
بسم الله الرحمن الرحيم

Dosage adjustment of psychotropic medications in hepatic impairment (HI)a

Antidepressants

MAOIs	Potentially hepatotoxic. Use is contraindicated in HI
SSRIs	Decreased clearance and prolonged half-life. Initial dose should be reduced by 50%; subsequent incremental increases should be made at longer intervals than usual. Target dosages will be lower than usual.
TCAs	Potentially serious hepatic effects. No dosing guidelines.
Bupropion	Decreased clearance. Mild HI: use reduced dosage and/or dosing frequency. In moderate to severe HI, do not exceed 75 mg/day for IR tablets, or 100 mg/day (SR) or 150 mg every other day (SR and XL).

Desvenlafaxine Primarily metabolized by conjugation. No adjustment in starting dose. Do not exceed 100mg/day in moderate to severe HI.

Duloxetine Reduced metabolism and elimination. Use is contraindicated in HI.

Mirtazapine, selegiline, trazodone Exercise caution in HI. No dosing guidelines.

Nefazodone May cause hepatic failure. Avoid use in patients with active liver disease.

Venlafaxine Decreased clearance of venlafaxine and its active metabolite O-desmethylvenlafaxine. Dosage should be reduced by 50% in mild to moderate HI.

Second-generation antipsychotics

Asenapine, cariprazine	No dosage adjustment needed in mild to moderate HI. Use in severe HI not recommended.
Brexpiprazole	Reduced maximum dose in moderate to severe HI; 2 mg/day for MDD; 3 mg/day for schizophrenia.
Clozapine	Discontinue in patients with marked transaminase elevations or jaundice. No specific dosing guidelines, but dosage reduction may be necessary.
Iloperidone	Pharmacokinetics in mild or moderate HI unknown. Use in severe HI not recommended. Lurasidone Reduce initial dosage in HI. Maximum dosage is 80 mg/day in moderate HI and 40 mg/day in severe HI.

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Olanzapine	Periodic assessment of LFTs is recommended.
Quetiapine	Clearance decreased 30%. For IR, start at 25 mg/day; increase by 25–50 mg/day; for XR, start at 50 mg/day; increase in 50-mg/day increments
Risperidone	Free fraction increased 35%. In severe HI, starting dosage and dose increments should not exceed 0.5 mg bid. Increases beyond 1.5 mg bid (3 mg/day) should be made at intervals of at least 1 week.
Ziprasidone	Increased half-life and serum level in mild to moderate HI. No dosage adjustments recommended.

First-generation antipsychotics

Haloperidol and others	All metabolized in the liver. No specific dosing recommendations. Phenothiazines (e.g., chlorpromazine, thioridazine) should be avoided. If nonphenothiazines are used, reduce dosage and titrate more slowly than usual.

Anxiolytic and sedative-hypnotic drugs

Alprazolam	Decreased metabolism and increased half-life. Reduce dosage by 50%. Avoid use in patients with cirrhosis.
Buspirone	Half-life prolonged; AUC increased 13-fold. Use in severe HI not recommended.
Chlordiazepoxide, clonazepam, diazepam, flurazepam, triazolam	Reduced clearance and prolonged half-life. Avoid use in HI if possible.
Lorazepam, oxazepam, temazepam	Metabolized by conjugation; clearance not affected. No dosage adjustment neededLorazepam is the preferred agent.

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Ramelteon	Exposure increased 4-fold in mild HI and >10-fold in moderate HI. Use with caution in moderate HI. Use in severe HI not recommended.
Zaleplon, zolpidem	Reduced clearance. Maximum dose is 5 mg in mildto moderate HI. Use in severe HI not recommended.
Eszopiclone	No dosage adjustment needed for mild to moderateHI. In severe HI, exposure is doubled; recommend 1 mg initial dose with a maximum of 2 mg.
Zopiclone	Initial dose 3.75 mg in mild to moderate HI; may increase to 5 mg with caution. Use contraindicated in severe HI.

Mood stabilizers/anticonvulsants

Carbamazepine	Perform baseline LFTs and periodic evaluations during therapy. Discontinue for active liver disease or aggravation of liver dysfunction.No dosing guidelines available.
Lamotrigine	Reduce initial, escalation, and maintenance dosages by 50% in moderate HI and by 75% in
Lithium	Rensaelvleyr eex HcrIe. ted; not metabolized. Dosage adjustment depends on fluid status.
Valproate	Reduced clearance and increased half-life. Reduce dosage and monitor LFTs. Avoid use in patients with severe HI. Use with caution in patients with history of hepatic disease.

