# POTENTIAL NEW PHARMACOTHERAPEUTIC DEVELOPMENTS FOR OPIOID AND STIMULANT USE DISORDERS

## APRIL 14TH, 2021

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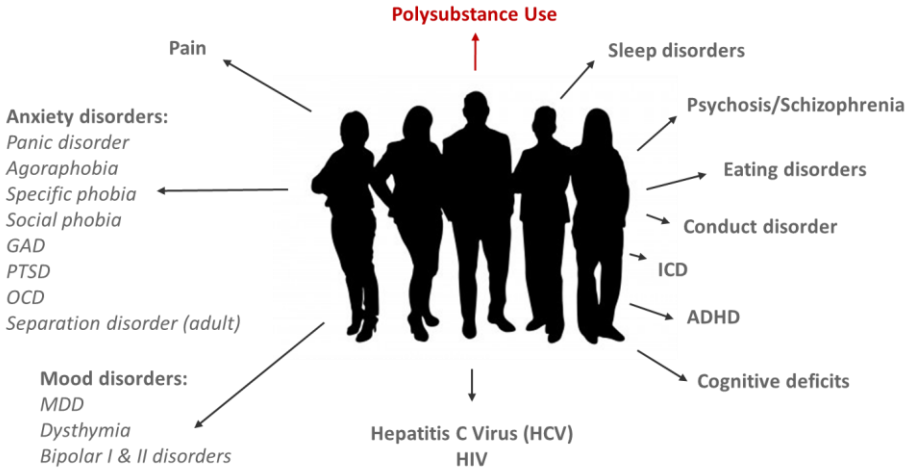
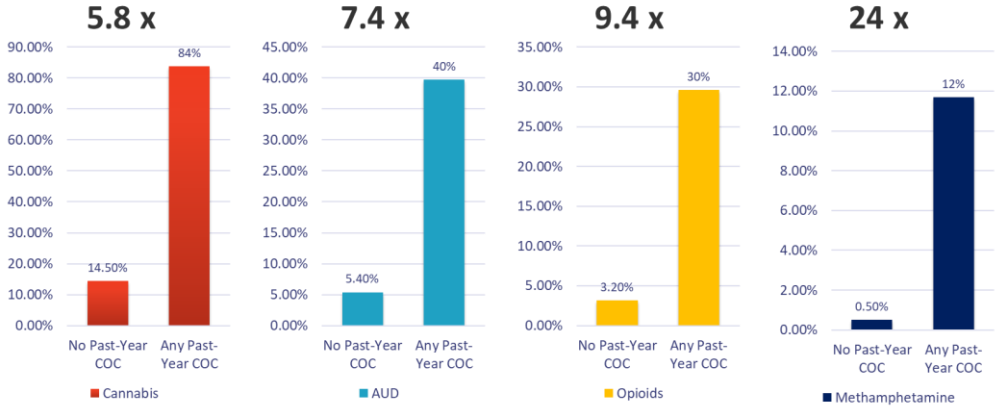
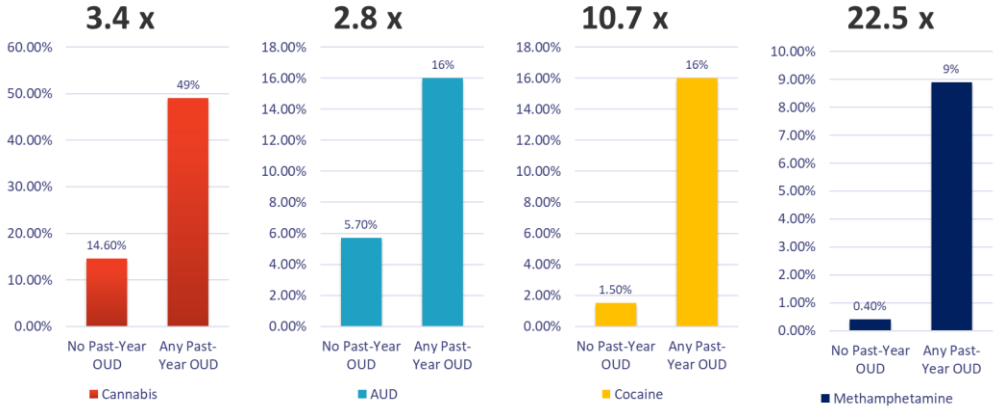
# POLYSUBSTANCE USE DISORDERS



