Addiction Therapy-2014

Chicago, USA

August 4 - 6, 2014





Kenneth Blum

Reward Deficiency Solution System: Translational Research

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Reward Deficiency Solution System

Over the last 50 years our laboratory has been engaged in developing a number of important tools to accurately diagnose, evaluate compliance to treatment medications, abstinence and enhance the quality of life of the “recovering” addict.

ASAM New Definition of Addiction

Addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biological psychological social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and **other behaviors**.

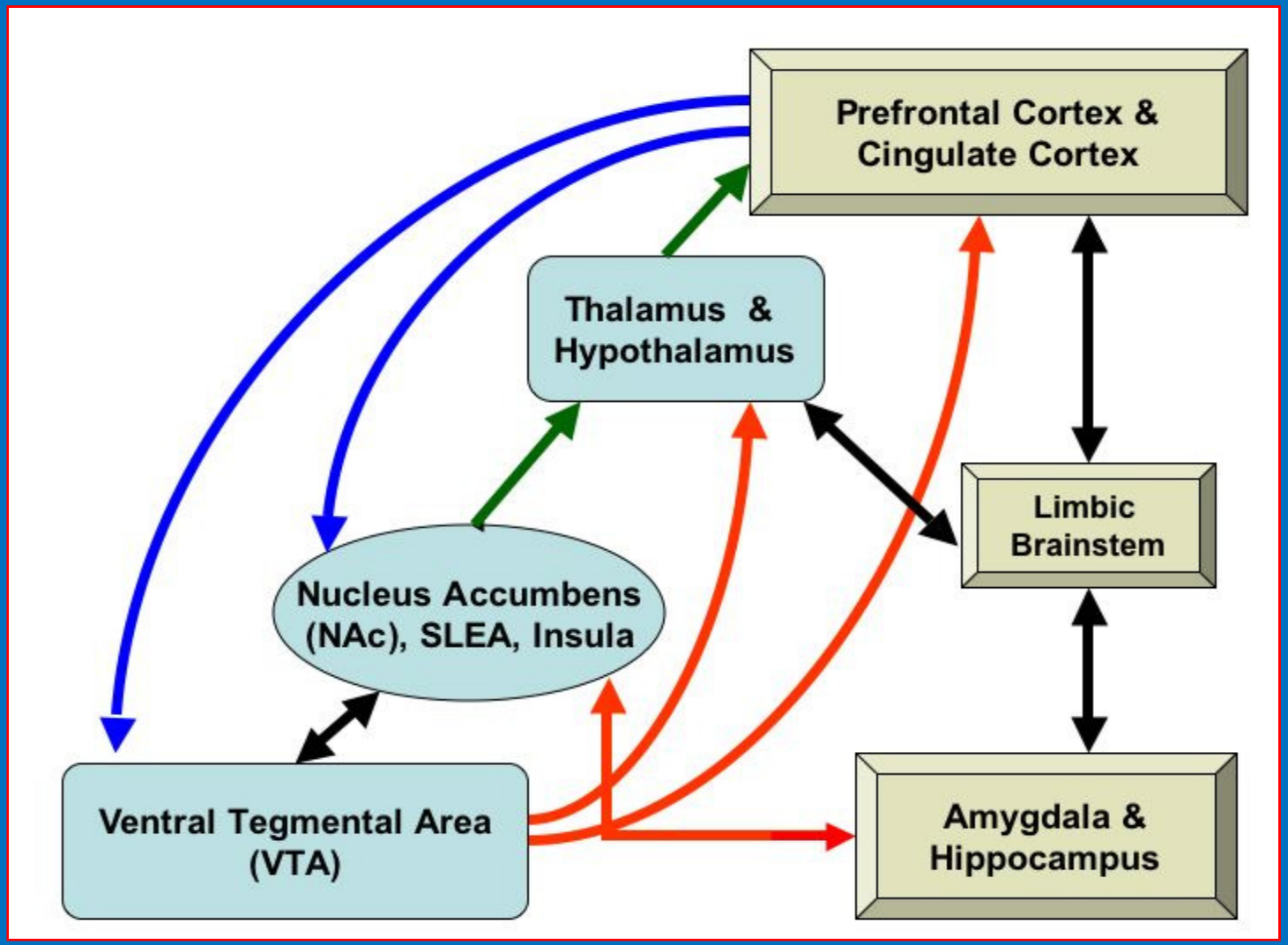
August 15,2011

Reward Deficiency Syndrome (RDS) Behaviors: A Function of the Reward Genes

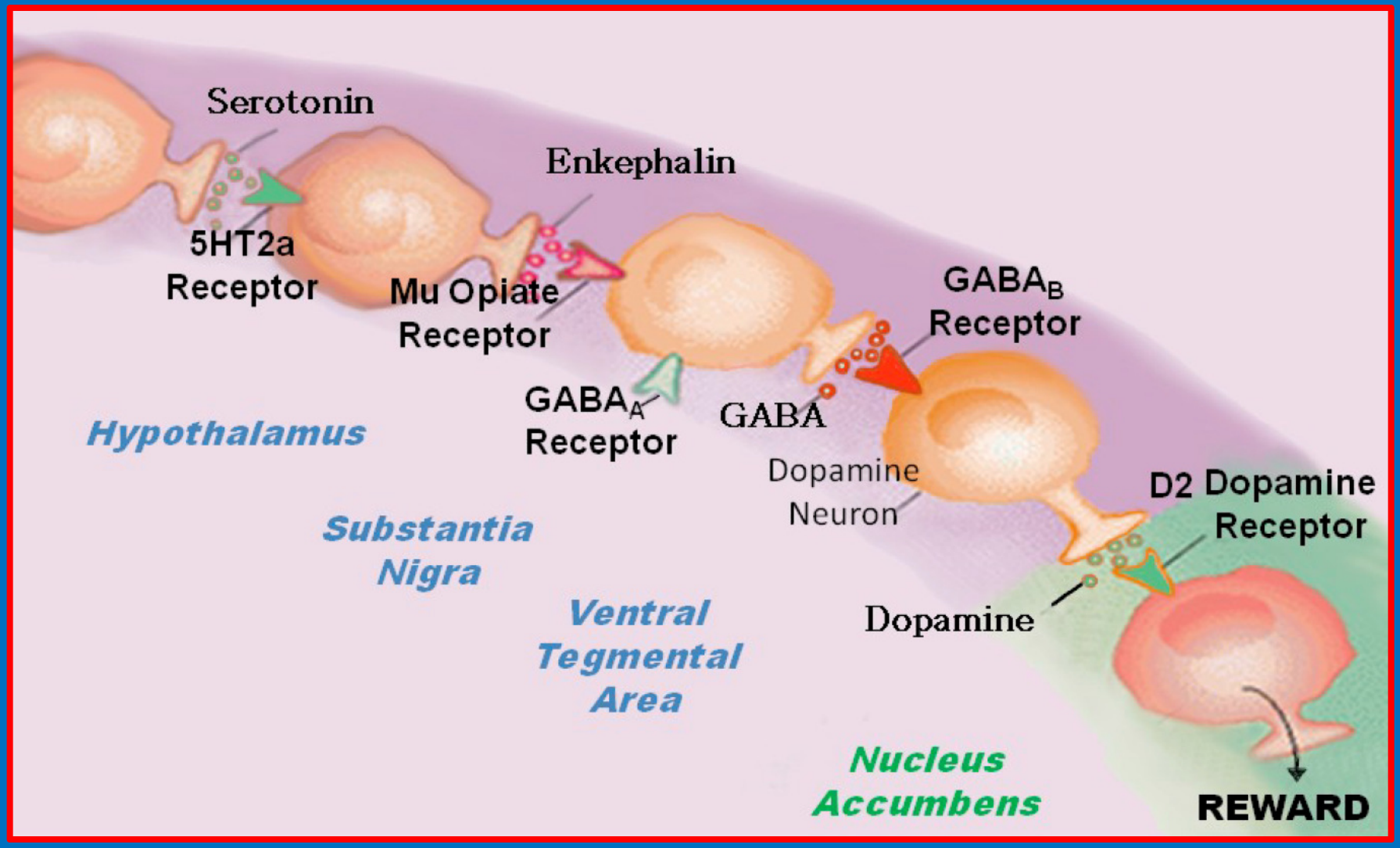
ADDICTIVE BEHAVIORS		IMPULSIVE BEHAVIORS		OBSESSIVE COMPULSIVE BEHAVIORS	PERSONALITY DISORDERS
Substance Related	**Non Substance Related**	**Spectrum Disorders**	**Disruptive Impulsive**		
Alcohol	Thrill seeking (novelty)	Attention-deficit Hyperactivity	Anti-social	Body Dysmorphic	Paranoid
Cannabis	Sexual Sadism	Tourette and Tic Syndrome	Conduct	Hoarding	Schizoid
Opioids	Sexual Masochism	Autism	Intermittent Explosive	Trichotillo-mania (hair pulling)	Borderline
Sedatives/ Hypnotics	Hypersexual		Oppositional Defiant	Excoriation (skin picking)	Schizotypal
Stimulants	Gambling		Exhibitionistic	Non-suicidal Self-Injury	Histrionic
Tobacco	Internet Gaming				Narcissistic
Glucose					Avoidant
Food					Dependant

Modified according to DSM-5 from Blum et al. 1996

BRAIN REWARD CIRCUITRY



BRAIN REWARD CASCADE



Addiction Medications

- FDA Approved
- Acamprosate (Campral)
- Disulfiram (Antabuse)
- Naltrexone (ReVia, Vivitrol, Depade)
- Topiramate (Topamax)
- Methadone
- Buprenorphine
- Suboxone
- Off Label
- Nefazodone (Serzone)
- Ondansetron (Zofran)
- Gabapentin

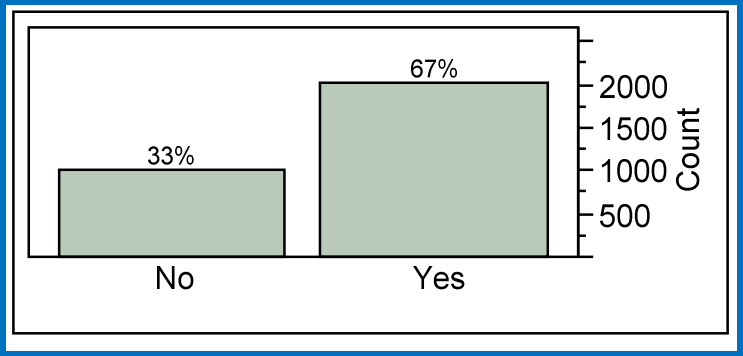
CARD Summary Reports

The Clinic receives a summary quarterly and annually that shows the following:

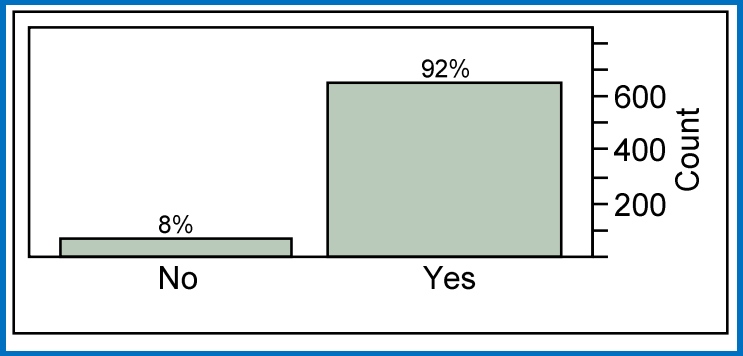
- Overall Summary of the Clinic
- Summary of NO treatment related medication prescribed and NO self reported use
- Adherence to Treatment Related Medication
- Self-Reported Misuse for Both Detected and Non-Detected
- Self-Reported Drug Misuse When Adherent to Medication both detected and non-detected
- A Summary as to why a CARD™ Analysis could not be completed

Comprehensive Analysis of Reported Drugs (CARD)

