What Psychiatrists Need to Know About Amphetamine-Type Stimulants

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Abbreviations

- Amphetamine-Type Stimulants (ATS) – includes amphetamines and Methamphetamine (MA)

Amphetamine

Methamphetamine

- RCT = Randomised Controlled Trial

Overview

- What is the epidemiology of ATS use?
- What are the mechanisms of action of ATS?
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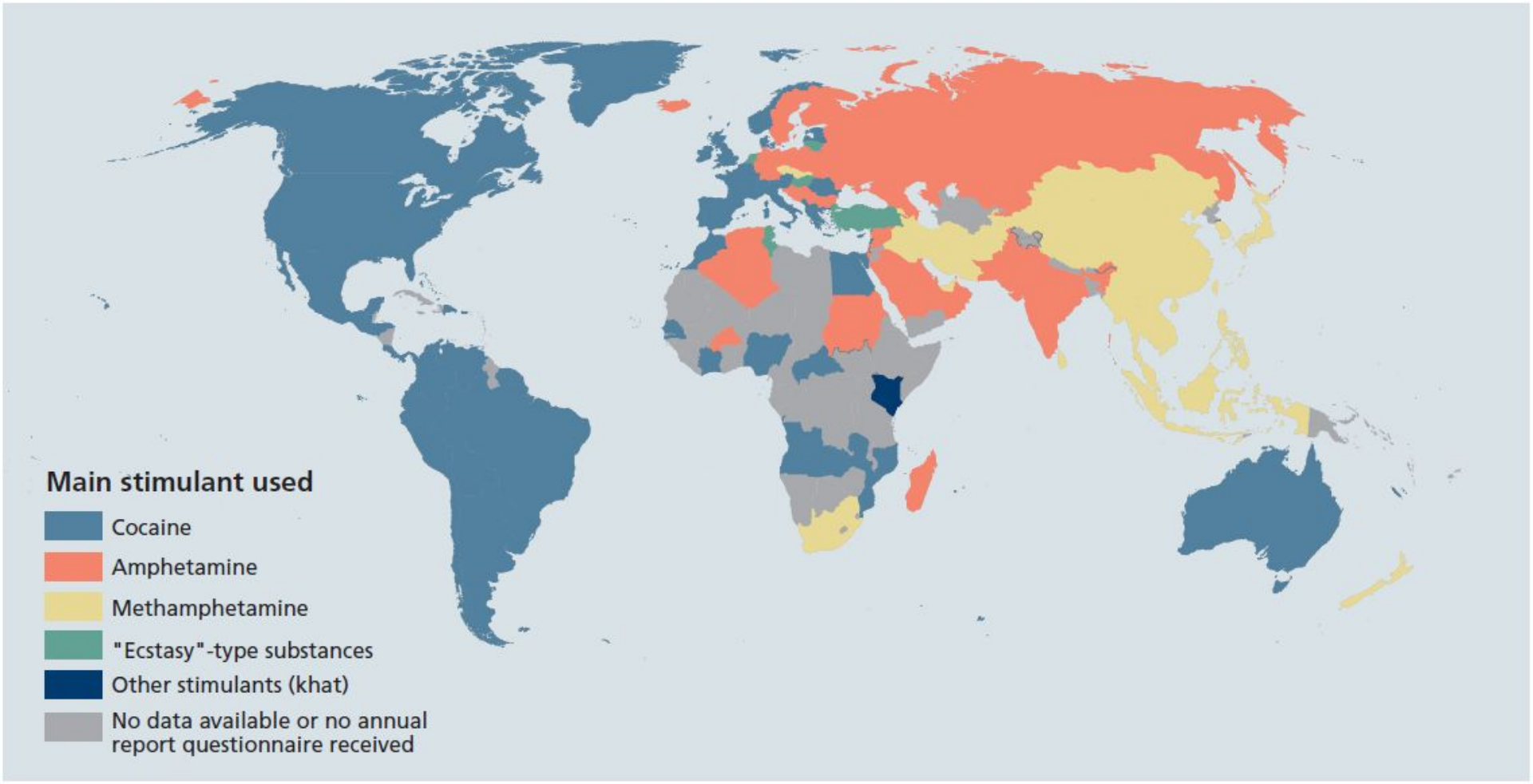
Main Stimulant Drug Used 2018

