Centre of Metabolism & Inflammation
Department of Inflammation & Rare Diseases
Division of Medicine
Royal Free Campus, London

UCL

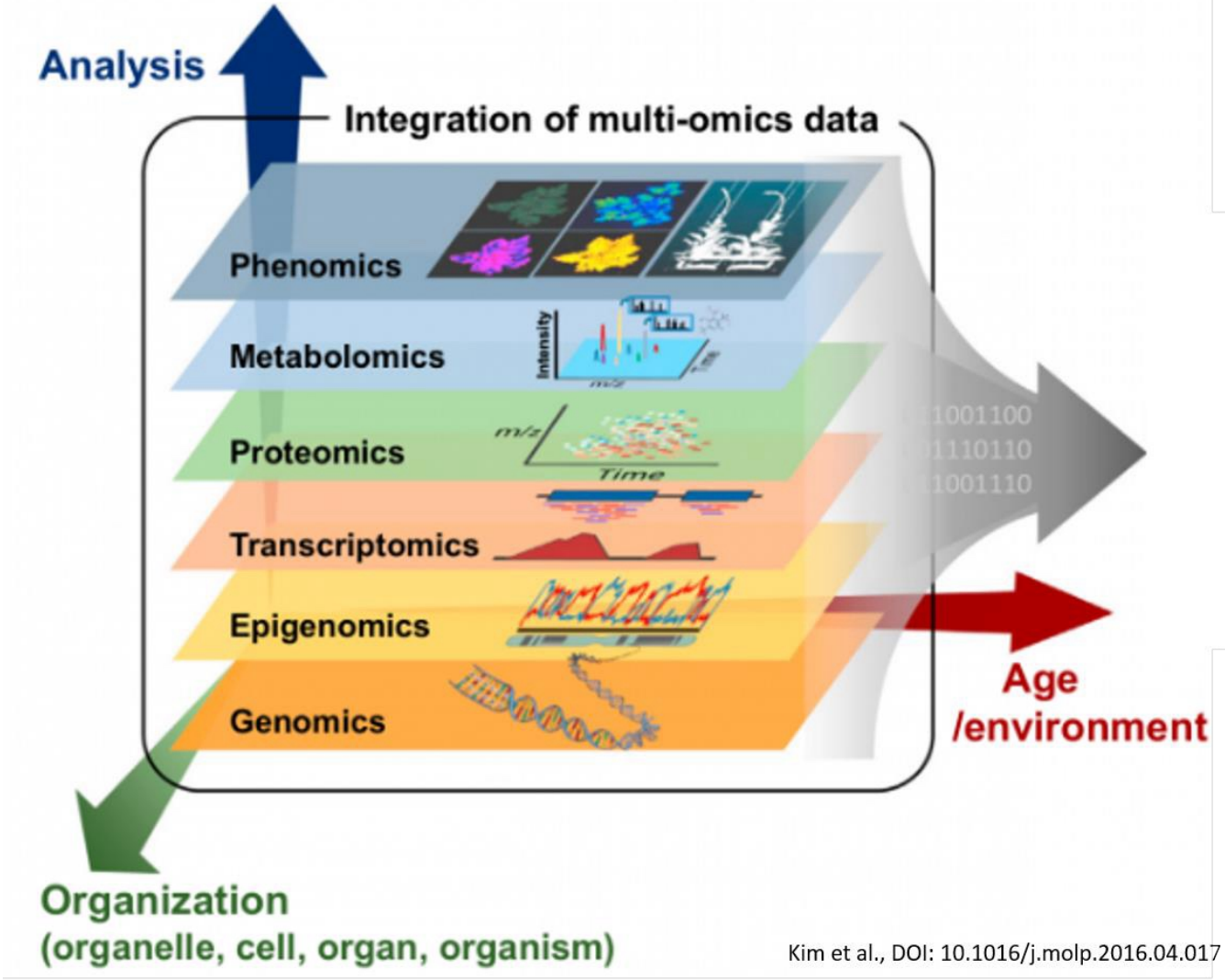
Multi-omics approach for the characterization of Substance Use Disorders

Vidya Mohamed-Ali
Mohammed Al-Maadheed

Aims of the presentation

- Omics for biomarkers discovery and mechanisms
- Drug discovery
- Critical appraisal of limitations
- Future – collaborations and consortia

Definitions



Kim et al., DOI: 10.1016/j.molp.2016.04.017

- omics - systematic measurement of DNA, epigenetic markers, RNA, proteins, metabolites,
- and detailed phenotyping, across large cohorts.
- Microbiome -

Epigenomic Signatures to Brain-Reward Circuits

- Parallel to GWAS, epigenomics showed that chronic exposure to substances, especially opioids, alcohol, and stimulants, leaves a molecular scar on the genome.
- In animal models, repeated exposure alters DNA methylation and histone modifications in key reward and stress circuits.
- As human postmortem brain banks matured, similar signals appeared in human tissue, reinforcing the idea that addiction is not just a behavioral state but a stable, experience-shaped epigenetic and transcriptional program.
- Implicated regions: nucleus accumbens, prefrontal cortex, amygdala, ventral tegmental area.

Postmortem OUD Brain: Neuroinflammation and Glia

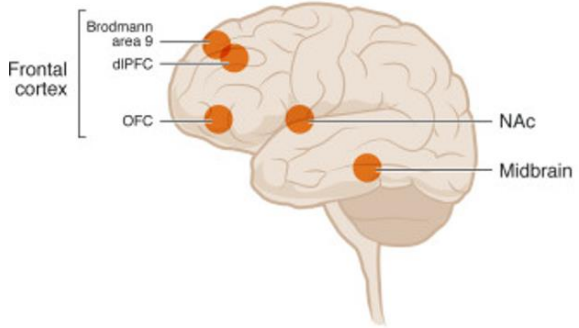
The Journal of Clinical Investigation

REVIEW SERIES: SUBSTANCE USE DISORDERS
Series Editor: Henry R. Kranzler

An emerging multi-omic understanding of the genetics of opioid addiction

Eric O. Johnson,[1,2] Heidi S. Fisher,[3] Kyle A. Sullivan,[4] Olivia Corradin,[5] Sandra Sanchez-Roige,[6,7] Nathan C. Gaddis,[1] Yasmine N. Sami,[5] Alice Townsend,[4] Erica Teixeira Prates,[4] Mirko Pavicic,[4] Peter Kruse,[4] Elissa J. Chesler,[3] Abraham A. Palmer,[6,8] Vanessa Troiani,[9] Jason A. Bubier,[3] Daniel A. Jacobson,[4] and Brion S. Maher[10]

- Cross-omics analyses of postmortem OUD brain tissue reveal coordinated immune-related gene modules and co-methylation networks that are enriched in glial and astrocytic pathways.
- This is a shift from viewing addiction purely as a neuronal dopamine disorder to a broader picture where neuroinflammation plays a central role.



