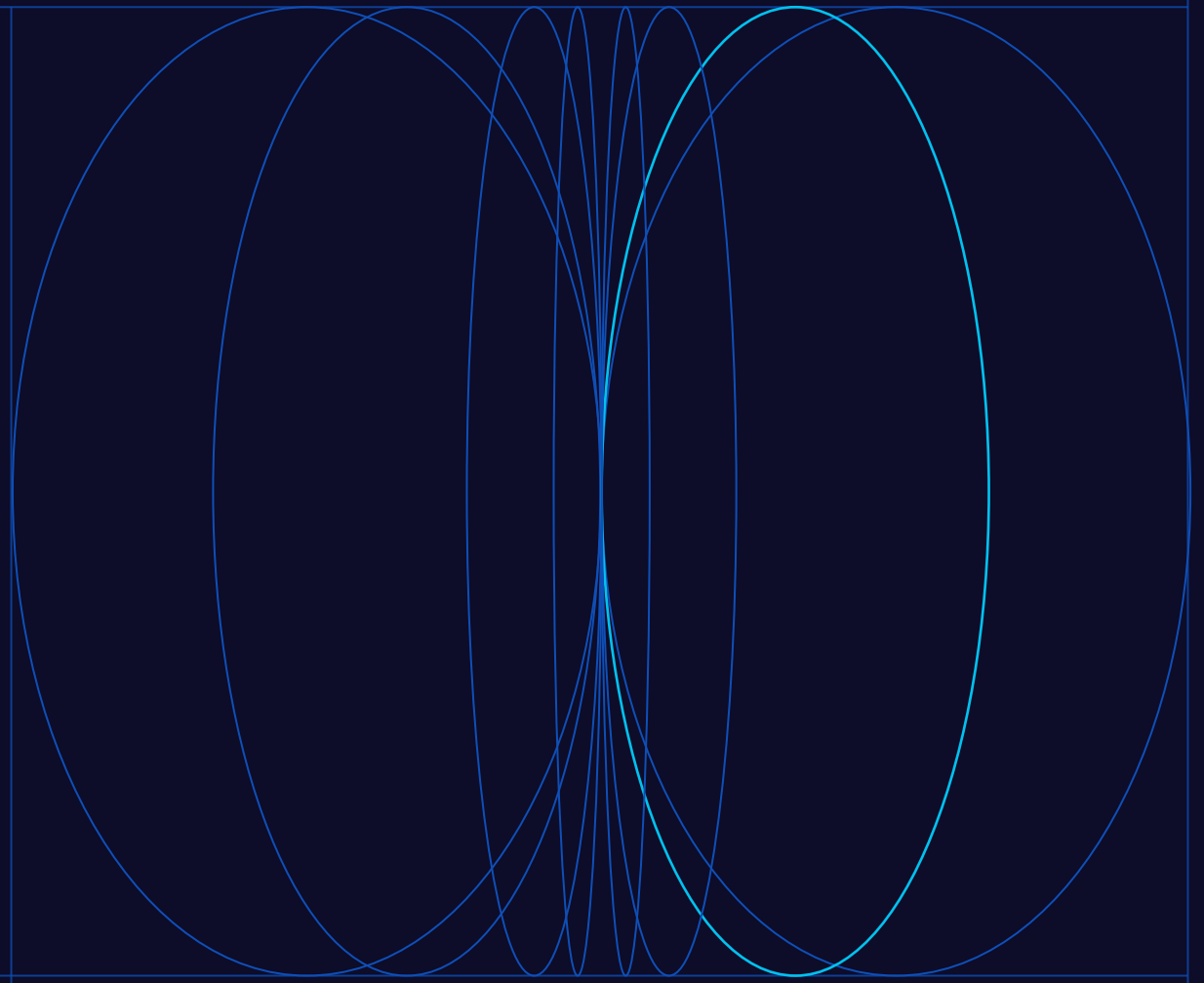
Sleuth



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