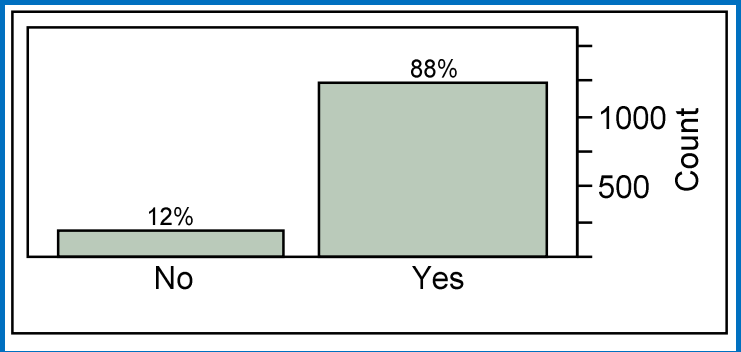
Compliance



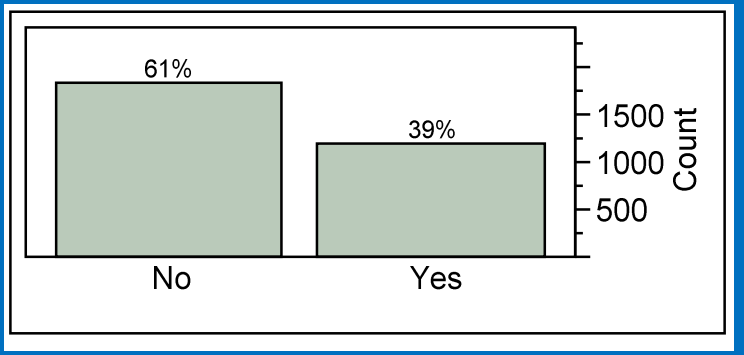
Methadone



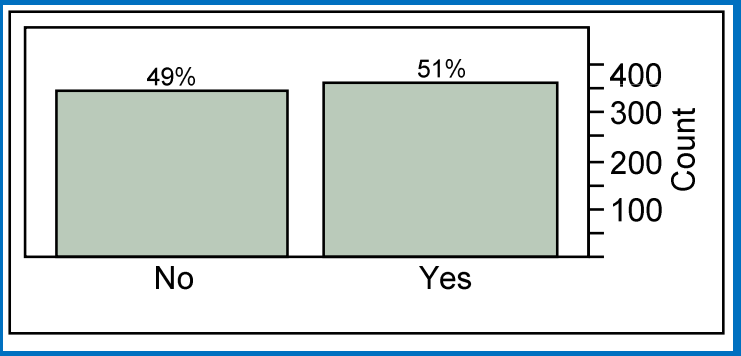
Suboxone



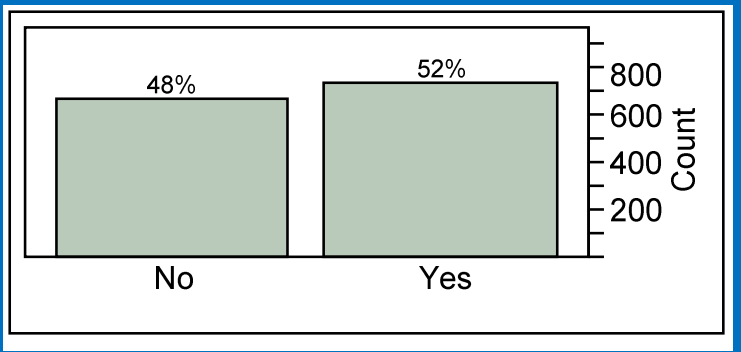
Abstinence



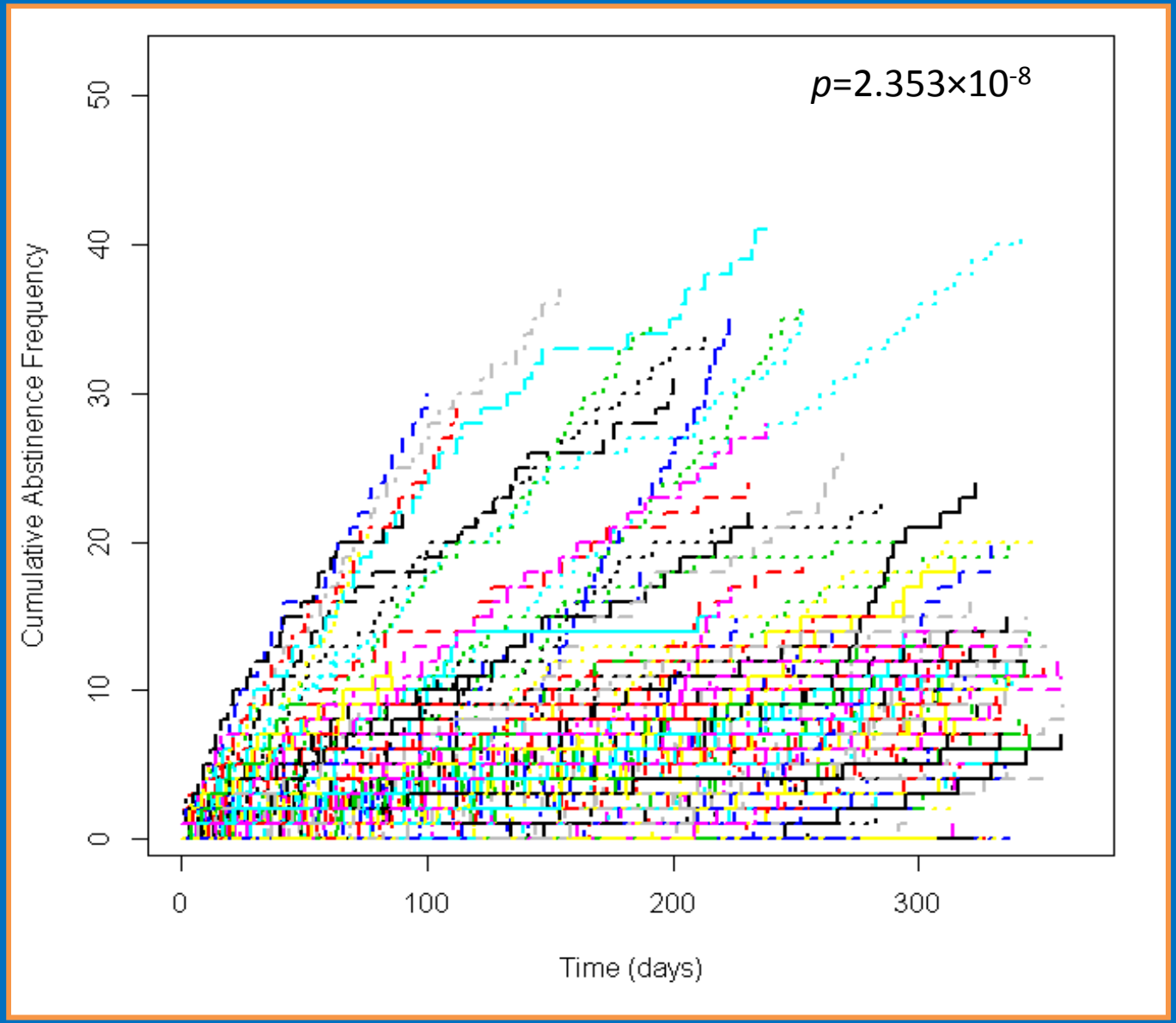
Methadone



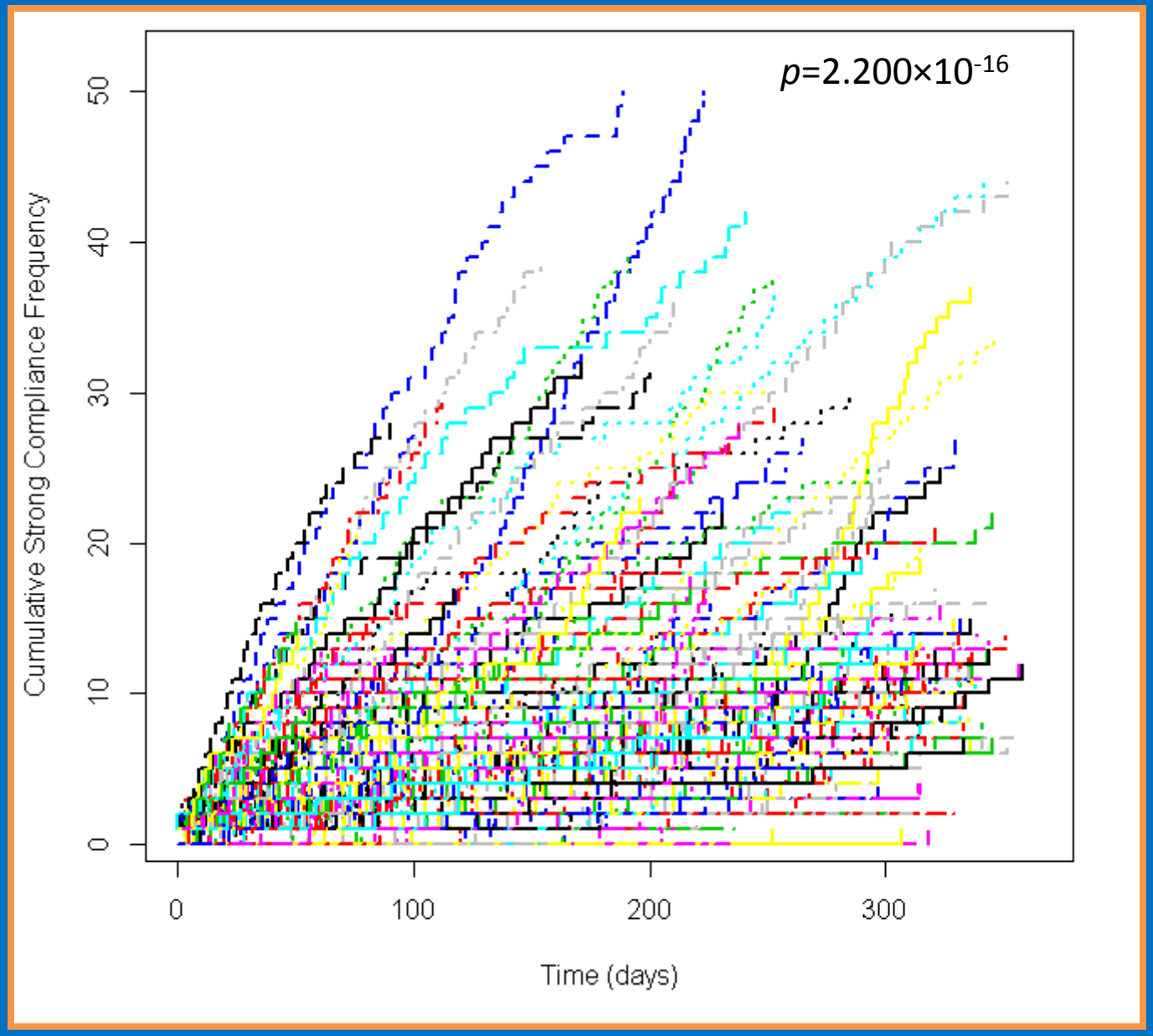
Suboxone



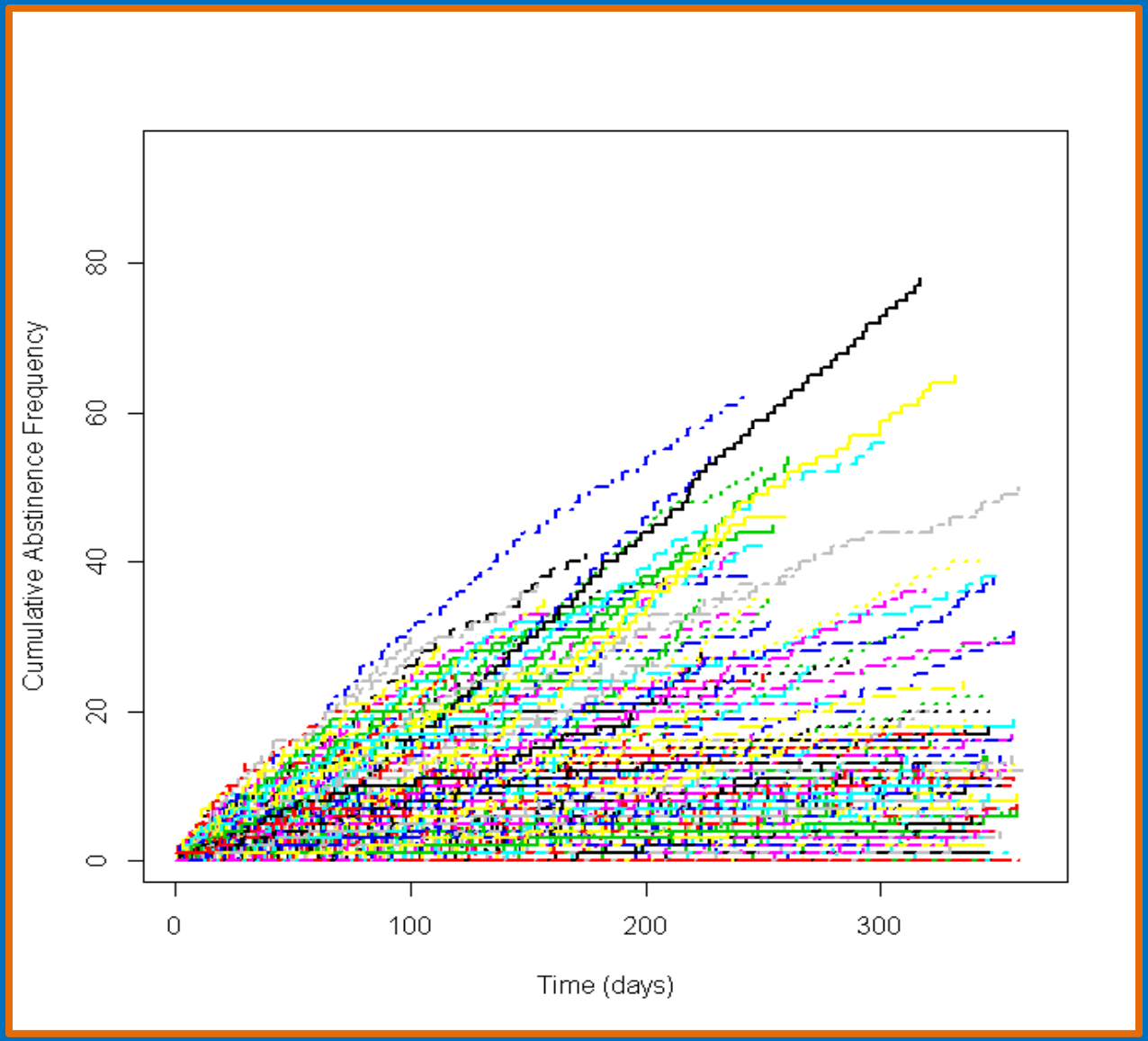
Cumulative Abstinence Frequency



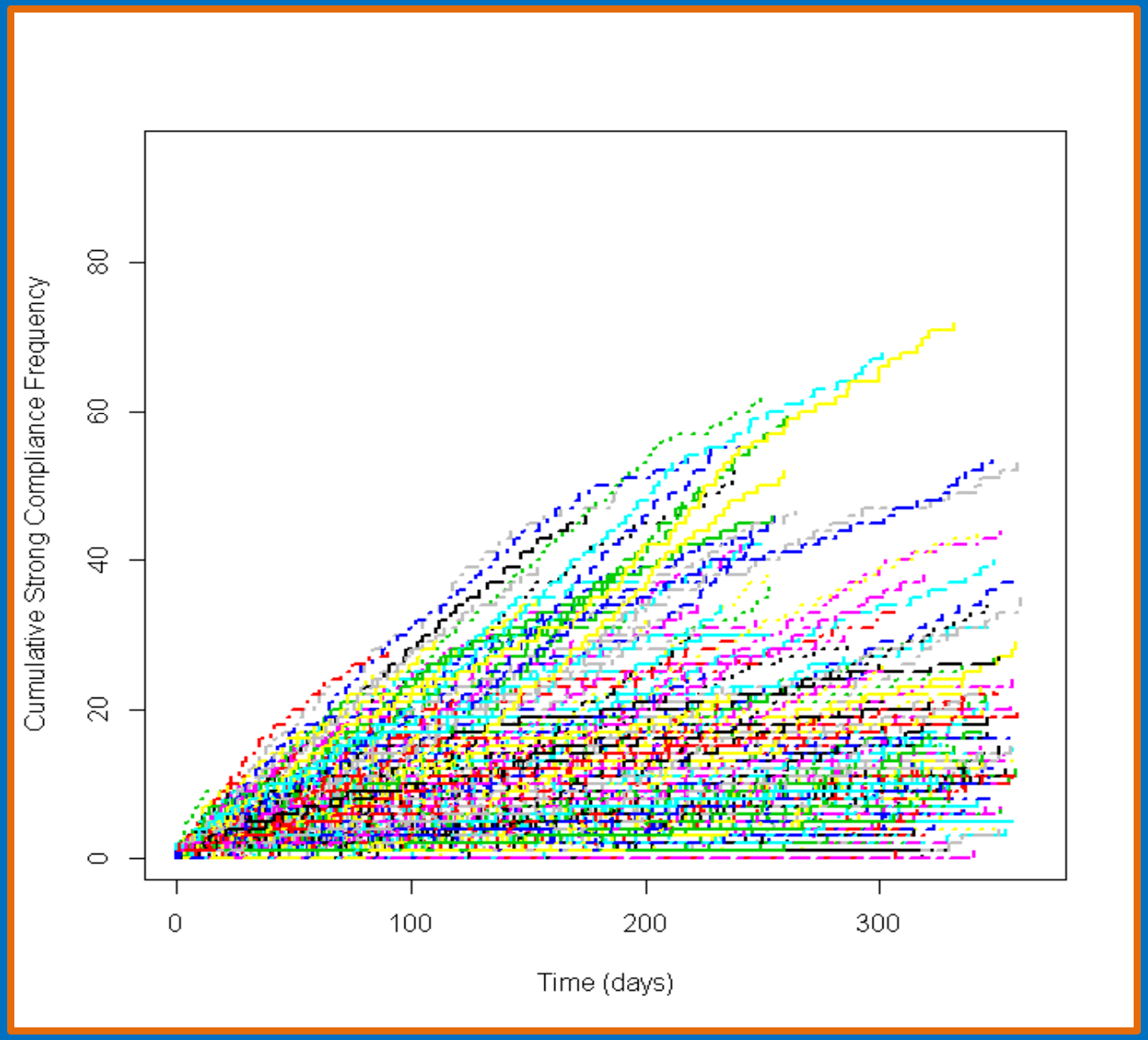
Cumulative Compliance Frequency



Suboxone: cumulative abstinence frequency 365 days 2011



Suboxone: cumulative compliance frequency 365 days 2011



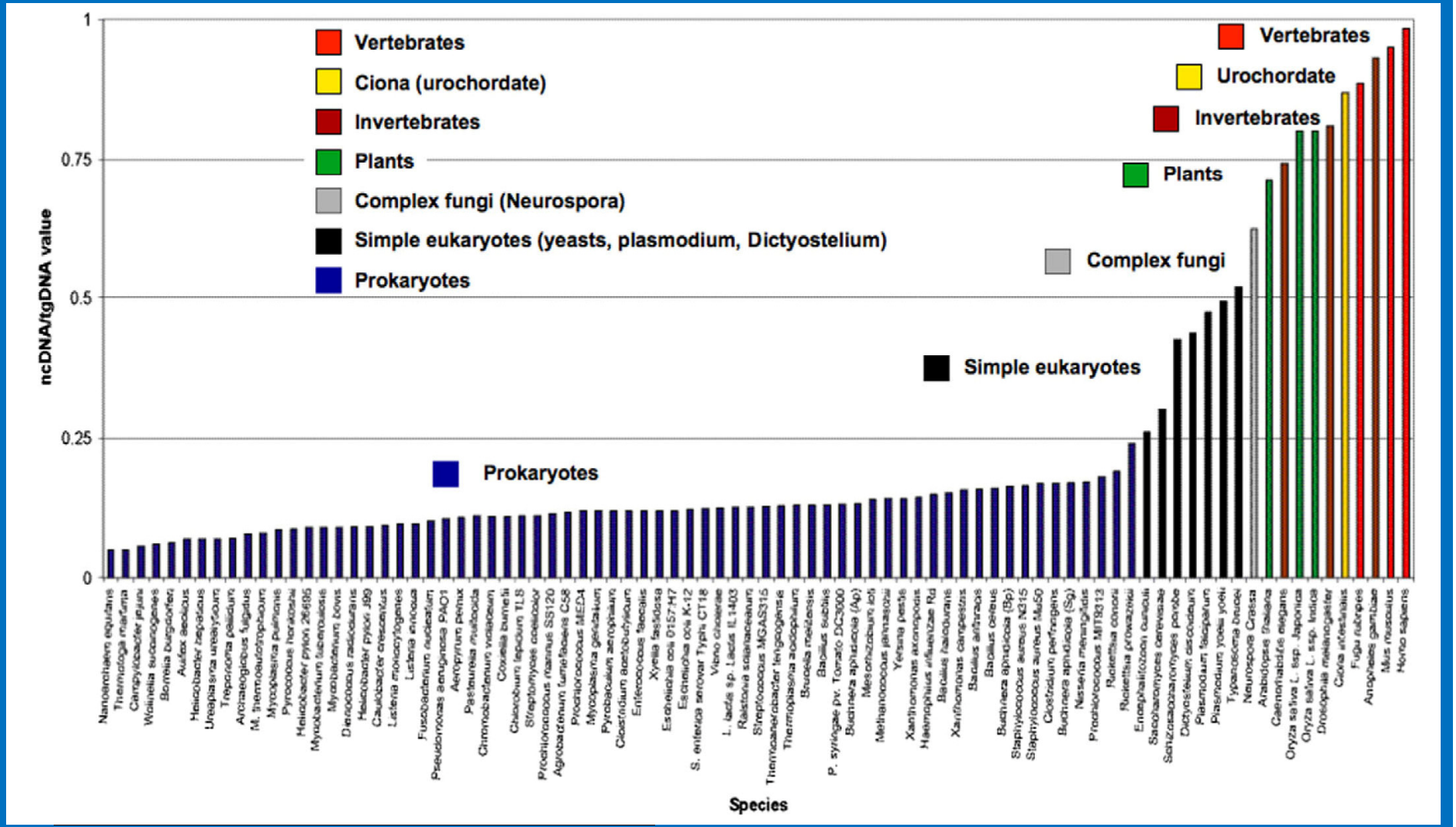
Targeting Brain DNA



I can’t Help It; its in my Genes



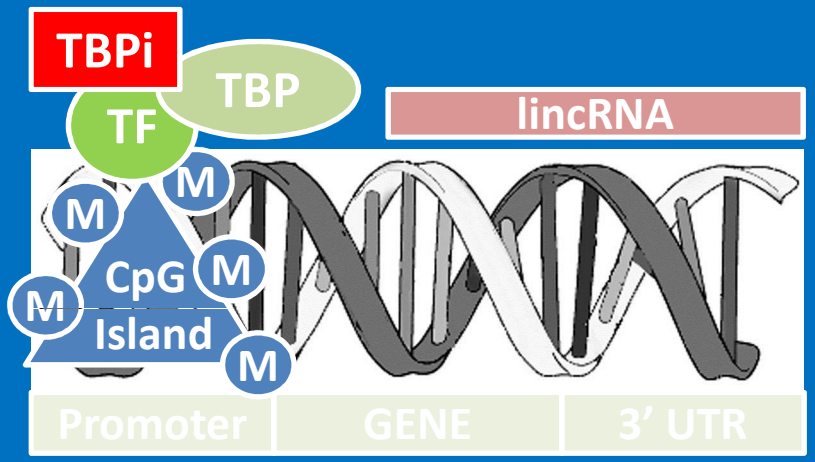
