

Trazodone Causes Amphetamine False Positives. Not on Every Immunoassay Platform.

Clinical Scenario

A 38-year-old woman prescribed trazodone for insomnia flags positive for amphetamines at her drug court program; GC-MS returns negative. The enzyme immunoassay her lab uses is performing as designed.

The Pearl

Trazodone is metabolized to meta-chlorophenylpiperazine (mCPP), a structural analogue that cross-reacts with enzyme immunoassay (IA) amphetamine antibodies on multiple high-throughput platforms.^{1,2} A 2026 retrospective study of 55 emergency-department urines screened by enzyme IA, confirmed by GC-MS, then re-tested by immunochromatography (IC, lateral flow) found **enzyme IA produced 11 false positives versus 2 for IC (a fivefold difference), with trazodone, phentermine, ephedrine, procainamide, and tetracaine driving the excess.**³ Neither method cross-reacted with methylphenidate or synthetic cathinones.

The data carry a counterpoint: IC frequently cannot discriminate amphetamine from methamphetamine, and the authors recommend reporting IC amphetamine-class positives as 'amphetamine derivatives' rather than assigning a specific identity.

Why It Matters

False amphetamine positives carry real consequences in drug court, OTP, and employment-testing settings: missed doses, program sanctions, and custody implications. Trazodone is widely prescribed in these populations; phentermine, ephedrine, and pseudoephedrine are present in weight-loss and OTC medications; tetracaine and procainamide appear in clinical procedures and cardiac settings. A 2026 systematic review of 61 studies confirms the enzyme IA cross-reactant list remains an active clinical hazard across platforms and settings; not a historical footnote.²

Bottom Line: When an enzyme immunoassay amphetamine positive does not fit the clinical picture, identify the platform and confirm by GC-MS or LC-MS/MS before acting. Trazodone (via mCPP), phentermine, ephedrine, tetracaine, and procainamide are enzyme IA cross-reactants that are typically negative on lateral flow and negative on LC-MS/MS.

References

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