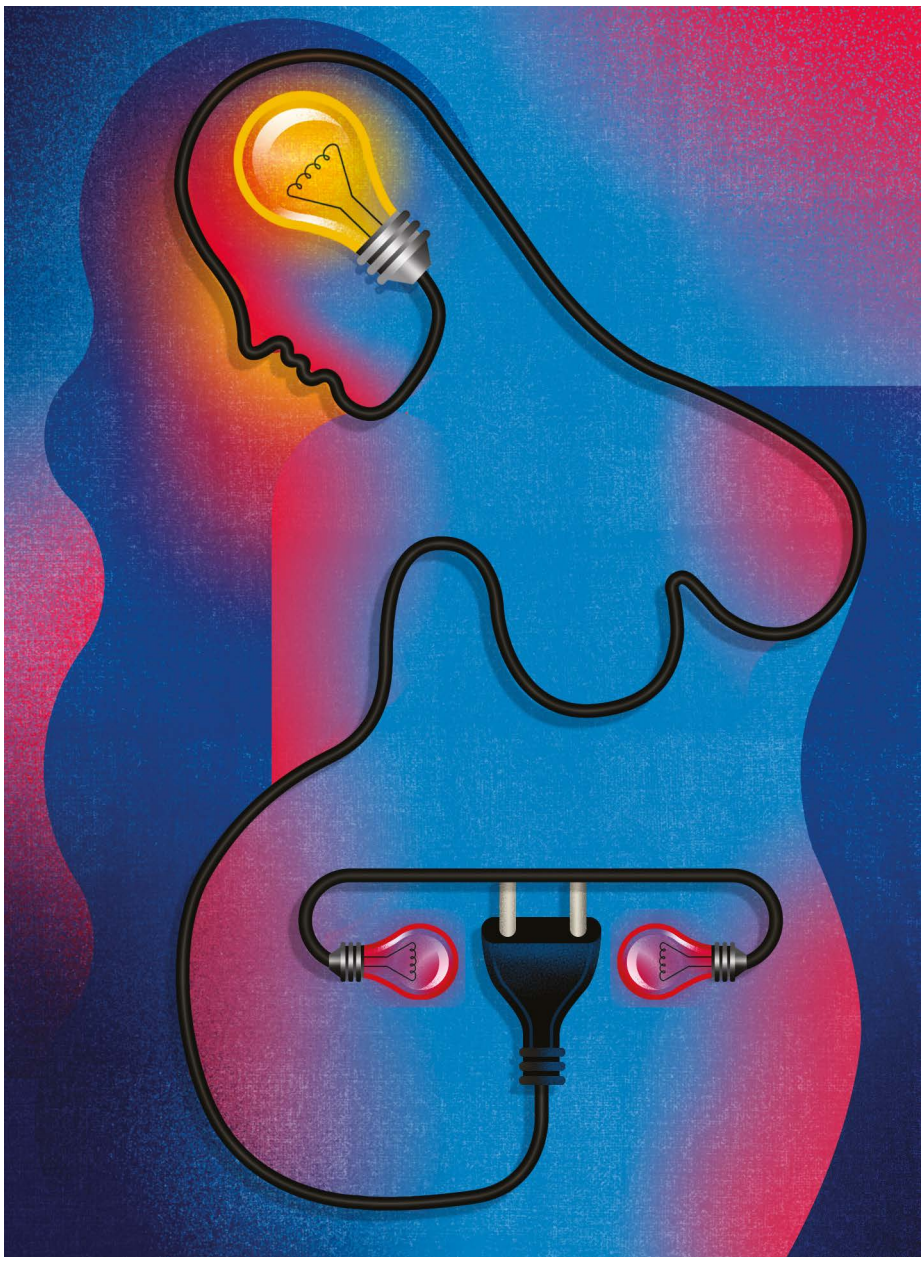


ILLUSTRATION BY MARIA CORTE

HOW THE RUN-UP TO MENOPAUSE CHANGES THE BRAIN

Women spend about one-third of their lives post-menopause. Researchers are only now learning how the transition to this phase affects brain health. **By Heidi Ledford**

When Naomi Rance first started studying menopause and the brain, she pretty much had the field to herself. And what she was discovering surprised her. In studies of post-mortem brains, she had found neurons in a region called the hypothalamus that roughly doubled in size in women after menopause[1]. "This was changing so much in postmenopausal women," says Rance, a neuropathologist at the University of Arizona in Tucson. "It had to be important."

