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Dr. Resch: How renal disease can alter pharmacotherapy

When to adjust the dosing of psychotropics in patients with renal impairment

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Renal disease can play a large role in altering the pharmacokinetics of medications, especially in elimination or clearance and plasma protein binding. Specifically, renal impairment decreases the plasma protein binding secondary to decreased albumin and retention of urea, which competes with medications to bind to the protein.[1]

Electrolyte shifts—which could lead to a fatal arrhythmia—are common among patients with renal impairment. The risk can be further increased in this population if a patient is taking a medication that can induce arrhythmia. If a drug is primarily excreted by the kidneys, elimination could be significantly altered, especially if the medication has active metabolites.[1]

Normal renal function is defined as an estimated creatinine clearance (eCrCl) of >80 mL/min. Renal impairment is classified as:

- mild: eCrCl, 51 to 80 mL/min
- moderate: eCrCl, 31 to 50 mL/min
- severe: eCrCl, ≤30 mL/min
- end-stage renal disease (ESRD): eCrCl, <10 mL/min.[2]

Overall, there is minimal information about the effects of renal disease on psychotropic therapy; our goal here is to summarize available data. We have created quick reference tables highlighting psychotropics that have renal dosing recommendations based on manufacturers' package inserts.

Antipsychotics

First-generation antipsychotics (FGAs). Dosage adjustments based on renal function are not required for any FGA, according to manufacturers' package inserts. Some of these antipsychotics are excreted in urine, but typically as inactive metabolites.

Although there are no dosage recommendations based on renal function provided by the labeling, there has been concern about the use of some FGAs in patients with renal impairment. Specifically, concerns center around the piperidine phenothiazines (thioridazine and mesoridazine) because of the increased risk of electrocardiographic changes and medication-

Practice Points

- Renal disease can play a significant role in **altering the pharmacokinetics of medications**, especially in elimination or clearance and plasma protein binding.
- **Most psychotropics can be used safely** in patients with mild or moderate renal impairment.
- **Dosage adjustment and caution** should be employed when using a psychotropic as severity of renal impairment increases.

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Table 1

Second-generation antipsychotics: Recommended dosage adjustments in renal impairment

Medication	Mild renal impairment	Moderate renal impairment	Severe renal impairment	ESRD or dialysis
Clozapine[8]	None	None	Dosage adjustment may be necessary in the setting of significant renal impairment	
Risperidone[9]	None	None	Initial dosage: 0.5 mg twice daily Increase in increments of ≤0.5 mg At a dosage of >1.5 mg twice daily, only increase at interval of ≥1 week	
Paliperidone[10]	Initial: 3 mg once daily (maximum dosage, 6 mg/d)	1.5 mg once daily initially (maximum dosage, 3 mg/d)		Use not recommended
Lurasidone[11]	None	Initial: 20 mg/d (maximum dosage, 80 mg/d)		

eCrCl: estimated creatinine clearance; ESRD: end-stage renal disease

induced arrhythmias in renal disease due to electrolyte imbalances.[3,4] Additionally, there is case evidence[5] that phenothiazine antipsychotics could increase a patient's risk for hypotension in chronic renal failure. Haloperidol is considered safe in renal disease because <1% of the medication is excreted unchanged through urine.[6]

Second-generation antipsychotics (SGAs). Overall, SGAs are considered safe in patients with renal disease. Most SGAs undergo extensive hepatic metabolism before excretion, allowing them to be used safely in patients with renal disease.

Sheehan et al[7] analyzed the metabolism and excretion of SGAs, evaluating 8 antipsychotics divided into 4 groups: (1) excretion primarily as an unchanged drug in urine, (2) changed drug in urine, (3) changed drug in feces, (4) and unchanged drug in feces.

- Paliperidone was found to be primarily excreted as an unchanged drug in urine.
- Clozapine, iloperidone, olanzapine, quetiapine, and risperidone all were found to be primarily excreted as a changed drug in urine.
- Aripiprazole and ziprasidone were found to be primarily excreted as a changed drug in feces.

The manufacturers' package inserts for clozapine, paliperidone, risperidone, and lurasidone have recommended dosage adjustments based on renal function (***Table 1***).[8-11]

Ziprasidone. Although ziprasidone does not have a recommended renal dosage adjustment, caution is recommended because of the risk of electrocardiographic changes and potential for medication-induced arrhythmias in patients with electrolyte disturbances secondary to renal disease. A single-dosage study of ziprasidone by Aweeka et al[12] demonstrated that the pharmacokinetics of ziprasidone are unchanged in patients with renal impairment.

