

Luck and serendipity in the time of scarcity

Gavin Bart, MD PhD FACP DFASAM
Division of Addiction Medicine
Hennepin Healthcare
Professor of Medicine
University of Minnesota Medical School
northstarnode.org

Financial Disclosure

Grants:

- National Institute on Drug Abuse (esp. UG1DA040316)

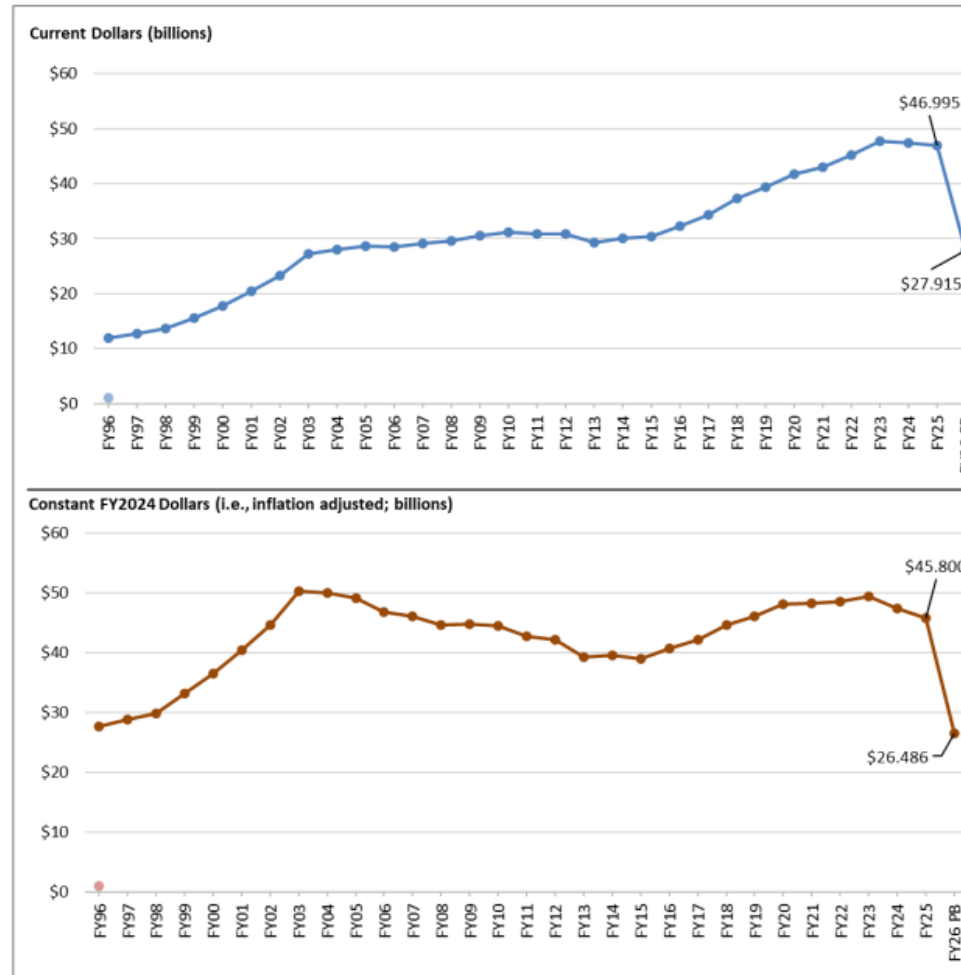
Honoraria:

- SAMHSA
- AHRQ

- The NIH budget is at an unprecedented low?
 - A. True
 - B. False

NIH Funding, FY 1996-2026 Request

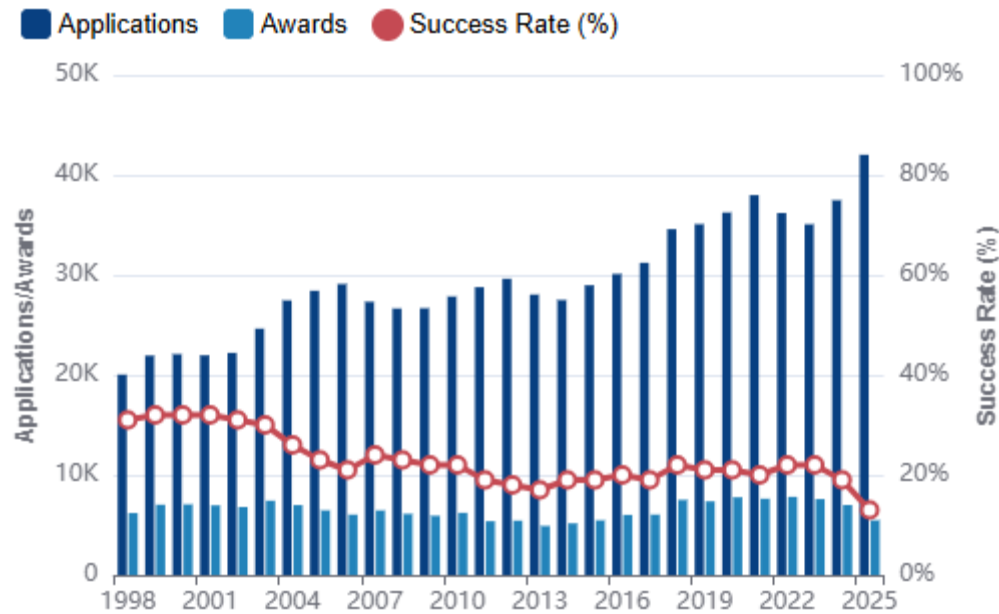
Program Level Funding in Current and Preliminary Constant (FY2024) Dollars



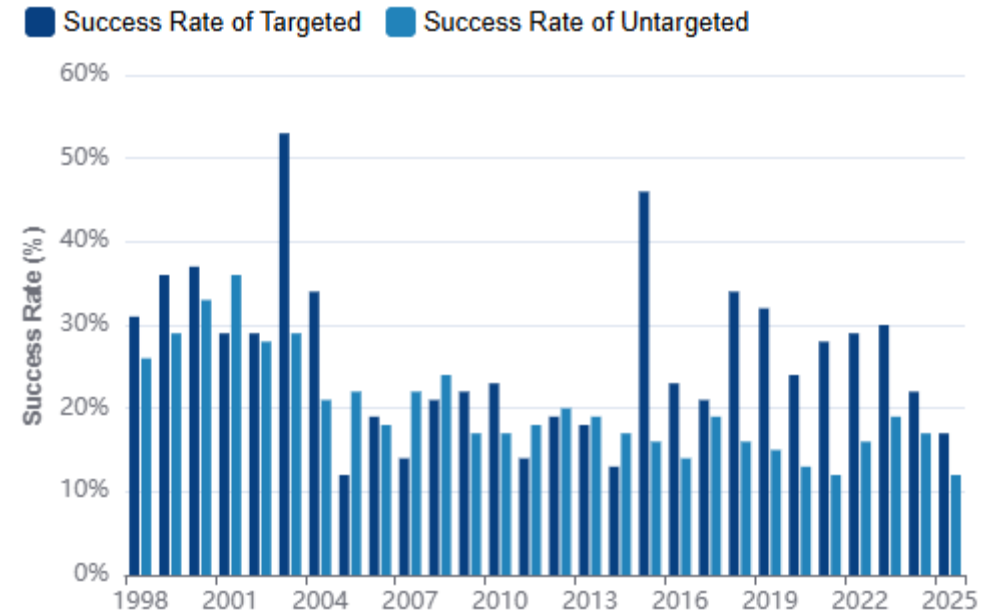
- Getting an NIH grant is harder than ever
 - A. True
 - B. False

