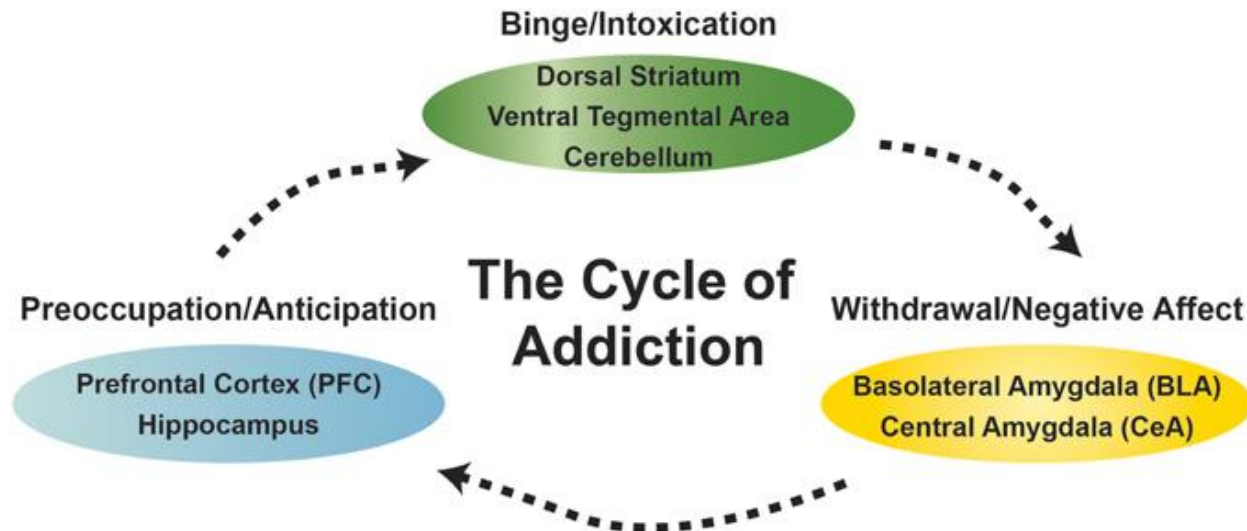


Citicoline in addictive disorders



Addictive disorders

- Addictive disorders are significant public health concerns because they are common, associated with poor outcomes, and result in significant health and economic burdens.



Back to History

- Smoking of Cannabis is known in India since 2000 B.C.
- The Code of Hammurabi (1792-1750 BC) the oldest known form of legal code, had guidelines and regulatory provisions for preventing alcohol abuse.



**King Hammurabi
(1792-1750 BC)**



Code of Hammurabi

Back to History

- By the middle of sixteenth century, drugs like cocaine, tobacco and hallucinogens were introduced from America to Europe, in exchange of wine, cannabis and narcotics.
- By the late 19th century cocaine kits were readily available in western world.
- Harrison Act (1914): made the possession of narcotics without a prescription a criminal offense.



Cocaine Kits

WHO Definitions

- **Drug Use:** is simply the ingestion of substance/substances without experiencing any negative consequences. It may be social use, like in parties; recreational or experimental use, dietary practice or may be religious ritual.
- **Drug abuse:** the use of any substance for purposes other than medical and scientific, including use without prescription, in excessive dose levels, or over an unjustified period of time.