Cholinesterase inhibitors

Donepezil	Mildly reduced clearance in cirrhosis. No specific recommendations for dosage adjustment.
Galantamine	Use with caution in mild to moderate HI. Dosage should not exceed 16 mg/day in moderate HI. Use in severe HI not recommended.
Rivastigmine	Clearance reduced 60%–65% in mild to moderate HI, but dosage adjustment may not be necessary.

Central nervous system stimulants

Atomoxetine	Reduce initial and target dosage by 50% in moderate HI and by 75% in severe HI.
Methylphenidate	Unclear association with hepatotoxicity, particularly when coadministered with other adrenergic drugs.
Armodafinil, modafinil	Decreased clearance. Reduce dosage by 50% in severe HI.

Note. AUC=area under the curve; IR=immediate release; LFTs=liver function tests; MAOI=mono-amine

oxidase inhibitor; MDD=major depressive disorder; SSRI=selective serotonin reuptake inhibitor;

SR=sustained-release; TCA=tricyclic antidepressant; XL=extended-release; XR=extended-release.

aHI severity rated as follows: mild HI=Child–Pugh class A (score <7); moderate HI=class B (score 7–9);

severe HI=class C (score 10–15).}

Source. Compiled from Asconapé 2014; Crone et al. 2006; Lexicomp 2017; Monti and Pandi-Perumal

2007; Park and Ishino 2013; Slim et al. 2016; and manufacturers' product information.

Dosage adjustment of psychotropic medications in renal insufficiency (RI)a

Antidepressants

Bupropion Water-soluble active metabolites may accumulate in ESRD. Consider reducing initial dosage.

Desvenlafaxine Approximately 45% of desvenlafaxine is excreted unchanged in urine. Mild RI: no dosage adjustment required. Moderate RI: dosage should not exceed 50 mg/day. Severe RI: 25 mg/day or 50 mg every other day.

Duloxetine Mild to moderate RI: population CPK analyses suggest no significant effect on apparent clearance. Not recommended for patients with ESRD or on dialysis.

Levomilnacipran Moderate RI: do not exceed dosage of 80 mg/day. Severe RI: do not exceed dosage of 40 mg/day. Use in ESRD not recommended.

Mirtazapine Moderate RI: clearance decreased by 30%. Severe RI: clearance decreased by 50%.

Paroxetine Mild RI: no dosage adjustment needed. Moderate RI: 50%–75% of usual dosage. Severe RI: initial dosage of 10 mg/day; increase as needed by 10 mg at weekly intervals to a maximum dosage of 40 mg/day. Controlled-release formulation: initial dosage of 12.5 mg/day; if needed by 12.5 mg at weekly intervals to a maximum of 50 mg/day.

Selegiline Active metabolite (methamphetamine) renally eliminated. Use with caution in RI. No dosing guidelines.

Venlafaxine Mild to moderate RI: 25%–50% of usual dosage. Severe RI or hemodialysis: 50–75% of usual dosage.

Second-generation antipsychotics

Asenapine, aripiprazole, clozapine, olanzapine, quetiapine	No dosage adjustment needed.
Brexpiprazole	If Clcr <60 mL/min, maximum dosage should not exceed 3 mg/day for schizophrenia or 2 mg/day for MDD.
Cariprazine	Dosage adjustment not needed in mild to moderate RI. Use in severe RI not recommended (not studied).
Iloperidone	Dosage adjustment not needed in mild to moderate RI. No recommendations for dosing in severe RI.

Lurasidone	Reduce initial dosage in moderate RI (Clcr 30–49 mL/min) and severe RI (Clcr <30 mL/min). Do not exceed 80 mg/day.
Paliperidone	Clearance decreased in RI. Mild RI: start at 3 mg/day, increasing to a maximum of 6 mg/day. Moderate to severe RI: start at 1.5 mg/day, increasing to 3 mg/day, as tolerated.
Paliperidone	palmitate requires dosage adjustment if Clcr <80 mL/min, and is contraindicated if Clcr <50 mL/min.
Risperidone	Clearance decreased in RI. Initiate therapy at 0.25–0.5 mg bid. Increases beyond 1.5 mg bid (3 mg/day) should be made at intervals of at least 1 week.

