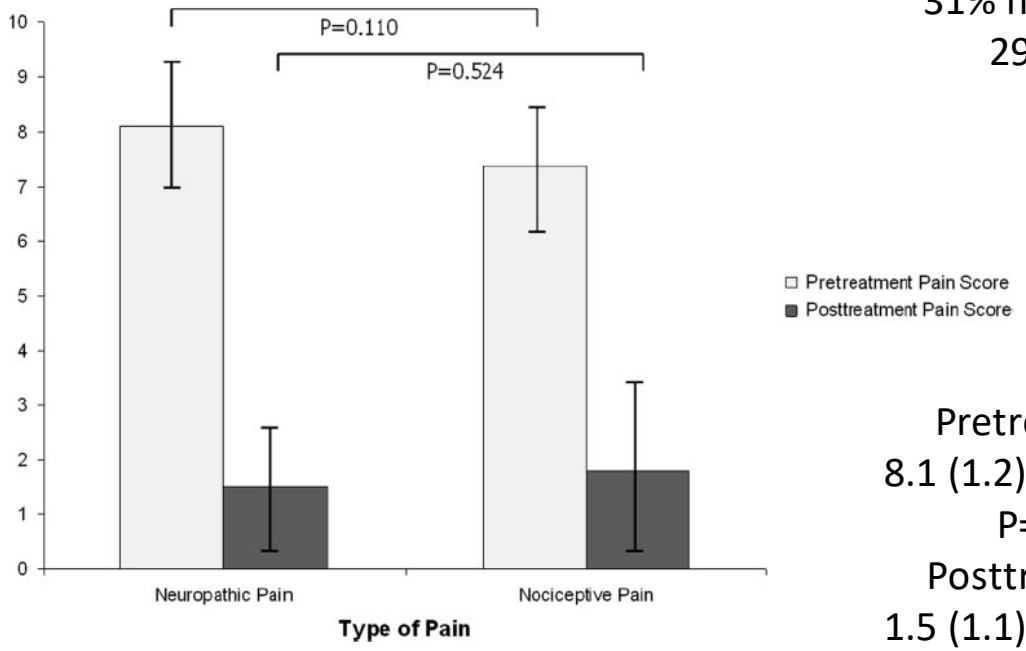
WHO pain ladder in ESKD

Launay-Vacher V et al.
J Pain 2005
6: 137–148



gabapentin 38%;
hydrocodone 27%
tramadol 24%
oxycodone 20%
nortriptyline 16%,
propoxyphene 2%

Barakzoy AS, Moss AH
JASN 17: 3198–3203,
2006



43/45 = 96%
adequate analgesia
defined as no or mild
post treatment pain
no opioid toxicity

N=45 adult HD
patients from 2 HD
units in Virginia
without pain
treatment, SF-MPQ
40% nociceptive
31% neuropathic
29% both

Pretreatment
8.1 (1.2) vs 7.4 (1.2)
P=0.11
Posttreatment
1.5 (1.1) vs 1.8 (1.5)
P=0.524

Acetaminophen and hip, knee OA –SR, MA

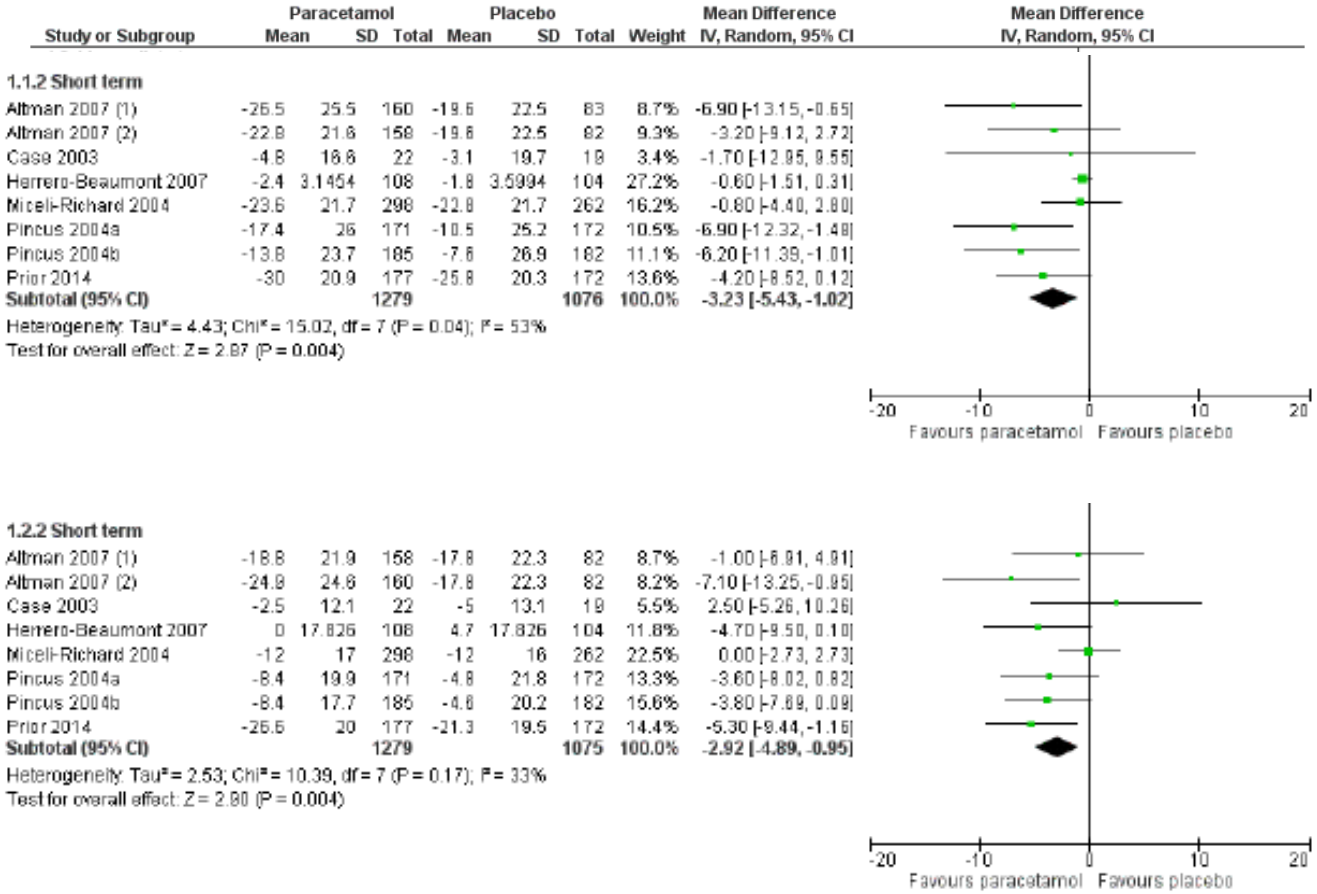
- RCT's paracetamol vs placebo
- hip or knee OA
- 10 RCT's n=3541 participants
- 1.95 g/day to 4 g/day
- short term – 3-12 weeks
- placebo = mean reduction in pain 23 points
- **pain: a small, likely clinically unimportant improvement**

= MD -3.23, 95% CI -5.43 to -1.02

- **physical function = WOMAC = a small likely clinically unimportant improvement**

