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A nasal spray reaches a woman's brain differently depending on the week, and it may explain why a promising brain drug looked like a failure

New research in Genomic Psychiatry shows that intranasal davunetide reaches the brain in higher amounts in female mice when estrogen peaks, with a parallel signal in healthy adults, raising the possibility that earlier trials mixing the sexes obscured a r

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TEL AVIV, Tel Aviv District, ISRAEL, 16 June 2026 — Consider what we ask of a clinical trial. We gather people who differ in nearly every way that matters, we give them the same drug at the same dose, and then we average the result and call the average truth. Most of the time the trick holds. Sometimes it lies. A new study published in Genomic Psychiatry makes the case that for at least one promising brain drug, the average has been lying to us, and that the lie has a mechanism, a schedule, and a sex.

The drug is davunetide, also known as NAP, a short fragment of a protein the brain makes to protect its own wiring. For years it carried the hopes of researchers working on tauopathies, the family of disorders, Alzheimer's disease among them, in which a protein called tau goes wrong and neurons falter. Davunetide stabilizes the microscopic scaffolding inside nerve cells, the microtubules along which cargo travels. In theory it should help. In the largest trial that tested it, in a brutal disorder called progressive supranuclear palsy, it did not. The result read like an ending.

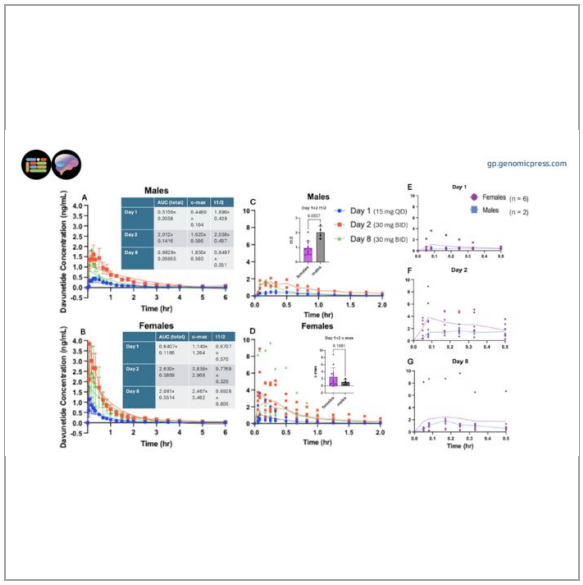

IMAGE:

SEX-DEPENDENT DAVUNETIDE CONCENTRATIONS OVER TIME IN HUMANS.

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The Average That Hid an Effect

But endings deserve scrutiny. The team led by Professor Illana Gozes, who directs the Elton Laboratory for Molecular Neuroendocrinology at Tel Aviv University, had already noticed something in the wreckage of those earlier trials. When the data were pulled apart by sex, women appeared to respond when men did not. That is the kind of observation that either dies as a statistical ghost or points to something real underneath. To find out which, the researchers did something deceptively simple. They watched the drug move.

Using a fluorescent tag on the peptide and a live imaging system, they followed intranasal davunetide as it traveled into the bodies and heads of mice. Five animals at a time, photographed at intervals across two and a half hours. And here the story turns on a detail that most drug studies ignore entirely. The female mice were not in a single state. They were cycling. The researchers tracked each animal's place in the estrous cycle, the rodent counterpart to the menstrual cycle, by reading vaginal smears under a microscope against a published template.

When Estrogen Is High, More Drug Reaches the Head

The pattern was clean enough to be unsettling. During proestrus and estrus, the phases when estrogen runs highest, female mice took up significantly more drug in the head region than males did. The contrast was sharpest in proestrus, where the head measurement separated males and females with a p-value of 0.00029, and the head-to-body ratio with a p-value of 0.000004. As the cycle moved into metestrus, when estrogen falls toward its minimum, the difference between the sexes faded toward nothing. The hormone was not incidental. It tracked the drug.