	Gene expression	DNA methylation	Alternative splicing	Chromatin modification
Frontal cortex				
Carter et al. (29)	●			
Corradin et al. (28)	●			●
Falconnier et al. (24)	●			
Huggett et al. (43)	●		●	
Mendez et al. (25)	●			
Rompala et al. (45)	●	●		
Seney et al. (26)	●			
Shu et al. (44)		●		
Sosnowski et al. (27)	●			
NAc				
Falconnier et al. (24)	●			
Huggett et al. (43)	●		●	
Seney et al. (26)	●			
Midbrain				
Huggett et al. (43)	●		●	
Saad et al. (42)	●			

567 and 1,305 DEGs in dorsolateral prefrontal cortex (dlPFC) and nucleus accumbens (NAc) tissues Identified nearly 400 DEGs and over 200 differentially expressed proteins and reported that four genes (LGALS3, SLC2A1, PCLD1, and VAMP1) were differentially expressed in RNA and protein.

Cell-Type–Specific Omics in SUDs

- Recent advances in single-cell and cell-type-specific omics have shown that drugs do not impact the brain uniformly.
- Dopaminergic, glutamatergic, and GABAergic neurons may respond differently,
- Microglia and astrocytes show their own distinct transcriptional and epigenetic signatures - they're dynamically sculpted by chronic opioid exposure, contributing to synaptic remodeling, stress reactivity, and even relapse vulnerability.
- This cell-type resolution is critical for precision drug discovery to pinpoint circuits and cell populations to target

Biomarker discovery

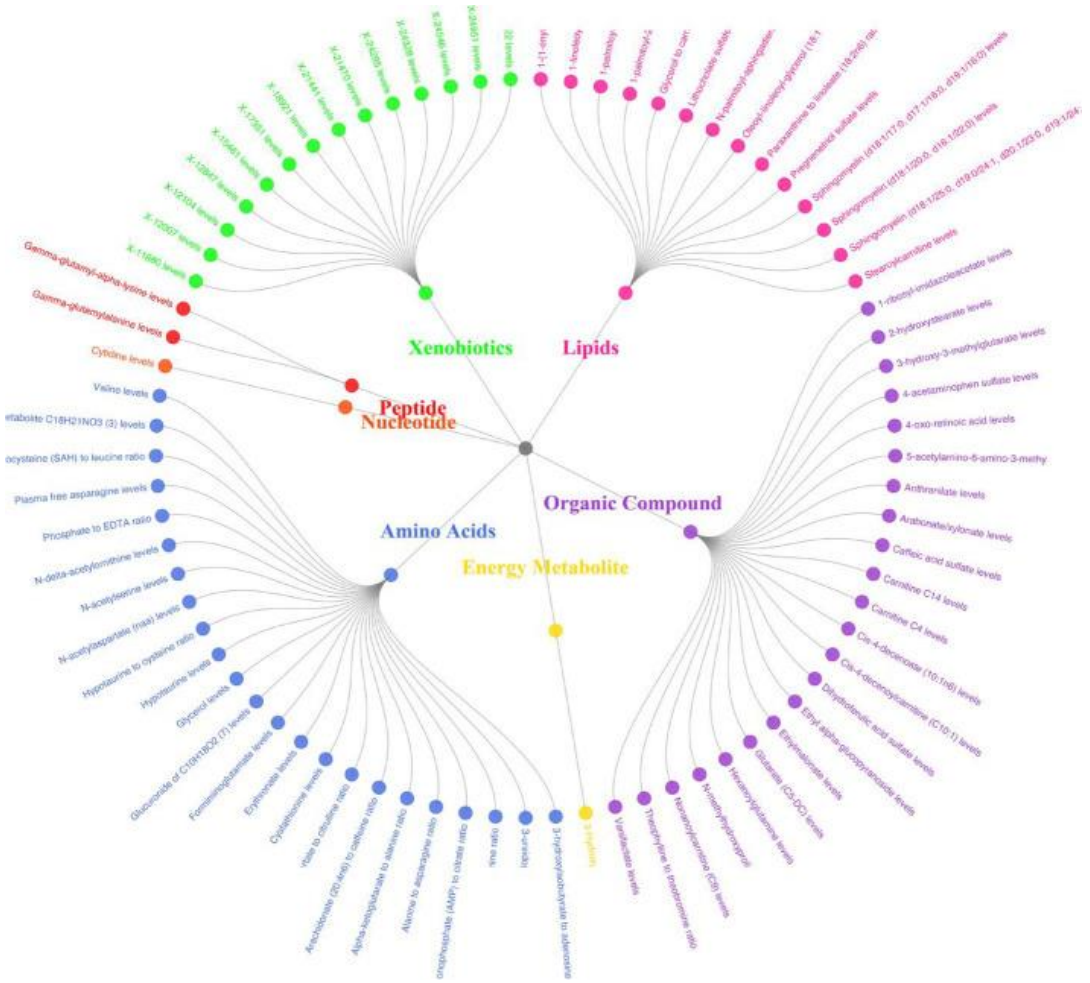
- Imbalanced metabolic homeostasis is be a predictor of substance addiction state with alterations in metabolites such as inositol-1-phosphate and serotonin, linked to reward-punishment mechanisms of heroin addiction
- Lipid signaling molecules (e.g., eicosanoids, sphingolipids, etc.), lipid trans porters (e.g., anandamide, etc.), and “lipid-based” ligands (e.g., arachidonoyl amino acid family of ligands, etc.) play a crucial role in the progression of SUDs.
- For example, the lipophilic compound tetrahydrocannabinol, which is the primary psychoactive component of the cannabis sativa plant, impedes production of neuronal growth factors in neurons and disrupts signaling cascades that are involved in synapse formation

LETTER ▸ Discov Ment Health. 2025 Aug 19;5(1):126. doi: 10.1007/s44192-025-00275-6

Investigating the causal role of serum metabolites in substance use disorder risk: a study integrating Mendelian randomization and synthesis analysis