= MD -2.92, 95% CI -4.89 to -0.95

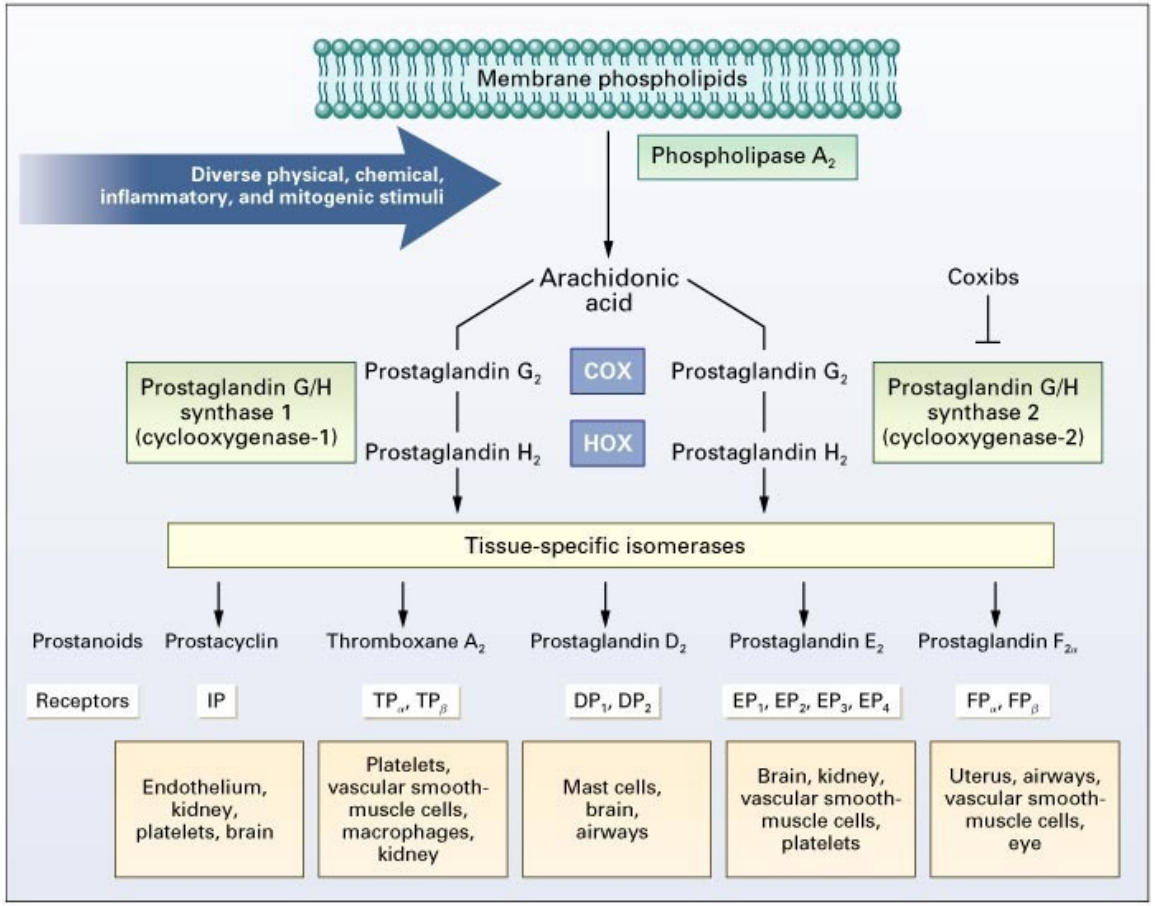
- no studies measured quality of life
- AE RR 1.01, 95% CI 0.92 to 1.11
- SAE RR 1.36, 95% CI 0.73 to 2.53
- abnormal liver function tests RR 3.79, 95% CI 1.94 to 7.39



Leopoldino et al.
Cochrane 2019 CD013273

NSAIDs

- adverse renal events in 1-5% of patients using NSAIDs
- AKI (ATN, AIN, NS)
- electrolyte (hyperkalemia, hyponatremia)
- edema, HTN, heart failure
- risk of AKI, progression of CKD but unclear if mediated by AKI
- prevention = avoid NSAID in high risk patients, no safe dose or duration
- other side effects = GI (dyspepsia, PUD), bleeding, CV events



Schlondorff D.
KI 1993 44:643

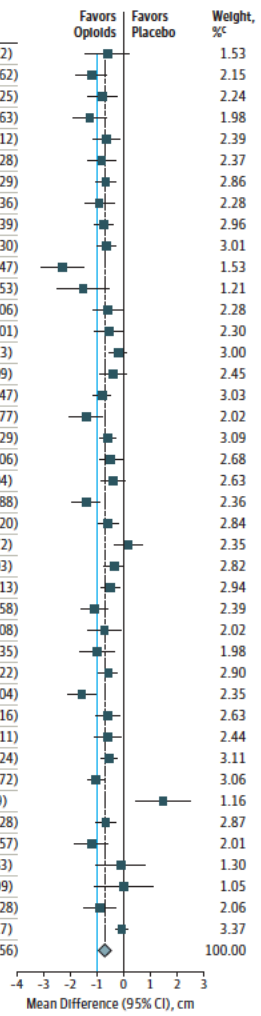
FitzGerald et al.
NEJM 2001; 345:433-442

Opioids for chronic non-cancer pain –SR, MA

Figure 2. Pain Relief on a 10-cm Visual Analog Scale Among Patients With Chronic Noncancer Pain Who Received Opioids vs Placebo in 42 High-Quality Randomized Clinical Trials

