

Managing Depression in Chronic Kidney Disease

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Learning Objectives

- **Recognize** the importance and potential causes of depressive symptoms in renal patients.
- **Identify** first-line treatments for Major Depressive Disorder in patients with renal disease.
- **Understand** considerations for pharmacotherapy when managing depressive symptoms in renal disease.



Outline



- Why mood is important in renal disease
- Causes of mood symptoms in renal disease
- Non-pharmacological treatments for renal disease
- Pharmacological treatments for mood Considerations for CKD

? Depressive symptoms in CKD are linked to:

- Worse Quality of Life
- Poor social support
- Risk of:
 - Hospitalization
 - Decline in renal function
 - Death
- Progression to dialysis
- Discontinuation of dialysis



? And rates of depression in CKD are high!

- Up to 3-4x general population!
 - 20-40% of patients at any given time
- Higher than other groups with chronic diseases



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MAJOR DEPRESSIVE EPISODE

- FIVE of the following present for >2 weeks:
 - Depressed for most of the day, nearly every day*
 - Markedly diminished interest or pleasure in all/nearly all activities*
 - Significant appetite changes (up or down)
 - Insomnia or hypersomnia
 - Psychomotor agitation or slowing
 - Feelings of worthlessness/excessive guilt
 - Concentration difficulties
 - Recurrent thoughts of death/suicide

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Not all depressive symptoms are from Major Depressive Disorder!



- Adjustment disorder
- Bipolar disorder
- Behavioral symptoms of dementia
- Personality disorder
- Mood disorder secondary to substance
 - Medication
 - Substance misuse
- Mood disorder secondary to medical condition
 - Uremia
 - Anemia
 - Hypocalcemia
 - Stroke
 - Myocardial infarction

Why do so many people with CKD have depression?

• People with depression are more likely to develop chronic renal disease!



Depression

- ↓ health care visits
- ↓ healthy behaviors
- ↓ socioeconomic well being
- psych med side effects (e.g. Lithium, Antipsychotics)

Decline in renal function

Why do so many people with CKD have depression?

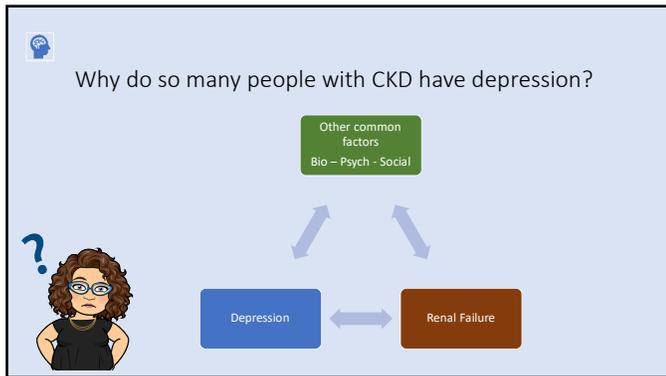


Renal decline

- Biological**
 - Uremia
 - ↓ pH
 - ↓ Ca
- Psychological**
 - Endocrine Distress
 - ↓ feelings of integrity, self-efficacy
 - ↓ job work
- Social**
 - change in family roles
 - ↓ self-efficacy

Increase risk of depression

*not exhaustive list



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Canadian Guidelines for Major Depression 1ST Line Management (CANMAT 2024)

Mild	Moderate	Severe
<ul style="list-style-type: none"> Medication OR* Psychotherapy OR* Exercise OR ?CAM 	<ul style="list-style-type: none"> Medication OR* Psychotherapy OR* Both Adjunctive exercise/CAM 	<ul style="list-style-type: none"> Medication AND Psychotherapy If psychotic, antidepressant + antipsychotic (occasionally ECT)

*OR
 • Patient preference
 • Availability
 • ?Risk of treatment

Line of treatment	Psychological treatment	Level of evidence
First line	Cognitive-behavioural therapy (CBT), Interpersonal therapy (IPT), Behavioural activation (BA).	●●●●
Second line	Cognitive behavioural analysis system of psychotherapy (CBASP), Mindfulness-based cognitive therapy (MBCT), Problem-solving therapy (PST), Short-term psychodynamic psychotherapy (STPP), Transdiagnostic psychological treatment of emotional disorders ^a	●●●●●
Third line	Acceptance & commitment therapy (ACT), Long-term psychodynamic psychotherapy (PDT), Metacognitive therapy (MCT), ^a Motivational interviewing (MI).	●●●●●

● Level 1; ● Level 2; ● Level 3; ● Level 4

Several small RCTs in patients with ESRD have shown positive results!