This was the 1990s, and few other researchers were interested. Rance forged ahead on her own, painstakingly unravelling what the neurons were doing and finessing a way to study menopause symptoms in rats by tracking tiny temperature changes in their tails as a measure of hot flushes, a common symptom of menopause that is thought to be triggered in the hypothalamus.

Thirty years later, a drug called fezolinetant, based on Rance's discoveries, is being evaluated by the US Food and Drug Administration, with an approval decision expected in the first half of this year. If approved, fezolinetant could be a landmark: the first non-hormonal therapy to treat the source of hot flushes, a symptom that has become nearly synonymous with menopause and one that is experienced by about 80% of women going through the transition. (This article uses 'women' to describe people who experience menopause, while recognizing that not all people who identify as women go through menopause, and not all people who go through menopause identify as women.)

For Rance and others in the field, fezolinetant's progress to this point is a sign that research into the causes and effects of menopausal symptoms is finally being taken seriously. In the next few years, the global number of postmenopausal women is expected to surpass one billion. But many women still struggle to access care related to menopause, and research into how best to manage such symptoms has lagged behind. That is slowly changing. Armed with improved animal models and a growing literature on the effects of existing treatments, more researchers are coming into the field to fill that gap.

They increasingly recognize that menopause and the transition to it, a phase labelled perimenopause, could set the stage for brain health in later life, and there are even hints that it could correlate with the risk of neurodegenerative diseases, such as Alzheimer's disease.

Fezolinetant and similar drugs in the pipeline also represent a shift in thinking: from menopause as a condition of the female reproductive organs, to one that focuses on neurological causes and effects. "We think of menopause as being driven by changes in the ovary," says Hadine Joffe, who studies mental health and ageing in women at Harvard

Medical School in Boston, Massachusetts. "The notion of the brain at the helm of menopause, that is a different concept."

Gradual halt

Menopause is defined as the cessation of menstruation for at least 12 successive months, and typically occurs between the ages of 45 and 55. But the shutdown of ovarian function associated with menopause rarely happens overnight: instead, many women will experience years of bumpy ovarian decline, with erratic production of key sex hormones such as oestrogen and progesterone. "It's not a night and day difference, it's a long, long process," says Ami Raval, who studies reproduction and neurology at the University of Miami in Florida. "The ovary is slowly sending the signal, 'hey, it's time to shut off our physiology.'"

That can mean years of fluctuating hormones that no longer rise and fall in their once-predictable patterns. During this time of perimenopause, circuits in the brain that previously relied on oestrogen signalling can be left floundering, says Roberta Brinton, a neurobiologist at the University of Arizona in Tucson.

Oestrogen does a lot for the brain: it stimulates glucose uptake and energy production. Once the transition to menopause is complete, neurons grow accustomed to its absence. But in the perimenopausal period, levels of the hormone can crash one week only to soar the next. The result can be a period of neuronal discord in which brain cells are periodically deprived of oestrogen, but not for long enough to forge the pathways needed to adapt to life without it, says Brinton.

Perimenopause is also when many of the characteristic symptoms of menopause occur. Hot flushes are the hallmark of perimenopause; other symptoms include irregular periods, anxiety, high blood pressure and the dreaded 'brain fog' that impedes concentration. "There is a notion that women in their perimenopause shouldn't be symptomatic, that they 'shouldn't be complaining yet'," says Joffe. "But it's actually the time when people are the most symptomatic, in some ways."

It could also be a key time to intervene using treatments that ease the transition into menopause, and which could slow the pace of age-related diseases that seem to accelerate afterwards. Raval and other researchers think that this perimenopausal transition could lay the groundwork for post-menopausal increases in the risk of conditions such as Alzheimer's disease and stroke.