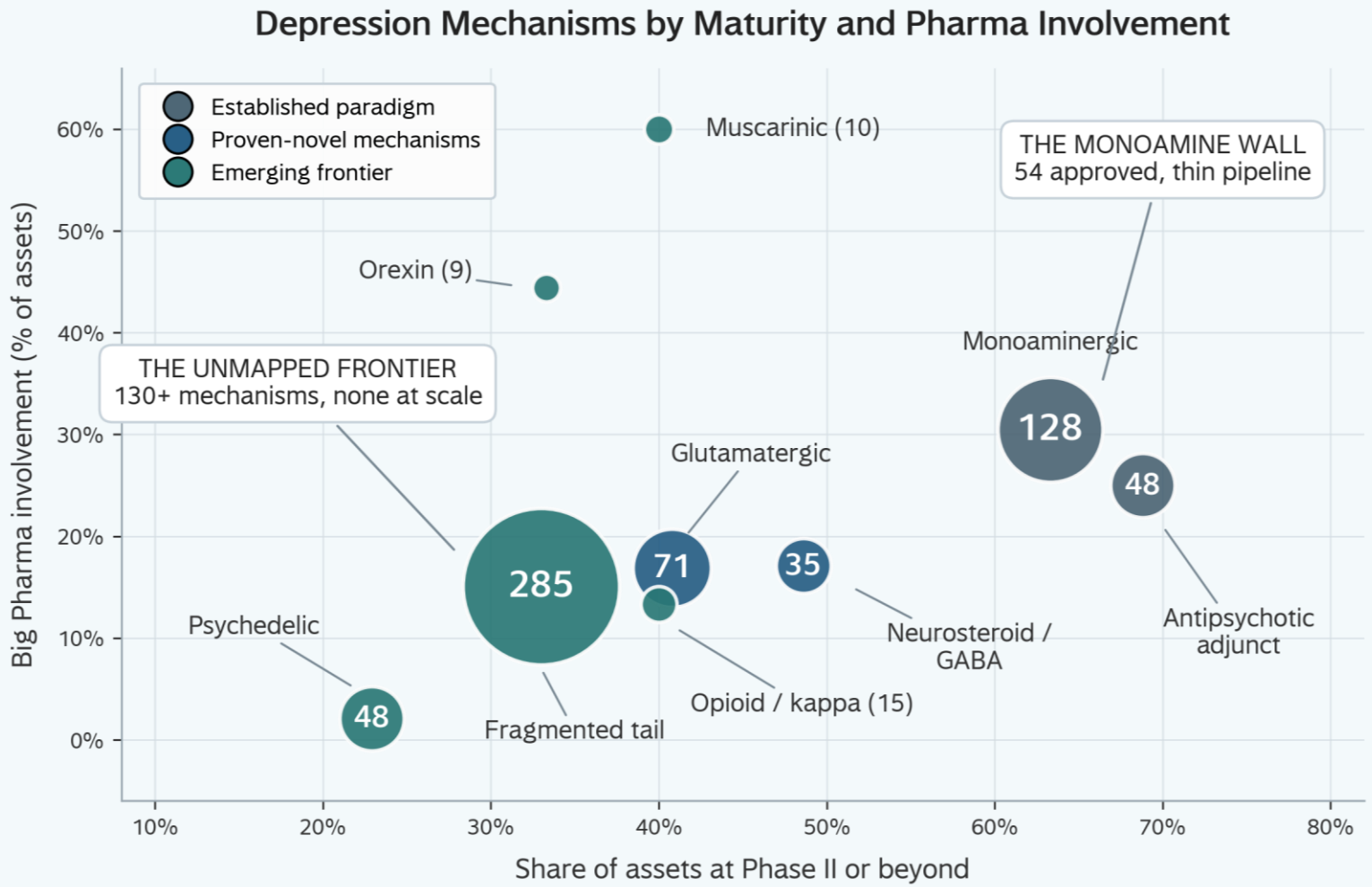
Biopharma insights
others miss