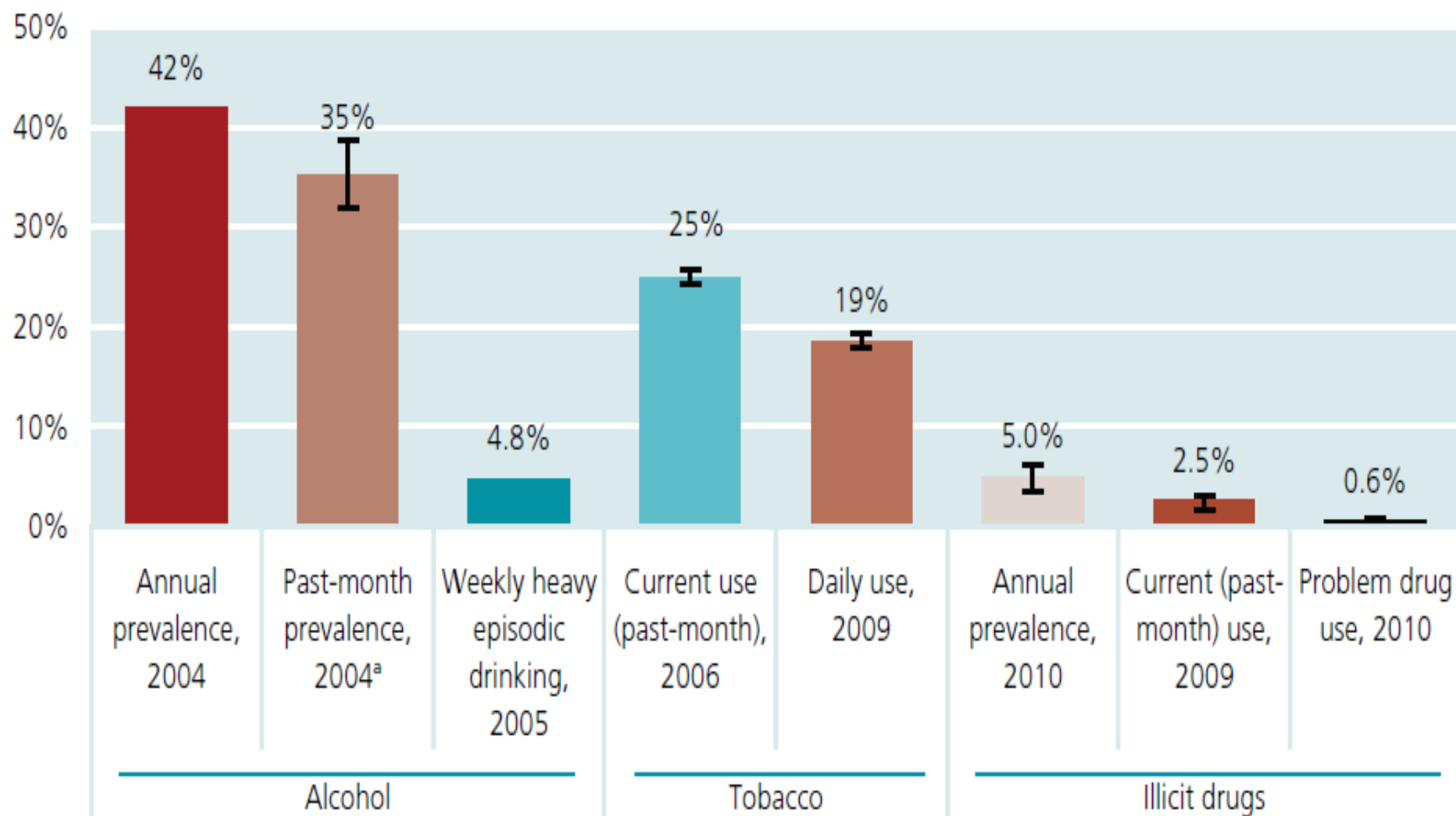
WHO Definitions

- **Addiction:** is defined as the repeated use of substance/drugs to the extent that the user is periodically or chronically intoxicated, shows a compulsion to take the preferred substance (or substances), has great difficulty in voluntarily ceasing or modifying substance use, and exhibits determination to obtain psychoactive substances by almost any means.
- **Dependence:** is defined as “a cluster of cognitive, behavioural and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems”.

Problem statement

- According to World Drug Report ≈230 million people, or 5% of the world's adult population, are estimated to have used an illicit drug at least once.
- 10-13 % of drug users continue to be problem users.
- The prevalence of HIV (20%), hepatitis C (46.7%) and hepatitis B (14.6 %) among injecting drug users continues to add to the global burden of disease.
- Annual prevalence of use of alcohol is 42 % (the use of alcohol being legal in most countries), which is 8 times higher than annual prevalence of illicit drug use (5%)
- Approximately 1 in every 100 deaths among adults is attributed to illicit drug use.

Fig. 1. Use of licit versus illicit psychoactive substances among youth and the adult population (Percentage)



Source: Estimates for illicit drugs based on UNODC data from the annual report questionnaire; alcohol statistics: World Health Organization, *Global Status Report on Alcohol and Health* (Geneva, 2011); and *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks* (Geneva 2009); tobacco statistics: World Health Organization, *World Health Statistics 2010* (Geneva 2010).

^aTentative estimate.

Table 1. Estimated number of drug-related deaths and rates per million population aged 15-64

Region	Number of all drug users (thousands)	Prevalence (percentage)	Number of drug-related deaths	Mortality rate per million aged 15-64
Africa	22,000-72,000	3.8-12.5	13,000-41,700	22.9-73.5
North America	45,000-46,000	14.7-15.1	44,800	147.3
South America	10,000-13,000	3.2-4.2	3,800-9,700	12.2-31.1
Asia	38,000-127,000	1.4-4.6	14,900-133,700	5.4-48.6
Europe	36,000-37,000	6.4-6.8	19,900	35.8
Oceania	3,000-5,000	12.3-20.1	3,000	123.0
Global	153,000-300,000	3.4-6.6	99,000-253,000	22.0-55.9