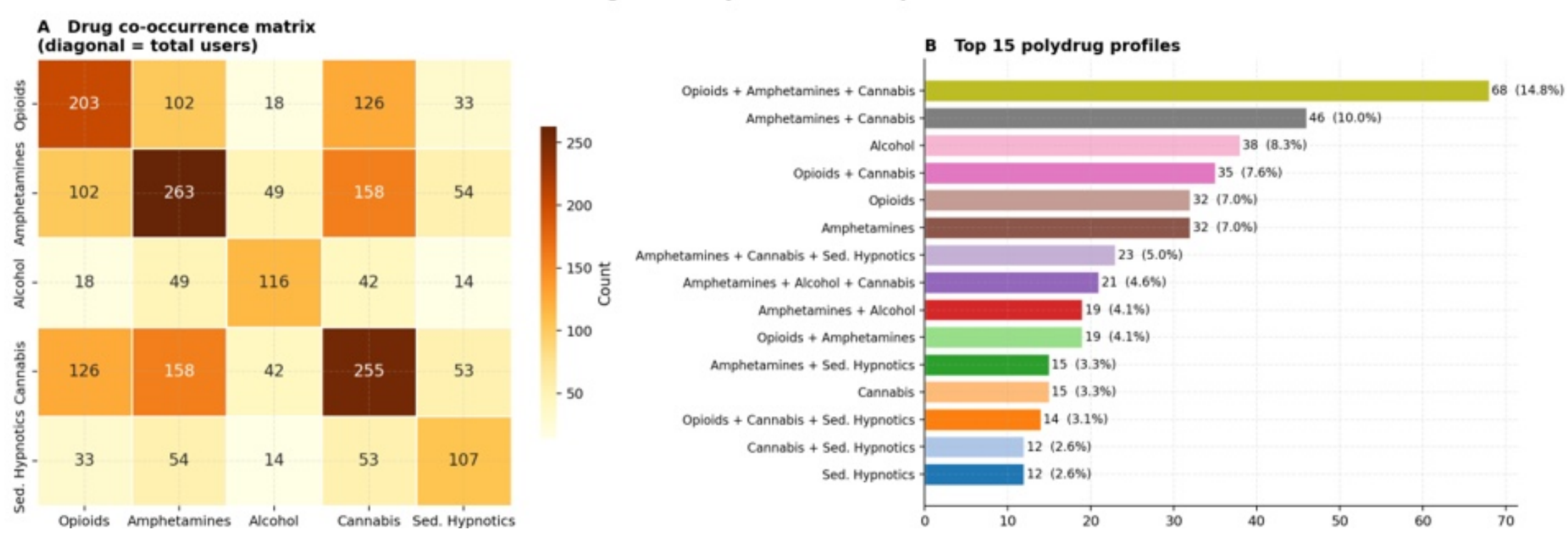
WeiXiong Xu [1,#], DanDan Xie [1,#], ZhenZhu Zhang [1,#], PiBo Du [1,#], YongJian Ye [1,#], XuBo Dai [1,✉,#]

- 77 metabolites showed initial causal associations with SUD - 14 metabolite ratios and 63 metabolites (49 known and 14 unknown).
- On validation - 57 metabolites (38 known, 6 unknown, 13 ratios), confirmed associations may indicate causal effects on SUD incidence.
- Synthesis analysis consistent with the primary analysis identified two as risk factors and four as protective factors for SUD.
  - gamma-glutamyl-alpha-lysine and ethyl alpha-glucopyranoside levels were positively correlated with disease incidence.
  - Erythronate levels, 1-(1-enyl-stearoyl)-2-oleoyl-GPE (P-18:0/18:1) levels, aspartate to citrulline ratios, and cis-4-decenoate (10:1n6) levels were negatively correlated with SUD



The microbiome and SUDs

In a cohort of 459 participants (420 males, 91.5%; 39 females), the median age was 32 years (IQR: 26–38.5) and the median BMI was 27.3 kg/m²; 73 participants reported intravenous drug use.



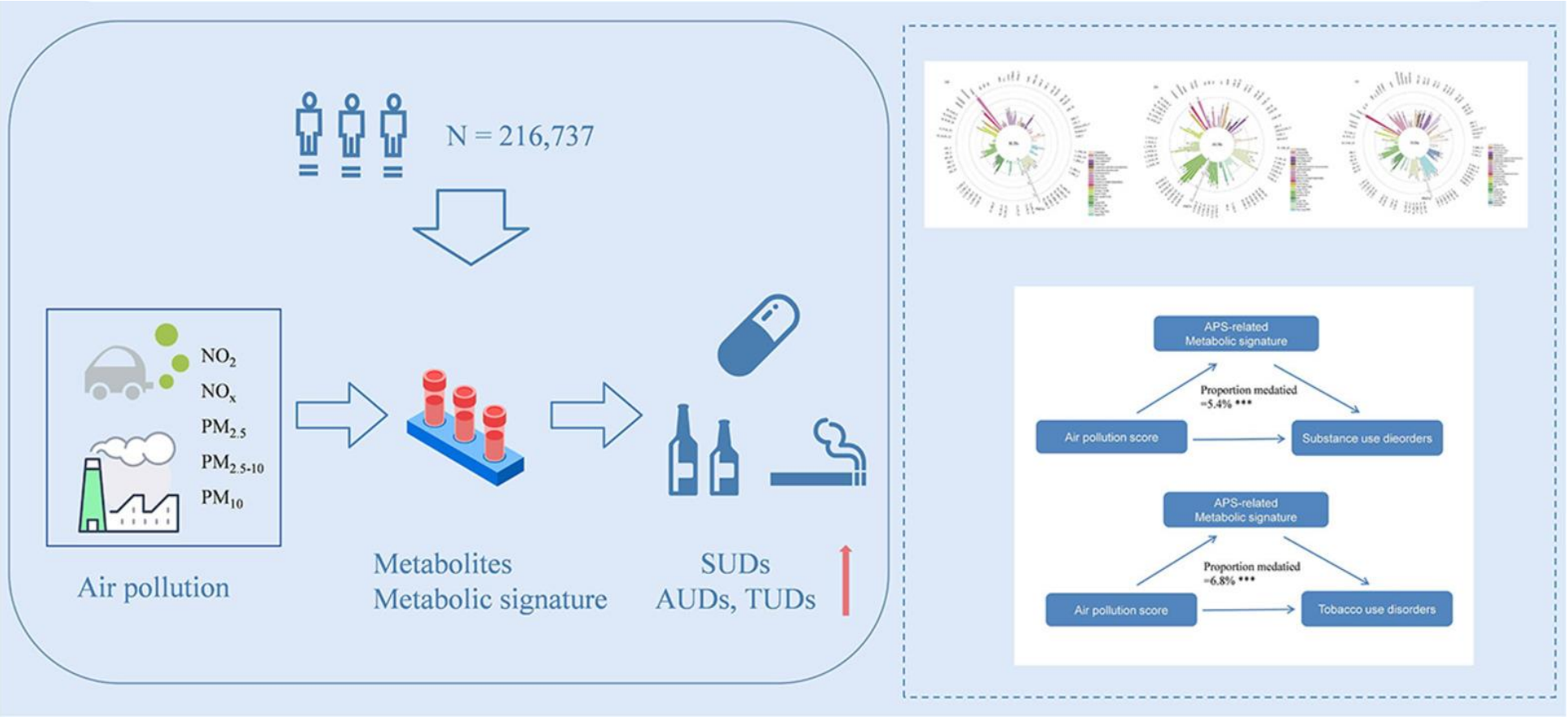
Each of the five primary substance classes (Opioids, Amphetamines, Alcohol, Cannabis, Sedative Hypnotics) was coded as a binary indicator variable (0 = not used, 1 = used in any of up to three recorded substance positions). This approach captures polysubstance use comprehensively and avoids the misclassification inherent in using only the primary substance label, given that 72.3% of participants reported use of more than one substance category.