Source	Opioids Group No. of Patients	Opioids Group Mean (95% CI), cm[a]	Placebo Group No. of Patients	Placebo Group Mean (95% CI), cm[a]	Between-Group Mean Difference (95% CI)[b]	Weight, %[c]
Fleischmann et al,[54] 2001	63	-1.53 (-2.10 to -0.95)	66	-0.93 (-1.53 to -0.32)	-0.60 (-1.42 to 0.22)	1.53
Bennett et al,[46] 2003	156	-1.90 (-2.34 to -1.46)	157	-0.70 (-1.09 to -0.31)	-1.20 (-1.78 to -0.62)	2.15
Ruoff et al,[69] 2003	151	-1.87 (-2.29 to -1.45)	142	-1.07 (-1.43 to -0.70)	-0.80 (-1.35 to -0.25)	2.24
Babul et al,[45] 2004	124	-3.04 (-3.50 to -2.58)	122	-1.77 (-2.23 to -1.31)	-1.27 (-1.91 to -0.63)	1.98
Emkey et al,[52] 2004	153	-2.75 (-3.11 to -2.39)	153	-2.12 (-2.49 to -1.75)	-0.63 (-1.14 to -0.12)	2.39
Peloso et al,[64] 2004	164	-1.36 (-1.77 to -0.94)	161	-0.56 (-0.87 to -0.24)	-0.80 (-1.32 to -0.28)	2.37
Gana et al,[56] 2006	806	-2.15 (-2.32 to -1.98)	205	-1.48 (-1.82 to -1.15)	-0.67 (-1.04 to -0.29)	2.86
Webster et al,[41] 2006	608	-3.40 (-3.58 to -3.23)	101	-2.50 (-3.02 to -1.98)	-0.90 (-1.44 to -0.36)	2.28
Burch et al,[48] 2007	393	-3.03 (-3.24 to -2.82)	196	-2.29 (-2.57 to -2.01)	-0.74 (-1.09 to -0.39)	2.96
Fishman et al,[53] 2007	311	-2.57 (-2.87 to -2.28)	224	-1.94 (-2.09 to -1.80)	-0.63 (-0.96 to -0.30)	3.01
Hale et al,[58] 2007	49	0.87 (0.27 to 1.47)	18	3.16 (2.55 to 3.77)	-2.29 (-3.11 to -1.47)	1.53
Katz et al,[62] 2007	71	1.09 (0.51 to 1.67)	47	2.60 (1.78 to 3.42)	-1.51 (-2.49 to -0.53)	1.21
Hanna et al,[59] 2008	163	-2.10 (-2.50 to -1.70)	165	-1.50 (-1.87 to -1.13)	-0.60 (-1.14 to -0.06)	2.28
Vorsanger et al,[78] 2008	256	0.42 (0.11 to 0.72)	126	0.96 (0.51 to 1.41)	-0.54 (-1.08 to -0.01)	2.30
Afilalo et al,[43] 2010	686	-1.51 (-1.70 to -1.32)	337	-1.31 (-1.58 to -1.04)	-0.20 (-0.53 to 0.13)	3.00
Breivik et al,[47] 2010	86	-0.90 (-1.29 to -0.51)	91	-0.50 (-0.81 to -0.19)	-0.40 (-0.89 to 0.09)	2.45
Buynak et al,[49] 2010	635	-2.90 (-3.10 to -2.70)	316	-2.10 (-2.36 to -1.84)	-0.80 (-1.13 to -0.47)	3.03
Hale et al,[57] 2010	133	0.20 (-0.25 to 0.65)	133	1.60 (1.15 to 2.05)	-1.40 (-2.03 to -0.77)	2.02
Katz et al,[60] 2010	171	0.10 (-0.11 to 0.31)	173	0.70 (0.47 to 0.93)	-0.60 (-0.91 to -0.29)	3.09
DeLemos et al,[51] 2011	599	-2.13 (-2.34 to -1.93)	200	-1.65 (-2.02 to -1.28)	-0.48 (-0.91 to -0.06)	2.68
Friedmann et al,[55] 2011	203	-0.70 (-0.98 to -0.42)	207	-0.30 (-0.64 to 0.04)	-0.40 (-0.84 to 0.04)	2.63
Schwartz et al,[70] 2011	196	0 (-0.37 to 0.37)	193	1.40 (1.03 to 1.77)	-1.40 (-1.92 to -0.88)	2.36
Steiner et al,[73] 2011	257	1.21 (0.93 to 1.49)	283	1.79 (1.53 to 2.05)	-0.58 (-0.96 to -0.20)	2.84
Vojtaššák et al,[77] 2011	132	-2.40 (-2.76 to -2.04)	143	-2.60 (-2.98 to -2.22)	0.20 (-0.32 to 0.72)	2.35
Rauck et al,[65] 2013	649	-2.25 (-2.47 to -2.03)	331	-1.90 (-2.21 to -1.59)	-0.35 (-0.73 to 0.03)	2.82
Rauck et al,[67] 2014	151	0.48 (0.23 to 0.73)	151	0.96 (0.71 to 1.21)	-0.48 (-0.83 to -0.13)	2.94
Vinik et al,[76] 2014	146	-0.04 (-0.36 to 0.28)	131	1.05 (0.65 to 1.45)	-1.09 (-1.60 to -0.58)	2.39
Aral et al,[44] 2015[d]	73	-0.02 (-0.44 to 0.40)	77	0.69 (0.22 to 1.16)	-0.71 (-1.34 to -0.08)	2.02
Aral et al,[44] 2015[d]	84	-0.03 (-0.49 to 0.43)	79	0.96 (0.50 to 1.42)	-0.99 (-1.63 to -0.35)	1.98
Hale et al,[38] 2015	191	-0.03 (-0.27 to 0.21)	179	0.55 (0.27 to 0.83)	-0.58 (-0.94 to -0.22)	2.90
Katz et al,[61] 2015	122	0.29 (-0.01 to 0.59)	100	1.85 (1.41 to 2.29)	-1.56 (-2.08 to -1.04)	2.35
Rauck et al,[66] 2015 and Weil et al,[79] 2017	146	0.60 (0.30 to 0.90)	134	1.20 (0.87 to 1.53)	-0.60 (-1.04 to -0.16)	2.63
Trenkwalder et al,[75] 2015	61	-2.30 (-2.67 to -1.93)	73	-1.70 (-2.04 to -1.36)	-0.60 (-1.09 to -0.11)	2.44
Wen et al,[80] 2015	296	-3.69 (-3.90 to -3.48)	292	-3.15 (-3.37 to -2.93)	-0.54 (-0.84 to -0.24)	3.11
Gimbel et al,[42] 2016	254	0.88 (0.66 to 1.10)	256	1.92 (1.69 to 2.15)	-1.04 (-1.36 to -0.72)	3.06
Mayorga et al,[63] 2016	50	-1.45 (-2.17 to -0.73)	48	-2.93 (-3.67 to -2.19)	1.48 (0.47 to 2.49)	1.16
Rauck et al,[68] 2016	209	0.94 (0.69 to 1.19)	211	1.59 (1.31 to 1.87)	-0.65 (-1.02 to -0.28)	2.87
Simpson and Wlodarczyk,[72] 2016	89	-3.30 (-3.76 to -2.84)	92	-2.10 (-2.55 to -1.65)	-1.20 (-1.83 to -0.57)	2.01
Tominaga et al,[74] 2016[d]	60	-3.00 (-3.51 to -2.49)	31	-2.90 (-3.71 to -2.09)	-0.10 (-1.03 to 0.83)	1.30
Tominaga et al,[74] 2016[d]	60	-2.60 (-3.18 to -2.02)	31	-2.60 (-3.57 to -1.63)	0 (-1.09 to 1.09)	1.05
Christoph et al,[50] 2017	123	-3.03 (-3.27 to -2.79)	125	-2.16 (-2.58 to -1.74)	-0.89 (-1.50 to -0.28)	2.06
Serrie et al,[71] 2017	650	Not reported[e]	337	Not reported[e]	-0.05 (-0.27 to 0.17)	3.37
Overall					-0.69 (-0.82 to -0.56)	100.00

Test for heterogeneity: $I^2 = 70.4\%$, $P < .001$



96 RCT's
26169 participants
25 neuropathic, 32 nociceptive, 33 central, 6 mixed
opioids vs placebo

reduced pain

- **WMD -0.69cm (95% CI -0.82cm to -0.56cm)**
  - **10cm VAS**
- **modeled risk difference for achieving the MID**
  - **11.9% (95% CI 9.7% to 14.1%)**

improved physical functioning

- **WMD, 2.04 points (95%CI, 1.41 to 2.68 points)**
  - **100-point SF-36 PCS**
- **modeled risk difference for achieving the MID**
  - **8.5% (95%CI, 5.9% to 11.2%)**

Busse JW et al.
JAMA 2018; 320:2448

Opioids: AE's and SAE's

- AE RR 1.42 (95% CI 1.22-1.66)
- SAE RR 2.75 (95% CI 2.06-3.67)
- The risks of specific adverse events were increased for **constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus, and vomiting**

Els C et al. Cochrane 2017
Issue 10
CD012509

Figure 2. Analysis 1.1: Opioids versus placebo, any adverse event. CI: confidence interval
df: degrees of freedom
M-H: Mantel-Haenszel method of meta-analysis
P: probability
Z: Z score (standard score)

