NEWS

New restrictions on epilepsy drug may do more harm than good

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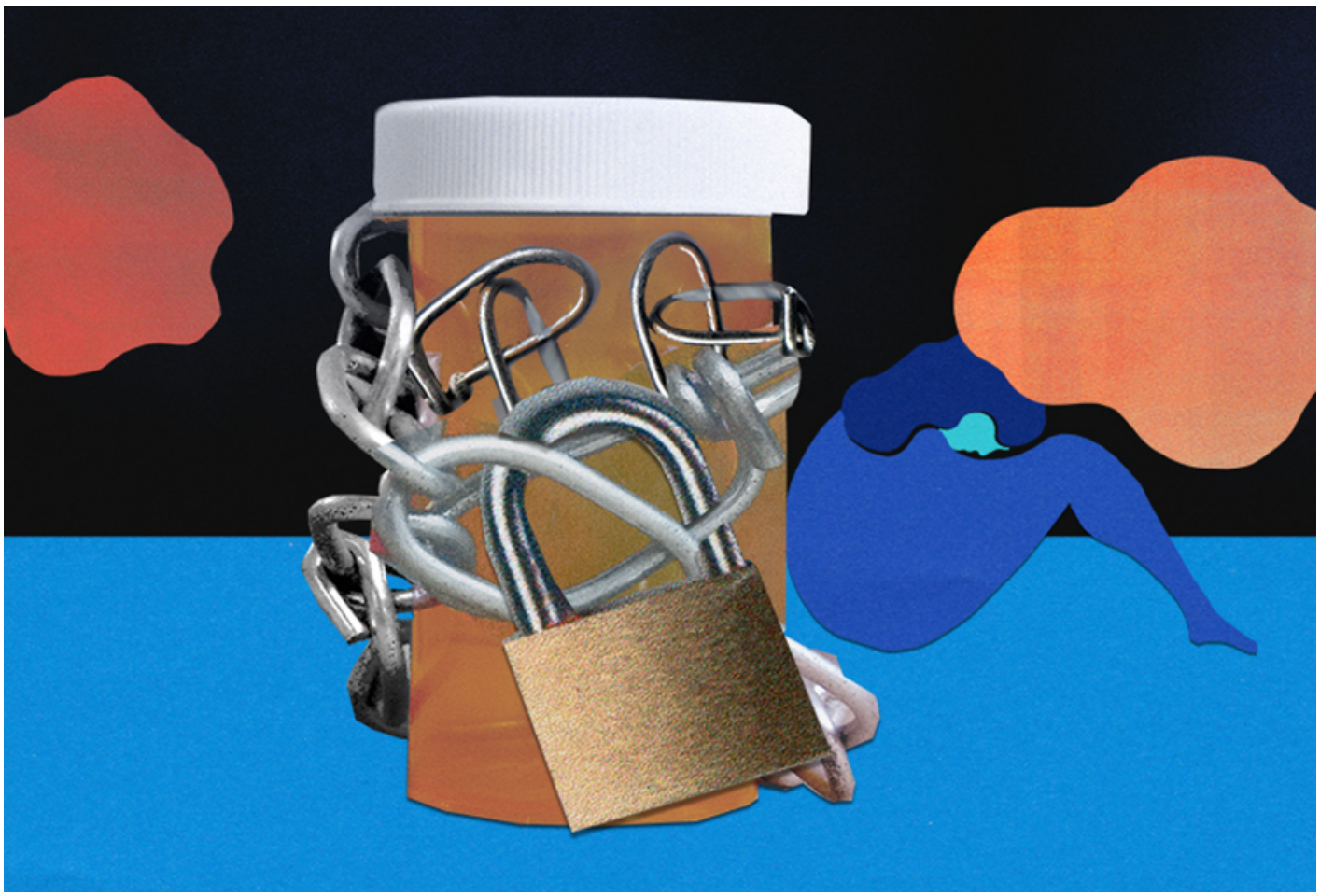

A partial ban in Europe on the use of a drug called valproate during pregnancy could deny women effective treatment for serious conditions.

Valproate is a widely used treatment for **epilepsy**, bipolar disorder and migraine. The drug's use during pregnancy is known to **increase the risk of birth defects** and neurodevelopmental conditions such as autism.

The ban went into effect 31 May and follows an official recommendation from the European Medical Agency (EMA) in February.

The **new measure** is legally binding in all 28 countries of the European Union (EU). It forbids valproate use during pregnancy for women with bipolar disorder or migraine, and allows it for women with epilepsy only if no other treatment is effective.

