ANTE
Associazione Nazionale Tecnici Emodialisi

XXXI Corso Nazionale ANTE - Dialisi e Tecnologia

"Evoluzione tecnologica nei trattamenti dialitici cronici e acuti: dalla teoria alla pratica"

La qualità di vita del paziente in emodialisi: nuovi approcci farmacologici per la gestione del prurito, della qualità del sonno e della depressione

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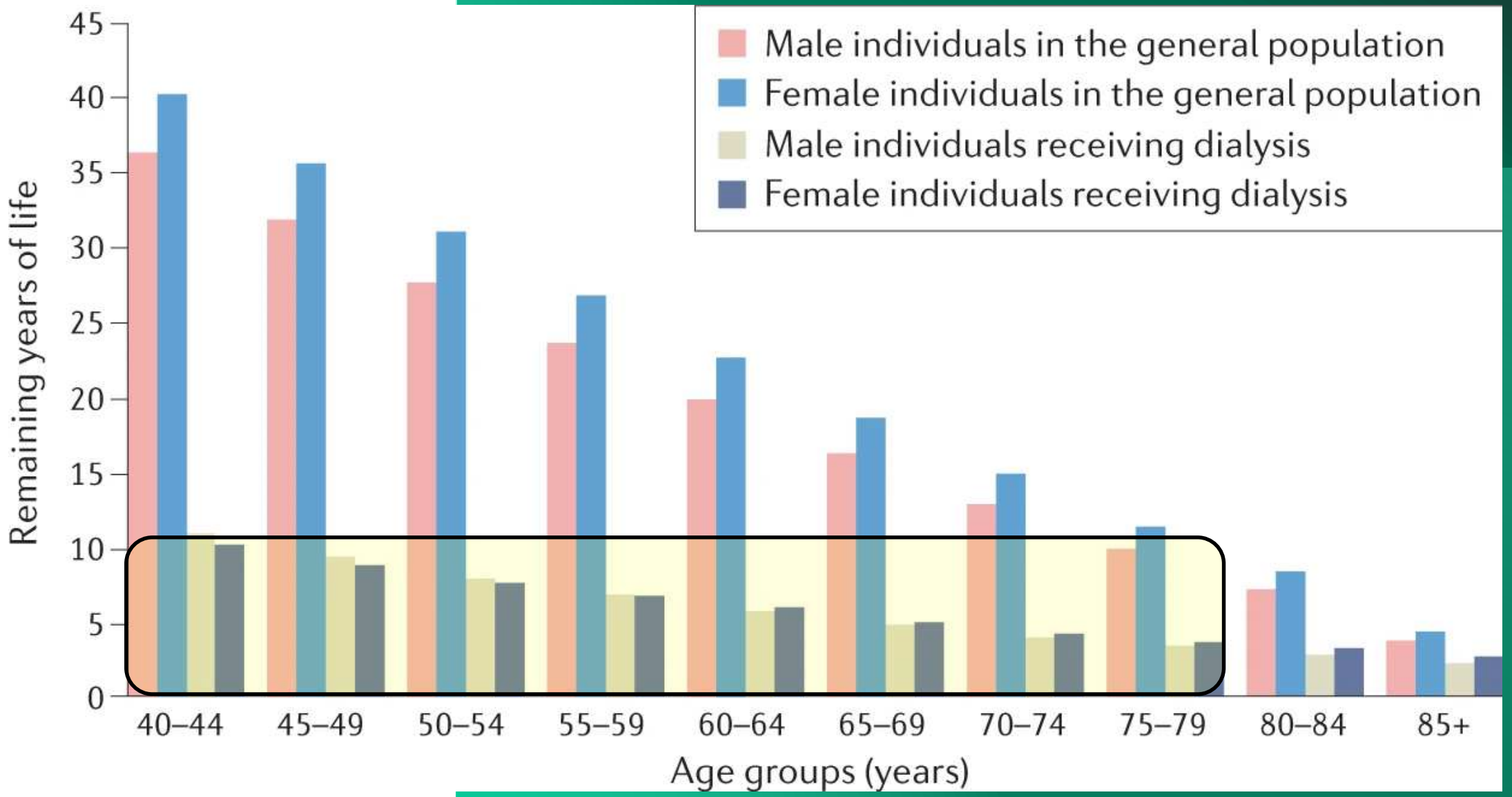
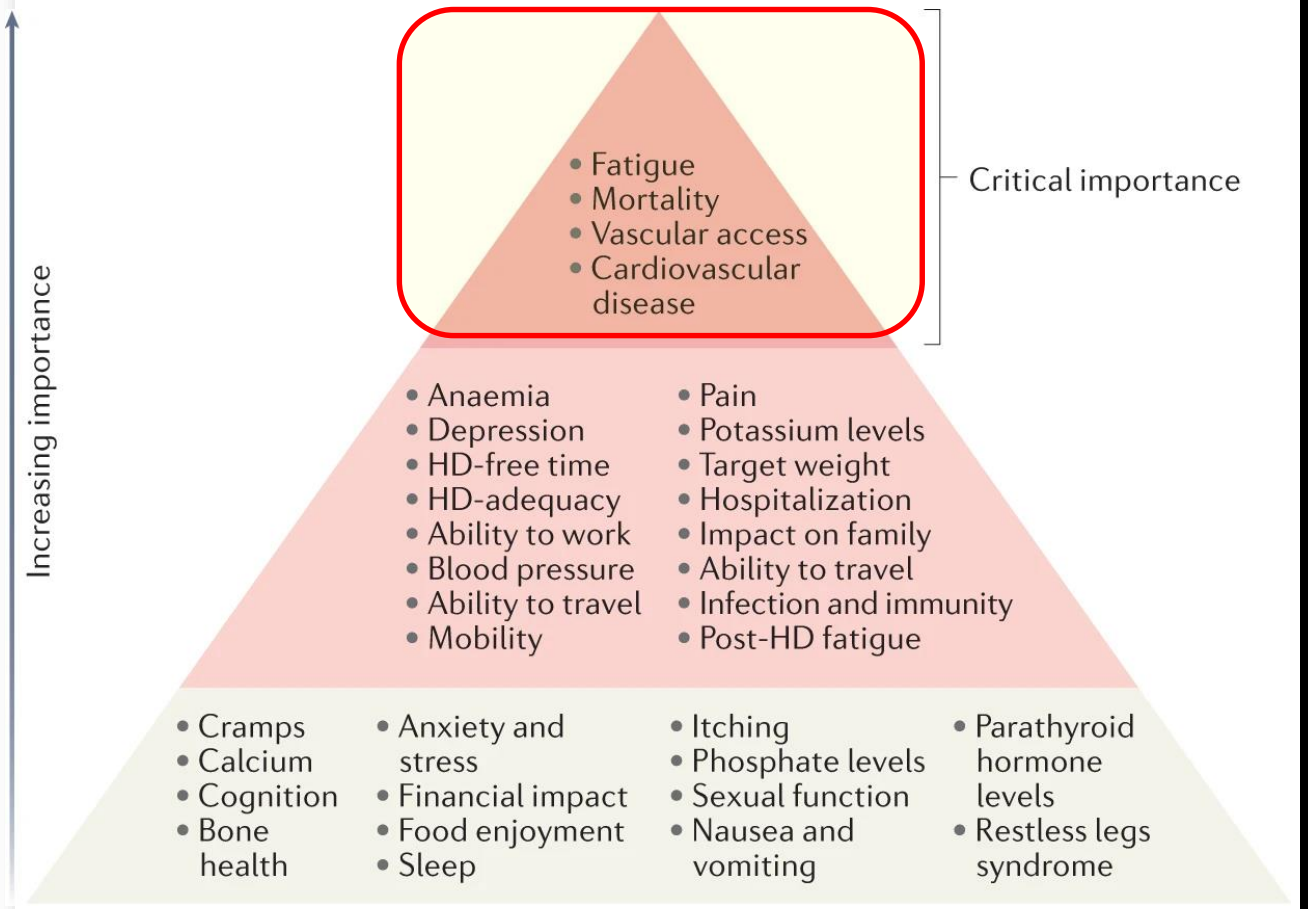


Nature Reviews Nephrology volume 18, pages378–395 (2022)

Hierarchy of importance of haemodialysis outcomes to patients, caregivers and clinicians.



Nature Reviews Nephrology volume 18, pages378–395 (2022)

Box 2 | **Risk factors for hospitalization in patients receiving haemodialysis**

Nutrition and inflammation

- Low body mass index (<20 kg/m²)
- Hypophosphataemia
- Hyponatraemia
- Hypoalbuminaemia
- Anaemia
- Poor malnutrition assessment scores (for example, malnutrition inflammation score or subjective global assessment of malnutrition)
- High p-cresol sulfate
- Poor or very poor self-reported appetite
- Hyperkalaemia owing to high dietary potassium intake

Comorbidities

- High Charlson comorbidity score
- Type 2 diabetes
- Cardiovascular disease
- Peripheral vascular disease
- Cerebrovascular disease
- Cancer
- Chronic obstructive pulmonary disease
- Hepatitis C virus infection
- Frailty

Demographic factors

- Limited health literacy
- Smoking
- Minority ethnicity
- Older age

Psychosocial factors

- Depression
- Anxiety symptoms
- Poor social support
- Low self-efficacy

Dialysis access and facility support

- Use of central venous catheter for vascular access
- Treatment in a centre with a high patient-to-staff ratio
- Non-adherence to dialysis treatment (missed or shortened dialysis sessions)

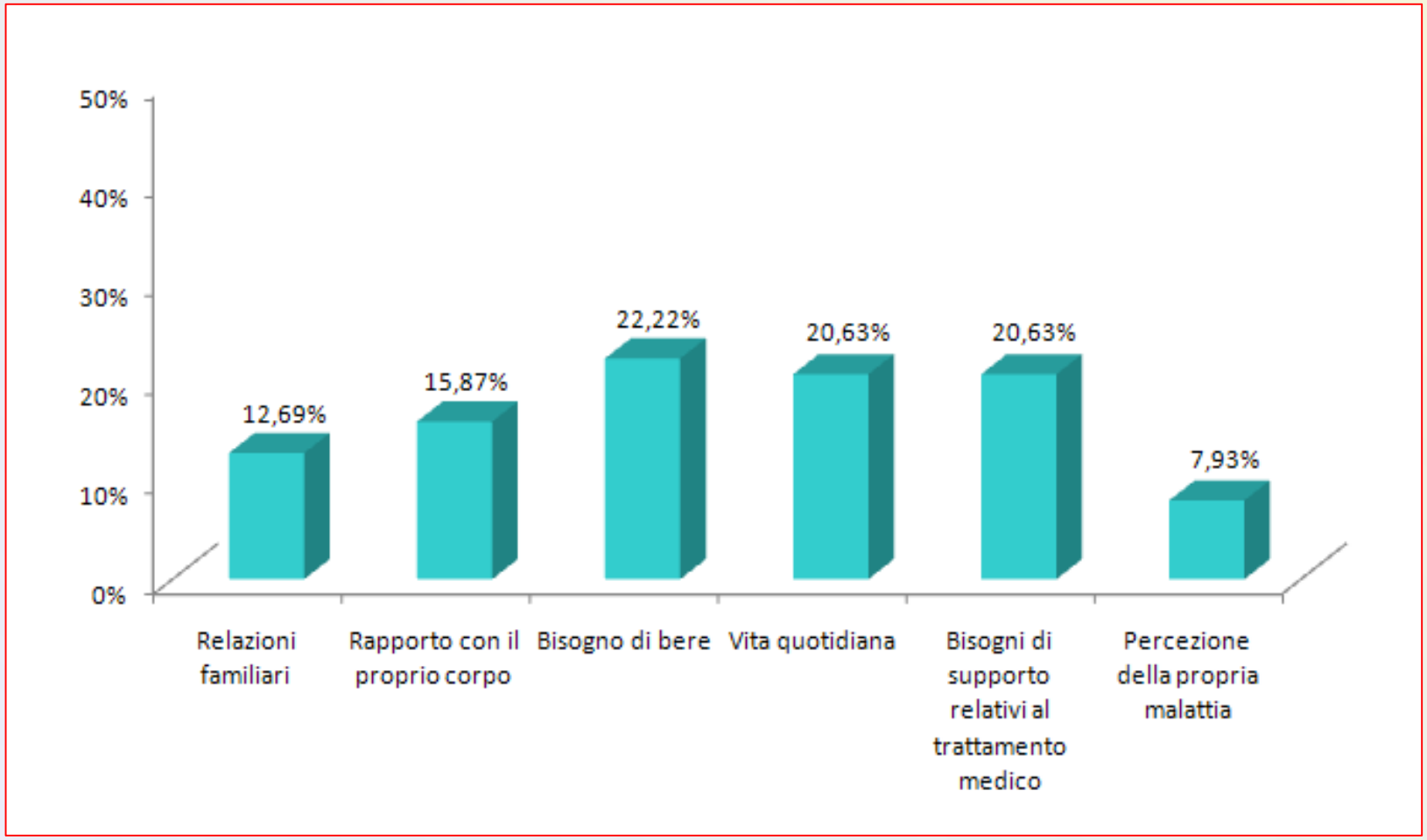
Others

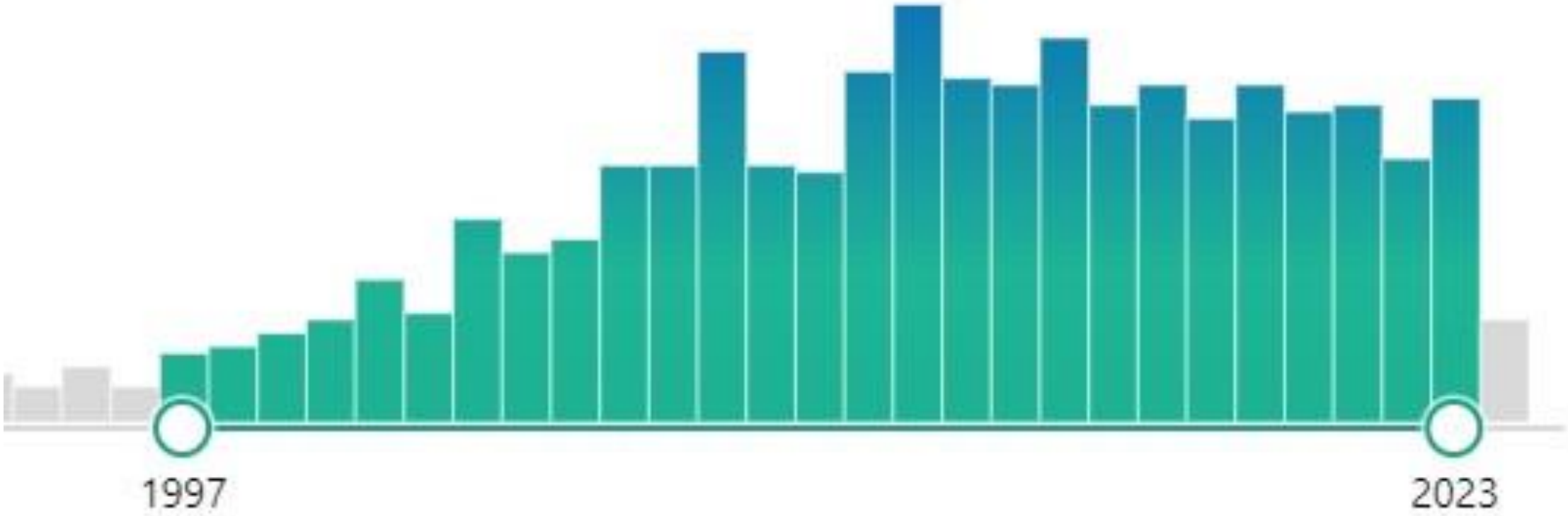
- High (>4%) inter-dialytic weight gain
- Previous history of hospitalization or emergency department visit
- Residence in a nursing facility