Depression R&D Is a Barbell, Consolidated and Fragmented at Once

Approvals locked on monoamines, the pipeline scattered across 130 mechanisms

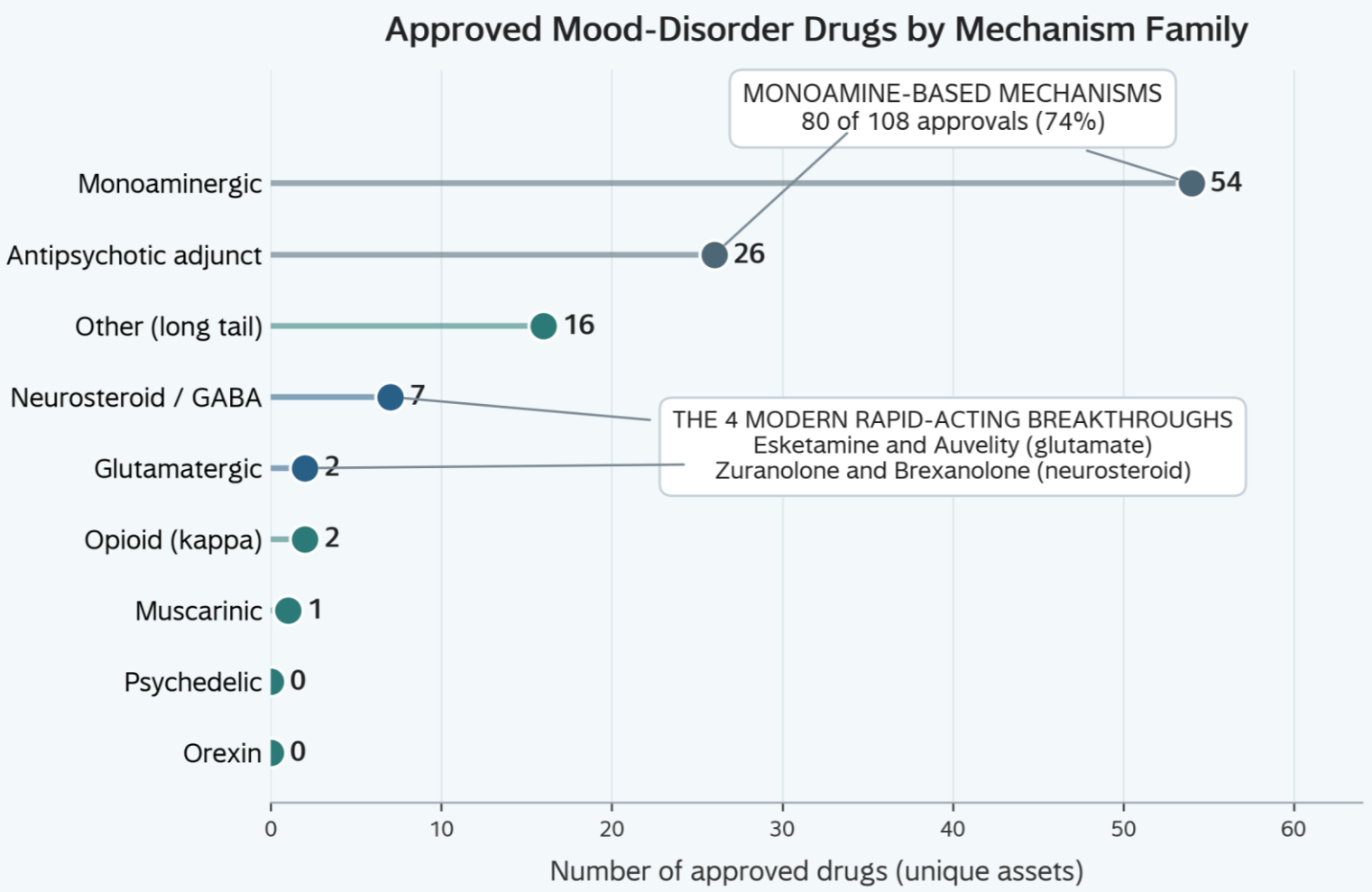


- The largest block in the pipeline is 130-plus distinct mechanisms, none holding more than a dozen assets.1
- 15 assets carry no disclosed mechanism at all, more than the entire psychedelic field.
- Big Pharma sits in 24% of that fragmented tail, versus 2% in psychedelics.
- The two monoamine families that hold nearly every approval are the consolidated end of the barbell.

Unique mood-disorder assets (n=649) counted once at their highest development phase across unipolar and bipolar depression indications. Imaging tracers, digital therapeutics, and microbiome assets excluded. The fragmented tail (285 assets) spans 130-plus disclosed mechanisms, led by ion channels, cannabinoids, HPA-axis, and metabolic targets, plus 115 assets with no disclosed mechanis

