AI-Driven Drug Repurposing for cocaine/ methamphetamine use disorder

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Disclosure Information (Required)

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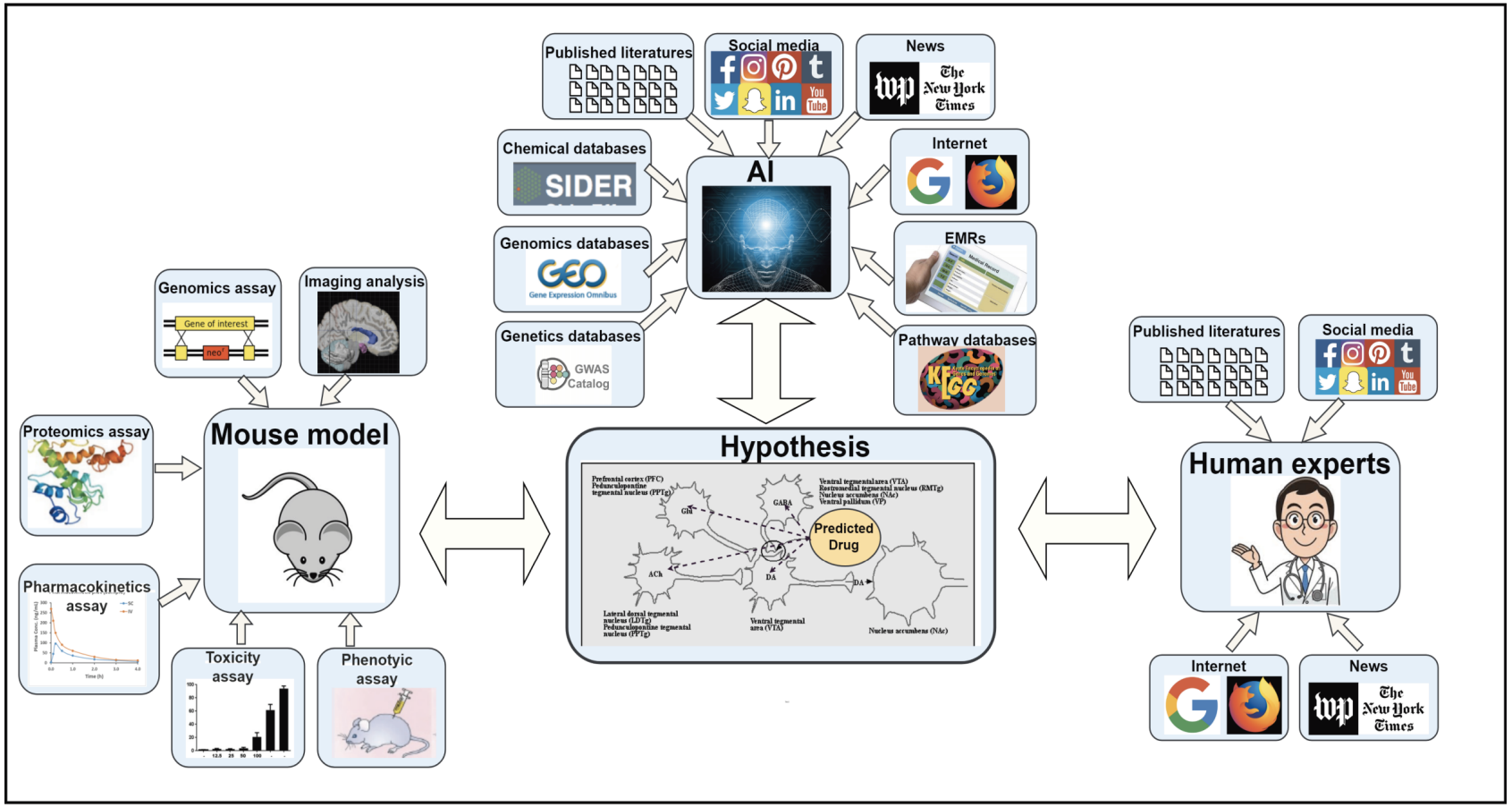
- No Disclosures

Learning Objectives (Suggested)

