CURRENT DRUG THERAPY

GSIPP 2013

PAD

Hans C. Hansen, MD

DISCLAIMER

HANS C. HANSEN MD

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Opioid Abuse

"The bottom line is there will never be enough specialists to deal with the problem."

Scott Fishman, MD

THIS IS NOT TRUE.....


painrelief
P.A.
Pain Management Specialists
OXYCONTIN

OXYCONTIN

- NO CEILING EFFECT
- NO ACETAMINOPHEN ISSUES
- TITRATABLE
- MINIMAL STREET USE

WATME 1998

WE'VE GOT AN EPIDEMIC HERE…..

IT'S LEGAL!

YOUR WAITING ROOM

3 p.m. Friday afternoon….

Ginger

Mary Ann

PHARMACEUTICAL REPRESENTATIVES

Medicine requires observation and conclusion

See

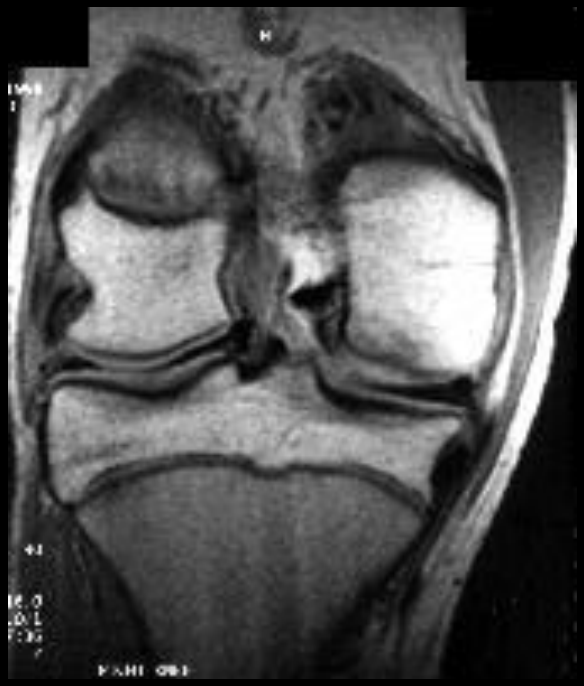
Hear

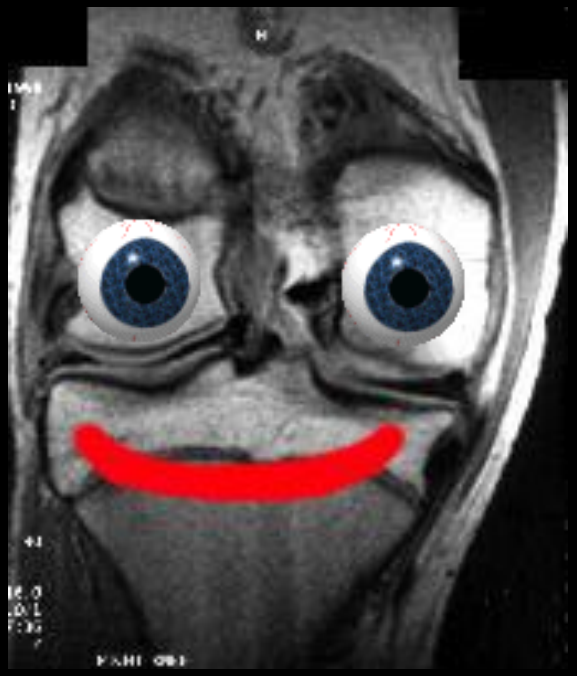
Touch

Measure

Observation verifies reality.

WE JUST WANT TO MAKE YOU HAPPY






Welcome To
Mount Airy
Historic Downtown

LIVE: White House Egg Roll
10:30 a.m. ET: President Barack Obama and first lady Miche annual White House Easter Egg Roll. More

Police Arrest 'Easter Bunny' On Drug Charges

Danville PD: Pills Seized From Man In Easter Bunny Costume

POSTED: 10:11 pm EDT April 7, 2012
UPDATED: 10:42 pm EDT April 7, 2012

DANVILLE, Va. -- A man who was working as the Easter Bunny at Danville's Piedmont Mall was arrested Friday after police said he was caught with pills without a valid prescription.

According to the Danville Police Department, 24-year-old Joshua Lee Bolling was charged with illegally possessing prescription narcotics.

Joshua Bolling

The investigation began after police said they received complaints from mall businesses and management of behavior suggestive of possible criminal drug activity involving the man working as the Easter Bunny.

Police said that Bolling was a contract worker for an outside company providing the Easter activities and was not employed by Piedmont Mall.

Bolling was asked to accompany officers away from the public area where he was working and he was escorted to a private changing area where he removed his costume and was arrested, officers said.

See Breaking News? Upload Pictures, Video | ulocal@wxii12.com

WHERE ARE WE GOING AND WHAT'S NEW

- *WHAT WE ARE*

- TERMINOLOGY
- ADDICTION OR PAIN
- EPRESSION AND PAIN- SAME THING, KINDA
- BIOLOGICS, AND OTHER DRUG THOUGHTS
- NEW IS AS NEW MIGHT BE

ARE WE BOTTOM FEEDERS?

OR…. ECCENTRIC AND INSPIRED

WATME

ASSUMPTIONS- CHRONIC PAIN

- A physician understands risks and management of addictive disease.
- Persistent failure to treat addiction is poor medical practice
- Failure to prescribe opioids when indicated is also poor medical practice
- Physicians traditionally receive little or no education about pain management or the treatment of addiction.

CHRONIC PAIN

- Pain is undertreated
  - Fear of patient harm
  - Fear of regulatory, legal or licensing penalties
  - Addictive disorder or risk for addiction
  - Divert or misuse of medications

‘PSEUDOADDICTION IS A PSEUDO REALITY’

HH

CHRONIC PAIN

- Most abused Prescription Drugs
  - Opioids
  - Central nervous system depressants
  - Stimulants

Source: National Institute on Drug Abuse, National Institute of Health, US Department of Health and Human Services. Abuse and Addiction, Research Report Series, 2005. NIH publication number 05-4881. Rockwell, MD

CHRONIC PAIN

Psychotherapeutic Prescriptions

- 6.4 million people used psychotherapeutic drugs non-medically
- 4.7 million use pain relievers
- 1.8 million use tranquilizers
- 1.1 use stimulants
- 272,000 use sedatives

PSEUDOADDICTION IS REALLY IAOTROGENIC ADDICTION

CHRONIC PAIN

- Chronic Pain

'***Rewires***' the nervous system to continue sending signals after the original cause has been healed or removed.

- Anxiety, depression, and insomnia make the pain unbearable. COMORBIDITY

5 RULES

1. Pain is a description and not an entity

2. YOU MUST HAVE A DIAGNOSIS

3. REFERRAL RULE

4. Know Thy Meds

5 CLASSES, PICK 5

From a *compassionate* standpoint
I want to relieve pain …

From a *realistic* standpoint I must
improve function

5. DO NOT CHASE PAIN!

Narcotics are not always our best choice

TERMINOLOGY

Opioid and Drug Speak

- **Definitions:**
  - **Abuse: use of medication for purposes other than those for which it was prescribed**
  - **Addiction: Impaired control over drug use, compulsive drug use and continued use despite harm and because of craving.**
  - **Tolerance: A physiologic state caused by regular use of an opioid in which increased doses are needed to maintain the same effect.**

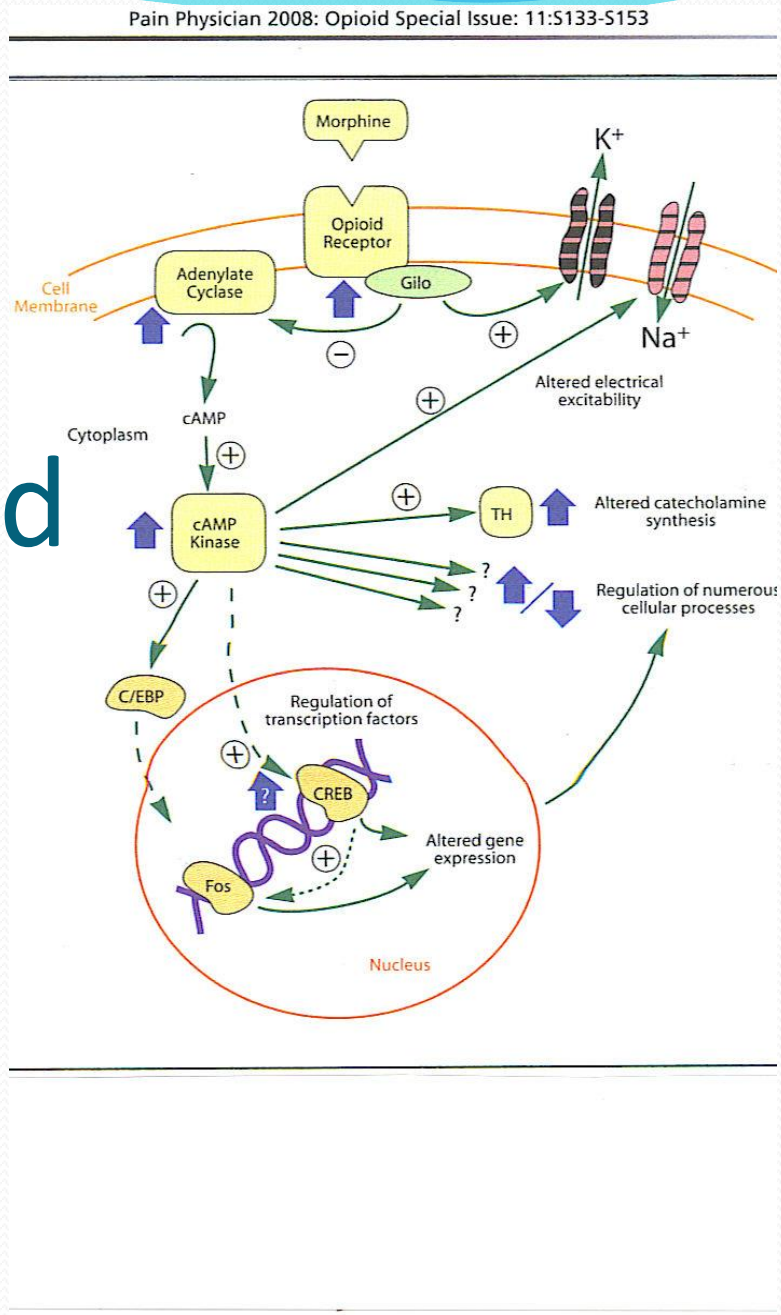
Opioid Use and Abuse

- **Physical Dependence** :
  - A normal physiologic state
  - An expected result of opioid use
  - Characterized by withdrawal
  - Highly variable in its onset
  - Sometimes coincides with addiction
  - Is not, by itself addiction

Opioid Use and Abuse

- **Tolerance**
  - Natural state of neuroadaptation to drug- induced changes
  - May result in increased analgesic needs
  - Varies among individuals
  - Varies according to the type of pain
  - Develops more quickly in younger people
  - Is not addiction

Drug use, Tolerance, and the Sensitized Cellular Enviornment



Pharmacokinetics

A drugs effect is directly related to its concentration at the site of action

What we do to the drug

Pharmacokinetic – **Drug movement and concentration**

- Blood
- Tissues
- Fluids

Concentration influenced by:

- Absorption
- Elimination/excretion
- Distribution
- Metabolism

Pharmacodynamics

Effect

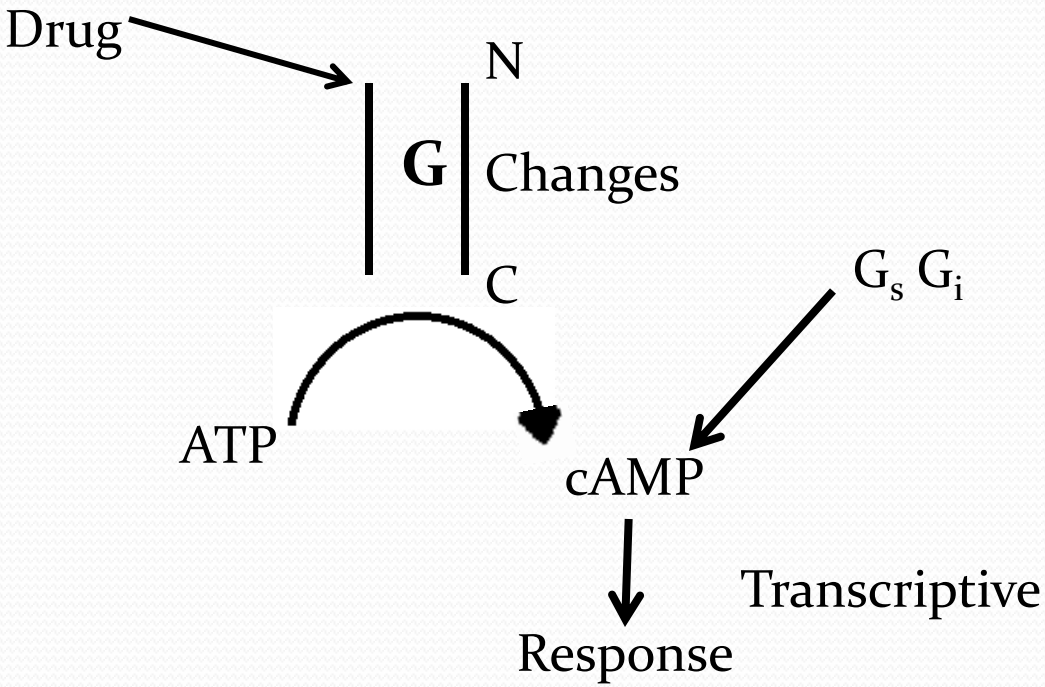
Biochemical, physiologic

What the drug does to us

Pharmacodynamics

Receptors

Ligand – Flow of ions
Effector – G Protein



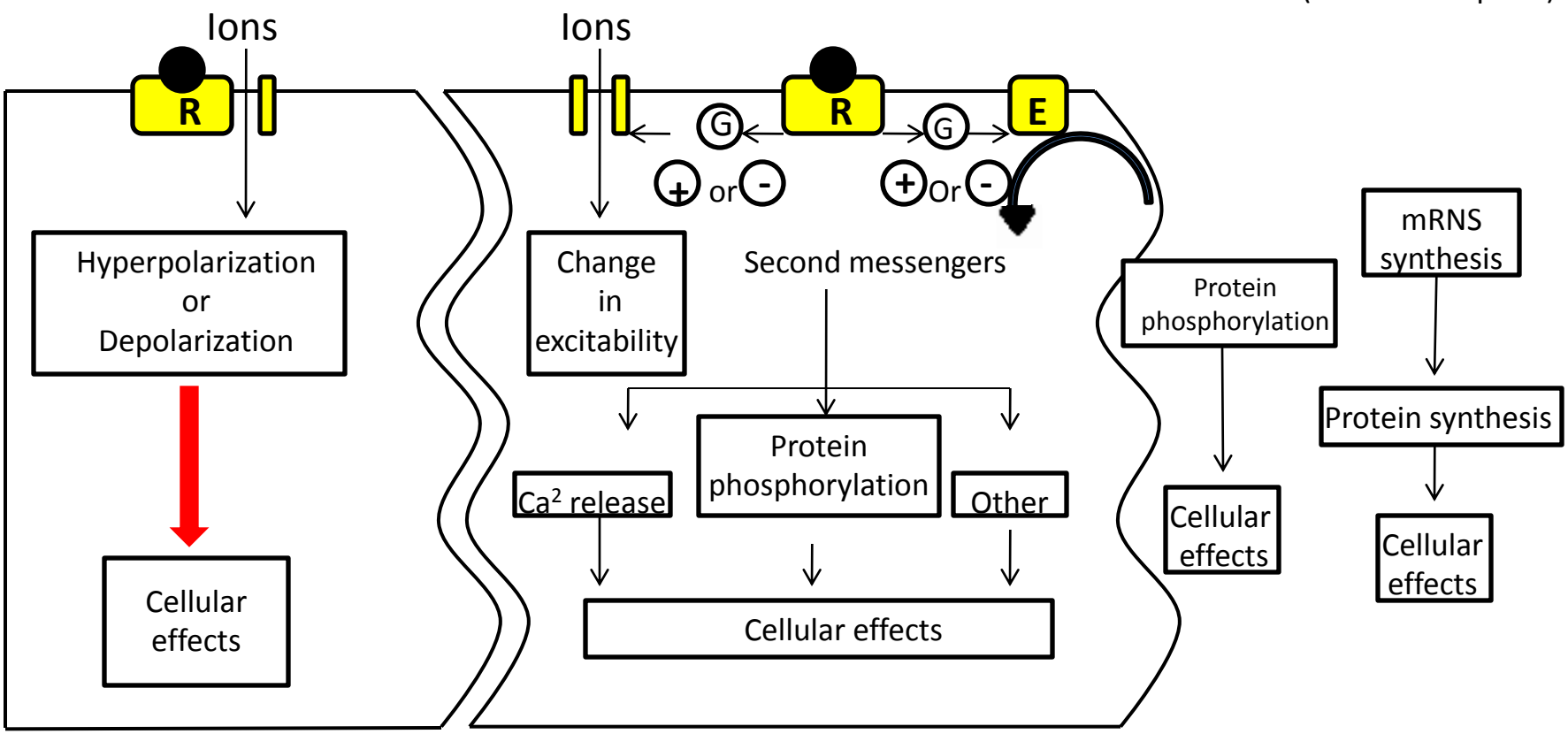
Active, inactive, partially active, selective