Patient-reported outcomes in patients receiving haemodialysis

Measure	Definition	Prevalence or Incidence	Clinical impact	Refs
Fatigue	Subjective, complex and multidimensional experience (for example, weakness and/or lethargy) that encompasses both physical and psychological domains	Widely variable prevalence; 60–97%	Reduced sleep quality; poor QOL; increased risk of CVD, hospitalization and all-cause mortality	
Life participation	Ability to engage in everyday life events (for example, work, travel, recreation, study and/or physical activity)	Prevalence is highly variable and difficult to measure; influenced by multiple factors: method of HD delivery (in-centre HD versus home HD), treatment schedule, need for repeated invasive procedures, HD symptoms (for example, post-dialysis fatigue) and complications (for example, pruritus, dizziness or headaches)	Affects patients' choices of treatment and modalities, as well as outcomes; can impact QOL	
Depression	A mood disorder that causes a persistent feeling of sadness and loss of interest in everyday life activities, and leads to a variety of emotional and physical consequences	Variable; global representative data suggest a prevalence of 22.8% (95% CI 18.6–27.6%) based on interview and 39.3% (95% CI 36.8–42.0%) based on self-report scales	Increased risk of mortality, hospitalizations, non-adherence to dialysis and lower HR-QOL	
Anxiety	Anticipation of a future concern; associated with muscular tension and avoidance behaviour	Variable; systematic review of 61 observational studies from Europe, North America, Asia and Africa reported a high prevalence (42%) of elevated anxiety symptoms	Increased risk of functional symptoms such as depression; affects mineral bone metabolism (decreased parathyroid hormone levels); increased length of hospitalization and decreased perceived QOL and vitality levels	
Cramps	Intradialytic painful involuntary musculature contraction	Incidence 24–86%	Reduced quality of dialysis (reduced time on treatment and interruptions); reduced QOL	
Pain	Localized or generalized unpleasant bodily sensation leading to mild to severe physical discomfort and emotional distress	A systematic review and meta-analysis of 48 studies involving 8,464 patients from 23 countries reported a 60.5% mean prevalence of chronic pain	Insomnia and depression; reduced QOL	
Pruritus	Unpleasant skin sensation that provokes a desire to scratch for relief	A large prospective study reported that 42% of 18,801 experienced moderate to extreme pruritus	Increased mortality risk; poor sleep; reduced QOL; depression	
Restless legs syndrome	Desire to move the extremities, associated with paraesthesias and/or dysaesthesias, motor restlessness and worsening of symptoms at rest with at least temporary relief by activity	Variably reported; prevalence 12–62%	Sleep disturbances; decreased QOL; premature withdrawal from dialysis; increased CVD morbidity and mortality	
Sexual dysfunction	Persistent, recurrent problems with sexual response, desire, orgasm or pain that affect sexual relationships	A systematic review found that the prevalence of erectile dysfunction in male patients was 75% (95% CI 72–77%) Only one study reported on sexual dysfunction in 138 female patients, and observed a prevalence of 29.7%	Decreased QOL; increased risk of CVD morbidity and mortality	
Sleep quality	A measure of whether sleep is restful and restorative	An assessment of sleep quality in 11,351 patients from 308 HD units in 7 countries reported a 49% prevalence of poor sleep quality	Increased mortality; increased risk of CVD; decreased QOL	

Qualità della vita rimane insoddisfacente anche per l'insorgenza di alterazioni psico-fisiche





Pubblicazioni Disturbi del Sonno e Dialisi

How does sleep disturbance affect hemodialysis patients?

Kidney Medicine

Methods and Cohort

Adults on maintenance HD with OSA **(n = 36)**

Polysomnogram & Epworth Sleepiness Scale (ESS)

Interview to explore patient experience **(n = 26)**

Findings

Severity of sleep apnea did not affect patients' sleep duration, sleep efficiency or ESS.

However,

70% reported broken sleep

62% felt unrefreshed upon wakening

Themes from Interview

Broken sleep

Feeling unrefreshed

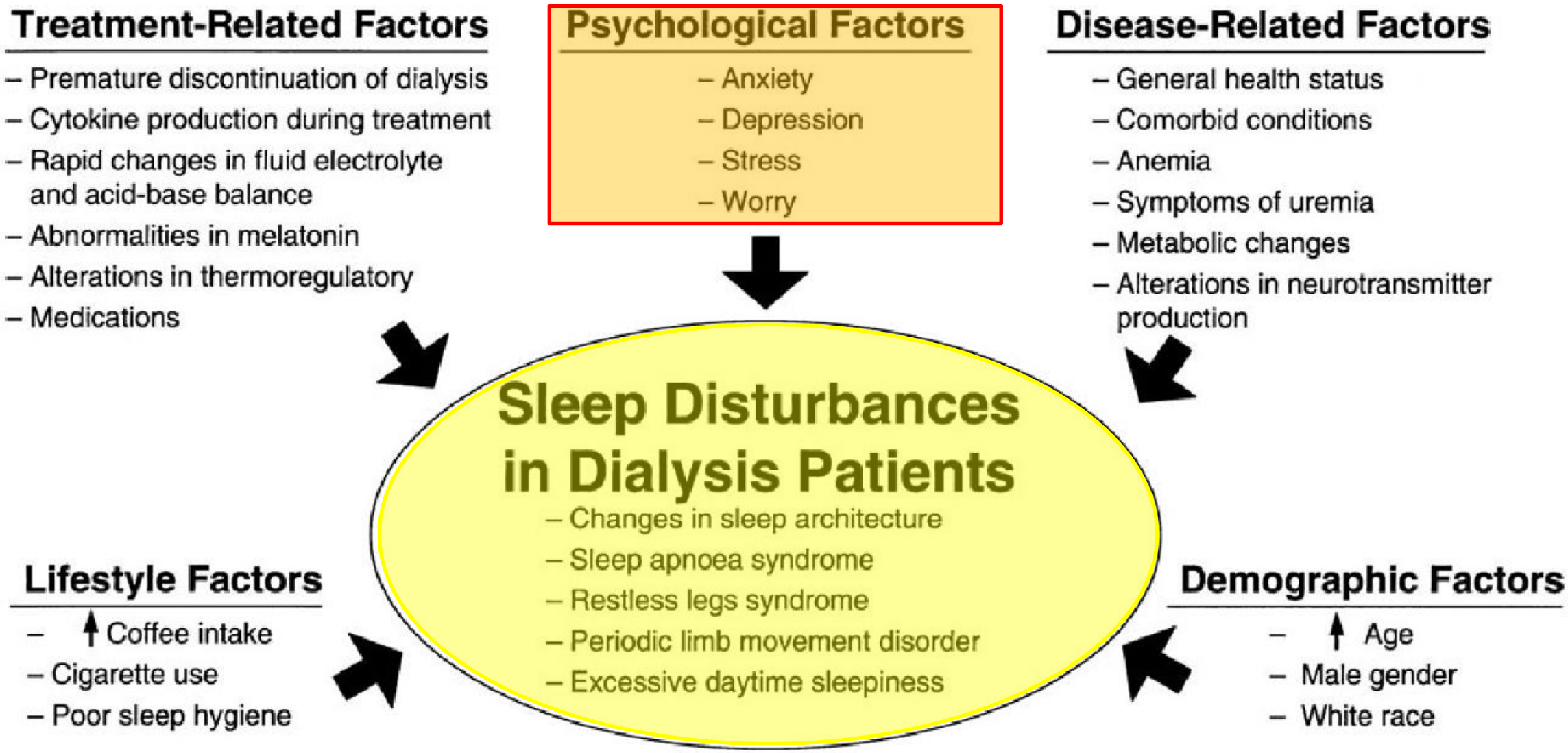
Impact of poor sleep

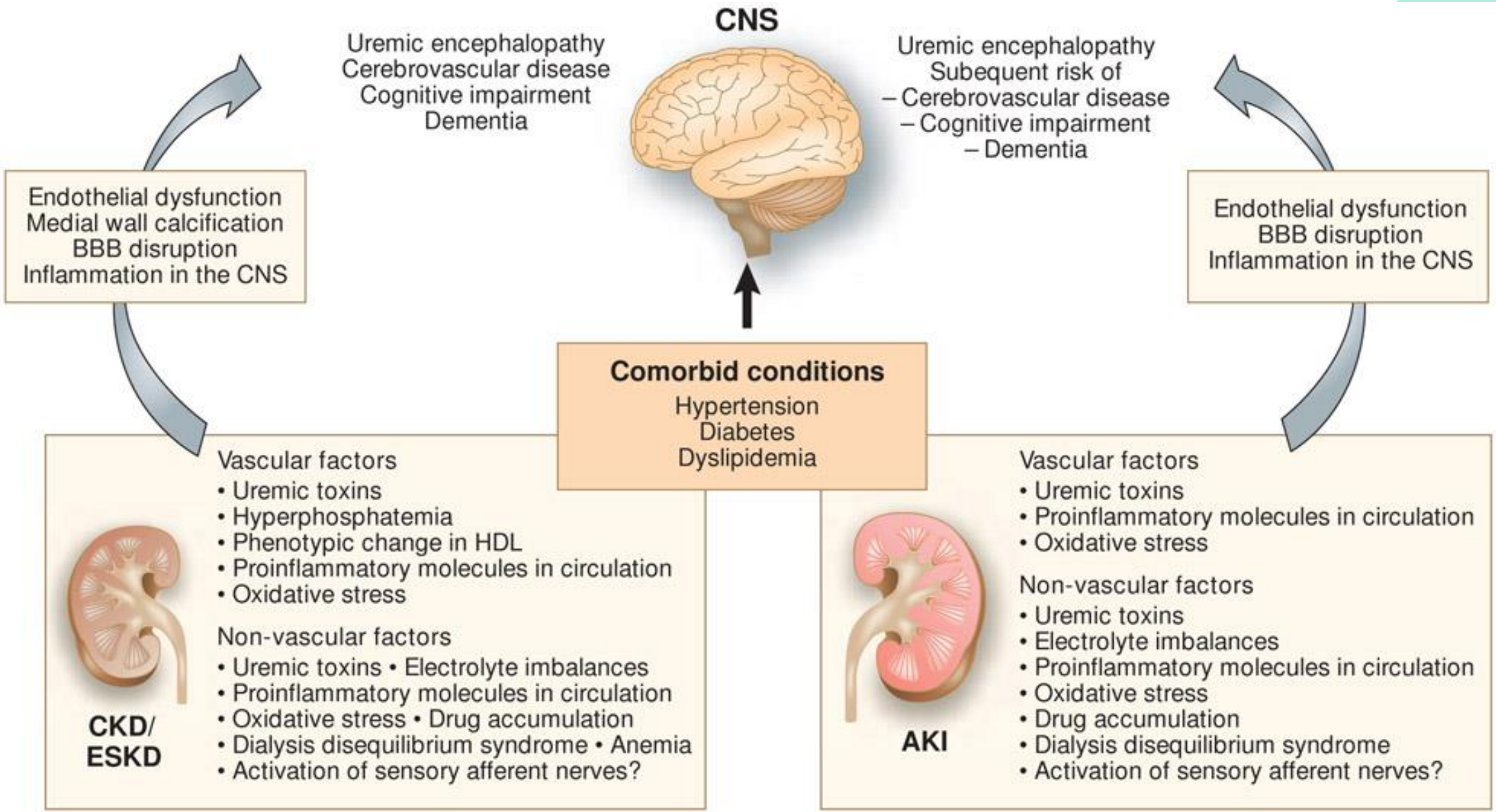
Having to "soldier on"

Conclusion: Sleep disturbance is common and has a profound impact on health and QoL of hemodialysis patients. The conflicting message between patient interview and self-reported questionnaires indicate a need for multidisciplinary approaches and improved patient communication to truly capture the health needs of individuals.

Reference: Chu G, Price E, Paech G, Choi P and McDonald V. Sleep apnea in maintenance hemodialysis: a mixed methods study. *Kidney Medicine*, 2020

Visual Abstract by Anna R Gaddy, MD @AnnaGaddy


Treatment-Related Factors
– Premature discontinuation of dialysis
– Cytokine production during treatment
– Rapid changes in fluid electrolyte and acid-base balance
– Abnormalities in melatonin
– Alterations in thermoregulatory
– Medications
Psychological Factors
– Anxiety
– Depression
– Stress
– Worry
Disease-Related Factors
– General health status
– Comorbid conditions
– Anemia
– Symptoms of uremia
– Metabolic changes
– Alterations in neurotransmitter production
Sleep Disturbances in Dialysis Patients
– Changes in sleep architecture
– Sleep apnoea syndrome
– Restless legs syndrome
– Periodic limb movement disorder
– Excessive daytime sleepiness
Lifestyle Factors
– ↑ Coffee intake
– Cigarette use
– Poor sleep hygiene
Demographic Factors
– ↑ Age
– Male gender
– White race


CNS
Uremic encephalopathy
Cerebrovascular disease
Cognitive impairment
Dementia
Uremic encephalopathy
Subequent risk of
– Cerebrovascular disease
– Cognitive impairment
– Dementia
Endothelial dysfunction
Medial wall calcification
BBB disruption
Inflammation in the CNS
Endothelial dysfunction
BBB disruption
Inflammation in the CNS
Comorbid conditions
Hypertension
Diabetes
Dyslipidemia
Vascular factors
• Uremic toxins
• Hyperphosphatemia
• Phenotypic change in HDL
• Proinflammatory molecules in circulation
• Oxidative stress
Non-vascular factors
• Uremic toxins • Electrolyte imbalances
• Proinflammatory molecules in circulation
• Oxidative stress • Drug accumulation
• Dialysis disequilibrium syndrome • Anemia
• Activation of sensory afferent nerves?
CKD/
ESKD
Vascular factors
• Uremic toxins
• Proinflammatory molecules in circulation
• Oxidative stress
Non-vascular factors
• Uremic toxins
• Electrolyte imbalances
• Proinflammatory molecules in circulation
• Oxidative stress
• Drug accumulation
• Dialysis disequilibrium syndrome
• Activation of sensory afferent nerves?
AKI

Quadro Clinico

Encefalopatia uremica:

alterazioni della personalità irritabilità
sindrome ansiosa
difficoltà all'attenzione
perdita della memoria

turbe del sonno

depressione maggiore, soprattutto nei pazienti che vanno incontro a trattamento sostitutivo (Levy NB et al 1994).