The genome is more complicated than we thought



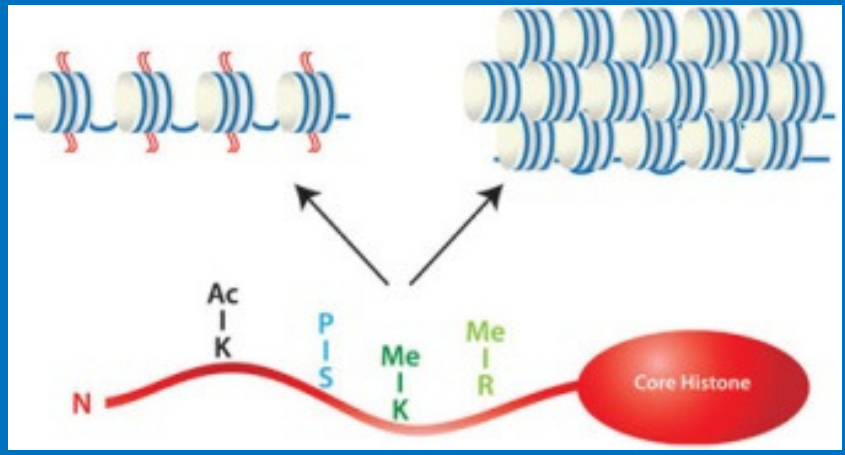
Mattick 2011

How much more complicated?

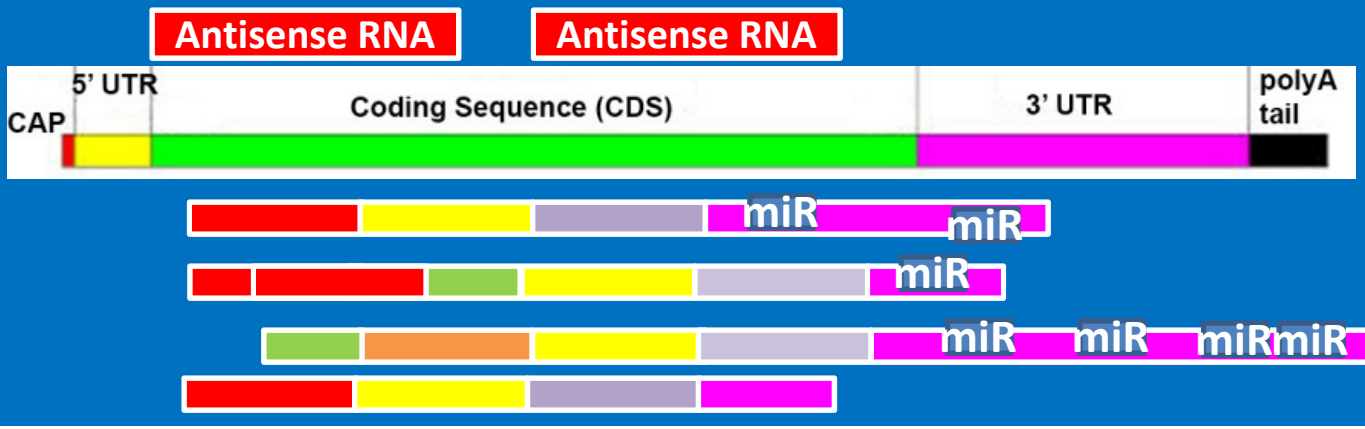
Transcriptional Regulation

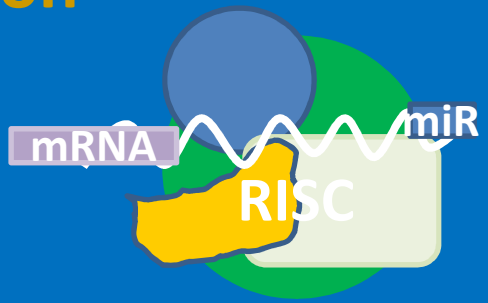


Chromatin Regulation



Post-translational Regulation





Genetic Addiction Risk Score (GARS) ™

Evaluated eleven genes and 22 Risk Alleles from Nine Addiction Treatment Centers in The United States (N= 393)

DNA COLLECTION PROCESS.

Collection Process

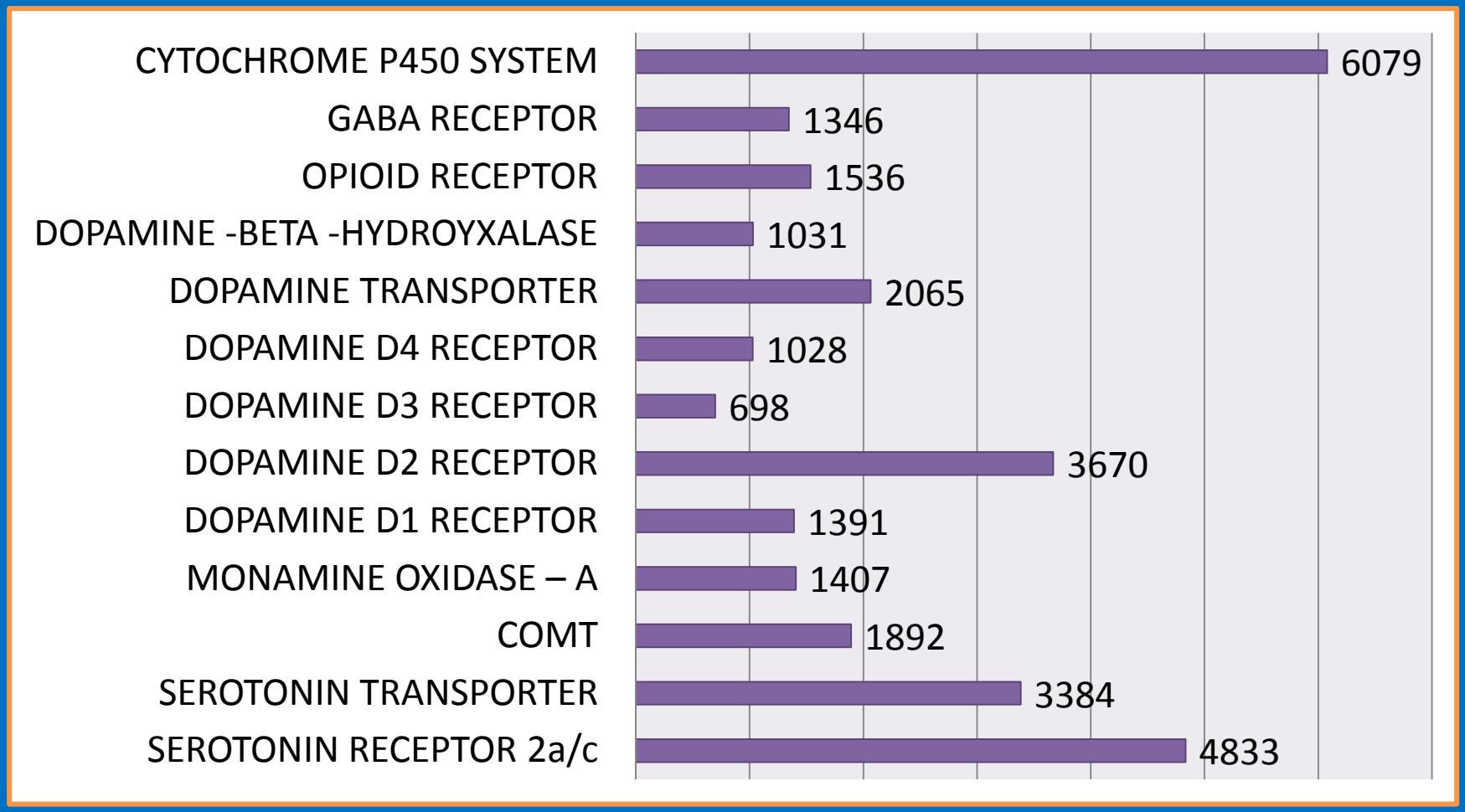
- Patient spit into tube
- Tube Sent for Genotyping
- Laboratory Tests for poly-genes
- Risk assessment sent to clinician/patient



Genetic Addiction Risk Score (GARS).