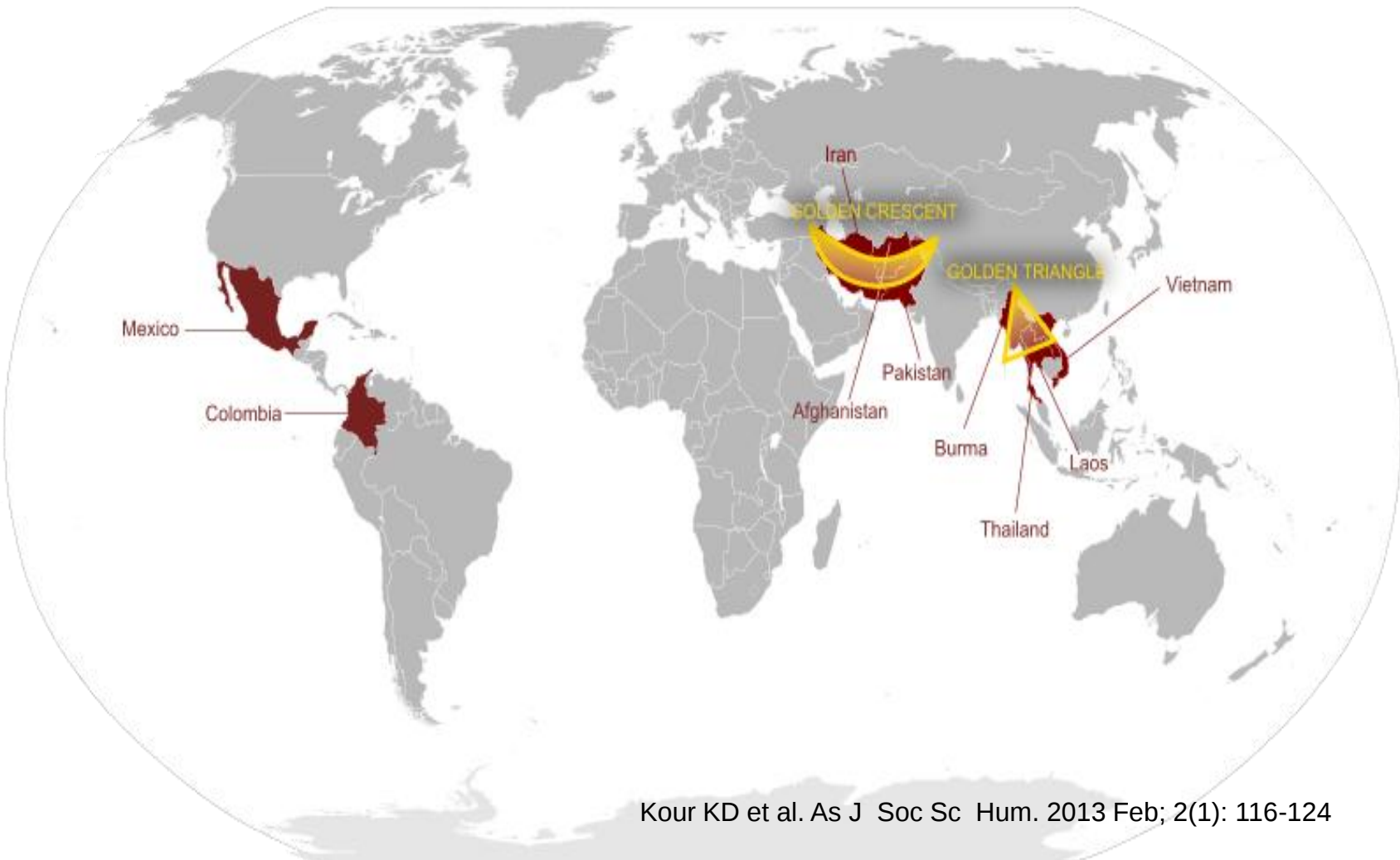
Source: UNODC, data from the annual report questionnaire; Inter-American Drug Abuse Control Commission; European Monitoring Centre for Drugs and Drug Addiction; Louisa Degenhardt and others, "Illicit drug use", in *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*, vol. 1, Majid Ezaati and others, eds. (Geneva, World Health Organization, 2004).

Note: Data for South America include data from Central America and the Caribbean. Data for Oceania are based on data from Australia only and therefore no range is given.

Problem statement

- India is located close to the major illicit opium growing areas of the world, with- “Golden Crescent” on the Northwest and “Golden Triangle” on the North–East.
- Illicit substances (alcohol and tobacco) are the most commonly used substances.
- Among illicit substances, cannabis and opiates are most frequently used.