Prevalenza

Table 2. Recent studies evaluating prevalence and outcomes of depression in CKD

First author, year, ref	Sample characteristics	Measurement tool for depression	Depression prevalence	Follow-up	Outcomes of depression
Hedayati, 2010[22]	267 Patients with stage 2–5 CKD	DSM-IV interview (MDE diagnosis)	21%	1 yr	- Composite of death, hospitalization, or ESRD: HR = 1.86 - Hospitalization: HR = 1.90 - ESRD: HR 3.51
Fischer, 2011[7]	628 Patients with stage 2–4 CKD	BDI-II score > 14 or ≥11	26 or 42%	5 yr	- Composite of CV death or hospitalization
Kop, 2011[19]	5785 Patients, average GFR 78	CES-D ≥ 8	21.2%	14 yr	- AKI
Cukor, 2012[4]	70 Patients with stage 1–4 CKD	BDI-II score ≥14	30%	6 mo	- Worse QOL, social support, community integration - Greater decline in GFR
Fischer, 2012[20]	3853 Patients with stage 2–4 CKD	BDI-II score ≥ 11	27.4%	None	
Tsai, 2012[8]	428 Patients with stage 3–5 CKD	BDI-II score ≥ 11	37%	4 yr	- Composite of ESRD or death: HR = 1.66 - First hospitalization: HR = 1.59 - Faster GFR decline - Initial dialysis at a higher GFR
Lee, 2013[5]	208 Patients with stage 3–5 CKD	HADS-D ≥ 8	47.1%	None	- Worse QOL
Chiang, 2015[23]	262 Patients (60.3% stage 4 and above)	Taiwanese Depression Questionnaire	21%	3 yr	- Composite of dialysis or death: HR = 2.95 - ESRD: HR = 2.25 - Mortality: HR 3.08

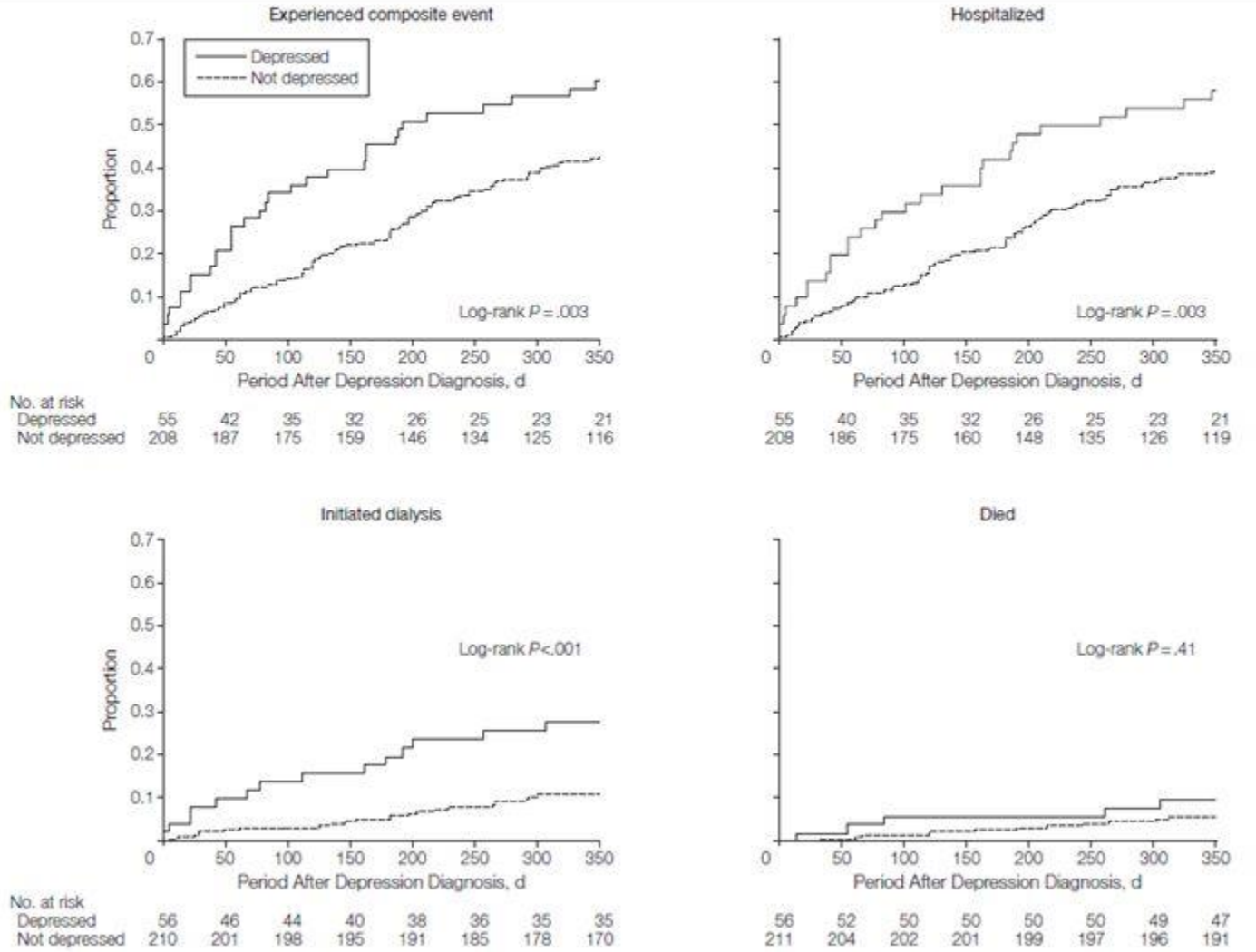
AKI, acute kidney injury; BDI, Beck Depression Inventory; CESD, Center for Epidemiologic Studies Depression Scale; CKD, chronic kidney disease; DSM IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HADS-D, Hospital Anxiety and Depression Scale—depression subscale; HR, hazard ratio; MDE, major depressive episode; QOL, quality of life; ref, reference.

The prevalence of depression is 3 to 4 times higher in patients with CKD and ESRD compared with the general population and 2 to 3 times higher compared to individuals with other chronic illnesses.

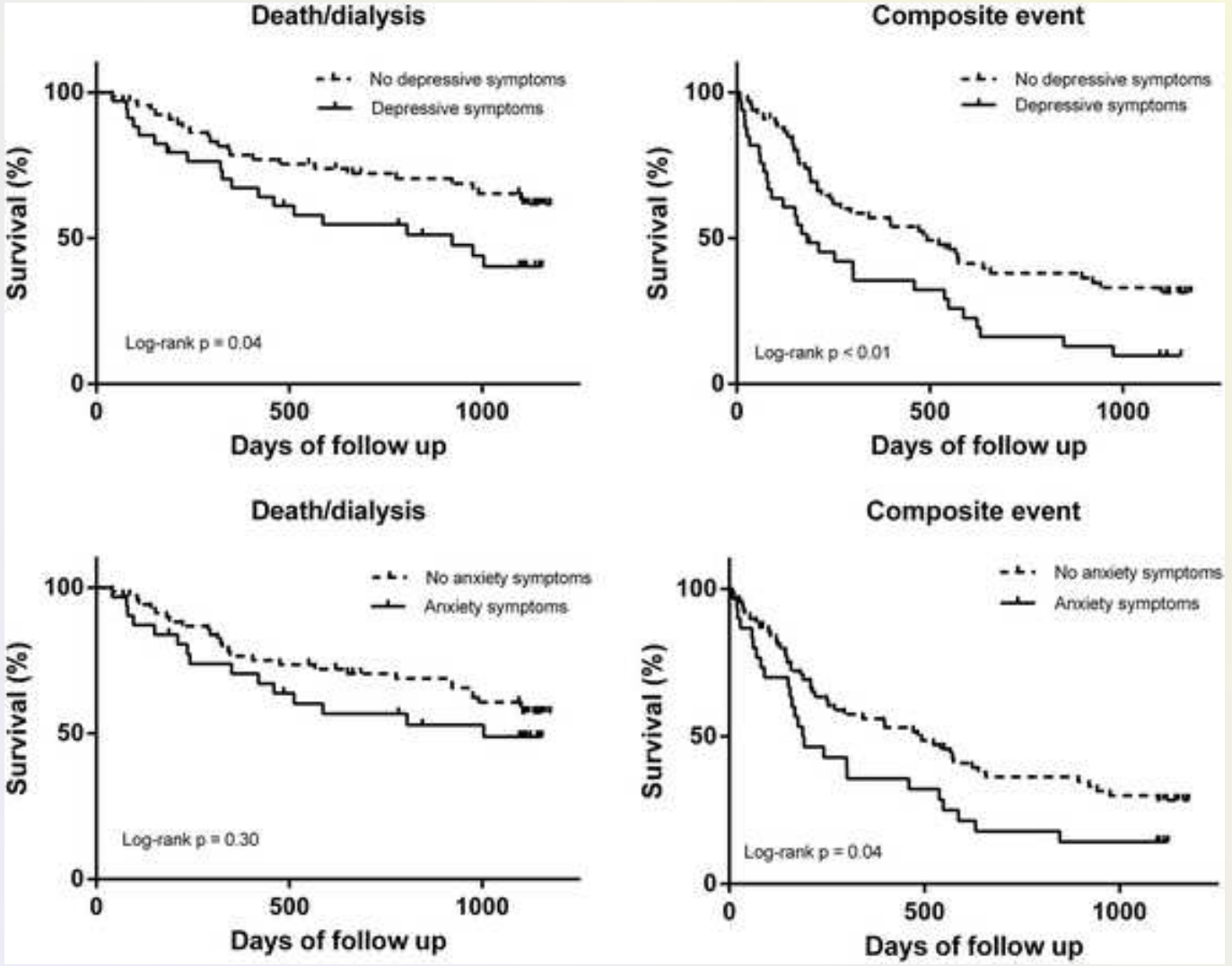
Kidney Int Rep (2017) 2, 94–107

Association Between Major Depressive Episodes in Patients With Chronic Kidney Disease and Initiation of Dialysis, Hospitalization, or Death

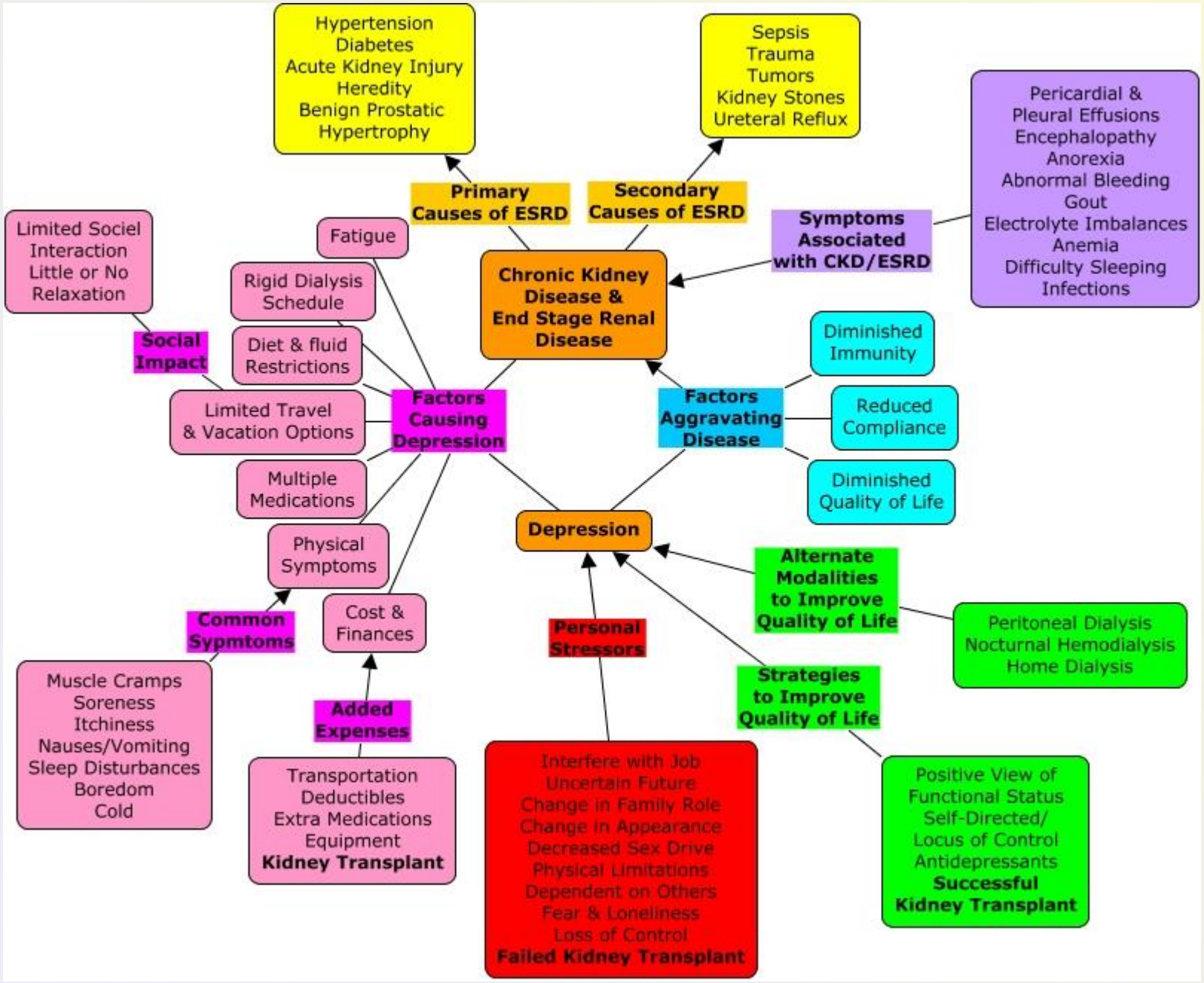
Figure 2. Survival Curves for Outcome Measures