MAP 2 Main stimulant drug used, 2018 or latest available data



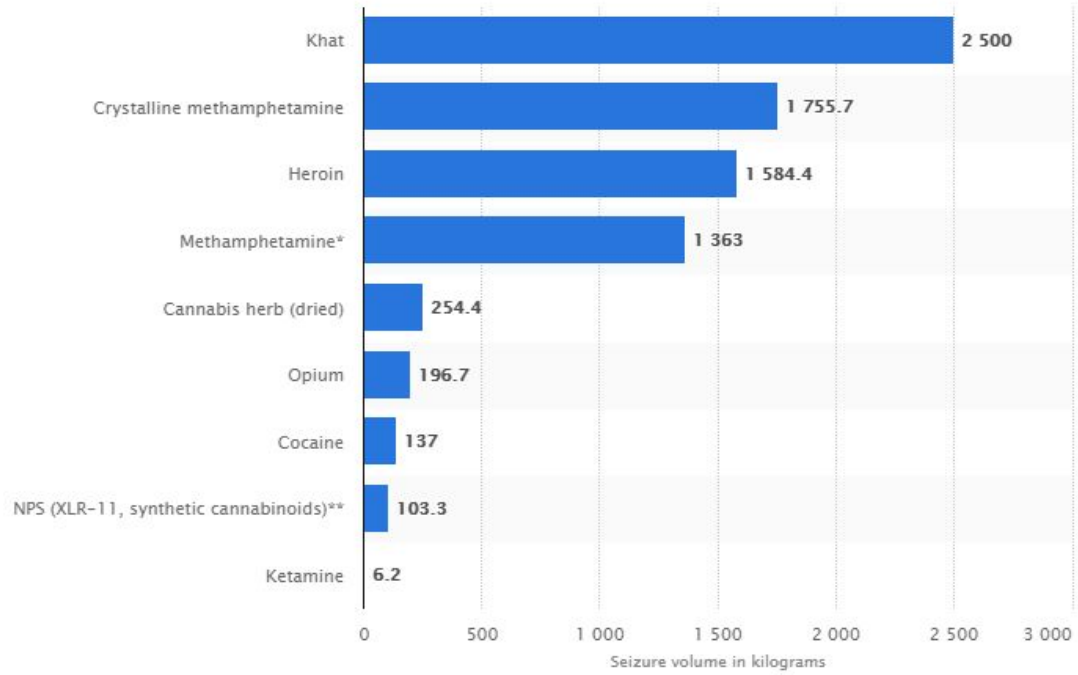
Source: UNODC, responses to the annual report questionnaire.

World Drug Report 2019 (United Nations publication)

Drug Seizures in Vietnam, 2018

Seizure volume of selected drugs in Vietnam in 2018, by drug type

(in kilograms)