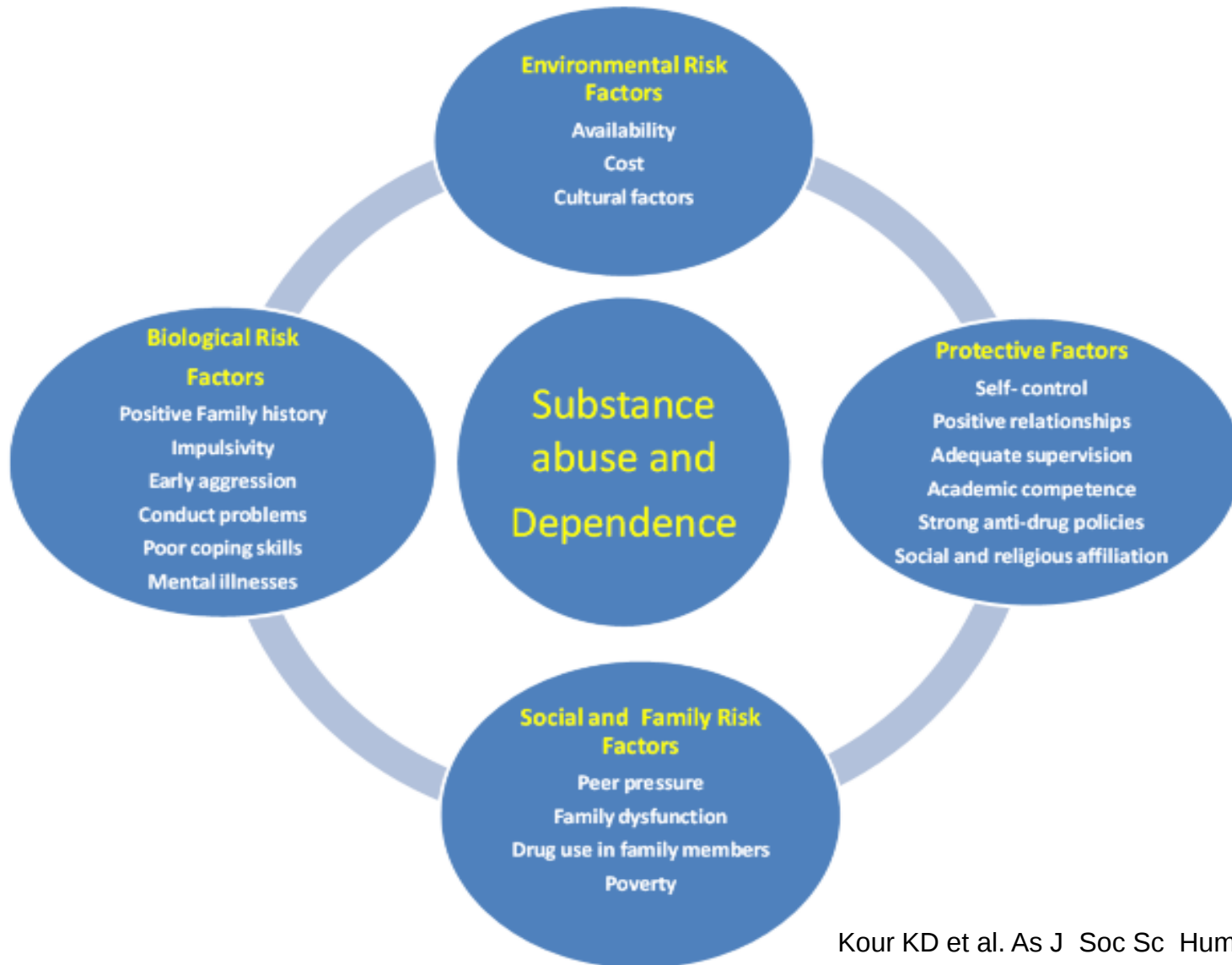
“Golden Crescent” and “Golden Triangle”



Drugs of Abuse

- The major categories include:
 - ▣ Alcohol
 - ▣ Nicotine and tobacco
 - ▣ Depressants (barbiturates, benzodiazepines)
 - ▣ Stimulants (amphetamines, cocaine)
 - ▣ Marijuana
 - ▣ Opioids (morphine, heroin, methadone)
 - ▣ Psychedelics (LSD, mescaline, ecstasy)

FACTORS INFLUENCING SUBSTANCE ABUSE AND DEPENDANCE



Substance-Use & Addictive Disorders (DSM-5)

Substance-Use Disorder

- The Severity of each Substance Use Disorder is based on:
 - 0 criteria or 1 criterion: **No diagnosis**
 - 2-3 criteria: **Mild Substance Use Disorder**
 - 4-5 criteria: **Moderate Substance Use Disorder**
 - 6 or more criteria: **Severe Substance Use Disorder**

- Among adolescents, **2 or 3 criteria** identify a group with severity of alcohol use disorder very close to that of adolescents with DSM-IV **alcohol abuse**, while **4 or more criteria** identify a group with severity very close to that of **DSM-IV dependence**. Using criterion counts results in much more homogeneous groups than DSM-IV's abuse and dependence groups.

- In the empirical research among adults, the proposed cutoff points have been shown to yield similar prevalence and high concordance in relation to the combined DSM-IV substance abuse and dependence diagnoses. **However, it is still unclear as to whether 4-5 or 6 or more constitute what used to be substance dependence in adults.**

DSM 5 CRITERIA FOR SUBSTANCE USE DISORDER

These symptom criteria must be present within the past 12 months and lead to “clinically significant impairment or distress.”

1. _____ is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control _____ use.
3. A great deal of time is spent in activities necessary to obtain _____, use _____, or recover from its effects.
4. Craving, or a strong desire or urge to use _____.
5. Recurrent _____ use resulting in a failure to fulfil major role obligations at work, school, or home.
6. Continued _____ use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of _____.