Sopravvivenza

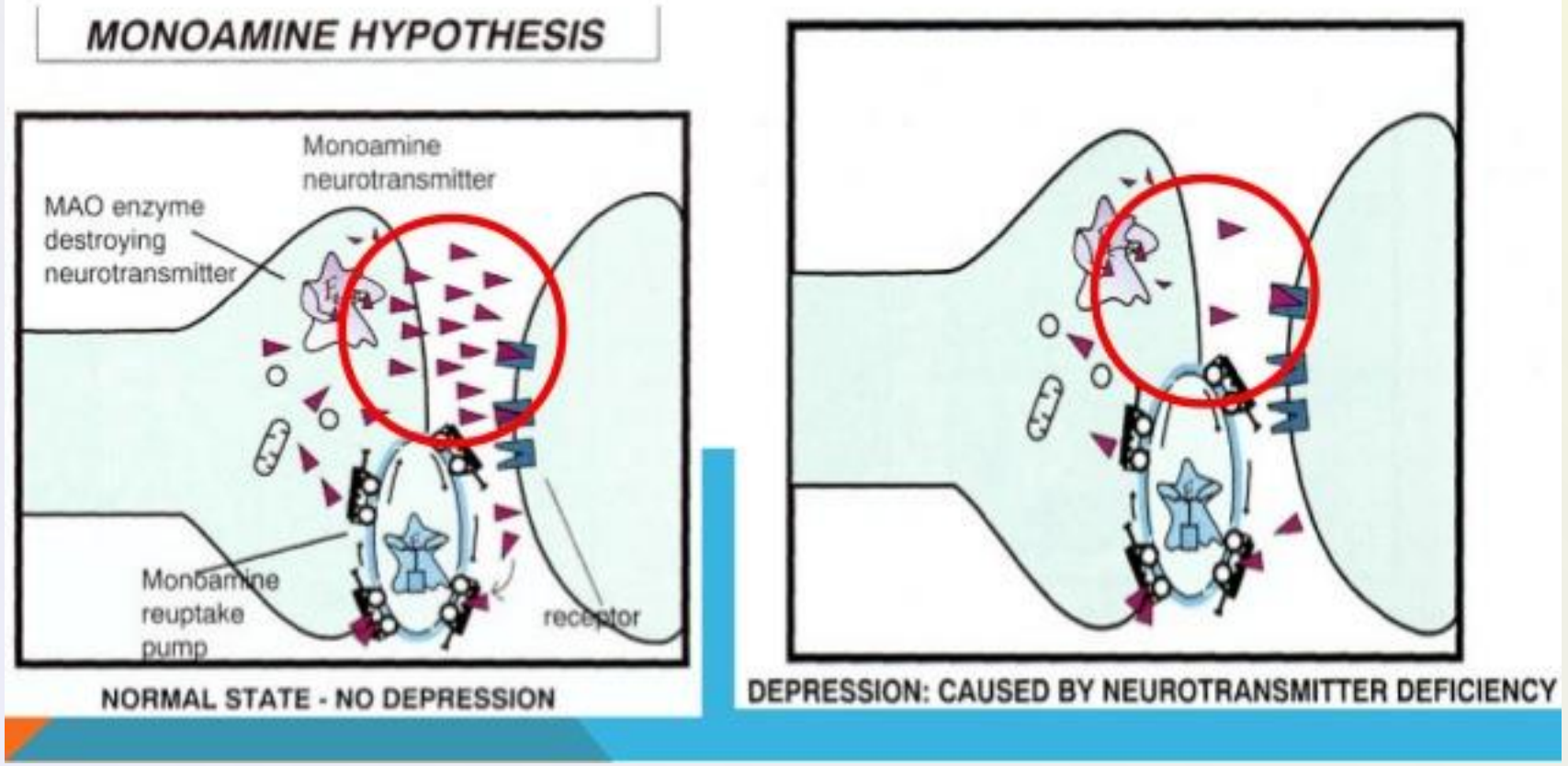


BMC Nephrology 2015; 16:155


Hypertension
Diabetes
Acute Kidney Injury
Heredity
Benign Prostatic Hypertrophy
Sepsis
Trauma
Tumors
Kidney Stones
Ureteral Reflux
Pericardial & Pleural Effusions
Encephalopathy
Anorexia
Abnormal Bleeding
Gout
Electrolyte Imbalances
Anemia
Difficulty Sleeping
Infections
Primary Causes of ESRD
Secondary Causes of ESRD
Symptoms Associated with CKD/ESRD
Chronic Kidney Disease & End Stage Renal Disease
Limited Societ Interaction
Little or No Relaxation
Fatigue
Rigid Dialysis Schedule
Diet & fluid Restrictions
Social Impact
Limited Travel & Vacation Options
Factors Causing Depression
Multiple Medications
Physical Symptoms
Cost & Finances
Diminished Immunity
Reduced Compliance
Diminished Quality of Life
Factors Aggravating Disease
Depression
Alternate Modalities to Improve Quality of Life
Peritoneal Dialysis
Nocturnal Hemodialysis
Home Dialysis
Common Sypmtoms
Muscle Cramps
Soreness
Itchiness
Nauses/Vomiting
Sleep Disturbances
Boredom
Cold
Added Expenses
Transportation
Deductibles
Extra Medications
Equipment
Kidney Transplant
Personal Stressors
Interfere with Job
Uncertain Future
Change in Family Role
Change in Appearance
Decreased Sex Drive
Physical Limitations
Dependent on Others
Fear & Loneliness
Loss of Control
Failed Kidney Transplant
Strategies to Improve Quality of Life
Positive View of
Functional Status
Self-Directed/
Locus of Control
Antidepressants
Successful Kidney Transplant

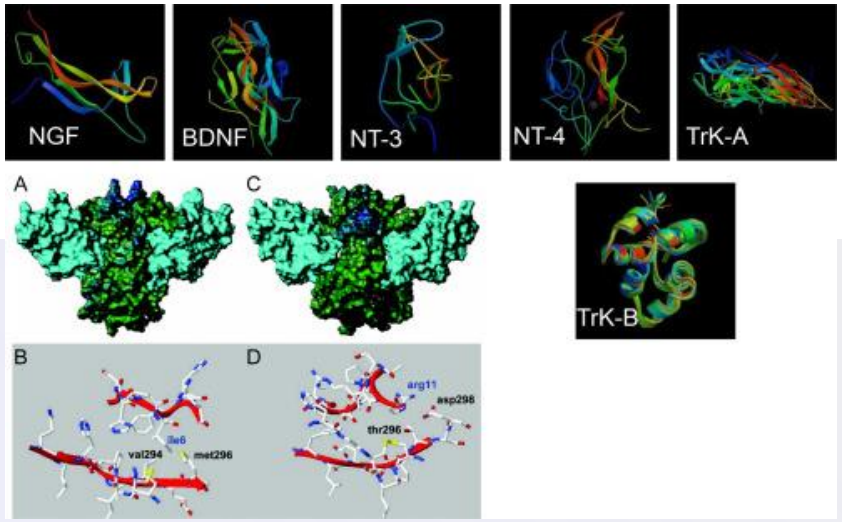
BIOCHEMICAL BASIS OF DEPRESSION

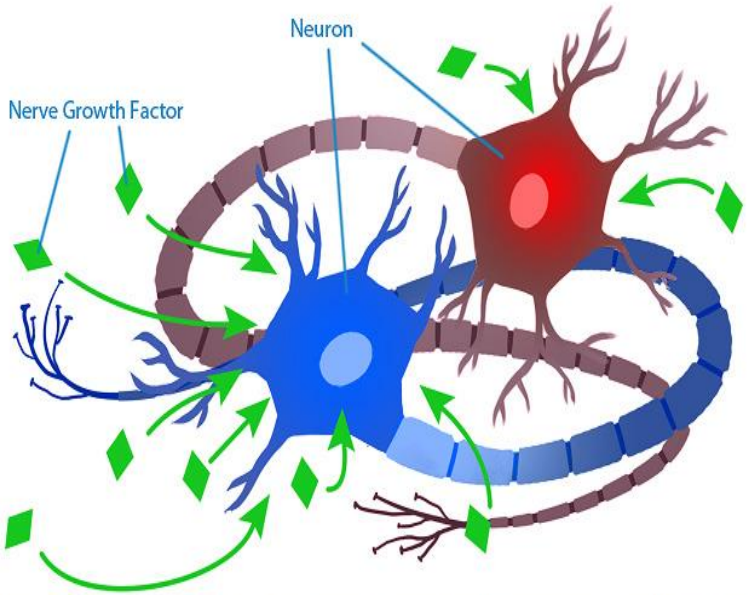
Monoamine Hypothesis: depression was due to a deficiency of monoamine neurotransmitters, notably nor-epinephrine (NE) and serotonin (5-hydroxytryptamine [5HT])



Neurotrophins

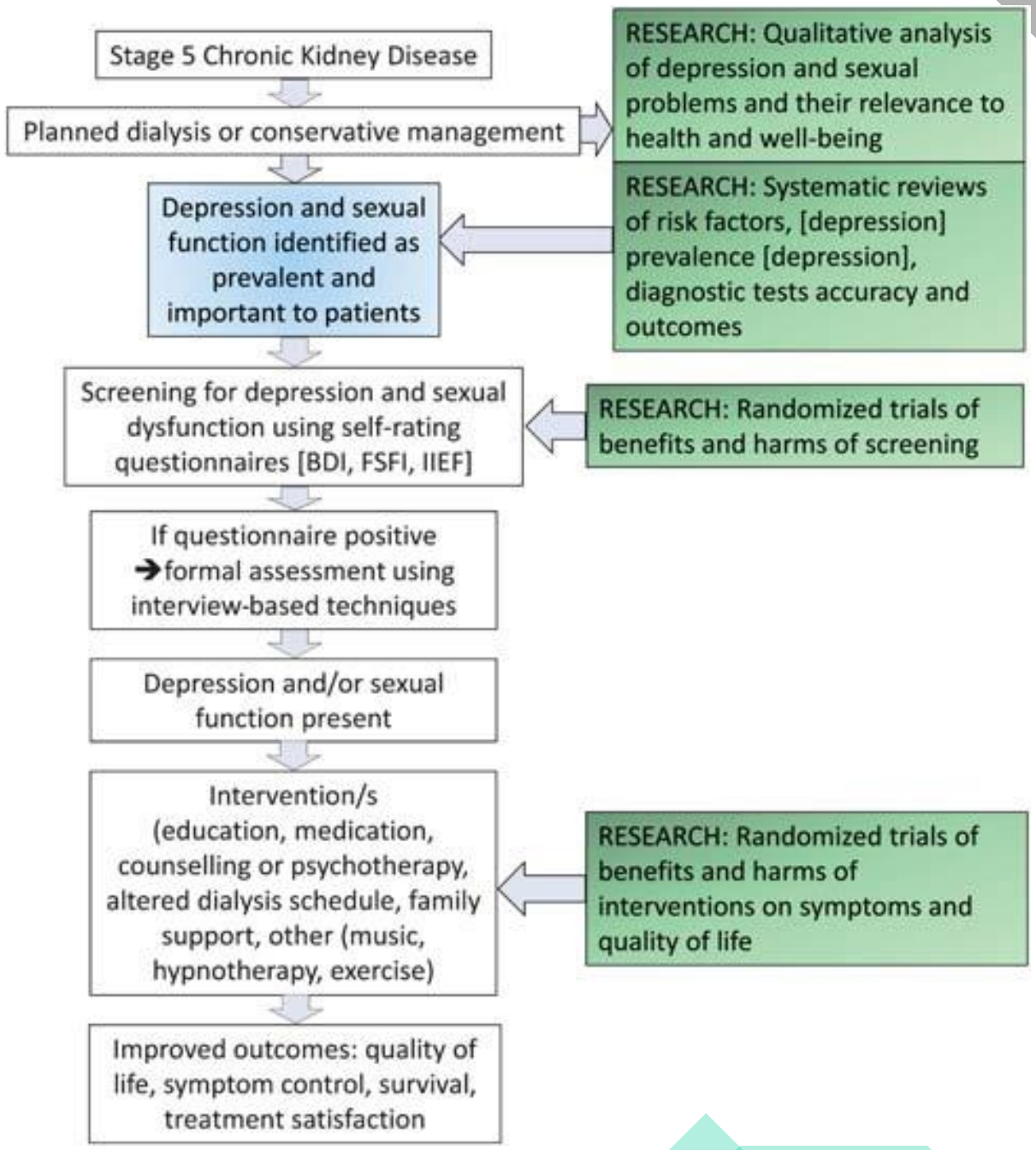
- The neurotrophins are a family of proteins that are essential for the development of the vertebrate nervous system.
  - NGF – Nerve growth factor
  - BDNF – Brain-derived neurotrophic factor
  - NT3 – Neurotrophin 3
  - NT4 – Neurotrophin 4

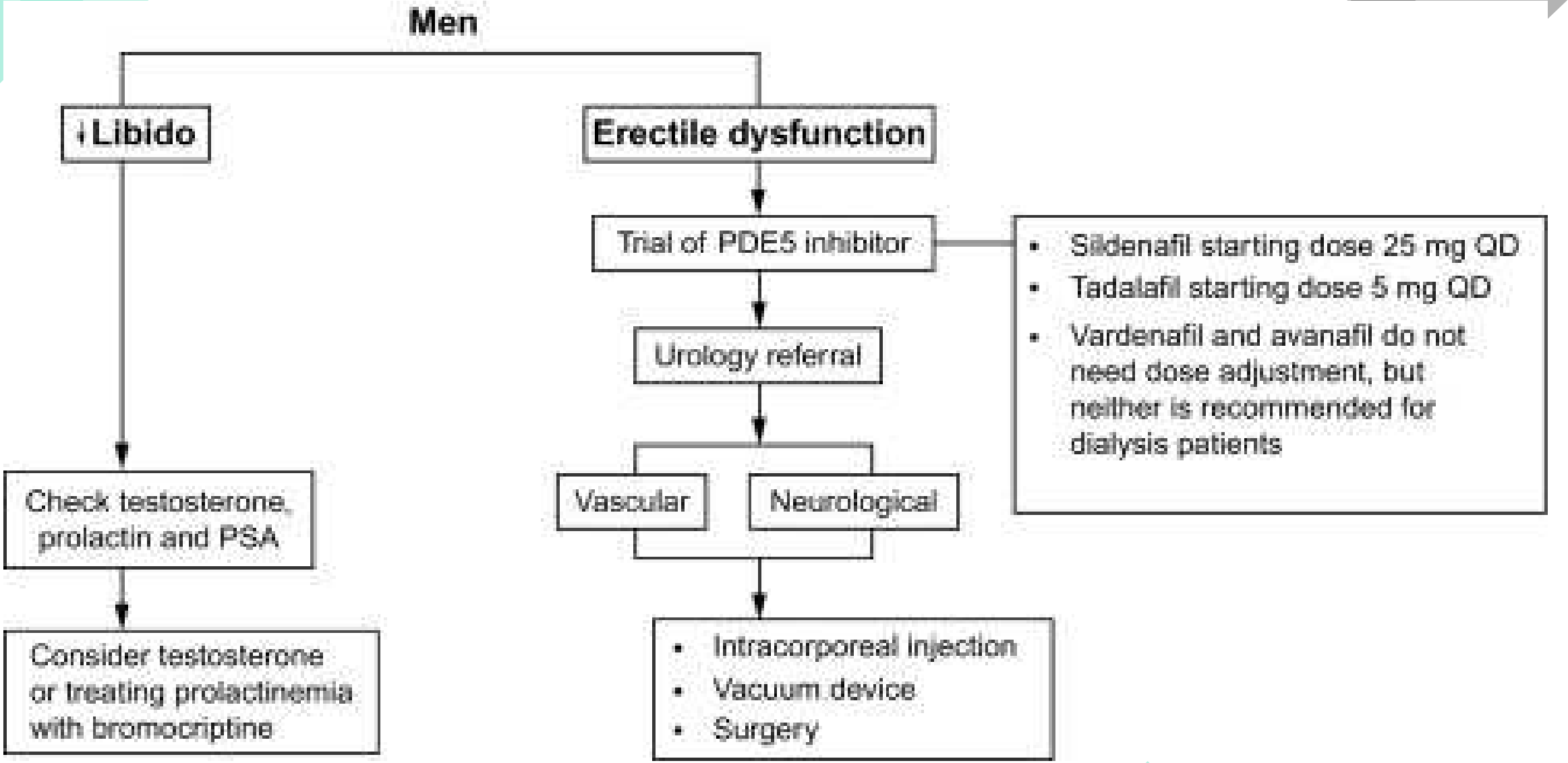




Nerve Growth Factors (shown in green) is required by neurons in order to survive. As they are a limited extracellular resource, some neurons (shown in blue) may uptake a disproportionate share of survival factors, leading to the eventual death of neighboring neurons (shown in red).

