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Flubromazolam - Deadly Designer Benzodiazepine

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Special Interest Articles:

- Flubromazolam
- PPIs and Dementia
- Ultra-Long Acting Pill

Did you know?

Twenty-five years ago, Eli Lilly's Prozac (fluoxetine) became the first selective serotonin reuptake inhibitor (SSRI) to be released to the market, where it quickly advanced in popularity for the treatment of depression. Soon, the drug was bringing in more than a billion dollars in earnings- at a time when the average American's income was $25,000.

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Flubromazolam is a triazole analog of flubromazepam and is a very high affinity, in-vitro benzodiazepine related compound. It contains a fluorine, a bromine, and a methylated triazole substituent on its core benzodiazepine structure. Flubromazolam is a novel designer drug that is a synthetic version of the benzodiazepine class. Many designer drugs are former research drugs or drugs that were previously approved in other countries. Flubromazolam is a former research drug that did not make it to clinical trials. It is still being sold as a research chemical but has found its way into the recreational drug marketplace.

Designer drugs are often many times stronger than the original substance due to its creation for abuse. Flubromazolam is one of the newer drugs that made its debut in 2014. The original designer drug, flubromazepam, was first synthesized in the 1960s, but was forgotten until it resurfaced in 2012. Flubromazolam is known as CAS 612526-40-6 in the research chemical world.

Flubromazolam has not been widely studied due to its lack of use in humans and animals. Exact pharmacology is speculation at this point. Due to its benzodiazepine-like structure, it is seen as binding to the benzodiazepine receptor site on the gamma amino butyric acid (GABA)-A receptor. By binding to the GABA-A receptor, the benzodiazepine is able to change the shape of the receptor's chloride channel. This change causes the cell to hyperpolarize and causes the inhibitory effect, which decreases the excitability of the brain's neurons.

The most common effect seen when taking flubromazolam is heavy sedation. Flubromazolam is a strong hypnotic with moderate anxiolytic and amnesic effects. According to Erowid Experience Vaults, several drug users report that flubromazolam would knock them out for most of the day, even on some of the lowest doses of 0.25mg. This is due to the drug's potency as well as a seemingly long half-life. The half-life is theorized to be around 18 hours long due to how long it takes people to come out of their sedated sleep.

Flubromazolam is very dangerous, especially if taken in combination with other hypnotics, barbiturates, and alcohol. The signs and symptoms of a possible overdose include shallow respiration, clammy hands, dilated pupils, rapid pulse, coma, and in the worst cases, death.

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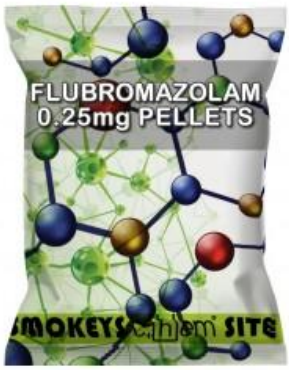

Proton Pump Inhibitors and the Development of Dementia

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"Current literature concludes that the avoidance of PPIs may contribute to the prevention of dementia, however, only statistical evidence associates the two."

Proton pump inhibitors (PPIs) account for one of the most commonly prescribed drug classes. In 2015, two PPIs were considered to be among the top 100 drugs in the United States – esomeprazole (Nexium®) and dexlansoprazole (Dexilant®) were prescribed a combined 19.9 million times which totaled over $6.5 billion in sales. Other PPIs include omeprazole (Prilosec®), lansoprazole (Prevacid®), pantoprazole (Protonix®), and rabeprazole (Aciphex®). These drugs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of duodenal ulcer disease, erosive esophagitis, and gastroesophageal reflux disease (GERD). Even though PPIs are frequently used for gastrointestinal disturbances, researchers now believe they have the potential to cause cognitive decline.