Addiction Redefined from DSM-IV to DSM-5

DSM-IV Abuse

- Failure to fulfill role obligations
- Hazardous use
- Recurrent legal problems due to use
- Continued use despite recurrent problems

DSM-IV Dependence (Abuse +)

- Tolerance
- Withdrawal
- Unintended use
- Unsuccessful attempts to cut down
- Excessive activity to obtain or recover
- Important activities reduced due to use
- Continued use despite problems caused by use

DSM-5 Substance Use

- Larger amounts than intended
- Unsuccessful efforts to cut down
- Excessive time to obtain, use or recover
- Craving or strong desire to use
- Failure to fulfill role obligations
- Continued use despite recurrent problems
- Important activities reduced due to use
- Hazardous use
- Continued use due to a problem caused by the substance
- Tolerance
- Withdrawal

- Mild (2-3 symptoms)
- Moderate (4-5 symptoms)
- Severe (6 or more symptoms)

Current Challenge

- Addictive disorders are significant public health concern.
- Associated with poor outcomes, and result in significant health and economic burdens.
- Developing effective treatments for addictive disorders remains a significant challenge
- Many patients still do not respond to either single or multiple treatment interventions, and effect sizes for these interventions remain modest

A Newer Paradigm

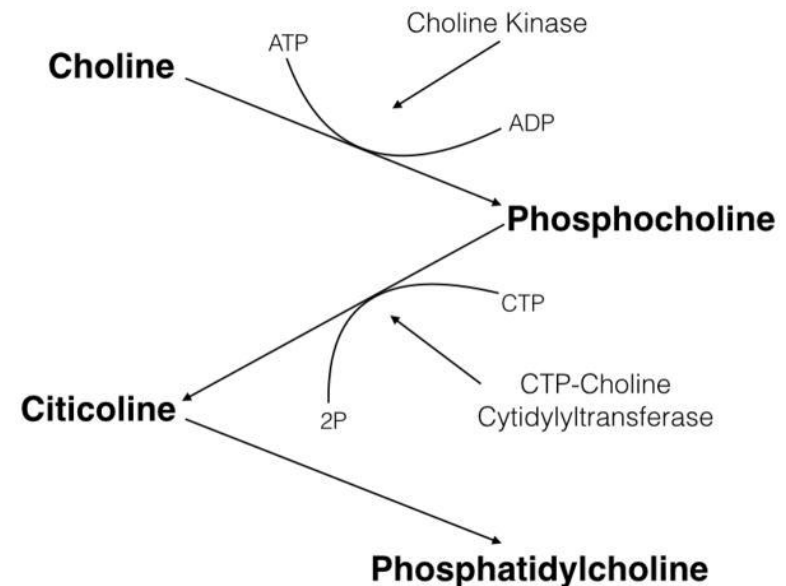
- Citicoline is a potentially promising pharmacological intervention for the addictive disorders population may be
- Citicoline, a dietary supplement widely studied
- Clinical applications have primarily focused on cognitive impairment and stroke recovery populations,
- Past several years have seen increased interest in citicoline as a novel agent in the treatment of addictive disorders.



Role of Citicoline

Citicoline

- Citicoline is useful in a *variety of neurological* disorders, because of its ability to enhance the integrity and function of neuronal membranes.
- Citicoline is a nucleotide composed of cytosine, choline, ribose, and pyrophosphate.
- After oral administration, citicoline has a greater than 90% bioavailability and is rapidly metabolized to cytidine and choline

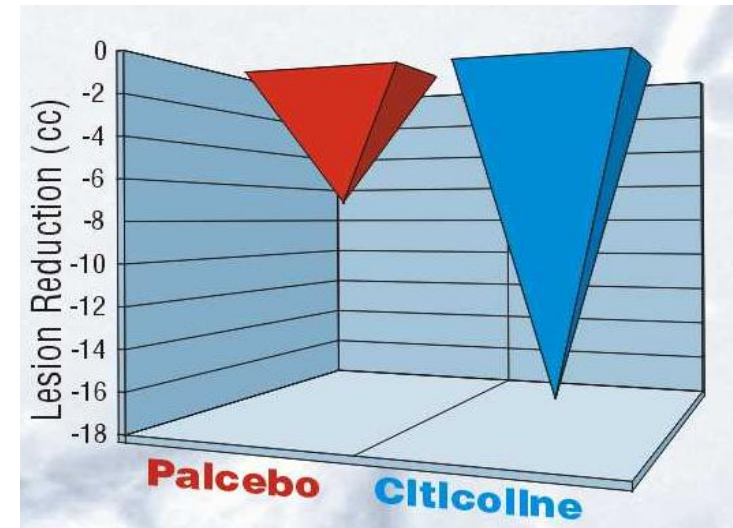


Citicoline in Neurological Diseases

- Citicoline is most widely used as a neuroprotective agent in neurological disorders, including:
 - ▣ Stroke
 - ▣ Traumatic brain injury
 - ▣ Dementia,
 - ▣ Parkinson's Disease,
 - ▣ Glaucoma

Citicoline in Stroke

- Since 1980's , 13 trials have been done with citicoline in stroke management
- 9 in Europe & Japan, 4 in the U.S.
- European trials showed citicoline improved global & neurological function, earlier motor & cognitive recovery
- Large multicenter studies in Japan showed citicoline improved global outcome rating scale
- Subsequent analysis showed citicoline treatment for 6 weeks improved overall recovery at week 12



N=100

Citicoline 500mg/day for 6 Wks

Significant decrease in lesion volume by 17.2 cc compared to placebo by 6.9 cc at 12 weeks as measured by MRI.