But perimenopause does not have a clear start and end, making it difficult to study. Large clinical trials of treatments such as hormone-replacement therapy have often focused on women who are post-menopausal, sometimes years beyond their last period, says Stacey Missmer, a population scientist at Michigan State University in Grand Rapids. "Some women have a short duration of perimenopausal symptoms, and others continue to be symptomatic for years or decades," she says. "And we don't know if this has anything to do with their health through the rest of their lives."

Meanwhile, a dearth of treatment options has left some women seeking unproven treatments, such as herbal supplements. "Women are frustrated that they're trying to function, and no one knows how to help them," says Susan Davis, an endocrinologist at Monash University in Melbourne, Australia.

Increasing attention

Momentum is building to address such questions. The taboo around discussing menopause — which combines the two historically sidelined subjects of ageing and women's reproductive health — is easing, says Kathryn Schubert, president of the Society for Women's Health Research in Washington DC. As discussions about both topics have become more acceptable, women are more vocal about the symptoms they experience during perimenopause.

Pharmaceutical and consumer-health firms are also working to raise awareness — and the size of their market. Behavioural scientist Vasiliki Michopoulos at Emory University in Atlanta, Georgia, says that she and her colleagues who study menopause in non-human primates were stunned to see a US advertisement about hot flushes during this year's Super Bowl, the biggest game of the season in American football. The ad was sponsored by Astellas Pharma, the Tokyo-based drug company that is developing fezolinetant. "The research team chat, it just blew up," Michopoulos says. "I said, 'Did I just see that? During a Super Bowl?'"

> "WE THINK THERE'S A WINDOW OF OPPORTUNITY DURING PERIMENOPAUSE."

Researchers hope that funding will follow these publicity boosts. The field has typically lacked long-term grant programmes, creating an uncertain funding environment and discouraging researchers from studying menopause. When a philanthropist approached Jennifer Garrison, a neuroscientist at the Buck Institute for Research on Aging in Novato, California, about funding research into reproductive ageing in 2018, Garrison struggled to find researchers to support. "It's not because there aren't interesting questions — it's one of the most fascinating problems that I can imagine," she says. "It's that there's not been funding."

Alongside this growing attention, research methods are also getting an upgrade. A few species of whale are the only animals known to undergo a natural menopause like humans. Most species remain capable of reproducing until they die. "Menopause is a human thing," says Teresa Milner, a neuroscientist at Weill Cornell Medicine in New York City. "That's why it's difficult to study."

To make up for this, the field has historically studied animals that have had their ovaries removed surgically. Researchers can then add back controlled quantities of oestrogen and progesterone, the two major hormones produced by the ovaries, to simulate the transition to menopause. But they rarely add back the other hormones that are found in the ovaries in smaller quantities, such as testosterone, says Joffe.