However, the ban applies to most women and girls: They may not start the drug without first trying alternatives — even if they are not yet of childbearing age or have no intention of getting pregnant. And those who do take the drug need to follow strict steps to avoid unintended pregnancy, including using contraceptives such as an intrauterine device or a progesterone injection administered by a doctor.

These rules go too far and endanger women's health, some experts say.

"I think it's actually a human-rights issue, because it is saying that we are giving more effective treatment to men in some circumstances rather than women because of their sex and their age range," says **Heather Angus-Leppan**, consultant neurologist and epilepsy lead at the Royal Free London NHS Foundation Trust. Angus-Leppan co-wrote an April editorial on the law in *BMJ*[1]. "[The law] is taking away autonomy and imposing one world view of women as basically great big baby incubators," she says.

Valproate may be the most effective treatment for some women with epilepsy or bipolar disorder. And switching women who are stable while taking valproate could trigger an unnecessary relapse.

"The consequences of stopping medicine are incredibly dire both for bipolar and for epilepsy," says **Sarah Spence**, pediatric neurologist and co-director of the Autism Spectrum Center at Boston Children's Hospital.

Drug dangers:

The EU measure originated in France, where **it went into effect** in July 2017. The French law was created following an investigation in which the French national agency for health and product safety reported that valproate had caused birth defects in as many as 4,100 children in France since it arrived on the market in 1967. In April, the United Kingdom approved its own ban in response to the EMA recommendation.

The EU ban is based on a substantial body of evidence on valproate's risks. A 2008 study

revealed that nearly 11 percent of children exposed to valproate in utero have birth defects such as a malformed spinal cord, compared with 2 percent of children born to women without epilepsy[2].

A study published in June reported that 10.3 percent of 1,381 women who took valproate during pregnancy had a child with birth defects. Children exposed in utero to a low dose of valproate had nearly three times the risk of birth defects as those exposed to a low dose of lamotrigine, the epilepsy drug with the lowest risk of birth defects[3].

Children exposed to valproate in the womb are also three to seven times **as likely to have autism** as those in the general population[4]. For nearly 20 years, researchers have used **rodents exposed to valproate** in utero as models for autism.

Many women taking valproate are not aware of the risks, and use of the drug in pregnant women has not declined over time[5]. This lack of awareness is what spurred the EMA to tighten recommendations, says **Angelika Wieck**, consultant psychiatrist at the Greater Manchester Mental Health NHS Foundation Trust. Wieck spoke at the EMA's public hearing on valproate last September on behalf of the European Psychiatric Association.

"The risk for children really is quite high, the damage to the children is not trivial, and the children have to live with it lifelong," Wieck says.

Health threat:

However, the dangers to women of stopping valproate use are often not trivial, either.

A 2016 study found that women with epilepsy who switch from valproate to another drug during pregnancy double their risk of seizures. And a 2012 study suggests that taking lamotrigine increases a woman's risk of sudden death from a seizure[6,7].

"To ban a potentially lifesaving medication for women of childbearing age is equivalent to saying that her potential unborn child is more important than she is," says **Jacqueline French**, professor of neurology at New York University.

Bipolar disorder, which is common among adults with autism, can also be exceedingly dangerous for both mothers and their babies if it goes untreated during pregnancy, says **Jennifer Payne**, director of the Women's Mood Disorders Center at Johns Hopkins University in Baltimore. For instance, it increases the risk of a condition called postpartum psychosis, in which women may experience delusions or hallucinations that occasionally lead to suicide or infanticide, Payne says.

And yet the EU ban stipulates that women with bipolar disorder must stop taking valproate during pregnancy, even if no other medication works for them.

“That’s a gross misunderstanding of bipolar disorder and how serious it can be,” Payne says.

The new measure was needed to minimize the risk of valproate exposure during pregnancy, says **Sabine Straus**, a Dutch representative of the EMA’s Pharmacovigilance Risk Assessment Committee, which proposed the ban.

“The pharmaceutical legislation doesn’t preclude an individual prescriber acting on their professional judgment in what they believe to be the best interests of their patient,” she says.

But language in the law does not explicitly recommend taking into account the risk to a woman’s own health.

The ban also does not allow doctors to prescribe valproate for women who are neither pregnant nor planning to become pregnant, unless other treatments have failed.

What constitutes ‘failure’ is open to interpretation, however.

“Some people may be taking that in a literal sense, meaning you have to go ahead and have seizures and smash your teeth and risk dying during a seizure before you can try valproate,” Angus-Leppan says.

This is especially of concern for girls, as having seizures earlier in life may affect cognition over the long term.

“Here we are trying to prevent cognitive problems in offspring, and yet you’re exposing young people who are at the prime time of learning — a time which is going to make a whole difference to their future — to less effective treatment,” Angus-Leppan says.

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