Four Drugs in Twenty Years Broke Depression's Monoamine Lock

Only four modern approvals broke the paradigm, and all act fast

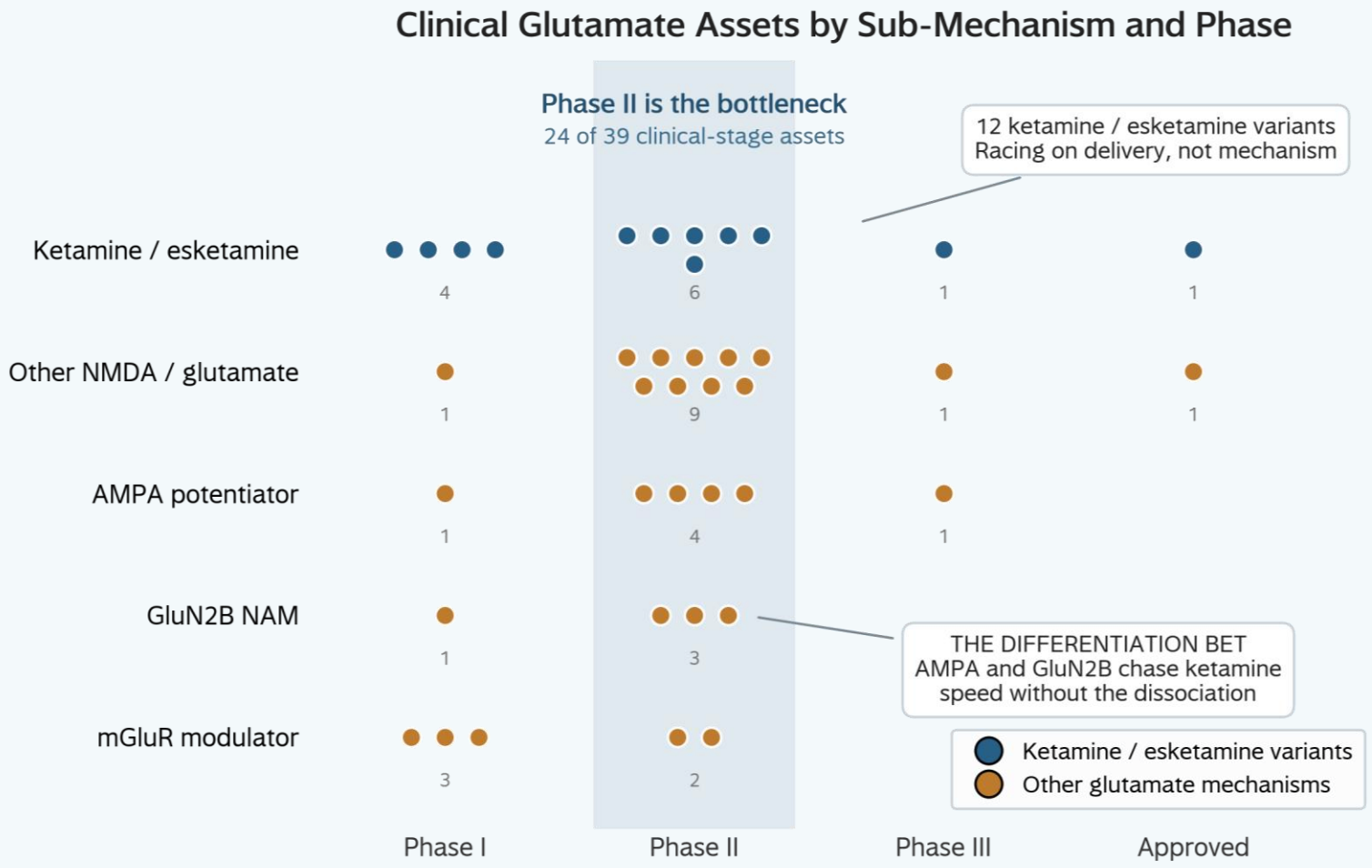


- Monoamines carry 80 of 108 approved depression drugs, three-quarters of the market on a 1990s playbook.
- The four exceptions share a rapid-relief claim, days to a week against an SSRI's four to eight weeks.
- One of them, brexanolone, was already pulled over its 60-hour infusion, undone by delivery not efficacy.
- Psychedelics and orexin have still produced zero approvals, despite deep and active clinical pipelines.

Approved unique assets in major depressive disorder and depressive disorder (n=108); excludes three approved digital therapeutics, plus imaging and microbiome. The neurosteroid total of seven includes five legacy combinations and anticonvulsants; of the modern novel-mechanism agents, brexanolone's FDA approval was withdrawn in April 2025 (its 60-hour infusion proved unviable), leaving oral zuranolone as the marketed neurosteroid.

