Medical and Biological Basis of Addiction: Gaining a Better Understanding of Addictive Illness

YNGVILD OLSEN, MD, MPH
MEDICAL DIRECTOR
INSTITUTES FOR BEHAVIOR RESOURCES, INC.

NOVEMBER 7, 2015
MARYLAND PSYCHIATRIC SOCIETY

Conflict of Interest

- No financial or advisory relationships related to this activity

Addiction Presentation Framework

"The study of disease and of identity cannot be disjoined.

To restore the human subject at the centre—the suffering, afflicted, fighting, human subject— we must deepen a case history to a narrative or tale; only then do we have a 'who' as well as a 'what', a real person, a patient, in relation to disease—in relation to the physical."

Oliver Sacks, Preface to *The Man Who Mistook His Wife for a Hat*

Learning Objectives

- Provide clinical observations
- Define terminology within a historical perspective
- Review risk factors for development of substance use disorders
- Brief review of pathophysiology
- Comments on language

Frank B.

- 28 yo male comes for a new patient visit on a Friday afternoon.
- You get a call from receptionist – “he’s 15 minutes late so I told him we would need to reschedule but he’s demanding to see you now and won’t leave.”
- Slightly disheveled, unshaven, wearing dirty jeans and a worn sweatshirt.
- Grumbles “this is f….. up” under his breath
- Demands a prescription for a controlled medication

Your initial reaction?

Physician Attitudes and SUD

- Attitudinal surveys of medical students and residents demonstrate low regard for patients with SUDs
  - Compared to htn, dyspepsia, pneumonia
  - Lowest for opioid use disorder compared to alcohol use disorder
- Low levels of satisfaction caring for addicted pts among physicians in practice
- Some evidence that attitudes towards patients with SUD degrade over course of training and practice

Public Perception of Addiction

- Barry et al 2014: National randomized public opinion survey on mental illness and addiction
- 54% to 90% of respondents thought employment and housing could be denied to those with addiction, did not want to have co-workers with addiction, or want them to marry into family
- 15% to 59% thought the same for mental illness
- 43% opposed insurance parity for addiction vs 21% for mental illness

Barry C et al. Psych Serv 2014

Brain Disease Model and Public Attitudes

- Australian social survey 2012*: Over 1,200 residents in Queensland
- Asked for level of agreement on a number of questions about: causality of addiction, disease models, role of coerced treatment, stigma, discrimination, and dangerousness

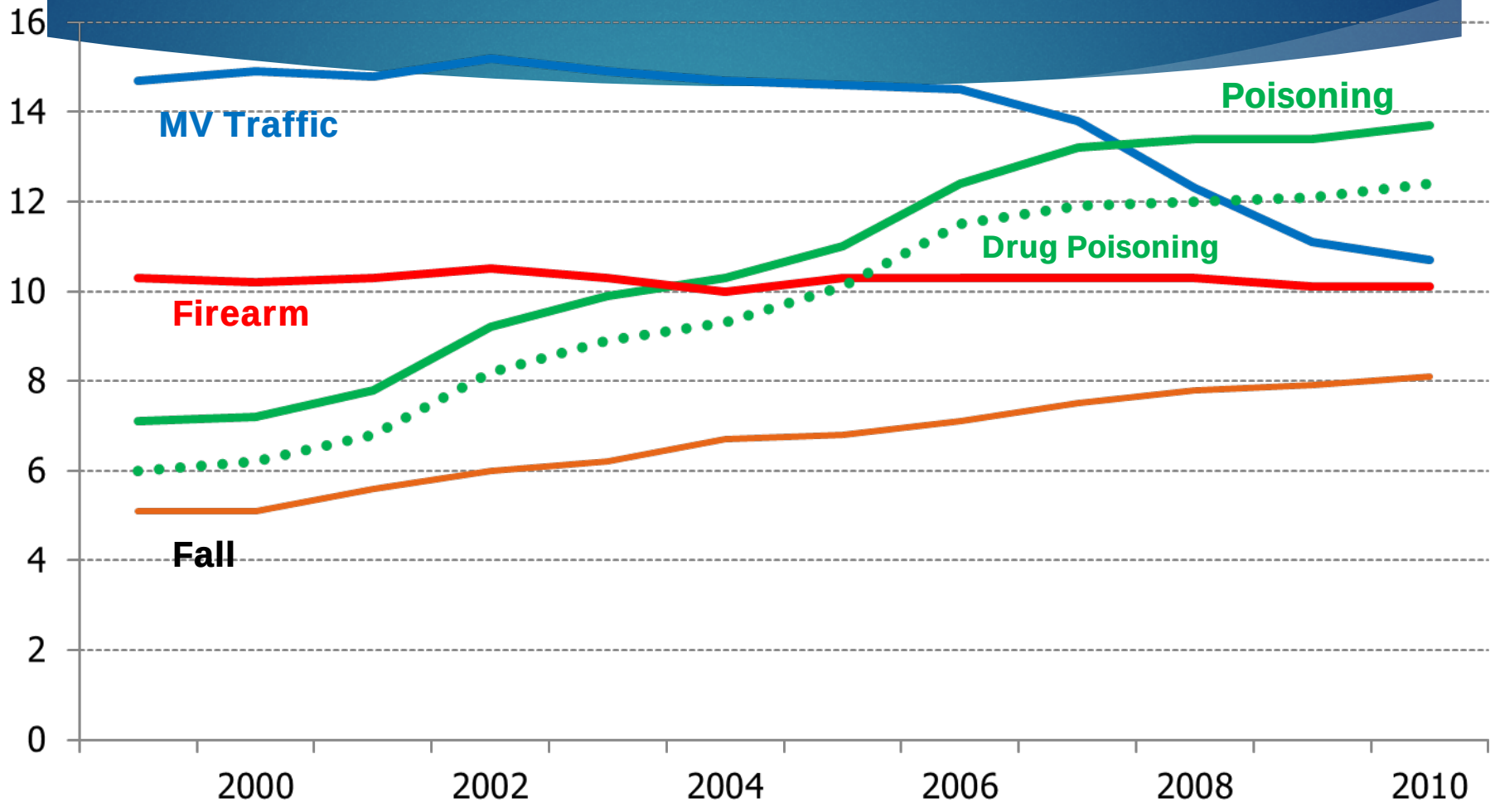
- Key Results:
  - Over 50% believed alcohol and heroin addiction was a disease; only about 30% thought both were a brain disease
  - 60% thought addiction was caused by "personal character qualities"

"Attitude is a little thing that makes a big difference"**

*Meurk et al. BMC Psychiatry, 2014.

**Ballon in Academic Psychiatry, 2008

United States: Injury Deaths by Cause, 1999-2010
Age adjusted rate per 100,000



Data Source: National Vital Statistics System-Mortality (NVSS-M), CDC/NCHS

Reversal of overall mortality rate among 45-54 white Americans

- Mortality rate in this age group decreased 2% per yr for 20 years since 1978
- Since 1998, increase in mortality rate per yr (34 per 100,000)
- Since 1998, decrease in mortality rate for AA and Latino (200 per 100,000 and 60 per 100,000)
- First increase in mortality rate among mid-life Americans since 1950

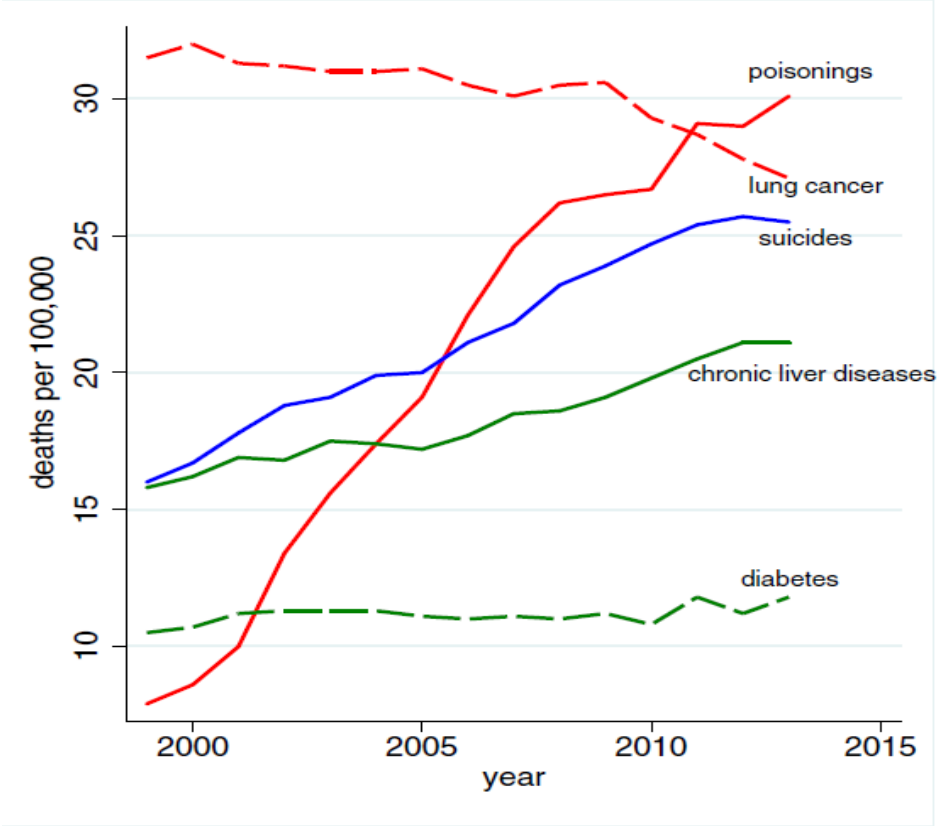
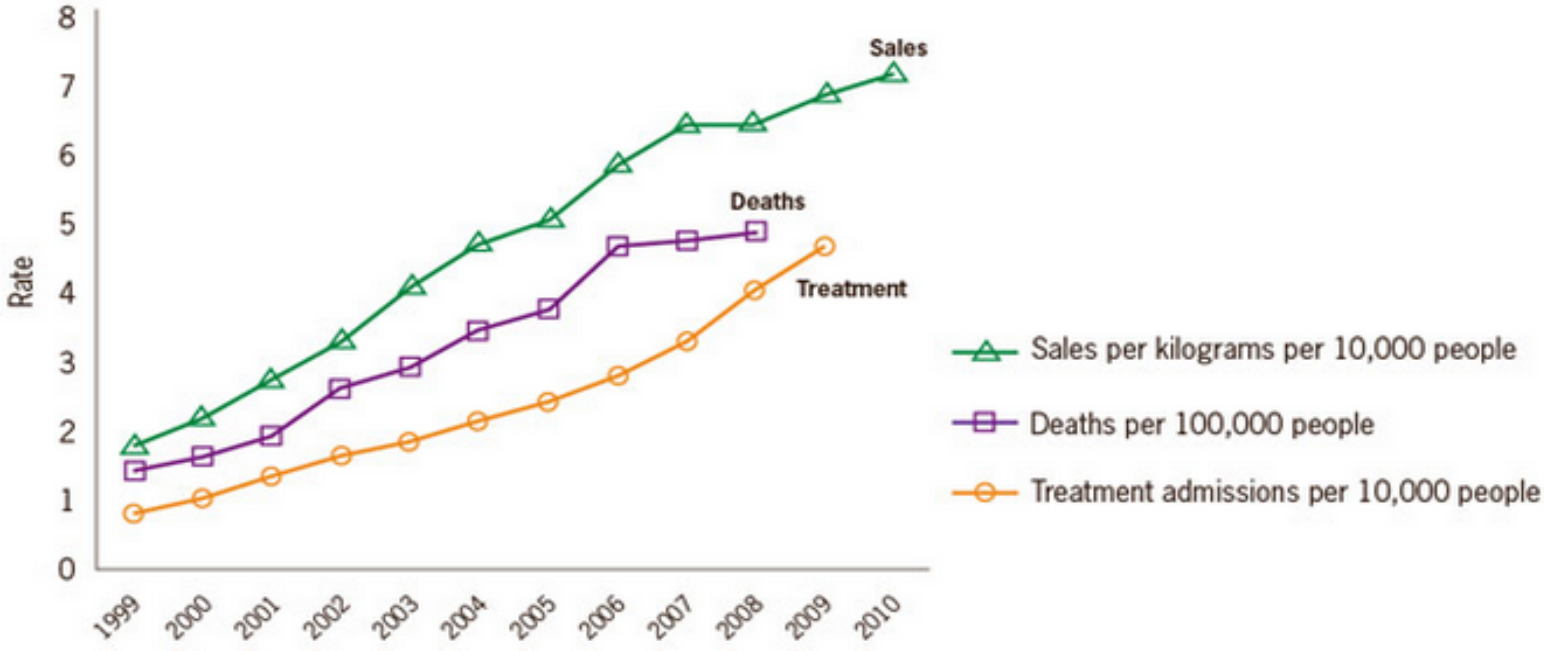