Study or Subgroup	Opioids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Stannard 2016	21	43	27	51	10.0%	0.92 [0.62, 1.38]
Derry 2016	72	84	56	79	23.0%	1.21 [1.02, 1.43]
da Costa 2014	2145	2725	837	1506	30.5%	1.42 [1.35, 1.49]
Whittle 2011	6	11	3	8	2.0%	1.45 [0.51, 4.13]
McNicol 2013	152	202	85	197	22.0%	1.74 [1.46, 2.09]
Gaskell 2016	40	48	22	50	12.5%	1.89 [1.35, 2.65]
Total (95% CI)		**3113**		**1891**	**100.0%**	**1.42 [1.22, 1.66]**
Total events	2436		1030			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 16.02$, df = 5 (P = 0.007); $I^2 = 69\%$
Test for overall effect: Z = 4.50 (P < 0.00001)

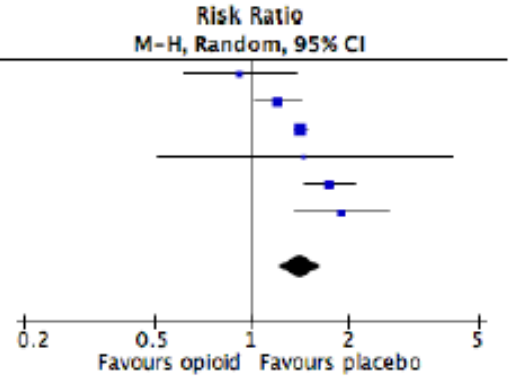
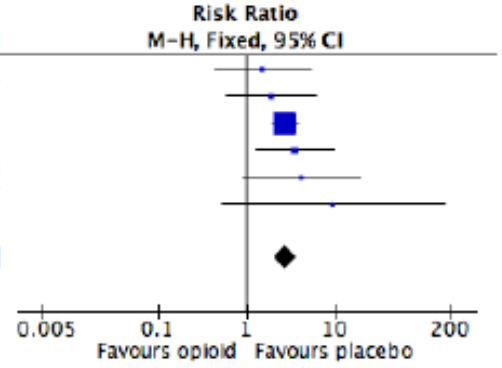


Figure 3. Analysis 1.2: Opioids versus placebo, any serious adverse event. CI: confidence interval
df: degrees of freedom
M-H: Mantel-Haenszel method of meta-analysis
P: probability
Z: Z score (standard score)

Study or Subgroup	Opioids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stannard 2016	6	134	4	134	6.6%	1.50 [0.43, 5.20]
Derry 2016	8	84	4	79	6.8%	1.88 [0.59, 6.00]
Cepeda 2006	116	505	43	505	71.2%	2.70 [1.94, 3.74]
Santos 2015	73	1767	4	337	11.1%	3.48 [1.28, 9.46]
da Costa 2014	9	355	2	326	3.5%	4.13 [0.90, 18.98]
Gaskell 2016	4	48	0	50	0.8%	9.37 [0.52, 169.45]
Total (95% CI)		**2893**		**1431**	**100.0%**	**2.75 [2.06, 3.67]**
Total events	216		57			

Heterogeneity: $Chi^2 = 2.52$, df = 5 (P = 0.77); $I^2 = 0\%$
Test for overall effect: Z = 6.90 (P < 0.00001)



Opioids and adverse outcomes

Ishida et al.
CJASN 13: 746–753, 2018

	Opioid exposure	LOC Adjusted HR (95% CI)	Fall Adjusted HR (95% CI)	Fracture Adjusted HR (95% CI)
	None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Lower dose ≤60mg morphine equivalents	**1.28 (1.23 to 1.34)**	**1.28 (1.21 to 1.36)**	**1.44 (1.33 to 1.56)**
	Higher dose >60mg morphine equivalents	**1.67 (1.56 to 1.78)**	**1.45 (1.31 to 1.61)**	**1.65 (1.44 to 1.89)**
	None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Recommended	*Hydromorphone*	**1.39 (1.23 to 1.57)**	**1.02 (1.01 to 1.04)**	**1.03 (1.02 to 1.04)**
Recommended	*Fentanyl*	**1.18 (1.11 to 1.25)**	1.06 (0.96 to 1.17)	1.03 (0.90 to 1.18)
Recommended	*Methadone*	**1.14 (1.01 to 1.29)**	1.08 (0.92 to 1.28)	1.08 (0.87 to 1.34)
Caution	*Hydrocodone*	**1.37 (1.29 to 1.47)**	**1.34 (1.27 to 1.41)**	**1.40 (1.32 to 1.48)**
Caution	*Oxycodone*	**1.31 (1.25 to 1.38)**	**1.13 (1.06 to 1.22)**	**1.25 (1.19 to 1.31)**
Caution	*Tramadol*	**1.48 (1.31 to 1.69)**	**1.42 (1.19 to 1.69)**	**1.65 (1.41 to 1.92)**
Avoid	*Codeine*	**3.65 (2.12 to 6.30)**	1.57 (0.64 to 3.83)	2.94 (1.00 to 8.66)
Avoid	*Morphine*	**1.40 (1.27 to 1.55)**	1.15 (0.99 to 1.32)	1.11 (0.90 to 1.38)

Opioids and more adverse outcomes

Table 6. Adjusted HRs of death, discontinued dialysis, and hospitalization in 2011–2012 associated with 2010 prescription for ≥90 days of an opioid in the 2010 prevalent dialysis cohort (*n*=149,757)

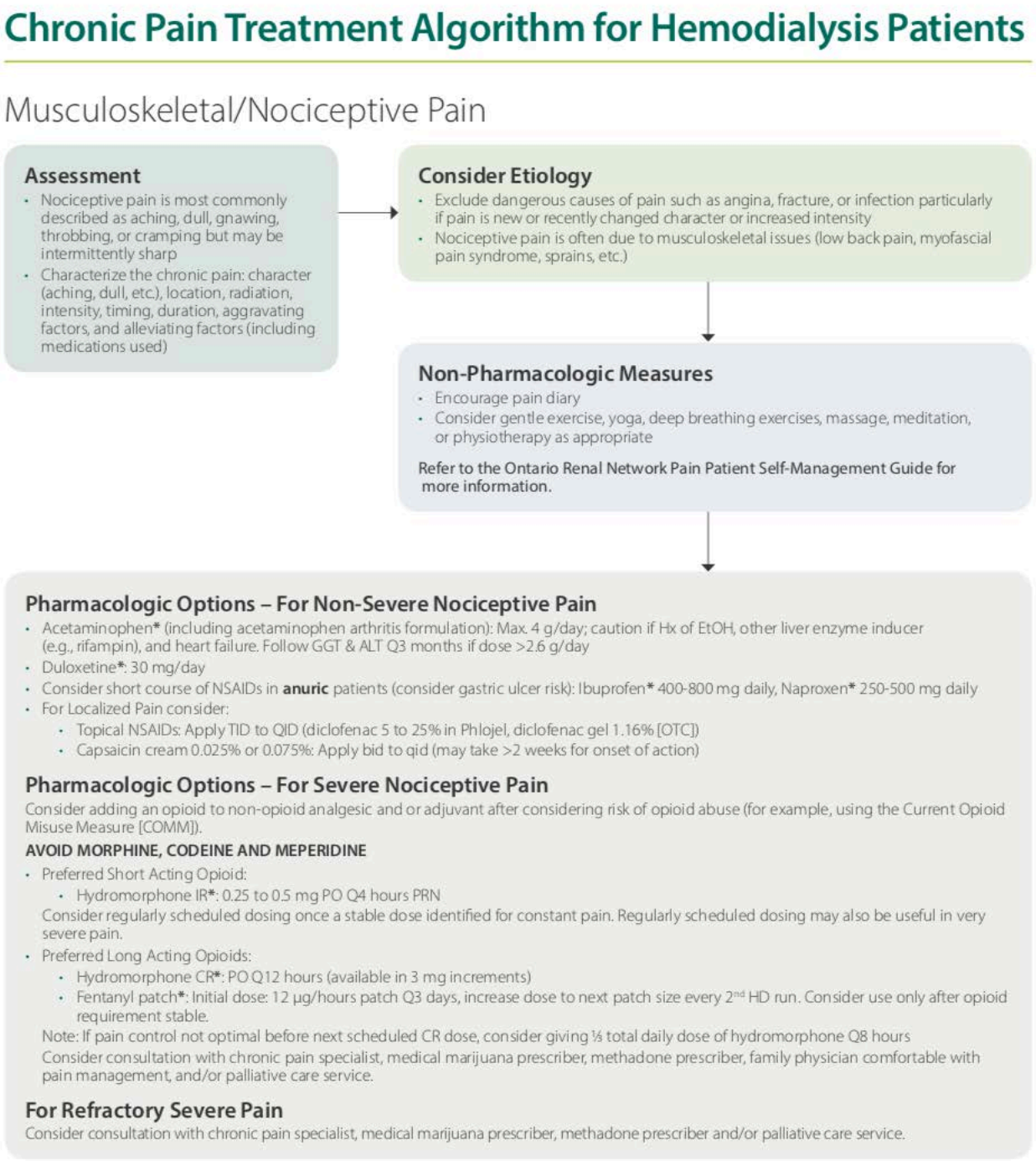
Characteristics	Outcome: Death			Outcome: Discontinued Dialysis			Outcome: Hospitalization		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Opioid prescription[a]									
None	1.00			1.00			1.00		
Short term	1.05	1.02 to 1.07	<0.001	1.13	1.05 to 1.22	0.002	1.13	1.11 to 1.14	<0.001
Chronic, <20 MME/d	1.16	1.11 to 1.21	<0.001	1.32	1.15 to 1.53	<0.001	1.26	1.22 to 1.29	<0.001
Chronic, 20–50 MME/d	1.26	1.22 to 1.30	<0.001	1.36	1.22 to 1.51	<0.001	1.29	1.27 to 1.32	<0.001
Chronic, 50+ MME/d	1.39	1.34 to 1.44	<0.001	1.47	1.30 to 1.66	<0.001	1.38	1.35 to 1.41	<0.001