Asenapine. A small study by Peeters et al[13] evaluated the pharmacokinetics of asenapine in hepatic and renal impairment and found no clinically relevant changes in asenapine's pharmacokinetics among patients with any level of renal impairment compared with patients with normal renal function.

Aripiprazole. Mallikaarjun et al[14] completed a small study evaluating the pharmacokinetics of aripiprazole in patients with renal impairment. They found that the pharmacokinetics of aripiprazole in these patients is no different than it is in patients

Clinical Point

Most SGAs undergo extensive hepatic metabolism before excretion, allowing them to be used safely in patients with renal disease

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with normal renal function who are taking aripiprazole.

Quetiapine. Thyrum et al[15] conducted a similar study with quetiapine, which showed no significant difference detected in the pharmacokinetics of quetiapine in patients with renal impairment. Additionally, quetiapine had no negative effect on patients' creatinine clearance.

Lurasidone. During clinical trials of lurasidone in patients with mild, moderate, and severe renal impairment, the mean C_{max} and area under the curve was higher compared with healthy patients, which led to recommended dosage adjustments in patients with renal impairment.[11]

As mentioned above, renal impairment decreases the protein binding percentage of medications. Hypothetically, the greater the protein binding, the lower the recommended dosage in patients with renal impairment because the free or unbound form correlates with efficacy and toxicity. Most FGAs and SGAs have the protein-binding characteristic of ≥90%.[16] Although it seems this characteristic should result in recommendations to adjust dosage based on renal function, the various pharmacokinetic studies of antipsychotics have not shown this factor to play a role in the manufacturers' recommendations.

Antidepressants

Comorbidity rates of depression in patients with renal disease range from 14% to 30%, making use of antidepressants in renal disease common.[4] Antidepressants primarily are metabolized hepatically and excreted renally. ***Table 2***[17-27] summarizes recommended dosing adjustments for antidepressants.

Selective serotonin reuptake inhibitors. Escitalopram is the (S)-enantiomer of the racemic antidepressant citalopram, both of which have been shown to decrease renal clearance in patients with mild or moderate renal impairment. However, according to the package insert, no dosage adjustments are needed.[17] No extensive studies have been conducted on escitalopram or citalopram, but each should be initiated at a reduced dosage and the titration schedule should be prolonged in patients with severe renal impairment or ESRD.[17,18]

The plasma concentration of paroxetine has been noted to be elevated in patients with severe renal impairment, and the half-life can increase to nearly 50%.[4] Paroxetine should be initiated at 10 mg/d, and then titrated slowly in patients with severe renal impairment.[19,28]

The pharmacokinetics of fluoxetine are unchanged in any stage of renal impairment. Patients in active renal dialysis report good tolerability and efficacy.[4]

Serotonin-norepinephrine reuptake inhibitors. Venlafaxine and its metabolite O-desmethylvenlafaxine (desvenlafaxine) are primarily excreted via renal elimination. Studies have shown that mild renal impairment can have an effect on plasma levels of the drug, and that moderate or severe impairment can increase the venlafaxine plasma concentration. According to the package insert, a dosage reduction of 50% is recommended for desvenlafaxine and venlafaxine.[20,21]

No significant pharmacokinetic changes with duloxetine have been noted in patients with mild or moderate renal impairment.[22] However, duloxetine's major metabolites, which are excreted renally, have been measured to be as much as 7 to 9 times higher in patients with ESRD compared with healthy subjects; therefore, it is recommended to avoid duloxetine in patients with severe renal disease.[4,22]

Our review of the literature produced limited recommendations on dosing milnacipran and its enantiomer levomilnacipran in renally impaired patients. The milnacipran package insert cautions its use in moderate renal impairment and recommends a 50% dosage reduction to 100 mg/d (50 mg twice daily) in patients with severe renal impairment.[23] Dosage recommendations for

Clinical Point

The plasma concentration of paroxetine has been noted to be elevated in patients with severe renal impairment

Table 2

Antidepressants: Recommended dosage adjustments in renal impairment

Medication	Mild renal impairment	Moderate renal impairment	Severe renal impairment	ESRD or dialysis
Escitalopram[17]	None	None	(eCrCl <20 mL/min) No information available Use caution: Start at a reduced dosage and titrate slowly	
Citalopram[18]	None	None	Use caution: Start at a reduced dosage and titrate slowly	
Paroxetine[19]	None	None	Initial dosage: 10 mg/d Maximum dosage: 40 mg/d	
Venlafaxine[20]	(GFR 10 to 70 mL/min) Decrease dosage by 25% to 50%			Decrease dosage by 50% and withhold until dialysis is complete
Desvenlafaxine[21]	None	50 mg/d (do not titrate)	50 mg every other day (do not titrate)	
Duloxetine[22]	None	None	(GFR <30 mL/min) Avoid use	
Milnacipran[23]	None	Use caution	Decrease dosage by 50%	Relative contraindication
Levomilnacipran[24]	None	80 mg/d	40 mg/d	Relative contraindication
TCAs[25]	None	Decrease by 50% in geriatric patients		
Bupropion[26,27]	(GFR <90 mL/min) Consider reducing the dosage or frequency	75 mg once daily		
	None		150 mg every 3 days	

eCrCl: estimated creatinine clearance; ESRD: end-stage renal disease; GFR: glomerular filtration rate; TCA: tricyclic antidepressants