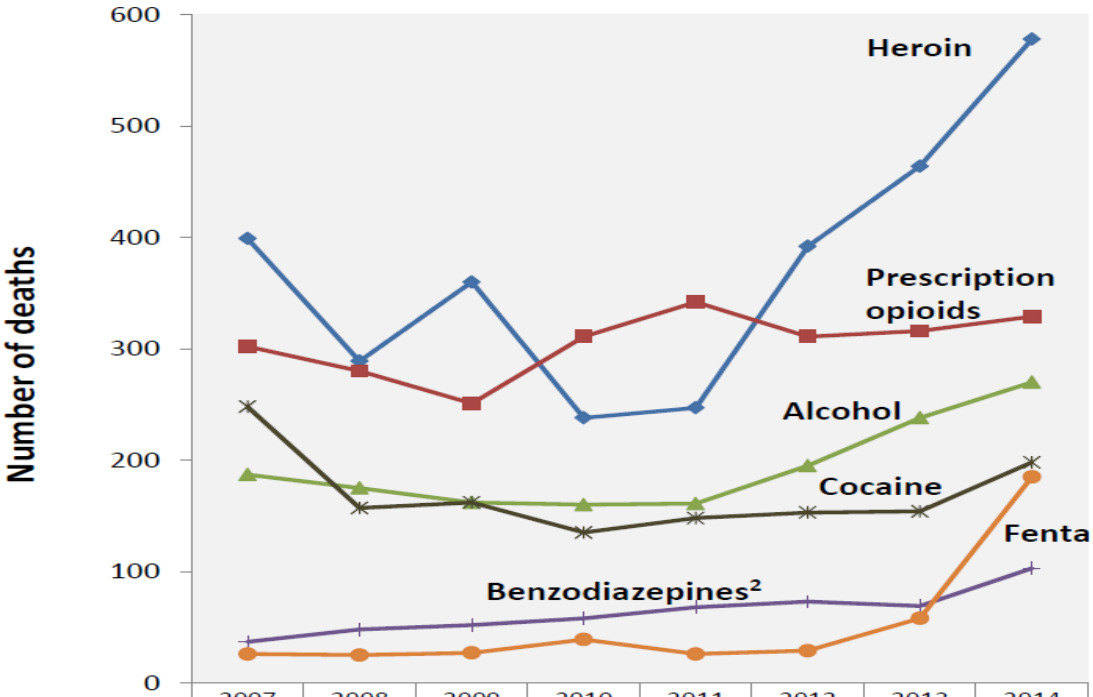
Fig. 2. Mortality by cause, white non-Hispanics ages 45–54.

Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)



SOURCES: National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009

Figure 5. Total Number of Drug- and Alcohol-Related Intoxication Deaths by Selected Substances[1], Maryland, 2007-2014.

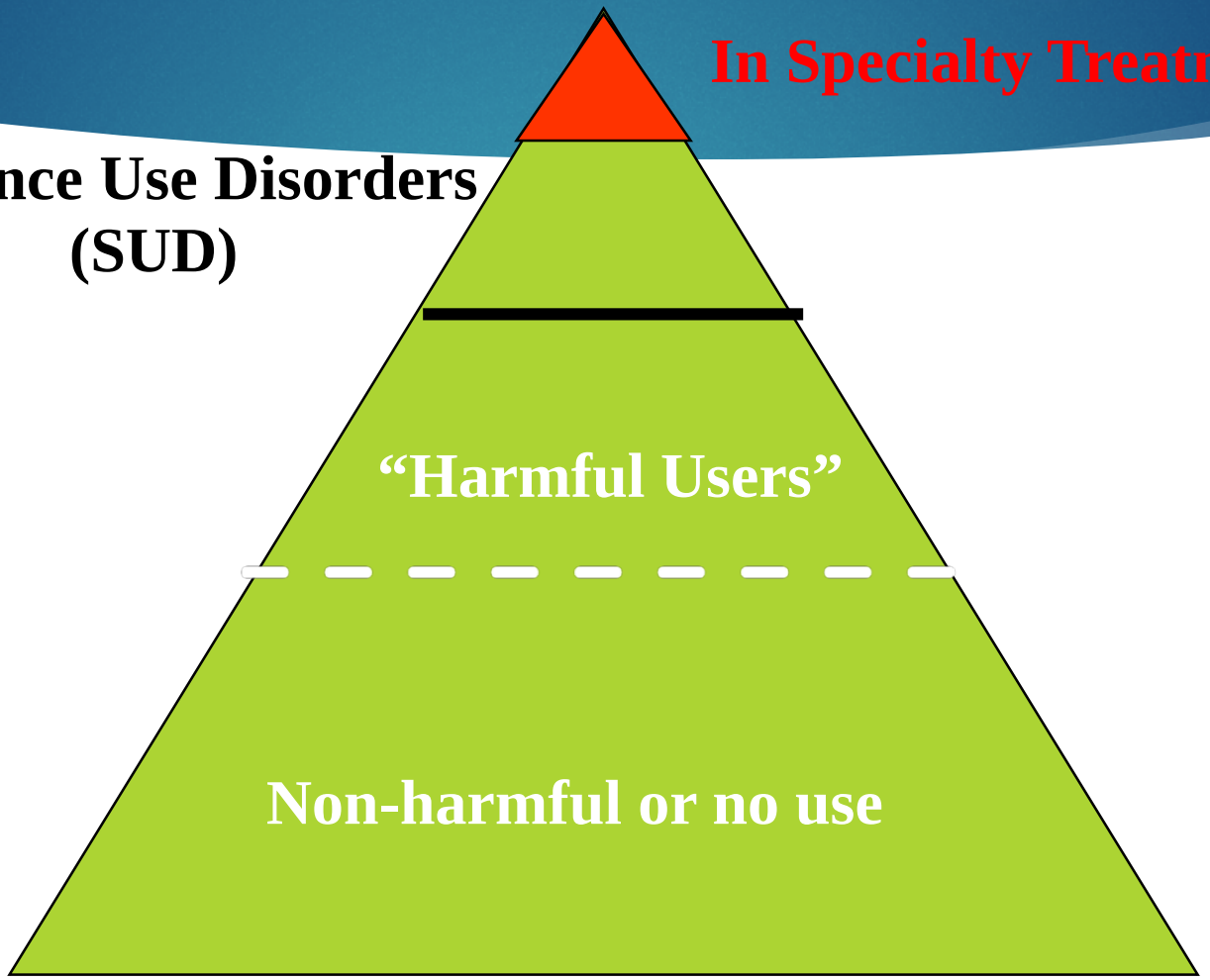


	2007	2008	2009	2010	2011	2012	2013	2014
Heroin	399	289	360	238	247	392	464	578
Prescription opioids	302	280	251	311	342	311	316	329
Alcohol	187	175	162	160	161	195	238	270
Benzodiazepines	37	48	52	58	68	73	69	103
Cocaine	248	157	162	135	148	153	154	198
Fentanyl	26	25	27	39	26	29	58	185

[1]Since an intoxication death may involve more than one substance, counts of deaths related to specific substances do not sum to the total number of deaths.
[2]Includes deaths caused by benzodiazepines and related drugs with similar sedative effects.

http://bha.dhmh.maryland.gov/OVERDOSE_PREVENTION/Documents/2015.05.19%20-%20Annual%20OD%20Report%202014_merged%20file%20final.pdf