Depression and sexual dysfunction in chronic kidney disease: A narrative review of the evidence in areas of significant unmet need




Men
↓Libido
Erectile dysfunction
Trial of PDE5 inhibitor
• Sildenafil starting dose 25 mg QD
• Tadalafil starting dose 5 mg QD
• Vardenafil and avanafil do not need dose adjustment, but neither is recommended for dialysis patients
Urology referral
Vascular
Neurological
Check testosterone, prolactin and PSA
Consider testosterone or treating prolactinemia with bromocriptine
• Intracorporeal injection
• Vacuum device
• Surgery

Treatment

- Non-pharmacological treatment
  - Electroconvulsive therapy (ECT)
    - Highly effective treatment for severe depression, including medication-resistant depression
    - Not studied in RCTs in CKD, but there are case reports of excellent response to ECT in patients with CKD and severe depression refractory to antidepressant medication
    - Special precautions: abrupt increases in blood pressure, adequate muscle relaxation, subsequent risk of fractures in an osteopenic patient
  - Change in dialysis regimen
    - It is not clear whether increasing the frequency of dialysis improves depression rates
    - FREEDOM study: Dialysis frequency three times weekly → six times weekly. Significant decrease in BDI values was found

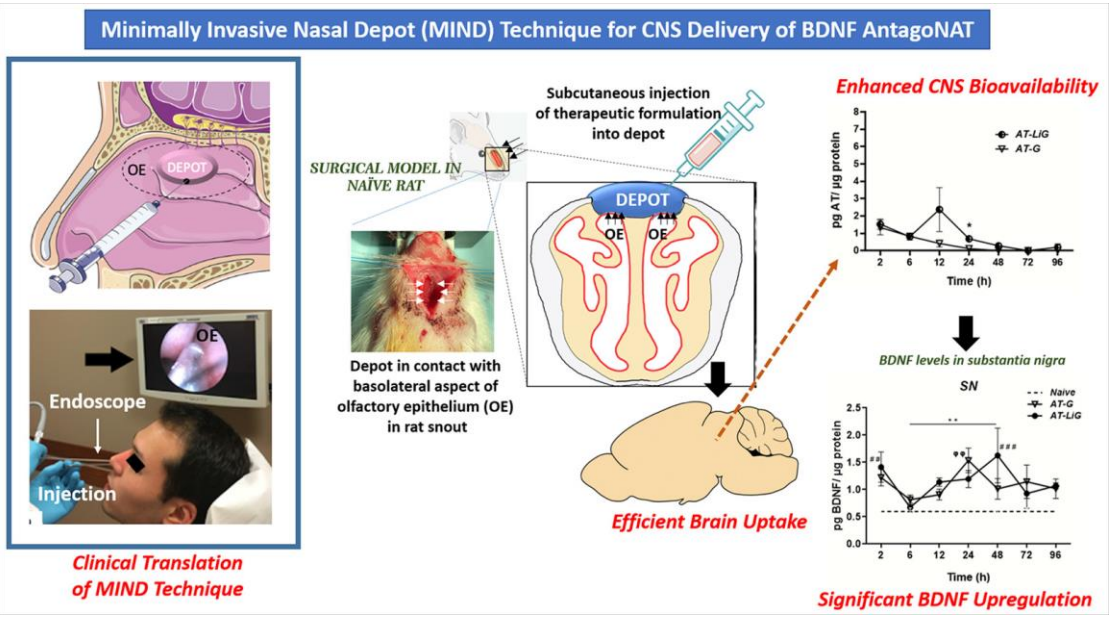
Australian & New Zealand Journal of Psychiatry
2014, Vol. 48(6) 530–541

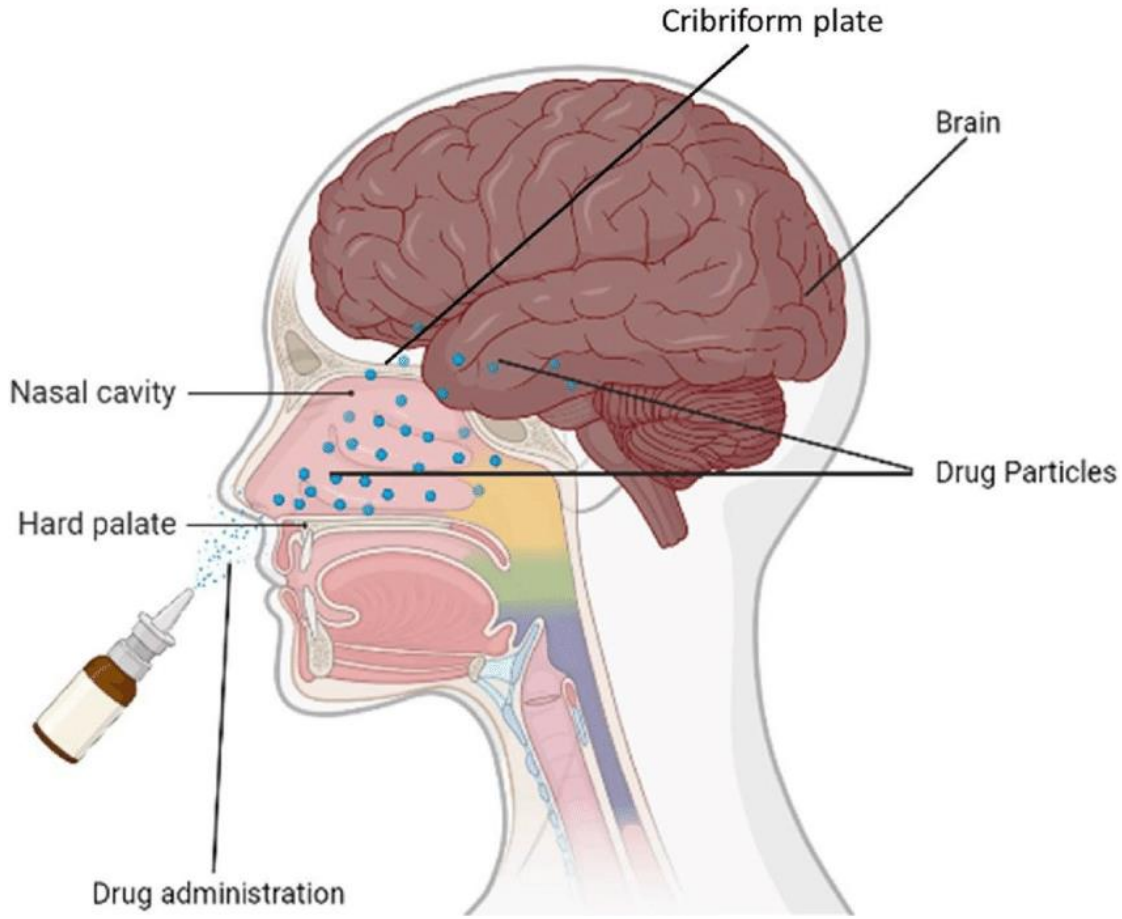
Treatment

- Pharmacological treatment
  - Patients with ESRD were often excluded from clinical trials because of safety concerns
    - Generally highly protein bound → Not removed significantly by the dialysis procedure/ Hepatically metabolized
    - Drug-drug interactions in the presence of polypharmacy
  - SSRI
    - Believed to be safer in patients with ESRD because of their more favorable adverse effect profiles
    - Fluoxetine is the only one completed RCT of antidepressant medication in CKD
    - If the diagnosis of an MDD is uncertain, they may enhance the risk for mania in patients who have bipolar disorder
    - SSRI may exacerbate preexisting uremic symptoms, bleeding risk

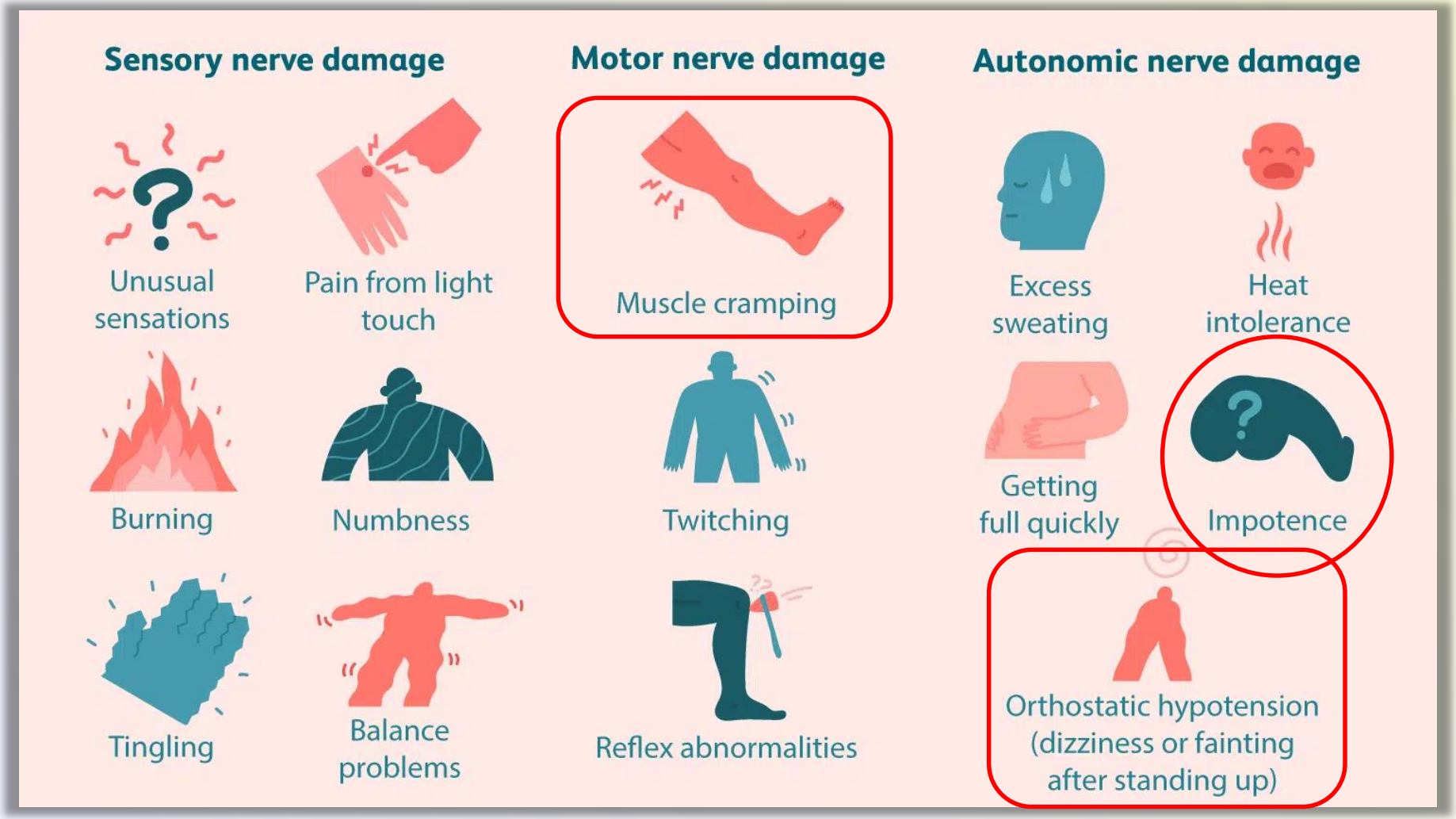
Clin J Am Soc Nephrol 2: 1332–1342, 2007

Class[a]	Drug	Dose/Day (MG)	Adverse Effects		Potential for Drug Interactions	Dose Change in Dialysis
			Common	Rare [b]		
SSRI	Fluoxetine	10-80	Insomnia, agitation, nausea, gastrointestinal effects, sexual dysfunction Mild sedation (fluvoxamine), mild weight gain	Movement disorders (parkinsonism, akathisia, TD), SIADH	Significant	None
	Paroxetine Paroxetine CR	10-60 12.5-75			Moderate	10-30 mg/daily
	Sertraline	25-200			Minimal	None
	Fluvoxamine	50-300			Significant	None
	Citalopram	10-60			Minimal	None
	Escitalopram	10-20			Minimal	No data
NDRI	Bupropion Bupropion SR	225-450 150-300 (divided dose if 300 mg)	Insomnia, agitation; mild anticholinergic effects, nausea, or gastrointestinal effects	Seizures (0.15% less than 300 mg/d, 0.4% 300-450 mg), psychosis	Moderate	100-300 mg daily
SNRI	Venlafaxine Duloxetine	75-375 40-60	Insomnia, agitation, nausea, gastrointestinal effects, sexual dysfunction	Hypertension (dose related) (venlafaxine)	Minimal	37.5-112.5 mg daily (venlafaxine) Not recommended (duloxetine)
NaSSA	Mirtazapine	15-60	Sexual dysfunction, severe sedation and weight gain, mild hypotension	Edema, neutropenia, Increased cholesterol	Minimal	7.5-22.5 mg daily


Minimally Invasive Nasal Depot (MIND) Technique for CNS Delivery of BDNF AntagoNAT
OE
DEPOT
Endoscope
Injection
Clinical Translation of MIND Technique
SURGICAL MODEL IN NAÏVE RAT
Subcutaneous injection of therapeutic formulation into depot
DEPOT
OE
OE
Depot in contact with basolateral aspect of olfactory epithelium (OE) in rat snout
Efficient Brain Uptake
Enhanced CNS Bioavailability
pg AT/ µg protein
AT-LIG
AT-G
Time (h)
BDNF levels in substantia nigra
SN
pg BDNF/ µg protein
Naive
AT-G
AT-LIG
Time (h)
Significant BDNF Upregulation


Cribriform plate
Brain
Nasal cavity
Drug Particles
Hard palate
Drug administration

NEUROPATIA PERIFERICA



Neuropatia Uremica

Neuropatia periferica: neuropatia periferica compare clinicamente nelle fasi più avanzate dell'IRC, si tratta di una neuropatia distale, generalmente simmetrica, di tipo misto, motoria e sensitiva.

Gli arti inferiori sono generalmente più interessati rispetto agli arti superiori.