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Release date

March 2019

Region

Vietnam

Survey time period

2018

Special properties

data covers first eleven months of 2018

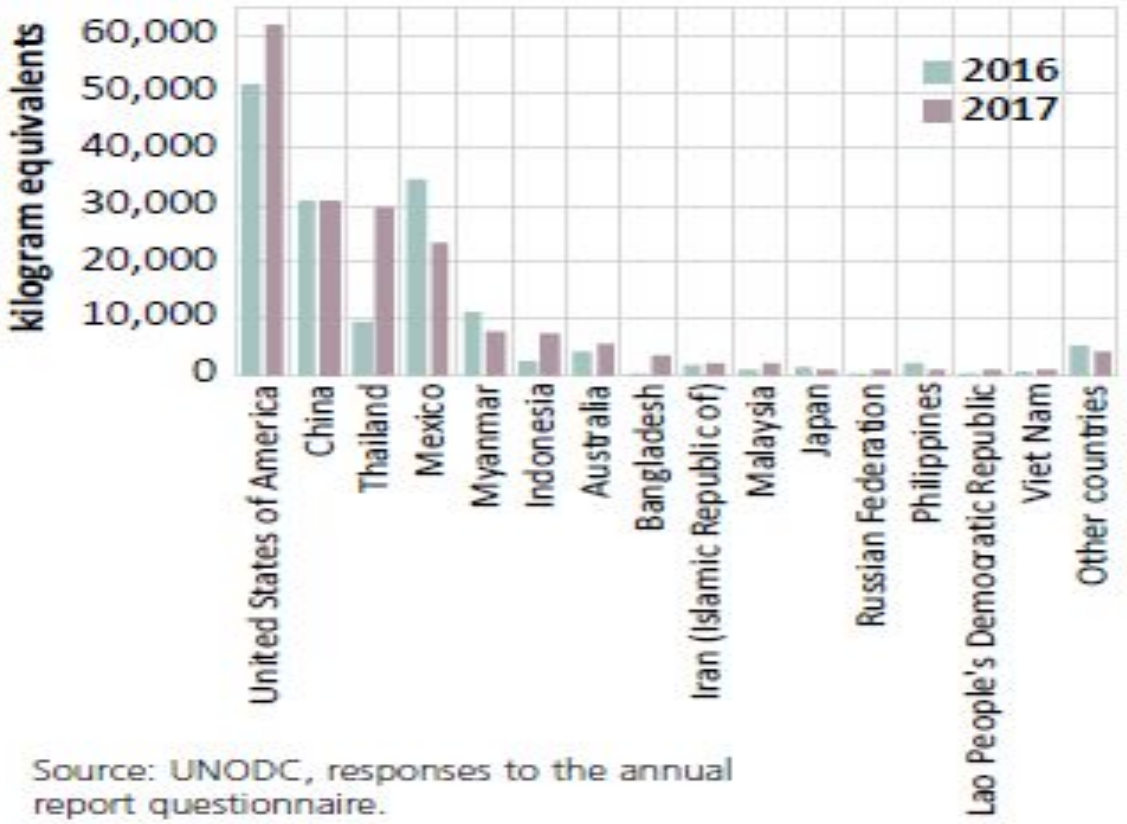
Supplementary notes

* Unit for methamphetamine in thousand tablets.

** As of June 2018.

https://www.statista.com/statistics/983363/vietnam-seizure-volume-drugs-by-type/

Drug Seizures in Vietnam, 2016-17



World Drug Report 2019 (United Nations publication)

Epidemiology of ATS use in Vietnam

- In 2018, there were 225,099 registered drug users in Vietnam
- In the past decade, a dramatic increase in the number of ATS dependent people
- 75% of drug users are ATS dependent people

Dublin Group Regional Report on South East Asia: October 2019
Vietnam Ministry of Public Security
Vietnam Ministry of Labour, Invalids and Social Affairs

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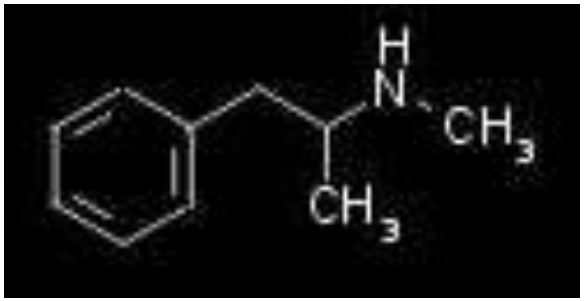
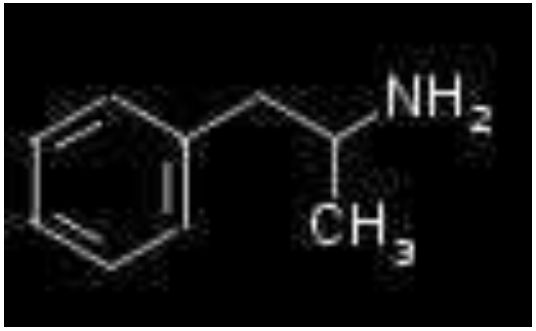
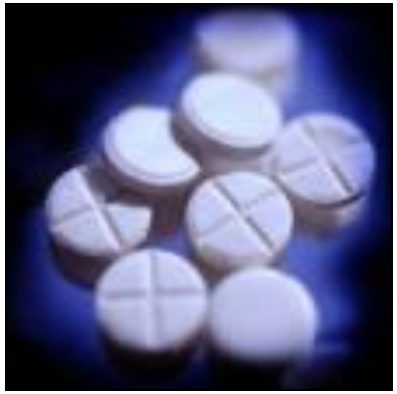
ATS Pharmacology