Substance Use Pyramid*

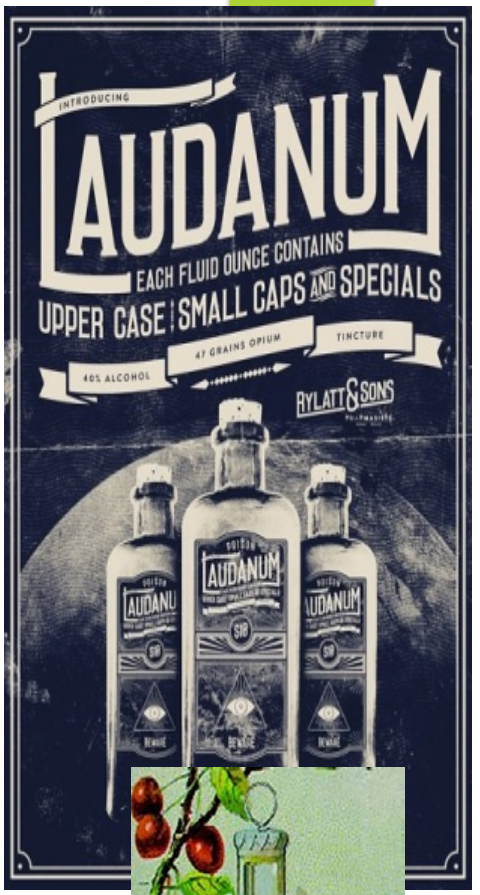


*Adapted from Dr. Tom McLellan

Not a New Phenomenon……


COCAINE
TOOTHACHE DROPS
Instantaneous Cure!
PRICE 15 CENTS.
Prepared by the
LLOYD MANUFACTURING CO.
219 HUDSON AVE., ALBANY, N. Y.
For sale by all Druggists.
(Registered March 1885.)
See other side.


DR. HAND'S REMEDIES FOR CHILDREN.
PUT UP IN
25¢ & $1.00 BOTTLES.
THE MOTHERS ADVISER & CHILDRENS FRIEND


INTRODUCING
LAUDANUM
EACH FLUID OUNCE CONTAINS
UPPER CASE | SMALL CAPS AND SPECIALS
40% ALCOHOL
47 GRAINS OPIUM
TINCTURE
RYLATT & SONS


A Good Friend
AYER'S
Don't take Ayer's Sarsaparilla if you are well. Don't take it simply because you are sick. Take it for what the doctors recommend it and you will like it, become fond of it, for it gives health, strength, vigor.
"I suffered terribly for twelve years. The doctors said my blood was all turning to water. I then tried Ayer's Sarsaparilla, and soon my health was fully restored." — Mrs. J. W. FIALA, Hadlyme, Conn.
All druggists.
J. C. AYER CO., Lowell, Mass.


1887
Mrs. Winslow's
SOOTHING SYRUP
FOR CHILDREN TEETHING


AYER'S
AYER'S CHERRY PECTORAL
Cures Colds, Coughs & all Diseases of the Throat and Lungs

Dr Benjamin Rush: The father of the American disease concept of alcoholism

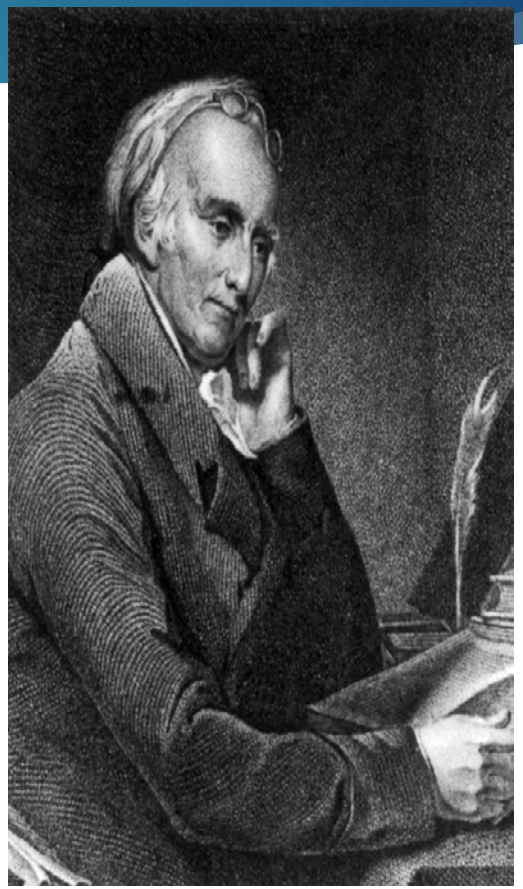
- Bylaws of the American Association for the Study and Cure of Inebreity (1870)

  1) Intemprance is a disease

  2) It is curable in the same fashion that other diseases are

  3) Its primary cause is a constitutional susceptibility to the alcoholic impression

  4) This constitutional tendency may be either inherited or acquired



TD Crothers

The increasing number of cases which become disabled and degenerate in almost every community from the use of alcohol suggests something more than moral lapses and sinful weakness.

In a large proportion of cases certain predisposing and favoring conditions are present. Of these heredity explains the largest number. In a study of many thousand cases over 60 per cent are found to have inebriate ancestors.

A careful clinical study and grouping of the history of many opium cases points out a neurotic diathesis or condition of brain and nerve defect which predisposes to the development of this disease. There is an opium diathesis or special inherited tendency to use opium or other narcotics.

The Drug Habits and Their Treatment, 1902

TELEPHONE
BROOKLINE 3620

CHARLES D. B. FISK,
SUPERINTENDENT

THE FISK HOSPITAL
FOR THE TREATMENT OF
ALCOHOLISM AND DRUG ADDICTION
(*By the Towns-Lambert method.*)

PRIVATE ROOMS —COMPETENT PHYSICIANS
TRAINED NURSES.

CONSULTING PHYSICIANS:
RICHARD C. CABOT, M.D., Boston, Mass.
FRANK G. WHEATLEY, M.D., North Abington, Mass.
WILLIAM OTIS FAXON, M.D., Stoughton, Mass.
LEONARD HUNTRESS, M.D., Lowell, Mass.
RUFUS W. SPRAGUE, M.D., Boston, Mass.

106 SEWALL AVENUE BROOKLINE, MASS.

The Modern Treatment of Alcoholism and Drug Addiction

ALCOHOLISM: The medical profession now recognize alcoholism as a disease; and as such, this vexed question has interest for physicians; and the best solution of its treatment is an important factor.

Boston Medical and Surgical Journal,
October, 1916

What Changed?..... Early 20th Century

- 1914 Harrison Narcotics Tax Act
  - Regulated manufacture and distribution of prescription opioids (and coca)
  - Licensing of pharmacists and physicians
  - Permitted dispensing opioids “to a patient in the course of [the physician’s] professional practice only”

Early 20th Century

- Supreme Court Cases – contesting/clarifying role of opioid prescribing for individuals with addiction
  - Webb et al., v. United States (1919)
  - United States v. Doremus (1919)
  - Jin Fuey Moy v. United States (1920)
- Criminalized prescribing/dispensing of opioids for individuals with opioid use disorders
- 1919 – 1935: 25,000 physicians indicted for Harrison Act violations
- All morphine maintenance clinics closed
- Medical treatment for opioid use disorders virtually disappears

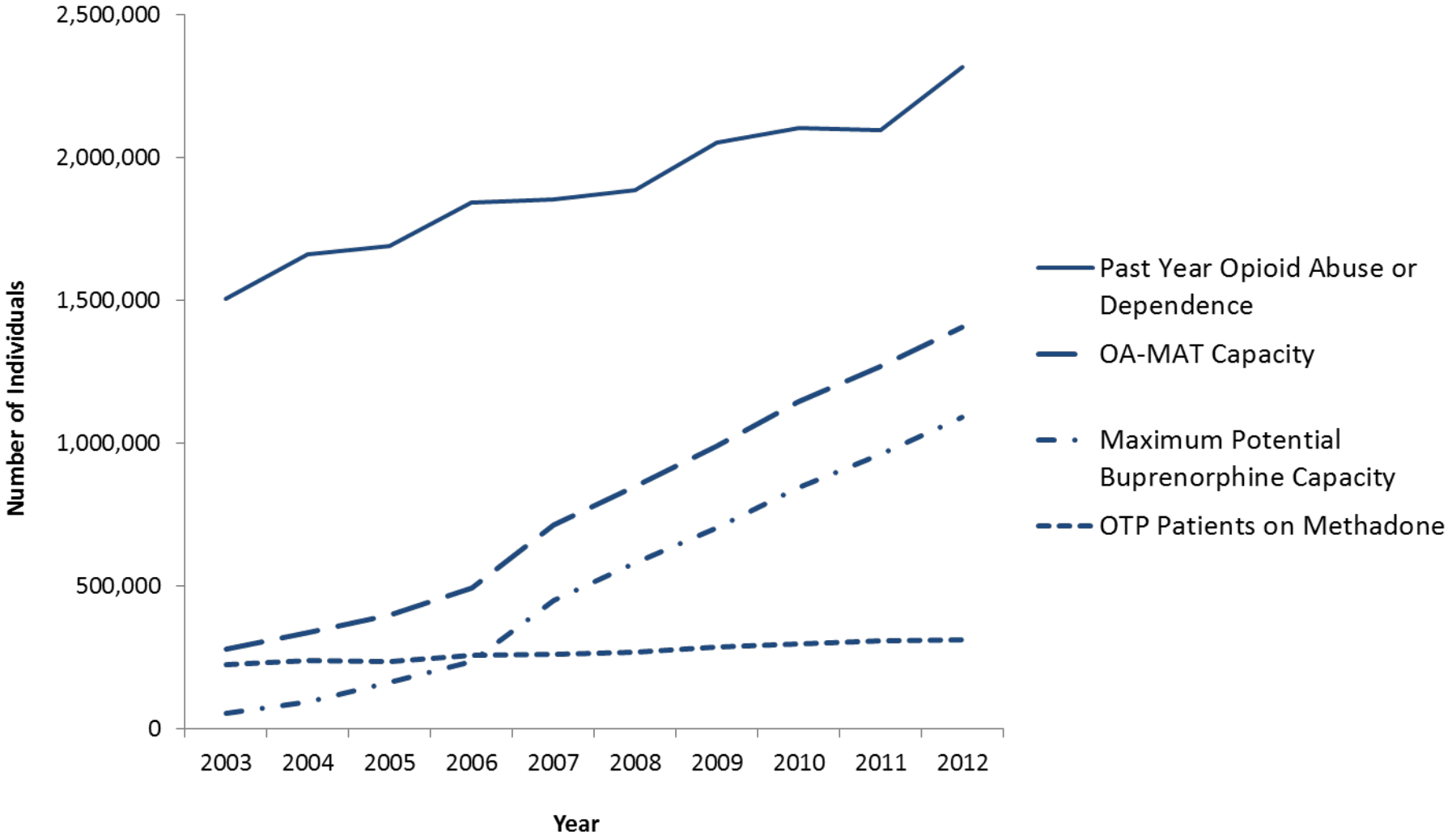
1920 to 1970 – Moral Failing

- Addiction no longer domain of medicine/public health – rather criminal justice and "lay providers"
- Addiction as a moral failing or lack of willpower: "heroin addicts spring from sin and crime"
- Vacuum:
  - Growth of mutual aid societies (AA)
  - Narcotic "farms": electroshock treatment, psycho-surgery, aversion therapy, forced sterilization
  - Medication only to be used for detox