Restless Legs Syndrome

anche conosciuta come la malattia di Willis-Ekbom

5-15%

La popolazione mondiale
che soffre di questo disturbo

I SEGNALI

- La necessità urgente di muovere gli arti inferiori
- Contrazioni notturne a piedi, polpacci e cosce (occasionalmente le braccia)
- Movimenti involontari (di grado lieve o intenso)
- Prurito, solletico e formicolii

GLI EFFETTI

- Stress elevato perché non si ha un sonno ristoratore
- Dolore agli arti inferiori

FATTORI SCATENANTI

- Anemia da carenza di ferro
- Gravidanza
- Malattie neurodegenerative come il Parkinson
- Insufficienza renale
- Diabete di tipo 2
- Lesioni al midollo spinale

Meta-analysis

Treatment of restless leg syndrome (RLS) in end stage kidney disease (EKSD)

Background

RLS is common in patients with ESKD. RLS affects quality of life, and is associated with increased cardiovascular events and mortality

There are possible benefits from nonpharmacological and pharmacological interventions

Methods

24 RCTs
2 independent reviewers

1252 ESKD patients on dialysis
14 nonpharmacological and pharmacological interventions

Treatment duration range: 3–24 weeks

Primary outcome
Reduction in RLS severity

Secondary outcome*
Improvement in sleep quality and treatment-related adverse events

Results

	Nonpharmacological interventions			Pharmacological interventions	
	Cool dialysate	Intradialytic stretching exercise	Reflexology	Aromatherapy massage	Gabapentin	Vitamins C + E
Mean difference (95% CI)	16.82 (10.63–23.02)	12.00 (7.04–16.97)	8.05 (2.73–13.37)	10.91 (6.96–14.85)	8.90 (1.95–15.85)	7.61 (0.05–15.17)

*No significant increase in adverse events, and gabapentin improved sleep quality (in comparison to control)

Conclusion

Non-pharmacological interventions, such as cool dialysate, are a useful treatment for RLS in ESKD. Gabapentin is the most effective pharmacological intervention.

NEPHROLOGY DIALYSIS TRANSPLANTATION

Chen et al. NDT (2021)
@NDTSocial

How prevalent is pruritus in non-dialysis CKD and how does it affect patients?

CJASN
Clinical Journal of American Society of Nephrology

3780 CKD stages 3-5

USA

Brazil

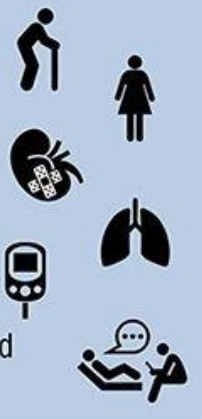
France

Prevalence of moderate to extreme itching

24%

Itching more likely in:

- Older patients
- Females
- Stage 5 CKD
- Lung disease
- Diabetes
- Physician-diagnosed depression



Patient-Reported Quality of life

not itchy

Extreme Pruritus

Health-Related Quality-of-Life Scores		Depression Symptoms	Restless Sleep
			
46.0	50.5	1.0 (ref)	1.0 (ref)
Physical Component Summary Score	Mental Component Summary Score	Prevalence Ratios	
38.4	44.3	2.6	2.1

Conclusions: There is a high prevalence of pruritus in non-dialysis CKD. Pruritus is associated with quality-of-life, self-reported depression symptoms, and self-reported restless sleep.

Nidhi Sukul, Elodie Speyer, Charlotte Tu, Brian Bieber, et al. ***Pruritus and Patient Reported Outcomes in Non-Dialysis Chronic Kidney Disease.*** CJASN doi: 10.2215/CJN.09600818. **Visual Abstract by Joel Topf, MD, FACP.**

International Comparisons of Prevalence, Awareness and Treatment of Pruritus in People on Hemodialysis

METHODS

Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Between 2012 and 2015

17 Countries

6256 Hemodialysis Patients

268 Medical Directors

OUTCOMES

18% of patients were very much or extremely bothered by itchy skin.

69% of medical directors underestimated the prevalence of pruritus in their facility.

Among patients nearly always or always bothered by itching, 18% used no treatment for pruritus.

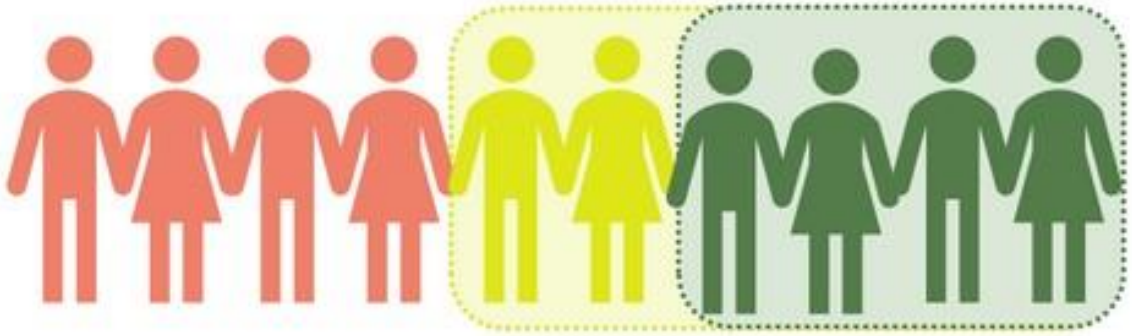
CONCLUSION

Many patients' lives could be improved by increased awareness and treatment of CKD-associated pruritus.

Hugh Rayner, Maria Larkina, Mia Wang, Matthew Graham-Brown, Sabine van der Veer, Tevfik Ecder, Takeshi Hasegawa, Werner Kleophas, Brian Bieber, Francesca Tentori, Bruce Robinson, and Ronald Pisoni. International Comparisons of Prevalence, Awareness and Treatment of Pruritus in People on Hemodialysis. CJASN doi:10.2215/CJN.03280317.

CJASN
Clinical Journal of American Society of Nephrology

KORSUVA[1] (Difelikefalin) Injection For CKD-associated Pruritus (CKD-aP) in Dialysis Patients



>500K[2]

patients on dialysis

60%

of ESRD patients have pruritus[3,4]

~40%

have moderate to severe pruritus

Serious intractable systemic pruritus

CKD-aP associated with worsening QoL, sleep disturbance, depressed mood/anxiety, socialization, increased mortality risk

KORSUVA granted Breakthrough Therapy Designation for CKD-aP

Significant unmet need

No FDA approved therapies

NDA Priority Review

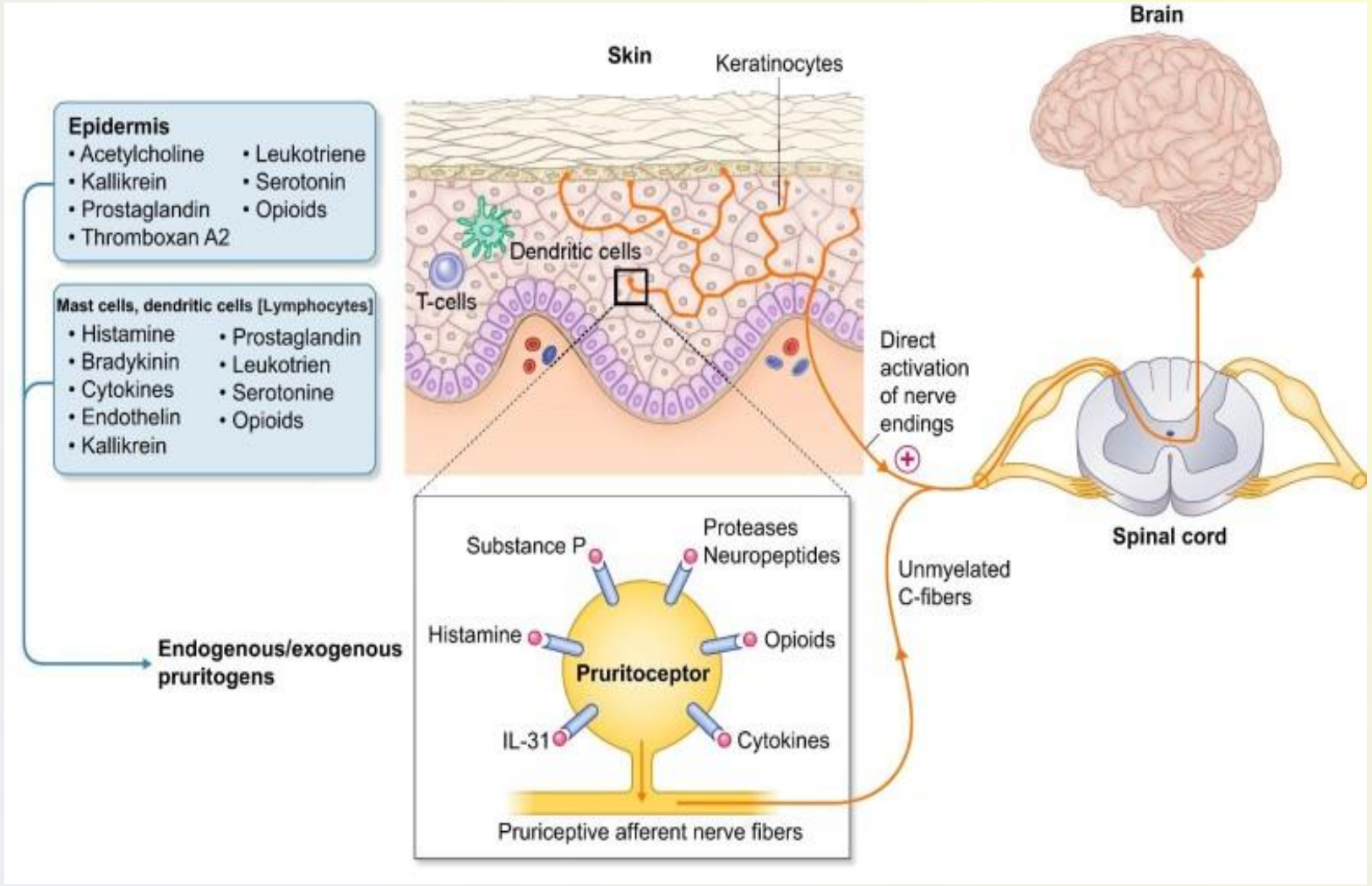
NDA filing – **PDUFA Aug 23 '21**[5]

U.S. launch - **2H, 2021**[5]

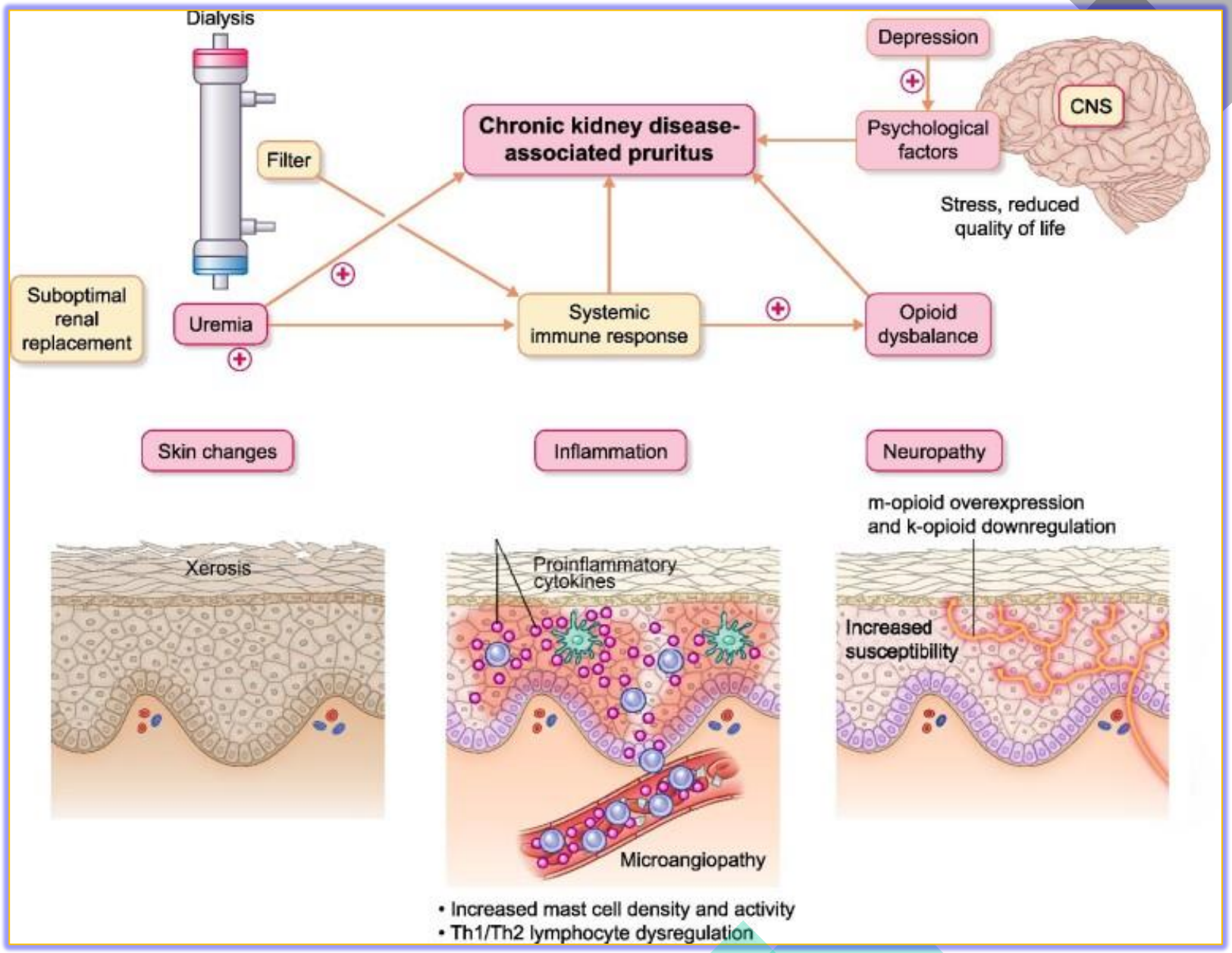
Reference: 1. The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. Difelikefalin injection is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority. **2.** National Kidney Foundation. . *3. Pisoni RL, Wikstrom B, Elder SJ, et al. Nephrol Dial Transplant. 2006;21:3495-3505. 4. Ramakrishnan et al. International Journal of Nephrology and Renovascular Disease. 2014:7 1–12* **5.** NDA accepted by FDA with priority review PDUFA date Q3 2021. Launch dependent on FDA approval

CARA THERAPEUTICS

Overview of the connections and signalling pathways in itch.



Overview of factors involved in CKD-associated pruritus.