methamphetamine



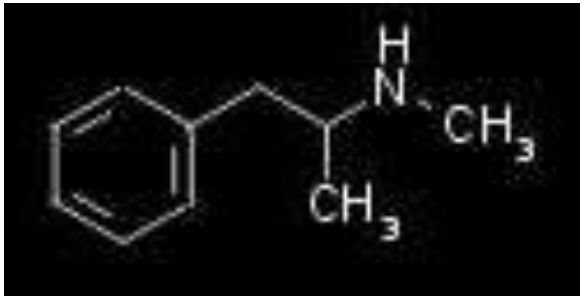
amphetamine



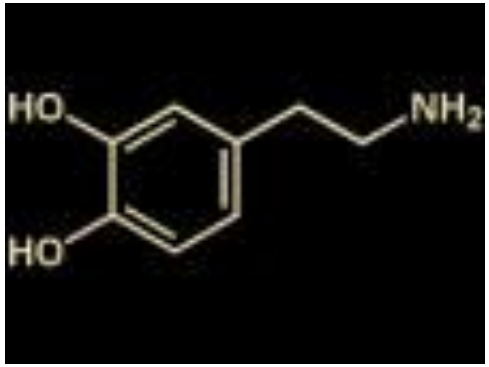
http://www.drugabuse.gov/NIDAHome.html

ATS Pharmacology

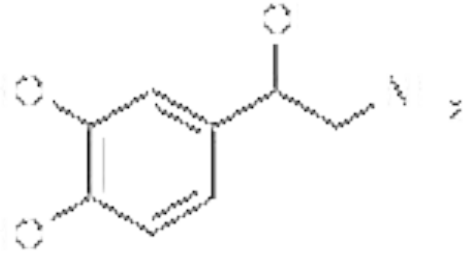
Methamphetamine is structurally similar to CNS monoamine neurotransmitters