1970 to Today

- 1974: Narcotic Addict Treatment Act
  - Recognized use of opioid agonist to treat opioid use disorder – defined “maintenance” treatment
  - Established NIDA
  - Separate DEA classification for physicians who dispense opioids for addiction treatment
- 2000: Drug Addiction Treatment Act (DATA 2000)
- 2002: Buprenorphine first drug approved by FDA under DATA 2000
- 2006 and 2010: FDA approval of injectable naltrexone for alcohol use disorder and then opioid use disorder relapse prevention

Treatment need for opioid abuse or dependence exceeds capacity for opioid agonist medication assisted treatment



Source: Jones CM, Campopiano M, Baldwin G, McCance-Katz E. National and state treatment need and capacity for opioid agonist medication assisted treatment. AJPH. 2015

Addiction Etiology Theories

- Moral failing or insufficient willpower

VS

- Reward deficiency syndrome
- Deficiency of inhibitory control
- Disorder of choice
- Conditioned learning and habituation
- Self-medication of unrecognized underlying psychiatric disorder
- Disorder of bonding and connectedness
  - To other humans
  - To spiritual being

Disorder of Hedonic Tone

Usual sense of well being, happiness, pleasure, contentment

Set by mesolimbic system

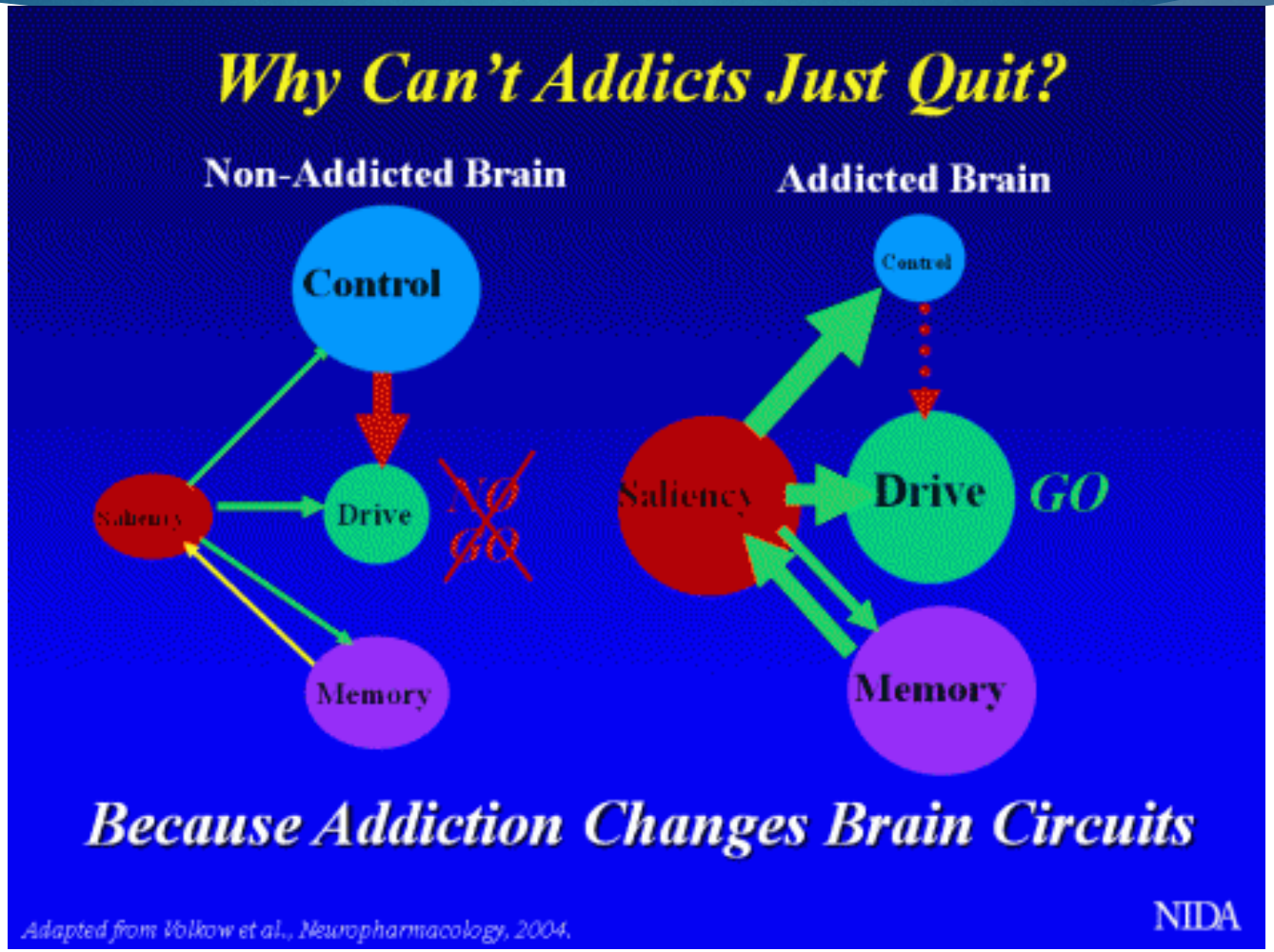
Range: Euphoria ← → Dysphoria

Altered in those vulnerable to SUDs

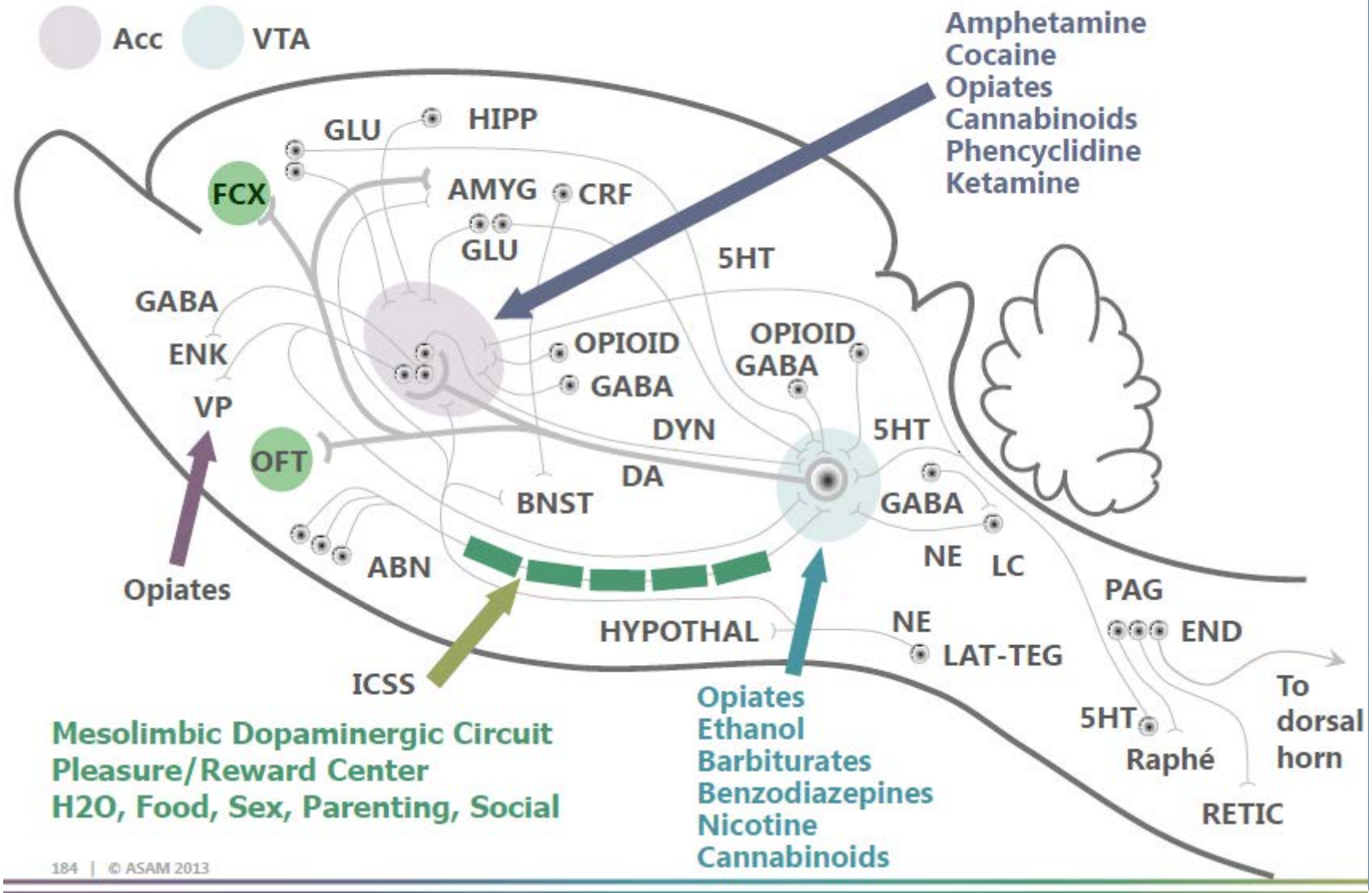
Further altered by addiction

Human Condition

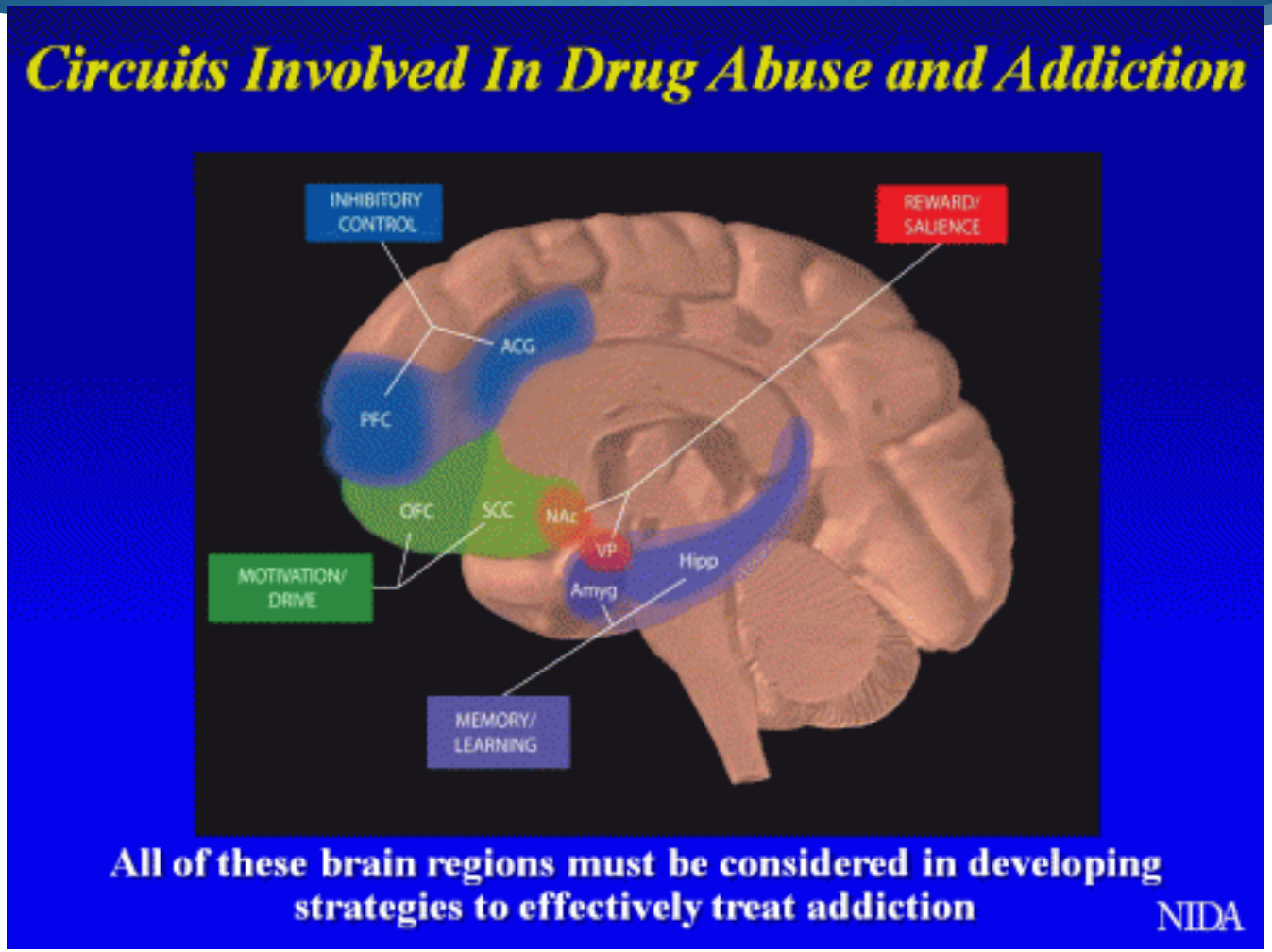
Pathophysiology of Addiction



Eliot Gardner



Connect and Disconnect



The Modern Chronic Disease Model Alternative

- Can incorporate multiple different etiological concepts
- Easier to explain than individual conceptual models
- Allows for more effective scientific discussion, discovery, and healthcare involvement
- Uses medical terminology