Kimmel PL et al.
JASN 28: 3658–3670,
2017

ORN symptom guide for chronic pain

Ontario Renal Network

https://www.ontariorenalnetwork.ca/en/kidney-care-resources/clinical-tools/symptom-management



Chronic Pain Treatment Algorithm for Hemodialysis Patients

Musculoskeletal/Nociceptive Pain

Assessment

- Nociceptive pain is most commonly described as aching, dull, gnawing, throbbing, or cramping but may be intermittently sharp
- Characterize the chronic pain: character (aching, dull, etc.), location, radiation, intensity, timing, duration, aggravating factors, and alleviating factors (including medications used)

Consider Etiology

- Exclude dangerous causes of pain such as angina, fracture, or infection particularly if pain is new or recently changed character or increased intensity
- Nociceptive pain is often due to musculoskeletal issues (low back pain, myofascial pain syndrome, sprains, etc.)

Non-Pharmacologic Measures

- Encourage pain diary
- Consider gentle exercise, yoga, deep breathing exercises, massage, meditation, or physiotherapy as appropriate

Refer to the Ontario Renal Network Pain Patient Self-Management Guide for more information.

Pharmacologic Options – For Non-Severe Nociceptive Pain

- Acetaminophen* (including acetaminophen arthritis formulation): Max. 4 g/day; caution if Hx of EtOH, other liver enzyme inducer (e.g., rifampin), and heart failure. Follow GGT & ALT Q3 months if dose >2.6 g/day
- Duloxetine*: 30 mg/day
- Consider short course of NSAIDs in **anuric** patients (consider gastric ulcer risk): Ibuprofen* 400-800 mg daily, Naproxen* 250-500 mg daily
- For Localized Pain consider:
  - Topical NSAIDs: Apply TID to QID (diclofenac 5 to 25% in Phlojel, diclofenac gel 1.16% [OTC])
  - Capsaicin cream 0.025% or 0.075%: Apply bid to qid (may take >2 weeks for onset of action)

Pharmacologic Options – For Severe Nociceptive Pain

Consider adding an opioid to non-opioid analgesic and or adjuvant after considering risk of opioid abuse (for example, using the Current Opioid Misuse Measure [COMM]).

AVOID MORPHINE, CODEINE AND MEPERIDINE

- Preferred Short Acting Opioid:
  - Hydromorphone IR*: 0.25 to 0.5 mg PO Q4 hours PRN

  Consider regularly scheduled dosing once a stable dose identified for constant pain. Regularly scheduled dosing may also be useful in very severe pain.
- Preferred Long Acting Opioids:
  - Hydromorphone CR*: PO Q12 hours (available in 3 mg increments)
  - Fentanyl patch*: Initial dose: 12 µg/hours patch Q3 days, increase dose to next patch size every 2nd HD run. Consider use only after opioid requirement stable.

  Note: If pain control not optimal before next scheduled CR dose, consider giving ⅛ total daily dose of hydromorphone Q8 hours

  Consider consultation with chronic pain specialist, medical marijuana prescriber, methadone prescriber, family physician comfortable with pain management, and/or palliative care service.

For Refractory Severe Pain

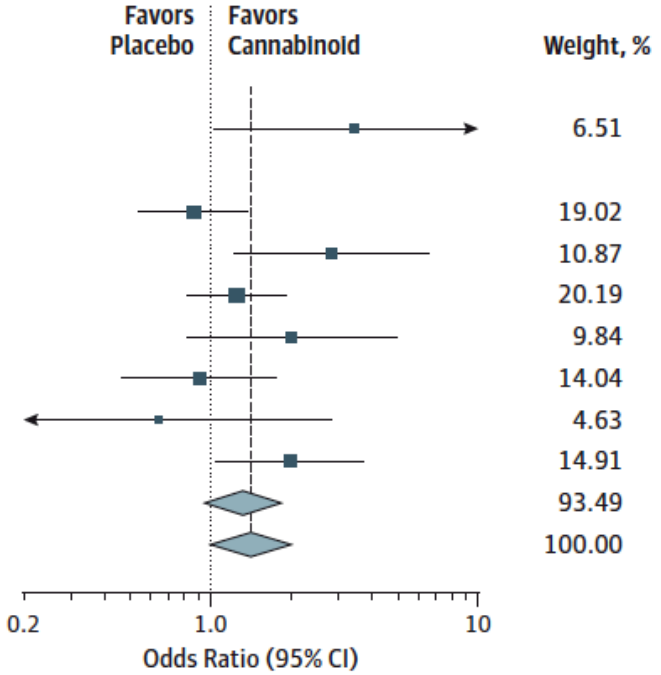
Consider consultation with chronic pain specialist, medical marijuana prescriber, methadone prescriber and/or palliative care service.

Cannabinoids for pain

Whiting et al.
JAMA 2015;313(24):2456-2473

Figure 2. Improvement in Pain

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal $I^2 = 44.5\%$, ($P = .0.94$)	241	660	209	660	1.32 (0.94-1.86)
Overall $I^2 = 47.6\%$, ($P = .0.64$)	254	685	215	685	1.41 (0.99-2.00)



Odds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).