Anxiolytics and sedative-hypnotics

Chlordiazepoxide Severe RI: 50% of usual dosage.

Buspirone Use in severe RI not recommended

Mood stabilizers/anticonvulsants

Carbamazepine Severe RI: 75% of usual dosage.

Gabapentin Dosing based on creatinine clearance: Clcr>60 mL/min: 1,200 mg/day (400 mg tid). Clcr 30–60 mL/min: 600 mg/day (300 mg bid). Clcr 15–30 mL/min: 300 mg/day. Clcr<15 mL/min: 150 mg/day (300 mg every other day). Hemodialysis: 300–400 mg loading dose in patients who have never received gabapentin, then 200–300 mg after each dialysis session.

Lamotrigine Reduced dosages may possibly be effective in significant RI but have not been adequately studied. Use with caution.

Levetiracetam Dosing based on creatinine clearance: Clcr 50–80

Ziprasidone	No recommendations regarding dosage adjustment.
	Use the short-acting injection cautiously in RI because cyclodextrin may accumulate.
	mL/min: 500–1,500 mg every 12 hours. Clcr 30–50 mL/min: 500–1,000 mg every 12 hours. Clcr<30 mL/min: 250–750 mg every 12 hours. Hemodialysis: 500–1,000 mg every 24 hours. Supplemental dose of 250–500 mg after each dialysis session.
Lithium	Moderate RI: 50%–75% of usual dosage.
	Hemodialysis: supplemental dose of 300 mg after each dialysis session.
Oxcarbazepine	Initiate therapy at 300 mg/day (50% of usual starting dosage).

Pregabalin	Dosing based on creatinine clearance: Clcr 30–60 mL/min: 50% of usual dosage. Clcr 15–30 mL/min: 25% of usual dosage. Clcr<15 mL/min: 12.5% of usual dosage. Hemodialysis: supplemental dose may be needed after each 4-hour dialysis session; see manufacturer's recommendations.
Topiramate	Mild RI: 100% of usual dosage. Moderate RI: 50% of usual dosage. Severe RI: 25% of usual dosage. Hemodialysis: supplemental dose may be needed after each dialysis session.
Valproate	No dosage adjustment needed in RI, but valproate level measurements may be misleading due to reduced protein binding.

Cholinesterase inhibitors and memantine

Galantamine	Moderate RI: maximum dosage 16 mg/day. Severe RI: use not recommended.
Memantine	Extensive renal elimination. Mild to moderate RI: no dosage reduction needed. Severe RI: reduce dosage to 5 mg bid.

Central nervous system stimulants

Lisdexamfetamine

Severe RI: maximum dosage 50 mg/day. ESRD: maximum dosage 30 mg/day.

Antiparkinsonian agents

Amantadine	Dosing based on creatinine clearance: Clcr 80 mL/min: 100 mg twice daily. Clcr 60 mL/min: alternating daily doses of 100 mg once daily and 100 mg twice daily. Clcr 40 mL/min: 100 mg/day. Clcr 30 mL/min: 200 mg twice weekly. Clcr 20 mL/min: 100 mg three times weekly. Clcr 10 mL/min: alternating weekly doses of 100 mg once weekly and 200 mg once weekly. Hemodialysis: 200 mg once weekly.
Pramipexole	90% renal elimination; clearance of pramipexole is 75% lower in patients with severe RI (Clcr 20 mL/min) and 60% lower in moderate RI (Clcr 40 mL/min) compared with healthy volunteers. Interval between titration steps should be increased to 14 days in RLS patients with moderate to severe RI (Clcr 20–60 mL/min).

Note. Clcr=creatinine clearance; CPK=creatine phosphokinase; ESRD=end-stage renal disease; MDD=

major depressive disorder; RLS=restless legs syndrome.

aRI severity rated as follows: mild RI: Clcr 50–80 mL/min; moderate RI: 30–50 mL/min; severe RI:

<30 mL/min.

Source. Compiled from Asconapé 2014; Baghdady et al. 2009; Cohen et al. 2004; Crone et al. 2006;

Eyler et al. 2015; Lexicomp 2017; Periclou et al. 2006; and manufacturer' product information.


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