1. Channel-linked receptors (Ionotropic)

2. G-protein coupled receptors (Metabotropic)

3. Kinase-linked receptors

4. Receptors linked to Gene transcription (nuclear receptors)



Time Scale

Milliseconds	Seconds	Minutes	Hours

Examples

Nicotinic Ach receptor	Muscarinic ACh receptors	Insulin receptor	Estrogen receptor

Adopted from Principles of Addiction Medicine 4th Edition

Acute Actions of Some Drugs of Abuse

Drug	Action	Receptor Signaling Mechanism
Opiates	Agonist at μ, δ and κ opioid receptors	Gi
Cocaine	Indirect agonist at Dopamine receptors by inhibiting dopamine transporters	Gi and Gs
Amphetamine	Indirect agonist at Dopamine receptors by stimulating Dopamine release	Gi and Gs
Ethanol	Facilitates $GABA_A$ receptor function and inhibits NMDA glutamate receptor function	Ligand-gated channels
Nicotine	Agonist at nicotinic acetylcholine receptors	Ligand-gated channels
Cannabinoids	Agonist at Cb_1 and CB_2 cannabinoid receptors	Gi
Phencyclidine	Antagonist at NMDA glutamate receptor channels	Ligand-gated
Hallucinogens	Partial agonist at $5HT_{2A}$ serotonin receptors	Gq
Inhalants	Unknown	

Metabolism

C Y P ( ) ( ) ( )

Family (Letter)

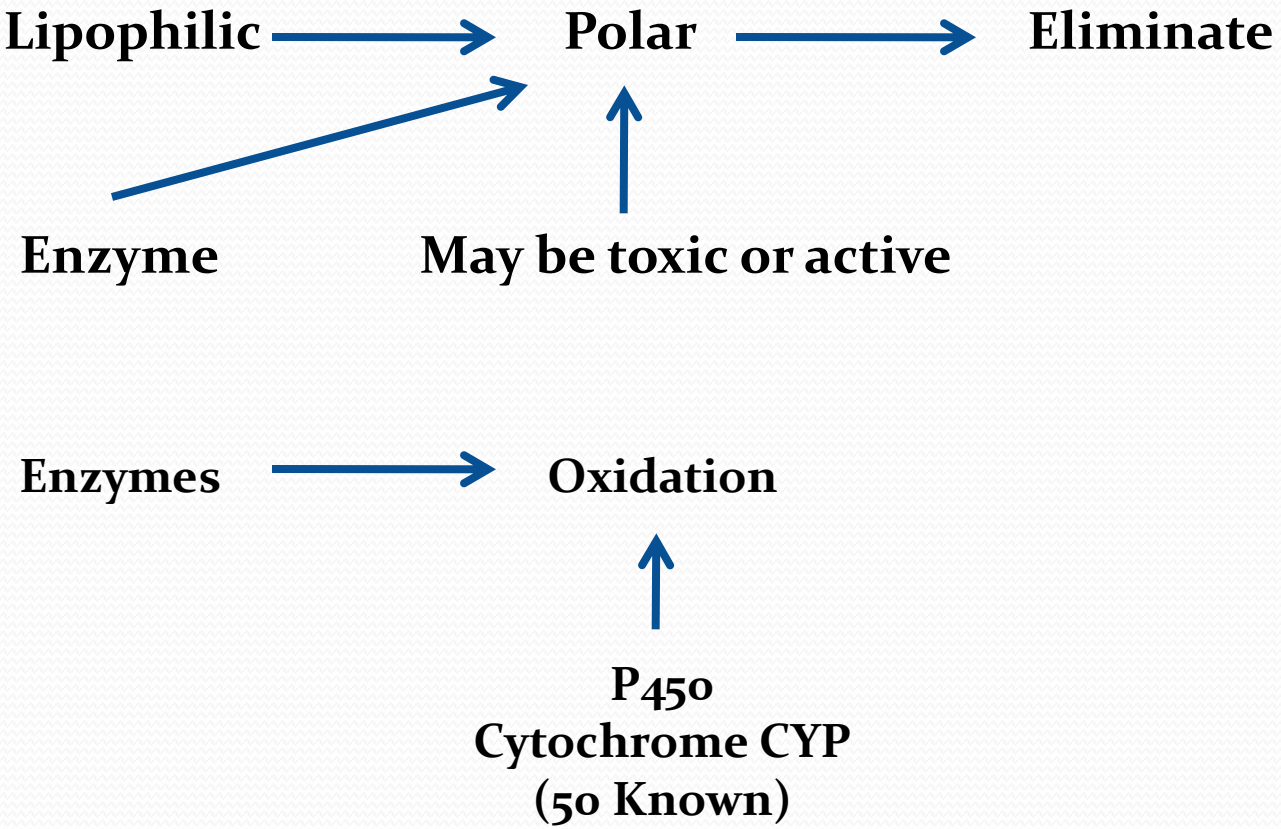
Subfamily (Letter)

Form (Number)

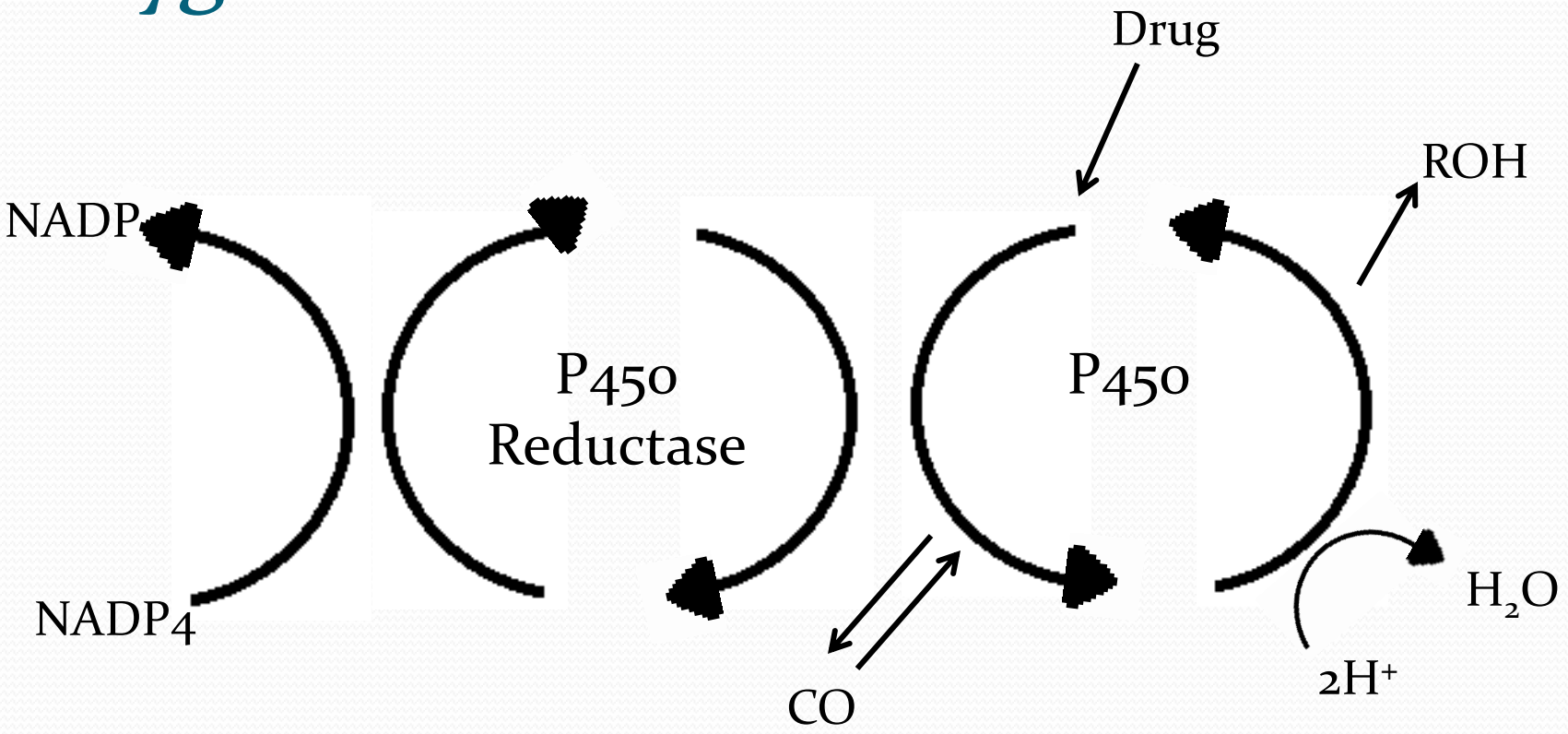
CYP3A – Metabolizes 50% of drugs.

May be broken down by genes and pseudogenes.

Metabolism


Lipophilic
Polar
Eliminate
Enzyme
May be toxic or active
Enzymes
Oxidation
P450
Cytochrome CYP
(50 Known)

1 Oxygen Molecule



Liver > Lung/GI/Skin/Kidney

Elimination/Excretion

Elimination – Metabolism or excretion of parent drug/metabolite

Excretion – Removal without changing the drug

Clearance – Rate that this occurs

t ½ - half life, 50% change, in time, to or from steady state

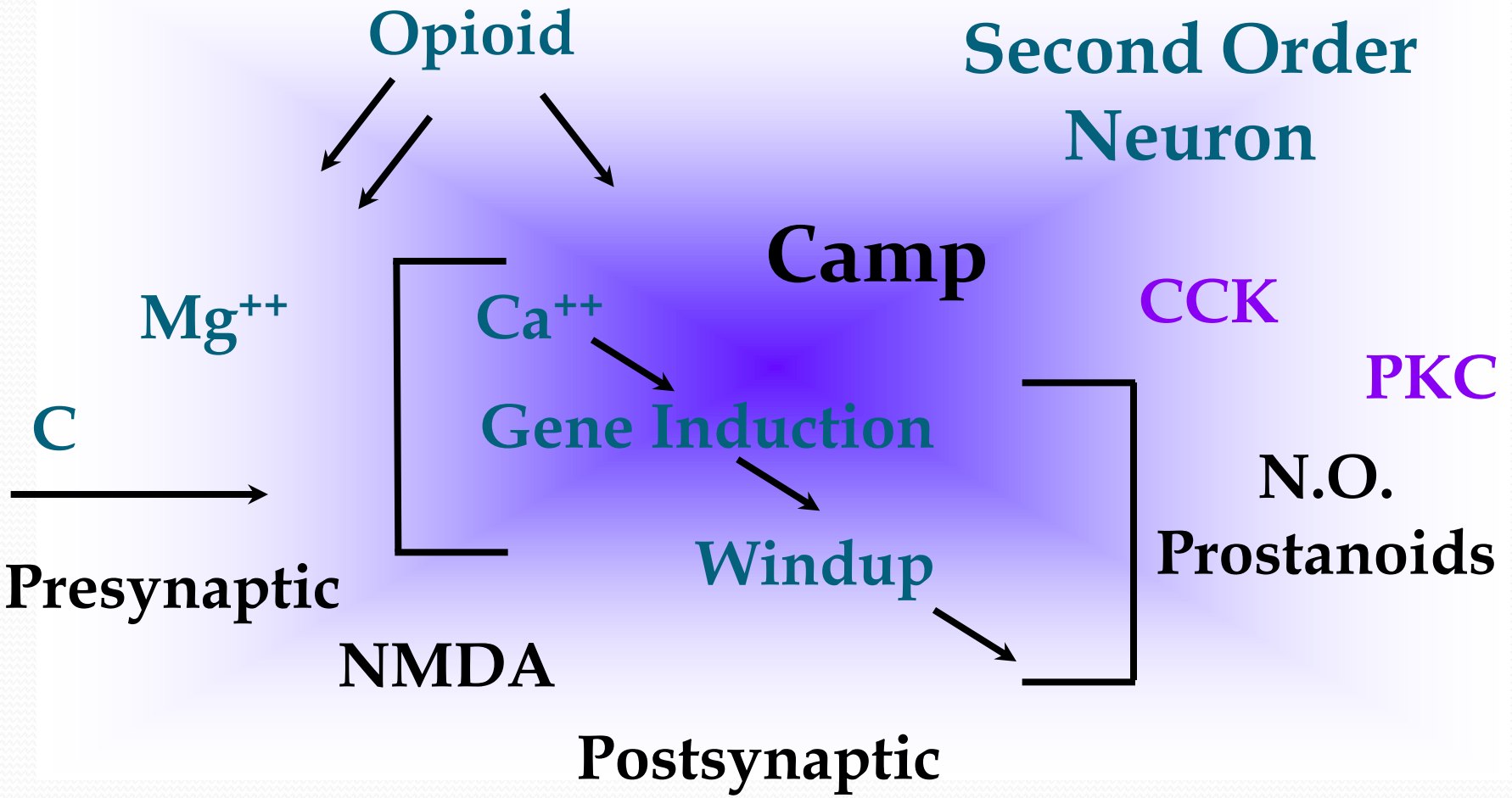
Opioid Interactions

-*Hyperalgesia*- persistant noxious stimulation and EAA activity (glutamate) = *neuroplasticity*