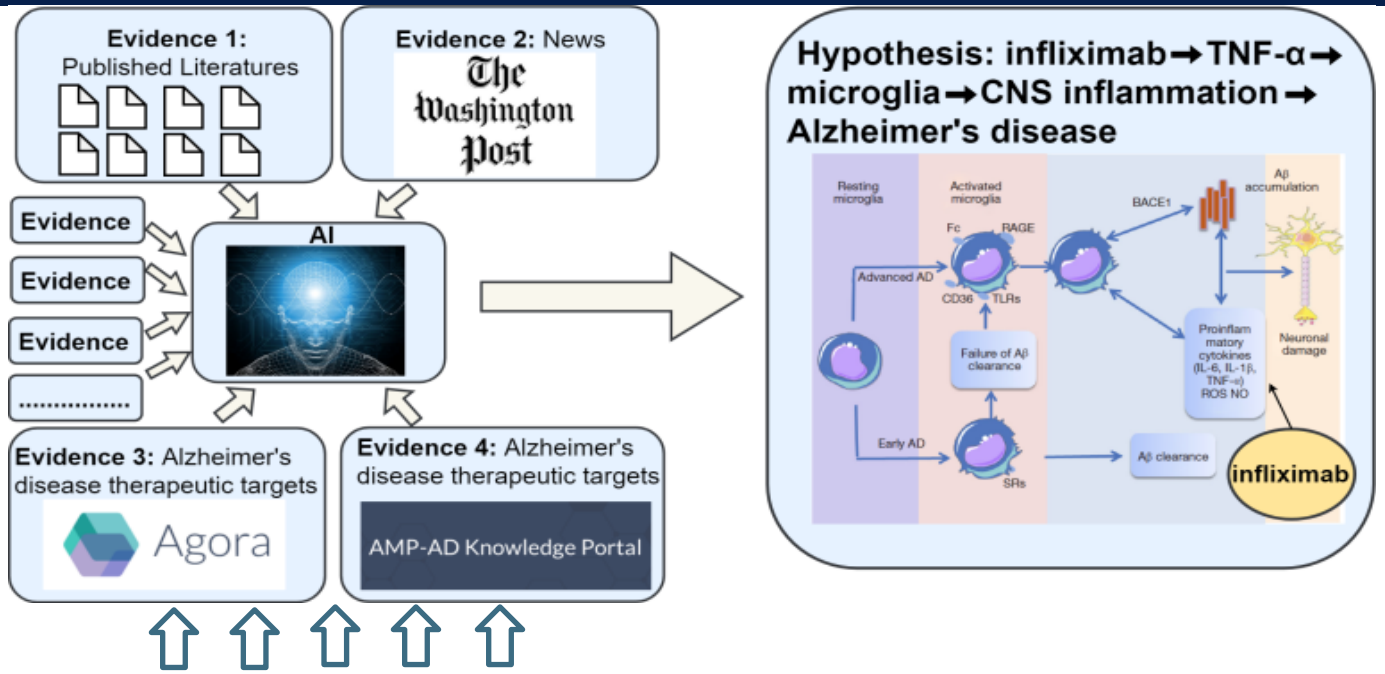
- To demonstrate the potential of advanced AI technologies in drug repurposing to treat stimulant use disorders

Knowledge-driven AI-Human-Animal Reinforcement Learning

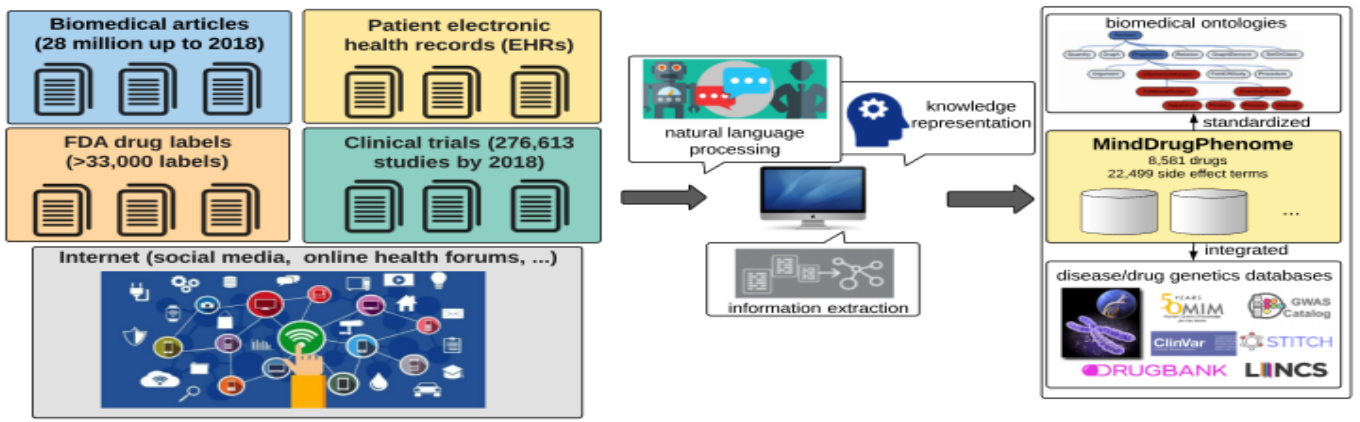


Knowledge-driven AI-Human-Animal Reinforcement Learning

The majority of biomedical knowledge is buried in free-text documents ("**wisdom of the crowd**")