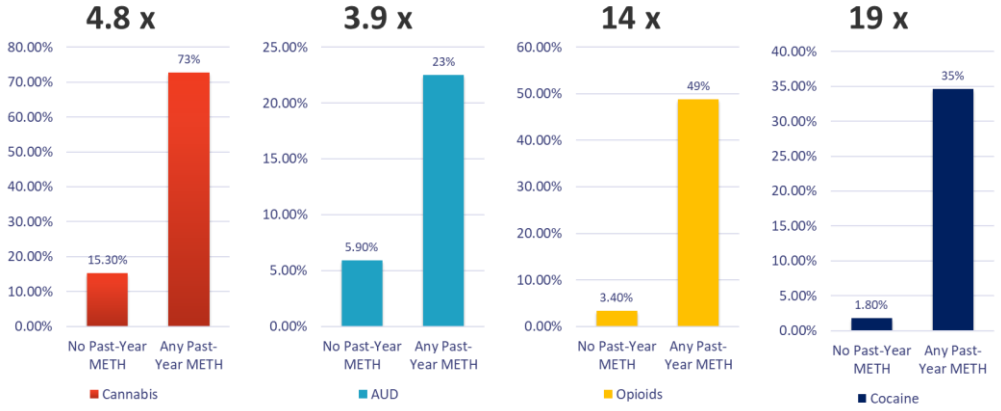

## Odds of drug use with No vs. Any past-year Cocaine Use




## Odds of drug use with No vs. Any past-year Opioid Use



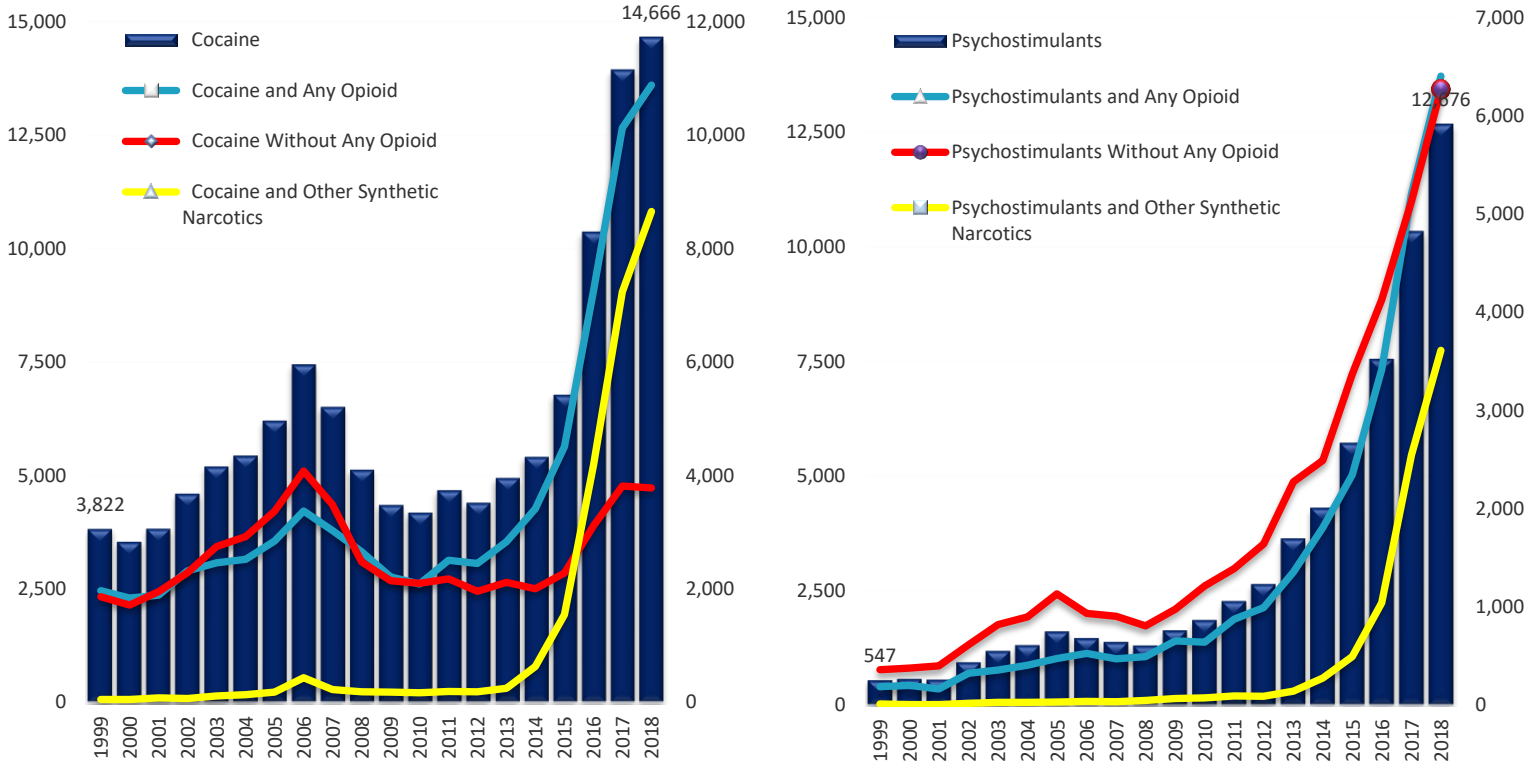

## Odds of drug use with No vs. Any past-year Methamphetamine Use




*Source: Substance Abuse and Mental Health Services Administration. (2019). Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/*

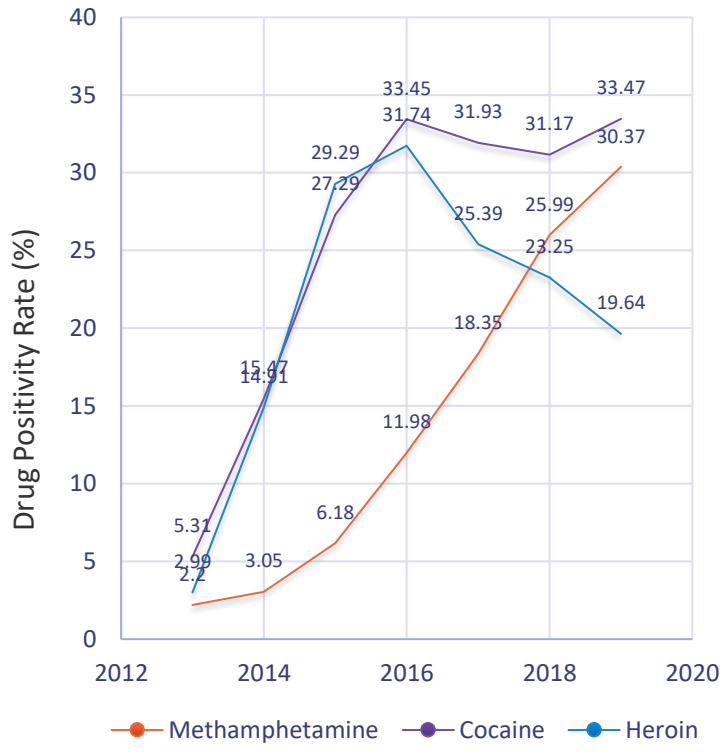
# CONCOMITANT MISUSE OF STIMULANTS & OPIOIDS IS A NEW "TWIN" EPIDEMIC

**Drug overdose deaths involving cocaine and amphetamine-type stimulants (1999-2018)**




*Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2018 on CDC WONDER Online Database.*

**FENTANYL-POSITIVE POPULATION**




*Source: Twillman RK et al. JAMA Network Open. 2020;3(1):e1918514. https://doi.org/10.1001/jamanetworkopen.2019.18514*