Comment on Addiction Language

- Current language focuses on labeling people rather than focusing on behaviors
- "Abuse"
  - Long implied the willful commission of an abhorrent (wrong and sinful) act
  - Involving forbidden pleasure
  - Come to characterize those of violent and contemptible character-those who abuse their partners, their children or animals
  - Defined in terms of immorality, not as health problem

White, The Rhetoric of Recovery Advocacy: An Essay on the Power of Language, 2006

"Substance Abuser vs Person with Substance Use Disorder"

- RCT using 2 vignettes – only difference was descriptive language of person portrayed
- 728 mental health professionals attending a conference – randomly presented with either vignette and a follow up questionnaire (response rate 71%)
- Measured extent of agreement with different causes of problem, social threat level of person, ability to self-regulate behavior, and appropriate response (therapeutic vs punitive action)
- Those assigned "substance abuser" vignette more likely to view the individual as personally culpable for condition, able to self-regulate behavior, and intervention should be punitive (jail)

Kelly et al Int J Drug Policy, 2010

Work from ADAA Learning Collaborative

Words to Never Use:

- Junkie
- Hostile

Words with possible alternatives

- Non-compliant or not ready
  - use descriptive terms
- Clean/dirty
  - urine toxicology test result is positive or negative OR expected or unexpected
  - Active recovery or symptomatic
  - Abstinent/abstaining from or ongoing/sporadic use
- Self-help
  - self-directed or mutual aid
- Graduated
  - stabilized

Modern Chronic Disease Model

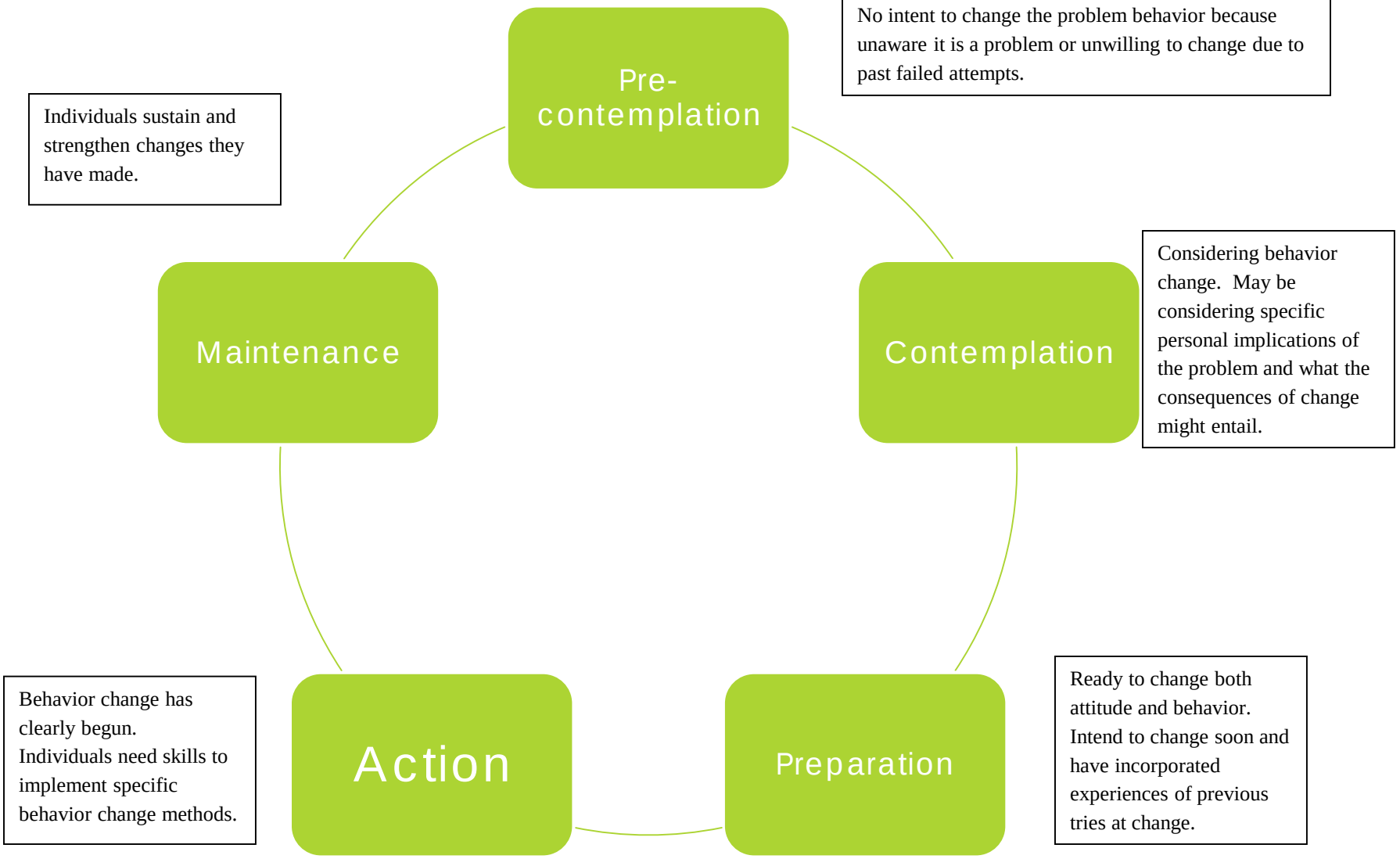
Criticism:

- Absolves the person of individual responsibility
- Too self-defeating or too lenient

Response:

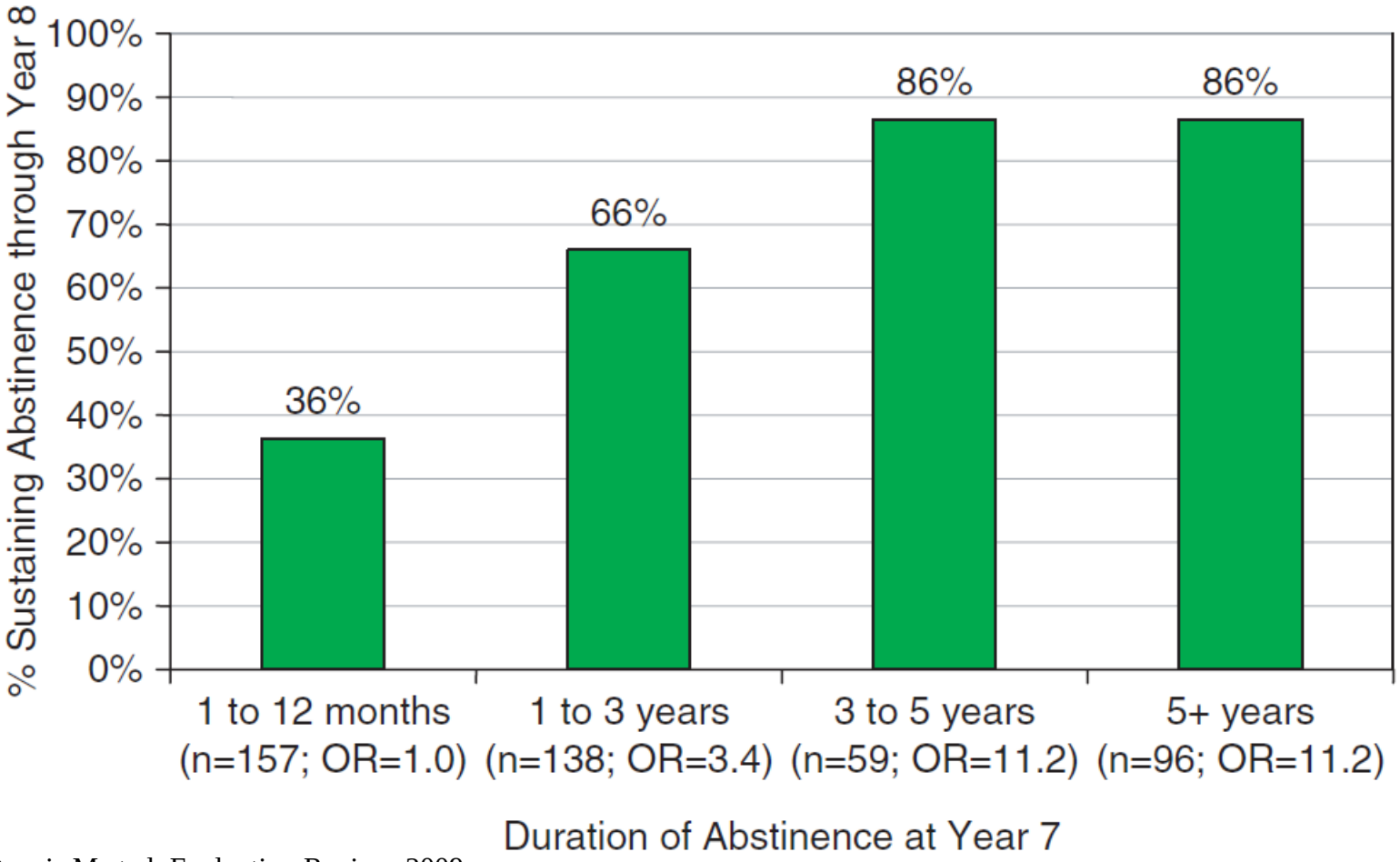
- No cure!
- Goal is life long management
- Disease severity may change over time but risk of symptom recurrence is always present
- Effective treatment often combines medications and behavioral interventions
- Behavior change is a key part of management
- Behavior change occurs in stages over time

Stages of Behavior Change



Prochaska and DiClemente TransTheoretical Model of Behavior Change

Figure 1
Percent Sustaining Abstinence Through Year 8
by Duration of Abstinence at Year 7



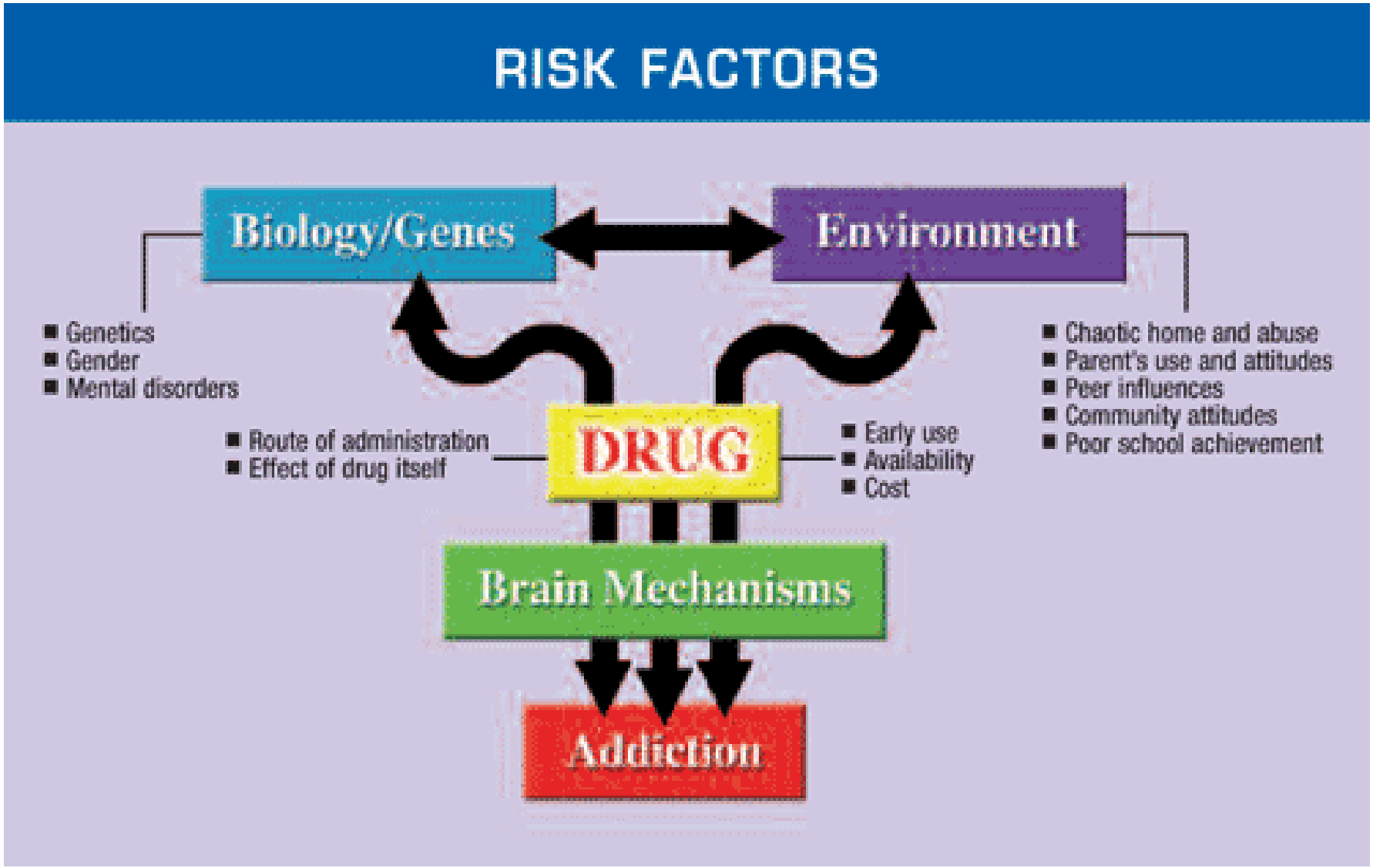
Source: Dennis M et al, Evaluation Review, 2009

Key Parts of Disease Definition

- Involves an impairment or dysfunction of one or more parts in a living animal
- The dysfunction interrupts or modifies the performance of vital functions
- Results in signs and symptoms
- Cause (or causes) in response to “environmental factors…, specific infective agents…., inherent defects of the organism…, or to combinations of these factors.” (Merriam-Webster Medical Dictionary)

Why do some people develop addiction?

The Perfect Storm!

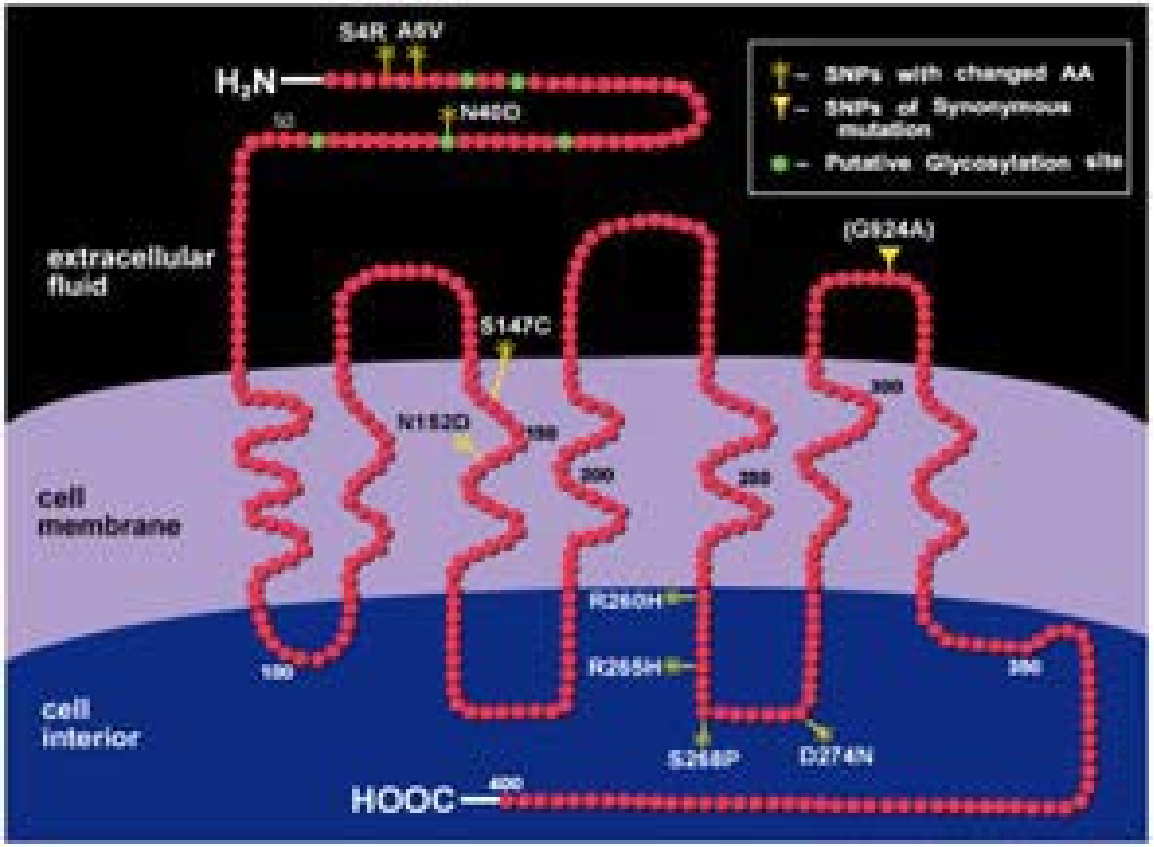


Genetic Variants of the Human Mu Opioid Receptor: Single Nucleotide Polymorphisms in the Coding Region Including the Functional A118G (N40D) Variant

