



Designer benzodiazepines etizolam and flubromazolam detected in patients with suspected opioid overdose



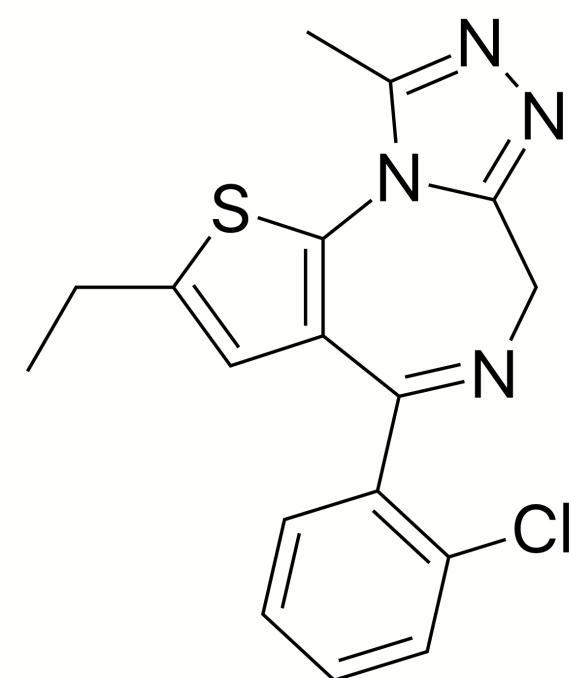
Adrienne Hughes¹, Robert Hendrickson¹, Kim Aldy², Alison Meyn², Sharan Campleman², Stephanie Abston², Alex Krotulski³, Barry Logan^{3,4}, Alexandra Amaducci⁵, Anthony Pizon⁶, Paul Wax², Jeffrey Brent⁷, Alex F Manini⁸; On behalf of the ToxIC Fentalog Study Group

Background:

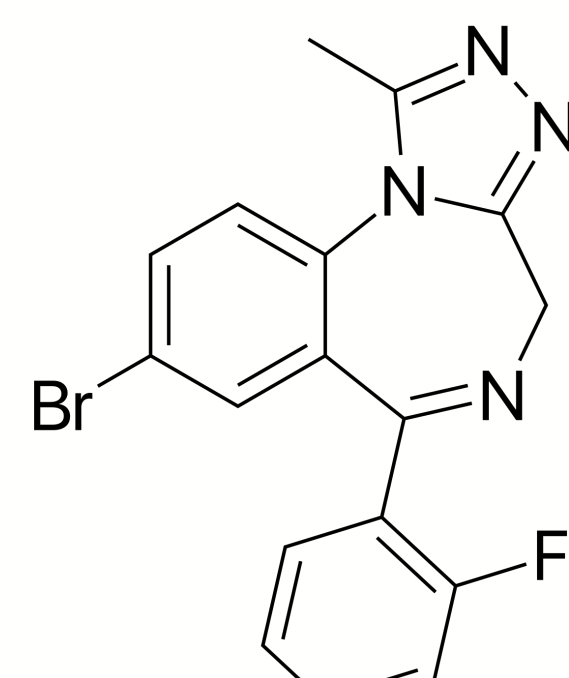
- A growing number of **novel psychoactive substances (NPS)**, including **designer benzodiazepines**, have become **available** on the illicit drug market and over the internet.
- **Etizolam**, a thienodiazepine, and **flubromazolam**, a triazolobenzodiazepine, have **recently emerged** on the **illicit drug market** in Europe and the US in recent years.
- Reports of non-medical use and detection of etizolam and flubromazolam drugs in counterfeit medications appear to be rising, as is their identification in drug-related deaths, often in combination with opioids and other CNS depressants.

Methods:

- **Case series: Adult ED patients** who presented to emergency departments within the ACMT's **Toxicology Investigators Consortium (ToxIC) fentalog study group** after a **suspected opioid overdose**.
- **Toxicological comprehensive testing** was performed on residual blood samples via **liquid chromatography quadrupole time-of-flight mass spectrometry** for the presence of over 900 psychoactive substances and their metabolites.
- **Cases with etizolam and flubromazolam identified in biologic samples were reviewed.**



Etizolam



Flubromazolam

Results:

- Between 10/6/20-3/9/21, 141 biological samples of patients suspected of opioid overdose were analyzed from 5 clinical sites encompassing 4 states (Missouri, Oregon, New York, & Pennsylvania).
- The **median age of subjects was 41.9 years** (range: 25-69); 80% were male.
- Etizolam was **detected in 10 samples (7%)** and **flubromazolam in 2 samples (1.4%)**.
- **Etizolam** was confirmed in **all states except Missouri** and **flubromazolam was detected only in Oregon**.
- **Oregon** had the **most exposures** overall (N= 5).
- In **all 10 cases** with confirmed presence of **etizolam**, **at least 1 opioid was also identified** in biological samples (methadone (n=6), Fentanyl (n=3), heroin (n=2), buprenorphine (n=1). Flubromazolam, was detected in 2 samples, both from Oregon.
- **Methamphetamine** (n=4) & **amphetamine** (n=3) were also commonly detected.
- The **primary reason for the exposure** was intentional in **all 10 cases**, the most common being misuse/abuse (n=5).
- No patients received flumazenil.
- **Naloxone** was administered in **7 cases**.
- The **most common indications for naloxone** administration were **depressed level of consciousness** (n=5), **respiratory depression** clinically (n=3), **decreased oxygenation** (n=1), & **decreased expired carbon dioxide** (n=1).

Results:

- In **5 cases**, the **response to naloxone was known: No response** (n=1), **increased respiratory rate** (n=2), **improved level of consciousness** (n=4), **iatrogenic withdrawal** precipitated (n=1).
- In **3 cases**, **3 or more doses of naloxone** was administered.
- **One patient was intubated for acute respiratory failure non-responsive to naloxone.**
- Nine patients were discharged without sequelae and 1 left against medical advice.
- There were **no deaths**.

Conclusion:

- **Combined designer benzodiazepine and illicit opioid use** can result in **synergistic toxicity** that may increase the risk of an overdose and/or death.
- In these preliminary data, **etizolam was always identified along with at least 1 opioid**, suggesting either **addition to the opioid supply or concomitant use**.

Author affiliations:

Oregon Health and Science University, Portland, OR, USA

American College of Medical Toxicology, Phoenix, AZ, USA

Center for Forensic Science Research and Education at the Fredric Rieders Family Foundation, Willow Grove, PA, USA

Toxicology Department, NMS Labs, PA, USA

Lehigh Valley Health Network, Allentown, PA, USA

University of Pittsburgh School of Medicine, Pittsburgh, PA

University of Colorado School of Medicine, Aurora, CO, USA

Icahn School of Medicine at Mount Sinai, New York, NY, USA