Gene	Allele	Prime Function
Dopamine D1 Receptor	48G	Regulation of Dopamine Release in Accumbens
Dopamine D2 Receptor (ANKKI/DRD2)	Taq I A1	Controls Synthesis of Dopamine D2 Receptors
Dopamine D3 Receptor (DRD3)	C	Carriers sensitive to cocaine; opioids, alcohol and nicotine
Dopamine D4 Receptor (DRD4)	7R	Pre-disposed to Novelty Seeking and ADHD
Dopamine Transporter (DAT1)	9R	Fast transport of synaptic Dopamine back into pre-neuron leading to Hypodopaminergic trait.
Serotonin Transporter (HTTLPR)	S	Fast transport of serotonin back into neuron
Mu-opiate Receptor (OPRM1)	G	Predisposes to heroin addiction and pain sensitivity
GABA –B_3 Receptor (GABAR3)	181.	Predisposes to anxiety disorders
Mono-Amine –Oxidase A (MAO-uVNTR)	3R	Fast catabolism of mitochondria Dopamine
Catecholamine –Methyl-Transferase (COMT-vall58met)	G	Val substitution leads to fast catabolism of synaptic Dopamine leading to RDS

Reward gene publications as of 3/16/2014



GARS Risk Stratification

	Caspi MAOA uVNTR	Caspi MAOA uVNTR	DRD4	DRD4	DAT	DAT	5HTTLR diallelic	COMT val/met G=val A=met	DRD2 TaqIA rs1800 497
XY	3R	3R	4R	5R	9R	10R	S/S	A/A	A2/A2
XY	3R	3R	4R	4R	10R	10R	S/S	A/G	A1/A1
XX	4R	5R	0	4R	9R	10R	L/L	A/G	A2/A2

DRD3 rs6280 C=Gly T=Ser	OPRM1 Rs179971 A=Asn G=Asp	GAB RA3	GAB RA3	# of ALLELES	SCORE	SEVERETY
C/T	A/A	181	181	8	0.44	Medium
C/C	A/A	181	181	12	0.7	High
T/T	A/A	181	193	5	0.29	L0w

Association Study Compared GARS & ASI

Evaluated a Subset of 220 Subjects who had also responded to the Addiction Severity Index - Media Version (ASI-MV) –Alcohol Severity Risk Score

Genes and Risk Alleles Tested

DRD1=G

DRD2=AI

DRD3=C

DRD4=C

DAT1=9R

DRD4=7-11R;

HTTLPR=
S or Lg

MAOA=3.5-5R

COMT=G

OPRM1=G and

GABRB3=181

Demographics.

		N	Mean	S.D.	Range
School	Males	129	13.4 years	+/- 2.24	8 - 20
	Females	94	14.6 years	+/- 2.22	9 - 20
Age	Males	129	34.46 years	+/- 12.21	18 - 67
	Females	94	38.00 **years**	+/- 13.96	18 - 70
Alcohol Risk Score	Males	129	4.47	+/- 2.66	1 - 9
	Females	94	4.91	+/- 2.64	1 - 9

GARS Score

6 or less Risk Alleles= 28.7%

7 or 8 Alleles =30.9%

9 or higher Alleles =40.4%

100% Carried at least one risk allele

Chi Sq Analysis of Association to Predict Severity

Mixed Gender with 7 Risk Alleles

Significantly Predicts ASI – Alcohol Severity Score

$\chi 2$ =8.38, df=1, P <0.003

Significant Association with ASI-Drug Severity

Illicit drug use as a function of alcohol risk severity score (0/1).

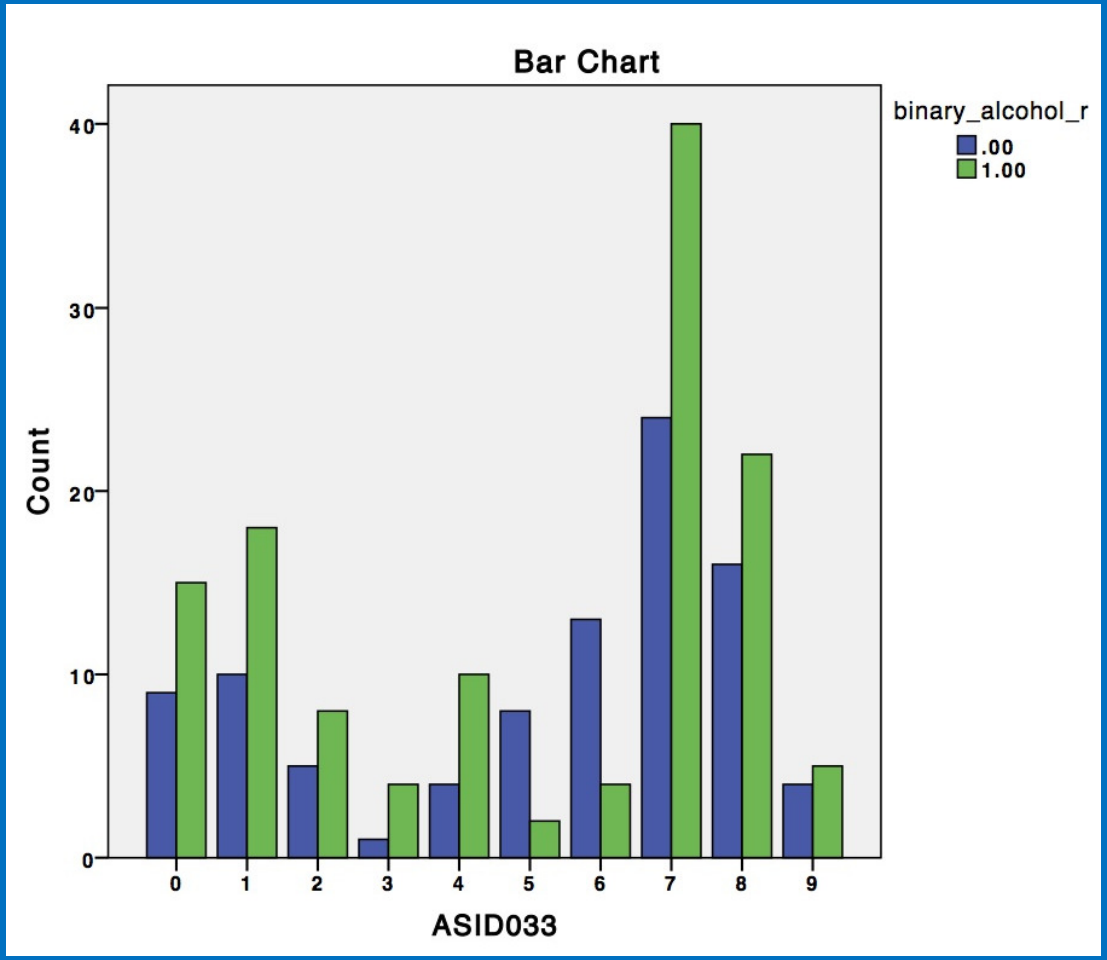
Higher severity risk scores for alcohol

also have

higher severity risk score for illicit drug use

compared with those with a lower alcohol risk

severity score (chi-square = 17.48, df = 9, p = 0.042)



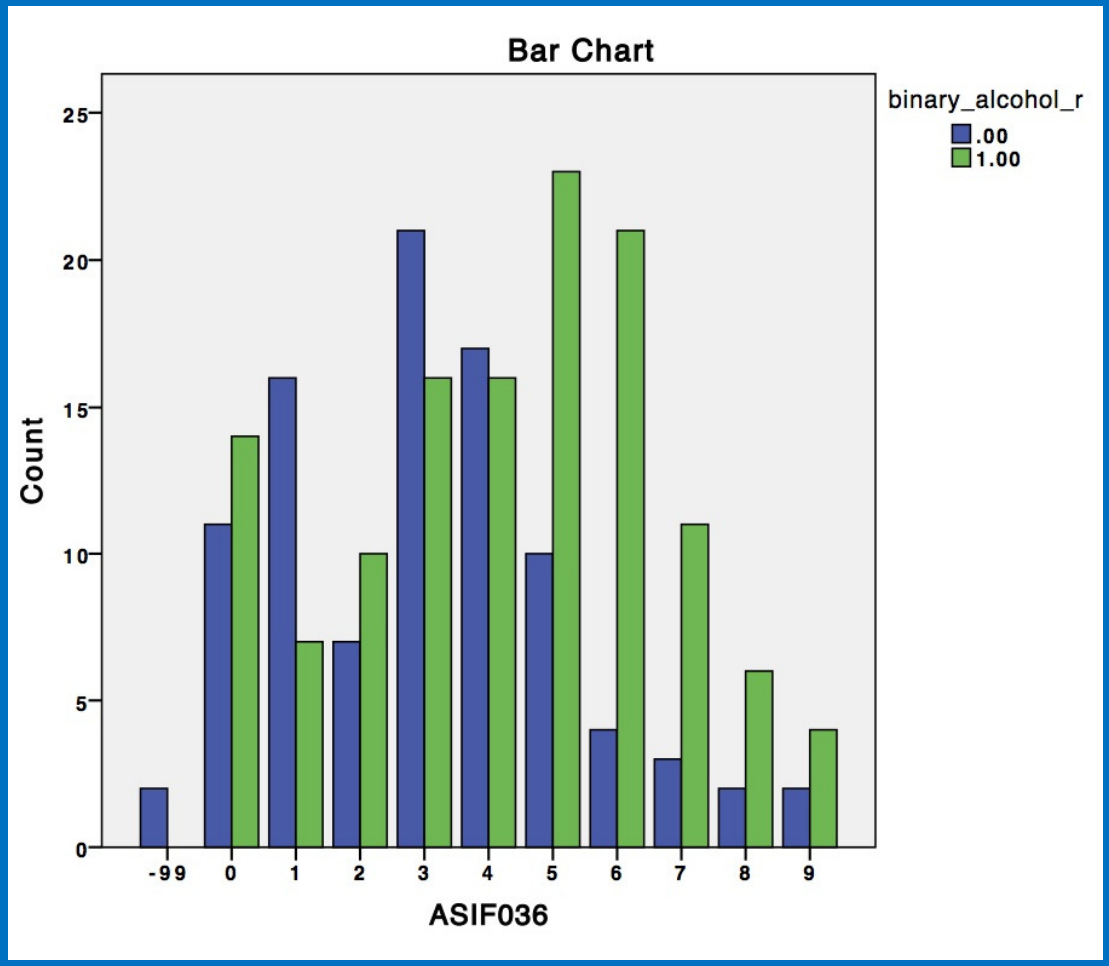
FAMILY PROBLEMS

Higher alcohol risk severity scores have

significantly higher number of family problems

as compared with those with lower alcohol severity risk scores.

(Chi-square = 26.73. df = 1-, p = 0.003).



RDS Risk Behaviors

High (score = 1) alcohol severity risk scores

more frequently report mood-related disorders such as

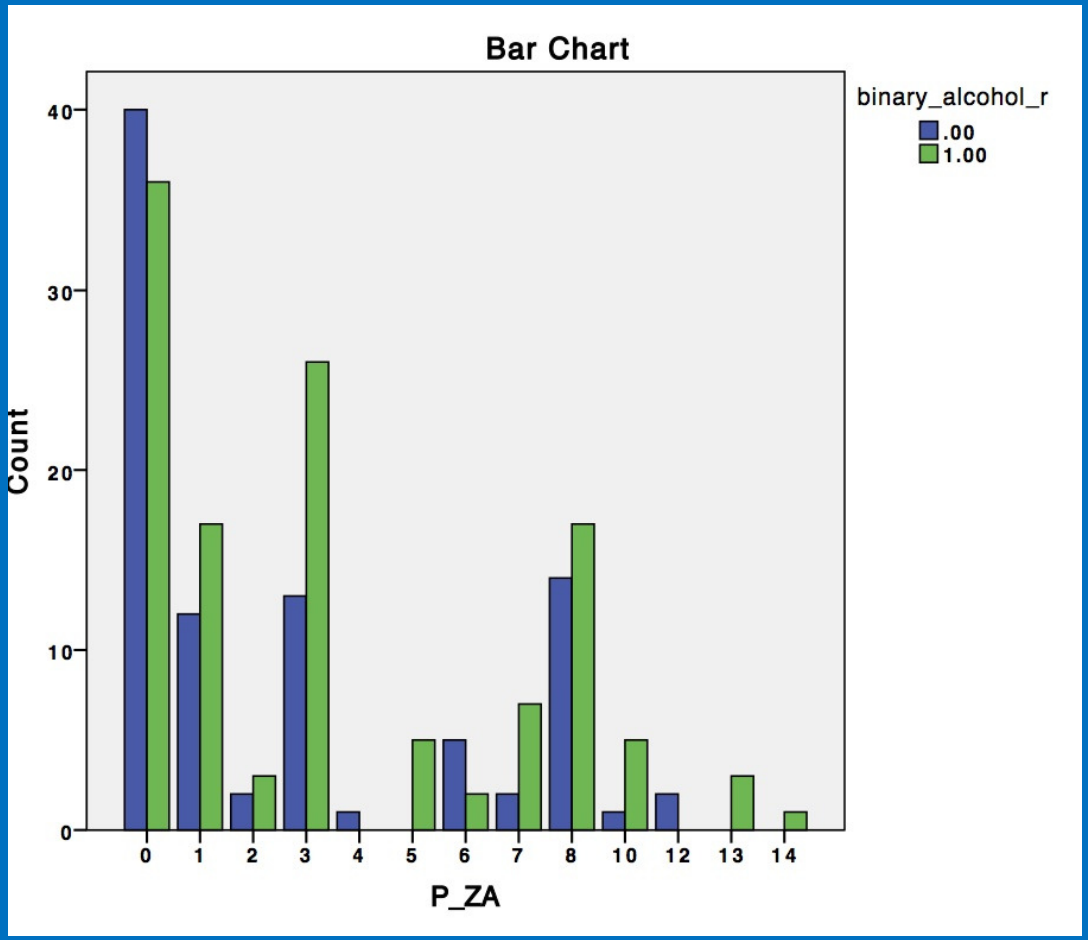
-DEPRESSION (#1 P< 0.05),

-ANXIETY (#3 P<0.05) and

-PTSD (8 P<0.05).