Barriers to Psychotherapy in CKD

- Cost
- Appointment burden/conflicts
- Accessibility challenges (ie. mobility, vision)
- Cognitive impairment

Other Evidence Based Non-Pharmacological Treatments

- Cardiovascular exercise
- Light therapy (seasonal depression)
- [St. John's Wort]
- Acupuncture (2nd line)
- Neuromodulation - treatment resistance
 - Electroconvulsive therapy
 - rTMS
 - tDCS
 - Magnetic Seizure Therapy
 - Surgical
 - Vagus Nerve Stimulation
 - Deep Brain Stimulation

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First Line Medications for MDEs (CANMAT 2024)

- SSRI**
 - Escitalopram (Cipralext)
 - Citalopram (Celexa)
 - Sertraline (Zoloft)
 - Fluvoxamine (Luvox)
 - Paroxetine (Paxil)
 - Fluoxetine (Prozac)
- SNRI**
 - Levomilnacipran (Fetzima)
 - Venlafaxine (Effexor)
 - Desvenlafaxine (Pristiq)
 - Duloxetine (Cymbalta)
- NaSSA:**
 - Mirtazapine (Remeron)
- NDRI**
 - Bupropion (Wellbutrin)
- Serotonin Reuptake Inhibitor**
 - Vortioxetine (Trintellix)
 - Vilazodone (Viibryd)
- (Milnacoprin, Mianserin, Agomelatine not available in Canada)**



Only a few are contraindicated in ESRD/dialysis

- SSRI**
 - Escitalopram (Cipralext)
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Many require dose reductions due to clearance

- SSRI**
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How do these medications work anyway?

SNRI Mechanism of Action

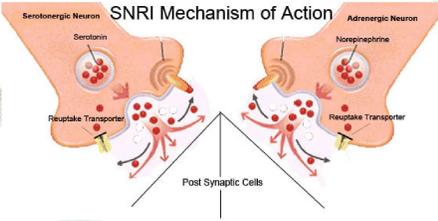


Image from MedBullets



What is the efficacy for MDE?

- 2009 Cochrane Review: SSRIs in depression
 - Number Needed to Treat – 7
- Placebo response in depression trials: 30-40%
- Perhaps slightly better efficacy for (Cipriani et al 2018):
 - Escitalopram
 - Paroxetine
 - Venlafaxine
 - Mirtazapine
 - Vortioxetine
 - [agomelatine]
 - [amitriptyline]



Are there any studies specific to CKD?

“...evidence for antidepressant medication in the dialysis setting is sparse and data are generally inconclusive.” (2016)

Which ones have been studied in CKD?

- Sertraline – positive results in 3 small studies
- Paroxetine
- Escitalopram
- Citalopram
- Fluoxetine (mixed results in RCT)
- All studies of dialysis patients specifically (Bossola et al. 2004)

Expert consensus for first line pharmacotherapy in CKD...

How do you choose an antidepressant?

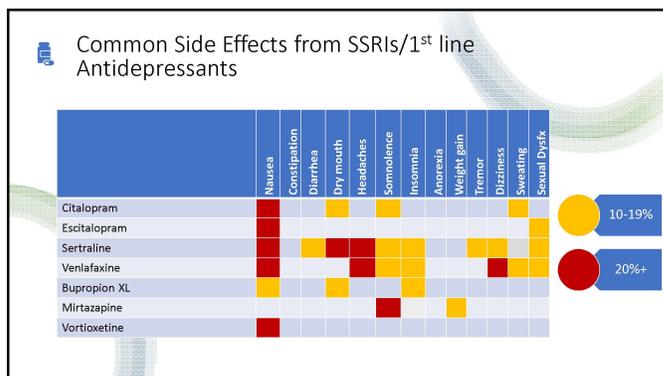
- Drug-drug interactions
- Side effect profile
- Cost
- Patient preference/previously successful treatments
- (Planning for potential decline in renal function in mild CKD)