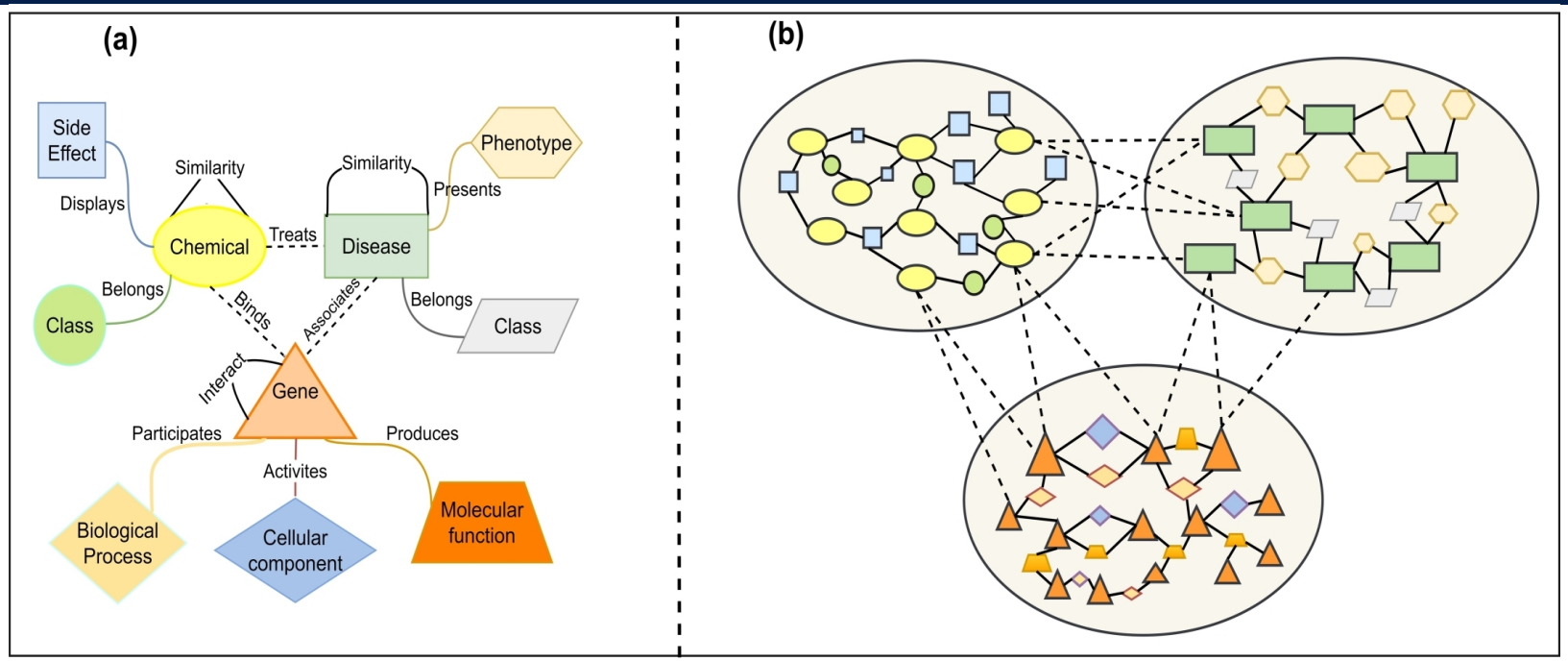


Use Natural Language Processing techniques to construct MindDrugPhenome



Wiring of the AI "brain"

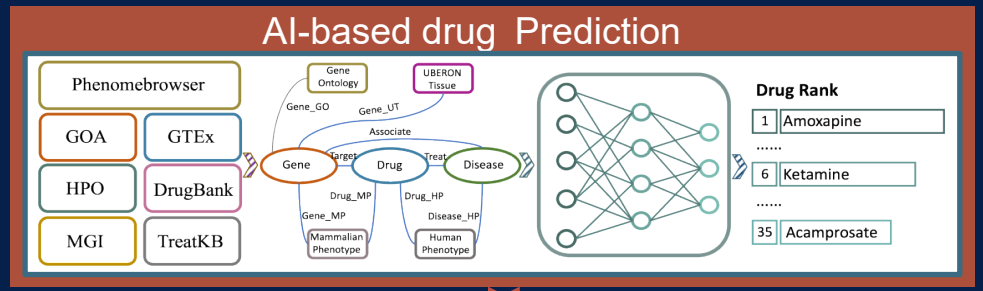
- Context-sensitive network, knowledge graph
- **Explainable, transparent**

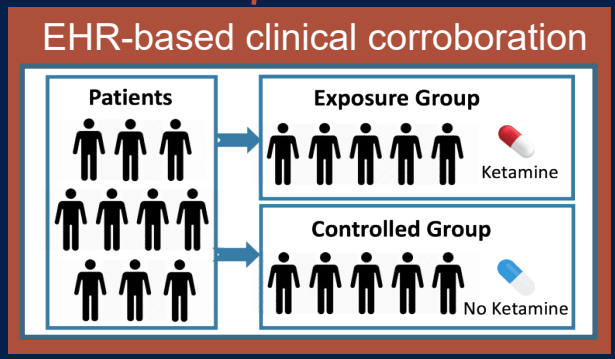


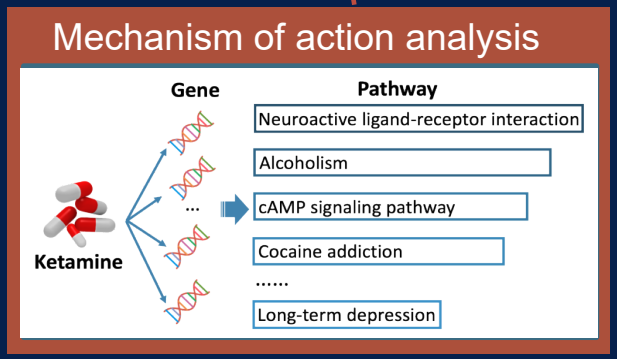
CUD "**is a comorbidity of**" opioid use disorder, depression "**is a risk factor for** " CUD, CUD "**is a risk factor for**" depression, BDNF "**is associated with**" CUD, ketamine "**targets**" BDNF, ketamine "**treats**" depression, ketamine "causes" hypertension, …..

Drug Repurposing for cocaine use disorder (CUD): integration of AI, human intelligence, clinical corroboration, and mechanism of action analysis

1. **AI-based Prediction**
2. **Expert review**
3. **Clinical evaluation**
4. **Mechanisms of action analysis**