Citicoline in HEAD INJURY

- Accelerates the recovery of neurological symptoms
- Accelerates the resolution of brain edema on CT
- Reduces hospital stay
- Better quality in the evolution
- Improves the global functional outcome
- Reduces post-concussional syndrome

Citicoline in DEMENTIA and PD

□ DEMENTIA

- Citicoline effective for cognitive impairment in vascular dementia and is well tolerated: Cochrane review

- Fioravanti M et al. The Cochrane database of systematic reviews. 2005; (2):CD000269.

- Citicoline therapy in elderly patients with mild cognitive impairment shows improvements in verbal memory

- Spiers PA et al. Archives of neurology. 1996; 53 (5):441–448

□ In Parkinson Disease

- Citicoline therapy shows improvement in bradykinesia, rigidity & tremors
- Allows reduction of levodopa ,hence reduces levodopa related adverse effects
- Discontinuation of citicoline worsens symptoms

Citicoline in Addictive Disorders

- Studies examined efficacy or potential mechanisms for citicoline in addictive disorders
- Interest has grown in citicoline as a treatment for addiction as it shows beneficial effects on
 - ▣ craving, withdrawal symptoms
 - ▣ cognitive functioning &
 - ▣ ability to attenuate the neurotoxic effects of drugs of abuse.



Possible Mechanisms of action

- ❑ Citicoline affects neurotransmitter levels primarily through modulation of catecholaminergic neurotransmission
- ❑ **Citicoline:**
 - increases 5-HT in the cerebral cortex, striatum, and hypothalamus
 - increases ACh in the hippocampus and neocortex
 - reduce brain glutamate activity by increasing expression of excitatory AA transporter-2 (EAAT2)
 - increases tyrosine levels in the striatum and also stimulates tyrosine hydroxylase activity and DA release

Short-term treatment with citicoline attenuates some measures of craving in cocaine-dependent subjects

- Outpatient study to assess the safety of citicoline (500 mg bid)
- To determine if short-term treatment alters mood states and cocaine craving in subjects with a history of cocaine dependence.
- Measures of drug craving and mood states after presentation of cocaine-related cues on two occasions: before and after 14 days of double-blind treatment with either citicoline or placebo.
- Results:
 - **Citicoline treatment was associated with decreases in self-reported mood states associated with cocaine craving**
 - **No side effects reported**

Randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence.

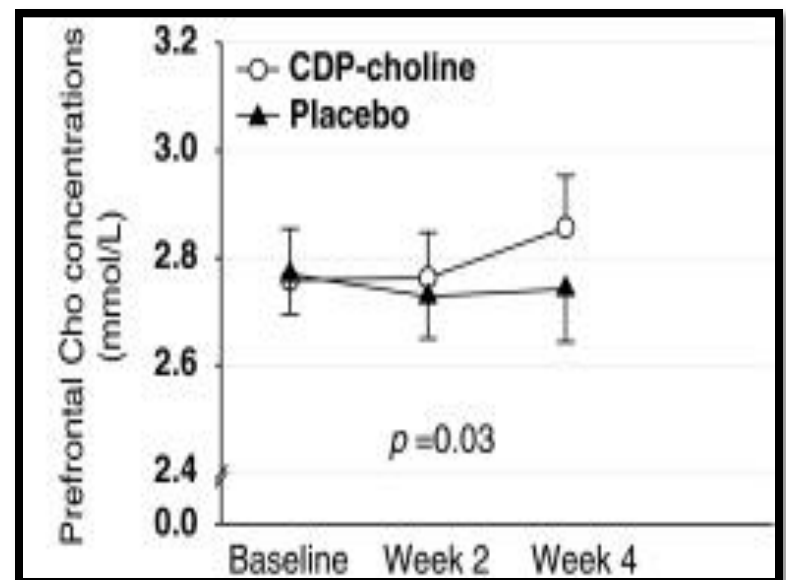
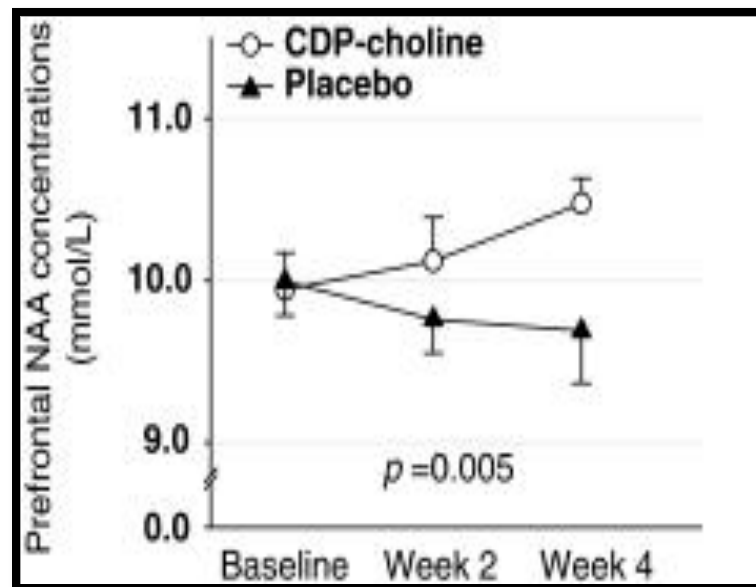
- A 12-week, randomized, placebo-controlled, parallel-group trial of citicoline
- N= 44 outpatients with a history of mania or hypomania and cocaine dependence
- Evaluation:
 - ▣ Structured diagnostic interview
 - ▣ Inventory of Depressive Symptomatology-Self-Report
 - ▣ Young Mania Rating Scale
 - ▣ Rey Auditory Verbal Learning Test
 - ▣ Cocaine use was assessed with urine drug screens