Drug-Drug Interactions of Antidepressants

	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Citalopram	0	0	0	+	0
Escitalopram	0	0	0	0/+	0
Fluoxetine	+	++	+ / ++	+++	+ / ++
Fluvoxamine	+++	++	+++	+	++
Paroxetine	+	+	+	+++	+
Sertraline	0	+	0	+ / ++	+
Venlafaxine	0	0	0	+	+
Duloxetine	0	0	0	++	+
Mirtazapine	0	0	0	+	0
Agomelatine	0	0	0	0/+	0
Vortioxetine	0	0	0	0	0

0 absence or minimal inhibition
 + low inhibition
 ++ moderate inhibition
 +++ expressed inhibition

Turovskaia, Ekaterina & Alekseeva, Lyudmila. (2023)



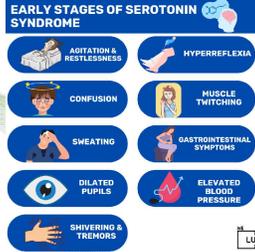
Additional Side Effects to Be Aware of:

Specific Drugs	More Globally
<ul style="list-style-type: none"> Bupropion – seizure risk Venlafaxine/Desvenlafaxine – Hypertension SSRIs – ?bleeding risks 	<ul style="list-style-type: none"> ↑ falls & cognitive risk in elderly ↑ suicidality in <25 years Mania Occasionally ↑ agitation



Serotonin Syndrome

EARLY STAGES OF SEROTONIN SYNDROME



- Very, very rare at therapeutic doses!
- Small risk with combined serotonergic medications
 - Multiple antidepressants +/- other psychotropics
 - Some opioids
 - MDMA, stimulants
 - ?Triptans
- If adding serotonergic agents, go slow

What about intentional overdose?

- SSRIs, SNRIs, NaSSAs, SRIs have low risk of death in overdose
 - Will generally still require hospitalization & telemetry
- To reduce risk:
 - Blister packs
 - Short dispense
 - Involving a family member to restrict access

***BUPROPION causes seizures in overdose



Are antidepressants addictive?

- They are not addictive – no fun immediate psychological effects
- HOWEVER many SSRI/SNRIs cause physiological withdrawal symptoms

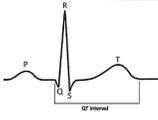
***BUPROPION can give euphoric effects when crushed

- Some diversion potential



Let's Talk About QT Interval!

- Most SSRIs can ↑ QTc
 - Theoretically ↑ risk of Torsades de pointe
 - Risk is mainly at QTc >500msec (AHA 2020)
- Dialysis patients likely higher risk
 - Multiple meds
 - Electrolyte fluctuations
 - Comorbidities




Let's Talk About QT Interval!

- Citalopram / Escitalopram are biggest culprits
 - Black box warning
- Other SSRIs are associated -5 to +4 msec changes

Medication and dose	QT prolongation (95% CI)
Citalopram 20mg daily	8.5 (6.2, 10.8)
Citalopram 40mg daily	12.6 (10.9, 14.3)
Citalopram 60mg daily	18.5 (16.0, 21.0)
Moxifloxacin 400mg daily	13.4 (10.9, 15.9)

Medication and dose	QT prolongation (95% CI)
Escitalopram 10mg daily	4.5 (2.5, 6.4)
Escitalopram 20mg daily	6.6 (5.3, 7.9)
Escitalopram 30mg daily	10.7 (8.7, 12.7)
Moxifloxacin 400mg daily	9.0 (7.9, 10.0)

Based on FDA data

How worried should we be about QTc in SSRIs?

- In general populations = negligible worry
- In ESRD, baseline ECG for QTc
 - Consider serial ECGs if borderline
 - Consider alternative drug class if >500msec
- Repeat ECG if major change in status or addition of other QTc prolonging drugs
 - Methadone
 - Antiemetics
 - Antiarrhythmics
 - Macrolides
 - Fluoroquinolones
 - ... and ...



Briefly, antipsychotics...

- Are often used as adjunctive tx in MDE
 - Aripiprazole (Abilify) and Brexpiprazole (Rexulti) are "1st line adjuncts"
- Some are renally cleared
 - Paliperidone (Invega) – 90% renally cleared!
 - Risperidone (Risperdal) – up to 70%
- Side effects merit special consideration in CKD
 - QT prolongation (except aripiprazole)
 - Postural hypotension (quetiapine, clozapine)
 - Metabolic derangements
 - Falls
 - Exacerbate Restless Leg Syndrome



Briefly, 2nd line agents...