Untargeted metabolomics identified 14 microbiome-related metabolites associated with at least one substance class at false discovery rate $q < 0.10$.

Significant associations were most frequent for opioids (n=7), followed by alcohol (n=4) and cannabis (n=3), whereas no significant associations were detected for amphetamines or sedative-hypnotics after FDR correction.

Substance	Metabolite	Pathway	β	FC	p	q
Opioids	Phenol sulfate	Tyrosine-related (microbiome associated)	-0.302	0.74	<0.001	0.003
	Kynurenine	Tryptophan/Indole/Kynurenine metabolism	0.119	1.13	<0.001	0.005
	Imidazole propionate	Histidine/Imidazole (microbiome associated)	0.256	1.29	<0.001	0.017
	Indolelactate	Tryptophan/Indole/Kynurenine metabolism	0.120	1.13	0.002	0.027
	o-Cresol sulfate	Benzoate/Phenolic (microbiome associated)	0.272	1.31	0.009	0.077
	Phenylacetate (PLA)	Phenylalanine-related (microbiome associated)	0.124	1.13	0.008	0.077
	Anthranilate	Tryptophan/Indole/Kynurenine metabolism	-0.330	0.72	0.006	0.077

Substance	Metabolite	Pathway	β	FC	p	q
Alcohol	Glycoursodeoxycholic acid sulfate	Secondary Bile Acids	0.461	1.59	0.003	0.064
	Butyrate/isobutyrate (4:0)	Short-Chain Fatty Acids	0.226	1.25	0.002	0.064
	Deoxycholic acid glucuronide	Secondary Bile Acids	0.420	1.52	0.002	0.064
	Isoursodeoxycholate sulfate	Secondary Bile Acids	0.555	1.74	0.004	0.067
Cannabis	Methyl-4-hydroxybenzoate sulfate	Benzoate/Phenolic (microbiome associated)	-0.423	0.66	0.003	0.075
	Anthranilate	Tryptophan/Indole/Kynurenine metabolism	-0.329	0.72	0.003	0.075
	Phenylacetate	Phenylalanine-related (microbiome associated)	-0.233	0.79	0.002	0.075



Psychiatry Research 361 (2026) 117124

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Original article

Metabolomics revealed novel associations between multiple ambient air pollutants exposure and substance use disorders: Evidence from a prospective cohort study

Xiao-Yu Jia, Jiang-Yan Wang, Chang Liu, Cun-Xian Jia *, Bao-Peng Liu *

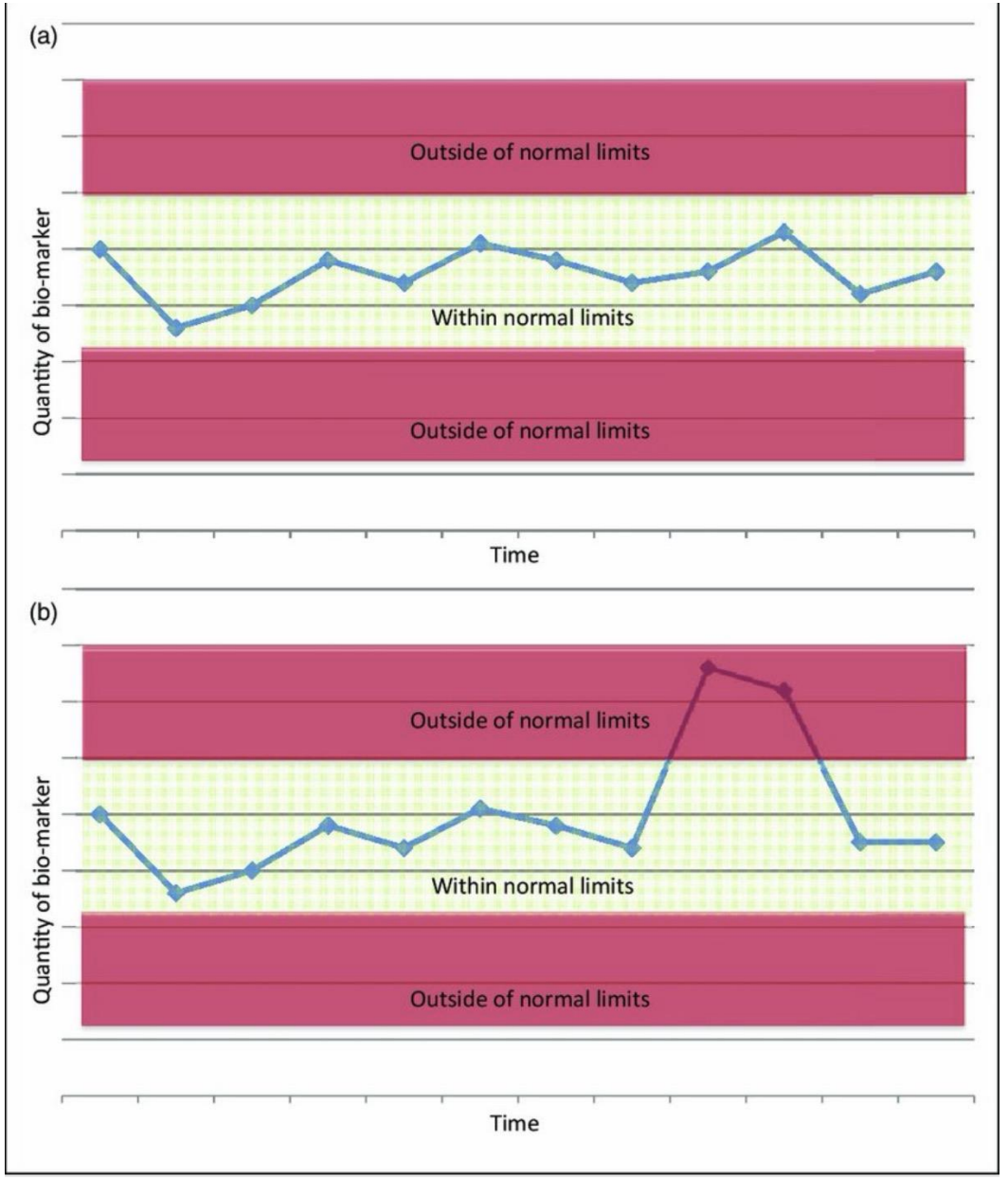
Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China