Clinical Point

TCAs are predominantly metabolized hepatically, glucuronidated, and then eliminated renally

levomilnacipran are 80 mg/d for moderate renal impairment and 40 mg/d for severe impairment. Both agents have relative contraindications for ESRD.[23,24]

Tricyclic antidepressants (TCAs) are predominantly metabolized hepatically, glucuronidated, and then eliminated renally. Desipramine, imipramine, and nortriptyline have nonspecific package insert recommendations for modified dosing in geriatric patients because of an age-related decrease in renal clearance.[29-31] Review articles assert that elevated glucuronidated metabolites could increase patients' sensitivity to side effects of TCAs. Because of concerns regarding elevated glucuronidated metabolites, it has been proposed to initiate TCAs at a low dosage, titrate slowly, and maintain the lowest effective dosage in patients with renal impairment.[25]

Monoamine oxidase inhibitors (MAOIs) and other antidepressants. The package inserts of the MAOIs isocarboxazid, phenelzine, selegiline, and tranylcypromine provide limited data and dosage recommendations for use in the context of renal impair-

Table 3

Mood stabilizers: Recommended dosage adjustments in renal impairment

Medication	Mild renal impairment	Moderate renal impairment	Severe renal impairment	ESRD or dialysis
Lithium[41]	None	None	Relative contraindication	
Lamotrigine[44]	None	None	Reduced maintenance dosage may be effective	
Oxcarbazepine[46]	None	None	IR: Initiate at 50% of the usual starting dosage (300 mg/d) and titrate slowly	
			ER: Initiate at 300 mg/d; may be titrated in increments of 300 to 450 mg/d weekly	

eCrCl: estimated creatinine clearance; ER: extended release; ESRD: end stage renal disease: IR: immediate release

Clinical Point

Extra vigilance is required when using MAOIs in patients with renal disease because of an increased risk of dialysis-induced hypotension

ment.[32-36] Isocarboxazid should not be used in patients with severe renal impairment, according to the prescribing information.[32] There are no dosing recommendations for transdermal selegiline in mild, moderate, or severe renal impairment.[37] Extra vigilance is required when using MAOIs in patients with renal disease because of an increased risk of dialysis-induced hypotension (orthostatic hypotension is a common adverse effect of MAOIs).[38]

Bupropion is primarily metabolized hepatically to the active metabolite hydroxybupropion. Plasma levels of this metabolite at steady state are reported to be 10 times greater than bupropion's concentration levels in healthy subjects; plasma levels are further increased in mild renal impairment.[26] Hydroxybupropion is not dialyzable, which can increase the risk of toxicity with bupropion therapy in patients with renal impairment.[3] If bupropion effectively treats depression in patients with declining renal function, specifically severe renal impairment and ESRD, then decreasing the dosage to 150 mg every 3 days is recommended to lessen the risk of toxicity.[27]

Mood stabilizers

Lithium has the most published literature on dosing adjustments with renal impairment. Many providers are inclined to discontinue lithium use at the first sign of any change in renal function; however, monitoring, prevention, and treatment guidelines for lithium are well established after many years of research and clinical use.[39] Lithium's prescribing information recommends dosage adjustment in mild to moderate renal impairment and lists severe renal impairment and ESRD as relative contraindications.[40]

A recent study proposes more assertive use of lithium in patients with renal impairment of any severity. Rej et al[41] compared continued lithium treatment to discontinuing treatment in geriatric patients with chronic renal failure, and reported (1) a statistically insignificant difference in renal function between groups at 2 years and (2) a "trending decrease" in renal function at 5 years in the lithium treatment group. With closely monitored plasma levels, lithium treatment is considered a workable treatment for patients with moderate renal impairment when mood stabilizer treatment has been effective.[42]

Lamotrigine and its main glucuronidated metabolite, lamotrigine-2N-glucuronide (L-2-N-G), are primarily excreted renally. In severe renal impairment and ESRD, the L-2-N-G levels are elevated but are not pharmacologically active and, therefore, do not affect plasma concentration or efficacy of lamotrigine.[43] Although data are limited regarding

the use of lamotrigine in severe renal impairment and ESRD, Kaufman[44] reported a 17% to 20% decrease in concentration after dialysis—suggesting that post-dialysis titration might be needed in these patients.

