Samidorphan: Discovery of an FDA-approved medication.

Samidorphan was discovered at Rensselaer Polytechnic Institute in the laboratories of Professor Mark Wentland. Samidorphan, a new chemical entity, combined with olanzapine was approved by the US FDA on 5/28/21 to treat schizophrenia and bipolar I disorder in adults. Named LYBALVI®, this combination drug (aka, ALKS 3831) was developed by Alkermes plc. Olanzapine is an established antipsychotic agent that can cause significant weight gain. The role of samidorphan is to mitigate this olanzapine-associated weight gain.

Samidorphan emerged from an effort at Rensselaer to identify orally available, long-acting modulators of opioid GPCRs as medications to treat opioid and cocaine use disorders in humans. Samidorphan is a high potency ($K_i = 0.052 \text{ nM}$) mu opioid receptor antagonist that first appeared in the literature in 2005. A 2009 publication provided further details on the design, crystallography and structure-activity relationships of samidorphan. Rensselaer licensed samidorphan to Alkermes in 2006 who subsequently sponsored numerous samidorphan clinical trials. In a recent publication, Alkermes described the human pharmacokinetic properties of samidorphan where they found the oral bioavailability and elimination half-life of the drug to be 69% and 7-8 h, respectively. The following press releases from Alkermes provides additional information:


Acknowledgments:

- Coworkers and collaborators:
  - Medicinal chemists at Rensselaer
  - Dr. Jean Bidlack and coworkers at the University of Rochester
  - Personnel at Alkermes, Inc.

- Funding: This research was supported by the National Institute of Drug Abuse of the National Institutes of Health under award numbers [DA012180](https://addictionrecovery.nih.gov/research-funding/search-awards?active_facilities=16&active_funding_program=DA&active_investigator=) and KO5-DA00360. [Funding from AMRI, Inc.](https://amri.com/) is also gratefully acknowledged.