

Tramadol is an odd, unpredictable opioid, scientists say

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In this Thursday, Oct. 31, 2019, photo, a recovering tramadol drug addict signs a register after taking her medication at a de-addiction center in Kapurthala, in the northern Indian state of Punjab. India has twice the global average of illicit opiate consumption. Researchers estimate 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan, where some of the most vulnerable are driven to drugs out of desperation. (AP Photo/Channi Anand)

Scientists who've studied the curious chemistry of the opioid tramadol use an array of adjectives to describe it: "unpredictable," "messy," "crazy."

Tramadol is unlike most other opioids in that it must pass through the liver to be metabolized into its most potent form. At the same time, it releases another type of drug that acts as an antidepressant because it increases levels of serotonin in the brain, which elevates mood.

But how much opioid and how much antidepressant is released is heavily dependent on users' genetics, said Bertha Madras, professor of psychobiology at Harvard Medical School. One person might get a potent dose of opioid, while the next gets nearly none.

Research has shown that some ethnic groups are prone to process tramadol as a far more potent opioid, upping the risk of addiction, Madras said. In a cruel twist, those groups are largely clustered in the areas that lack access to other opioid medications, so are dependent on tramadol for pain relief: Africa, the Middle East and parts of Asia. Studies suggest nearly 30% of North Africans metabolize tramadol to the most active opioid potency, she said, compared with about 1 percent of northern Europeans.



In this Thursday, Oct. 31, 2019, photo, recovering drug addicts eat a meal at a de-addiction center in Kapurthala, in the northern Indian state of Punjab. India has twice the global average of illicit opiate consumption. Researchers estimate 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan, where some of the most vulnerable are driven to drugs out of desperation. (AP Photo/Channi Anand)



In this Thursday, Oct. 31, 2019, photo, a recovering drug addict shows his veins at a de-addiction center in Kapurthala, in the northern Indian state of Punjab. India has twice the global average of illicit opiate consumption. Researchers estimate about 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan. The country scheduled tramadol in April 2018. But regulators acknowledge that the vastness of the pharmaceutical industry and the ingenuity of traffickers makes curtailing abuse and illegal exports all but impossible. Tramadol is still easy to find. (AP Photo/Channi Anand)



In this Oct. 31, 2019, photo, an Indian drug addict lies unconscious by the side of a road in Kapurthala, in the northern Indian state of Punjab. Mass abuse of the opioid tramadol spans continents, from India to Africa to the Middle East, creating international havoc some experts blame on a loophole in narcotics regulation and a miscalculation of the drug's danger. Punjab, the center of India's opioid epidemic, was among the latest to crack down on the tramadol trade. Researchers estimate about 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan. (AP Photo/Channi Anand)



In this Thursday, Oct. 31, 2019, photo, a recovering tramadol addict waits for her medication at a de-addiction center in Kapurthala, in the northern Indian state of Punjab. The pills were everywhere, as legitimate medication sold in pharmacies, but also illicit counterfeits hawked by itinerant peddlers and street vendors. India has twice the global average of illicit opiate consumption. Researchers estimate about 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan. (AP Photo/Channi Anand)



In this Oct. 30, 2019, photo, people walk past drugstores where tramadol was once easily accessible in Amritsar, in the northern Indian state of Punjab. The pills were everywhere, as legitimate medication sold in pharmacies, but also illicit counterfeits hawked by itinerant peddlers and street vendors. India has twice the global average of illicit opiate consumption. Researchers estimate about 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan. (AP Photo/Channi Anand)



In this Oct. 31, 2019, photo, Indian boys ride a motorcycle in Kapurthala, in the northern Indian state of Punjab. India has twice the global average of illicit opiate consumption. Researchers estimate 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan, where some of the most vulnerable are driven to drugs out of desperation. (AP Photo/Channi Anand)



In this Thursday, Oct. 31, 2019, photo, a medic sits at a drug de-addiction center, where many cases of tramadol are reported, in Kapurthala, in the northern Indian state of Punjab. India scheduled tramadol in April 2018. But regulators acknowledge that the vastness of the pharmaceutical industry and the ingenuity of traffickers makes curtailing abuse and illegal exports all but impossible. Tramadol is still easy to find. Researchers estimate about 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan. (AP Photo/Channi Anand)