Based on a large prospective cohort study, long-term exposure to multiple ambient air pollutants was significantly associated with markedly elevated risks of SUDs, including AUDs and TUDs.

Metabolic signature reflecting air pollution exposure was associated with SUDs and TUDs and mediated the association between air pollution and these disorders.

SUD Passport

Faced with challenge of identifying known and unknown illicit substances, especially NPS, as well poly substance abuse, an analogous approach to the one taken by the World Anti-doping Agency (WADA) with the Athlete's Biological Passport (ABP), which monitors selected biological variables over time that indirectly reveal the effects of doping, rather than attempting to detect the doping substance itself, may be fruitful



Precision Prevention and Personalized Treatment

- In prevention, genetic addiction risk scores are being explored to identify high-risk individuals, such as adolescents in high-risk families, before full-blown dependence emerges.
- In treatment, omics-guided repurposing may yield tailored medications: dopamine-modulating agents for reward-driven phenotypes, anti-inflammatory drugs for those with neuroinflammatory signatures, and stress-modulating agents for those with high allostatic load.

Need for drug repurposing

- There are few medications for SUD and while effective they are limited by limited utilization and high relapse rates.
- There are no approved medications to treat cocaine, marijuana, methamphetamine, benzodiazepine, or inhalant use disorders.
- The traditional drug discovery process for medication development is lengthy and costly.
- In addition, the very modest investment from the pharmaceutical sector in SUDs has limited the discovery of new medications to a greater extent than for other neuro-psychiatric disorders.
- Thus, novel strategies to evaluate the potential for repurposing existing drugs to treat SUD could accelerate access to additional medications.

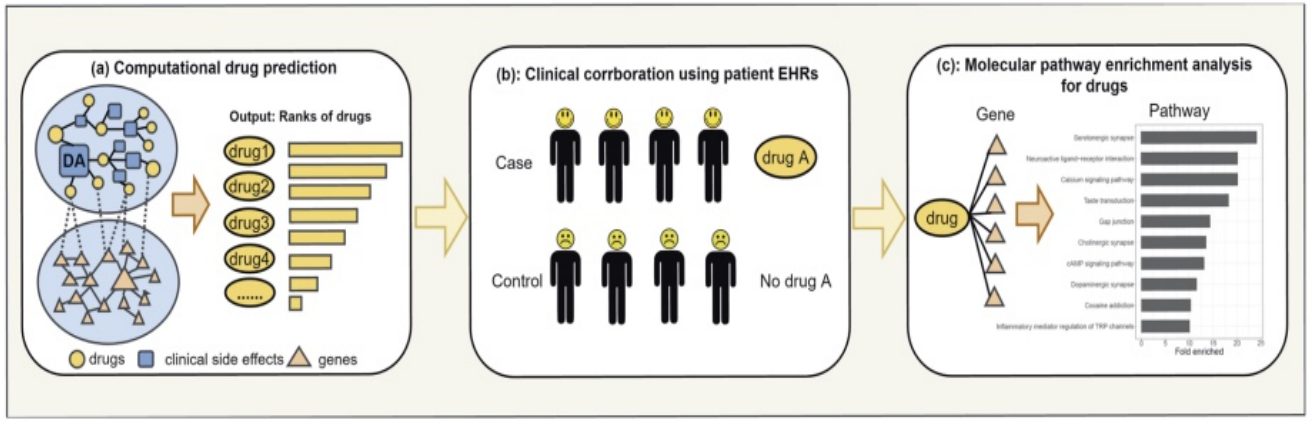
Network-Based Drug Repurposing

Molecular Psychiatry (2021) 26:5286–5296
https://doi.org/10.1038/s41380-020-01011-y

ARTICLE

Drug repurposing for opioid use disorders: integration of computational prediction, clinical corroboration, and mechanism of action analyses

Mengshi Zhou[1,2] · QuanQiu Wang[1] · Chunlei Zheng[1] · A. John Rush[3,4,5] · Nora D. Volkow[6] · Rong Xu[1]



Drug	Total target genes	Target OUD genes	OUD genes
Atomoxetine	11	3	BDNF, CYP2D6, SLC6A4
Bupropion	22	2	CYP2D6, SLC6A4
Mirtazapine	30	5	CYP2D6, DRD2, DRD4, OPRK1, SLC6A4
Olanzapine	62	7	BDNF, CYP2D6, DRD2, DRD4, HTR1B, POMC, SLC6A4
Tramadol	16	5	CYP2D6, OPRD1, OPRK1, OPRM1, SLC6A4

Buprenorphine, methadone, naltrexone and naloxone all ranked in the top 0.91 – 3.2%

Network-Based Drug Repurposing

- Beyond biomarkers, omics is now feeding into drug discovery - if a drug reverses the addiction-associated gene-expression signature, it might reverse the underlying biology.
- Several FDA-approved dopamine-modulating and anti-inflammatory agents emerged as candidates for opioid and cocaine addiction.