NIH funding line

R01 Equivalent

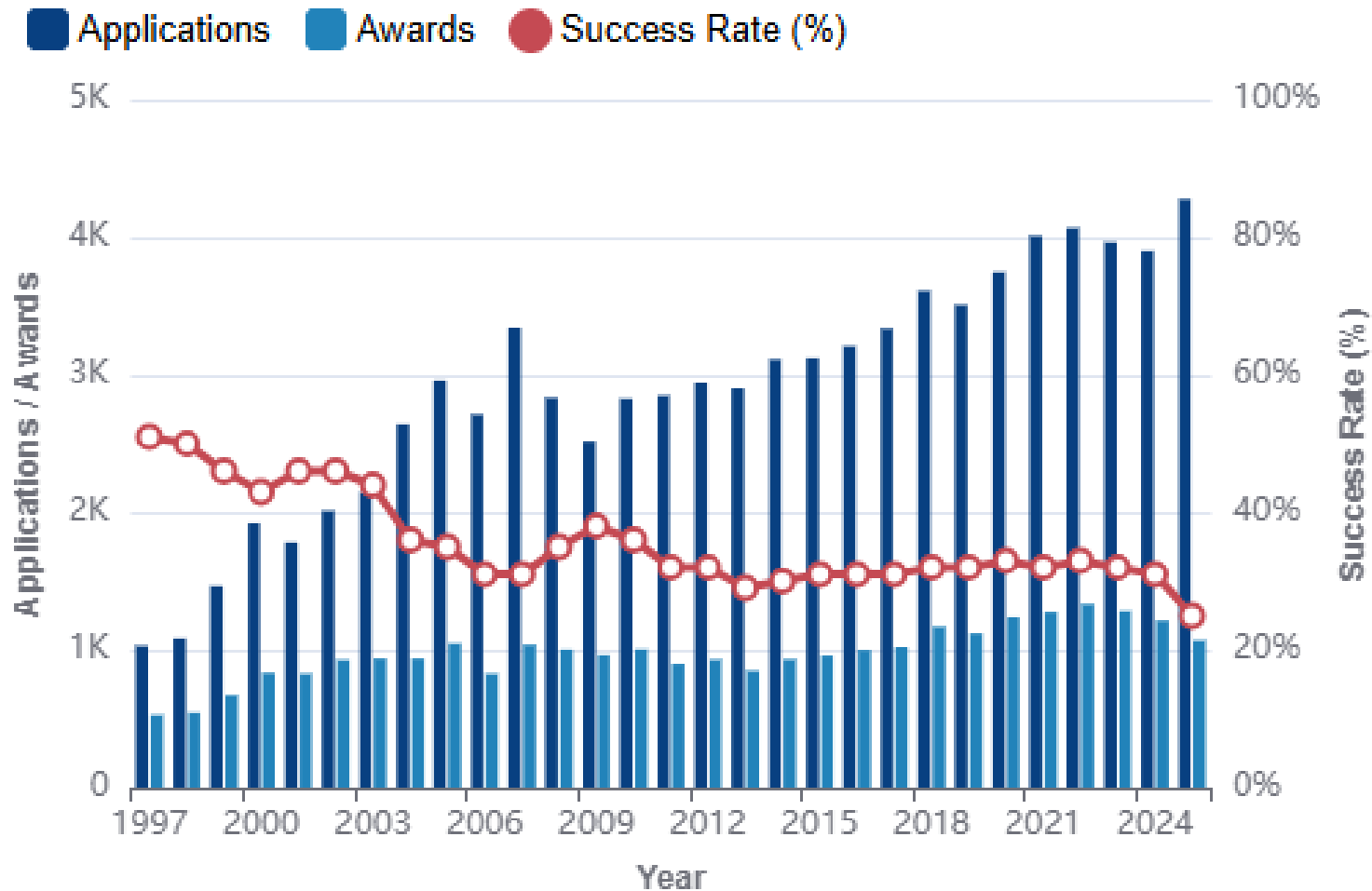


NIDA New applications



- Getting an NIH career development award is harder than ever
 - A. True
 - B. False

Career development awards



When I started

- Join Hennepin County Medical Center September 2005
- Urban safety-net hospital
- Addiction Medicine faculty n=2
- Addiction medicine services = OTP



Choose your own adventure

- A. Khat chewing in East African refugees
- B. Alcohol in American Indian adults
- C. Hospital-based SBIRT
- D. Methadone

Methadone

- Capitalize on local strengths
 - A. University of MN is a leader in tobacco research
 - B. Unique Southeast Asian population in our OTP

- Without research funding, I can't do research
 - A. True
 - B. False

Surveys and data dives are free

- Smoking survey
 - Patterns
 - Dependence scales
 - Quit attempts
 - Desire to quit
 - Setting for quitting (OTP or elsewhere)
- Data dive
 - Retention
 - Dosing history
 - Drug test results
 - Psychiatric comorbidities
 - ASI scores

What was timely



Methadone-Associated Mortality: Report of a National Assessment



Summary Report of the Meeting:

Methadone Mortality – A Reassessment

Sponsored by the
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services
Administration

Washington, DC
July 20, 2007

| BRIEF COMMUNICATION

Torsade de Pointes Associated with Very-High-Dose Methadone

Mori J. Krantz, MD; Laurent Lewkowicz, MD; Helen Hays, MD; Mary Ann Woodroffe, BScN; Alastair D. Robertson, PhD;
and Philip S. Mehler, MD

Annals of Internal Medicine

| CLINICAL GUIDELINES

QTc Interval Screening in Methadone Treatment

Mori J. Krantz, MD; Judith Martin, MD; Barry Stimmel, MD; Davendra Mehta, MD; and Mark C.P. Haigney, MD

Methadone and QTc

Characteristic (N = 211)	ECG On Methadone	ECG Off Methadone	P
Age at time of ECG, yrs (SD)	47.6 (9.7)	46.5 (10.0)	NS
Male, %	57.4	57.4	—
Race, %			—
Caucasian	46.5	—	
African American	37.4	—	
Asian	5.2	—	
Other	10.9	—	
ECG setting, %			NS
Emergency department	64.0	66.4	
Inpatient	22.3	24.2	
Outpatient	13.7	9.5	
QTc, ms (SD)	440 (35)	429 (34)	<0.001
QTc ≥500 ms, %	10 (4.8)	4 (1.9)	NS
Dose, mg (range) (SD)*	74.5 (15–140) (26.5)	—	—

- 7064 person years total
 - 44 total events = 630 per 100,000 patient years
- But only 18 events plausibly linked SCD
 - 250 per 100,000 patient years
 - Actual SCD 42 per 100,000 patient years
 - State age-adjusted SCD 134 per 100,000

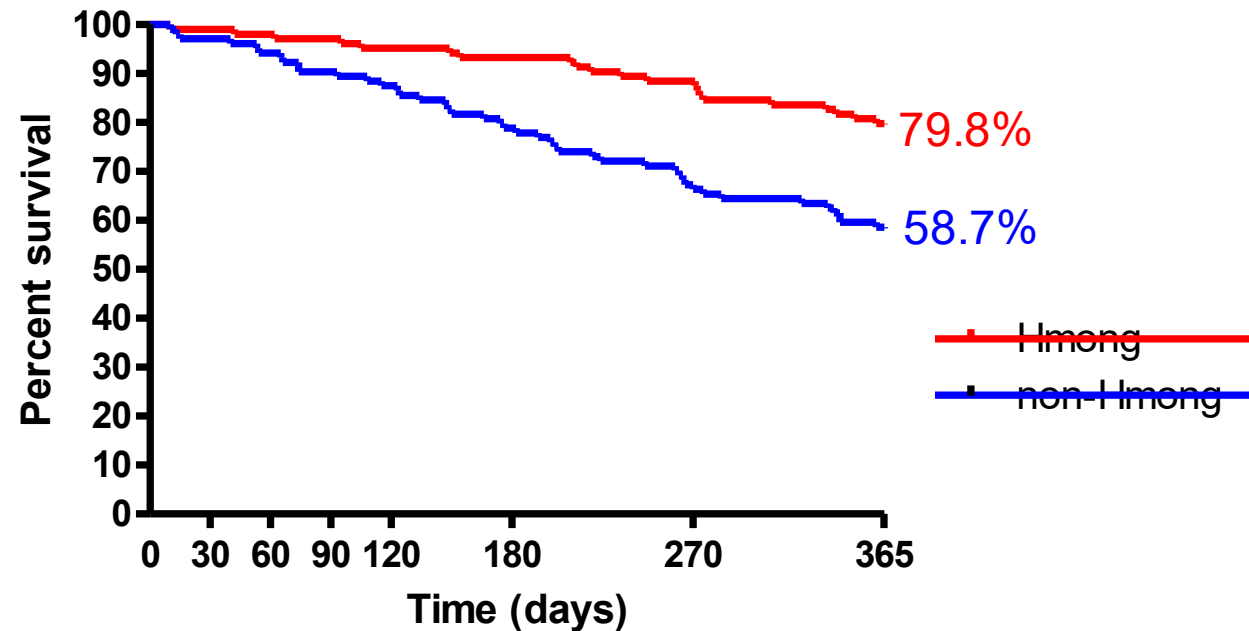
ICD-9 Code	Diagnosis	N
426.12	MOBITZ (TYPE) II ATRIOVENTRICULAR BLOCK	1
426.13	WENCKEBACH'S PHENOMENON, HEART BLOCK	1
426.13	HEART BLOCK AV SECOND DEGREE	1
426.82	LONG Q-T SYNDROME	2
426.9	HEART BLOCK	1
427.1	IDIOPATHIC VENTRICULAR TACHYCARDIA	1
427.1	VENTRICULAR TACHYARRHYTHMIA	1
427.31	ATRIAL FIBRILLATION	5
427.31	PAROXYSMAL ATRIAL FIBRILLATION	1
427.41	VENTRICULAR FIBRILLATION	1
427.5	CARDIAC ARREST	3
427.61	PAC (PREMATURE ATRIAL CONTRACTION)	1
427.69	PVC (PREMATURE VENTRICULAR CONTRACTION)	3
427.81	SICK SINUS SYNDROME	1
427.89	BRADYCARDIA	12
427.89	SINUS TACHYCARDIA	1
427.89	SVT (SUPRAVENTRICULAR TACHYCARDIA)	2
427.89	OTHER SPECIFIED CARDIAC DYSRHYTHMIAS	1
427.9	CARDIAC DYSRHYTHMIA, UNSPECIFIED	9