Cannabinoids and AE's

- **Any AE OR 3.02 95% CI 2.42-3.80**
- **SAE OR 1.41 95% CI 1.04-1.92**
- Withdrawal OR 2.94 2.18-3.96
- MedDRA high level grouping = GI, psychiatric, nervous system, general, ear and labyrinth, renal and urinary
- **Individual AE = dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, diarrhea, disorientation, asthenia, drowsiness, confusion, balance, hallucination**

Whiting et al.
JAMA 2015;313(24):2456-2473

Table 3. Summary Estimates From Meta-analyses for Each AE Assessed: Odds of Participants Experiencing AE With Cannabinoid vs Placebo or Active Comparison

	No. of Studies (No. of Patients)	Summary OR (95% CI)	I^2, %
General AE categories			
Any	29 (3714)	3.03 (2.42-3.80)	31
Serious	34 (3248)	1.41 (1.04-1.92)	0
Withdrawal due to AE	23 (2755)	2.94 (2.18-3.96)	2
MedDRA high-level grouping[164]			
Gastrointestinal disorders	10 (1960)	1.78 (1.43-2.22)	0
Infections and infestations	7 (1681)	1.13 (0.87-1.46)	0
Psychiatric disorders	8 (1672)	3.10 (1.81-5.29)	55
Nervous system disorders	10 (1521)	3.17 (2.20-4.58)	46
Musculoskeletal and connective tissues disorders	7 (1310)	1.32 (0.75-2.32)	34
General disorders and administration site conditions	6 (1208)	1.78 (1.34-2.36)	0
Death	5 (929)	1.01 (0.51-2.00)	0
Ear and labyrinth disorders	3 (922)	2.72 (1.55-4.75)	0
Respiratory, thoracic, and mediastinal disorders	5 (851)	0.80 (0.46-1.39)	0
Cardiac disorders	7 (833)	1.42 (0.58-3.48)	0
Blood disorders	3 (543)	1.42 (0.20-10.25)	18
Injury, poisoning and procedural complications	3 (543)	1.18 (0.48-2.93)	0
Renal and urinary disorders	3 (470)	2.45 (2.27-2.65)	0
Investigations	2 (427)	1.55 (0.36-6.71)	0
Metabolism and nutrition	2 (427)	2.37 (1.00-5.61)	0
Neoplasms, benign, malignant, and unspecified	2 (427)	0.99 (0.47-2.08)	0
Skin and subcutaneous	3 (405)	0.85 (0.34-2.13)	0
Eye disorders	1 (339)	1.42 (0.46-4.33)	NA
Reproductive system	1 (246)	1.55 (0.20-11.92)	NA
Hepatobiliary disorders	1 (181)	3.07 (0.12-76.29)	NA
Mental status change	3 (106)	2.49 (0.49-12.64)	0
Other body systems	1 (42)	2.59 (0.34-19.47)	NA
Injection site pain	1 (32)	2.49 (0.92-6.68)	NA
Individual AEs			
Dizziness	41 (4243)	5.09 (4.10-6.32)	18
Dry mouth	36 (4181)	3.50 (2.58-4.75)	28
Nausea	30 (3579)	2.08 (1.63-2.65)	0
Fatigue	20 (2717)	2.00 (1.54-2.62)	0
Somnolence	26 (3168)	2.83 (2.05-3.91)	27
Euphoria	27 (2420)	4.08 (2.18-7.64)	49
Depression	15 (2353)	1.32 (0.87-2.01)	0
Vomiting	17 (2191)	1.67 (1.13-2.47)	0
Diarrhea	17 (2077)	1.65 (1.04-2.62)	15
Disorientation	12 (1736)	5.41 (2.61-11.19)	0
Asthenia	15 (1717)	2.03 (1.35-3.06)	0
Drowsiness	18 (1272)	3.68 (2.24-6.01)	44
Anxiety	12 (1242)	1.98 (0.73-5.35)	54
Confusion	13 (1160)	4.03 (2.05-7.97)	0
Balance	6 (920)	2.62 (1.12-6.13)	0
Hallucination	10 (898)	2.19 (1.02-4.68)	0
Dyspnea	4 (375)	0.83 (0.26-2.63)	0
Paranoia	4 (492)	2.05 (0.42-10.10)	0
Psychosis	2 (37)	1.09 (0.07-16.35)	25
Seizures	2 (42)	0.91 (0.05-15.66)	0

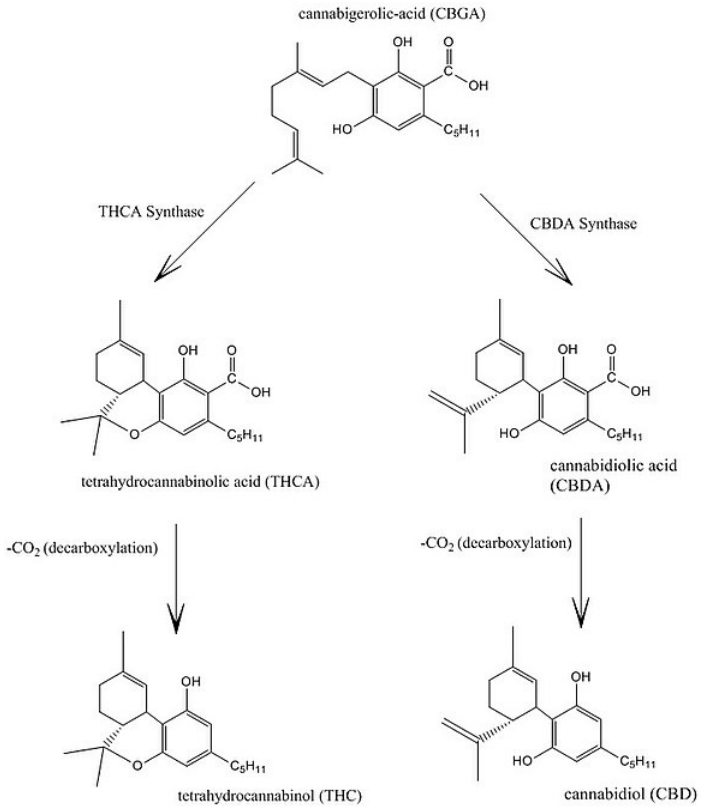
Cannabinoids in CKD, dialysis

- symptom management is a top research priority for dialysis patients
- cannabis has the biologic rationale for many symptoms and some evidence from the general population
- recent legalization of cannabis in Canada
- cultural acceptability
- our patients are using it
- we don’t know if it works
- we don’t know if its safe

- Research projects:
  - patient and physician surveys
  - PK study = single dose, multiple dose
  - pilot trials
  - RCT’s

Cannabinoids

- >100 cannabinoids are found in cannabis
- THC=delta-9 tetrahydrocannabinol = psychoactive effects
- CBD=cannabidiol = no psychoactive effects
- CB1, CB2 = endogenous G-protein couple cannabinoid receptors
- routes = inhaled, oral, transdermal
- THC and CBD are metabolized primarily by hepatic cytochrome P-450 3A4, 2C9
- THC, CBD and their metabolites are excreted in the urine 20-35% and feces 65-80% with <5% of a THC dose excreted unchanged in the urine
- No PK or PD data in dialysis