Oxcarbazepine is metabolized by means of cytosolic enzymes in the liver to its primary pharmacologically active metabolite, 10-monohydroxy, which is further metabolized via glucuronidation and then renally excreted. There are no dosage adjustment recommendations for patients with an eCrCl >30 mL/min.[45] Rouan et al[46] suggest initiating oxcarbazepine at 50% of the recommended dosage and following a longer titration schedule in patients with an eCrCl 10 to 30 mL/min. No dosing suggestions for severe renal impairment and ESRD were provided because of study limitations; however, the general recommendation for psychotropic agents in patients in a severe stage of renal impairment is dosage reduction with close monitoring.[46]

Table 3[41,44,46] summarizes dosage adjustments for mood stabilizers in patients with renal impairment.

Related Resources

- Cohen LM, Tessier EG, Germain MJ, et al. Update on psychotropic medication use in renal disease. Psychosomatics. 2004;45(1):34-48.
- Baghdady NT, Banik S, Swartz SA, et al. Psychotropic drugs and renal failure: translating the evidence for clinical practice. Adv Ther. 2009;26(4):404-424.

Drug Brand Names

Aripiprazole • Abilify
Asenapine • Saphris
Bupropion • Wellbutrin
Citalopram • Celexa
Clozapine • Clozaril, Fazaclo
Desipramine • Norpramin
Desvenlafaxine • Pristiq
Duloxetine • Cymbalta
Escitalopram • Lexapro
Fluoxetine • Prozac
Haloperidol • Haldol
Iloperidone • Fanapt
Imipramine • Tofranil
Isocarboxazid • Marplan
Lamotrigine • Lamictal
Levomilnacipran • Fetzima
Lithium • Eskalith, Lithobid
Lurasidone • Latuda
Mesoridazine • Serentil
Milnacipran • Savella
Nortriptyline • Pamelor
Olanzapine • Zyprexa
Oxcarbazepine • Trileptal
Paliperidone • Invega
Paroxetine • Paxil
Phenelzine • Nardil
Quetiapine • Seroquel
Risperidone • Risperdal
Selegiline • EMSAM, Eldepryl
Thioridazine • Mellaril
Tranylcypromine • Parnate
Venlafaxine • Effexor, Effexor XR
Ziprasidone • Geodon

Clinical Point

Monitoring, prevention, and treatment guidelines for lithium are well established after many years of research and clinical use

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This month's quickpoll

Mr. R, age 35, begins clozapine treatment for treatment-refractory schizophrenia during his inpatient stay. He has no significant medical history. Screening labs and baseline electrocardiogram (ECG) are within normal limits. Three days after initiating clozapine, Mr. R develops tachycardia with an otherwise normal physical exam and negative review of systems. A repeat ECG is notable only for sinus tachycardia. **What is the best next step?**

- ☐ Stop clozapine
- ☐ Wait and monitor
- ☐ Initiate propranolol
- ☐ Initiate atenolol

See "**Rediscovering clozapine: Adverse effects develop—what should you do now?**" *pages 40-46,48,49*

Visit CurrentPsychiatry.com to answer the Quick Poll and see how your colleagues responded.

JUNE POLL RESULTS

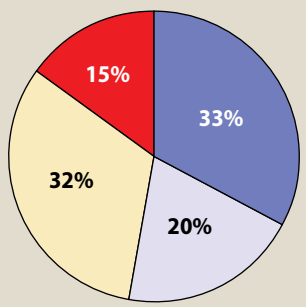
Ms. B, age 29, reports that fatigue, sadness, and feelings of worthlessness have compromised her work and eroded her friendships. You make a diagnosis of major depressive disorder; prescribe citalopram, 20 mg/d; and refer her for cognitive-behavioral therapy. At 2-month follow-up, you notice that Ms. B has gained 10 lb. **What would you do to address Ms. B's weight gain?**

33% Recommend that she reduce portion size at meals and exercise 45 minutes a day

20% Stop citalopram and switch to vortioxetine, 10 mg/d, and titrate to 20 mg/d

32% Refer her to a nutritionist for education on making healthy diet choices

15% Add bupropion, 100 mg, 3 times a day




How to control weight gain when prescribing antidepressants

Address diet and exercise first, then consider switching antidepressants or prescribing an adjunctive agent

SUGGESTED READING:

MacDaniels JS, Schwartz TL. Current Psychiatry. 2015;15(6):30-32,35,36,38,39,47,48.

Data obtained via CurrentPsychiatry.com, June 2016

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