-Increase protein kinase C (PKC) intracellularly

--PKC increases with prolonged opioid exposure

Hyperalgesia

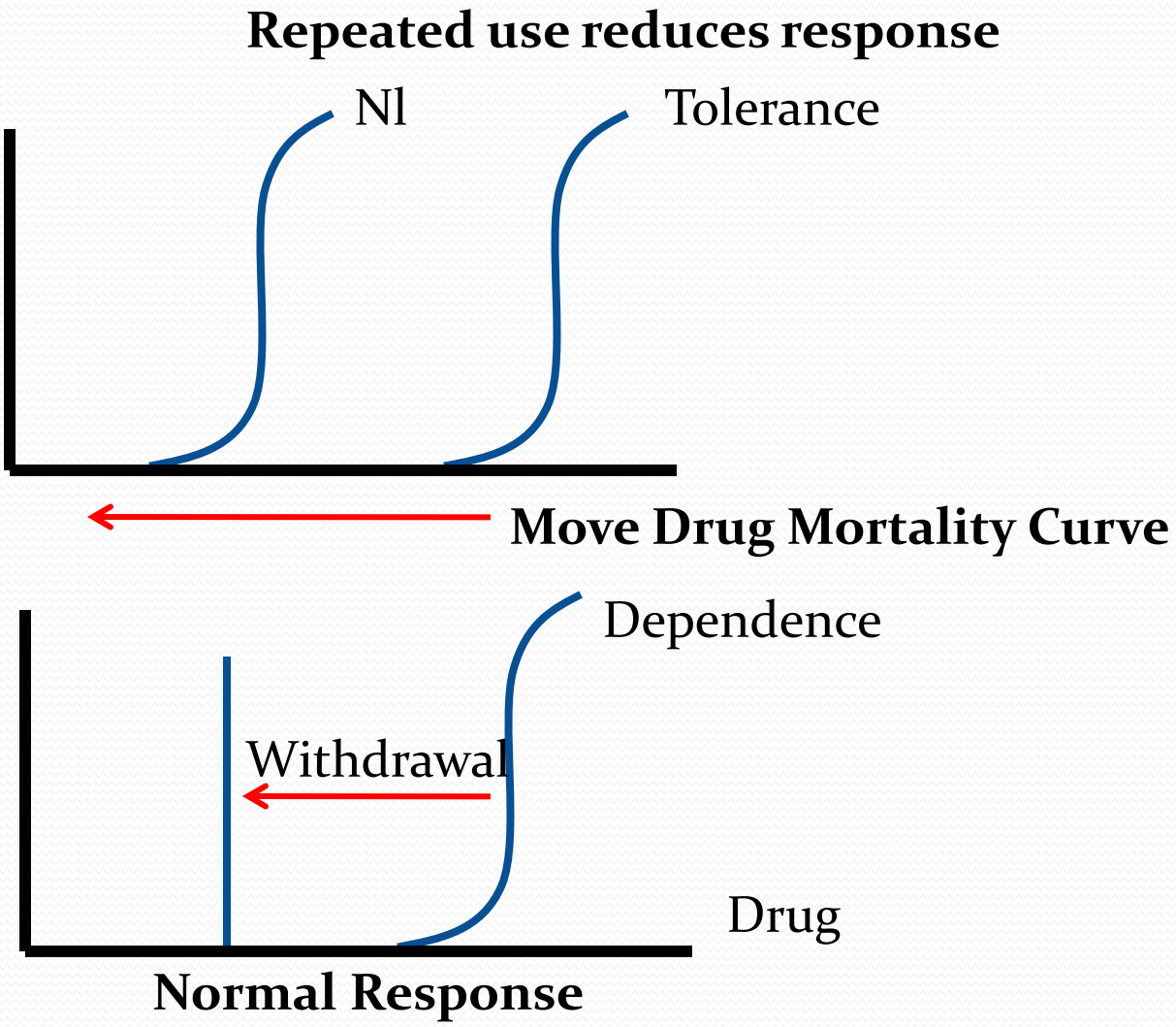


Increase PKC

Increases NMDA receptor sensitivity to EAA's

Decreases opioid responsiveness

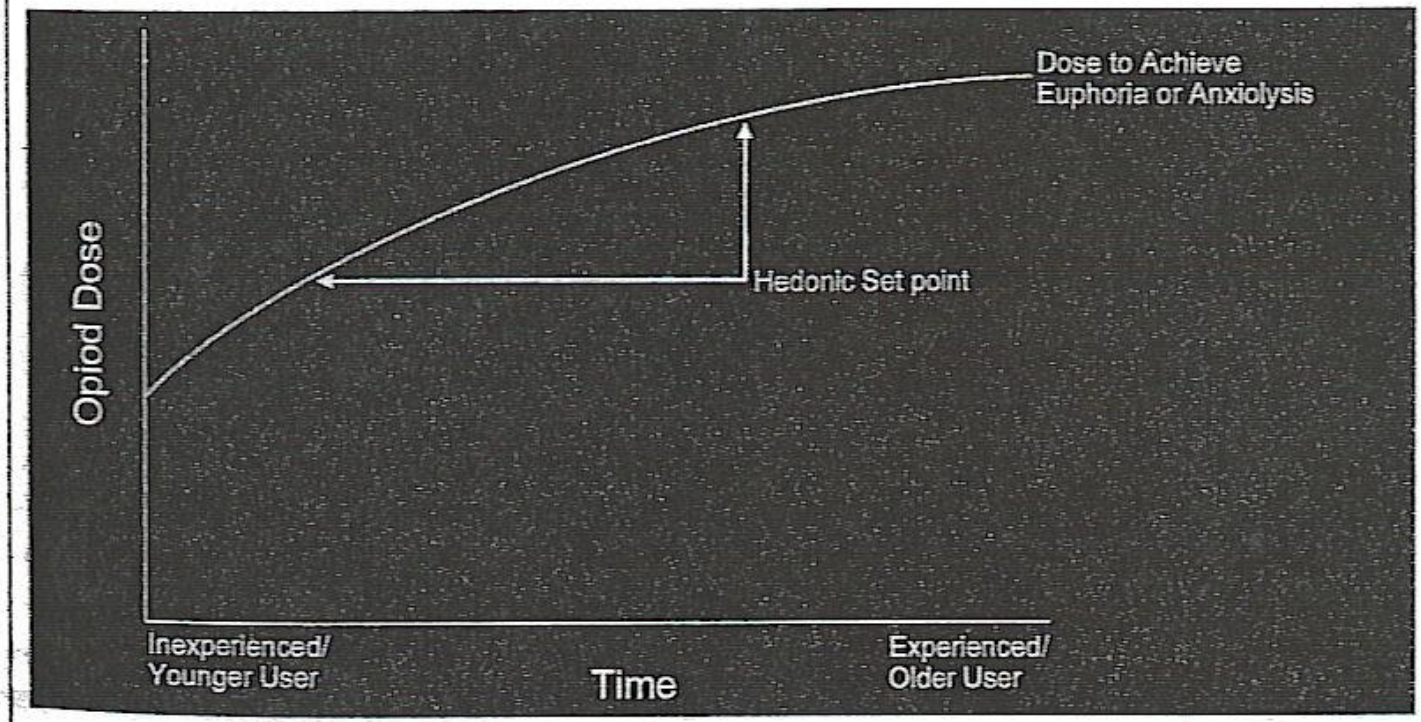
Tolerance/Dependence



CONCEPT OF TOLERANCE

L. WEBSTER M.D.

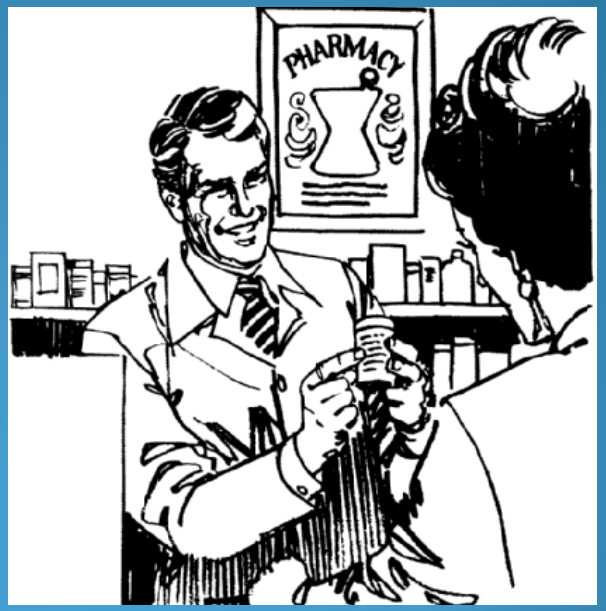
Figure II:7 The Development of Tolerance to Opioids in Humans



Over time, the dose of opioid required to produce the same euphoric or anxiolytic effect must be increased. This effect is defined as an increase in tolerance and a change in the hedonic set point.

ASSESSMENT

WELL, IS IT PAIN, OR IS IT ADDICTION?



RISK MANAGEMENT

Water, taken in moderation, cannot hurt anybody.

Mark Twain

UNLESS YOU ARE A PHYSICIAN OR PHARMACEUTICAL COMPANY….

IF WATER WAS INTRODUCED TODAY, A *BLACK BOX WARNING* WOULD BE REQUIRED…

YOU CAN DROWN

How to tell if your doctor is A SERIAL KILLER

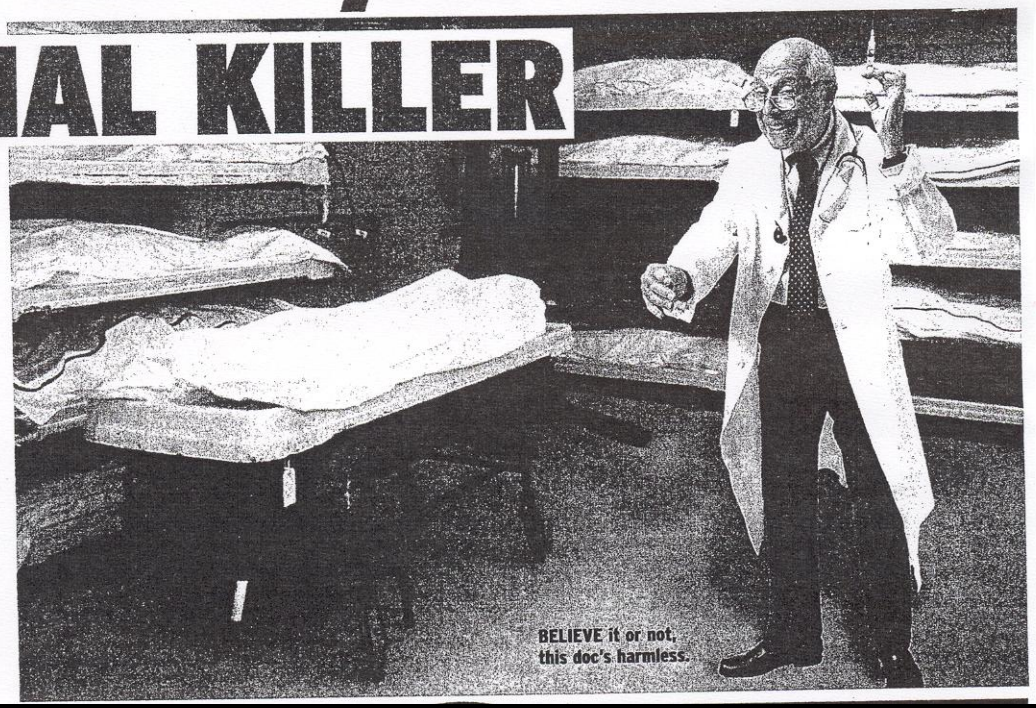
By BECKY TODD

YOUR doctor could be a serial killer and you'd never suspect a thing!

"Most physicians are dedicated to saving lives, and they do a heroic job," says Professor Gary Givens, a member of the government's Medical Crime Investigative Service (MCIS).

"But more often than the AMA would like to admit, a psychopathic monster slips through the cracks. After all, doctors are only human, and it's well documented that roughly 50 percent of the population is totally bonkers."

Givens says homicidal maniacs often get away with their crimes because they have access



BELIEVE it or not, this doc's harmless.

Opioid Abuse

4 C's

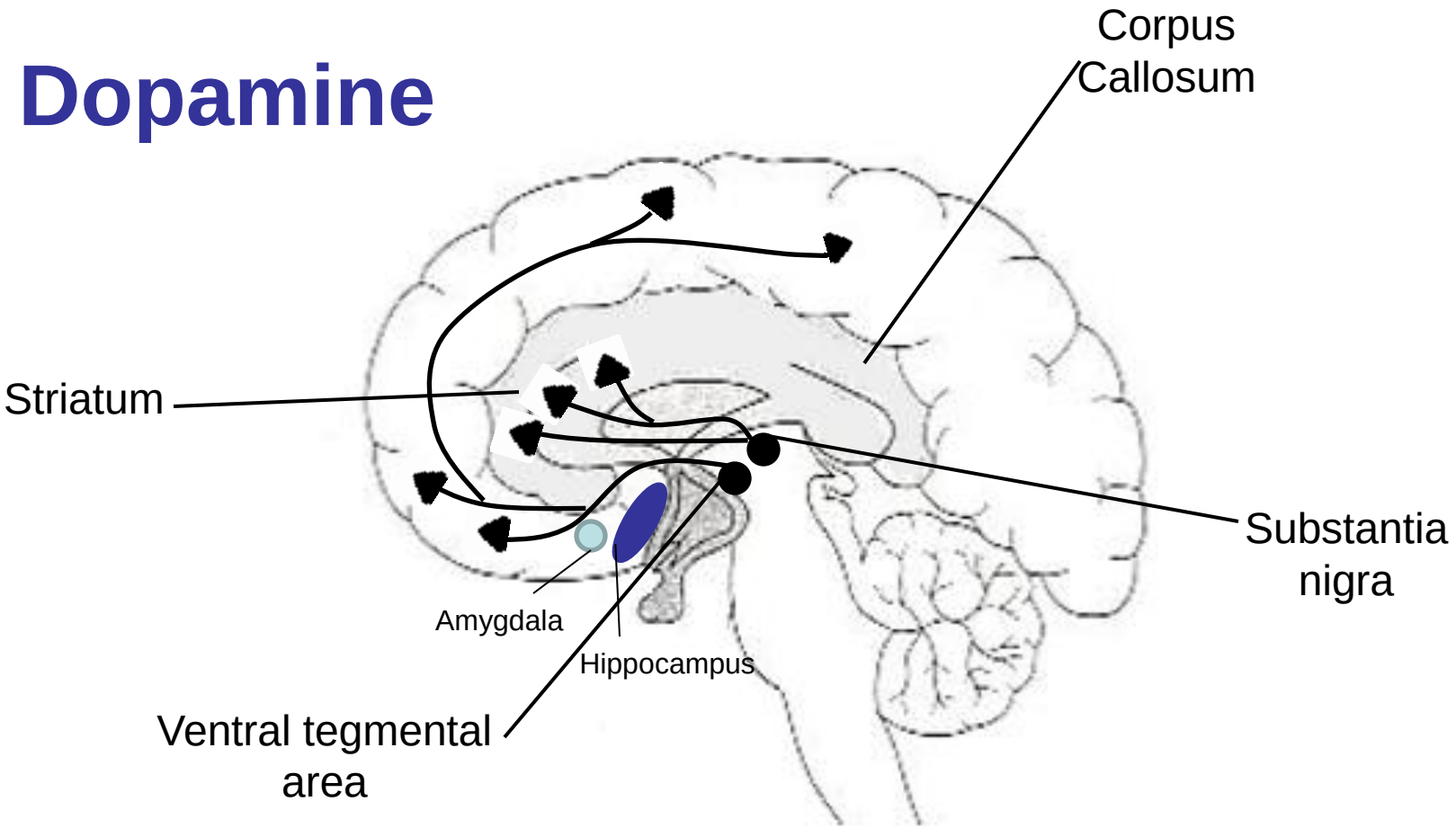
- **Addicted behaviors**
  - Impaired **c**ontrol over drug use
  - **C**ompulsive use of the drug
  - **C**ontinued use of the drug despite harm
  - **C**raving for the drug

ADDICTION

- REWARDING
- REINFORCING
- PLEASURE
- ACTIVATE BRAIN CIRCUITRY
- DEGREE OF ACTIVATION CORRELATES WITH ADDICTION TENDANCY
- REWARD NEUROTRANSMITTER IS.....