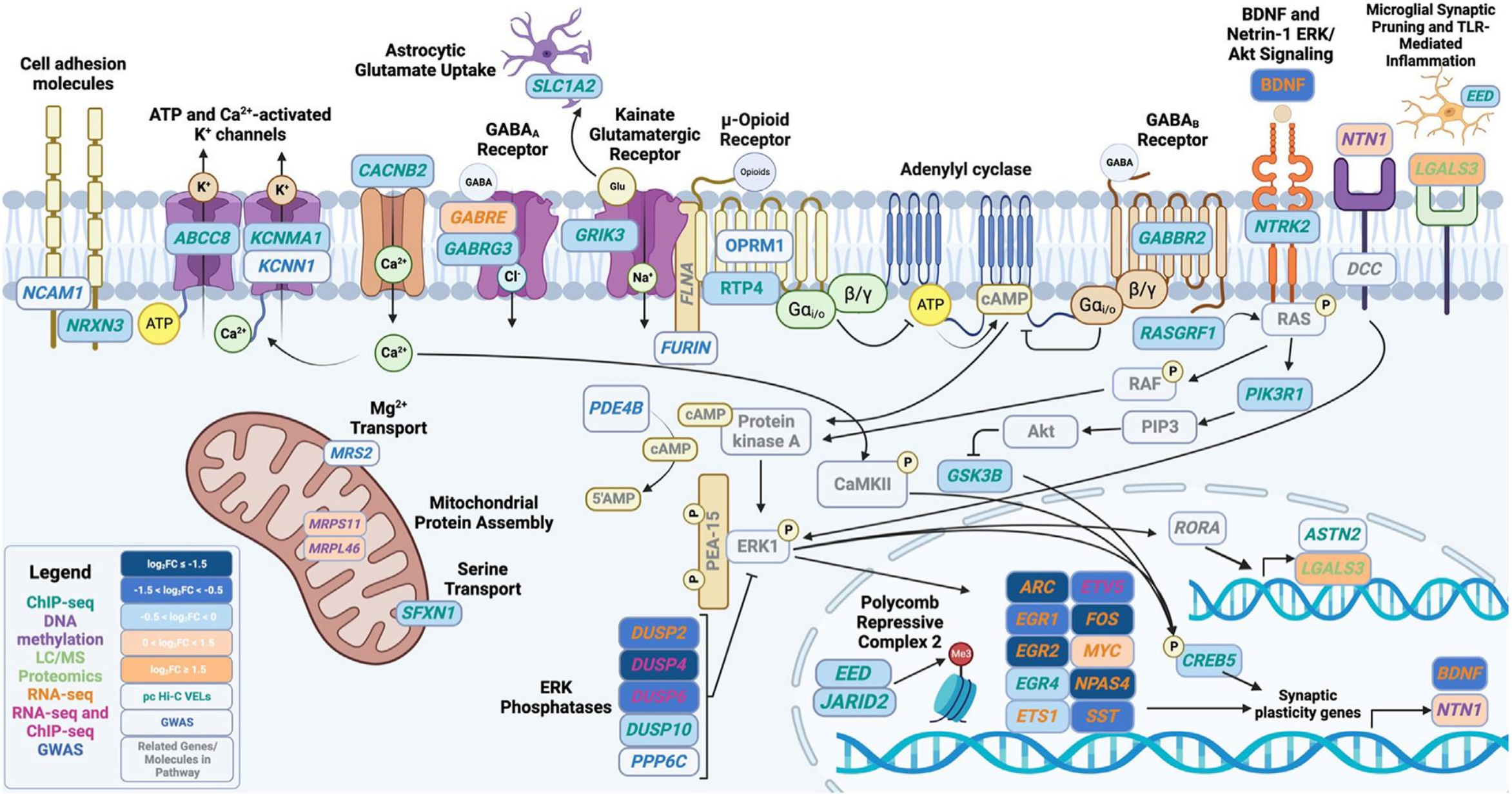
▸ Biol Psychiatry. Author manuscript; available in PMC: 2025 Jul 1.

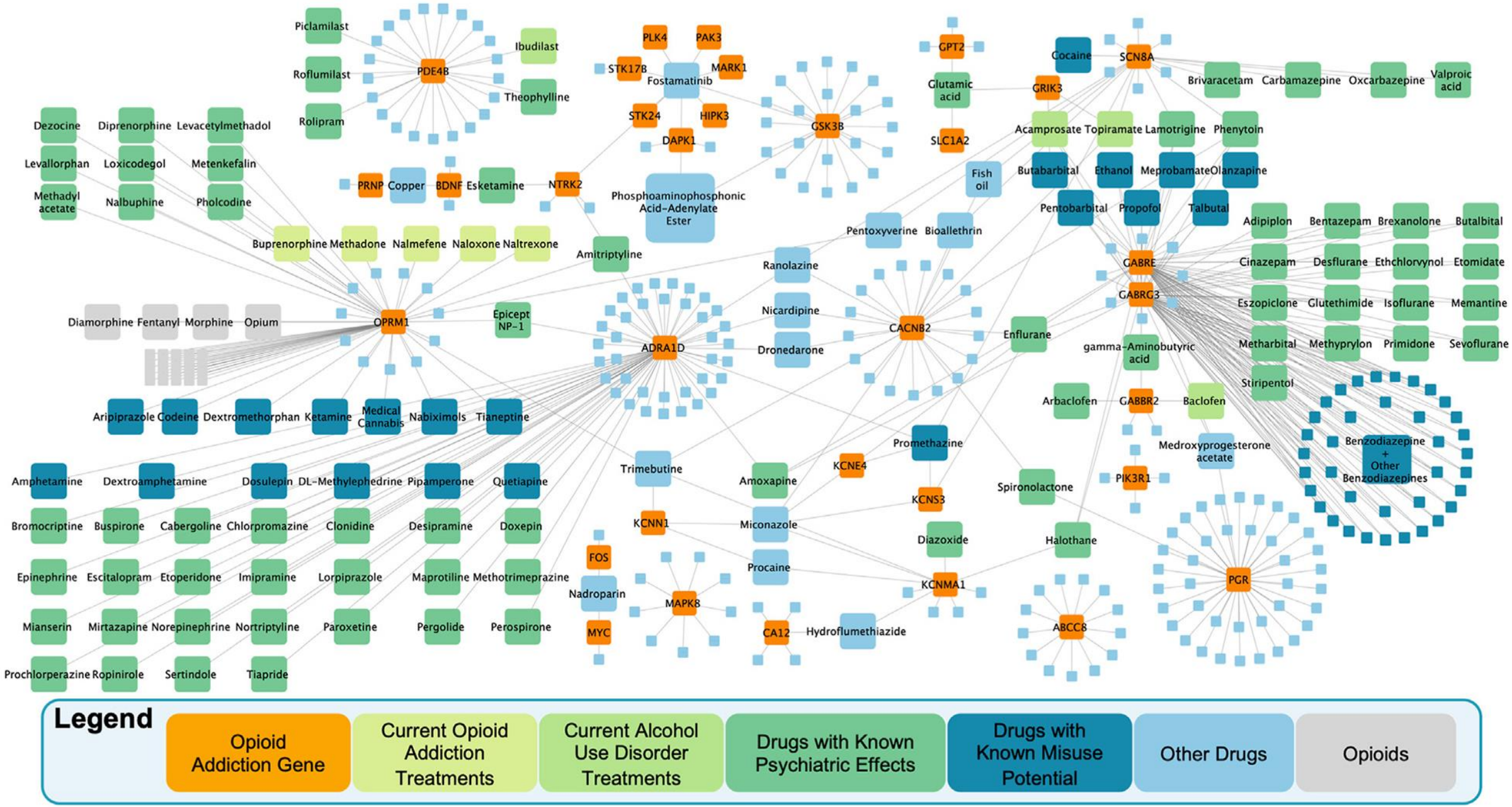
Published in final edited form as: Biol Psychiatry. 2024 Nov 29;98(1):11–22. doi: 10.1016/j.biopsych.2024.11.013