Although the sample size is small, there appears to be a trend for

-HIGHER RATES OF EATING disorders (#7 P<0.06).

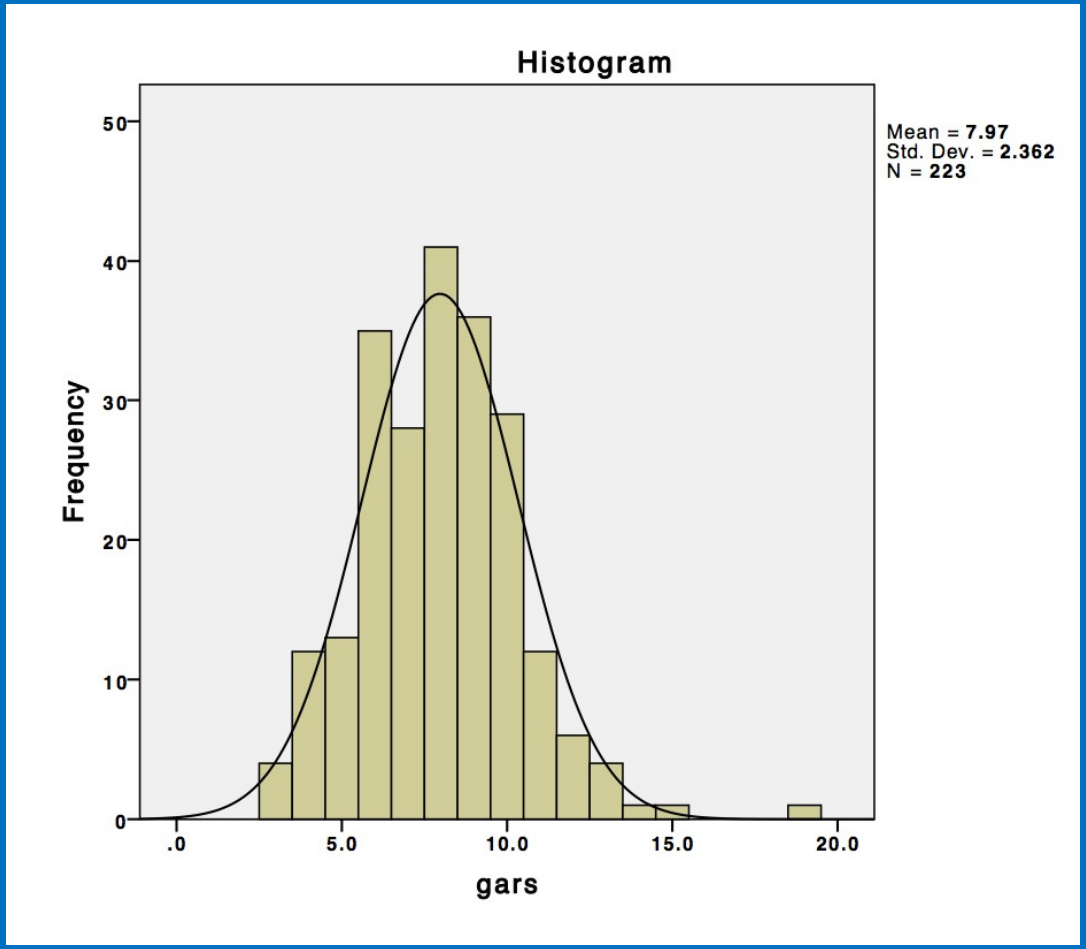


Hardy-Weinberg Distribution

Genetic risk is normally distributed

in the population,

with the average individual carrying roughly 8 risk alleles.



Logistic regression results.

Alcohol risk severity score has a cut off at 5 or fewer symptoms = 0; Binary genetic risk score has a cut off at 7 or fewer risk alleles = 0.

	B	S.E.	Wald χ^2	df	P-value
Constant	-1.23	0.60	4.28	1	0.039
Gender	-0.34	0.30	1.38	1	0.240
Age	0.03	0.01	8.45	1	0.004
Race	0.16	0.27	0.32	1	0.571
Genetic Risk Score	0.70	0.60	4.28	1	0.015

Genetic Addiction Risk Score (GARS)

GENE
DRD1
DRD2
DRD3
DRD4
DAT
COMT
MAOA
5HTTLLR
OPRM1
GABRA3

GARS results of a total of 393 subjects	GARS Predicts ASI
Number of Subjects	223
Low Risk	28.7%
Moderate Risk	30.9%
High Risk	40..4%
ASI –Alcohol Severity Risk Score	GARS Predicts at P<.0.003 Age adjusted P<0.012
Nine Treatment centers	393

GARS Predicts ASI –Drug Severity Risk Score

- Linear Regression using 223 Patients from Nine Diverse Addiction Treatment Centers
- Hypothesis Higher GARS Predicts Higher ASI-033 Drug Score .
- Log Transformation (10) .
- P<0.028 Unadjusted—Indicting significant association.
- Log Transformation (10).
- P<0.044 adjusted for age -Indicting significant association.

Proposed Clinical Tree For GARS

- Reduce patient guilt
- Reduce patient denial of disease
- Reduce overall stigma
- Stratify genetic risk for “reward deficiency” (Addiction)
- Provide information of “relapse chance” (e.g. DRD2 A1 allele increases risk for relapse)
- DNA-directed therapeutic targets based on gene polymorphisms

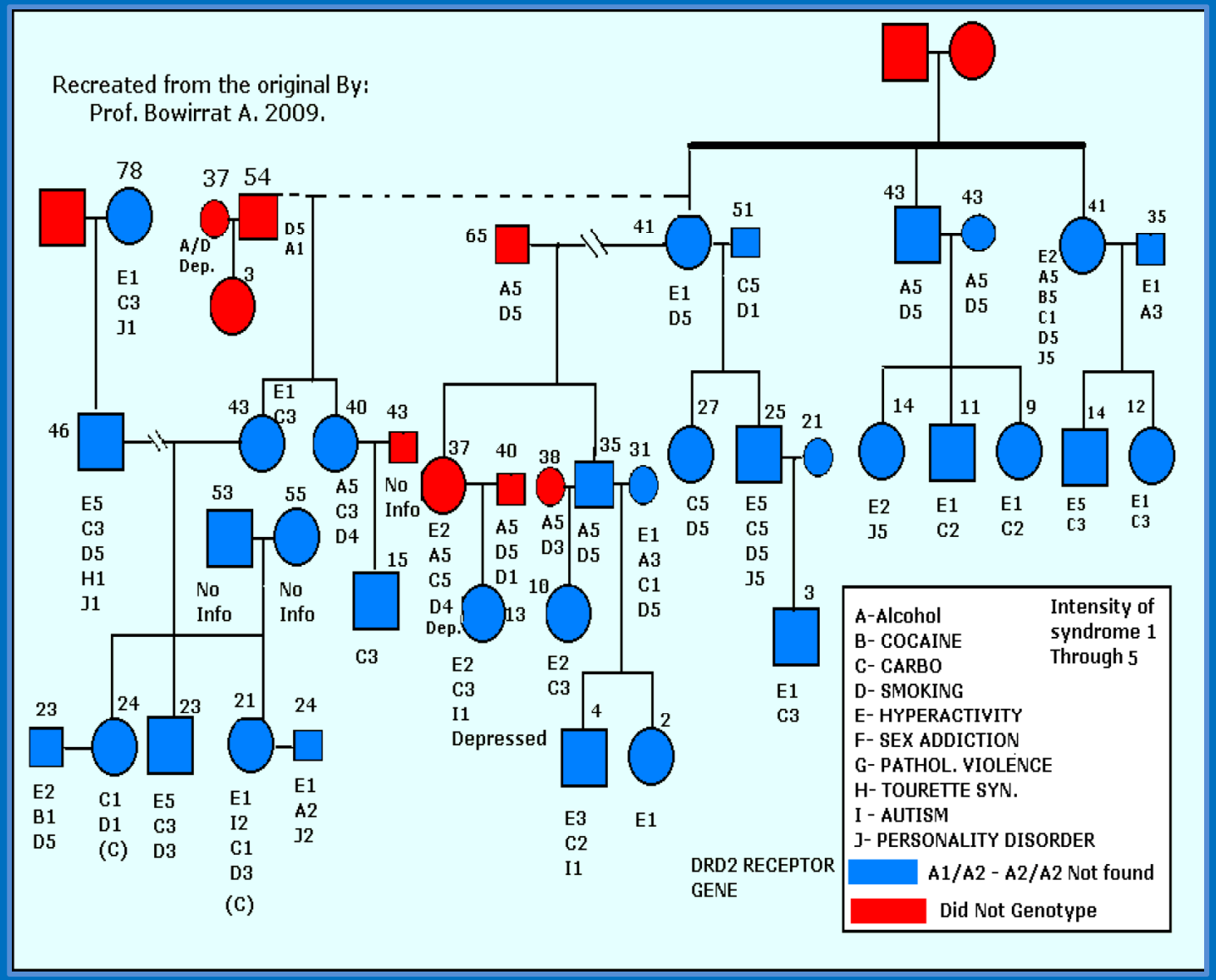
Proposed Clinical Tree For GARS cont'

- Provide medical monitoring based on pharmacogenetics (differential genotypes and pharmaceutical outcomes – Vivatrol, Antidepressants etc.)
- Provide medical necessity for insurance payments in terms of days required for treatment based on risk
- Provide medical necessity for level of care (e.g. Detox, Intensive Out Patient, Residential etc.)