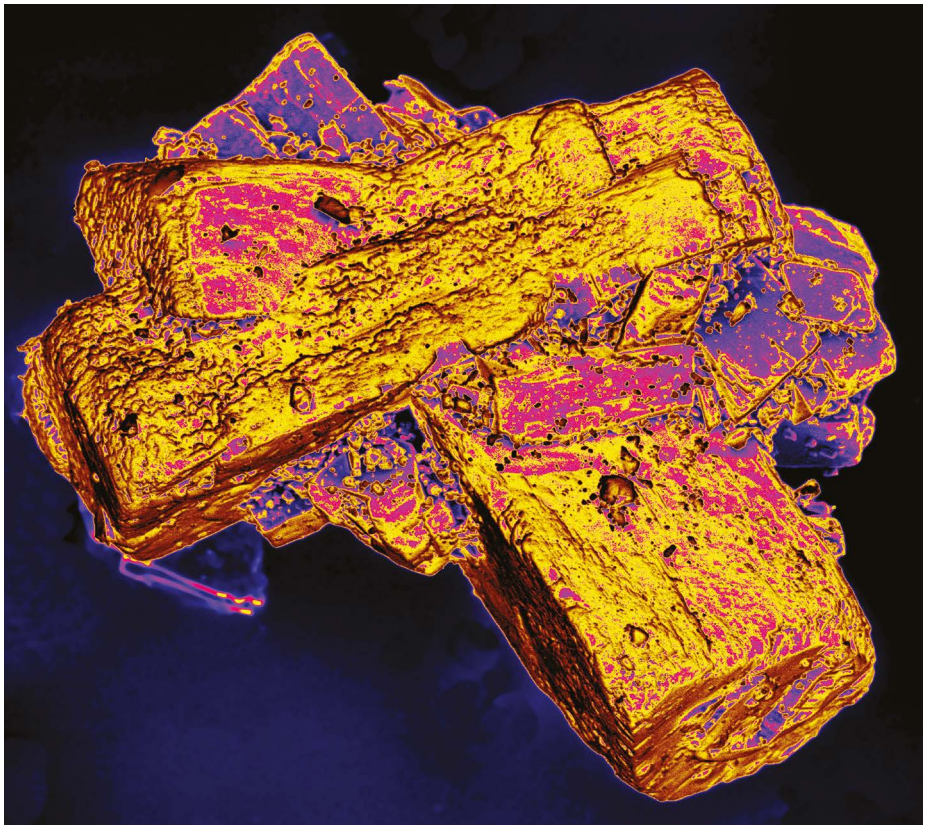
In recent years, research funders have been pushing the field to step away from this model. One alternative is to use ageing female mice; a more nuanced option is to treat mice with 4-vinylcyclohexene diepoxide, a chemical used in rubber tyre manufacturing and other industrial processes. It kills the primary follicles of the ovary and induces a period of fluctuating oestrogen that mimics perimenopause.

Better remedies

Milner hopes that such models can be used to develop better treatments for menopausal symptoms. At present, the main option is to replace oestrogen and sometimes progesterone, which begin to diminish during perimenopause. But not every person is a candidate for hormone replacement therapy (HRT), particularly those who are at risk for blood clots or who have had breast cancer, says Davis.

And when it comes to HRT, researchers are a long way from understanding the best doses and timings to use for individual women. In 2002, a large US study called the Women's Health Initiative stopped a trial of HRT early, after finding that women with menopause who were taking oestrogen and progesterone were at greater risk of invasive breast cancer than those in the control group. Another arm of the trial was halted in 2004 after finding increased rates of stroke in women who were taking oestrogen alone[2]. The ensuing controversy caused many women to stop taking HRT.

Critics raised many concerns about the study[3]: participants had been given relatively high levels of synthetic hormones, and many of the participants were more than 60 years old and had long since completed their transition to menopause. When the data were parsed, the increased risk of invasive breast cancer was limited to those who had been taking HRT for more than ten years, and some data suggest that stroke risk can be minimized by using topical forms of oestrogen, such as in a patch or gel, rather than oral tablets[4]. The ensuing debates over HRT have consumed researchers



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A crystal of oestradiol, a naturally occurring form of the hormone oestrogen.

and clinicians, leaving little room for exploring other ways to treat symptoms, says Missmer.

Since 2002, a smattering of smaller studies has suggested that HRT could be beneficial not only for easing hot flushes but also for preventing cardiovascular disease and preserving bone health, if given earlier during the menopause transition. The older women in the Women's Health Initiative were years past the perimenopausal stage and their bodies had adapted to life without oestrogen, says Milner. "You're trying to treat with oestrogen at a time when most of the oestrogen receptors don't remember what oestrogen is supposed to do," she says. "We think that there's a window of opportunity during perimenopause."

So far, however, that window has not been defined, and even starting HRT during perimenopause does not alleviate all symptoms. "HRT is not a perfect fix," says Garrison. "That tells me that there's other things going on there."

Rance was among the first to pull at that thread. Her tiny temperature gauges helped her to establish in 2011 that activating the receptor for a molecule called neurokinin B in rats triggered hot-flush-like changes[5]. The work caught the attention of endocrinologist Waljit Dhillo at Imperial College London, who had been studying neurokinin B for other reasons. Dhillo and his colleagues moved Rance's studies into the clinic, and found that a compound that prevents neurokinin B from binding to its cellular receptor reduced hot flushes in women who were experiencing at least seven of them daily[6].