Hmong Paradoxical Response to Methadone?

- Estimated 10% Hmong refugees with OUD
- ~75% relapse with behavioral treatment only
 - Minnesota model
 - Culturally specific

- Hmong mean dose 49 mg (± 17)
- Non-Hmong mean dose 77 mg (± 25)



What should I do next?

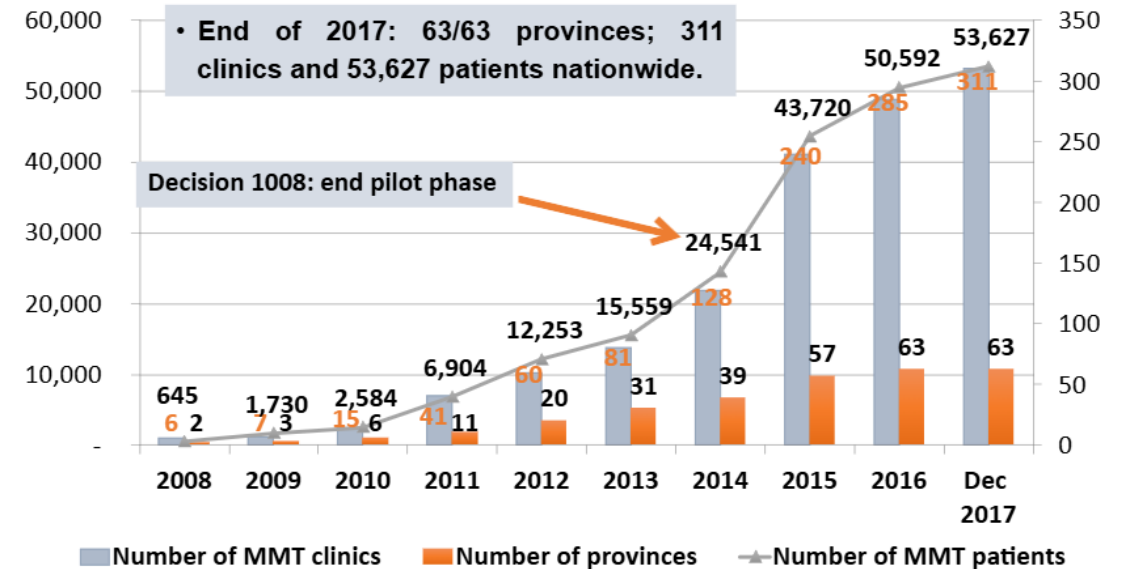
- NIDA K23
 - Coursework
 - Mentorship
 - Research time
- SAMHSA technical assistance Vietnam
 - Teaching/workforce development
 - Program building
 - Program evaluation

- Deviating from publish-grant-publish cycle is harmful to your career
 - A. True
 - B. False