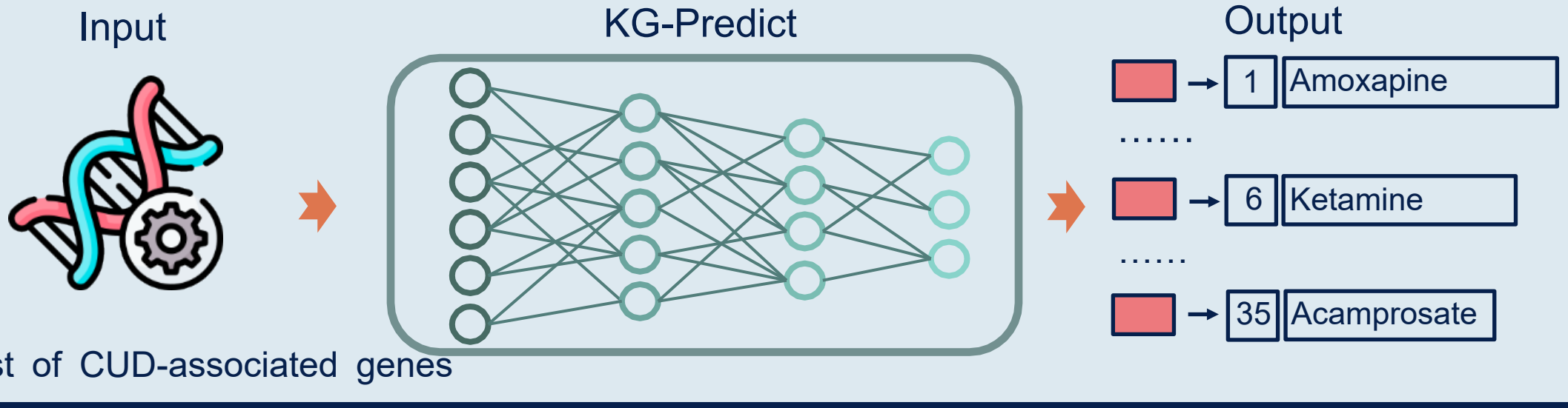




Gao et al. Addiction. 2023

Step 1: AI-based drug repurposing for CUD

Input: a list of CUD-associated genes.
Output: a list of prioritized candidate drugs
Algorithm: KG-Predict

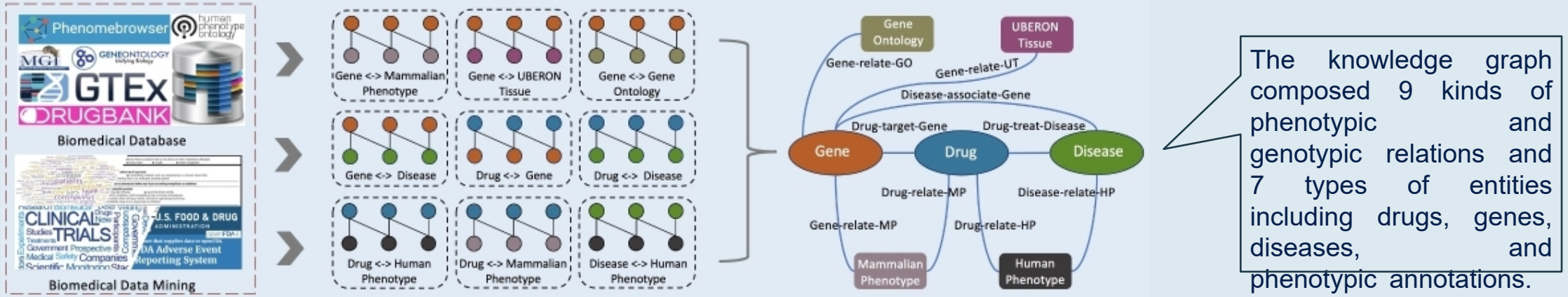


KG-Predict: knowledge graph-based prediction

Phase 1: Flow chart of knowledge graph construction

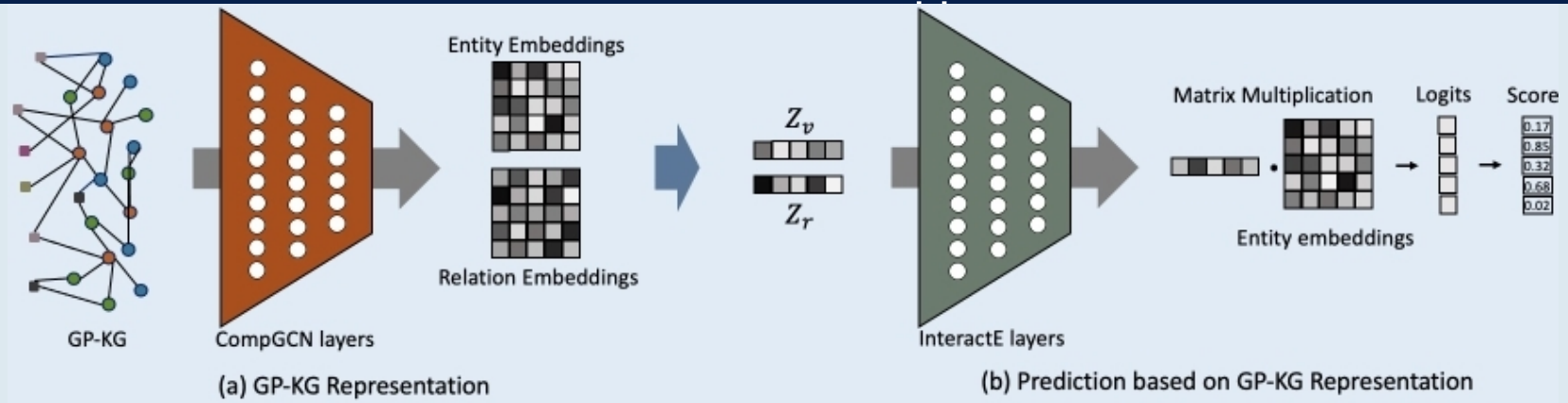
(a) Extracted raw interactions from biomedical databases and text-mined knowledge base

(b) Mapped entities into standard identifiers and merged raw interactions into a knowledge graph



The knowledge graph composed 9 kinds of phenotypic and genotypic relations and 7 types of entities including drugs, genes, diseases, and phenotypic annotations.