Researchers working with Astellas Pharma have since shown that fezolinetant, a similar compound, also reduces the frequency of the symptom in women experiencing moderate-to-severe hot flushes associated with menopause[7]. That could have a significant impact on health, given how common this symptom is during perimenopause, says neuroendocrinologist Stephanie Correa at the University of California, Los Angeles.

A reduction in hot flushes (rather than stopping them altogether) means that there is room for improvement, she adds, but that requires understanding more about the body's temperature regulation. "That drug was based on 30-year-old basic-science research," she says. "As far as the next step, I feel like we're really far away." Furthermore, Correa has had to fight pushback from funding agencies and colleagues for her choice of topic. "Because hot flashes are not life-threatening, they're perceived as being not as important," she says.

Constellation of symptoms

Hot flushes can be more than an inconvenience. As well as being distressing and a hindrance to everyday life , they are a key contributor to the sleep disturbances that many women experience during perimenopause. And interrupted sleep could be feeding into other unwanted hallmarks of menopause, including high blood pressure, metabolic changes and anxiety, says Joffe. Some studies suggest that low levels of oestrogen can also contribute to waking at night, independently of hot flushes[8].

That's just one of many impacts that reduced oestrogen levels can have on the brain, says Brinton. She and her collaborators have found that declining sex-hormone levels have enormous effects on the metabolism and immune status of the brain in both rodents[9] and humans[10]. Key to this is oestrogen's role in regulating the uptake of glucose, the brain's principal food source. Brinton and her colleagues have found that when oestrogen levels decline, metabolic activity in the brain initially plummets, says Brinton. "That starvation response is sending out an SOS — 'I'm starving out here; I need another fuel.'"

In response, Brinton says, the brain starts to shift its metabolism from glucose to lipids. This transition, she thinks, can trigger inflammation, which in turn could contribute to the brain fog experienced during menopause and the increased risk of Alzheimer's disease and Parkinson's disease women face after menopause. "Perimenopause is a very important part of this transition," she says. "It really depends on how that perimenopausal transition goes, whether you come out with a heightened risk generated by inflammation, or whether you come out and you're OK." Brinton and her collaborators are conducting brain-imaging studies in perimenopausal women to extend their findings beyond animal models. Results so far suggest that after a period of neurobiological unrest, glucose use in the brain settles into a post-menopausal 'new normal', and people's performance on memory and cognitive tests improves[10].

Ongoing epidemiological studies might also firm up the relationship between perimenopause and brain health. The US Study of Women's Health Across the Nation, for example, is tracking women aged 42 to 52 using clinical visits, blood tests and bone-density imaging, and so could capture some aspects of the perimenopausal transition.

As for Rance, she retired and closed her lab last year, leaving a field that was a bit more populated than when she started, she says. "But not as much as you might think," she adds. "There's still a lot of room for people to do basic research."

Heidi Ledford is a senior reporter for *Nature* in London.

1. Rance, N. E. & Young, W. S. III *Endocrinology* **128**, 2239–2247 (1991).
2. Manson, J. E. *et al. JAMA* **310**, 1353–1368 (2013).
3. Lobo, R. A. *Nature Rev. Endocrinol.* **13**, 220–231 (2017).
4. Renoux, C., Dell'Aniello, S, Garbe, E. & Suissa, S. *BMJ* **340**, c2519 (2010).
5. Dacks, P. A., Krajewski, S. J. & Rance, N. E. *Endocrinology* **152**, 4894–4905 (2011).
6. Prague, J. K. *et al. Lancet* **389**, 1809–1820 (2017).
7. Johnson, K. A. *et al. J. Clin. Endocrinol. Metab.* https://doi.org/10.1210/clinem/dgad058 (2023).
8. Coburn, J. *et al. J. Clin. Endocrinol. Metab.* **107**, e4144–e4153 (2022).
9. Yin, F. *et al. Neurobiol. Aging* **36**, 2282–2295 (2015).
10. Mosconi, L. *et al. Sci. Rep.* **11**, 10867 (2021).