According to a pharmacoepidemiological analyses published in February of 2016 in *JAMA Neurology*, researchers have come up with several proposed mechanisms that could increase the risk of a dementia diagnosis. The first mechanism presented was a mouse model that showed an increase in the levels of β-amyloid plaque in the brain – a protein that contributes as a major pathological sign of dementia. More specifically, some PPIs have been reported to cross the blood-brain barrier and interact with the enzymes β- and γ-secretase which leads to the accumulation of β-amyloid.
The second mechanism involves lysosomes that induce the degradation of β-amyloid in the microglia by acidification. The acidification process is pH-dependent and is also mediated by proton pumps therefore if the proton pumps are inhibited by PPIs, then the clearance of β-amyloid is diminished while accumulation furthers until severe cognitive impairment.

Lastly, the third mechanism that can potentially increase the risk of dementia is a vitamin B_{12} deficiency. It is theorized that PPIs may inhibit secretin of intrinsic factor which promotes neurologic damage due to impaired DNA synthesis. According to a study published in August of 2016, the clinical significance of a B_{12} deficiency caused by acid suppression is inconclusive and longer prospective studies are needed.

Although the underlying mechanism to which PPIs can cause dementia is yet to be determined, it can be speculated that acid suppression works throughout the body instead of just the parietal cells within the stomach. Increased β-amyloid plaque, pH disturbances, and the absence of vitamin B_{12} are all potential risk factors that may contribute to dementia – all because of a very commonly prescribed and misused medication. Current literature concludes that the avoidance of PPIs may contribute to the prevention of dementia, however, only statistical evidence associates the two. In order to formulate a direct cause and effect, randomized, prospective clinical trials are needed.

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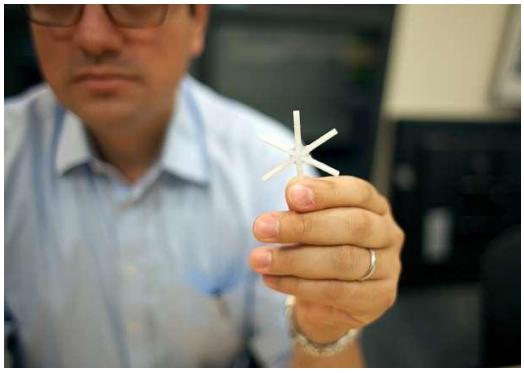
Slow-Breaking, Ultra Long- Acting Pill: Medical Breakthrough



A new pill, developed by researchers at MIT, demonstrates promise in allowing for effective long-term delivery of drugs, with the ability to stick to the gastrointestinal tract for lengthy periods of time. One side of the pill is designed to hold it in place, while the other repels liquid and food that could otherwise displace it. This type of drug delivery could oust inconvenient regimens that require repeated doses, which would help to overcome one of the major obstacles to treating and potentially eliminating diseases such as malaria. In a recent study, an ingested “ultra long-acting” capsule was able to deliver a controlled release of a malaria drug to pigs for up to 14 days. The pill is about the size of a vitamin and when ingested, after five seconds in the stomach, the pill opens to the shape of a star. The star shape prevents the pill from being passed, allowing it to release a drug for days to weeks. At a calculated point in time, the pill then breaks down and safely passes through the gastrointestinal tract, thanks to the dissolution of pH- and time-dependent linkers. In the design, researchers used a mucoadhesive polymer called Carbopol for one side of the pill and for the other, used cellulose acetate to repel stomach contents. The repellant side was textured to imitate a lotus leaf, which has tiny protrusions that make it extremely hydrophobic. Once the texturing was complete, the surface was fluorinated and lubricated to make it repel practically anything it comes into contact with.

The technology could improve patient adherence in various indications and slash health costs. Approximately 50% of patients in the developed world do not take their medicines as prescribed - a statistic that is even more challenging in the developing world. Long-acting pills could be especially helpful for elderly patients or those with mental conditions who often fail to follow prescription instructions. Scientists plan to investigate potential applications beyond infectious disease, including chronic diseases such as psychiatric disease, heart disease, and renal disease.

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Basaglar - New Brand of Glargine

Basaglar® is a new brand of long-acting insulin that will be available in mid-December. It is given once daily and is a new option of glargine U-100. It is not a Lantus® generic, but many hospital formularies are expected to drop Lantus in 2017 and replace it with Basaglar. Basaglar is slightly less expensive than Lantus and its duration is 24 hours with no pronounced peak. Basaglar will be available in a 3 ml prefilled KwikPen®.

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