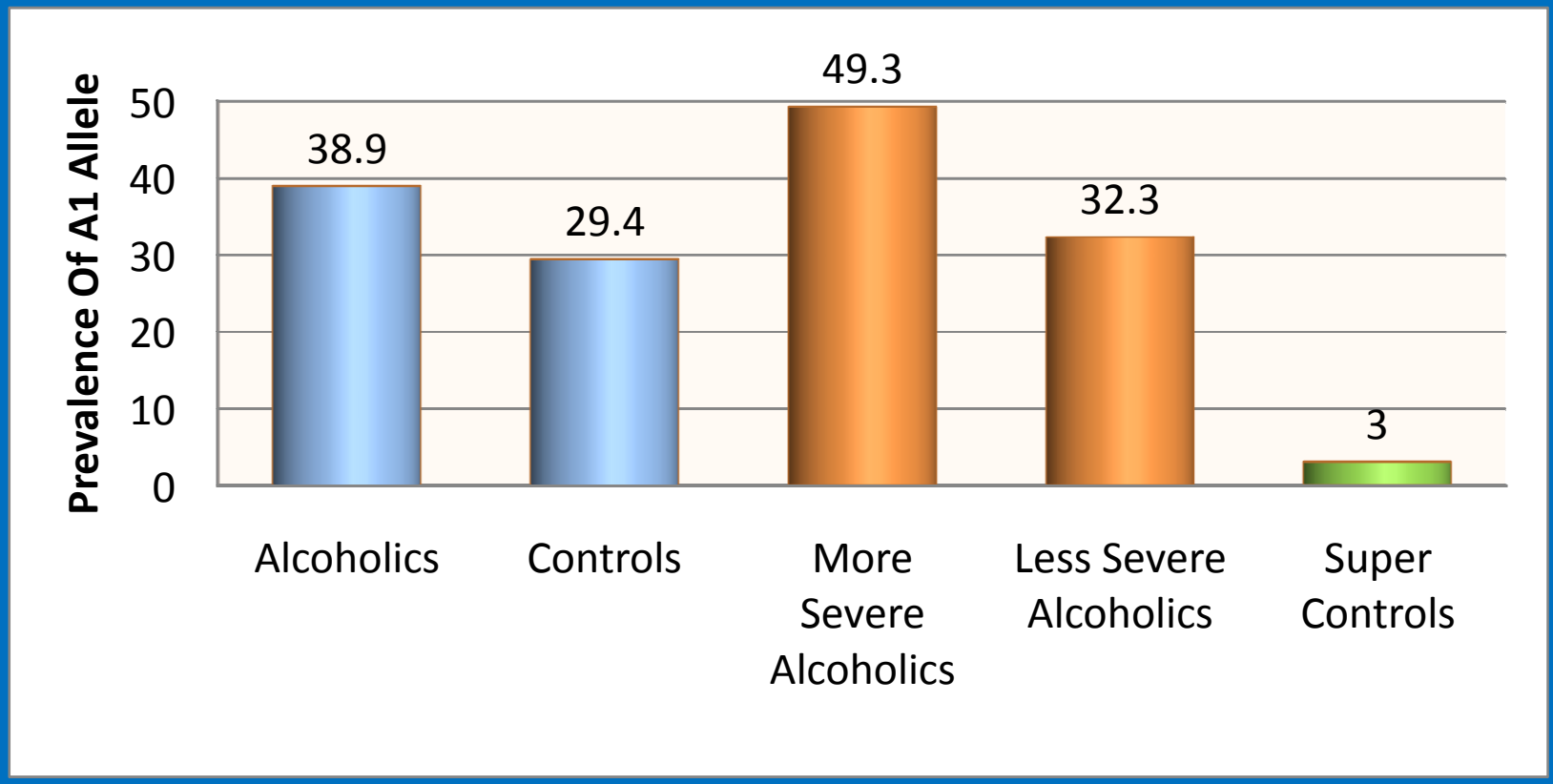
The necessity for SUPER CONTROLS

REWARD DEFICIENCY SYNDROME IS THE TRUE PHENOTYPE

Reward Deficiency Syndrome in the Generational



D_2 Dopamine Receptor Gene Association Studies

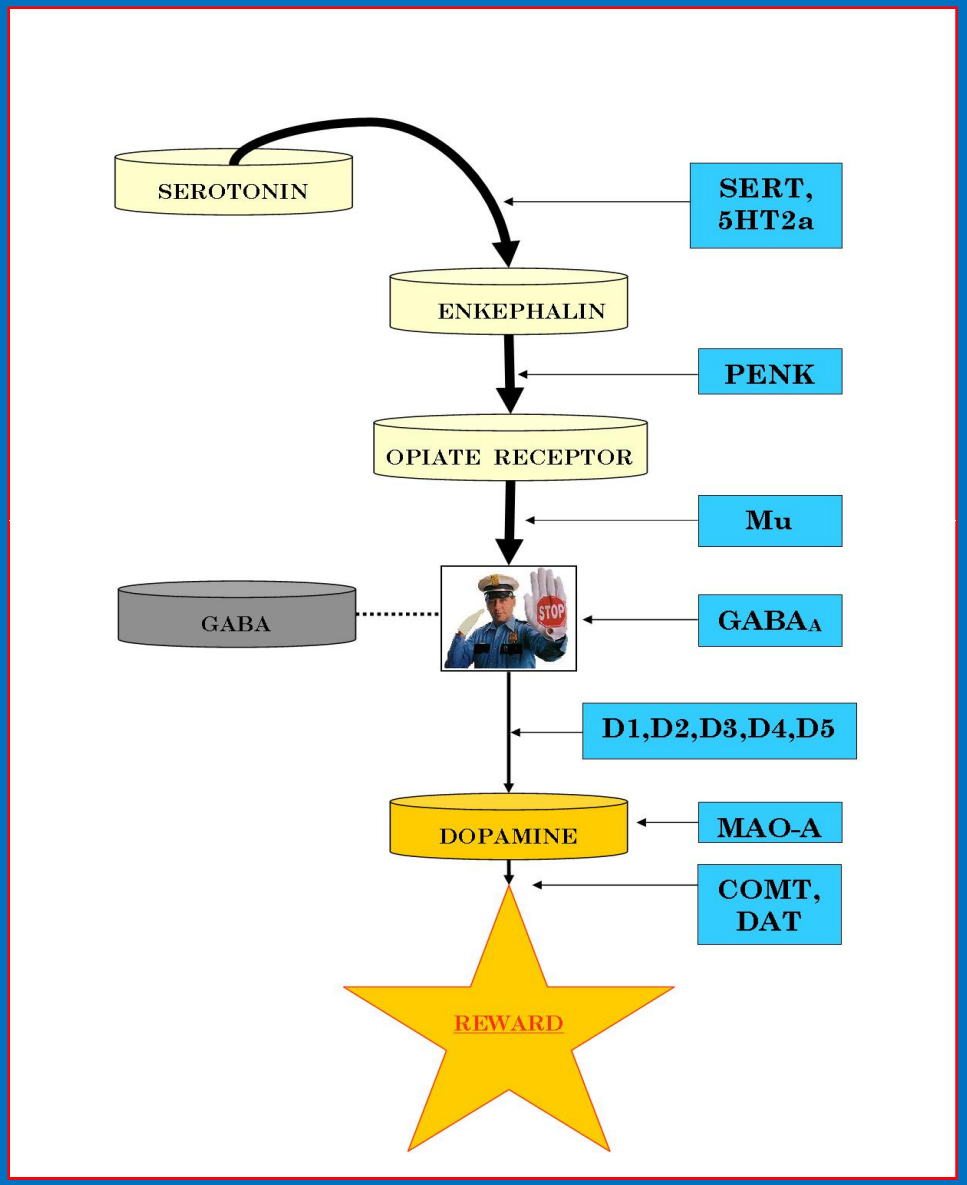


n=3329 **n=748** **n=30**

Noble, E.P. (2003). D_2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. *American Journal of Medical Genetics*, 116B, 103-125.
Chen, *et al. Gene Therapy & Mol Biology,* 11A: 93-112

The Brain Reward Cascade

Gene Targets in the Brain Reward Cascade

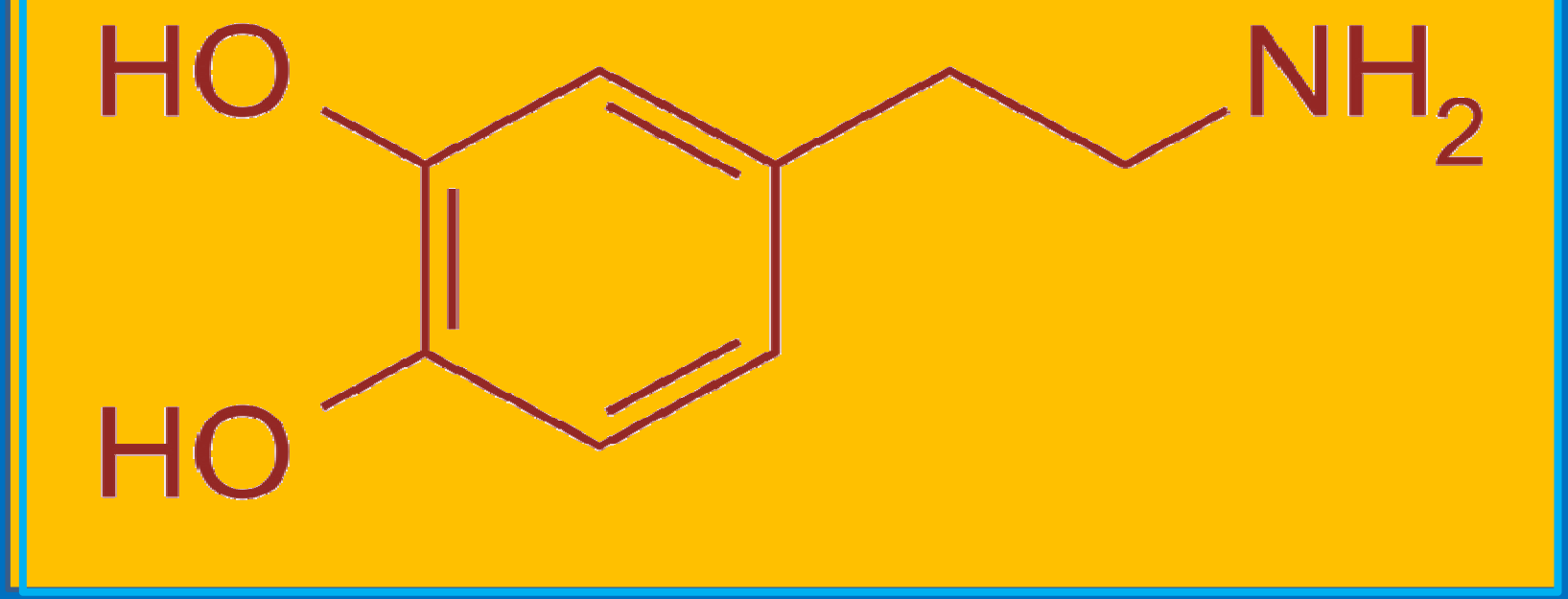


Neuroadaptagen Amino-Acid Therapy (NAAT)

GRAS NUTRIENT	PATHWAY
D-Phenylalanine	Opioid peptides
L-Phenylalanine	Dopamine
L-Tryptophane	Serotonin
L-Tyrosine	Dopamine
L-Glutamine	GABA
Chromium	Serotonin
Rhodiola rosea	COMT
Pyridoxine	Enzyme catalyst
Glycoside	Immune

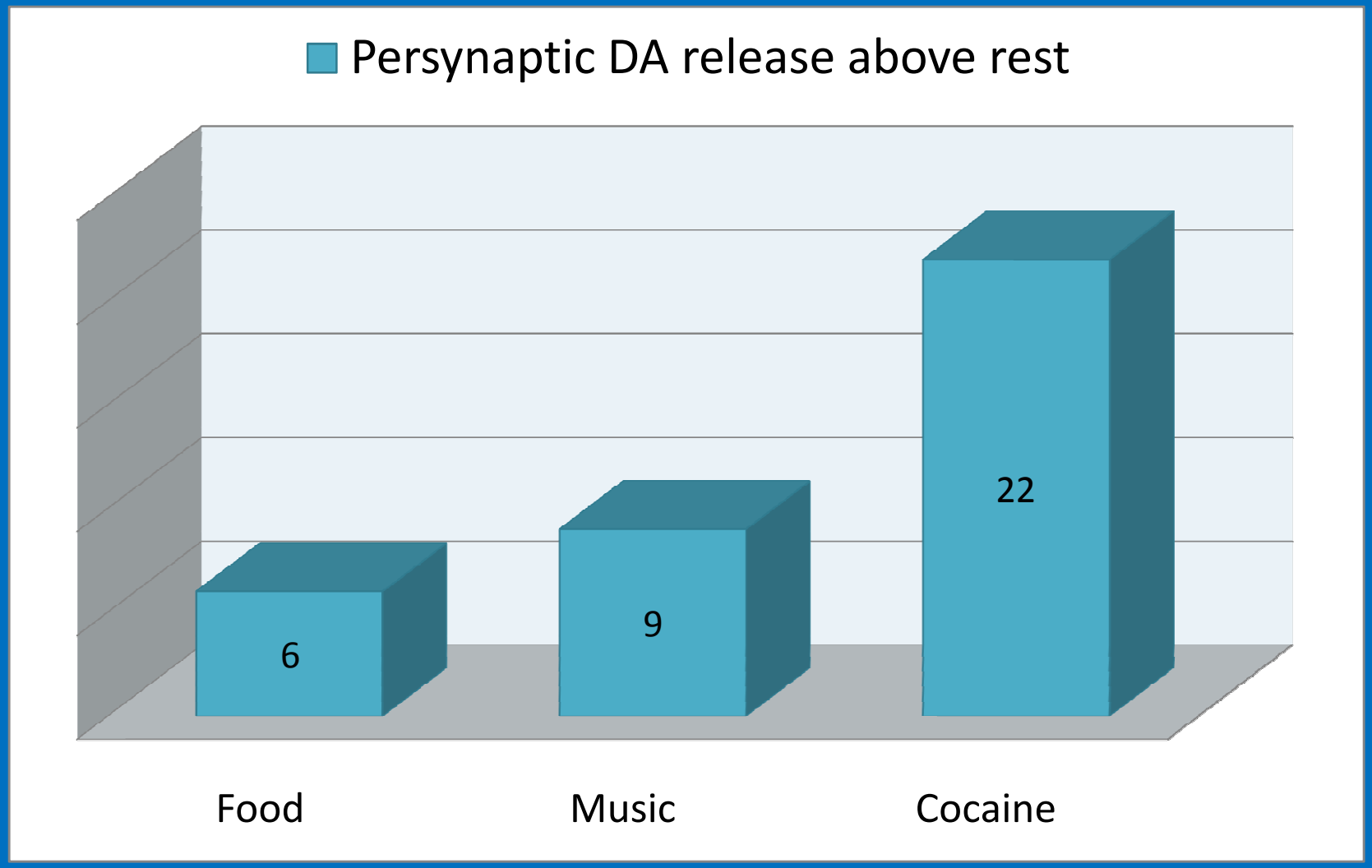
27 Published Clinical Trials of KB220 Variants