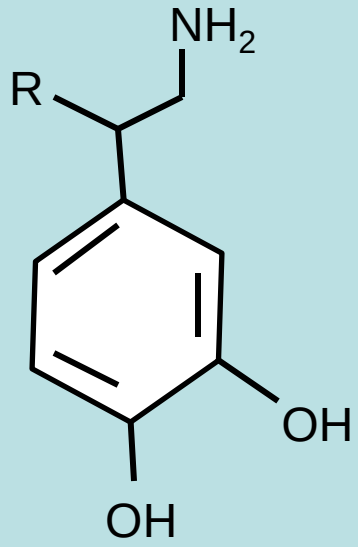
DOPAMINE (DA)

Dopamine

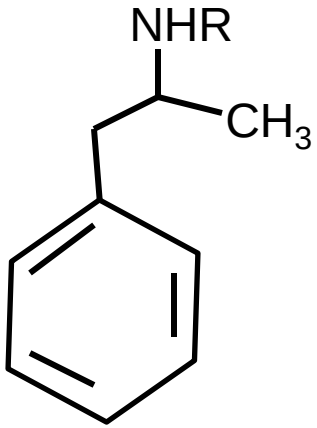


MOTHER OF ALL ADDICTIVE THINGS

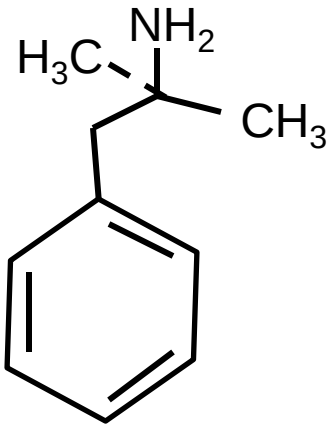
Adopted from Principles of Addiction Medicine 4th Editio



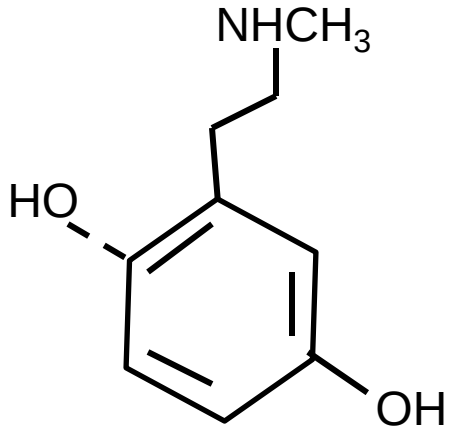
Dopamine; R=H
Norepinephrine; R=OH



Amphetamine; R=H
Methamphetamine; R=CH3
Benzphetamine; R=benzyl



Phentermine



Phenylephrine

Avoiding Opioid Abuse

- **Brain Reward Circuitry**
  - **Nucleus accumbens**
  - **Ventral tegmental area**
  - **Amygdala**
  - **Locus ceruleus**
  - **Dopamine, NE, enkephalin, GABAergic,**
  - **Dynamic outflow circuitry**

ADDICTION

NUCLEUS ACCUMBENS (NUACC) AND DOPAMINE (DA)

- DOPAMINERGIC REWARD RELATIONSHIP
- ENCODES RECIEPT OF REWARD
- DEGREE OF REWARD
- ANTICIPATION
- EXPECTANCY
- PREDICTION
- DISSAPOINTMENT

ADDICTION

- ALMOST ALL ADDICTIVE DRUGS ARE **DA** ACTIVATORS
- **DOPAMINE** AGONISTS ARE IMPORTANT- NEUROLEPTICS- BUT PROBLEMATIC
- **DOPAMINE** ANTAGONISTS DIMINISH DESIRE
- **DOPAMINE** ANTAGONISTS- CAN INCREASE DRUG INTAKE TO COMPENSATE
  - **NUCLEUS ACCUMBENS** ON **FIRE** W/DRUG DESIRED

DOPAMINE IS AN ADDICTS GASOLINE

Receptors/Genes

Decreased D_2 receptors, decreased metabolism in CG, no longer inhibit drive to use substances. **“ADDICT”**

People with increased D_2, less likely to develop Substance Abuse Disorder (SUD).

ADDICTION

D3 Receptor only found in pleasure -Reward

D2 is dysphoric when blocked

Addicts have circuitry and reward deficiency

D3 –”Block”-- Diminish drug seeking, drug triggered relapse, cue, trigger, incubation, craving

The Mechanistic Classification of Drugs of Abuse

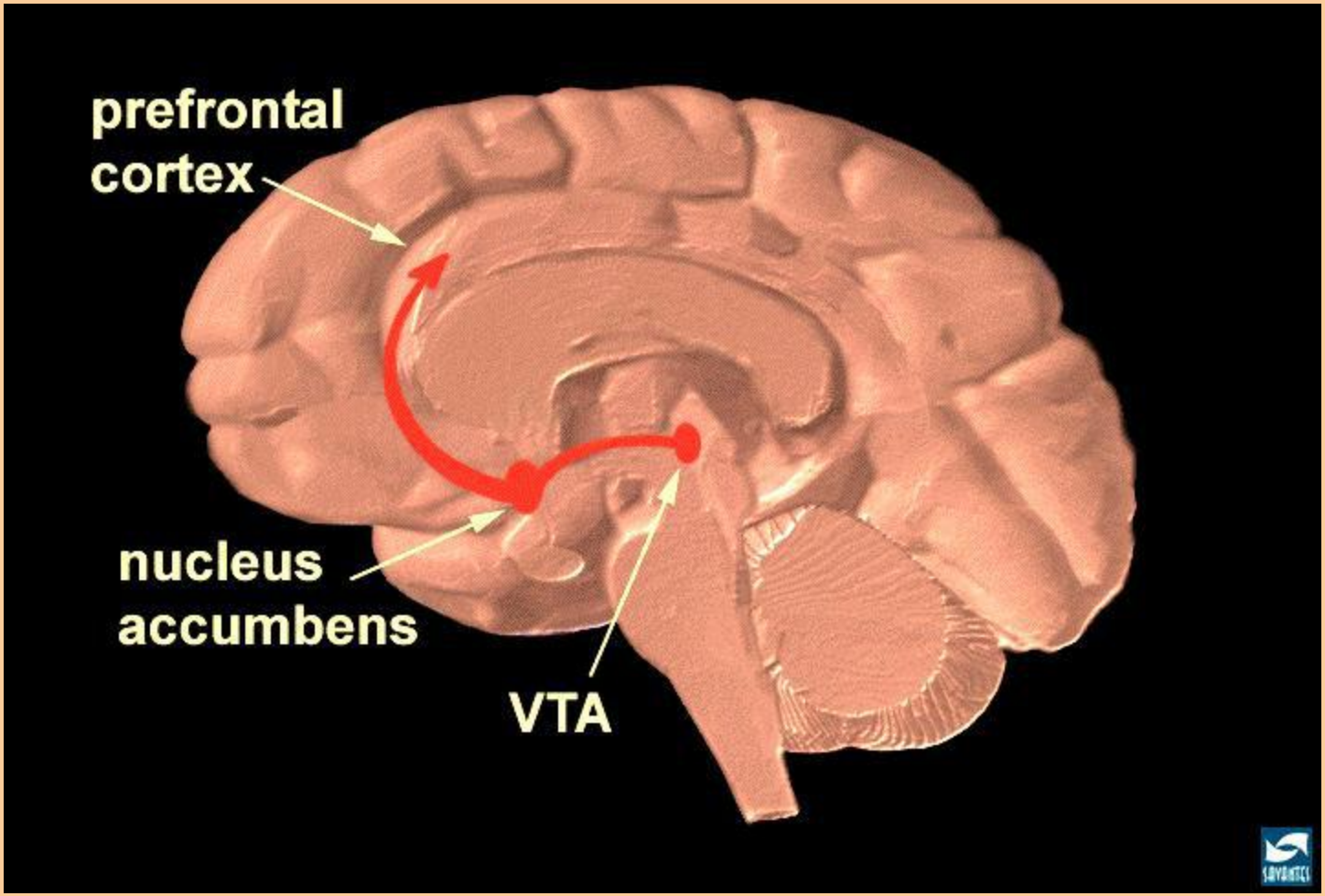
Name	Main molecular target	Pharmacology	Effect on dopamine (DA) neurons
Drugs that bind to ionotropic Receptors and ion channels			
Nicotine	nAChR	Agonist	Disinhibition
Alcohol	$GABA_AR$, $5\text{-}HT_3R$, nAChR, NMDAR, Kir3 channels	--------	Disinhibition
Benzodiazepines	$GABA_AR$	Positive modulator	Disinhibition
Phencyclidine	NMDAR	Antagonist	---------
Drugs that activate G protein-coupled receptors			
Opioids	-OR (G_{io})	Agonist	Excitation, disinhibition (?)
Cannabinoids	CB1R (G_{io})	Agonist	Excitation, disinhibition (?)
LSD, mescaline, psilocybin	$5\text{-}HT_{2A}R$ (G_q)	Partial Agonist	--------
Drugs that bind to transporters of biogenic amines			
Cocaine	DAT, SERT, NET	Inhibitor	Blocks DA uptake
Amphetamine	DAT, NET, SERT, VMAT	Reverses transport	Blocks DA uptake, synaptic depletion
Methylenedioxymethamphetamine (MDMA)	SERT>DAT, NET	Reverses transport	Blocks DA uptake, synaptic depletion

Neurobiology of Addicition

- The Reward Pathway

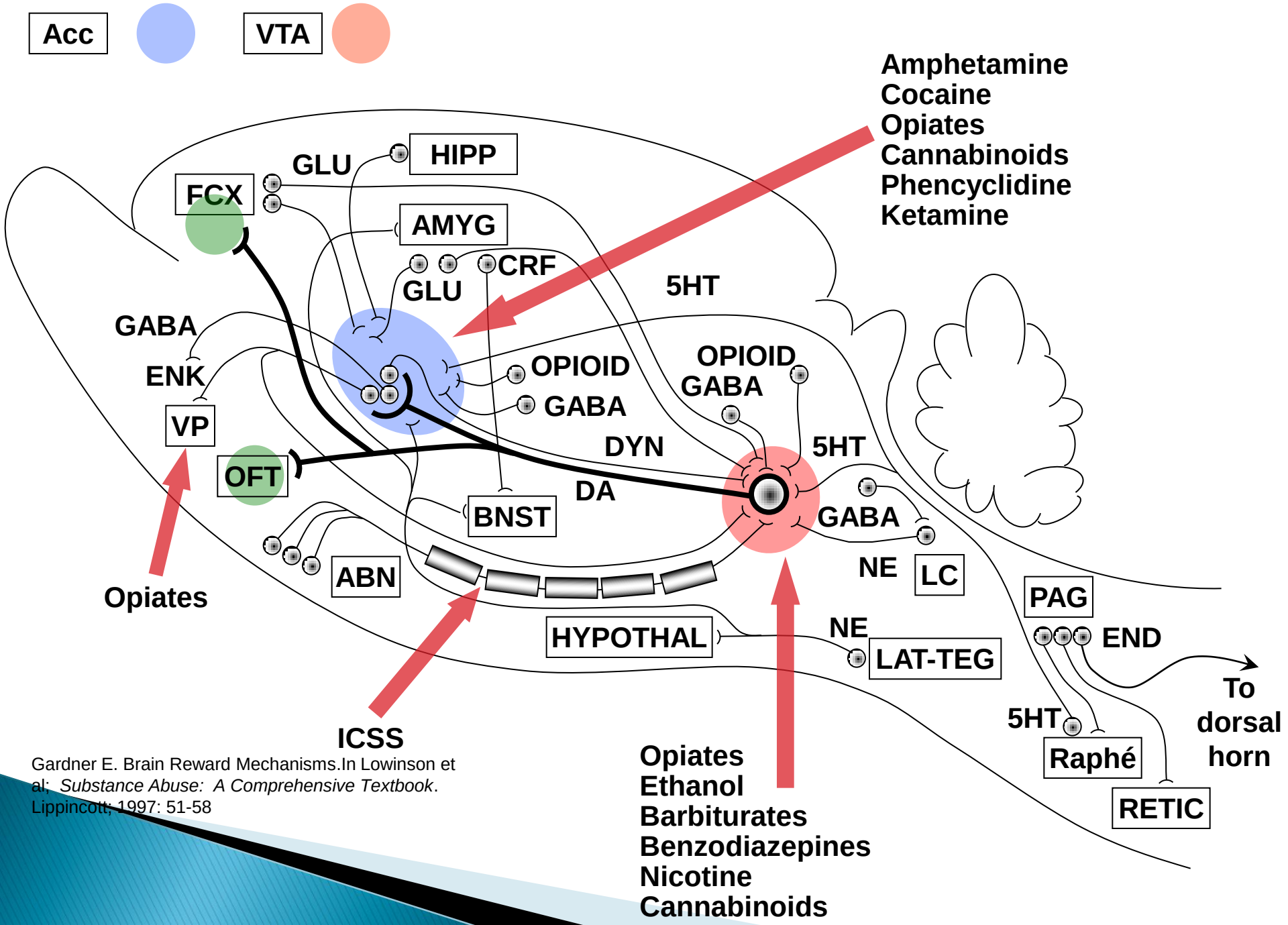
THE STUPID CENTER

"The seat of the addict's soul lies in the nucleus accumbens"
-Griffith Edwards



MEDIAL FOREBRAIN BUNDLE

- Ventral tegmental area (VTA)
- Lateral hypothalamus (LH)
- Nucleus accumbens (Nacc)
- Frontal cortex (FC)*
- Prefrontal cortex (PFC)
- Orbitofrontal cortex (OFC)



Gardner E. Brain Reward Mechanisms.In Lowinson et al; *Substance Abuse: A Comprehensive Textbook*. Lippincott; 1997: 51-58

The "Hijacked" Brain Hypothesis

- Addictive drugs act on the same brain-reward substrates and mechanisms as do natural biologically-essential rewards (e.g., food, sex, etc)
- Addictive drugs derive much of their addictive power by activating these brain-reward substrates and mechanisms more powerfully than natural biologically-essential rewards (e.g., food, sex, etc)

- Experimental evidence for this

Opioids

Nucleus Accumbens

The brain’s reward center

Mediates motivation to behavior associated incentive

Dopamine transmission

Opioid

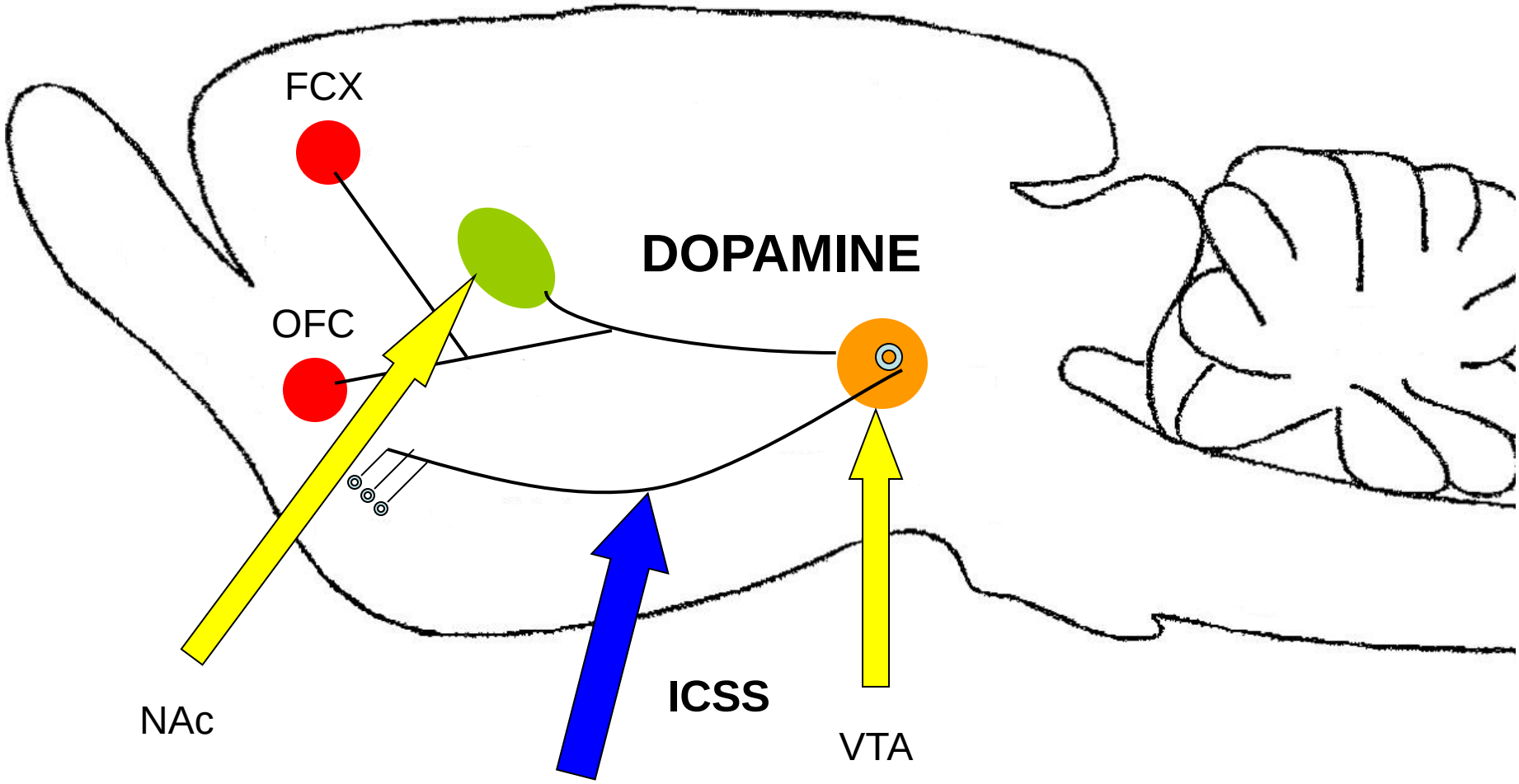
Anterior Cingulate Gyrus = Anticipated reward