# NEW & OLD CHALLENGES

# NEW CHALLENGE: NOVEL SYNTHETIC OPIOIDS (NSO)

| | Potency Ratio to Morphine [14] | Administration Route Associated with Overdose | Blood Concentration (ng/mL) | Other Concentrations (Site, ng/mL) |
|---|---|---|---|---|
| Acetylfentanyl [53,58,80,88] | 15.7 | Nasal, intravenous | 153–260<br>247.5–285 (heart) | Liver 100–2400 ng/g; urine 2.6–2720 ng/mL; stomach content 880 ng/mL; vitreous humor 131–240 ng/mL. |
| Alpha-Methylfentanyl [89] | 56.9 | Intravenous | 3.1 | liver 78 ng/g; bile 6.4 ng/mL. |
| Butyrylfentanyl [59,71] | 1.5–7.0 | Nasal, rectal, intravenous, sublingual | 66–99 ng/mL;<br>39–220 ng/mL (heart) | liver 41–57 ng/g; kidney 160 ng/g, muscle 100 ng/g; vitreous humor 32 ng/mL; bile 260 ng/mL; urine 64 ng/mL; gastric contents 590 ng/mL; brain 93 ng/g. |
| Carfentanil [90] | 10,000 | | 0.11–0.88 | |
| 4-Fluorobutyrfentanyl [91] | Unknown | By smoking | 91–112 | urine, 200–414 ng/mL; liver, 411–902 ng/g; kidney 136–197 ng/g. |
| Furanylfentanyl [49,60] | Unknown | Nasal, intravenous | 0.43–26 | |
| 3-Methylfentanyl [83,92] | 48.5–7000 | Intravenous | 0.3–1.9 | |
| Ocfentanil [62,93] | 90 | Nasal, by smoking | 9.1–15.3;<br>23.3–27.9 (heart) | vitreous humor 12.5 ng/mL; urine 6.0 ng/mL; bile 13.7 ng/mL; liver 31.2 ng/g; kidney 51.2 ng/g; brain 37.9 ng/g; nasal swabs 2999 ng/swab. |
| AH-7921 [5,44,64,66] | Unknown | Oral, nasal, by smoking, intravenous | 330–6600<br>480–3900 (heart) | urine 760–6000 ng/mL; bile 17,000 ng/mL; liver 530–26,000 ng/g; kidney 7200 ng/g; brain, 7700 ng/g; vitreous humor 190 ng/mL; stomach content, 40 µg/mL. |
| U-47700 [5,49,94,95] | 7.5 | Oral, nasal, intrarectal, smoking, intravenous | 59–525<br>1347 (heart) | Urine 360–1393 ng/mL; liver 430–1700 ng/g; kidney 270 ng/g; lung 320 ng/g; brain 97 ng/g. |
| MT-45 [5,66,96] | Unknown | Oral, nasal, intrarectal, intravenous | 520–660<br>1300 (heart) | Urine 370 ng/mL; vitreous humor 260 ng/mL; gastric content 49 µg/mL; liver 24 µg/g. |
| Fentanyl [70,82,86,87,97,98] | 100 | Oral, transdermal, nasal, intravenous | 0.5–383 | Urine 2.9–895 ng/mL; gastric content 31.6–745 µg/mL; liver 5.8–613 µg/g. |

NSO-related deaths are associated with drugs of abuse such as:

→ other opiates (up to 64%)

→ cocaine (up to 65%)

→ cannabinoids (up to 50%)

→ benzodiazepines (up to 52.2%)

→ antidepressants (up to 48%)

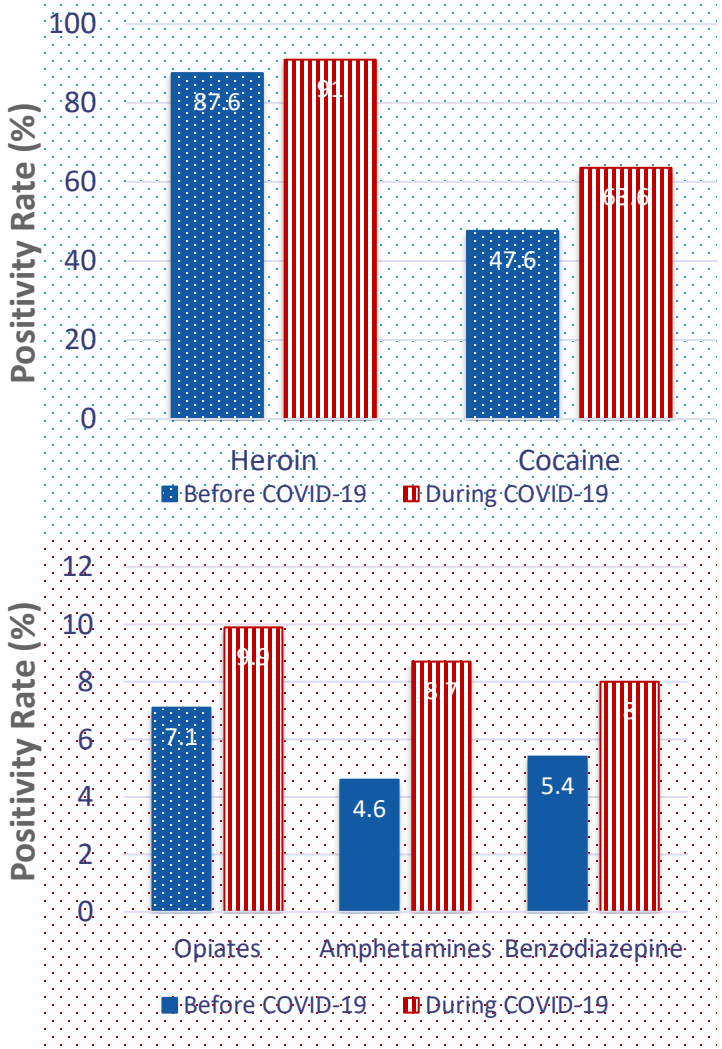
→ amphetamines (up to 40%)