Phase 2: From knowledge graph to entity/relation embedding to prediction, i.e. Drug



Gao et al, Journal of Biomedical Informatics, 2022; Gao et al, AMIA 2022

Step 2: Expert Panel Review of top candidates

The CTN-0114 advisory committee members

- Kathleen Brady, MD, PhD
- Todd Korthuis, MD, MPH
- Sean Luo, PhD
- Edward Nunes, MD
- John Rotrosen, MD
- Andrew Saxon, MD
- Steven Shoptaw, PhD.

Expert Panel Review

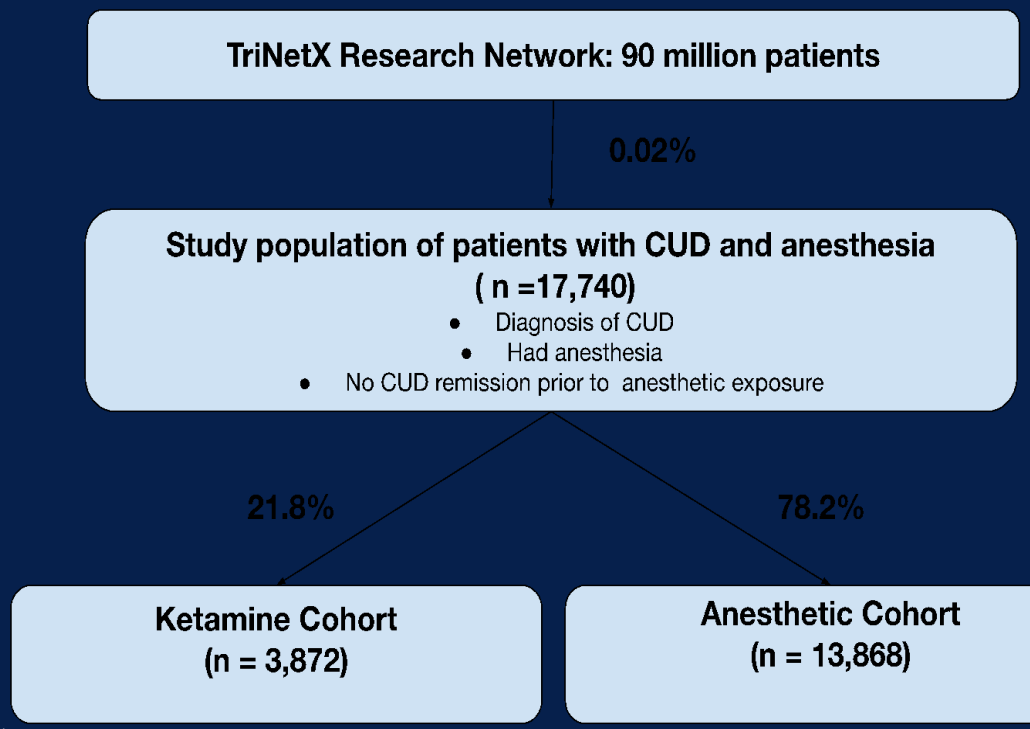
Should each of the **top 35** drug candidates (out of a ranked list of **1,430** drugs) be included in the EHR analysis taking into account **:**

- Existing pre-clinical and clinical trials evidence
- Likely challenges with clinical utilization
- Potential to address co-occurring substance use and/or phenotypes which patients frequently report as being prominent barriers to their recovery
- On-going (or soon to start investigations)

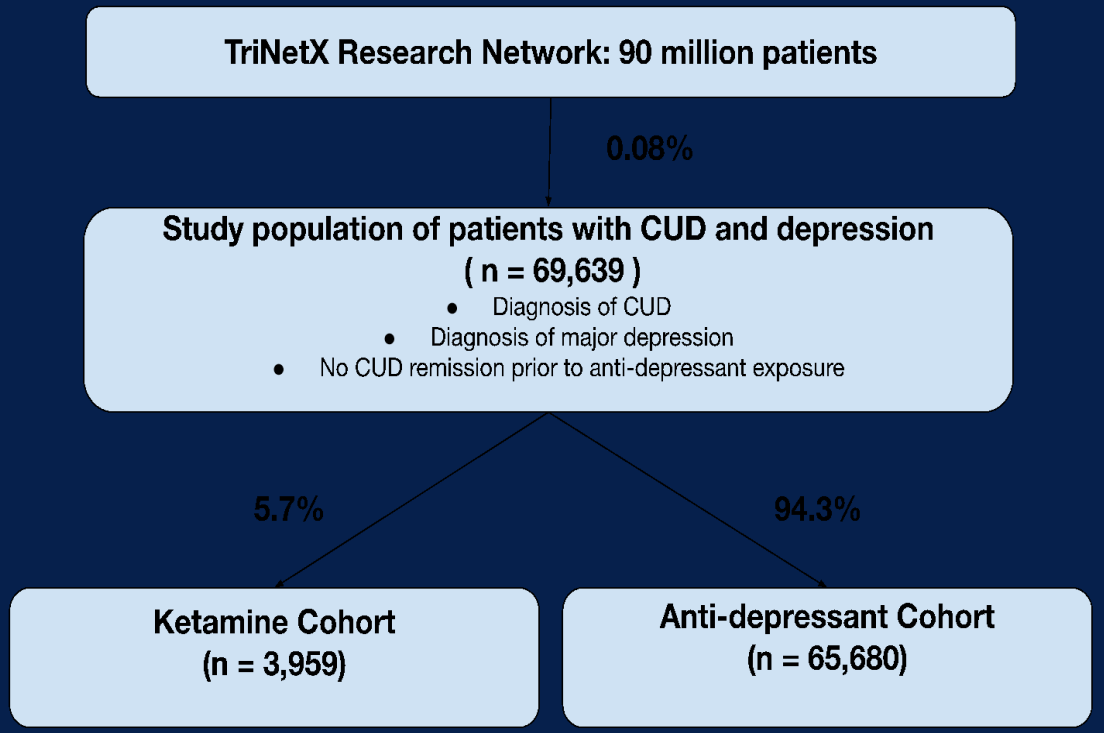
Drug	Likely Poor Adherence? No*	Likely helpful for co-occurring substance use? Yes*	Likely helpful for phenotypes that are barriers to recovery? Yes*	EHR analysis? Yes*
Ketamine	7 (100%)	7 (100%)	6 (85.7%)	7 (100%)

