The Neuroscience of “Addiction”: From Diagnosis to Treatment - Updated

Carlton Erickson, Ph.D.
- Distinguished Professor of Pharmacology
- Director, Addiction Science Research and Education Center
- Associate Dean for Research and Graduate Studies
College of Pharmacy
The University of Texas
Austin, TX  USA

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Points to cover in this brief workshop

• criteria to **diagnose** drug use disorders
  - DSM-5 (*value of this diagnostic guide to users and staff*)
• **review** of neuroscience 101
  - new information (*what this means to you*)
• **programs and treatments** for drug use disorders
  - traditional
  - evidence-based - CENAPS model
• ways to **improve treatment** in the future?
The take-home message this evening:

- People around the world do not agree that addiction is a disease.
- People around the world do not agree on whether addiction requires treatment.
- People around the world do not agree that treatment is effective in treating addictions.

Science is showing clearly that addiction is a brain disease, that it can be overcome, and that deaths and suffering can be reduced by finding the causes of addiction and more effective ways to help those who are suffering.
Problem: What IS “addiction”?  

What we see in the media and on the Internet  

Addiction:  
- is synonymous with “drug abuse” or “habit”  
- occurs anytime something is taken/done “too much, too often, for too long”  
- is a serious health problem (heroin)  
- is not so serious (exercise)  
- is preventable (“just say no….”)  
- scientifically includes all compulsive behaviors  
  (actually, all of these are confusing and wrong)
Actually, people tend to be uninformed

- There are really **two major DIFFERENT** drug overuse problems:
  1. drug overuse that **can be controlled** by the user
  2. drug overuse that **cannot be controlled** by the user
- They are “**handled**” differently by society and professionals
  1. these users **have the ability to stop** when they need to do so – punishment, adverse effects, lose interest
  2. these users **have a brain disease** that requires treatment (this is closest to “addiction”)
The problem with “addiction”

• confusion due to misunderstanding and miscommunication about “addiction”
  - “sugar cookies are addicting”
  - “antidepressants are addicting”
  - “marijuana is not addicting”
  - “I’m addicted to you baby, you’re a hard habit to break..” (Chicago singing group)
WHERE IS THE CORRECT INFORMATION ABOUT THESE MYTHS?

www.utexas.edu/research/asrec

(The most famous academic website on the science of addiction in the world! 😊)
First, we need to clarify what “addiction” is, and what it is not. (This is because the word is non-scientific and overused, so it is not the best word to describe the disease.)
DIAGNOSTIC CRITERIA
FOR “ADDICTION”
Major Diagnostic Instruments

- DSM-IV, 1994, 2000 (old)
- DSM-5, 2013 (current)
- ICD-10, 2003, 2010 (current)
- ICD-11, 2017 (projected)

DSM = Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association

ICD = International Classification of Mental and Behavioural Disorders, World Health Organization
(Old) DSM-IV Diagnosis of Drug Problems

• drug abuse is diagnosed by 1 (or more) out of 4 criteria, within the previous 12 month period (“Bad choice behavior”)

• chemical dependence is diagnosed by 3 (or more) of 7 criteria, within the previous 12 month period (“Brain disease”)

The **main symptom** of chemical dependence (a.k.a. “addiction”) is “impaired control over the use of a drug”.

It is **NOT** hangover, blackouts, amount of drug taken, withdrawal signs, criminal behavior, or anything else (DSM-IV).  *(This is still true in DSM-5.)*
DSM-IV Weaknesses

- subjective
- not accurate for adolescent diagnoses
- not accurate for geriatric or infant diagnoses
- often used for diagnosis by computer (e.g., SCID)
- often used by untrained personnel

**Better:**

- trained assessment counselor/technician
- use as part of a battery of diagnostic tests

(most of these weaknesses remain in DSM-5)
Why is DSM important?