→ barbiturates (up to 27%)

→ ethanol (up to 22.9%)

*Lethal concentrations of novel synthetic opioids reported in the literature*
*Source: Frisoni P et al. Brain Sci. 2018, 8: 170; https://doi.org/10.3390/brainsci8090170*

# NEW CHALLENGE: COVID-19 PANDEMIC IS ENHANCING NON-PRESCRIBED FENTANYL POSITIVITY RATE IN SPECIMENS POSITIVE FOR OTHER DRUGS




## Changes in drug market

- → Shortages of numerous types of drugs at the street level
- → Price increases for consumers on the black market
- → Reductions in purity, likelihood of adulteration, and contamination of heroin supply with synthetic opioids such as fentanyl and fentanyl-derivatives

## Changes in drug use patterns

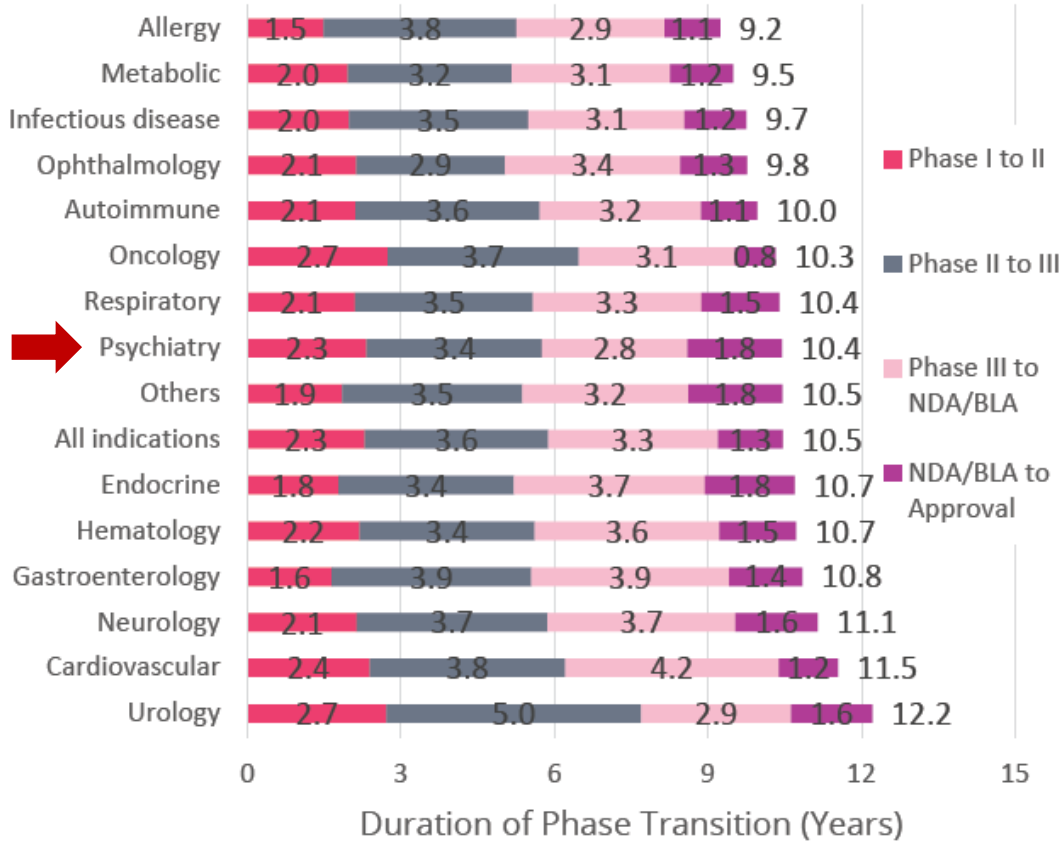
Shifts to more at-risk drug using behaviors and polysubstance use:

- → Street benzodiazepines
- → Synthetic cannabinoids
- → Quetiapine
- → Gabapentinoids
- → Z-drugs (e.g., zolpidem)
- → Over-The-Counter (OTC) medications, such as codeine, ephedrine and pseudoephedrine, and the antidiarrheal loperamide (“poor man’s methadone”).