Step 3: EHR-based clinical evaluation: cohort selection

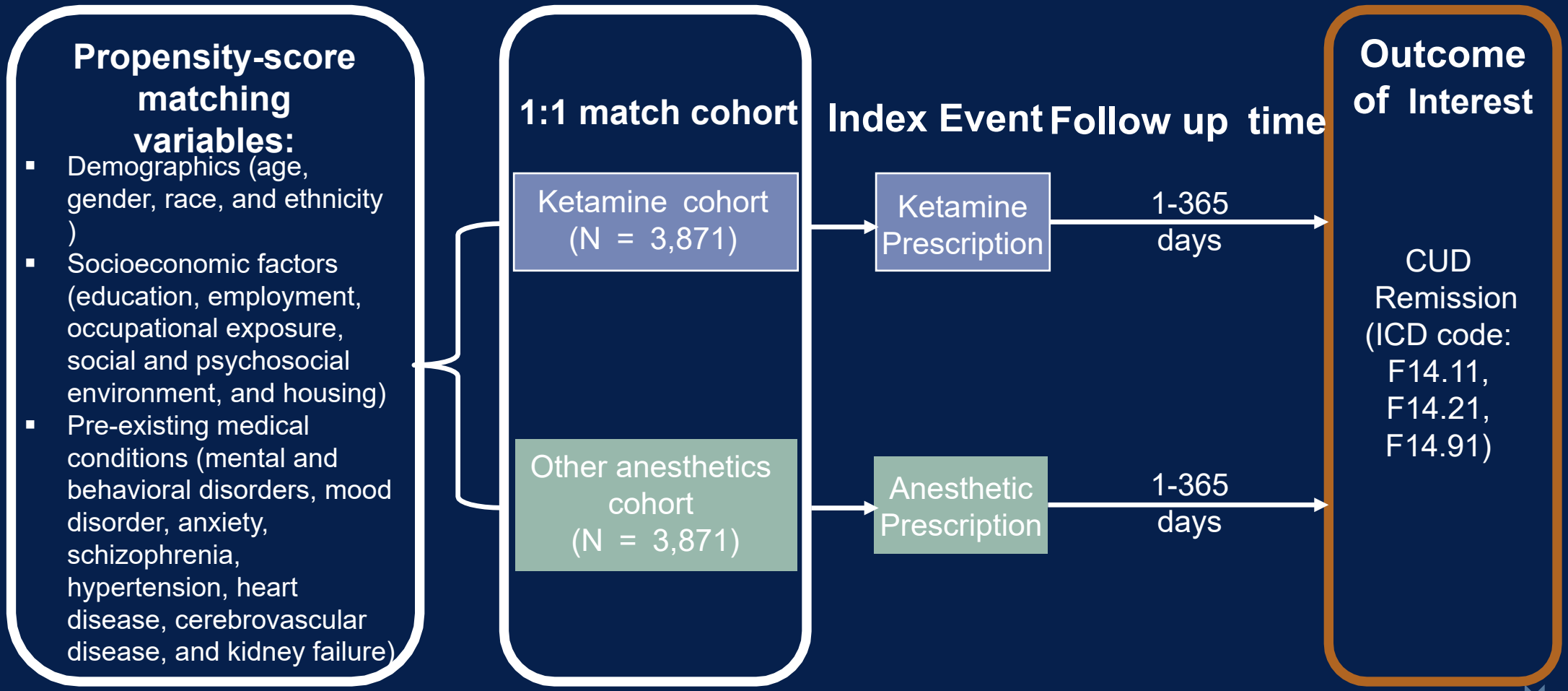
Study population #1:
patients with CUD + anesthesia



Study population #2:
patients with CUD + major depression



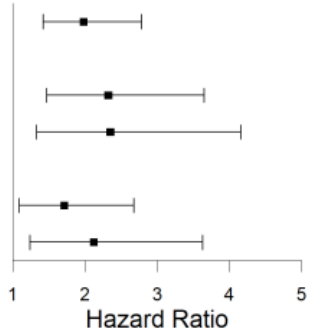
Comparing hazard rate of CUD remission within 1-year following ketamine vs. anesthetic prescription between matched cohorts



Ketamine was associated with improved CUD remission compared with other anesthetic or anti-depressants

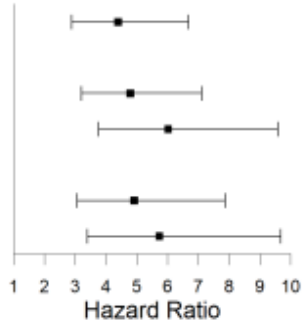
- **Ketamine is associated with greater remission from CUD in patients prescribed ketamine as an anesthetic (HR=1.98, CI=1.42-2.78)**