Results:

- A significant group effect ($P = 0.006$) favoring citicoline on RAVLT alternative word list.
- No significant between-group differences on the IDS-SR or YMRS
- The citicoline group had a significantly lower probability of a cocaine-positive urine at exit ($P = 0.026$).
- The covariate-adjusted odds ratio estimate was 6.41, suggesting that those who took placebo had 6.41-times higher odds of testing positive for cocaine at exit than those who took citicoline.
- Citicoline was well tolerated, with no discontinuation due to adverse effects

Neurochemical Alterations in Methamphetamine Dependent Patients Treated with citicolin

- 4-week, double-blind, placebo-controlled study
- Neurochemical effects and the efficacy of CDP-choline in MA-dependent subjects.
- Generalized estimating equation regression analyses showed that the rate of change in prefrontal NAA ($p=0.005$) and Cho ($p=0.03$) levels were greater with CDP-choline treatment than with placebo.



Neurochemical Alterations in Methamphetamine Dependent Patients Treated with citicoline

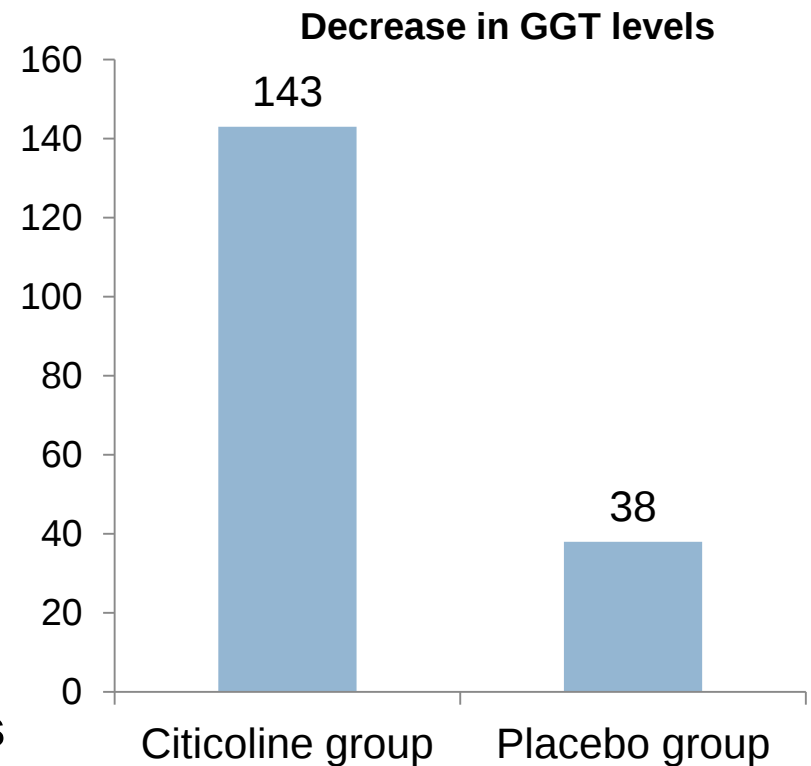
- In the CDP-choline-treated patients, changes in prefrontal NAA levels were positively associated with the total number of negative urine results ($p=0.03$).
- Changes in the prefrontal Cho levels, however, were not associated with the total number of negative urine results.

CONCLUSION:

- **CDP-choline treatment exert potential neuroprotective effects directly or indirectly because of reductions in drug use by the MA-dependent patients.**

Citicoline in an alcohol dependent population

- Randomized 20 volunteers with alcohol dependence to citicoline or placebo.
- After 60 days citicoline group showed greater improvement than placebo on measures of
 - Attention
 - concentration
 - temporo-spatial orientation,
 - Significant decrease in gamma-glutamyltransferase (GGT) levels



Citicoline in Addictive Disorders

Authors	Substance	N	Design	Dosing	Findings of interest
Chinchilla et al., 1995	Alcohol	20	Double-blind, placebo-controlled	1,000 mg/day	Improved attention, concentration, and orientation in the citicoline group.
Renshaw et al., 1999	Cocaine	14	Double-blind, placebo-controlled	500 mg/day	Increased control and decreased craving with citicoline compared to placebo.
Lukas et al., 2001	Cocaine	8	Double-blind, placebo-controlled, crossover	1,000 mg/day	Citicoline safe and well tolerated but no changes in cocaine use.
Brown et al., 2007	Cocaine	44	Double-blind, placebo-controlled	2,000 mg/day	Citicoline associated with less cocaine use, increased declarative memory performance, and increased treatment retention.