Dopamine

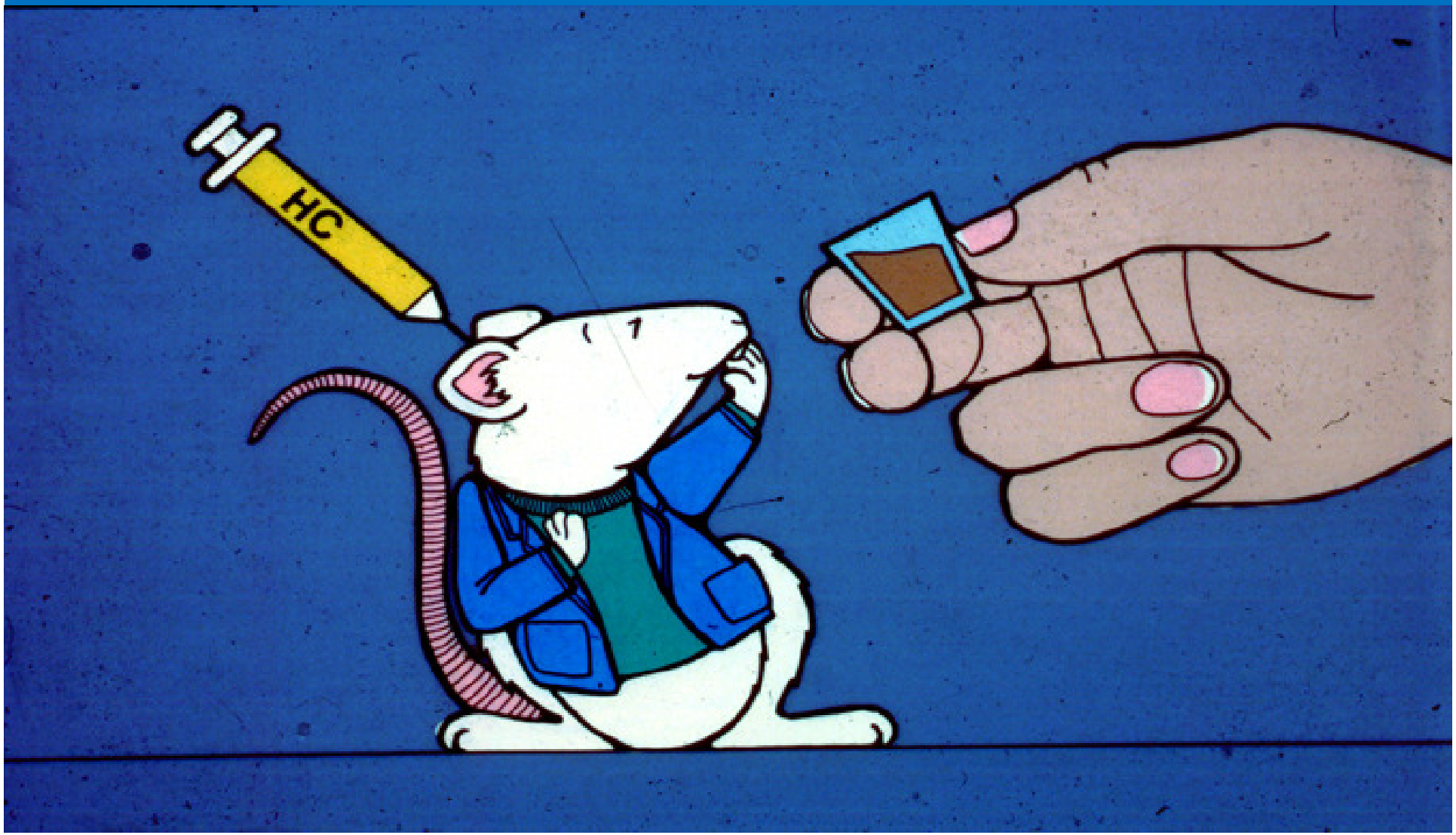



SELF MEDICATION
ROLLING ROCK
SAMUEL ADAMS

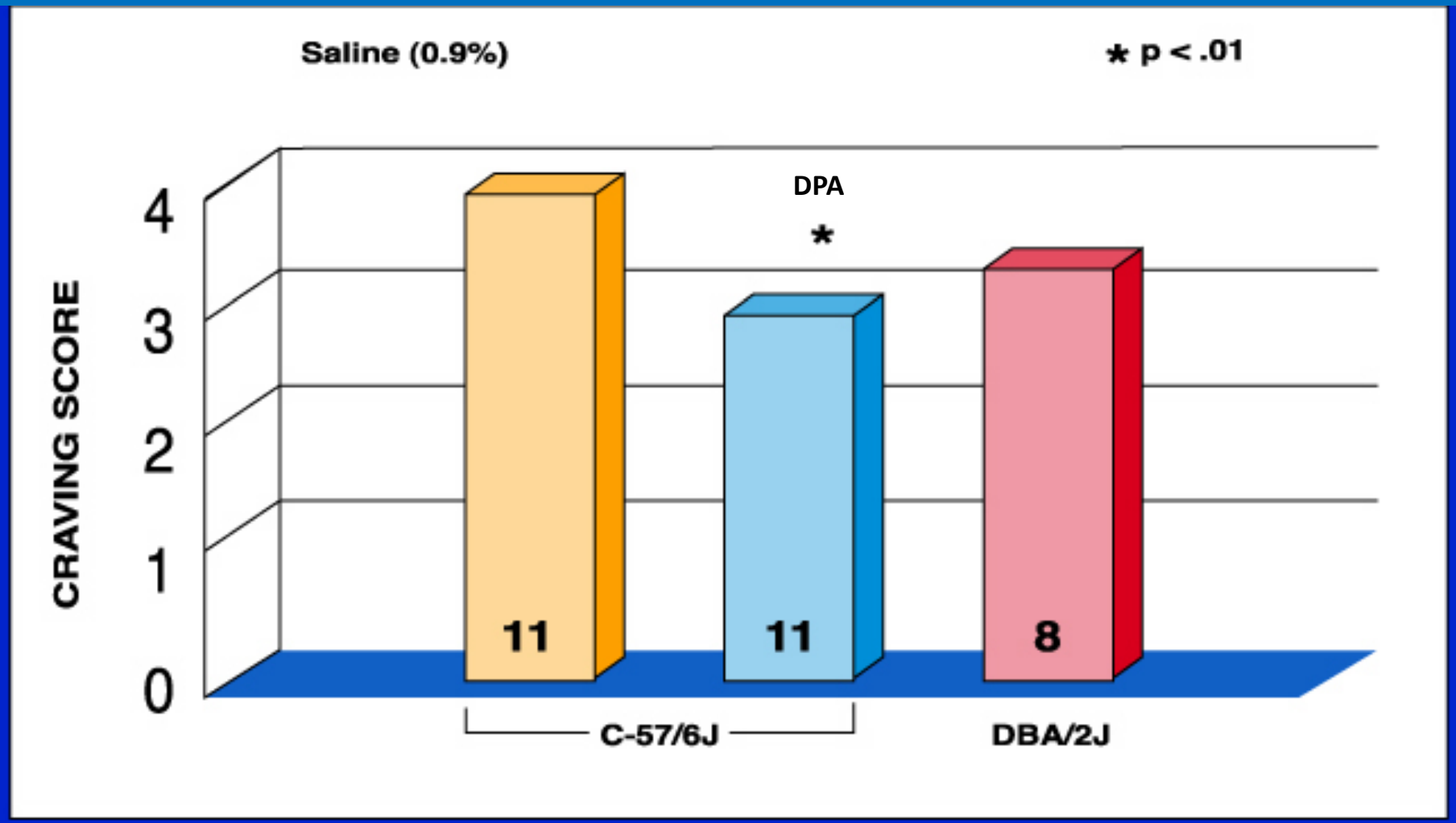
fMRI of Caudate Region of Brain following food, Music & Cocaine



D-Phenylalanine raises brain endorphins and stops cravings

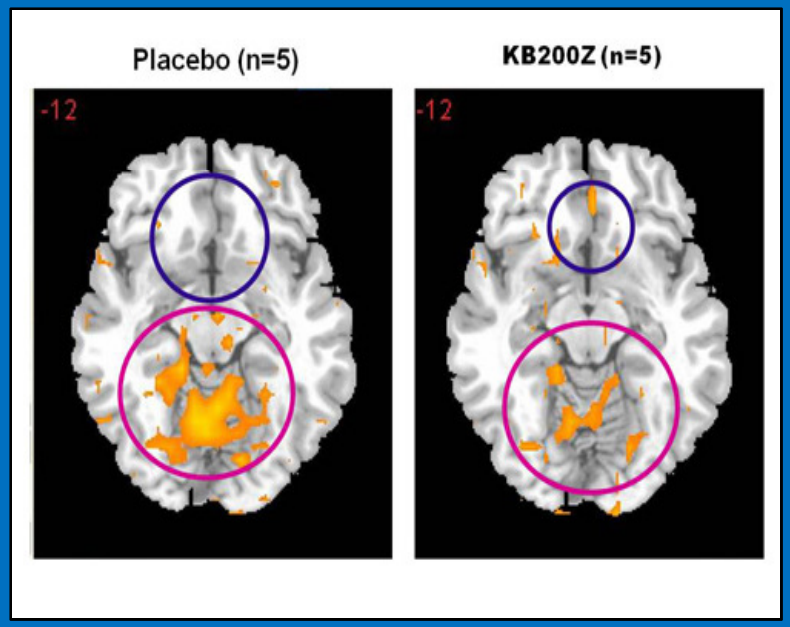


Pharmacogenetic conversion of high craving to low craving mice

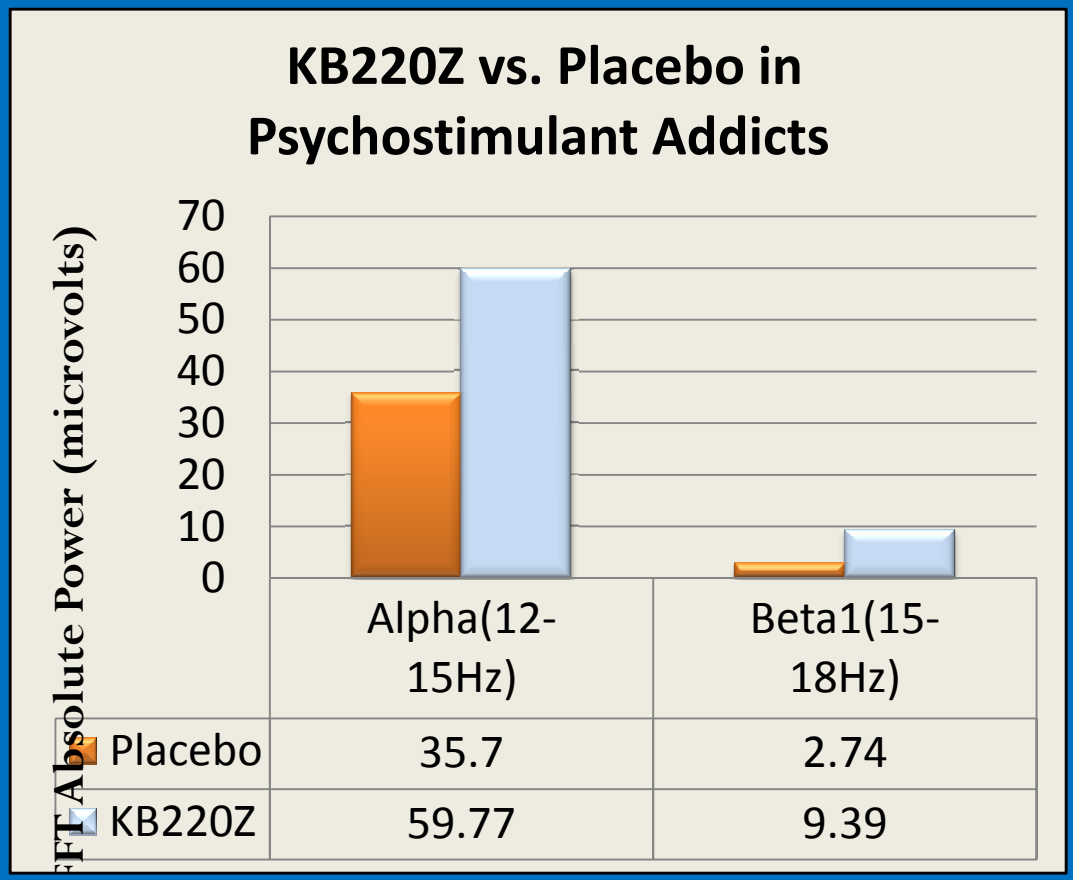


KB220Z Neuroadaptogen Complex

KB220Z compared to Placebo in five abstinent heroin dependent patients using fMRI