Multiomic Network Analysis Identifies Dysregulated Neurobiological Pathways in Opioid Addiction

Kyle A Sullivan [1], David Kainer [1], Matthew Lane [1], Mikaela Cashman [1], J Izaak Miller [1], Michael R Garvin [1], Alice Townsend [1], Bryan C Quach [1], Caryn Willis [1], Peter Kruse [1], Nathan C Gaddis [1], Ravi Mathur [1], Olivia Corradin [1], Brion S Maher [1], Peter C Scacheri [1], Sandra Sanchez-Roige [1], Abraham A Palmer [1], Vanessa Troiani [1], Elissa J Chesler [1], Rachel L Kember [1], Henry R Kranzler [1], Amy C Justice [1], Ke Xu [1], Bradley E Aouizerat [1], Dana B Hancock [1], Eric O Johnson [1], Daniel A Jacobson [1]; for the VA Million Veteran Program[1]

- Differentially expressed genes in human postmortem dorsolateral prefrontal cortex (dlPFC) from control subjects and subjects who died of an opioid overdose.
- Omics - H3K27ac chromatin immunoprecipitation sequencing (ChIP-seq), DNA methylation, liquid chromatography-mass spectrometry (LC/MS), and bulk RNA-seq


Cell adhesion molecules
NCAM1
NRXN3
ATP and Ca2+-activated K+ channels
ABCC8
KCNMA1
KCNN1
ATP
Ca2+
Astrocytic Glutamate Uptake
SLC1A2
CACNB2
Ca2+
GABAA Receptor
GABA
GABRE
GABRG3
Cl-
Kainate Glutamatergic Receptor
Glu
GRIK3
Na+
FLNA
FURIN
μ-Opioid Receptor
Opioids
OPRM1
RTP4
Gαi/o
β/γ
Adenylyl cyclase
ATP
cAMP
GABAB Receptor
GABA
GABBR2
Gαi/o
β/γ
RASGRF1
BDNF and Netrin-1 ERK/ Akt Signaling
BDNF
NTRK2
RAS
P
RAF
P
PIK3R1
PIP3
Akt
Microglial Synaptic Pruning and TLR-Mediated Inflammation
EED
NTN1
LGALS3
DCC
PDE4B
cAMP
Protein kinase A
cAMP
5'AMP
Mg2+ Transport
MRS2
Mitochondrial Protein Assembly
MRPS11
MRPL46
Serine Transport
SFXN1
CaMKII
P
GSK3B
P
PEA-15
P
ERK1
P
RORA
ASTN2
LGALS3
Polycomb Repressive Complex 2
EED
JARID2
Me3
ERK Phosphatases
DUSP2
DUSP4
DUSP6
DUSP10
PPP6C
ARC
ETV5
EGR1
FOS
EGR2
MYC
EGR4
NPAS4
ETS1
SST
P
CREB5
Synaptic plasticity genes
BDNF
NTN1
Legend
ChIP-seq
DNA methylation
LC/MS
Proteomics
RNA-seq
RNA-seq and ChIP-seq
GWAS
log2FC ≤ -1.5
-1.5 < log2FC < -0.5
-0.5 < log2FC < 0
0 < log2FC < 1.5
log2FC ≥ 1.5
pc Hi-C VELs
GWAS
Related Genes/ Molecules in Pathway


Piclamilast
Roflumilast
Rolipram
PDE4B
Ibudilast
Theophylline
PLK4
PAK3
STK17B
MARK1
Fostamatinib
STK24
HIPK3
DAPK1
GSK3B
GPT2
Glutamic acid
SLC1A2
Cocaine
SCN8A
GRIK3
Brivaracetam
Carbamazepine
Oxcarbazepine
Valproic acid
Acamprosate
Topiramate
Lamotrigine
Phenytoin
Butabarbital
Ethanol
MeprobamateOlanzapine
Pentobarbital
Propofol
Talbutal
Dezocine
Diprenorphine
Levacetylmethadol
Levallorphan
Loxicodegol
Metenkefalin
Methadyl acetate
Nalbuphine
Pholcodine
PRNP
Copper
BDNF
Esketamine
NTRK2
Phosphoaminophosphonic Acid-Adenylate Ester
Fish oil
Pentoxyverine
Bioallethrin
Buprenorphine
Methadone
Nalmefene
Naloxone
Naltrexone
Amitriptyline
Ranolazine
Nicardipine
Dronedarone
CACNB2
GABRE
GABRG3
Adipiplon
Bentazepam
Brexanolone
Butalbital
Cinazepam
Desflurane
Ethchlorvynol
Etomidate
Eszopiclone
Glutethimide
Isoflurane
Memantine
Metharbital
Methyprylon
Primidone
Sevoflurane
Stiripentol
Diamorphine
Fentanyl
Morphine
Opium
OPRM1
Epicept NP-1
ADRA1D
Enflurane
gamma-Aminobutyric acid
Arbaclofen
GABBR2
Baclofen
Medroxyprogesterone acetate
Benzodiazepine + Other Benzodiazepines
Aripiprazole
Codeine
Dextromethorphan
Ketamine
Medical Cannabis
Nabiximols
Tianeptine
Promethazine
KCNE4
KCNS3
Spironolactone
PIK3R1
Amphetamine
Dextroamphetamine
Dosulepin
DL-Methylephedrine
Pipamperone
Quetiapine
Trimebutine
Amoxapine
Bromocriptine
Buspirone
Cabergoline
Chlorpromazine
Clonidine
Desipramine
Doxepin
KCNN1
Miconazole
Diazoxide
Halothane
Epinephrine
Escitalopram
Etoperidone
Imipramine
Lorpiprazole
Maprotiline
Methotrimeprazine
FOS
Nadroparin
MAPK8
Procaine
KCNMA1
PGR
Mianserin
Mirtazapine
Norepinephrine
Nortriptyline
Paroxetine
Pergolide
Perospirone
MYC
CA12
Hydroflumethiazide
ABCC8
Prochlorperazine
Ropinirole
Sertindole
Tiapride
Legend
Opioid Addiction Gene
Current Opioid Addiction Treatments
Current Alcohol Use Disorder Treatments
Drugs with Known Psychiatric Effects
Drugs with Known Misuse Potential
Other Drugs
Opioids