*Source: Niles JK et al. Population Health Management. 24: S1 Published Online: 5 Feb 2021. https://doi.org/10.1089/pop.2020.0230*

# OLD CHALLENGE:
# LIKELIHOOD OF APPROVAL (LOA) & DRUG DEVELOPMENT TIMELINES

| Likelihood of Approval | Phase I to Approval | | Phase II to Approval | | Phase III to Approval | | NDA/BLA to Approval | |
|---|---|---|---|---|---|---|---|---|
| | LOA n | Phase LOA | LOA n | Phase LOA | LOA n | Phase LOA | LOA n | Phase LOA |
| Hematology | 352 | 23.9% | 260 | 34.4% | 154 | 71.5% | 72 | 93.1% |
| Metabolic | 399 | 15.5% | 263 | 25.0% | 114 | 55.7% | 48 | 87.5% |
| Infectious disease | 1170 | 13.2% | 767 | 22.8% | 353 | 59.4% | 156 | 92.9% |
| Others | 541 | 13.0% | 387 | 20.5% | 159 | 53.0% | 69 | 88.4% |
| Ophthalmology | 415 | 11.9% | 327 | 16.6% | 127 | 46.7% | 45 | 91.1% |
| Autoimmune | 1305 | 10.7% | 892 | 19.3% | 421 | 61.4% | 202 | 94.1% |
| Allergy | 201 | 10.3% | 146 | 18.3% | 54 | 64.7% | 20 | 100.0% |
| Gastroenterology* | 186 | 8.3% | 141 | 17.8% | 68 | 51.9% | 33 | 90.9% |
| All indications | 12728 | 7.9% | 8314 | 15.1% | 3381 | 52.4% | 1453 | 90.6% |
| Respiratory | 501 | 7.5% | 322 | 13.5% | 107 | 61.6% | 45 | 95.6% |
| Psychiatry | 442 | 7.3% | 292 | 13.8% | 128 | 51.4% | 57 | 91.2% |
| Endocrine | 887 | 6.6% | 568 | 15.2% | 275 | 57.1% | 124 | 86.3% |
| Neurology | 1411 | 5.9% | 895 | 12.3% | 391 | 46.0% | 165 | 86.7% |
| Oncology | 4179 | 5.3% | 2551 | 10.8% | 819 | 43.9% | 324 | 92.0% |
| Cardiovascular | 651 | 4.8% | 437 | 9.6% | 185 | 45.6% | 80 | 82.5% |
| Urology | 88 | 3.6% | 66 | 8.8% | 26 | 58.6% | 13 | 84.6% |




→ The overall likelihood of approval (LOA) from Phase I for all developmental candidates over 2011-2020 was 7.9%.