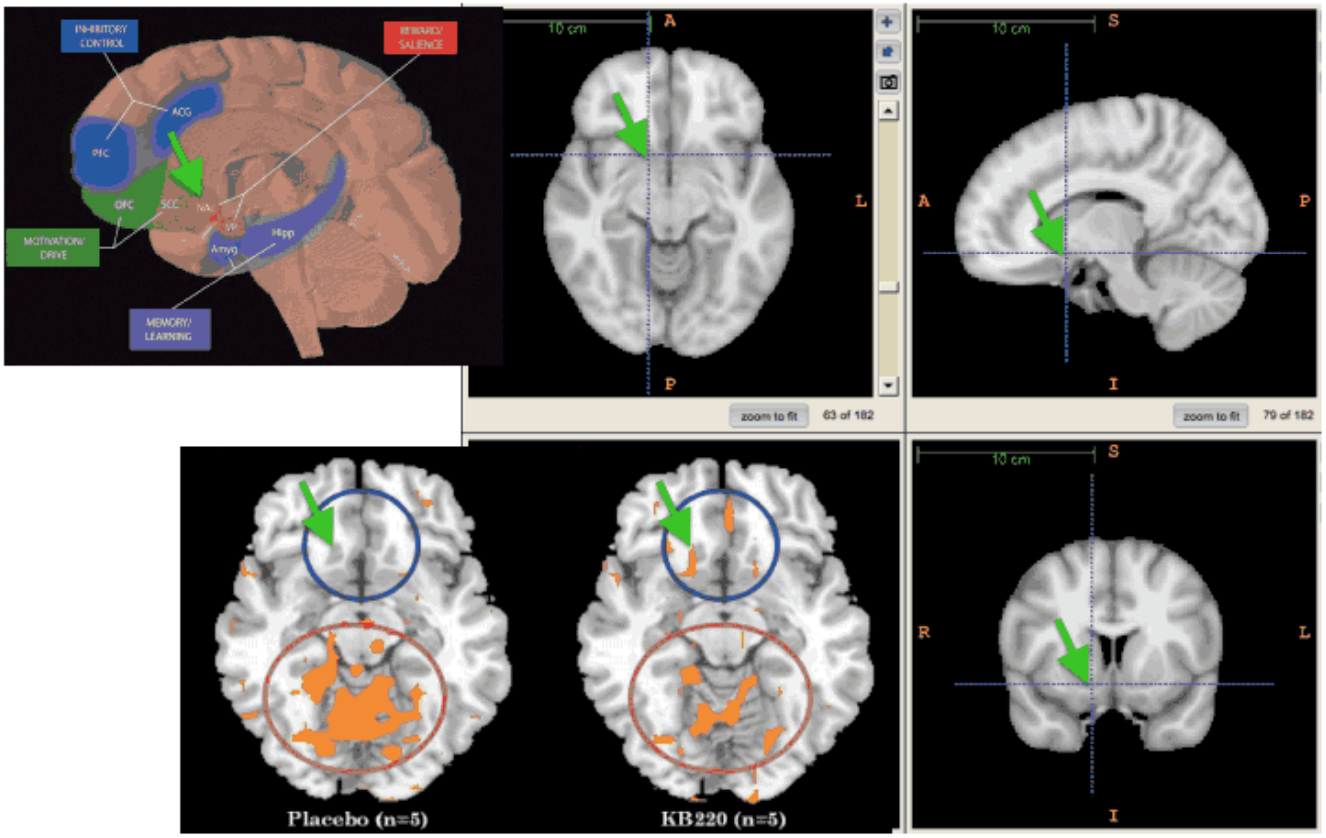
KB220Z normalizes qEEG Dysregulation



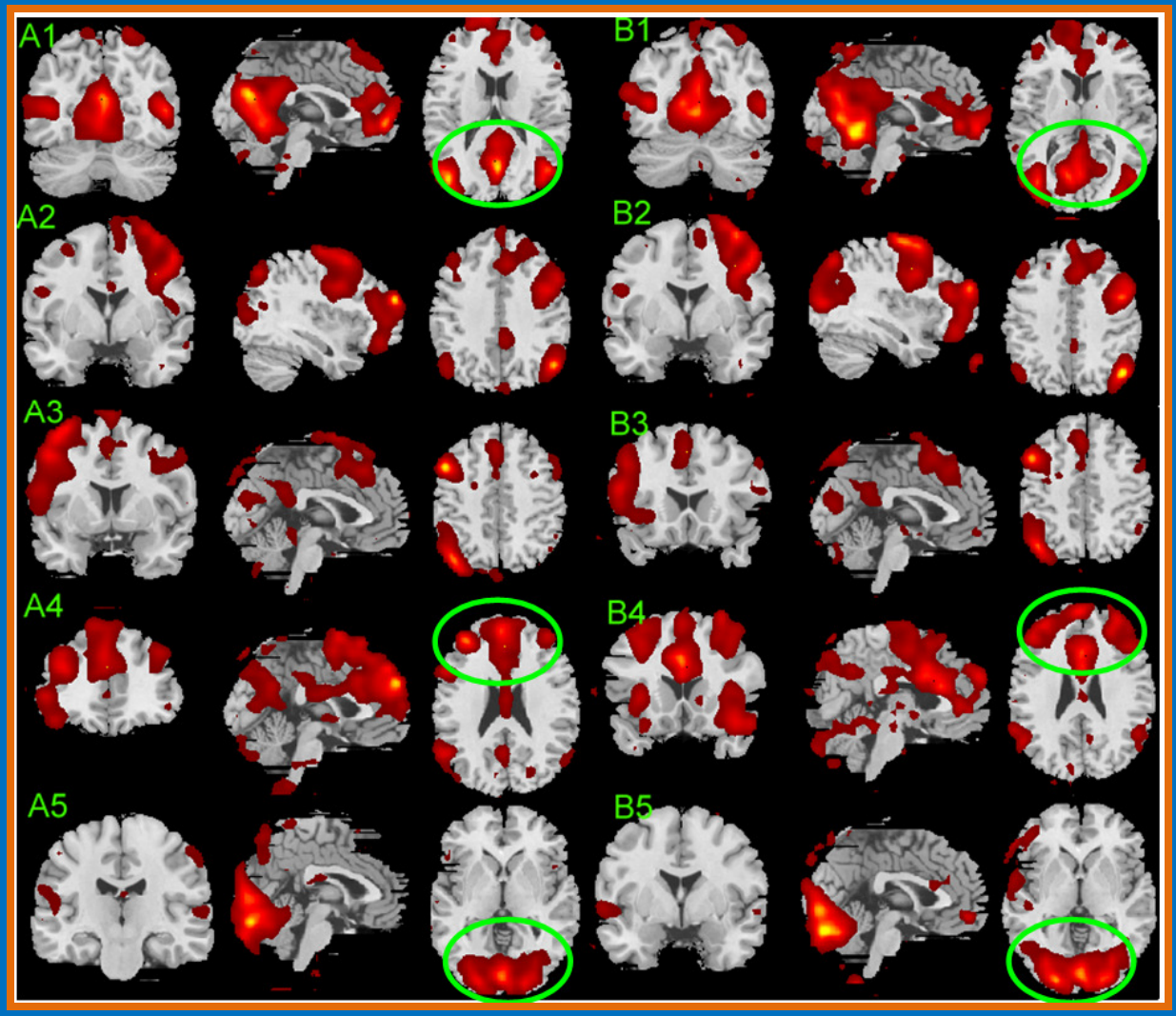
fMRI and qEEG results one-hour post administration compared placebo to KB220Z

Human brain map

Location of the nucleus accumbens in human CNS



Placebo VS KB220Z

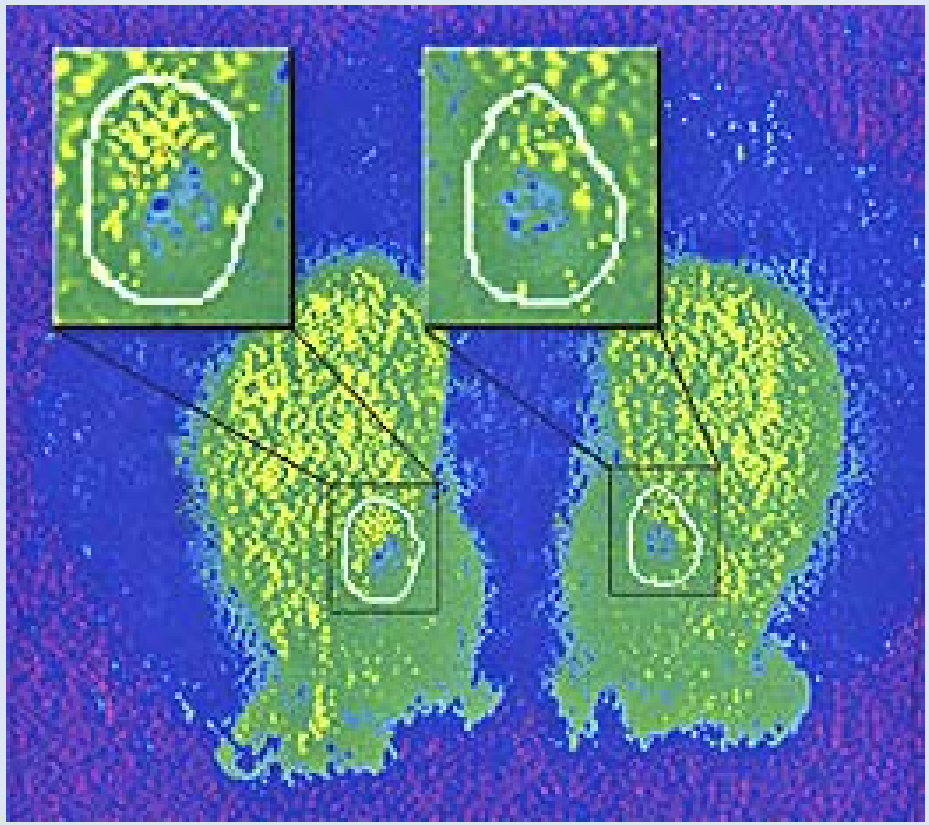


Areas of Significance

- Dorsal Anterior Cingulate
- Medial Frontal Gyrus
- Nucleus Accumbens
- Posterior Cingulate
- Occipital Cortical
- Cerebellum

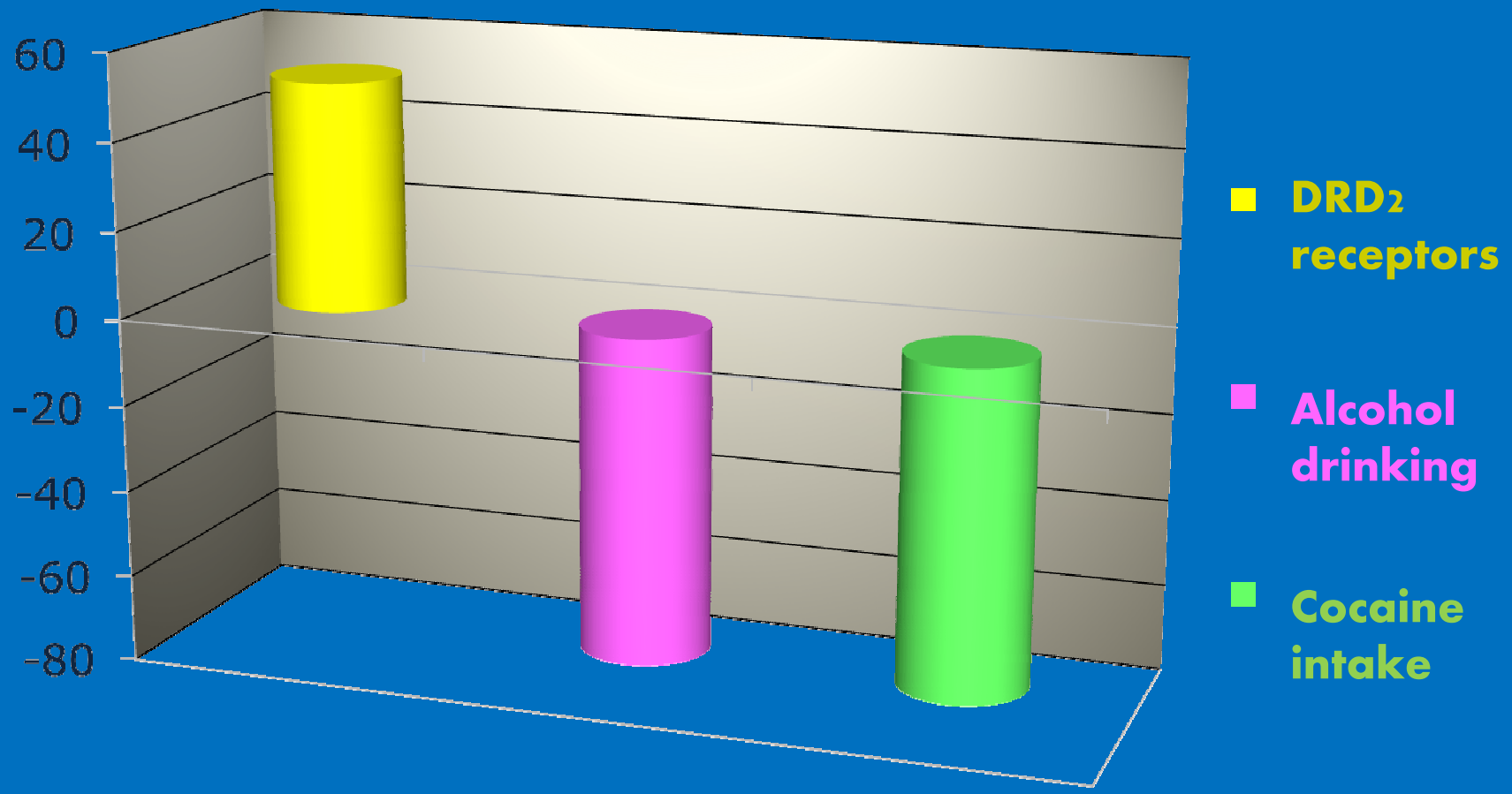
GENE THERAPY

The insets in this image of a rat's brain show increased expression of dopamine D2 receptors in the nucleus accumbens on the left side, which was injected with the D2 gene, compared with the right side, which was not injected with the receptor gene.



Thanos et al. Neurochemistry, 2004

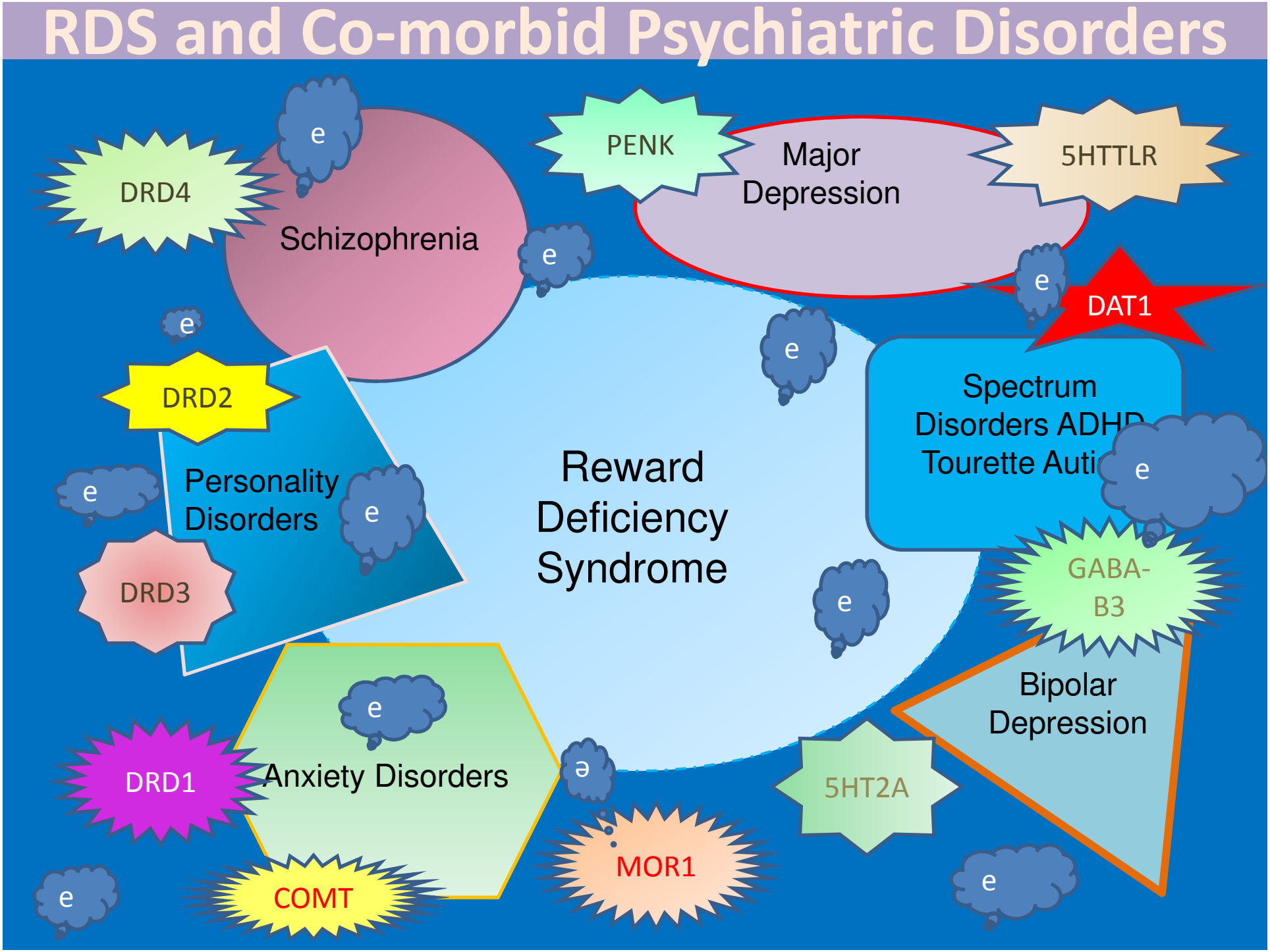
DRD2 Repletion Therapy is one key to unlocking the cause of RDS



Reward Deficiency Solution System

To this end we have:

- **utilized the CARD [urine screen] to determine treatment outcomes**
- **developed Genetic Addiction Risk Score (GARS), a DNA based panel of candidate genes to stratify risk for all reward dependent behaviors;**
- **evaluated the first ever natural dopamine D2 receptor activator (KB220Z) to provide enhancement of "dopamine sensitivity" using neuroimaging in animals and humans;**
- **propose using mRNA to determine reward gene expression pre and post treatment.**


RDS and Co-morbid Psychiatric Disorders
DRD4
Schizophrenia
PENK
Major Depression
5HTTLR
DAT1
DRD2
Personality Disorders
DRD3
Reward Deficiency Syndrome
Spectrum Disorders ADHD Tourette Auti
GABA-B3
Bipolar Depression
5HT2A
DRD1
Anxiety Disorders
COMT
MOR1
e

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