Phenotype Heterogeneity: A Central Limitation

- Despite progress, phenotype heterogeneity remains a core critique.
- SUD diagnoses are behaviorally defined, often lumping different substances, severities, and treatment states into one category.
- This dilutes omics signals: a ‘heavy-drinker’ and a ‘recovery-oriented’ person occupy the same diagnostic box, yet their molecular signatures may differ substantially.
- Many studies rely on retrospective or postmortem data, which limits our ability to infer causality and track molecular trajectories from initiation to addiction.

Sample Size, Power, and Overfitting

- Power and consortia lag are another major critique.
- GWAS and epigenomic studies for opioids and stimulants typically have smaller sample sizes than those for alcohol or tobacco, which increases the risk of false negatives and reduces generalizability.
- Multi-omics consortia for SUDs are also behind those in schizophrenia and depression, slowing biomarker validation.
- When you combine high-dimensional omics data with relatively small subsamples, you invite overfitting, exciting ‘biomarkers’ that fail to replicate in independent cohorts.
- Many early-phase pilot studies fall into this trap.

Correlation Without Causal Mechanism

- A closely related criticism is mechanism versus association.
- Many omics-derived signatures are epidemiologically robust but mechanistically vague.
- We see consistent methylation or transcriptomic changes, but without clear functional validation in relevant circuits or model systems, it's hard to know if they're drivers or byproducts.
- Consequently, very few biomarkers have crossed the threshold into clinical use as diagnostic tests or predictors of treatment response.
- This is a brake on translational impact.

Multi-Omics Integration and AI-Driven Modeling

- Looking forward, the field is moving toward dense, longitudinal ‘patient fingerprints.’ The vision is to integrate multiple omics layers with detailed clinical, behavioral, and digital-phenotyping data, like mobile-based mood and craving tracking or geospatial exposure data.

- Machine learning and network models are being used to stratify SUDs into subtypes, reward-driven, self-medication, stress-related, and to predict trajectories of relapse, treatment response, and even overdose risk.

- This is the promise of precision addiction medicine

Longitudinal, Real-World Cohorts

- Realizing this vision requires big, longitudinal cohorts. We need large, prospective studies with repeated biosampling, blood, saliva, and, where ethical and feasible, CSF, paired with neuroimaging, wearable data, and digital phenotyping.

- Such cohorts would allow us to map dynamic omics trajectories across stages: from initiation to regular use, dependence, recovery, and relapse.

- These designs are crucial for testing whether omics signatures can serve as early-warning signals or response markers in clinical trials

Collaboration and Consortia

HEALTH DATA RESEARCH UK

- **A national multi-omics consortium to inform disease aetiology and prediction - 2020**
- One of HDR UK's research priorities is to understand the causes of disease at a deeper than biological level, to enable better prediction of the onset and progression of ill-health and to tailor medicines for sub-types of disease. The Consortium brings together multiple cohorts and uses advanced data methods to interrogate the complex data layers, going from genomics through multi-omics to health and disease outcomes.

- **Solution**
- The Consortium initially involved nine longitudinal UK population cohorts within the HDR UK network, comprising over 750,000 participants to considerably improve the statistical power, molecular breadth, and generalizability, compared to analyses of individual cohorts.
- The nine cohorts are:

- **AIRWAVE Health Monitoring** investigates whether there are any long-term health impacts of **Airwave use on police** personnel in this study of 53,000 participants. Lead institution: Imperial College London
- **COMPARE Study** is determining the best method for **measuring iron levels in blood donors**. Lead institution: University of Cambridge
- **EPIC-Norfolk** is a study of over 25,000 people living in Norfolk, looking to provide data-based evidence for health policies to prevent or delay **disease onset and maintain health and independence in older people**. Lead institution: MRC Epidemiology
- **The Fenland Study** investigates the interaction between environmental and genetic factors in determining **obesity, type 2 diabetes, and related metabolic disorders.** Lead institution: MRC Epidemiology
- **Generation Scotland** is a resource of human biological samples and data which are available for medical research. Lead institution: University of Edinburgh
- **GoDARTS** identified 18,000 patients with **diabetes** within the wider Tayside region, through electronic record linkage, in order to improve health care over and above that which was practical through existing general practice lists alone. Lead institution: University of Dundee
- **INTERVAL Study** of 50,000 blood donors across England have joined the INTERVAL study to help our researchers compare the **effects of donating blood at different time intervals**. Lead institution: University of Cambridge
- **UCLEB Consortium** of 40,000 participants works to explain the precise relationship between the **genes and biological changes that precede cardiovascular disease**. Lead institution: University College London
- **UK Biobank** a national and international open access resource following the health and wellbeing of 500,000 volunteer participants, aims to improve the **prevention, diagnosis and treatment of a wide range of illnesses**.

Future Directions: A Research Agenda

Omics has the potential to transform our mechanistic understanding of SUDs, but we must confront its limitations and ethical risks.

- First, integration: multi-omics tightly linked with **longitudinal** clinical, social-exposome, and digital-pheno-typing data.

- Second, scalable, real-time phenotyping: decentralized biosampling, wearables, and mobile apps that capture craving, context, and treatment engagement.

- Third, and most importantly, co-design with people with lived experience and policy makers.

Without these, even the most elegant omics-based models will fail to address the real-world needs of people with SUDs.

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