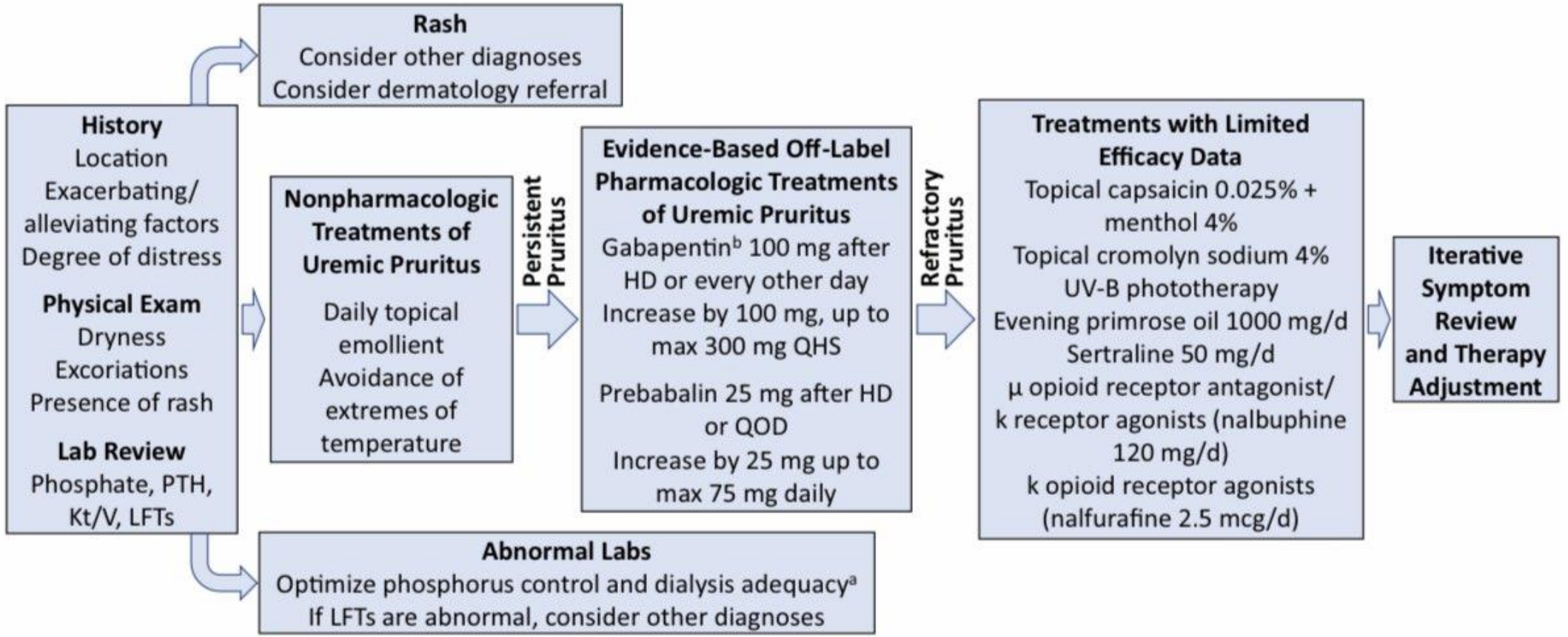
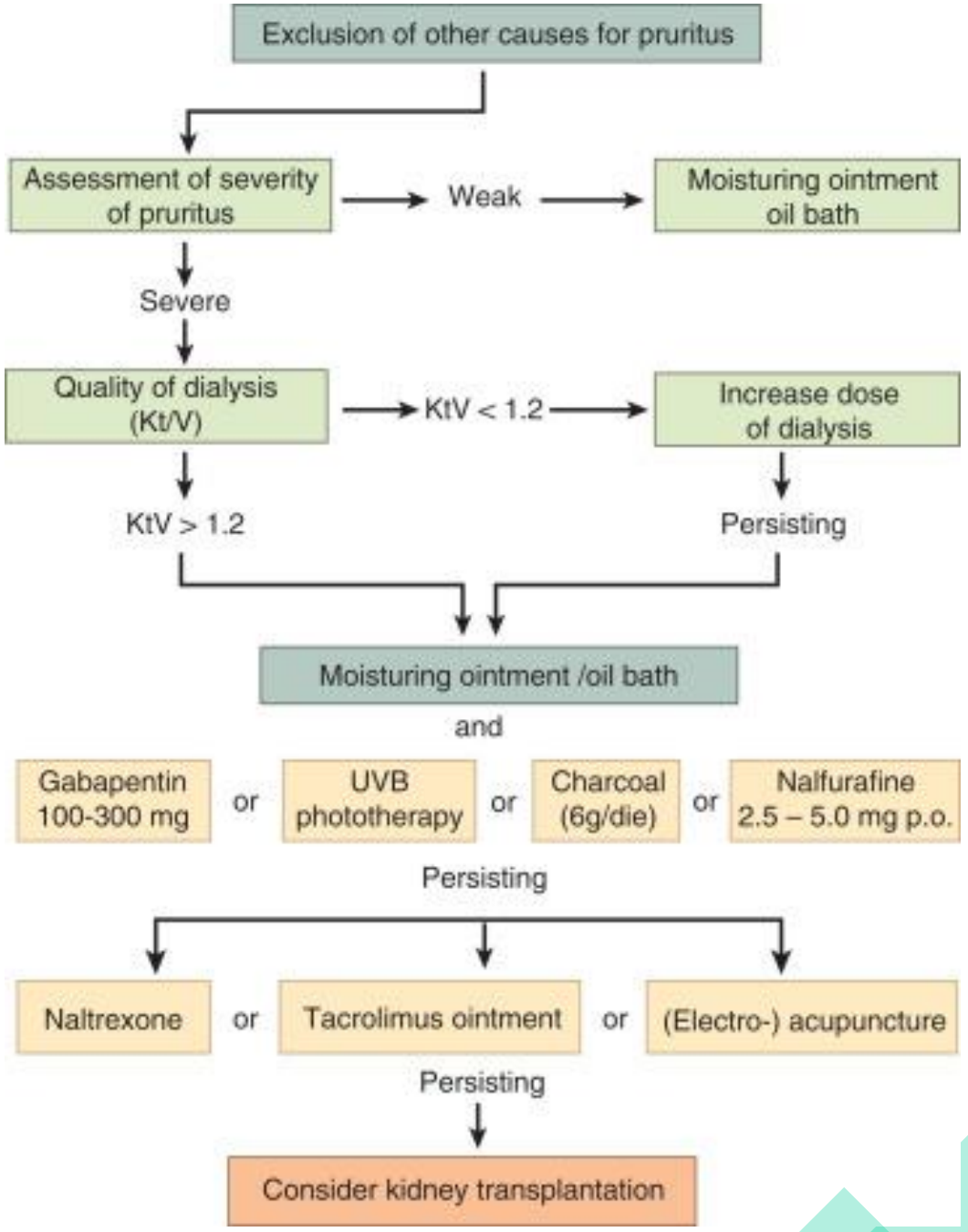
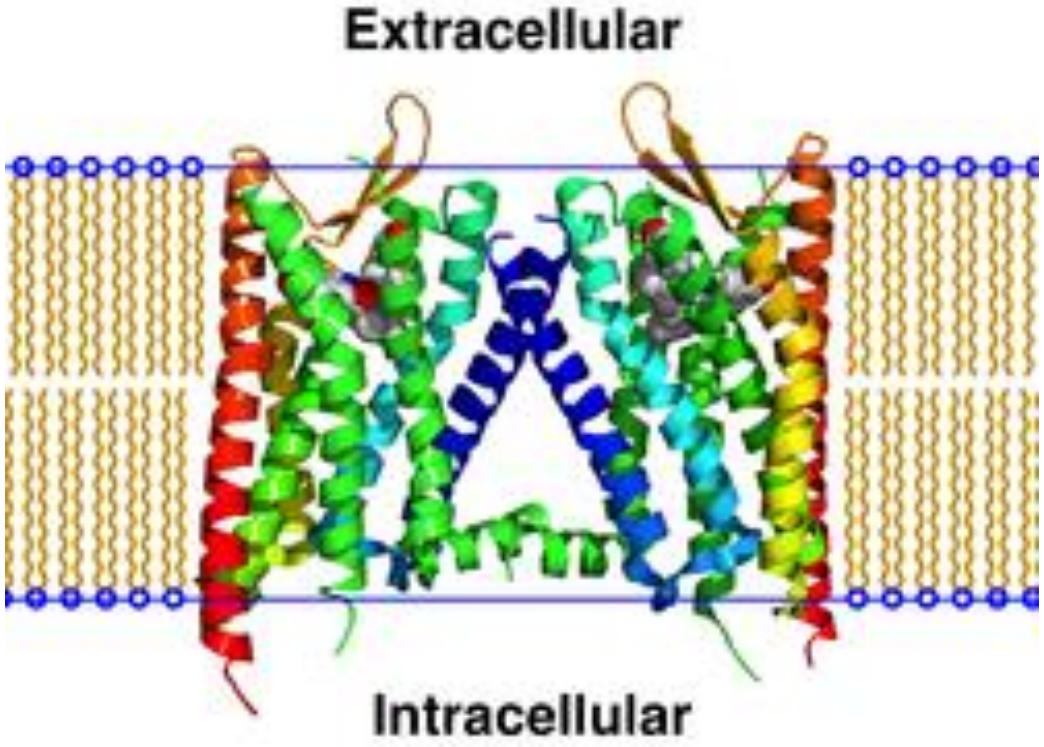
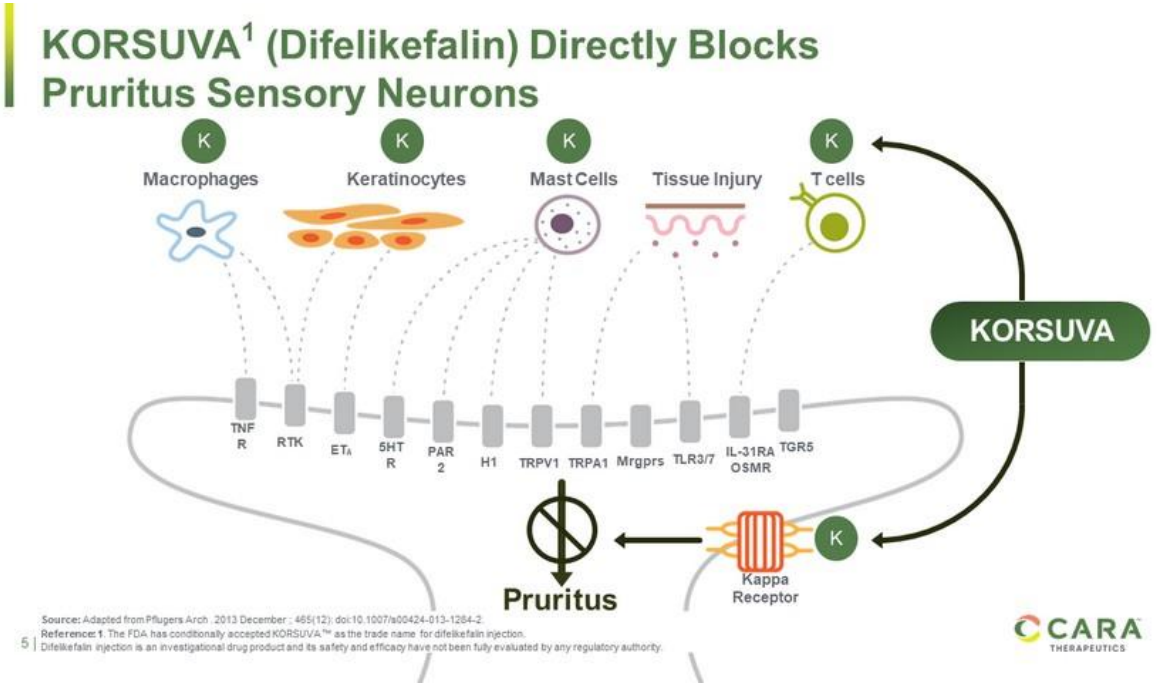


Figure 2. Treatment approach for uremic pruritus. [a]Common clinical practice despite lack of evidence that hyperphosphatemia, hyperparathyroidism, or increasing Kt/V over usual adequacy standards has any relationship to the sensation or alleviation of pruritus. [b]Caution and close monitoring is recommended with any off-label use of calcium channel alpha-2-delta ligands. Abbreviations: HD, hemodialysis; Lab, laboratory; LFTs, liver function tests; PTH, parathyroid hormone; QHS, every bedtime; QOD, every other day.


Exclusion of other causes for pruritus
Assessment of severity of pruritus
Weak
Moisturing ointment oil bath
Severe
Quality of dialysis (Kt/V)
KtV < 1.2
Increase dose of dialysis
KtV > 1.2
Persisting
Moisturing ointment /oil bath
and
Gabapentin 100-300 mg
or
UVB phototherapy
or
Charcoal (6g/die)
or
Nalfurafine 2.5 – 5.0 mg p.o.
Persisting
Naltrexone
or
Tacrolimus ointment
or
(Electro-) acupuncture
Persisting
Consider kidney transplantation

Difelikefalin is an opioid peptide used for the treatment of moderate to severe itch. It acts as a peripherally-restricted, highly selective agonist of the κ-opioid receptor (KOR)





Cara Therapeutics Pipeline

Program	Indication*	STAGE OF DEVELOPMENT: Phase I / Phase II / Phase III / NDA Review	Commercialization Rights† (ex-Japan and S. Korea)‡
KORSUVA™ Injection	Pruritus CKD-HD§	FDA Priority Review	US-Vifor EU / Other-VFMCRP‖
Oral KORSUVA™	Pruritus AD	EOPII Meeting Q3 '21	Cara
Oral KORSUVA™	Pruritus NDD-CKD		Cara
Oral KORSUVA™	Pruritus PBC		Cara
Oral KORSUVA™	Pruritus NP		Cara

*Cara Therapeutics has investigated KORSUVA™ for post-operative pain.
†Vifor has commercial rights in Non-US Fresenius Medical Care dialysis clinics under a profit-share arrangement.
‡Commercialization rights to KORSUVA™ in defined indications—Japan: Maruishi Pharma; South Korea: CKD Pharma.
§PDUFA date is August 23, 2021.
‖VFMCRP and Cara have rights to promote in Fresenius clinics in the US under a profit-share agreement.
CKD-HD: Chronic Kidney Disease-Hemodialysis; NDD—CKD: Non-Dialysis Dependent-Chronic Kidney Disease; AD: Atopic Dermatitis; PBC: Primary Biliary Cholangitis; NP: Notalgia Paresthetica.

The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection.
Difelikefalin injection is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority.

CARA THERAPEUTICS

Does difelikefalin reduce uremic pruritus in dialysis patients? The Kalm-1 Trial

Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. N Engl J Med. 2019;

#NephJC

378 patients
With moderate to severe itching

N=189

Placebo
3x/wk

12 weeks → **28%**

N=189

Difelikefalin
0.5 mcg/kg
3x/wk

12 weeks → **49%**

Clinically relevant decrease in itching

Increased adverse reactions with difelikefalin

Diarrhea
10 vs 4%

Vomiting
5 vs 3%

Dizziness
7 vs 1%

No signal for dependence or withdrawal

Conclusions Patients treated with difelikefalin had a significant reduction in itch intensity and improved itch-related quality of life as compared with those who received placebo.