- provides **diagnostic criteria** for mental disorders and **drug problems**
- influences **how doctors diagnose and treat** their patients
- insurance companies use it to **determine coverage and reimbursement** (U.S.)
- determines how pharmaceutical companies **design clinical trials and how research is done**
- determines how **funding agencies decide** which research to fund
(New) DSM-5(1)

• the terms “abuse” and “dependence” have been dropped
• instead, the phrase “substance-use disorder” (SUD) is described under the general heading “Addiction and Related Disorders”
• there is one longitudinal category, with 11 criteria
• there are severity specifiers: mild = 2-3 criteria; moderate = 4-5 criteria; severe = 6 or more
but do not count tolerance or withdrawal if medications are under medical supervision (!?)

the new category includes one non-substance addiction: gambling disorder

“internet addiction” and “caffeine addiction” will be considered if more research indicates (until then, placed in an Appendix in DSM-5)
An “addiction” challenge!

• For anyone **who wishes to call** the following “addictions”:
  - pornography  - religion
  - bicycling  - oil (as in petroleum oil)
  - Tivoli Gardens  - tanning booths

• **Are you aware** that science is **not** on your side? What is the **incidence** of the problem? Where are the **genetic** causes?

• Instead of **trying to describe these as having qualities similar to drug addiction**, is there another way?

• **Why not “obsession”?** Or “compulsion”? Why is it important **to call them** an “addiction”?

(Dilemma: It’s not whether compulsive behaviors exist with some of these, it’s what to call them!)
Problems with the DSM-5 changes

• **not agreed upon** by the National Institute of Mental Health (NIMH, U.S.) – too symptom-driven
• felt by some to be biased in favor of the **pharmaceutical industry**
• the research cited in making these decisions is **scanty** (severity, craving)
• where is **the disease** in the new definition?
DSM-5: Substance use disorders (SUDs) lie on a continuum of severity that ranges from “no substance problem” to “severe substance problem”

- no more “abuse” or “dependence” terms
- severity specifiers: mild, moderate, severe
- a separate monograph for each drug/group
- includes gambling, for the first time (but no other compulsive behaviors)
How do we merge the two DSM editions?

This seems to be happening:

• mild – moderate: similar to DSM-IV category of “abuse”

• severe: similar to DSM-IV category of “dependence”

But the emphasis in DSM-5 is on the idea that “disease” develops somewhere along the continuum – perhaps at different times for different patients. (In my opinion, this reduces the clarity of the diagnosis.)
WHAT DOES THIS MEAN FOR CLINICIANS AND TREATMENT PROFESSIONALS?

(the terminology of “addiction” is changing....)
RESEARCH VALIDITY ESTIMATE (RVE)

(A Thoughtful Appraisal of High-Quality Scientific Research)

High RVE
• many large, well-controlled studies
• replicable results
• much peer-reviewed, published literature

Low RVE
• few replicable studies
• highly speculative results
• little peer-reviewed, published literature
Who develops a severe SUD?
Drug Users Who Developed Chemical Dependence*

(U.S. Epidemiological Estimates, 1992-98):

- nicotine - 32%
- heroin - 23%
- cocaine - 17%
- alcohol - 15%
- stimulants other than cocaine - 11%
- cannabis - 9%
- “sedatives” - 9%
- analgesic opioids – 9%
- psychedelics - 5%
- inhalants - 4%

(*Now, SUD patients with 6 or more diagnostic criteria)

Anthony et al., 1994
Chen & Anthony, 2004
Hughes et al., 2006
WHERE CAN I GET THESE REFERENCES?

www.utexas.edu/research/asrec
NEUROSCIENCE UPDATE
The bottom line first.....

A severe SUD occurs because of neurochemical dysregulation of the mesolimbic dopamine system (MDS)*

* a.k.a. Medial Forebrain Bundle (MFB) or “Pleasure Pathway” or “Reward Pathway”
What are you doing?