In this Thursday, Oct. 31, 2019, photo, a medic administers medicine to a recovering drug addict at a de-addiction center in Kapurthala, in the northern Indian state of Punjab. Researchers estimate about 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan. These pills, the world had been told, were safer than the OxyContin, the Vicodin, the fentanyl that had wreaked so much devastation. But now they are the root of what the United Nations named "the other opioid crisis," an epidemic featured in fewer headlines than the American one, as it rages through the most vulnerable places on the planet. (AP Photo/Channi Anand)



In this Thursday, Oct. 31, 2019, photo, Jyoti Rani, a recovering tramadol drug addict, breaks down while narrating her story at a de-addiction center in Kapurthala, in the northern Indian state of Punjab. Rani's addiction began with heroin. When her 14-year-old son died, she fell into depression. "I wanted to kill myself, but I ended up becoming an addict," she cried. A doctor prescribed tramadol to help kick the habit, instead, she formed a new one. She locked herself in her room, not eating or taking care of two children. Rani used tramadol until she ran out of money and entered treatment. Now her family tells her she's her old self again. (AP Photo/Channi Anand)



In this Thursday, Oct. 31, 2019, photo, Amandeep Kaur, a former tramadol addict, covers her face at the de-addiction center in Kapurthala, in the northern Indian state of Punjab. Kaur was pregnant when her husband died of a heart attack. She turned to the sex trade to make ends meet. She wanted not to feel, and a fellow sex worker suggested tramadol. She had no idea she'd get addicted, but eventually needed three pills to get through the day. "If I didn't have it I felt lifeless, my body ached as if I was going to die," she said, and joined the line stretching from the addiction clinic's doors. (AP Photo/Channi Anand)



In this Thursday, Oct. 31, 2019, photo, recovering drug addicts eat a meal at a de-addiction center in Kapurthala, in the northern Indian state of Punjab. India has twice the global average of illicit opiate consumption. Researchers estimate 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan, where some of the most vulnerable are driven to drugs out of desperation. (AP Photo/Channi Anand)



In this Thursday, Oct. 31, 2019, photo, recovering drug addicts perform yoga at a de-addiction center in Kapurthala, in the northern Indian state of Punjab. India has twice the global average of illicit opiate consumption. Researchers estimate 4 million Indians use heroin or other opioids, and a quarter of them live in the Punjab, India's agricultural heartland bordering Pakistan, where some of the most vulnerable are driven to drugs out of desperation. (AP Photo/Channi Anand)

Grunenthal, the German pharmaceutical company that originally synthesized tramadol, also points to its strange chemistry to defend its claim that the drug is less prone to be abused. As people begin to abuse most opioids, they move to higher doses, then to snorting or shooting up as they build up tolerance and no longer feel the same high from the same dose. But tramadol, one recent survey suggests, might naturally

deter that trajectory because as doses increase, nasty side effects become more pronounced. And since it must pass through the liver to reach full effect, users do not transition to snorting or injecting.

Tramadol taken at high doses—particularly when combined with other drugs—can cause the respiratory depression that leads to overdose deaths. The United Kingdom, for example, decided to regulate the drug in 2014, after researchers found that as the number of tramadol prescriptions increased, so did the number of times it was mentioned on death certificates. But it has not as routinely caused overdose as more traditional opioids. Users who take too much often first have a side effect different than other opioids: an overload of serotonin that causes seizures.

"Tramadol is most likely not as problematic as some of the big gun opioids like oxycodone and fentanyl and heroin," Madras said. "But it certainly can be in certain populations and it certainly can be if it's abused by a wider and wider swath of the population."

When people who've become dependent try to stop taking tramadol, they have withdrawal symptoms like those of traditional opioids, including pain, sweating, diarrhea and insomnia, according to the World Health Organization. But the serotonin crash adds other problems: hallucinations, panic, paranoia and confusion.

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