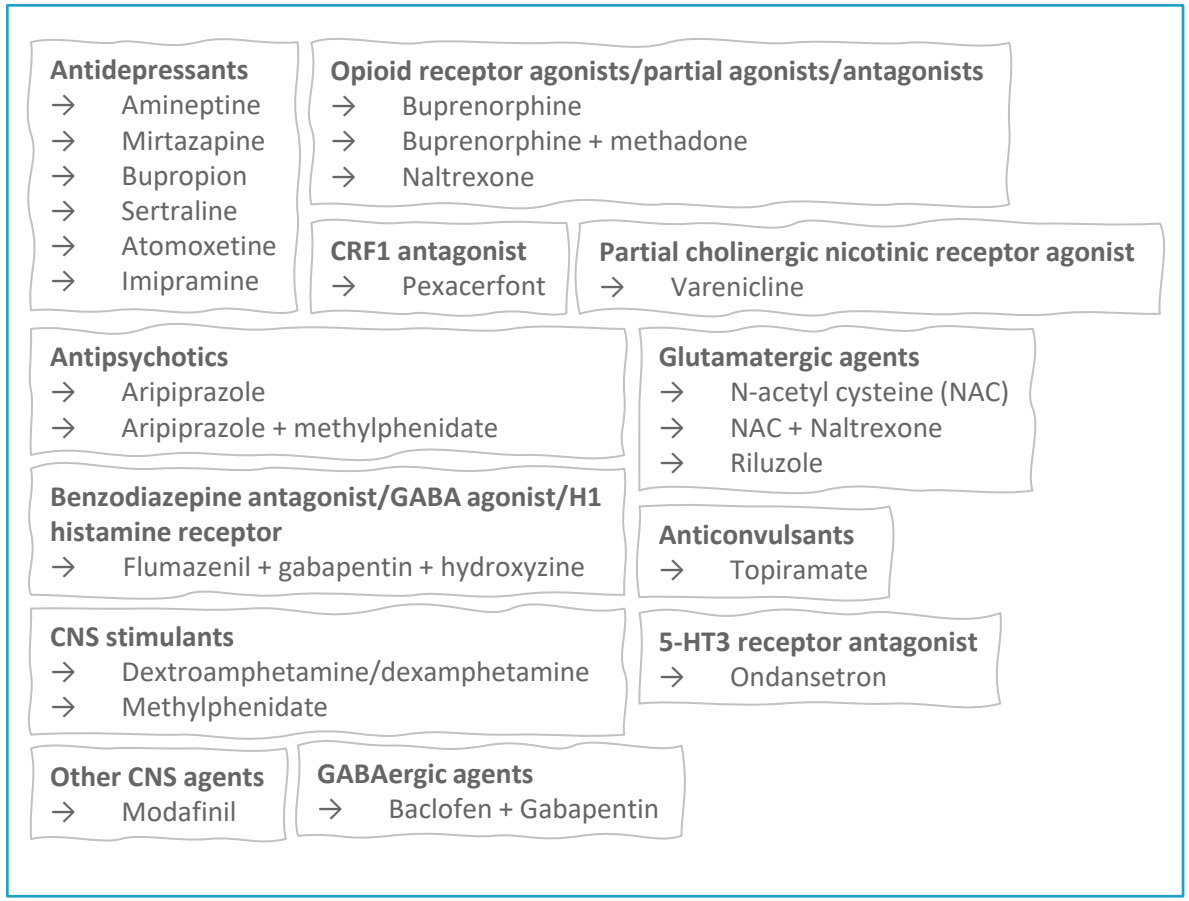
→ Phase II development remains the largest hurdle in drug development, with just 28.9% of candidates achieving this critical phase transition.

→ On average, it takes 10.5 years for a Phase I asset to progress to regulatory approval.

*Source: BIO | QLS Advisors | Informa UK Ltd February 2021*

# A FEW POSSIBLE OPTIONS

# 1 REPURPOSING OF KNOWN CHEMICAL ENTITIES (OUD/STUD)




**Reduction in use:**

→ Overall weak signals - few consistent positive findings – significant inter-individual variability in treatment response.

**Treatment of withdrawal symptoms:**

→ No robustly convincing results

**Major limitations of all studies:** Almost 80 % of studies excluded participants with co-morbid mental health diseases. HOWEVER:

→ 40% of methamphetamine users suffer from transient psychotic symptoms (Glasner-Edwards S, Mooney LJ. CNS Drugs 2014; 28(12):1115–26).

→ Most methamphetamine users suffer from lifetime prevalence of depression and anxiety (Darke S et al. Drug Alcohol Rev. 2008; 27(3):253–62).

→ Treatment compliance and retention still a major challenge

**Opportunities for medication combinations & long-acting injectable formulations:**

→ CURB: XR-NTX + transmucosal buprenorphine (for cocaine) (Ling et al. Addiction. 2016;111(8):1416-27.

→ ADAPT-2: XR-NTX + bupropion (for methamphetamine) (Trivedi et al. N Engl J Med. 2021;384(2):140-153.

→ BUP-XR: Future studies

→ XR-NTX + BUP-XR: Future studies

*Source: Siefried KJ et al. CNS Drugs (2020) 34:337–365. https://doi.org/10.1007/s40263-020-00711-x*

# 2 DEVELOPMENT OF NEW CHEMICAL ENTITIES (OUD/STUD)

| Target receptors | Drug development | Reference |
|---|---|---|
| **Metabotropic glutamate (mGluR)** | → NAMs of postsynaptic mGluR5<br>→ PAMs of presynaptic mGluR2 and possibly mGluR7 | Caprioli D et al. Biol Psychiatry. 2018; 84(3):180-192 |
| **Nociceptin/orphanin FQ receptor (NOR) or nociceptin (NOP)** | → Nonpeptide small-molecule agonists | Lutfy K, Zaveri NT. Prog Mol Biol Transl Sci. 2016; 137:149-81 |
| **Dopamine D3** | → Selective Dopamine D3 receptor antagonists | Heidbreder CA, Newman AH. Ann N Y Acad Sci. 2010; 1187:4-34 |
| **GABAb** | → GABAb PAM | Evenseth LSM et al. Molecules. 2020; 25(13):3093 |
| **Orexin 1** | → Selective Orexin 1 receptor antagonists | James MH et al. Neuropharmacology. 2021; 183:108359 |
| **Atypical pan-opioid/complex receptor pharmacology** | → Mitragynine (Kratom) | Eastlack et al. Pain Ther. 2020; 9:55–69 |
| **Epigenetic-related drugs** | → HDAC3-selective inhibitor (RGFP-966)<br>→ HDAC inhibitor suberoylanilide hydroxamic acid (SAHA)<br>→ BET inhibitor (JQ1)<br>→ Development of PET ligands for multiple histone-modifying proteins (measure target engagement and brain biomarkers in SUD patients) | Sartor GC. Biochem Pharmacol. 2019; 168: 269–274 |

