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## Popular Pain Medication Associated with Greater Risk of Hypoglycemia

**Tramadol, an opioid, is widely used to treat moderate or severe pain, but patients may be at risk of low blood sugar levels**

Since its approval in 1995, the opioid tramadol (marketed as ConZip and Ultram) has become a widely prescribed remedy for osteoarthritis and other painful indications, in part because it presents a lesser risk for some side effects and has a lower abuse potential when compared to other opioids. It is currently ranked among the top five prescribed opioids and top 60 prescribed medications in the country.

But as tramadol has grown in popularity so too have documented cases of adverse effects among its users. In a new paper, published August 28, 2019 by [\*Scientific Reports\*](#), researchers at Skaggs School of Pharmacy and Pharmaceutical Sciences at University of California San Diego show that patients who take tramadol are at greater risk for developing hypoglycemia, or abnormally low blood sugar.

The research team, led by senior author Ruben Abagyan, PhD, professor of pharmacy, analyzed more than 12 million reports from the FDA Adverse Effect Reporting System (FAERS) and Adverse Event Reporting System (AERS) databases, which chronicle voluntary reports of adverse effects while taking a medication. The period studied ranged from January 2004 to March 2019.

“The impetus was the recent dramatic surge in tramadol popularity and prescriptions,” said first author Tigran Makunts, PharmD, a researcher in Abagyan’s lab. “We wanted to have an objective data-driven look at its adverse effects and bumped into a dangerous, unlisted and unexpected hypoglycemia.”

Recognized adverse drug reactions associated with tramadol include dizziness, nausea, headaches and constipation — all common side effects of opioids. More serious but rarer adverse drug reactions include serotonin syndrome and increased seizure risk. The link to

hypoglycemia is relatively new, though it had been previously suggested by case studies and animal model testing.

Hypoglycemia is often related to the treatment of diabetes, but can also occur in persons without diabetes. Untreated, hypoglycemia can lead to serious complications of its own, such as neurocognitive dysfunction, vision loss, greater risk of falls and loss of quality of life.

The researchers also looked at other widely prescribed opioids and similar acting, non-opioid medications, such serotonin and norepinephrine reuptake inhibitors (Cymbalta, Effexor XR) and NMDA receptors (ketamine and memantine). Only tramadol produced a significant risk of developing hypoglycemia in patients. In fact, there was a 10-fold greater risk of hypoglycemia using tramadol than virtually every other opioid. The only other drug identified with comparable effect was methadone, an opioid most commonly used to help persons reduce or quit addictions to heroin or other opiates.

While this study underscores an association between tramadol and hypoglycemia, a large, randomized, controlled clinical trial would be needed to definitively establish causality.

“The takeaway message is to warn physicians about the likelihood of low blood sugar (and/or high insulin content), in particular if the patient is predisposed to diabetes,” said Abagyan, “and to motivate research about the unique molecular mechanism leading to that side effect. It is particularly important for tramadol or methadone that are used widely and, often, chronically.”

Co-authors include Andrew U and Rabia S. Atayee, both at UC San Diego.

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