Amygdala= Emotions

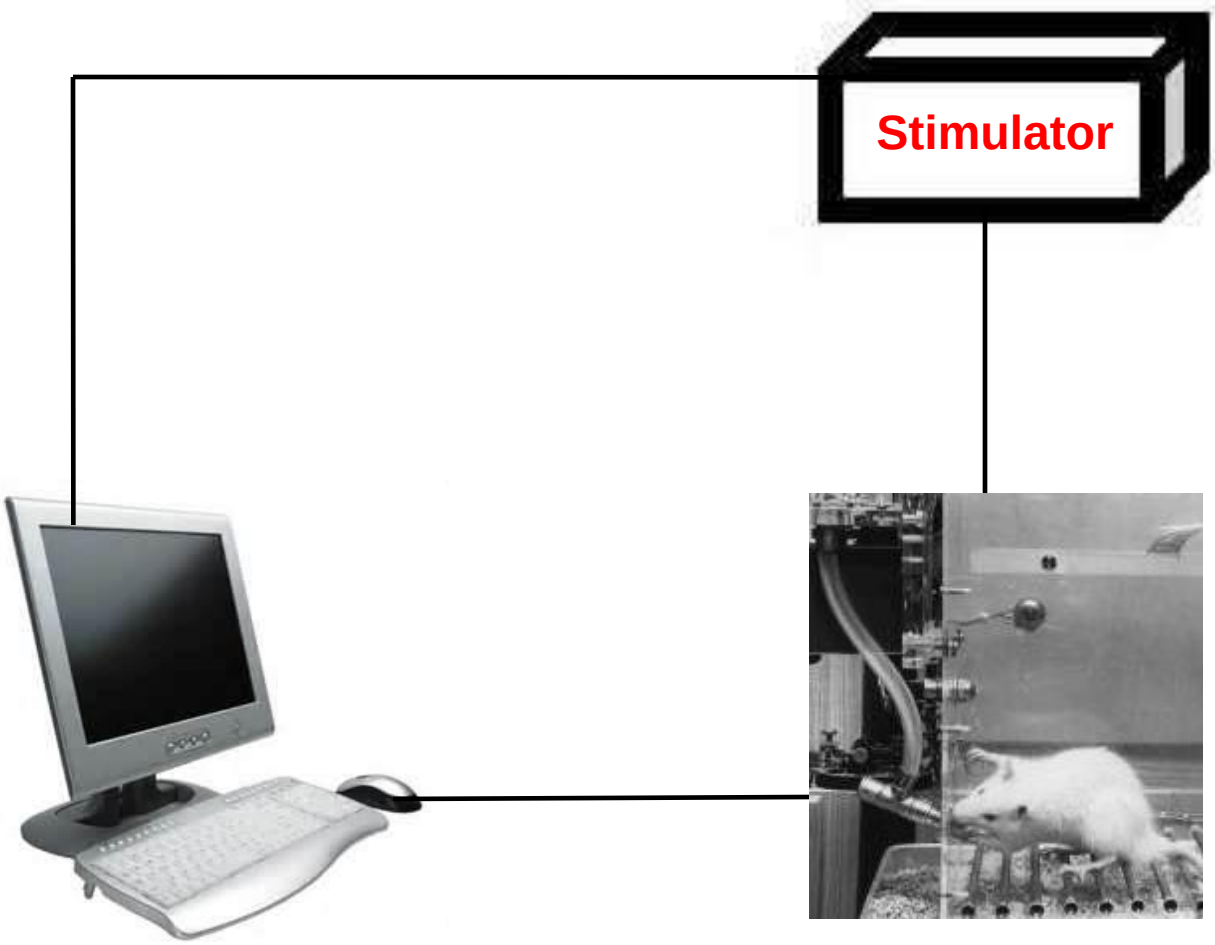
Nucleus Accumbens= Motivation

Progressive Ratio Self-Administration

- Designed to progressively increase the workload on the experimental animal i.e. first push yields injection, then requires 2 pushes for injection, then 4, 8, 16, 32
- Break point is defined as the ratio when the animal will abruptly STOP pushing to get injection



Electrode Stimulation


Stimulator

Reward Pathway

Most drugs of abuse have a relationship to the limbic system

Addictions alter neurochemistry in the limbic system

Drug seeking is driven by **emotion, not logic**

Progression of the Disease of Addiction

- Recreational occasional use
- Recreational steady use
- Reward-driven use → Habit-driven use
  - No longer rewarding or only with first use of day
  - Transition from ventral striatum to dorsal striatum
- Habit-driven use → Compulsive use
- Denial, the "Crash," "Bottoming Out"
- Treatment and achievement of abstinence
- Persistent vulnerability to craving and relapse

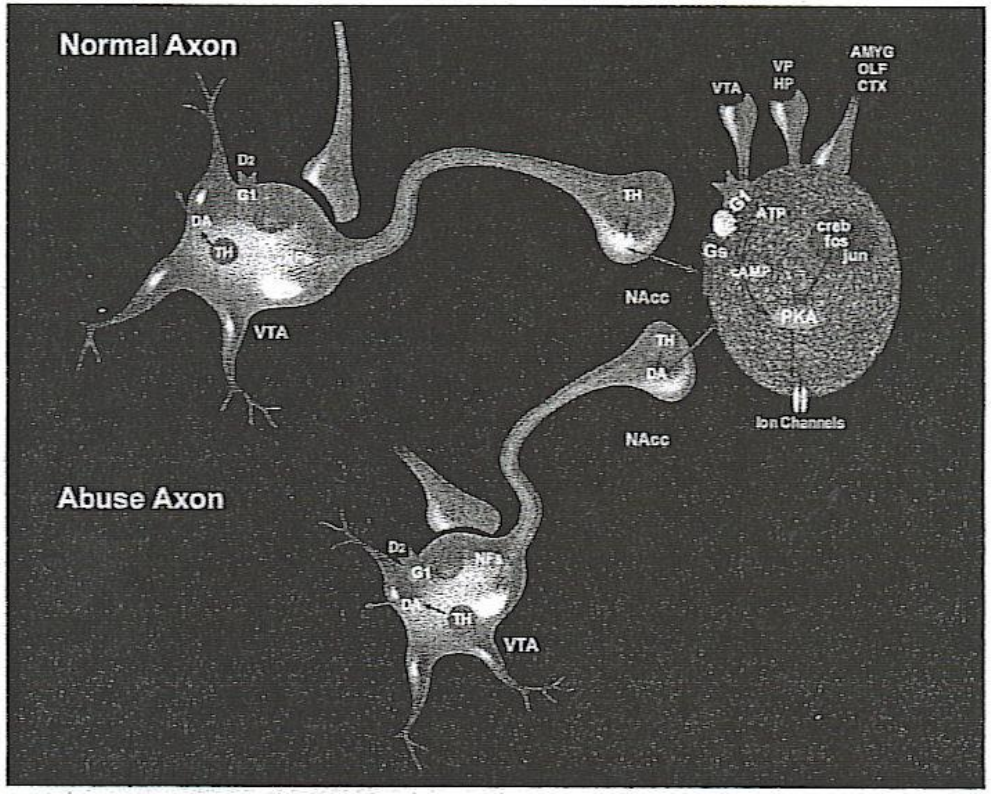
EXPECT A RELAPSE

DEPRESSION, PAIN, AND THE SICK NEURON!

SICK NEURON

Figure II:6

Axons of Normal and Opioid Abuser States



The projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) changes over time after continued opioid exposure or in patients who are genetically predisposed to the disease of addiction. The left VTA neuron shows a robust connection to the NAcc neuron, and the stimulus of the NAcc has normal structure and function. The right VTA neuron illustrates the effects of long-term opioid exposure or opioid addiction in an individual who is genetically vulnerable to the disease of addiction. The connection to the NAcc on the right shows less structure and function than that of a healthy VTA neuron. This in turn affects the function of the NAcc.

Concept of Neurodegeneration

Neurodegeneration Disorders

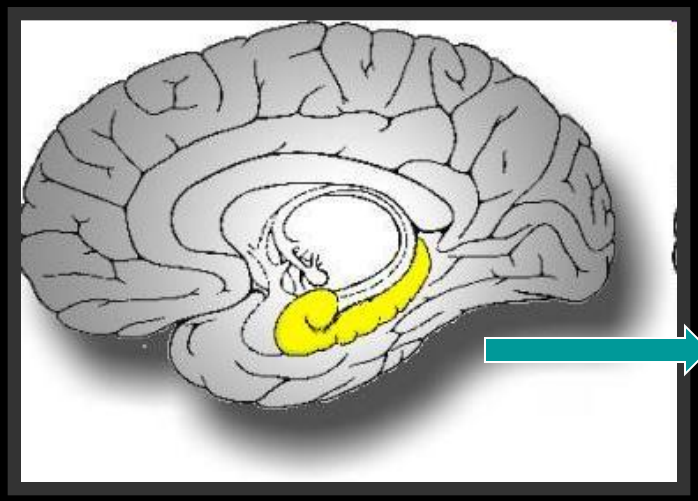
Atrophy and loss of neurons and glial cells

Treatment Resistant Depression (TRD)

Mood, Receptors, Depression

Medieval	Depression and Humors (Black Bile)
17th Century	Duelism – Mind, body, social environment
Early 20th Century	Sigmund Freud – Brain would describe mental illness
Current	Receptor technology

BDNF



Hippocampus

Connections to amygdala and prefrontal cortex

Learning and Memory

Cognitive Emotion

BDNF supports health of brain cells and promote new Neurons

NEUROGENESIS

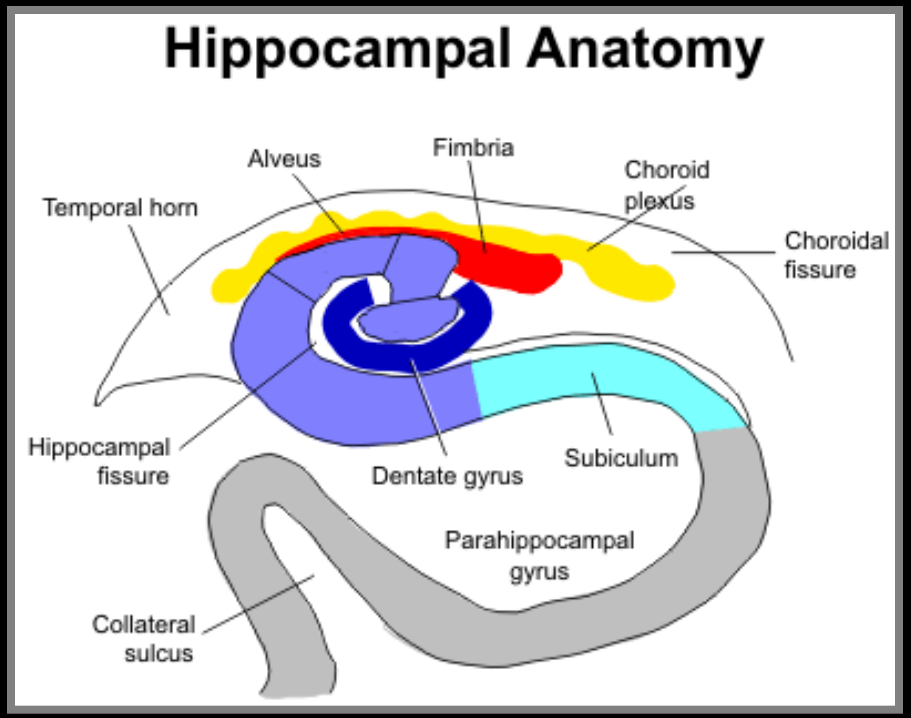
BRAIN DERIVED NEUROTROPHIC FACTOR

Stress and Depression

Neurogensis —— Hippocampus

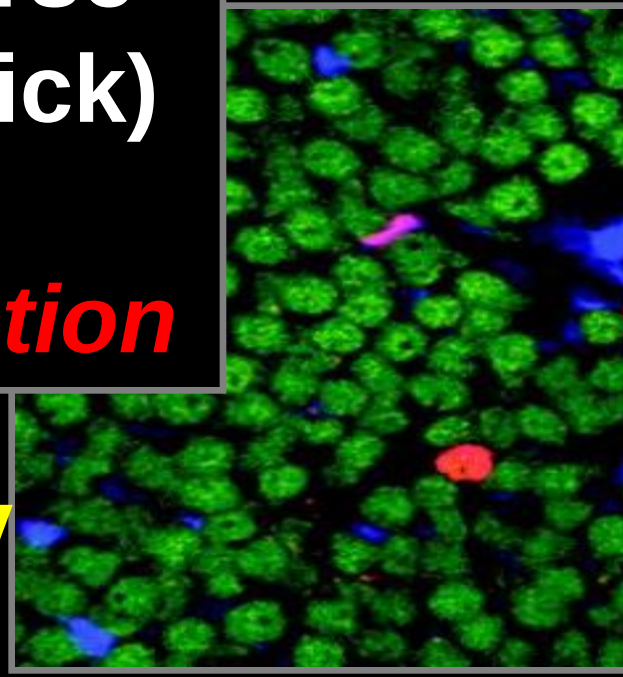
Rats, Monkeys, Humans

Neurons continue to be born in dentate gyrus of hippocampus



Neurogensis Happens
(only in select areas)

Up-regulation of neurogenesis with antidepressants reverse atrophy of neurons (sick) that are present in *depression*, and *addiction*