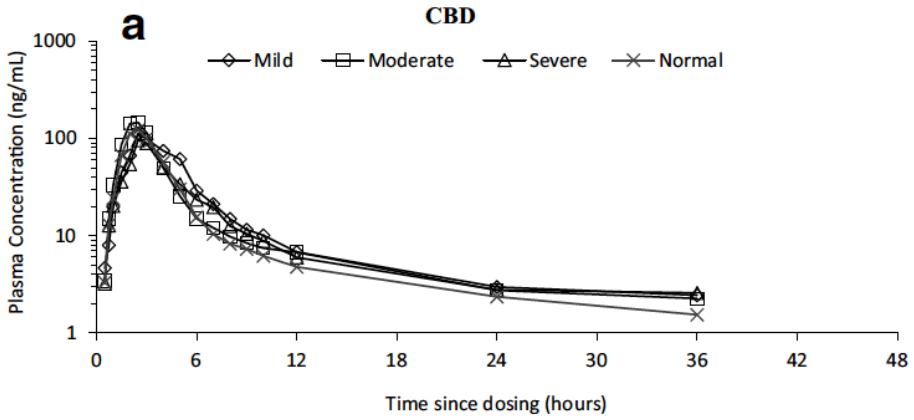


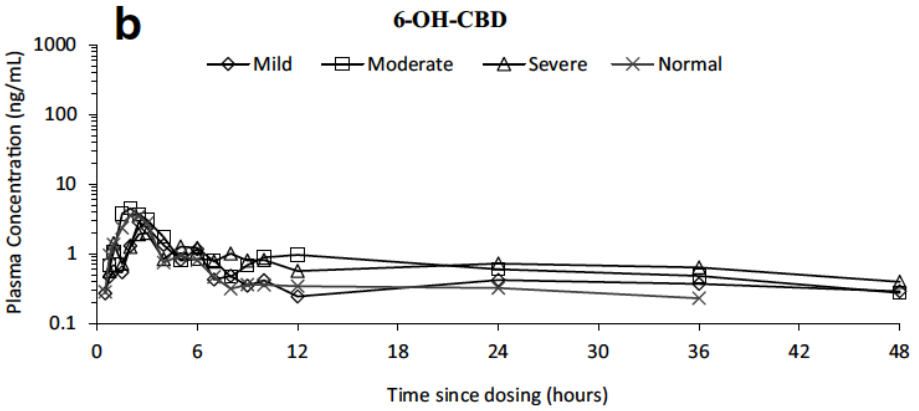
Grotenhermen F.
Clinical Pharmacokinetics
2003;42(4):327-60

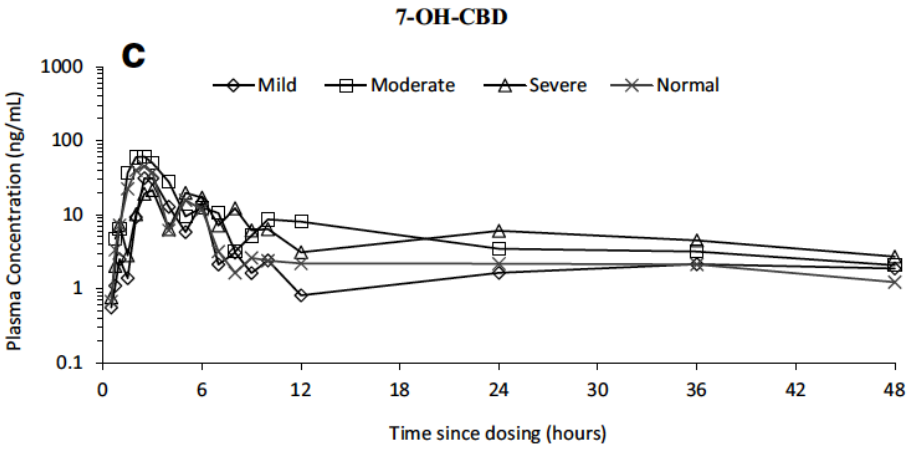
Lucas et al. BJCP 2018
Nov;84(11):2477-2482

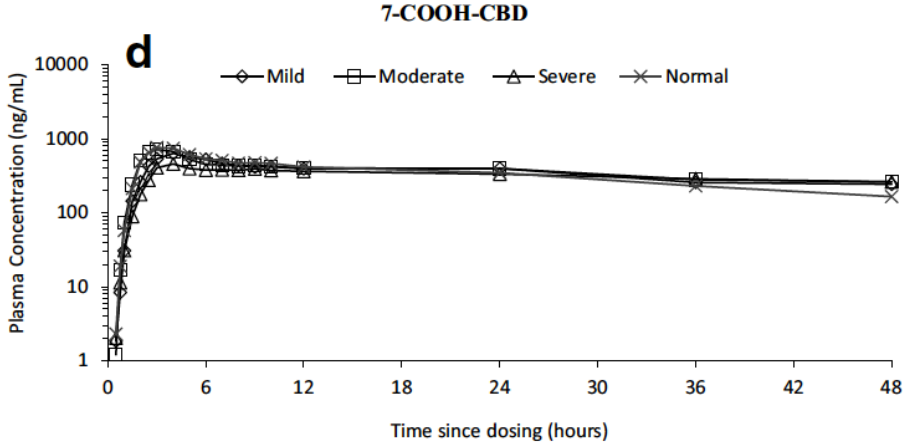
Pharmacokinetics of CBD

No difference in Cmax, tmax, AUC for CBD or its metabolites
No AE's in mild, moderate renal insufficiency









N=8 "normal"
CrCl 111.7 (31.8)
N=8 "mild"
CrCl 66.9 (8.3)
N=8 "moderate"
CrCl 40.0 (6.1)
N=8 "severe"
CrCl 21.7 (6.0)
matched by:
age, sex, BMI

Tayo et al.
Clinical Pharmacokinetics
2019

Cannabis for medical use

- chronic pain (cancer, neuropathic)
- chemotherapy induced nausea and vomiting
- multiple sclerosis associated spasticity
- HIV/AIDS
- seizure disorders (children)
- other

- CB1 and CB2 receptors
- central and peripheral nervous systems
- interact with many nerve pathways
- interact with many neurotransmitters
- many targets
- many effects

Cannabinoids in CKD and dialysis: physician survey

- n = 151 = 43.4% response rate
- 4/5 clinical experience with medicinal cannabinoids
  - chronic pain, appetite stimulation
- 1/5 prescription experience with medicinal cannabinoids
  - chronic pain, appetite stimulation
- 9/10 experience with non-prescription cannabis
  - recreational
  - symptoms
- 4/10 personal use of cannabis
- 1/10 recent use of cannabis since legislation
- multilevel linear regression: only symptom and province were independent predictors, not practice vintage, sex/gender, clinical experience, prescription experience, personal use