# 2 DEVELOPMENT OF NEW CHEMICAL ENTITIES (RESPIRATORY DEPRESSION)

| Target receptors | Drug development | Reference |
|---|---|---|
| **Opioid** | → New formulations of nalmefene<br>→ Novel selective and potent μ-opioid receptor antagonists: NAQ; NAN | Han et al. Translational Psychiatry 2019 ; 9:282 |
| **Ampakines** | → Positive allosteric modulators of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor that stimulate respiratory drive, particularly under hypoventilatory conditions: CX717; CX1739; LCX001 | Imam MZ et al. F1000Research 2020, 9:91 |
| **α4β2 nicotinic acetylcholine receptor** | → Receptor agonist A85380 | |
| **TWIK-related acid-sensitive K+-channels (TASK)** | → Doxapram (restricted to its positive enantiomer) | |
| **Other** | → PKA inhibitors (e.g., H8936)<br>→ GIRK inhibitors (e.g., tertiapin-Q36)<br>→ Thyrotropin-Releasing Hormone (TRH) analogs (e.g., taltirelin) | |

# 3 MACHINE LEARNING (ML)

Hundreds of online publicly, curated databases that can be integrated modularly to drug development:

- → Genomic data (disease-gene associations; SNP reporting)
- → Interaction data (Protein-protein or pathway information; Biological models of gene and pathway interactions; Drug signatures (genewise expression changes due to treatment)
- → Drug-Disease associations
- → Repositories of clinical trial settings, status, and results (e.g., ClinicalTrials.gov; RepoDB; etc…)
- → Chemical and drug data (Protein-related; Drug-related; ADME drug properties)
- → Healthcare datasets (WHO; CDC; data.gov; Medicare; HCUP; etc…)

Select valid, discriminatory features for prediction or decision model inputs

ML algorithm = any computational method where results from past actions or decisions, or past observations, are used to improve predictions or future decision-making.

- → Supervised learning: aims at predicting the label of new observations given a large database of labelled examples (e.g., Support Vector Machines or (Deep) Neural Networks).
- → Unsupervised learning: aims at detecting underlying relationships or patterns in unlabeled data (e.g., Principal Component Analysis (PCA), density estimation, clustering or collaborative filtering.
- → Sequential learning: algorithms rely on trial-and-error, and iteratively use external observations in order to find the best decision with respect to the environment they interact with.

*Source: Reda C et al. (2020) Computational and Structural Biotechnology Journal. 18: 241-252. https://doi.org/10.1016/j.csbj.2019.12.006*

# IN SUMMARY

- Polysubstance use is complex and depends on drug use patterns (concurrent/simultaneous, sequential, or a combination of both), which can vary across demographics, study periods, and study structure.
- Given that nearly 80%* of fatal opioid overdoses also involved another substance, it appears that there is a greater risk of death when opioids are used in combination with other opioids and/or other drugs.
- New synthetic opioids, the COVID-19 pandemic and its associated changes in drug market dynamics and polysubstance use patterns are new challenges to the development of valid treatment options.
- Repurposing of known chemical entities in the CNS area has been broadly unsuccessful – exclusion criteria, treatment compliance and retention are still challenging.
  - New opportunities for combination of medications and new LAI formulations.
- Several opportunities for the development of new chemical entities across a wide range of biological systems.
  - But remember the “old” challenge (LOA + timelines).
- The availability of a fast-growing amount of biological and medical data, along with well-established machine learning algorithms, may promote data-driven decision making and has the potential to speed up the process and reduce failure rates in drug discovery and development.

* *Source: Jones CM et al. (2018). JAMA 319: 1819–1821. https://doi.org/10.1001/jama.2018.2844*

# THANK YOU !