Matched Patients	CUD Remission in Ketamine Group	CUD Remission in Anesthetic Group	Hazard Ratio
All			
N = 3,871	2.58% (100)	1.32% (51)	1.98 (1.42, 2.78)
Gender			
Male (N = 2,453)	2.49% (61)	1.10% (27)	2.32 (1.47, 3.65)
Female (N = 1,415)	2.76% (39)	1.20% (17)	2.35 (1.33, 4.16)
Race			
Caucasian (N = 2,287)	2.23% (51)	1.31% (30)	1.71 (1.09, 2.68)
African American (N = 1,231)	3.25% (40)	1.63% (20)	2.12 (1.24, 3.63)



- **Ketamine is associated with greater remission from CUD in patients prescribed ketamine as an antidepressant (HR=4.39, CI=2.89-6.68)**

Matched patients	CUD Remission in Ketamine Group	CUD Remission in Antidepressant Group	Hazard Ratio
All			
N = 3,955	2.93% (116)	0.68% (27)	4.39 (2.89, 6.68)
Gender			
Male (N = 2,228)	2.92% (65)	0.49% (11)	4.78 (3.21, 7.11)
Female (N = 1,726)	2.96% (51)	0.58% (10)	6.01 (3.76, 9.58)
Race			
Caucasian (N = 2,382)	2.73% (65)	0.51% (12)	4.91 (3.06, 7.87)
African American (N = 1,021)	3.63% (37)	0.98% (10)	5.73 (3.39, 9.68)



Step 4: Mechanisms of action analysis of ketamine in the context of CUD

- Ketamine targets CUD-associated genes

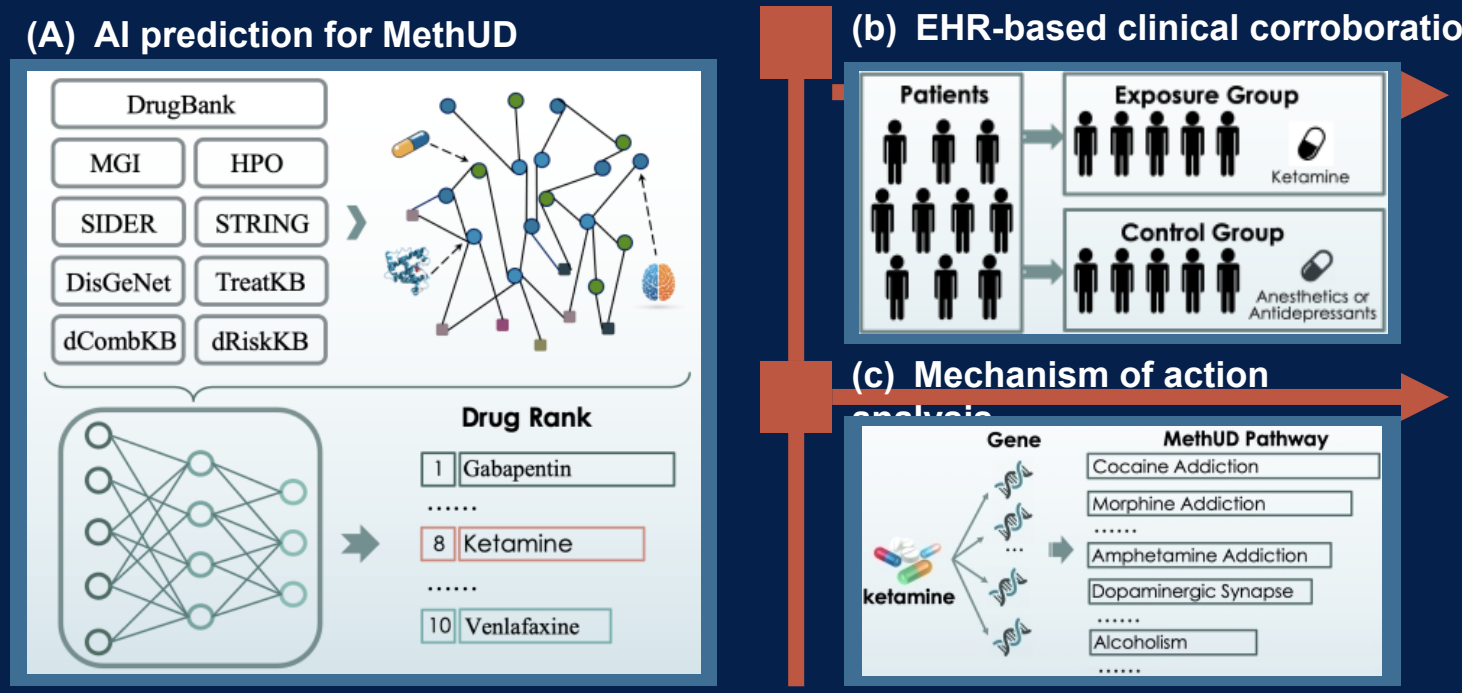
Drug	Total Target Genes	Target CUD Genes	CUD Genes
Ketamine	154	10	BDNF, CNR1, DRD2, GABRA2, GABRB3, GAD1, OPRK1, OPRM1, SLC6A3, SLC6A4