BDNF protein, encoded by the BDNF gene

Stress and Depression

Increased expression of **BDNF** up regulate connectivity in Hippocampus

Positive Metaplasticity

STEM CELLS

Hippocampus

Basal Forebrain

Addicts

BDNF

Cortex

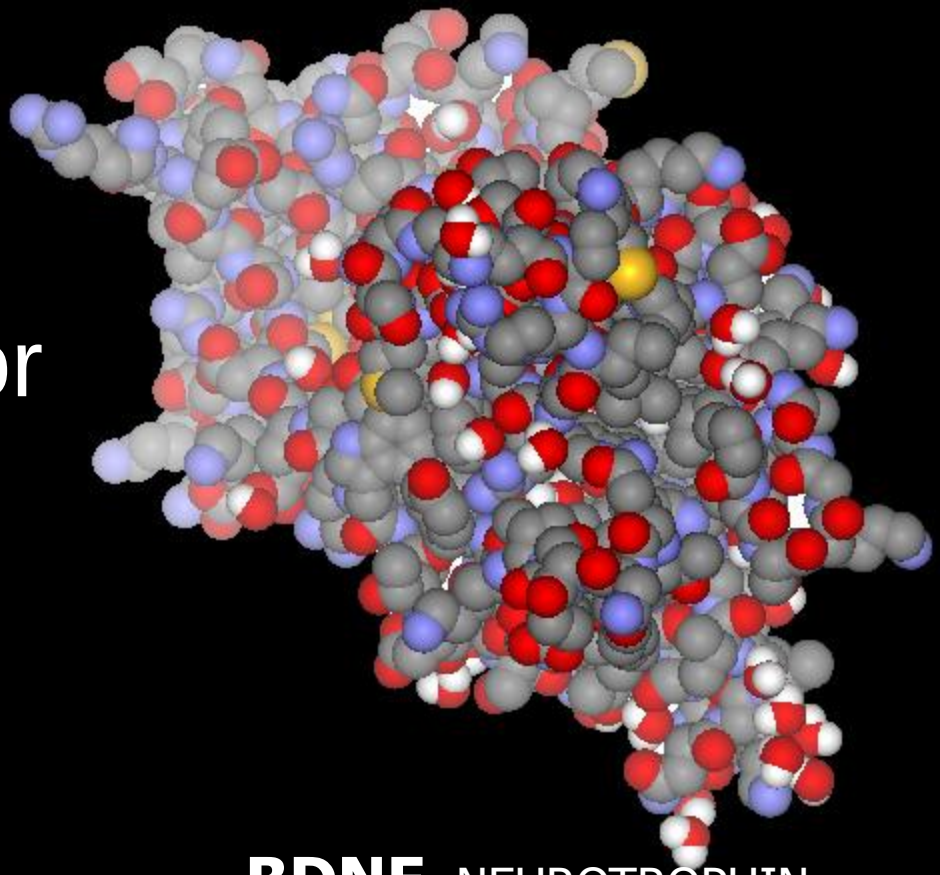
NEUROGENESIS

Loss of BDNF contributes to depression

Stress is a precursor to mood disorders

Stress *decreases*
BDNF
Environment
Genetic

BDNF



BDNF- NEUROTROPHIN FAMILY
NGF
SUPPORTS NEURON **SURVIVAL** AND **SYNAPSES**

Stress and Depression

Increased *Glucocorticoids*

Down regulate Hippocampal synaptic activity

Negative Metaplasticity

Increase pain, cognition, dementia, amyloid, obesity epilepsy

MEMORY DISTURBANCES,POOR LEARNING

Stress and Depression

Glucocorticoids and steroids suppress Dentate Gyrus neurogenesis – Gould

5-HT1a - Serotonin/receptors high concentration in Dentate Gyrus of Hippocampus

Exercise stimulates neurogenesis

Stress and Depression

BDNF mRNA

Up regulated in hippocampus with physical activity and antidepressants -**GOOD**

Stress = Depression

Neuronal atrophy – cellular level

Decreased BDNF and Neurogenesis (Hippocampus)

BAD

BDNF

Blocking NMDA receptor stops eukaryotic elongation factor 2

↓ (eEF2) Kinase phosphorylation (inactivated) → Rapid increase in ***BDNF***

↑ Translation

Inhibit eEF2 kinase, get rapid antidepressant effect

eEF2 kinase suppresses BDNF production

Background Noise and Depression

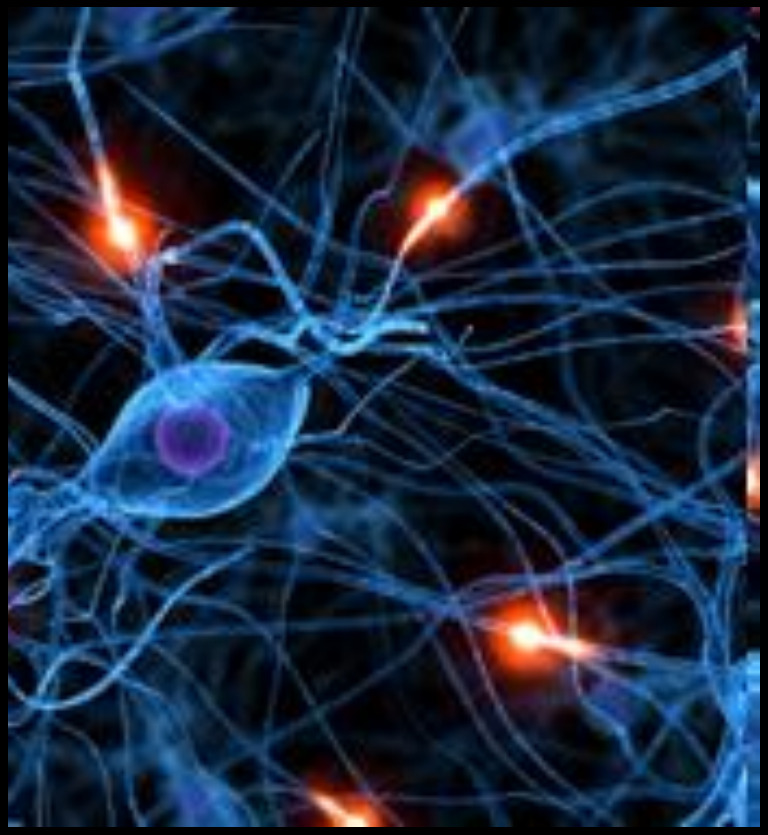
BDNF

eEF2 effect background activity

Spontaneous nerve firing is important

ECT

strong role in plasticity

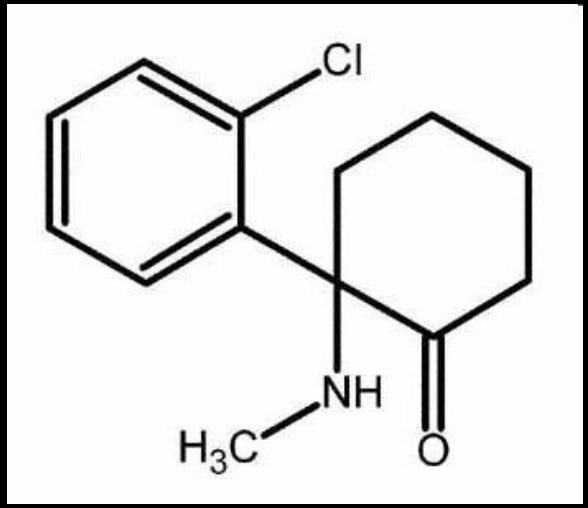


Ketamine

Ketamine
NMDA receptor antagonist

Noncompetitive
Decreases effectiveness of neurotransmitter

Glutamate
Binds opioid receptors

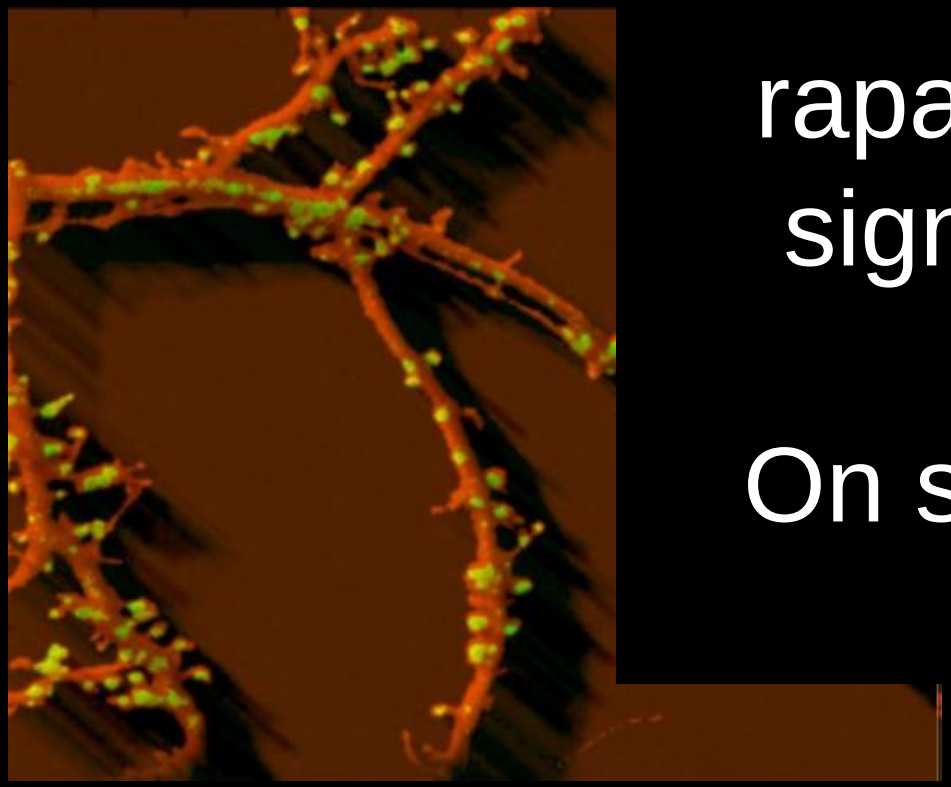


Ketamine

Does not block NMDA activity

Does block background noise
link between
spontaneous noise and depression

Ketamine



1 dose of Ketamine activates mammilian target of rapamycin (mTOR) signaling pathway

On switch to mTOR catabolism

Mood, Receptors, Depression

SYNAPTOGENESIS

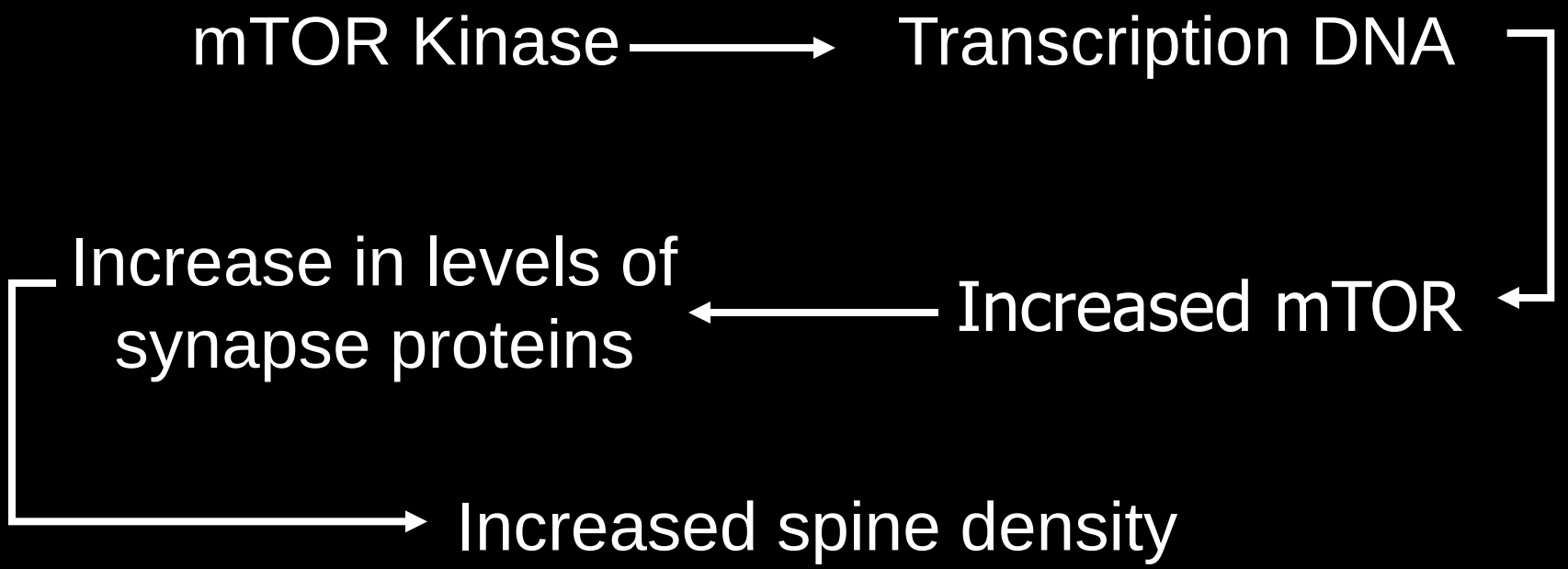
Depression results from brain's failure to grow new neurons at key regions

Receptor regulated

Ketamine/Synaptogenesis

Ketamine activates mTOR, a ubiquitous protein kinase
involved in protein synthesis and synaptic plasticity

Synaptogenesis



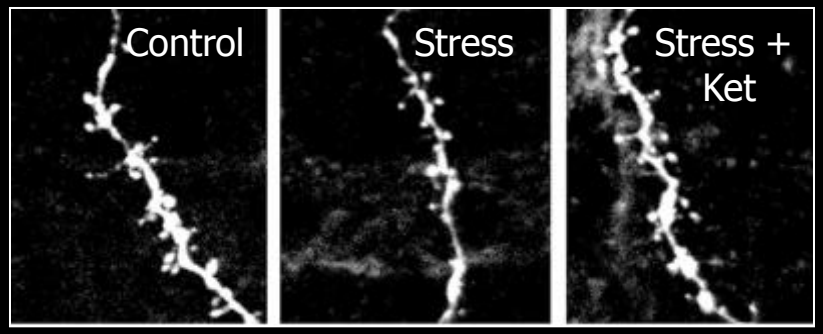
Synapses and spine morphology necessary for learning and memory

Ketamine

Depression occurs when a cell is sick
--- poor dendritic spine formation

Ketamine induces spine formation in hours

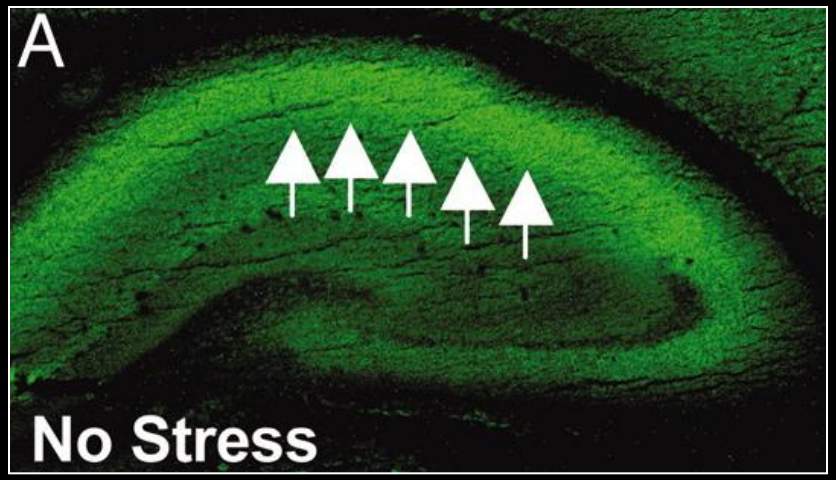
Aberrant **TOR** activity also seen in
Diabetes Mellitus, obesity, heart disease,
cancer, pain and addiction