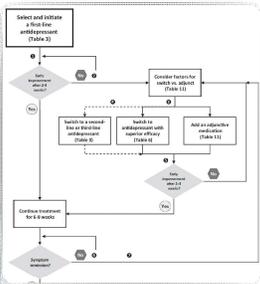
Tricyclic (TCA)	RIMA	SRI	Atypical antipsychotic
<ul style="list-style-type: none"> Amitriptyline, nortriptyline, doxepin, imipramine etc. ++ s/e Longer QTc More cardiac 	<ul style="list-style-type: none"> Moclobemide (Manerix) Not approved in US Drug-drug interactions Cardiovascular risk 	<ul style="list-style-type: none"> Trazodone ++++ sedating at therapeutic doses Recent study show increased mortality in dialysis patients 	<ul style="list-style-type: none"> Quetiapine (Seroquel) monotherapy See antipsychotic side effects Quite sedating

Most antidepressants take at least 4-6 weeks to work!

And side effects tend to be worse when starting



What if it doesn't work?



The flowchart outlines a systematic approach to treatment-resistant depression. It begins with 'Select and initiate a first-line antidepressant (Table 2)'. If there is 'No response', it branches into two paths: 'Switch to a second-line antidepressant (Table 2)' or 'Consider treatment with an antidepressant (Table 2)'. The 'Switch to a second-line antidepressant' path leads to 'Switch to a second-line antidepressant (Table 2)', which then leads to 'Add an adjunctive medication (Table 2)'. The 'Consider treatment with an antidepressant' path leads to 'Consider treatment with an antidepressant (Table 2)', which then leads to 'Add an adjunctive medication (Table 2)'. Both paths converge at 'Add an adjunctive medication (Table 2)', which then leads to 'Continue treatment for 6 weeks'. If there is still 'No response', it leads to 'Consider treatment with an antidepressant (Table 2)'. If there is a 'Response', it leads to 'Continue treatment for 6 weeks'.



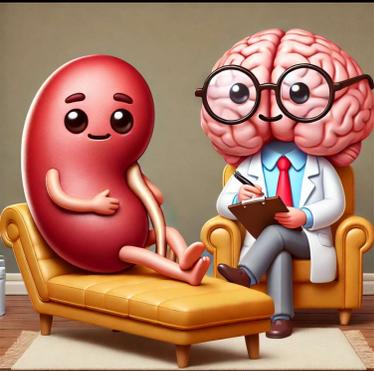
Ketamine

- 2nd line for treatment-resistant depression
- Good evidence for treatment efficacy, anti-suicide
- IV and intranasal (esketamine)
- Availability?



Psychedelics

- Still investigational
- Early evidence for single dose psilocybin assisted psychotherapy
- No evidence for micro-dosing



How long should someone stay on an antidepressant ?



- 6-12 months
 - 1st episode
- 2 years +
 - Frequent episodes
 - Severe episodes (psychosis, suicidality)
 - Chronic episodes
 - Residual symptoms
 - Presence of comorbid conditions

Wean vs. Sudden Stop

Discontinuation:

- Unpleasant, but not life-threatening
- GI, headache, mood lability, sleep changes, "zaps" (venlafaxine)



More Discontinuation Syndrome	Less Discontinuation Syndrome	STOP QUICKLY IF:
<ul style="list-style-type: none"> • Most SSRIs & SNRIs • Vilazodone 	<ul style="list-style-type: none"> • Fluoxetine • Bupropion • Mirtazapine • Vortioxetine 	<ul style="list-style-type: none"> • Mania • Serotonergic side effects • ?Suicidality in youth • ?GI bleed

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Approach to Renal Patient with Depressive Symptoms



- Make sure the diagnosis is right!
- Optimize medical parameters
- Discuss patient preferences
 - Consider psychotherapy for mild-moderate
- ++ Psychoeducation
- Select a 1st line med that does the least harm
 - Start low and go slow
 - Monitor side effects including ECG
 - Monitor response
 - Switch if needed

Take Home Points re: Depression in CKD



- Depressive symptoms are common and multifactorial
- Medications are only 1 option
 - Psychotherapy
- Most antidepressants are fairly safe
 - No duloxetine or levomilnacipram!
 - Often ↓ doses
 - Watch side effects & interactions
 - Evidence is limited



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