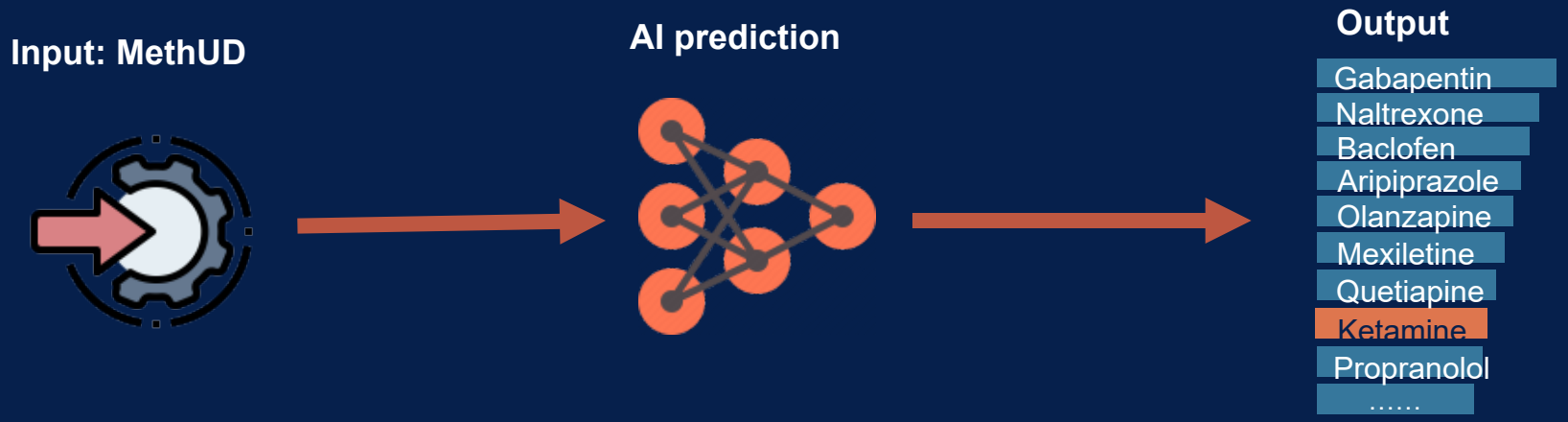
- Ketamine targets CUD-related pathways

Pathways			
1	Neuroactive ligand-receptor interaction	2	Alcoholism
3	cAMP signaling pathway	4	Cocaine addiction
5	Dopaminergic synapse	6	Amphetamine addiction
7	GABAergic synapse	8	Morphine addiction
9	Serotonergic synapse	10	Nicotine addiction
11	Retrograde endocannabinoid signaling	12	Long-term depression

Does the AI system work for other StUDs?

Drug Repurposing for methamphetamine use disorder (MethUD)

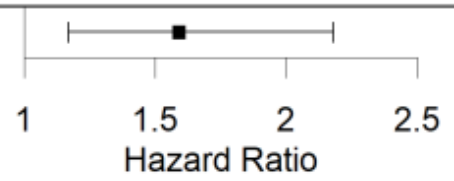




Results: Ketamine is associated with higher rate of MethUD remission compared with other anesthetic or anti-depressants

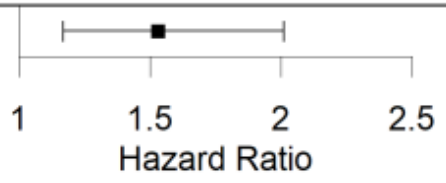
- **Ketamine is associated with greater remission from MethUD in patients prescribed ketamine as an anesthetic (HR=1.59, CI=1.17-2.18)**

Drug	Remission Ratio in Exposure Cohort	Remission Ratio in Control Cohort	Hazard Ratio
Ketamine vs Other anesthetics	5.56% (104/1,872)	3.45% (65/1,886)	1.59 (1.17, 2.18)



- **Ketamine is associated with greater remission from MethUD in patients prescribed ketamine as an antidepressant (HR=1.53 , CI=1.17-2.01)**

Drug	Remission Ratio in Exposure Cohort	Remission Ratio in Control Cohort	Hazard Ratio
Ketamine vs Antidepressants	5.76% (129/2,240)	3.82% (86/2,253)	1.53 (1.17, 2.01)



Mechanisms of action analysis of ketamine in the context of MethUD

- Ketamine targets MethUD-associated genes

Drug	Total Target Genes	Target MethUD Genes	MethUD Genes
Ketamine	154	12	NPY1R, HTR3A, GRM2, BDNF, ACHE, OPRM1, SLC6A4, GABRG2, SLC6A3, ADORA2A, DRD2, FOS

- Ketamine targets MethUD-related pathways

Pathways	
1 Cocaine addiction	2 Morphine addiction
3 Neuroactive ligand-receptor interaction	4 Amphetamine addiction
5 Dopaminergic synapse	6 cAMP signaling pathway
7 Gap junction	8 Serotonergic synapse
9 Neurotrophin signaling pathway	10 Fluid shear stress and atherosclerosis
11 Relaxin signaling pathway	12 Alcoholism
13 MAPK signaling pathway	14 Chemical carcinogenesis - receptor activation
15 Chemical carcinogenesis - reactive oxygen species	

Summary, limitations and future directions

Summary:

- This study demonstrates the potential of knowledge-driven AI in drug discovery for substance use disorders including StUD
- Findings suggest the potential of ketamine for treating CUD/MethUD

Limitations:

- AI-prediction: Incomplete, noisy, evolving knowledge
- Expert evaluation: time-consuming
- Cohort studies: confounders and biases
- Mechanism of action analysis: in-silico

Future works:

- Other substance use disorders
- Polysubstance use disorders
- Substance use disorders with comorbidities.

Gao Z, Winhusen TJ, Gorenflo M, Ghitza UE, Davis PB, Kaelber DC, Xu R*. Repurposing ketamine to treat cocaine use disorder: Integration of artificial intelligence-based prediction, expert evaluation, clinical corroboration, and mechanism of action analyses. Addiction. 2023 Feb 15. doi: 10.1111/add.16168.*

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  - Kathleen Brady, MD, PhD
  - Todd Korthuis, MD, MPH
  - Sean Luo, PhD
  - Edward Nunes, MD
  - John Rotrosen, MD
  - Andrew Saxon, MD
  - Steven Shoptaw, PhD
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QUESTIONS?

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