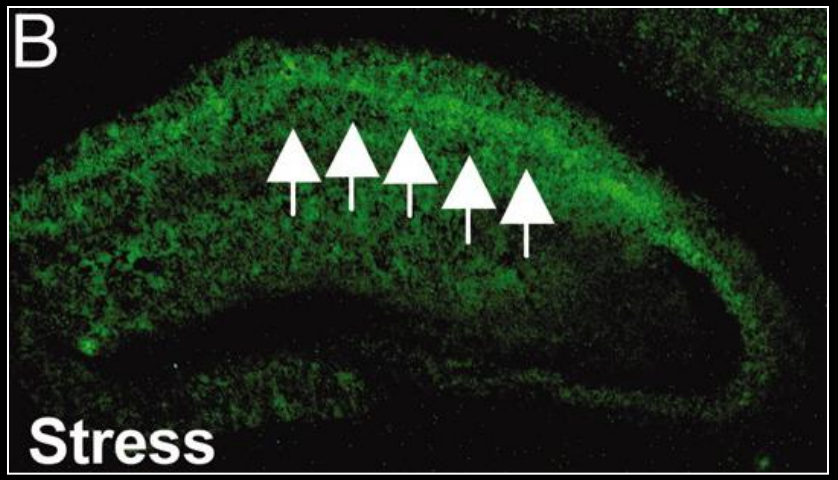


Synaptogenesis

Proteins associated with synapses like Glutamate receptors (**NMDA**) and synapsin 1 are reduced during stress --- sick

Ketamine increases them



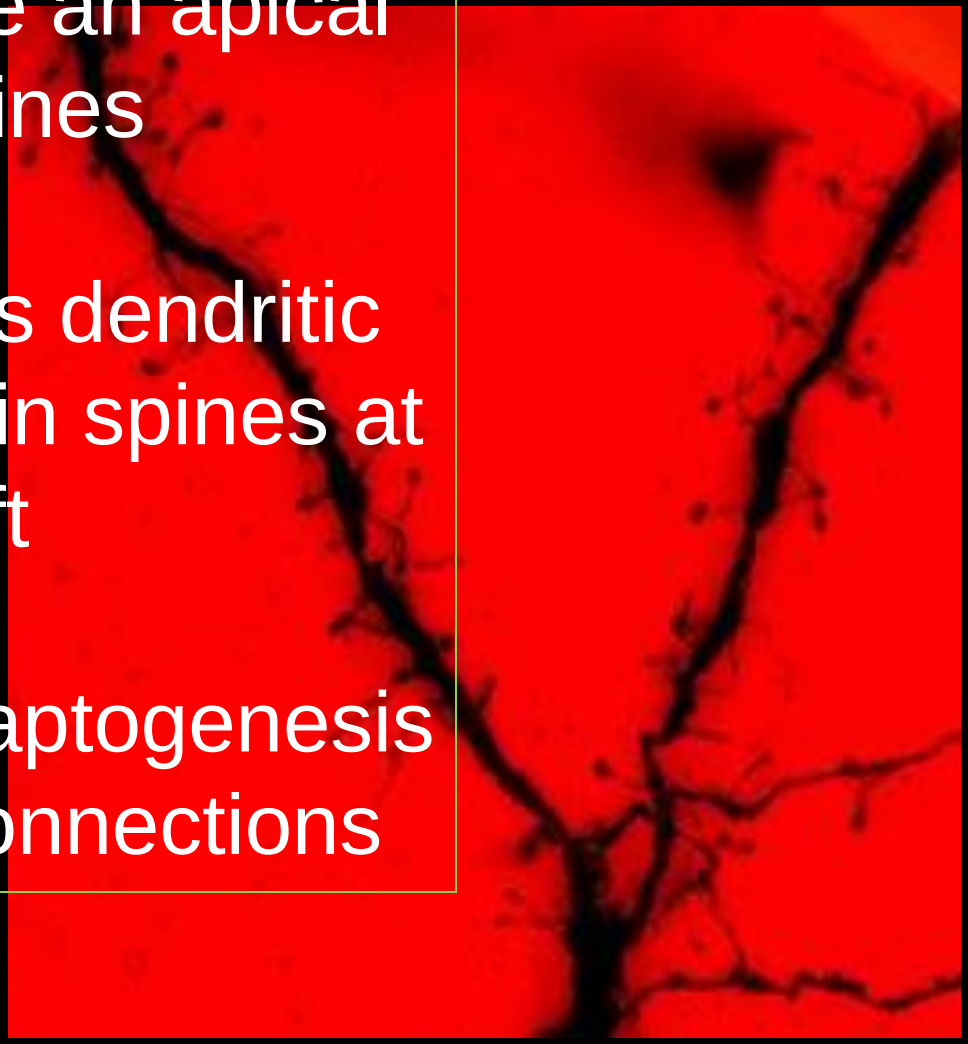


Synaptogenesis

Neurons in PFC create an apical tuft, creating spines

Depression – There is dendritic atrophy, and decrease in spines at the apical tuft

Ketamine induces synaptogenesis ---restores synapse connections

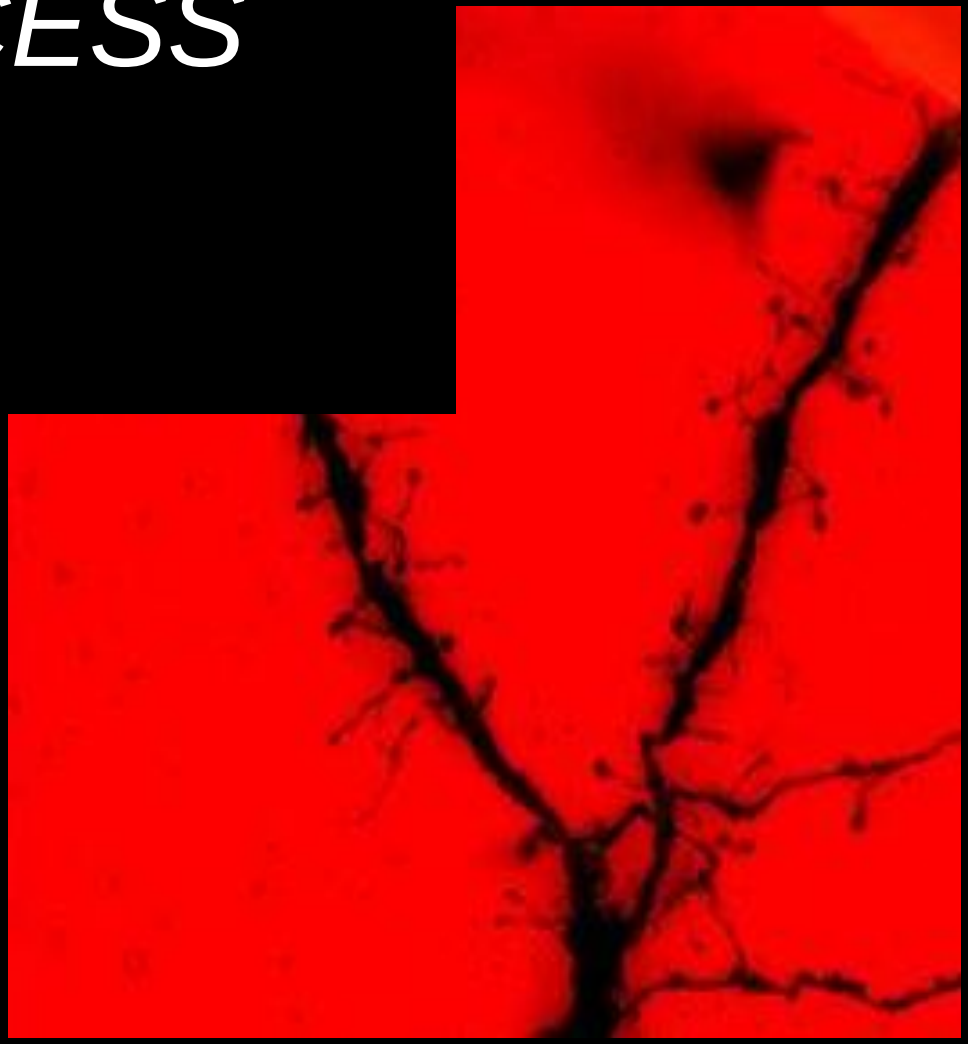


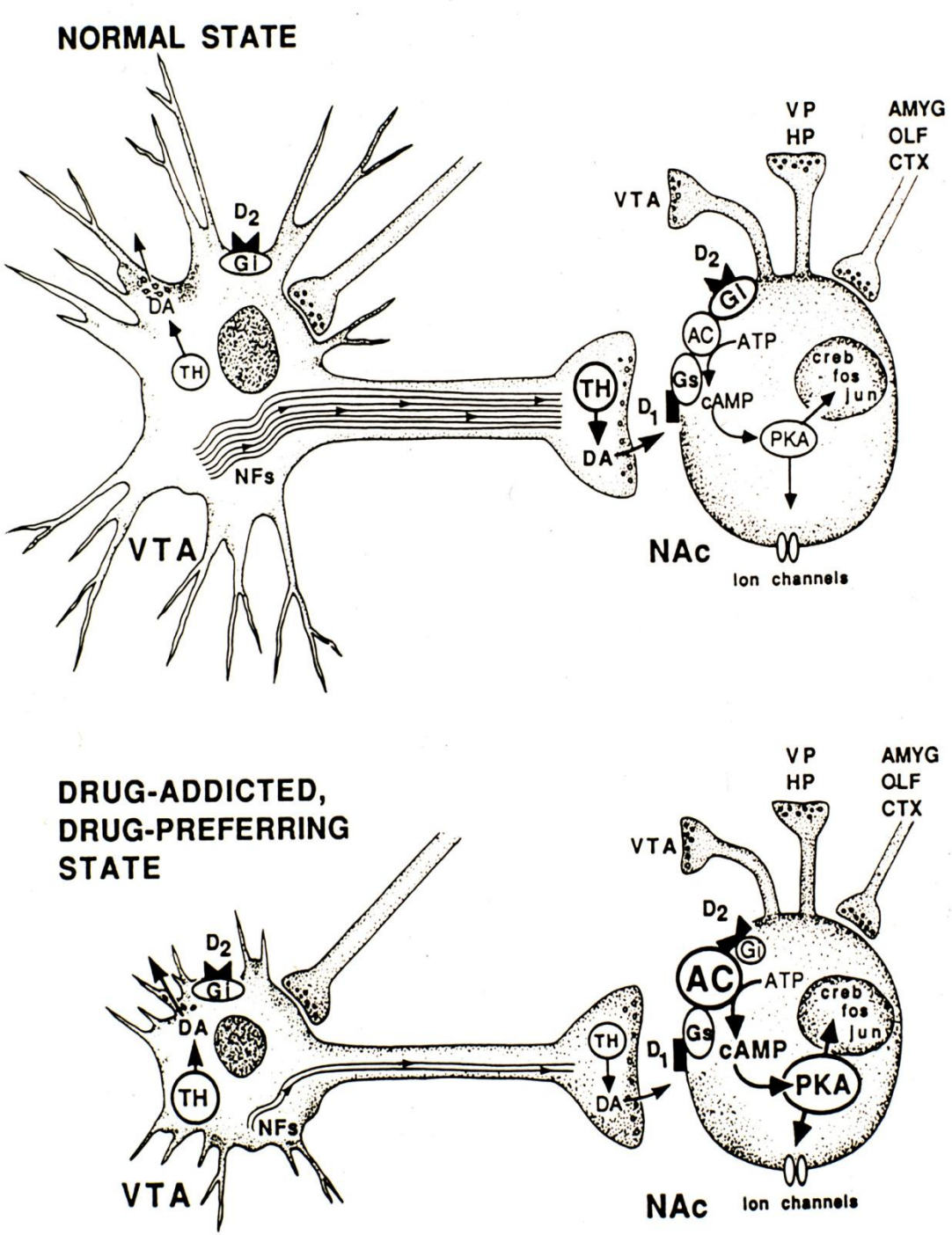
Synaptogenesis

SAME PROCESS

PAIN

ADDICTION




NORMAL STATE
VP
HP
AMYG
OLF
CTX
VTA
D2
Gi
DA
TH
AC
ATP
Gs
cAMP
creb
fos
jun
D1
PKA
NFs
VTA
NAc
Ion channels
DRUG-ADDICTED,
DRUG-PREFERRING
STATE

SICK

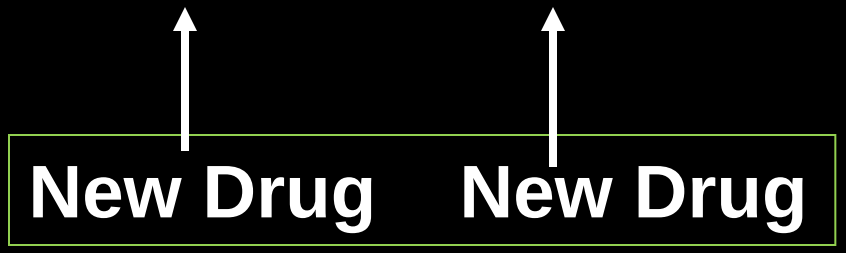
Ketamine

Low dose --- distortion space/time, occasional hallucination, mildly dissociative

0.1-0.5 mg/kg

High dose --- severe distortion disconnect

Rapid Jump → **Time**



Benzodiazepine- GABA Ketamine
Dopamine- Stimulants
Serotonin- Hallucinogen
Excitatory- Glutamate NMDA
Neurotransmitter- indirect antagonist

Ketamine

Works where PCP does

ECT and Ketamine reset background noise/activity

Protein eEF2 that activate NMDA effect on spontaneous activity

New Drugs

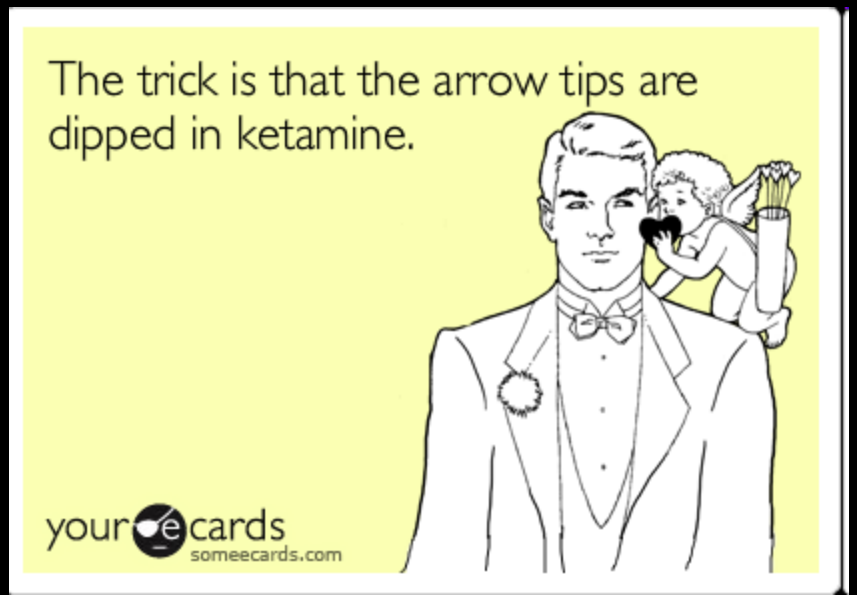
Ketamine Dextromethorphan

2/3 patients who do not respond to other antidepressants improved hours after *Ketamine* exposure

40% - Antidepressants do not work

TRD – treatment resistant depression

Ketamine



Duman -2011 Neurotrophic Theory of Depression

Brain derived neurotrophic factor (BNDF) 1995 – Antidepressant Effect

Neuronal Growth Factors

↓

Depression → Serotonin → cAMP → Signal Transduction

↓

cAMP activation → cAMP dependant protein kinase (Regulator) → Regulated cAMP response to element bringing protein (CREB)