Randomized controlled trial of difelikefalin for chronic pruritus in hemodialysis patients

Patient Selection

174 patients

- ≥ 18 years
- Hemodialysis 3x per week for ≥ 3 months
- Moderate-to-severe pruritus (mean Baseline WI-NRS >4)
- Followed for 8 weeks

Worst Itching Numeric Rating Scale (1-10) (WI-NRS)

Treatment Randomization

Placebo (n=45)

Difelikefalin
0.5 μg/kg (n=44)
1.0 μg/kg (n=41)
1.5 μg/kg (n=44)

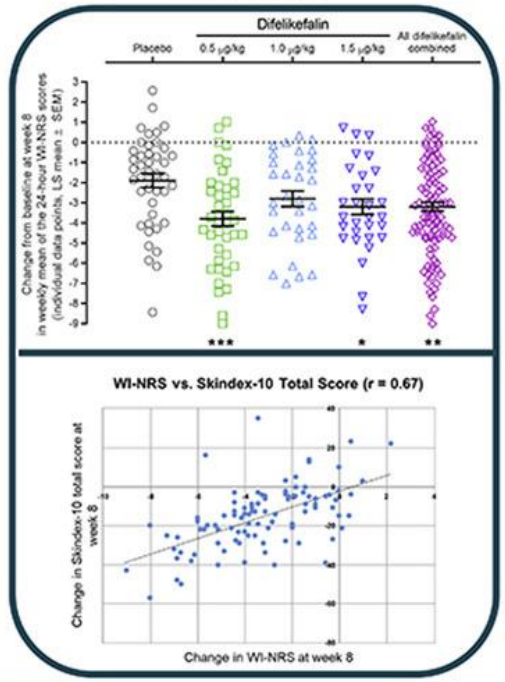
Endpoints

Primary endpoint
Weekly Mean of Daily WI-NRS scores

Secondary endpoint
Skindex-10 (QoL)

Other endpoints
5-D Itch (QoL), Sleep, Itch Severity and Impression of Change

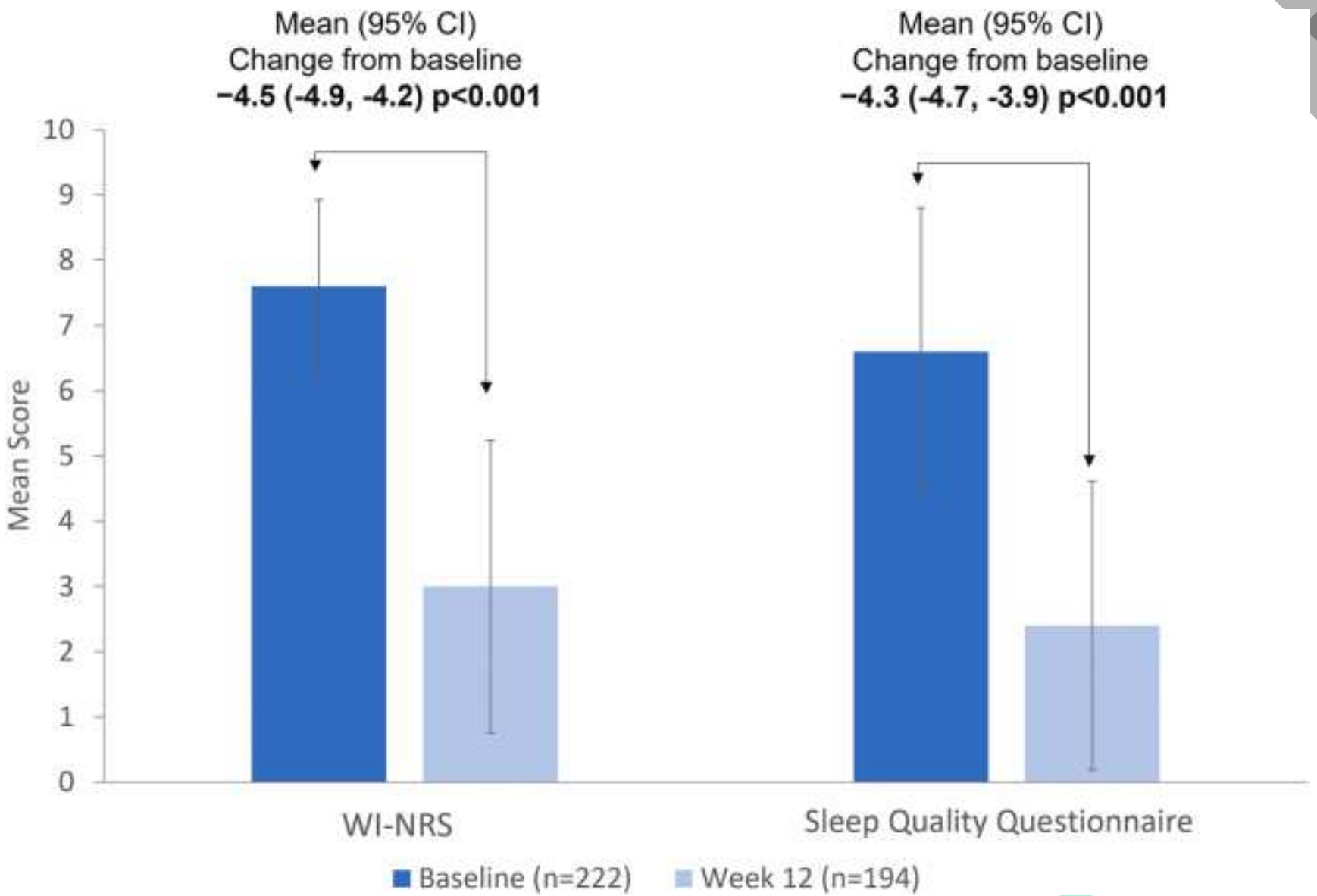
Results



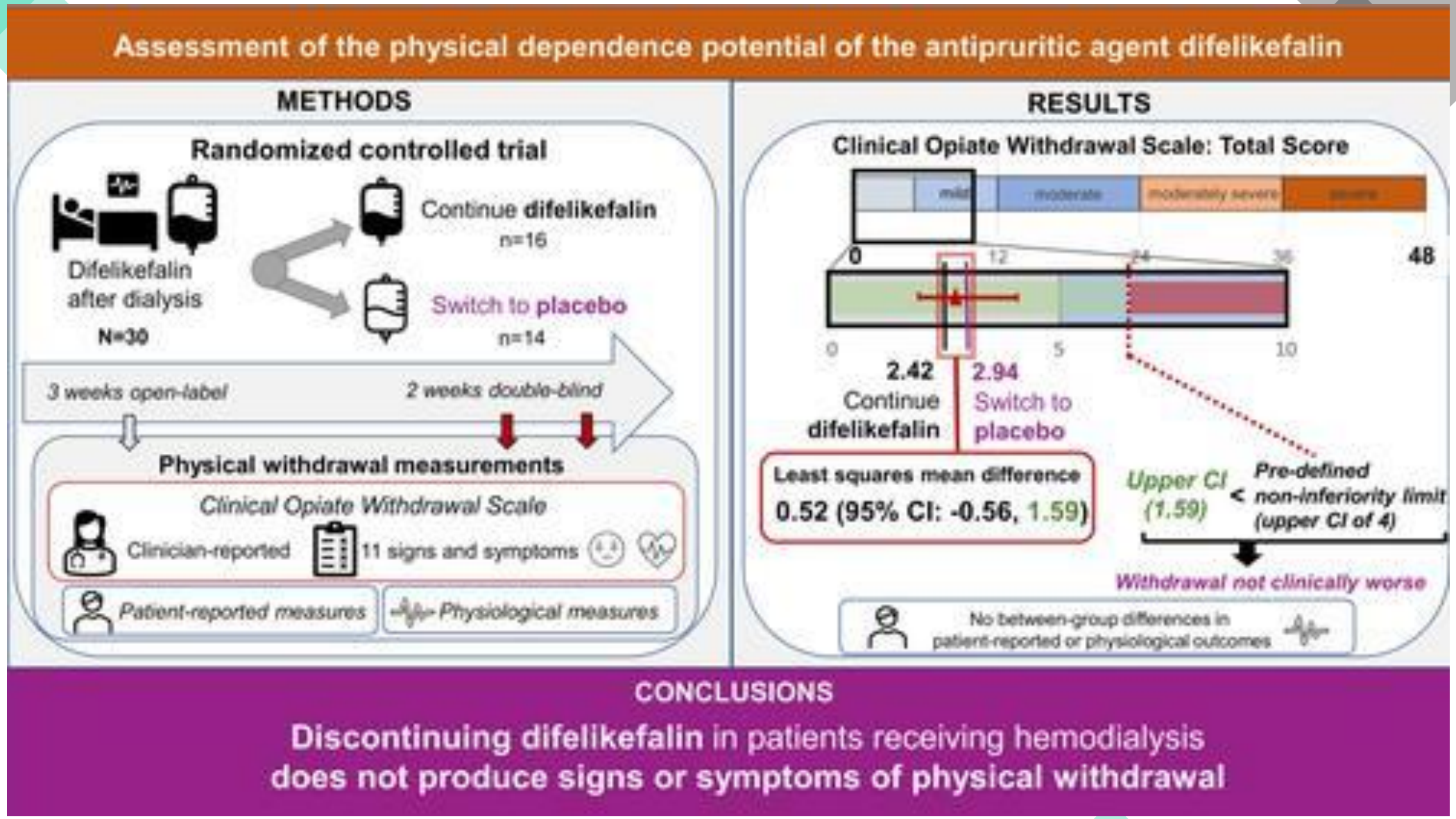
CONCLUSION:
Difelikefalin was effective at reducing the severity of pruritus in hemodialysis patients with chronic moderate-to-severe pruritus and improving sleep, mood, and social functioning.

KI REPORTS
KIReports.org

Fishbane et al, 2020

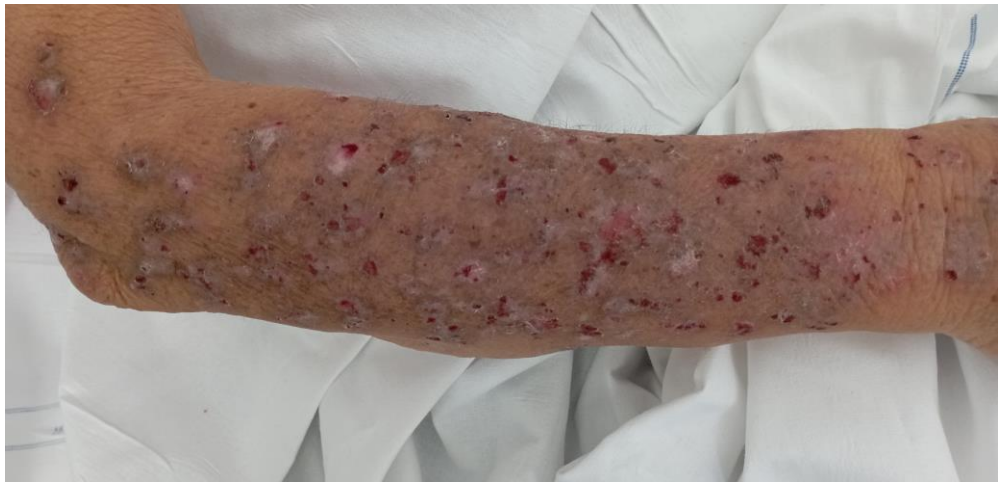

Mean (95% CI)
Change from baseline
−4.5 (-4.9, -4.2) p<0.001
Mean (95% CI)
Change from baseline
−4.3 (-4.7, -3.9) p<0.001
Mean Score
10
9
8
7
6
5
4
3
2
1
0
WI-NRS
Sleep Quality Questionnaire
Baseline (n=222)
Week 12 (n=194)

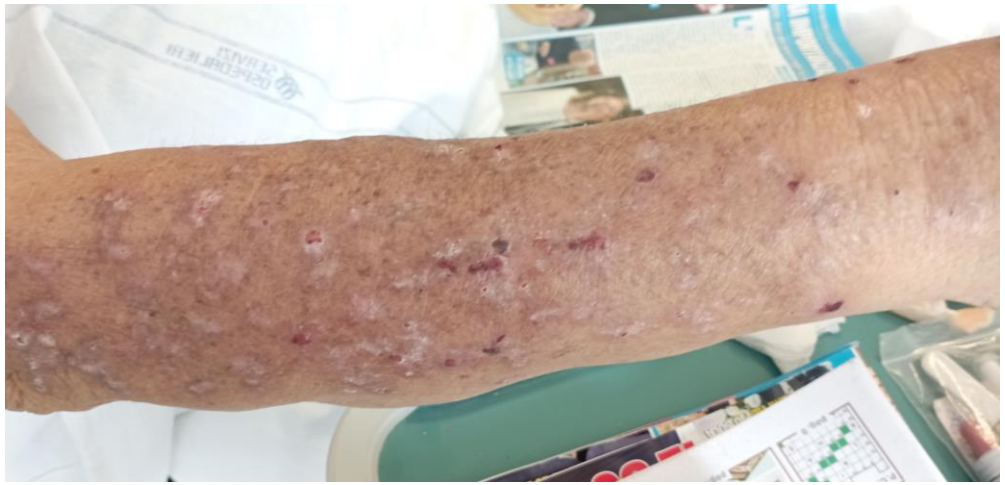
Assessment of the physical dependence potential of the antipruritic agent difelikefalin

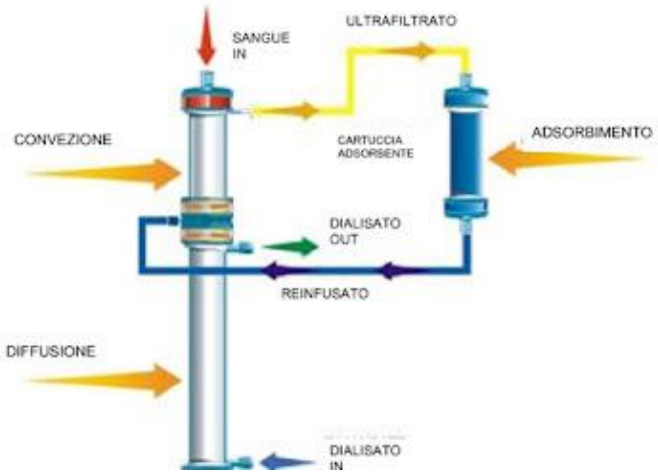


CONCLUSIONS

Discontinuing difelikefalin in patients receiving hemodialysis **does not produce signs or symptoms of physical withdrawal**






SANGUE
IN
ULTRAFILTRATO
CONVEZIONE
CARTUCCIA
ADSORBENTE
ADSORBIMENTO
DIALISATO
OUT
REINFUSATO
DIFFUSIONE
DIALISATO
IN


HA130
Disposable
Service
STERILE
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Grazie per l’attenzione