Do both and look for opportunity

Parameter R-Methadone	Estimate	95% CI
CL/F (L/h)	7.6	7.0-8.3
Hmong	0.713	0.625-0.801
(Age/48) ^{0.2}	-0.359	-0.550--0.168
ABCB1 2677GG	0.820	0.734-0.906
V/F (L)	311	277-345
Parameter S-Methadone	Estimate	95% CI
CL/F (L/h)	10.2	8.9-11.4
Hmong	0.676	0.592-0.760
ABCB1 2677 GG	0.787	0.694-0.880
CYP2B6 516GT	0.810	0.717-0.903
V/F (L)	224	206-253

- 12 years
- 7,000 trained
- 33 provinces visited
- University faculty engagement and partnership



MAPS

Methadone & Antiretroviral Pharmacokinetics Study



Synergy of effort

R-Methadone

R-methadone	Estimate (%RSE)	95% CI
CL (L/hr)	6.11 (2.7%)	[5.79, 6.43]
V (L)	316 (2.9%)	[298, 334]
CL if HIV+ART-	7.86 (6.8%)	[6.82, 8.80]
CL if HIV+ART+	13.4 (3.3%)	[12.5, 14.3]
CL if ABCB1 2677AA	5.54 (3.7%)	[5.14, 5.94]
CL if ABCB1 2677xT	6.66 (4.1%)	[6.11, 7.21]
CL if NR113 and ART+	7.15 (5.4%)	[6.42, 7.88]
V if HIV+	392 (4.0%)	[360– 423]
BSV CL (%)	28.9 (5.7%)	-
BOV CL (%)	15.5 (5.2%)	-
BSV V (%)	28.8 (7.2%)	-

Bart et al, 2021

Notice of Special Interest (NOSI): Pharmacogenomic Approaches to Enhancing HIV and Substance Use Disorder (SUD) Treatment Strategies, A jump into Precision Medicine.

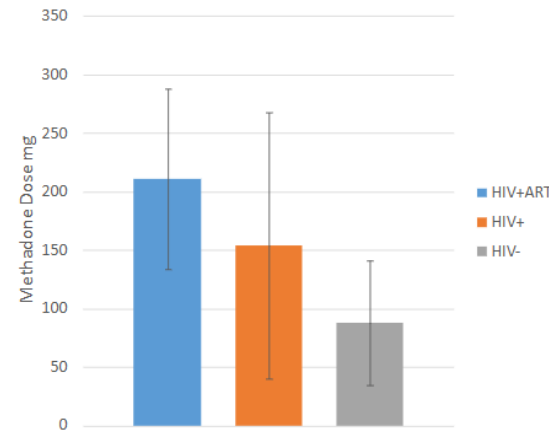
Notice Number:
NOT-DA-24-001

Purpose

Background:

Variable responses to ART are due at least in part to [human genetic variants](#) that affect drug metabolism, drug disposition, and off-site drug targets. Defining effects of human genetic variants on HIV treatment toxicity, efficacy, and pharmacokinetics has far-reaching implications. Substances of abuse (opioid, stimulants, nicotine, anxiolytics, alcohol, etc.) and its treatments (methadone, buprenorphine, extended naltrexone, etc.) may interact with ART, altering its bioavailability, its safety, and its efficacy. It is known that nevirapine and efavirenz increase methadone clearance. New evidence demonstrates that variabilities in responses to ART depend in part on genetic variants for certain drugs of abuse and its therapies. For instance, a NR113 gene variant affected methadone clearance only in those taking efavirenz. Two other genetic variants in the *ABCB1* and *CYP2B6* genes decreased methadone clearance. More research, though, is necessary to better understand the role of pharmacogenomics in people with HIV (PLWH) with substance use disorders (SUD).

Does HIV itself alter methadone and buprenorphine pharmacokinetics?