HYPOTHESIS

Gene variants:

- **Alter physiology "PHYSIOGENETICS"**
- **Alter response to medications "PHARMACOGENETICS"**
- **Are associated with specific addictions**



Bond, LaForge… Kreek, Yu, PNAS, 95:9608, 1998; Kreek, Yuferov and LaForge, 2000

Slide Source: Dr. Kreek

Lifetime Prevalence and Odds Ratios of Mental Disorders by Substance Use Disorder: ECA

	Alcohol		Drug	
Comorbid Disorder	%	O.R.	%	O.R.
Any mental	36.6	2.3	53.1	4.5
Schizophrenia	3.8	3.3	6.8	6.2
Affective	13.4	1.9	26.4	4.7
Anxiety	19.4	1.5	28.3	2.5
Antisocial	14.3	21.0	17.8	13.8

(Regier et al., JAMA 264:2511-2518, 1990)

Trauma Impact

- Adverse Childhood Experiences Study: Over 8,000 adult men and women (mean age 57 and 55, respectively)
- Assessed history until age 18 of abuse/neglect, level of household dysfunction, health-related behaviors, and illicit drug use using standardized questionnaires
- Each participant assigned an ACE score based on number of experiences (analyzed as 0-5+)
- 67% had at least ACE; 42% had 2 or more

Dube et al. Pediatrics, 2003

ACE Study Results: Initiation of Illicit Drug Use

TABLE 4. Prevalence and Adjusted OR* for the Relationship Between the ACE Score and Age at Initiation of Illicit Drug Use and Lifetime Use

ACE Score†	Age at Initiation of Drug Use								
	N	≤14 Years		15–18 Years		Adult (≥19 Years)		Lifetime	
		%	OR	%	OR	%	OR	%	OR
0	2812	0.7	1.0 (Referent)	3.8	1.0 (Referent)	4.8	1.0 (Referent)	9.4	1.0 (Referent)
1	2205	1.5	1.5 (0.9–2.7)	6.5	1.4 (1.1–1.8)	7.2	1.4 (1.1–1.8)	15.2	1.5 (1.2–1.8)
2	1338	3.1	2.9 (1.6–5.0)	9.3	1.8 (1.3–2.4)	9.8	1.9 (1.5–2.4)	22.3	2.3 (1.9–2.8)
3	849	4.7	4.0 (2.3–7.1)	10.6	1.9 (1.4–2.6)	10.3	1.9 (1.4–2.6)	25.6	2.5 (2.0–3.2)
4	507	4.1	3.8 (2.0–7.2)	13.4	2.7 (1.9–3.8)	11.2	2.1 (1.5–3.0)	28.8	3.1 (2.4–4.0)
≥5	902	9.9	9.1 (5.4–15.2)	14.3	2.5 (1.9–3.3)	13.2	2.5 (1.9–3.2)	37.4	4.3 (3.5–5.4)
Total	8613	2.8	—	7.7	—	8.0	—	18.5	—

* ORs adjusted for gender, baseline age, race, and educational attainment.

† The trend for increasing ORs as the ACE score increases is significant ($P < .05$) in each model.

ACE Study Results: Substance Use Disorder

TABLE 5. Relationship of the ACE Score to Ever Having a Drug Problem, Ever Being Addicted to Drugs, or Injecting Illicit Drugs

ACE Score†	N	Ever Had Drug Problem		Ever Addicted to Drugs		Ever Injected Drugs	
		%	OR*	%	OR*	%	OR*
0	2812	1.3	1.0 (Referent)	0.8	1.0 (Referent)	0.3	1.0 (Referent)
1	2205	3.0	1.9 (1.3–2.9)	2.1	2.3 (1.4–3.8)	0.5	1.6 (0.7–4.0)
2	1338	3.9	2.0 (1.3–3.2)	3.1	2.7 (1.6–4.7)	1.2	3.0 (1.3–7.1)
3	849	5.0	2.5 (1.6–4.0)	4.1	3.5 (2.0–6.0)	1.4	3.5 (1.4–8.7)
4	507	7.5	4.2 (2.6–6.9)	3.9	3.4 (1.8–6.4)	1.0	2.4 (0.8–7.4)
≥5	902	12.0	6.5 (4.3–9.6)	9.2	7.7 (4.7–12.7)	4.3	10.1 (4.6–22.0)
Total	8613	4.0	—	2.9	—	1.1	—

* ORs adjusted for gender, baseline age, race, and educational attainment.

† The trend for increasing ORs as the ACE score increases is significant ($P < .05$) in each model.

Age of First Use

- Multiple studies across different methodologies demonstrate higher risk of adult onset substance use disorders with early onset of use – before age 14
- Higher vulnerability of adolescent brain -- significant developmental changes
  - Changes in dopaminergic system
  - Growth in prefrontal cortex
  - Refinement of limbic neurocircuits
- Differential gene expression during adolescence compared to adulthood

Neighborhood Associations

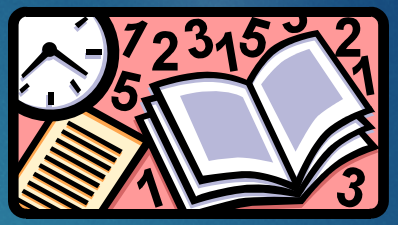
- National Survey on Drug Use and Health (NSDUH) secondary data analysis of adolescent perceptions (N=38,000 youth ages 12-17))
  - Neighborhood disorganization
  - Social capital
- Outcomes: adolescent substance use and diagnostic SUD
- Teens with high levels of perceived neighborhood disorganization had 2.6 times odds of diagnostic SUD
- Medium and high levels of social capital associated with lower odds of diagnostic SUD (OR 0.77 (95% CI 0.71-0.83), .06 (95% CI 0.54-0.67)

Winstanley et al. Drug Alcohol Depend 2008

Addictive Potential Determinants

- The faster a drug gets to the brain, the higher addictive potential
- The shorter acting a drug is, the higher addictive potential
- More potent drugs have higher addictive potential
  - Takes less of drug to achieve effect

Addiction Definition



- 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.*

- A chronic, relapsing disease characterized by compulsive drug seeking and use despite harmful consequences as well as neurochemical and molecular changes in the brain.**

- A brain disease whose symptoms are overwhelming cravings and resultant behaviours.

*American Society of Addiction Medicine

**National Institute on Drug Abuse (NIDA)

Substance Use Disorder Diagnostic Criteria, DSM-V

More use than intended	Excessive time spent in acquisition
Unsuccessful efforts to cut down	Craving for the substance
Activities given up because of use	Continued use despite consistent social or interpersonal problems
Failure to fulfill major role obligations	Tolerance*
Use despite negative effects	Withdrawal*
Recurrent use in hazardous situations	

Severity measured by number of symptoms; 2-3 mild, 4-6 moderate, 7-11 severe

*** These do not apply if the medication is prescribed and no other diagnostic criteria are met**

Physical Dependence Vs. Addiction

- "Physical dependence is neither sufficient nor necessary to diagnose addiction." Dr. Howard Heit
- Physical dependence is a neuropharmacological phenomenon while addiction is both a neuropharmacological AND behavioral phenomenon.
- Physical dependence occurs with many different categories of medications and substances.

Heit HA. Addiction, Physical Dependence, and Tolerance: Precise Definitions to Help Clinicians, Evaluate, and Treat the Patient with Chronic Pain. J Pain and Palliative Care Pharmacotherapy. March/April 2003;26:655-667

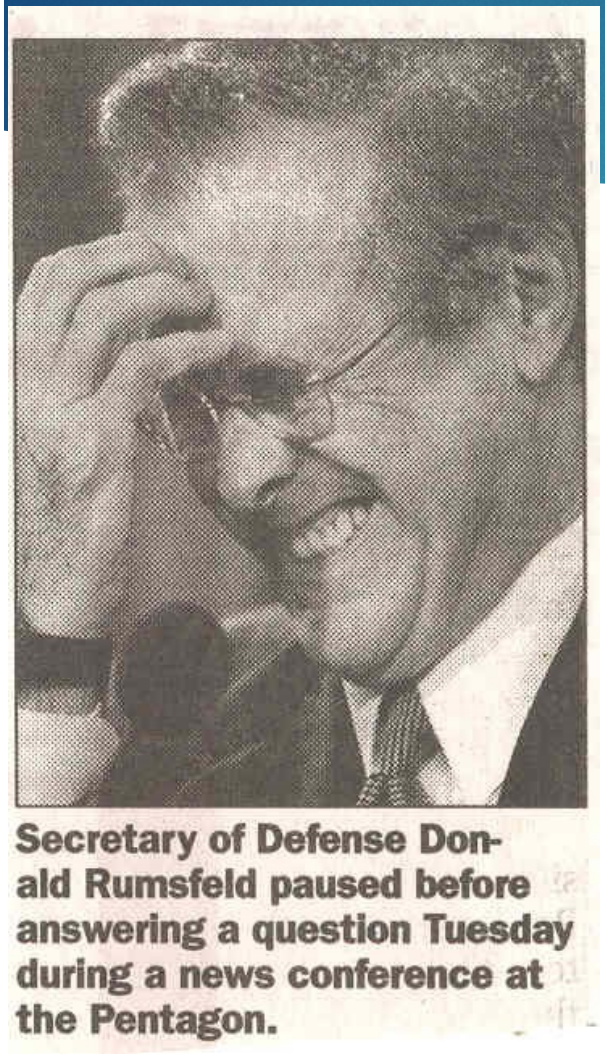
Physical Dependence

- "Physical dependence is the physiological adaptation of the body to the presence of an opioid. It is defined by the development of withdrawal symptoms when opioids are discontinued, when the dose is reduced abruptly or when an antagonist (e.g., naloxone) or an agonist-antagonist (e.g., pentazocine) is administered. "

