

# Amantadine

Gocovri, Osmolex ER, Symmetrel (discontinued)

*Dopamine-enhancing NMDA antagonist used for drug-induced extrapyramidal symptoms, parkinsonism, levodopa dyskinesia and fatigue.*

## USUAL ADULT DOSE

**100 mg PO BID (max 300 mg)**

## HALF-LIFE

**10-25 h; far longer in CKD**

## METABOLISM

**Minimal; renal excretion**

## ONSET

**EPS relief within days**

✔ **No FDA boxed warning** on the current US label.

## INDICATIONS

- FDA-approved for drug-induced extrapyramidal reactions in adults, which is the indication that matters most in psychiatric practice.
- FDA-approved for parkinsonism, including idiopathic, post-encephalitic and arteriosclerotic forms, usually as an adjunct rather than monotherapy.
- The extended-release capsule is approved for levodopa-induced dyskinesia and for OFF episodes in Parkinson disease on levodopa.
- Retains an approved influenza A indication, but CDC no longer recommends it because circulating strains are almost universally resistant.
- Used off-label for antipsychotic-induced parkinsonism and akathisia when adding anticholinergic burden is undesirable.
- Off-label for fatigue in multiple sclerosis and for apathy, irritability and aggression after traumatic brain injury, with modest evidence.

## DOSING & TITRATION

- Drug-induced extrapyramidal reactions: **100 mg** twice daily, increasing to 300 mg/day in divided doses if response is inadequate.
- Parkinsonism: **100 mg** once or twice daily, with doses up to 400 mg/day in divided doses only under close supervision.
- Extended-release capsules for levodopa-induced dyskinesia: **137 mg** at bedtime for one week, then **274 mg** at bedtime.
- Reduce for renal impairment: 100 mg daily at creatinine clearance 30-50, 100 mg every other day at 15-29, and 200 mg every 7 days below 15.
- Start patients over 65 at **100 mg** once daily, since age-related decline in creatinine clearance is the usual cause of toxicity.
- Do not stop abruptly in Parkinson disease, where withdrawal can precipitate a parkinsonian crisis or a syndrome resembling NMS.

## MECHANISM OF ACTION

- Weak non-competitive NMDA receptor antagonist, the property that underlies its anti-dyskinetic effect and its benefit for fatigue.
- Increases presynaptic dopamine release and blocks dopamine reuptake, raising striatal dopamine without direct receptor agonism.
- Mild anticholinergic activity contributes to relief of drug-induced parkinsonism and also to confusion in vulnerable patients.
- Its antiviral action comes from blockade of the influenza A M2 proton channel, now largely irrelevant because of resistance.
- Unlike benztropine it does not worsen tardive dyskinesia and produces much less cognitive impairment, which drives its psychiatric use.

## PHARMACOKINETICS

- Oral bioavailability is high at **86-94%** with peak concentrations 2-4 h after immediate-release dosing and no meaningful food effect.
- Elimination half-life is **10-25 h** with normal renal function but can extend to a week or more in end-stage renal disease.
- Amantadine is not appreciably metabolized: roughly **90%** is excreted unchanged in urine by filtration and active tubular secretion.
- Because clearance is renal, accumulation in kidney disease produces delirium, myoclonus, hallucinations and livedo reticularis.
- Hemodialysis removes only small amounts, so dialysis neither substitutes for dose reduction nor rescues toxicity quickly.

## ADVERSE EFFECTS

- Nausea, dizziness, insomnia, dry mouth and anorexia occur in roughly **5-10%** and are usually mild at standard doses.
- Livedo reticularis of the lower limbs and ankle edema are characteristic, dose-related, benign and reversible on stopping.
- Confusion, visual hallucinations and frank delirium occur most often in older patients, in renal impairment or with other anticholinergics.
- Anticholinergic effects including urinary retention, constipation and blurred vision matter in men with prostatic hypertrophy.
- Impulse control disorders such as gambling and hypersexuality, and worsening of psychosis, follow from its dopaminergic action.
- Rare but serious effects include corneal edema, leukopenia, suicidal ideation and a neuroleptic malignant-like syndrome on abrupt withdrawal.

## MONITORING

- Creatinine clearance at baseline and periodically, because renal function alone determines the correct dose.
- Mental status, hallucinations and sleep at each visit, particularly in patients over 65 or with cognitive impairment.
- Inspect the legs for livedo reticularis and check for peripheral edema, which are easily mistaken for vasculitis or heart failure.
- Track extrapyramidal response with a Simpson-Angus or Barnes akathisia rating when treating antipsychotic-induced symptoms.
- Ask directly about gambling, spending, sexual behavior and suicidal ideation, none of which patients report spontaneously.

## INTERACTIONS & CAUTIONS

- Additive anticholinergic burden with benztropine, tricyclics, diphenhydramine and oxybutynin, which markedly raises delirium risk.
- Other dopaminergic drugs increase both benefit and the risk of psychosis, especially in patients with schizophrenia.
- Triamterene-hydrochlorothiazide, quinine and quinidine compete for renal tubular secretion and raise amantadine concentrations.
- Alcohol and other central nervous system depressants add to dizziness, confusion and orthostatic symptoms, particularly in older adults.
- Live attenuated influenza vaccine should be separated from amantadine by about 2 weeks because of residual antiviral activity.

## SPECIAL POPULATIONS

- Pregnancy: avoid where possible, since first-trimester case reports describe cardiovascular and limb malformations.
- Lactation: amantadine enters human milk and may suppress lactation through its dopaminergic action, so it is not recommended.
- Pediatric use is established only for the influenza indication from age 1 year; there is no established pediatric dose for extrapyramidal symptoms.
- Geriatric patients need lower doses and closer surveillance for delirium, hallucinations, urinary retention and falls.
- Renal impairment drives every dose adjustment, down to **200 mg every 7 days** in end-stage disease including patients on hemodialysis.

## ☆ PRESCRIBING PEARLS

- Dose it by creatinine clearance; accumulation shows up first as confusion and hallucinations.
- Livedo reticularis of the legs is benign and dose-related, not vasculitis; do not panic.
- Good choice for antipsychotic EPS when anticholinergic burden must be kept down.

# References

- Adamas Pharmaceuticals. (2023). *GOCOVRI (amantadine) extended-release capsules [Prescribing information]*. U.S. Food and Drug Administration. <https://dailymed.nlm.nih.gov/dailymed/>
- American Psychiatric Association. (2020). *The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia* (3rd ed.). American Psychiatric Association Publishing.
- National Institute for Health and Care Excellence. (2017). *Parkinson's disease in adults* (NICE Guideline NG71). <https://www.nice.org.uk/guidance/ng71>
- National Library of Medicine. (2023). Amantadine. In *MedlinePlus*. <https://medlineplus.gov/druginfo/meds/a682064.html>
- Pahwa, R., Tanner, C. M., Hauser, R. A., Isaacson, S. H., Nausieda, P. A., Truong, D. D., ... Went, G. T. (2017). ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson disease (EASE LID study): A randomized clinical trial. *JAMA Neurology*, 74(8), 941-949. <https://doi.org/10.1001/jamaneurol.2017.0943>
- Stahl, S. M. (2021). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (5th ed.). Cambridge University Press.

## NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.