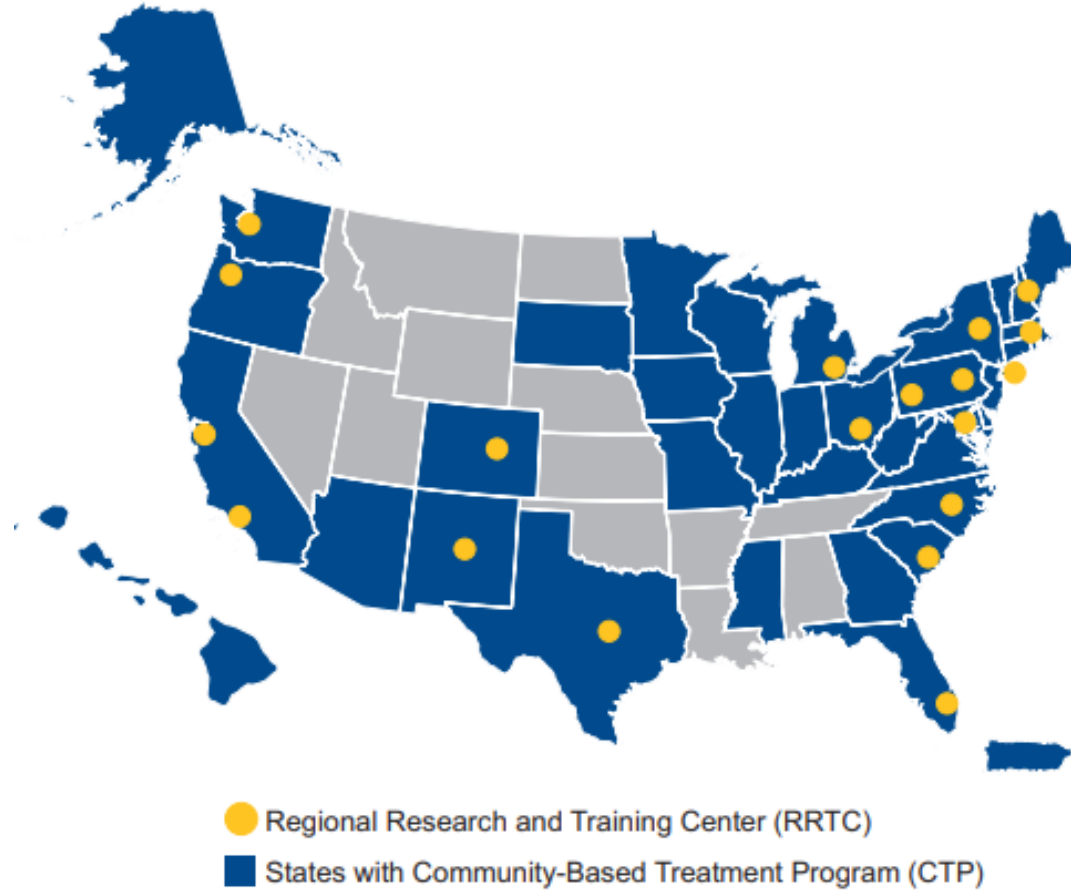
- HIV independently lowered bioavailability
 - Methadone
 - Buprenorphine

Bart and Mai unpublished data; Bart et al. 2021; Bart et al. 2022



In the meantime...

CTN Across the Nation



One thing led to another

- NorthStar node of the NIDA CTN (UG1 Bart, renewed twice)
 - XR-BUP v consult service TAU (Bart)
 - Hospital-based MOUD implementation (Bart and Saitz)
 - Primary care clinical decision support (Bart and Rossom)
 - Black Church Faith Leaders SUD Collaborative (Bart, Hagle, and Tyus)
 - Facebook intervention for American Indian Women in Recovery (Patten)
 - XR-NTX plus bupropion for methamphetamine (ADAPT-2) (Trivedi)
 - XR-BUP plus XR-NTX for cocaine (CURB-2) (Trivedi)
 - Office-based methadone (Fiellin and Joudrey)
 - XR-BUP plus bupropion for stimulant use and opioid use disorder (Oliveto, Shoptaw, Trivedi)
- Family MOUD (R61/R33 Gustafson)
- Buprenorphine v methadone for OUD in people with HIV (R01 Korthuis)
- XR-NTX plus bupropion for methamphetamine replication (NIDA IRP)
- International workforce and treatment capacity
 - Vietnam
 - Southeast Asia
 - China

- Showing up is ___% of success
 - A. 99
 - B. 80
 - C. 50
 - D. 25

Showing up

- Conferences
 - University
 - State
 - National
- Societies
- Cast a wide net of mentors (does not need to be formal)

Balance

Scale of taking from one and giving from one to another



Integration

Aligning your priorities and managing boundaries