- "Physical dependence is a normal and expected response to continuous opioid therapy. Physical dependence may occur within a few days of dosing with opioids, although it varies among patients. Physical dependence (indicated by withdrawal symptoms) does not mean that the patient is addicted. "

O'Brien CP. Drug addiction and drug abuse. In: *Goodman and Gilman's The pharmacological basis of therapeutics. 9th edition.*

The Clinical Conundrum

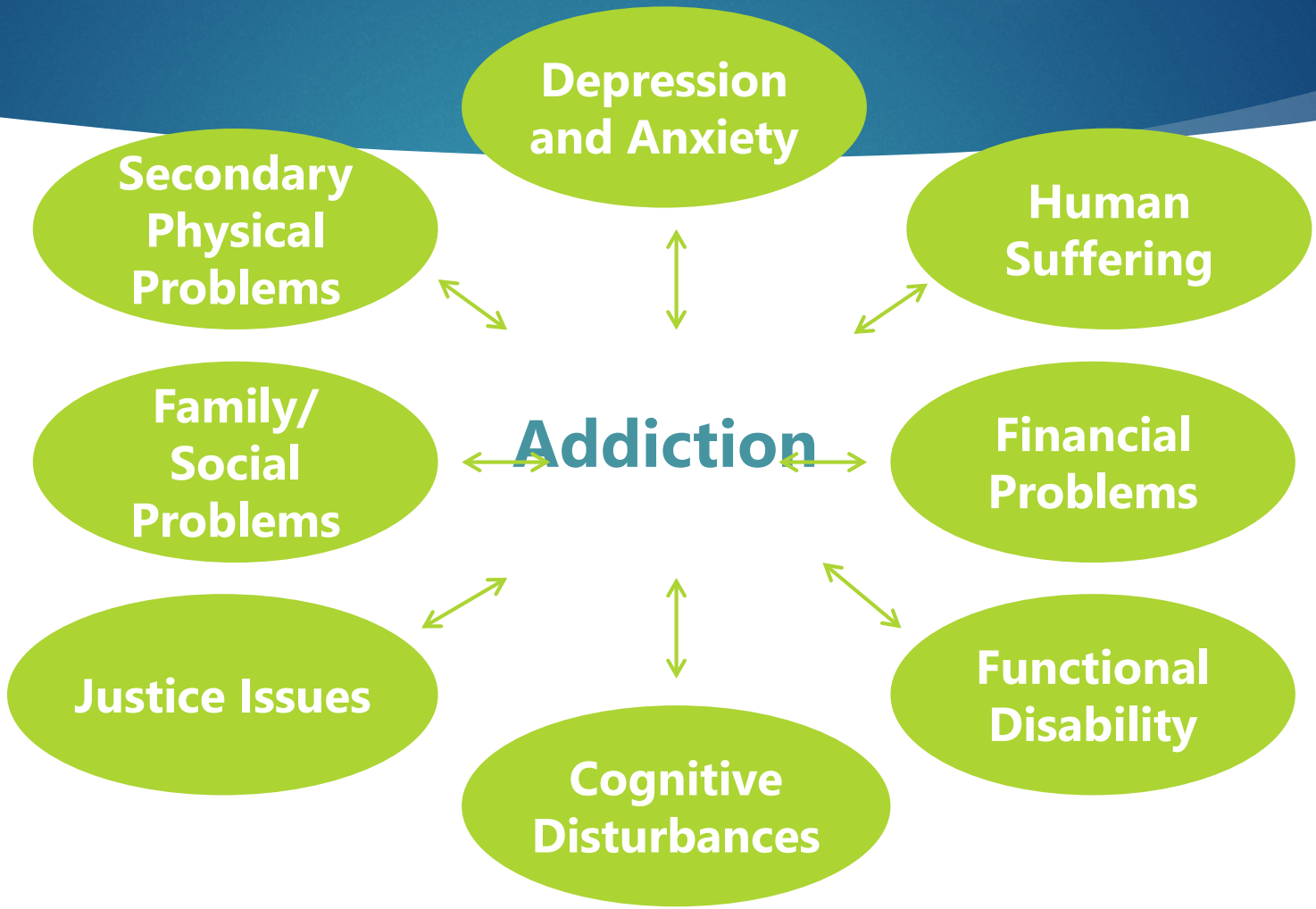


Secretary of Defense Donald Rumsfeld paused before answering a question Tuesday during a news conference at the Pentagon.

"…as we know, there are known knowns, there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don't know."

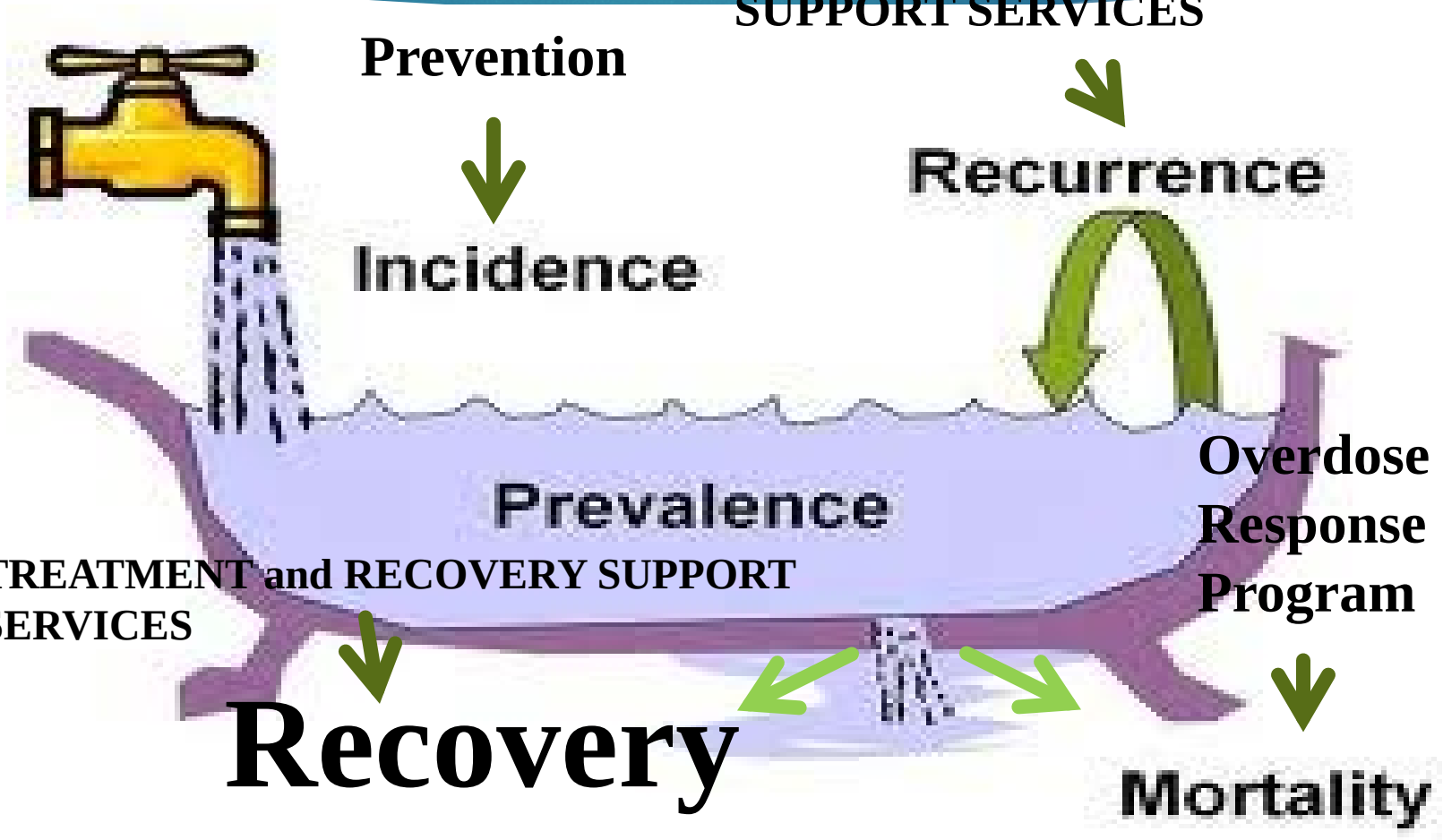
– Donald Rumsfeld

Addiction



Adapted from Ann Quinlan-Colwell, PhD, PCSS-O Webinar 2011

Public Health Approach



Frank B.

- History
  - Has severe opioid use disorder
  - Past history of alcohol and cocaine use disorder
  - Head trauma as a child
  - Multiple incarcerations, on probation
  - Living with girlfriend – also with opioid use disorder, in treatment
  - Has PCP and psychiatrist but was not keeping appointments
- Exam: paranoid but not delusional
- Starts Suboxone
- Now at 4 months – keeps all appointments, expected test results and film counts, PDMP without surprises
- Smiles, shows pictures of self and girlfriend at family events

NARCOTIC ADDICTION — A SYSTEMIC DISEASE CONDITION

ERNEST S. BISHOP, M.D.

VOLUME LX
NUMBER 6

I

realized that the patients were people sick of a definite disease condition, and that until we recognized, understood and treated this condition, and removed the stigma of mental and moral taint from those cases in which it did not exist, we should make little headway toward the solution of our problem.

JAMA. 1913;60(6):431-434.