Trying to regulate my dysregulation.
“Addiction” Brain Areas - Historically

- mesolimbic dopamine system
- “key elements of a basal forebrain macrostructure”

**extended amygdala**
- central nucleus of amygdala
- bed nucleus of the stria terminalis
- transition zone, medial (shell) of the nucleus accumbens
“Addiction” Brain Areas - Newer

**binge/intoxication stage:** ventral tegmental area, ventral striatum

**withdrawal/negative affect stage:** extended amygdala

**preoccupation/anticipation stage:** craving: orbitofrontal cortex-dorsal striatum, prefrontal cortex, basolateral amygdala, hippocampus, insula; **disrupted inhibitory control:** cingulate gyrus, dorsolateral prefrontal, inferior frontal cortices

Koob and Volkow (2010)
Circuits Involved In Drug Abuse and Addiction

All of these brain regions must be considered in developing strategies to effectively treat addiction
WHERE IS THE PROBLEM WITHIN THESE BRAIN AREAS?
What happens?

Drug actions reveal vulnerable brain chemicals

- cocaine, amphetamines - dopamine (DA)
- LSD - serotonin (SER)
- heroin - endorphins (END)
- benzodiazepines – gamma-aminobutyric acid (GABA)
- nicotine - acetylcholine (ACH)
- alcohol (ETOH) - glutamate (GLU)
  - substance P (SUBP)
- marijuana - endocannabinoids (ENCB)
Emerging “drugs of choice” groupings

- DA - amphetamines, cocaine, ETOH
- END - opioids, ETOH
- ACH - nicotine, ETOH
- GABA - benzodiazepines, ETOH
- SER - LSD, ETOH
- GLU - ETOH
- SUBP - ETOH
- ENCB - marijuana, ETOH
Thus, drugs are associated with specific neurotransmitters.

- We assume that genetics + drug-use lead to "dysregulation" of MDS neurotransmitter systems.
- When people use, the drugs "connect" with the specific dysregulated neurotransmitter system.
- This may be why people have "drugs of choice"
WHAT DOES THIS MEAN FOR CLINICIANS AND TREATMENT PROFESSIONALS?

(neurobiology explains a lot...)
Let’s think “outside the box”

What causes the disease?
(compare with Parkinson’s disease)
Dysregulation =

- **continued exposure** of the MDS pathways to a drug leads to changes (adaptations) in nerve function, called “neuroadaptations”
- the changes reach a **threshold**
- ….leading to **compulsive use** over which the individual has **impaired control** (symptom of the disease)
Current research suggests that the site of dysregulation is the **cell receptor**!

(With nicotine, we are now even discovering **subunits** of the nicotinic receptor!)
What causes the neurotransmitter systems to become “dysregulated”?

• genetic vulnerability
• exposure to a drug
• other aspects of the environment, besides drugs?
RATIONALE BASED ON GENETICS

abnormal genes → abnormal proteins

abnormal transmitter synthesizing enzymes
abnormal transmitter breakdown enzymes

ABNORMAL RECEPTORS

neurotransmitter dysregulation in the pleasure pathway

impaired control over drug use
WHAT DOES THIS MEAN FOR CLINICIANS AND TREATMENT PROFESSIONALS?

(dysregulation of the MDS is the problem, and genetics helps us better understand the cause of the disease)
Severe SUD –
A Brain Chemistry Disease!

• “addicting” drugs “match” the transmitter system that is not normal
• genetic susceptibility is clearly involved - but onset time is variable
• cases of SUD range from mild to severe
• remember, this is not mild SUD!
• methadone and nicotine maintenance is evidence that some people require a chemical to overcome the non-normal transmitter system
TREATMENT OF SUBSTANCE USE DISORDERS
HARM REDUCTION
What IS harm reduction?

- assuming a person will use drugs; attempt to reduce harm to the user and those around the user
  - methadone
  - needle exchange programs
  - safe injection neighborhoods
  - controlled drinking
What IS harm reduction?