Citicoline in Addictive Disorders

Authors	Substance	N	Design	Dosing	Findings of interest
Yoon et al., 2010	Methamphetamine	31	Double-blind, placebo-controlled	Up to 2,000 mg/day	Decrease in positive UAs with citicoline; increased NAA and Cho with citicoline.
Killgore et al., 2010	Food	16	Double-blind, placebo-controlled	500 vs 2,000 mg/day	Greater declines in appetite ratings and increased functional brain response to food stimuli in 2,000 mg/day group compared to 500 mg/day group.
Bracken et al., 2011	Cocaine	12	Double-blind, placebo-controlled	1,000 mg/day	No association between citicoline and sleep/wake disturbances.
Licata et al., 2011	Cocaine	29	Double-blind, placebo-controlled	1,000 mg/day	Citicoline safe and well tolerated but no changes in cocaine craving.
Brown & Gabrielson, 2012	Methamphetamine	48	Double-blind, placebo-controlled	2,000 mg/day	Citicoline group had a reduction in depressive symptoms, increased treatment retention,

Conclusion

- Citicoline appears to be a promising potential treatment for addictive disorders
- It is generally safe and well tolerated, even at higher doses
- Evidence suggests that citicoline may be useful in reducing cocaine use and possibly alcohol and cannabis use.
- Finally, future research may benefit from investigating the effects of citicoline in various stages of addiction;
 - because of its potential cognitively enhancing properties efficacy especially during the relapse prevention stage of treatment.

A word cloud featuring the phrase "Thank You" in numerous languages and colors. The central and largest text is "thank you" in red. Other prominent words include "danke" (blue), "gracias" (green), "merci" (orange), "dziękuję" (pink), "obrigado" (green), "sukriya" (purple), "arigatō" (pink), "terima kasih" (yellow), "mochchakkeram" (blue), "maith agat" (purple), "sagolun" (blue), "kop khun krap" (green), "najes tuke" (blue), "kam sah hammida" (blue), "rahmat" (blue), "xixie" (blue), "eucharistō" (blue), "dank je" (green), "misaotra" (blue), "matondo" (blue), "paldies" (blue), "grazzi" (blue), "mahalo" (blue), "tapadh leat" (blue), "hvala" (blue), "maururu" (blue), "kösönöm" (blue), "dhanyavad" (blue), "kiitos" (blue), "dankie" (blue), "nandri" (blue), "nanni" (blue), "spas" (blue), "welalin" (blue), "tack" (blue), "barka" (blue), "kia ora" (blue), "mersi" (blue), "vinaka" (blue), "spasibi" (blue), "blagodaram" (blue), "faafetai lava" (blue), "Баярлалаа" (blue), "спасибо" (blue), "рахмат" (blue), "teşekkür ederim" (pink), "ngiyabonga" (orange), "chnorakaloutioun" (blue), "gratias ago" (blue), "gracies" (blue), "sulpáy" (blue), "dijere dieuf" (blue), "tau" (blue), "dyaкую" (blue), "mamnun" (blue), "chokrane" (blue), "murakoze" (blue), "asante" (blue), "manana" (blue), "tenki" (blue), "trugarez" (blue), "merci" (orange), "shukriya" (blue), "merce" (blue), "merci" (orange), "arigatō" (pink), "takk" (blue), "dakujem" (blue), "go raibh maith agat" (purple), "sagolun" (blue), "sukriya" (purple), "kop khun krap" (green), "najes tuke" (blue), "kam sah hammida" (blue), "rahmat" (blue), "xixie" (blue), "eucharistō" (blue), "dank je" (green), "misaotra" (blue), "matondo" (blue), "paldies" (blue), "grazzi" (blue), "mahalo" (blue), "tapadh leat" (blue), "hvala" (blue), "maururu" (blue), "kösönöm" (blue), "dhanyavad" (blue), "kiitos" (blue), "dankie" (blue), "nandri" (blue), "nanni" (blue), "spas" (blue), "welalin" (blue), "tack" (blue), "barka" (blue), "kia ora" (blue), "mersi" (blue), "vinaka" (blue), "spasibi" (blue), "blagodaram" (blue), "faafetai lava" (blue), "Баярлалаа" (blue), "спасибо" (blue), "рахмат" (blue), "teşekkür ederim" (pink), "ngiyabonga" (orange), "chnorakaloutioun" (blue), "gratias ago" (blue), "gracies" (blue), "sulpáy" (blue), "dijere dieuf" (blue), "tau" (blue), "dyaкую" (blue), "mamnun" (blue), "chokrane" (blue), "murakoze" (blue), "asante" (blue), "manana" (blue), "tenki" (blue), "trugarez" (blue), "merci" (orange), "shukriya" (blue), "merce" (blue), "merci" (orange).