Figure 1: Likelihood of supporting treatment with cannabinoids

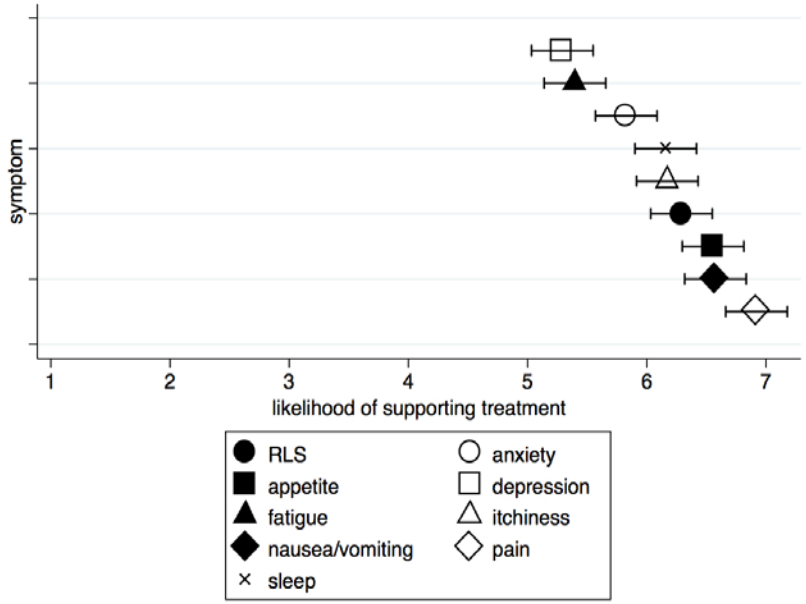
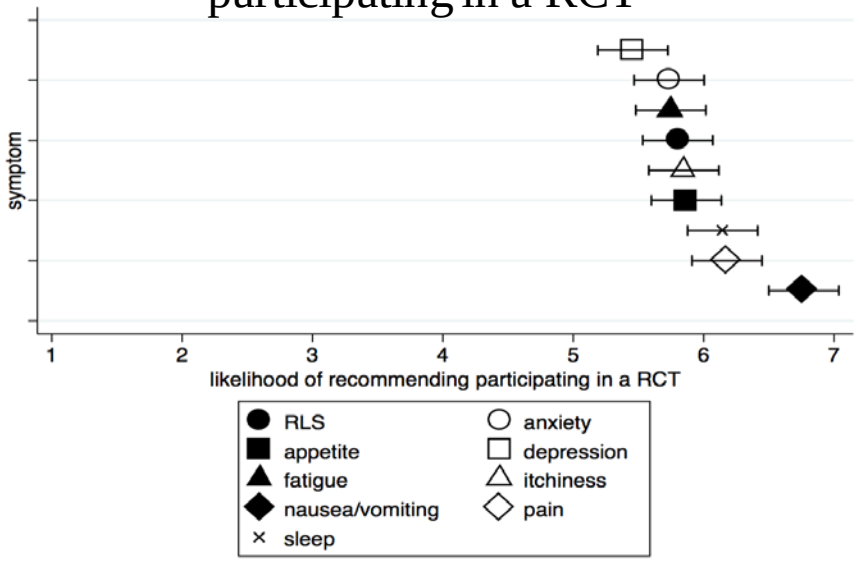
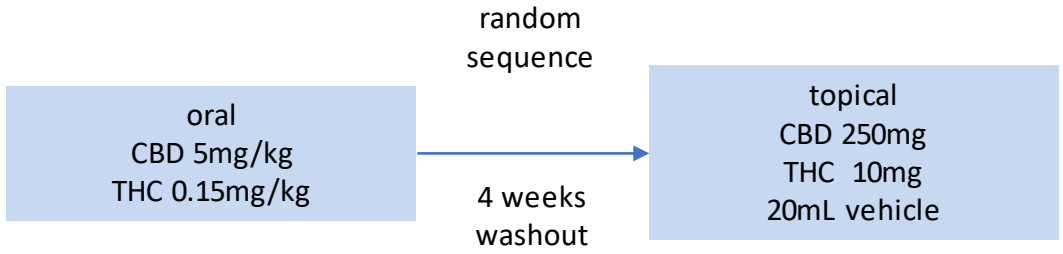


Figure 2: Likelihood of recommending participating in a RCT



PK Study of THC, CBD in dialysis



n=10 (5 men, 5 women)
prevalent ICHD with tunneled catheter
no liver dysfunction
no recent cannabis <30 days
no pregnancy or breastfeeding
no safety concerns
(dependency, CV, psychiatric, tolerability)

Time	-4 hours	-3 hours	-2 hours	-1.5 hours	-1 hour	-0.5 hours	HD Start t = 0	+1 hours	+2 hours	middle of HD	+3 hours	HD finish	HD finish +15 mins	HD finish +60 mins	+24 hours	pre-HD +48 hours
Blood cannabinoids	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dialysate cannabinoids										X						
24 hour urine cannabinoids							X	X	X	X	X	X	X	X	X	

THC, 11-OHTHC, THCCOOH, THC-glucuronide, THCCOOH-glucuronide, CBD and its metabolites measured by MSI-CE-MS

DISCO-POT

Eligibility Assessment

Key inclusion criteria: age≥18 years on in-center hemodialysis ≥3x weekly for >90 days with generalized uremic pruritus >2 days per week and VAS ≥50mm, able to provide informed consent

***Key exclusion criteria*:** etiology of pruritus secondary to primary dermatologic condition, liver disease, hematologic malignancy or allergy, hospitalization within previous 4 weeks, pregnancy, planned kidney transplantation, travel or relocation in the next 6 months

Informed Consent

Run-in Period
Open label oral CBD for 4 weeks

Final Eligibility Assessment
Adherence>24/28 days by pill counts
Tolerates oral CBD

2 weeks washout

Treatment A = oral CBD+topical placebo
Treatment B = oral placebo+topical CBD
Treatment C = oral placebo +topical placebo

Randomization

Treatment A	Treatment B	Treatment C	2 weeks
Treatment B	Treatment C	Treatment A	2 weeks
Treatment C	Treatment A	Treatment B	2 weeks

Each 2 week treatment period is followed by a 2 week washout period prior to crossover

Possible sequences: ABC, ACB, BAC BCA, CAB, CBA

Follow-up
Cycle 1: weeks 1, 2, 4, 5, 6, 8, 9, 10, 12
Cycle 2: weeks 13, 14, 16, 17, 18, 20, 21, 22, 24
Cycle 3: weeks 25, 26, 28, 29, 30, 32, 33, 34, 36

Schedule of follow-up

				Treatment period = 12 weeks*									
				Sequence 1 = 4 weeks			Sequence 2 = 4 weeks			Sequence 3 = 4 weeks			End of study visit
Visit	Recruitment	Run-in	Rand	3 weeks	Dialysis sessions between 3-4 weeks°	4 weeks	3 weeks	Dialysis sessions between 3-4 weeks°	4 weeks	3 weeks	Dialysis sessions between 3-4 weeks°	4 weeks	1 week
Window		+3 days	0	-3 to +5 days	N/A	-3 to +5 days	-3 to +5 days	N/A	-3 to +5 days	-3 to +5 days	N/A	-3 to +5 days	+5 days
Informed Consent	X												
Eligibility Criteria	X		X										
Demographics	X												
Adherence		X		X		X	X		X	X		X	
Drug Dispension		X	X			X			X			X	
Medications	X		X			X			X			X	
Co-interventions	X		X			X			X			X	
VAS	X	X	X	X	X	X	X	X	X	X	X	X	
NRS		X	X	X	X	X	X	X	X	X	X	X	
VRS		X	X	X	X	X	X	X	X	X	X	X	
DLQI		X	X	X		X	X		X	X		X	
EQ-5D-5L		X	X	X		X	X		X	X		X	
HADS		X	X	X		X	X		X	X		X	
IRLS		X	X	X		X	X		X	X		X	
PSQI		X	X	X		X	X		X	X		X	
ESAS		X	X	X		X	X		X	X		X	
SAE Assessment			X	X		X	X		X	X		X	X
Drug intolerance			X	X		X	X		X	X		X	X
Blinding Assessment				X			X			X			

Future trials of cannabinoids for symptoms in dialysis

- chronic pain
- nausea/vomiting
- cachexia/appetite stimulant NCT03664141
- sleep
- RLS
- ???mood disorders
- ???fatigue

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- KRESCENT
- DISCO investigators, participants

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

McMaster University

Can-SOLVE CKD Network

Michael G. DeGroote
CENTRE FOR MEDICINAL CANNABIS RESEARCH

CNTN|RCEN
Canadian Nephrology Trials Network
Réseau canadien d'essais cliniques en néphrologie

Krescent
Kidney Research Scientist Core Education and National Training Program