• assuming a person will use drugs; attempt to reduce harm to the user and those around the user
  - methadone
  - needle exchange programs
  - safe injection neighborhoods
  - controlled drinking
  - educating the public about the dangers of drunk driving
METHADONE
Characteristics of a Good Methadone Program

Example: to replace street use of heroin with use of an oral opioid in a controlled environment

- methadone taken in front of an employee
- regular drug screens
- steady job
- counseling to get off the medication
Treatment of SUD in different countries

• I am most familiar with treatment in the U.S.
• From what I can tell, treatment in Denmark is similar
• What are some of the characteristics of treatment in Denmark? Scandinavia?
• U.K.?
• Greece?
• Other countries?
• evidence-based
• broad range of diagnosis and treatment
• mainly abstinence-based
• diagnosis through DSM criteria
• relapse prevention
• education about prevention, diagnosis, and treatment
What is “recovery”? 

Recovery from *substance dependence* is a *voluntarily maintained lifestyle* characterized by: 

- **sobriety** - abstinence from *alcohol and all other non-prescribed drugs* (including nicotine)

*Betty Ford Institute Consensus Panel (2007)*
What is “recovery”?

AND

- **personal health** - improved quality of personal life as defined and measured by scores on the physical health, psychological health, independence, and spirituality scales of the WHO QOL inst.

- **citizenship** - improved quality of social function as defined and measured by scores on the social function and environment scales of the WHO QOL instrument
3 - What is “recovery”?

• “**Sobriety** is best achieved through the practice of abstinence from alcohol and all other drugs of abuse.” There is not yet agreement regarding recovery facilitated by **psychosocial and pharmacological** treatments.

• **Early sobriety** = 1 - 11 months

  - **Sustained sobriety** = 1 - 5 years
  - **Stable sobriety** = 5 years or more
WHAT DOES THIS MEAN FOR CLINICIANS AND TREATMENT PROFESSIONALS?

(new research might change what we know about recovery)
Treatment options in the 1960’s (U.S.)

- 12-step programs
- the beginning of inpatient treatment
- the beginning of outpatient treatment
- emergency rooms and jails where people could “sleep it off” – and then go back on the street again
Today’s treatment options
(Options to initiate recovery....)

- traditional (in U.S.): **12 step programs** (abstinence)
- behavioral: individual/group counseling
- misunderstood (U.S.): **harm reduction**, MM
- new: **motivational interviewing**, CBT, MET, primary care management, vouchers
- **medications**: detox meds, meds to enhance abstinence/reward blockers, methadone, buprenorphine, vaccines

*(evidence-based, or “research proven”)*

(MM= Moderation Management, CBT= cognitive behavioral therapy, MET= motivational enhancement therapy)
Current Medications

• naltrexone (ReVia, Vivitrol*) - alcohol
• acamprosate (Campral, Fr.-Aotal) – alcohol
* Also used in opioid treatment
• methadone (generic) - opioids
• buprenorphine (Subutex, Suboxone) - opioids, such as heroin
• bupropion (Zyban) - nicotine
• varenicline (Chantix, Champix) – nicotine
• disulfiram (Antabuse) - works on the liver, generally not effective for treating alcohol dependence
What’s new in medication development?

**Alcohol**
- nalmefene (END, no other major use)
- topiramate (Topamax, GABA/GLU, migraine etc.)
- ondansetron (Zofran, SER, nausea/vomiting)
- quetiapine (Seroquel, DA?, antiSZP, bipolar)
- aripiprazole (Abilify, DA?, antiSZP, bipolar)

**Cocaine**
- disulfiram (Antabuse, DA, GABA?)
- methadone (generic, END)
- gabapentin (Neurontin, GABA, anticonvulsant)
- baclofen (generic, GABA, muscle relaxant)
- modafinil (Provigil, GLU, anti-narcolepsy)
What about electronic cigarettes (e-cigarettes)?
Pharmacogenetics!

- the “personalization” of pharmacotherapy, based upon genetic factors – i.e., predictors of drug response, or to target medication effects.
- controversial as to whether pharmacogenetic testing in the clinic should be started, with such preliminary studies.
  