Glutamate's Novel Wave Is a Twelve-Way Ketamine Race

Twelve ketamine variants in the clinic, feeding a 24-asset Phase II logjam

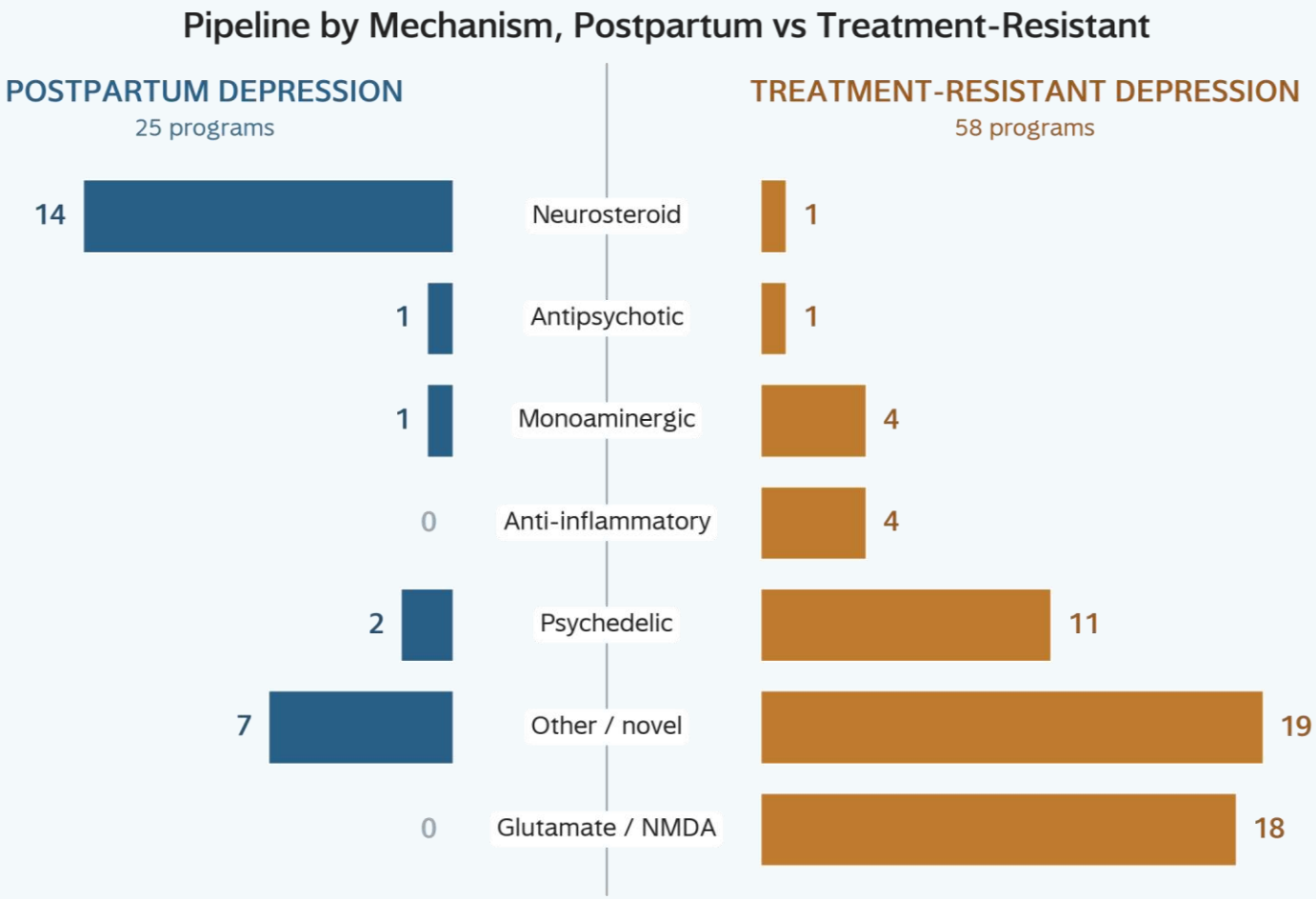


- Glutamate has 39 clinical assets, and 24 are stuck at Phase II, the obvious bottleneck.
- Twelve are ketamine or esketamine in another form, competing on how it is dosed rather than on biology.
- The real differentiation sits with ten AMPA and GluN2B programs chasing ketamine's speed without the dissociation.
- Inside glutamate, the winning question is no longer the target. It is tolerability and route of delivery.

Clinical-stage glutamatergic mood-disorder assets (n=39), counted once at highest phase; 32 preclinical assets and four PET imaging tracers excluded. Ketamine variants include racemic, R-enantiomer, oral, and intranasal forms across separate developers

Postpartum and Treatment-Resistant Are Two Different Games

One has a settled mechanism, the other has none



- Postpartum depression is a neurosteroid monoculture: 14 of 25 programs share one mechanism, so price and convenience decide.
- Treatment-resistant has no settled mechanism. Its 58 programs scatter across glutamate, psychedelics, anti-inflammatories, and a long novel tail.
- In postpartum, the win is a better oral neurosteroid, on a fast path into a commoditizing field.
- Treatment-resistant offers open biology and the deepest unmet need, against one of the toughest endpoints in the field.

Programs by mechanism family within each indication (postpartum depression n=25; treatment-resistant depression n=58); digital therapeutics, imaging, and microbiome excluded. 5-MeO-DMT agents classified as psychedelic. Brexanolone, the IV neurosteroid first approved for PPD, had its approval withdrawn in April 2025; oral zuranolone remains, which is why the PPD race is now about oral convenience and price.