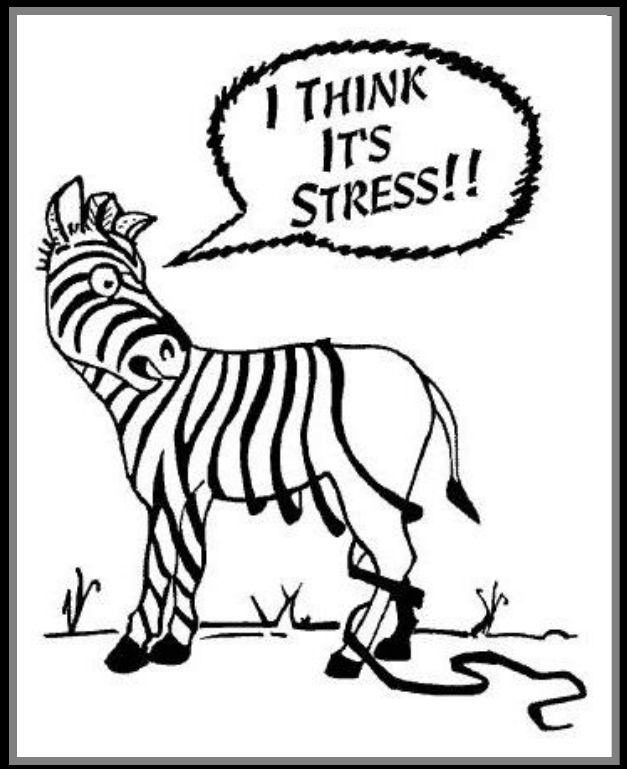
↓

Increased CREB mRNA and protein in hippocampus (just like antidepressants) → Antidepressant effect

A link between antidepressants and cAMP pathway (CREB) regulating genes in the hippocampus producing antidepressant effect

Stress and Depression

Ketamine and antidepressant medications restore cell density and regulate higher order synaptic plasticity in hippocampus



WHERE ARE WE GOING AND WHAT'S NEW

- WHAT WE ARE
- TERMINOLOGY
- ADDICTION OR PAIN
- EPRESSION AND PAIN- SAME THING, KINDA
- *BIOLOGICS, AND OTHER DRUG THOUGHTS*
- NEW IS AS NEW MIGHT BE

Biologics

DMARD	Disease modifying anti-rheumatic drugs
TNF	Block Embrel, Humira, Simponi, Cimzia
BRM	Biologic response modifiers stimulate or restore system

THE OPIOID SPARING DRUGS

Biologics

Unlike chemical medicine, biologics are large and complex

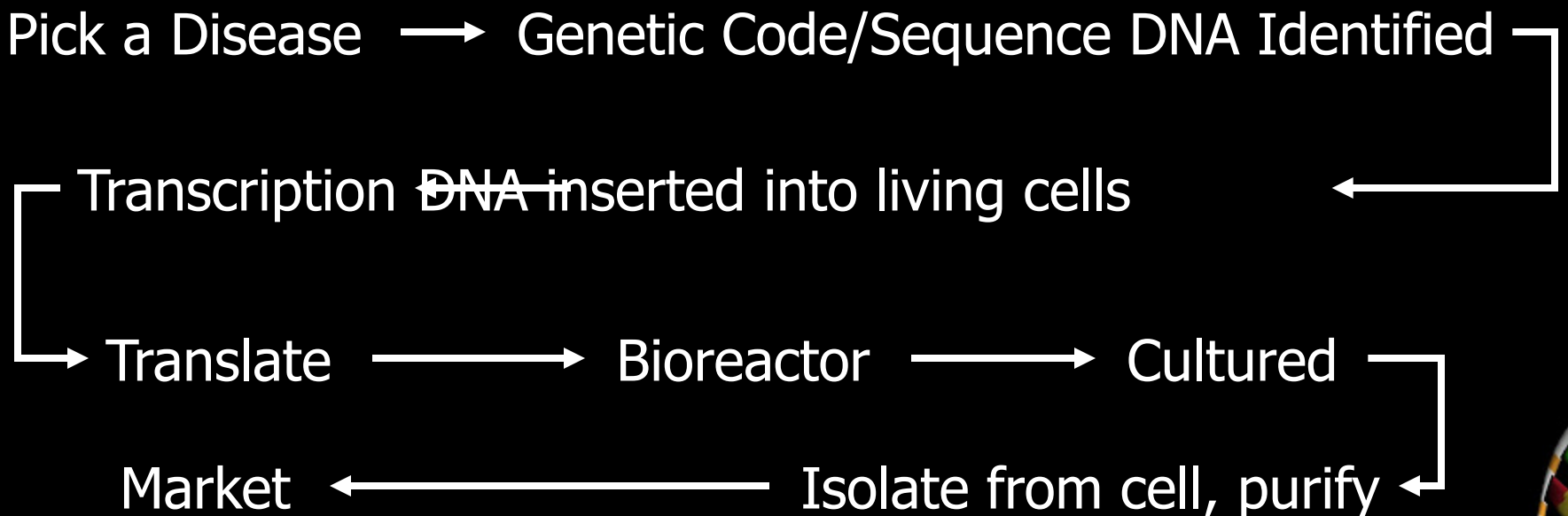
Can be unstable

May produce an immune response

Biologics

Similar to complex body proteins

Derived from recombinant DNA



Biologics

DMARD – Disease modifying anti-rheumatic drug
NOT anti-inflammatory.

They modify the immune system.

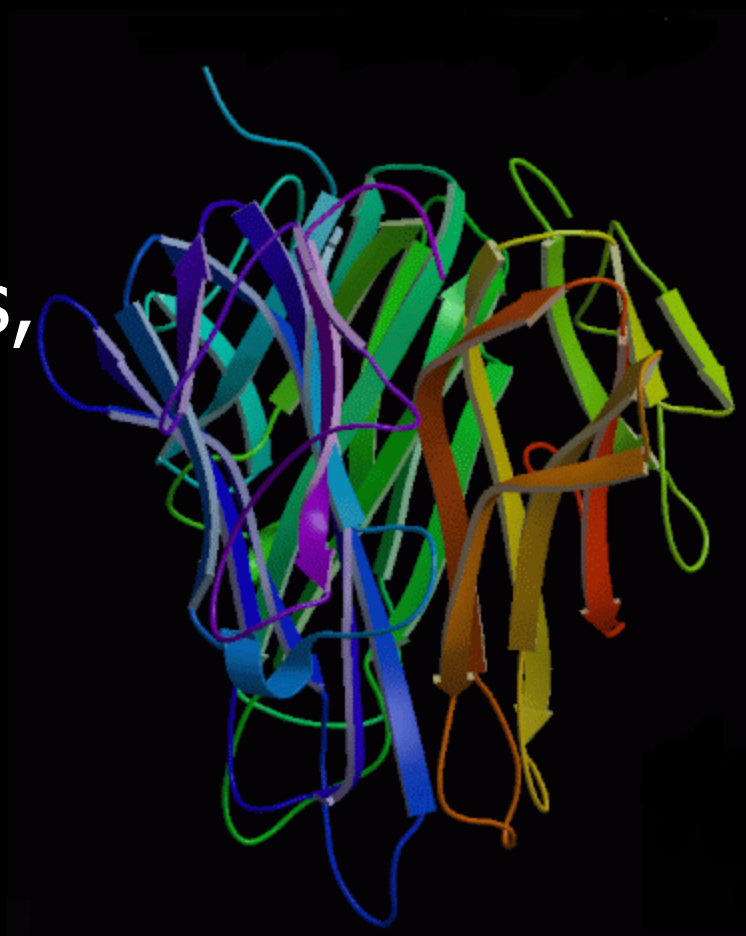
Plaquenil, Gold Penicillamine, Methotrexate, Sulfasalazine, Minocin, Cytoxan

Biologics/Risk

Tumor Necrosis Factor --- α TNF α

DMARD Infection – 4%

Biologic – 7% at 3 years, risk is at baseline



Biologics

TNF – α **- TNF – α and IL-1 are macrophage derived cytokines Associated with inflammation**

TNF blockers bind to TNF – α, now Inactive, interfering with inflammatory cascade (Beware of TB/infections)

Biologics

Actemra (Tocilizumab) – Blocks IL-6

(Cytokine) – IL-6 is inflammatory

Orencia (Abatacept) – Depresses T Cells

Rituxan (Rituximab) – Depletes B Cells

WHERE ARE WE GOING AND WHAT'S NEW

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Biologics

Platelet Rich Plasma Regeneration

Fraction plasma – contains multiple growth factors

Stimulates

- Cell prolifertion
- Proteoglycans
- Collagen

A New Disc

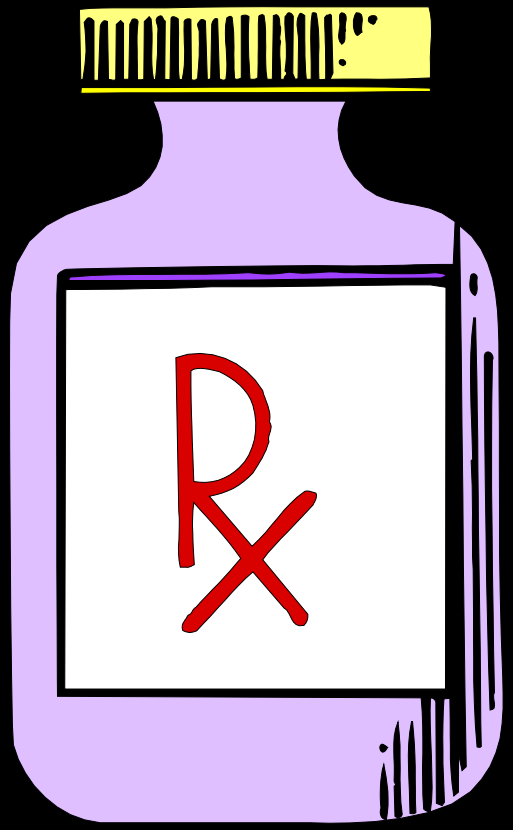
Platelet Rich Plasma

Gelatin hydrogel microspheres

Mobilize growth factor β1

Intervertebral disc cell proliferation and proteoglycan synthesis

Benzodiazepines
AKA Valium®-like drugs



Wildly overprescribed-

#1 class in U.S.

AN UNAPPRECIATED KILLER

Benzodiazepines

Serotonin is inhibited

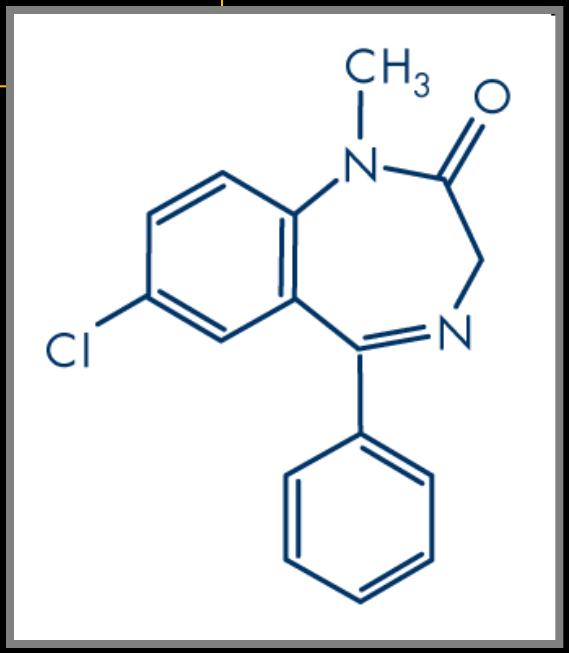
- Pain threshold reduced
- Further decays natural sleep
- Further promotes depression

Dopamine release inhibited

Stage 4 sleep impaired

Benzodiazepine

- Potentiates activity if $GABA_A$
- Opens chloride channel
- Membrane hyperpolarizes
- Inhibits cellular excitation
- Similar effect ETOH



BARBITURATE

NSAIDS

Cox I

Number of Deaths in the United States

Hodgkins	1,400
Cervical cancer	4,400
Multiple myeloma	10,500
AIDS	16,500
Leukemia	20,000
Drunk drivers	23,000

Cox I

NSAID Toxicity 16,500

As many people die from NSAID toxicity as AIDS

15th most common cause of death in the United States

"Silent epidemic"

Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs

NEJM 340 No.24

U.S. Mortality Data 1997

MOBIC

GET LUCKY

Singh et al. study

- ***4 fold increase CV risk for patients on Mobic***

<60 days versus >60 days

Graham et al. (retrospective) study

- Analyzed data from California's Medicaid program of over 15,000 heart attack patients
- ***37% increase heart attack risk w/ Mobic***
- 32% increase w/ Vioxx
- 0.9% increase w/ Celebrex

Is CV risk related to pro/anti thrombotic mediation?

- **Thromboxane A_2—*COX I***
  - Pro-thrombotic
- **Prostaglandin I_2 (prostacyclin)—*COX II***
  - Anti-thrombotic

COX-2 Cardiovascular Effects

Hypothesis

Inhibition of vascular prostacyclin synthesis

AND

Lack of effect on platelet thromboxane synthesis

IMBALANCE

Prothrombotic state

Increased thromboembolic cardiovascular events

McAdam et al. *Proc Natl Acad Sci USA*. 1999;96:272-277.

If COX II anti-thrombotic PGI_2 is blocked, TXA_2 pro-thrombotic is unopposed.

Conceivably, a CV thrombotic event may evolve.

EXAMPLE OF RULE 4

PGE inhibits release of NE in many tissues

CRPS

GIVE AN NSAID—MAKE THE PROBLEM WORSE?

RULE 2 RULE 4

CANNABINOIDS

IS MARY J OK?

MAYBE SO….

CANNABINOIDS

- Definitive analgesic properties- E. Gardner
- There is a role for treatment of pain
- Speeds bone healing by endo cannabinoid regulation of osteoclastic activity
- Stroke – infarct reduction

CANNABINOIDS

- Ubiquitous – CB1, CB2 Receptors
- CB1 antagonists are anti-addictive (cocaine)
- All pain models (hot plate,caragein,familia) demonstrate analgesia
- CB2 is an antinflammatory
- 2AG,JZC184 receptors isolated to analgesia
- Can vaporize to eliminate smoking issues
- Therapeutic in many disorders- HIV, ALS etc
- Cannabis indica (not sativa) 5-HT1 agonist,CBD:THC ratio effects alertness, sedation,hunger, stimulation. Sativa- high. Indica-mellow

ADDICTION MEDICINE

- OAT (opioid agonist therapy)
  - Use of opioid to taper off from abused opioid
  - Methadone
  - Buprenorphine
  - Others?

Opioid Abuse
Suboxone

- **Suboxone**
  - MU partial agonist
  - Ceiling effect
  - Safer than methadone
  - Schedule III
  - Naloxone 4:1 ratio- poor activity PO, Potent IV
  - High dose methadone more effective
  - Retention, not as quick as Methadone therapy
  - Oral substitute – less aberrant behavior
  - Cochrane review supported (evidence based)

Opioid Abuse

- **Methadone**
  - Inhibitor ascending pathways
  - Diminished pain response
  - Preferred opioid agonist treatment
  - Plasma levels 400mg/ml to diminish craving
  - Remedies criminal behavior
  - Improved social structure

THIS DRUG IS A VERY DIFFICULT DRUG TO MANAGE – CAUTION

Medications for Treating Drug and Alcohol Addiction

Clinical Target	Medication	Biological Target
Alcoholism FDA Approved	Disulfiram	Aldehyde Dehydrogenase
	Naltrexone	Mu Opioid Receptor
	Acamprosate	Glutamate Related
Under Investigation	Valproate	GABA/glutamate
	Nalmefene	Mu Opioid Receptor
	Rimonabant	CB1 Receptor
Smoking Cessation	Nicotine Replacement	Nicotinic Receptor
	Varenicline	Nicotinic Receptor
	Bupropion	DA Transporter Blocker
Under Investigation	Deprenyl	MAO-B Inhibitor
	Rimonabant	CB1 Receptor
	Methoxsalen	CYP2A6
Heroin/Opiate Addiction	Naltrexone	Mu Opioid Receptor
	Methadone	Mu Opioid Receptor
	Buprenorphine	Mu Opioid Receptor
Cocaine Addiction Under Investigation	Topiramate	GABA Agonist
	Gabapentin	GABA/Glutamate
	Tiagabine	GABA Transporter

Thank You