  E.g., mu-opioid receptor gene **OPRM1**; carriers of the G-allele of the **A118G** polymorphism showed a **better response to naltrexone in treating alcohol dependence**.
2. Alcohol-dependent patients with LL genotype of SERT had a better response to ondansetron

3. CYP2A6 rapid metabolizers are less likely to achieve a positive result with NRT

4. ANKK1 Taq1A polymorphism predicts bupropion vs. NRT response

Sturgess et al., 2011
Johnson et al., 2011
12-Step Philosophy Questions

“Once abstinent, one must avoid all mood-altering drugs”

- Is this still good advice?
- What about people in recovery with chronic pain?
- What about 12-step meetings that do not allow people to attend when they are taking antidepressants?
- What about “liberal” groups that take in anyone with an “addiction”?
WHAT DOES THIS MEAN FOR CLINICIANS AND TREATMENT PROFESSIONALS?

(although medications can help, counseling and 12-steps still predominate in the U.S., because medications have not yet proven themselves, and physicians are not yet as involved as they should be)
Medical education trends (U.S.)

SBIRT:
- **Screening** (At least, SBI...)
- **Brief Intervention**
- **Referral to Treatment**

Also:
- **SIMS:** Summer Institute for Medical Students
  (1 week, Hazelden Betty Ford, others)
- some schools: training in addiction medicine during **residencies** (U.S.)
Overall validity of today’s story

• Individual validities add up:
  - neurotransmitter story = medium RVE
  - genetics story = medium RVE
  - medication mechanisms = medium RVE

Three stories independently supporting neurotransmitter dysregulation = very high validity!
Science is Compatible with the Big Book!

- “addiction is an illness” (p. 18)
- “people drink to overcome a craving beyond their mental control” (p. xxviii)
- “no controlled drinking for us” (p. 31)
- “some drinkers can drink moderately” (p. 34)

Alcoholics Anonymous, Third Edition
Is there a common mechanism of action for “talk therapies” and medications?
If chemical dependence is a brain disease and people get better with treatment, logic says that:

**Behavioral Therapies Probably Change Brain Chemistry!**
BRAIN IMAGING STUDIES ARE HELPFUL
New Brain Scan Research...

- **Psychotherapy** and **meds** work on the basal ganglia in the treatment of **depression**  
  *Martin et al., 2001*

- **CBT** and **meds** work on the same brain areas in treating **social anxiety**  
  *Furmark et al., 2002*

- **CBT** appears to modify “bad circuits” associated with **anxiety disorders**  
  *Paquette et al., 2003*
Pre-treatment  Post-treatment

Z = -2
Z = -2
SO, IT APPEARS THAT THE MDS DYSREGULATION BEGINS TO MOVE BACK TOWARDS NORMAL WITH TREATMENT

It cannot be totally normalized - just “pushed back” towards normal, in much the same way that medications change brain chemistry.

(For some people, spirituality – or “revelation” – seems to be a very effective way to do this!)
WHAT DOES THIS MEAN FOR CLINICIANS AND TREATMENT PROFESSIONALS?

(The way treatment works is becoming better understood through research)
CONCLUSIONS
We now have a choice

- there is now research evidence for the effectiveness of the 12-step mutual-help programs (Donovan, Galanter, Humphreys, Kaskutas, Kurtz, Laudet, McCrady, Miller, Moos, Tonigan, others)
- there have been many other research advances, mostly in neurobiology/genetics
- yet some say our field (U.S.) has not moved forward much in the past 70+ years (I disagree)
- choices: continue what works, or look to the science for new ideas to help those still suffering...... (or both!)
Finally, please remember...

- Our field is in transition, and previously erroneous folklore is becoming clearer - through new research.
- For the latest science: www.pubmed.gov
- This new information requires an open mind and the curiosity to learn new things - while we continue to help those who are still suffering....
References

- bibliography: www.utexas.edu/research/asrec
TAK!