In a larger mixed group, five males and five females imaged without sorting by cycle phase, the females still showed higher head uptake at every time point and a significantly higher head-to-body ratio, with a p-value of 0.000009. The body told a different story than the head, which is itself a clue. What reaches the brain is not the same as what circulates.

A Signal in People, Within the Limits of a Small Study

Mice are not women. The authors know this, and they say so plainly. So they turned to a human pharmacokinetic dataset from an earlier study of intranasal davunetide in healthy adults, two men and six women. The numbers are small, and the paper does not pretend otherwise. Yet the direction matched. Women trended toward higher peak concentrations, with the highest female peak more than double the highest male peak. Men, meanwhile, held the drug longer. When the first two days were grouped, the longer half-life in men reached statistical significance with a p-value of 0.0057, while the roughly two-fold higher peak concentration in women remained a trend, with a p-value of 0.1081.

“These sex-specific differences likely reflect a combination of hormonal regulation, tissue distribution, nasal physiology, and blood-brain barrier function,” the authors write, describing a picture in which no single factor decides the outcome. The drug crosses the delicate vessels of the nose and rides the circulation toward the brain, and that passage depends on the tone of the blood vessels, which depends, in turn, on estrogen.

What the Mice Made Visible

One observation in the study refuses to stay quiet. In the experiments on elderly animals, the male mice kept dying during the procedure. The authors report it directly, noting increased male vulnerability, and they fold it into the methods rather than dressing it up. It is the kind of asymmetry that makes an abstract claim about sex differences suddenly physical. Whatever is different between these bodies, it is different enough to matter at the edge of life.

The mechanistic threads the authors gather point in a consistent direction. Estrogen shapes blood-brain barrier integrity. The microtubules that davunetide targets help build that barrier, and estrogen restrains their excess growth. The protein behind davunetide, ADNP, is itself regulated by the estrous cycle and in turn helps regulate sex hormones. None of this is loose association reaching for significance. It is a network in which sex and hormone and drug are bound together, and the study is careful to mark where it is reporting a finding and where it is reaching toward an interpretation.

Why a Footnote Becomes a Warning

The honest limitations are considerable, and the paper does not bury them. Davunetide remains investigational. The mouse experiments often compared two or three females against a single male. The human cohort was tiny. The estrous staging relied on judgment calls made by eye. The authors name each of these, and the restraint is part of what makes the larger argument credible. They are not claiming a cure. They are claiming that the variable everyone averaged away was carrying information.

If they are right, the implication runs past this one molecule. Alzheimer's disease, the major tauopathy, strikes women at roughly twice the rate of men. A field that designs trials and doses without accounting for sex and hormonal state may keep producing flat averages that conceal living effects, and may keep shelving drugs that work for someone, just not for everyone at once. “Optimizing neuroprotective strategies will require purposeful accounting for biological sex as a core variable,” the authors conclude, and the sentence reads less like a flourish than like a correction owed.

We have spent a long time pretending the body is one body. This peer-reviewed work, modest in scale and careful in its claims, suggests something the clinic has been slow to absorb. A drug can be right for a person and wrong for the week. The woman in the trial and the man beside her were never taking the same medicine. They only thought they were.

The peer-reviewed research article in Genomic Psychiatry titled “Intranasal bioavailability is estrous-cycle regulated: Davunetide as a case study,” is freely available via Open Access, starting on 16 June 2026 in Genomic Psychiatry at the following hyperlink: https://doi.org/10.61373/gp026r.0039.

The full reference for citation purposes is: Blatt J, Guz LS, Shabat D, Gozes I. Intranasal bioavailability is estrous-cycle regulated: Davunetide as a case study. Genomic Psychiatry 2026. DOI: https://doi.org/10.61373/gp026r.0039. Epub 2026 Jun 16.

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COI STATEMENT

IG serves as VP Drug Development at Exonavis Therapeutics, developing davunetide for the ADNP syndrome (under patent protection, IG inventor). Other contributors have confirmed that no conflict of interest exists. The manuscript has been read and approved by all authors.

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