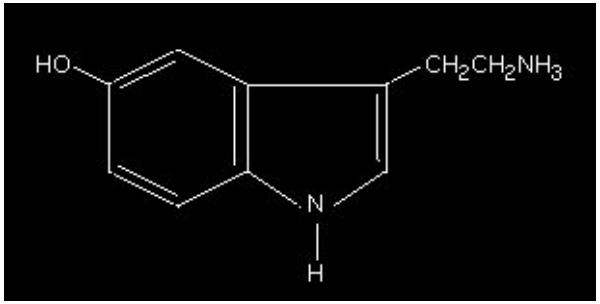
methamphetamine



dopamine

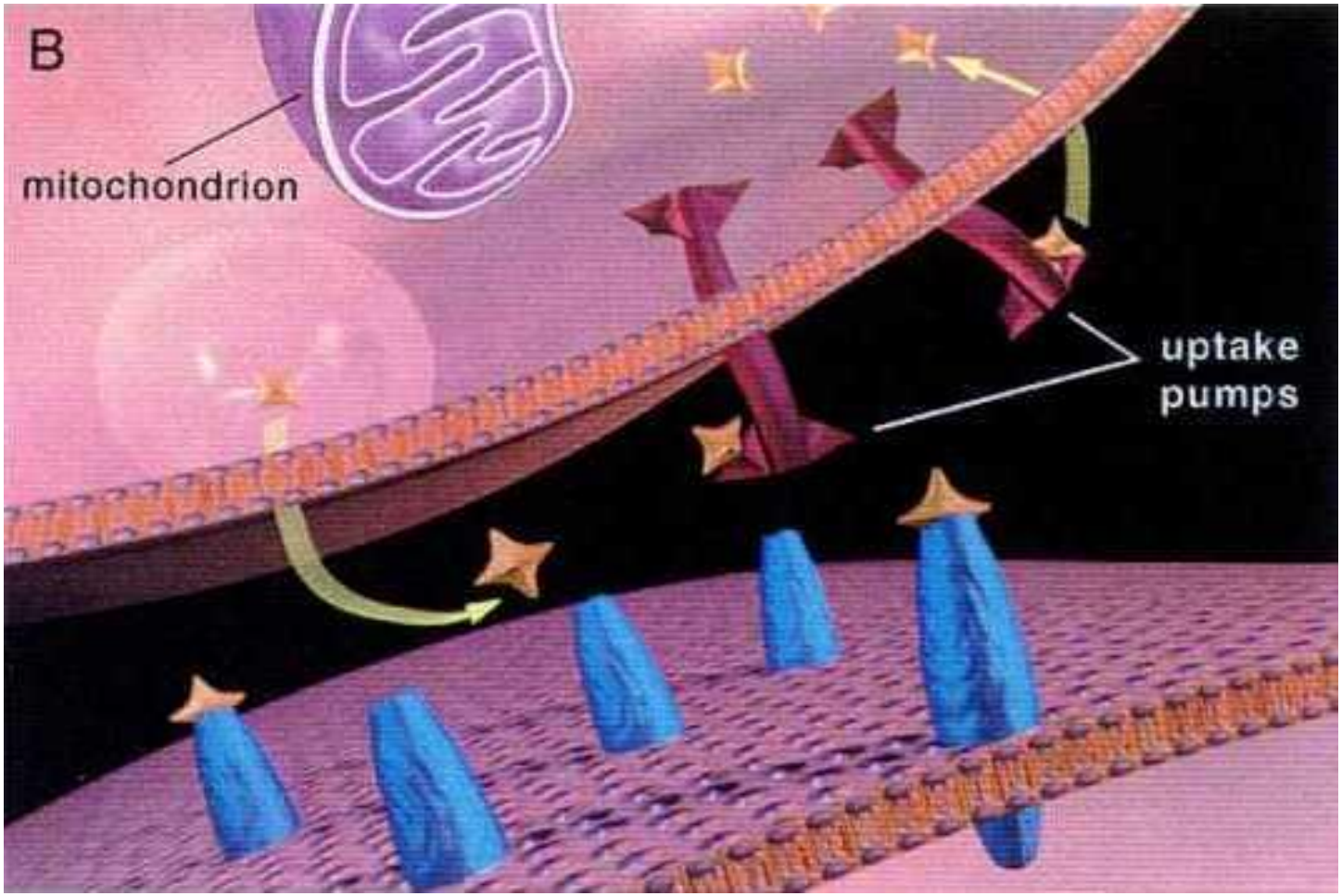


noradrenaline



serotonin

Mechanisms of Action of ATS



http://www.drugabuse.gov/NIDAHome.html

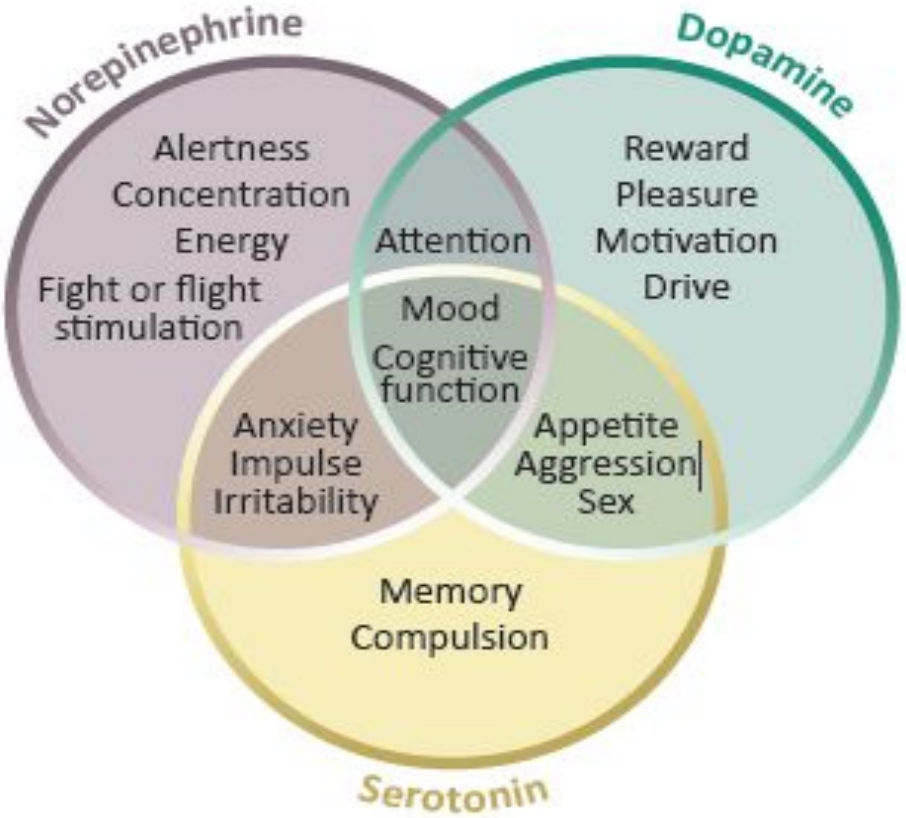
Mechanisms of Action of ATS

- Greatest effect is on dopamine but also effects noradrenaline and serotonin

- Direct release mechanisms
  - displaces monoamines from storage vesicles
  - increases release via passive diffusion

- Inhibits reuptake of monoamines
- Reverses dopamine transporter function

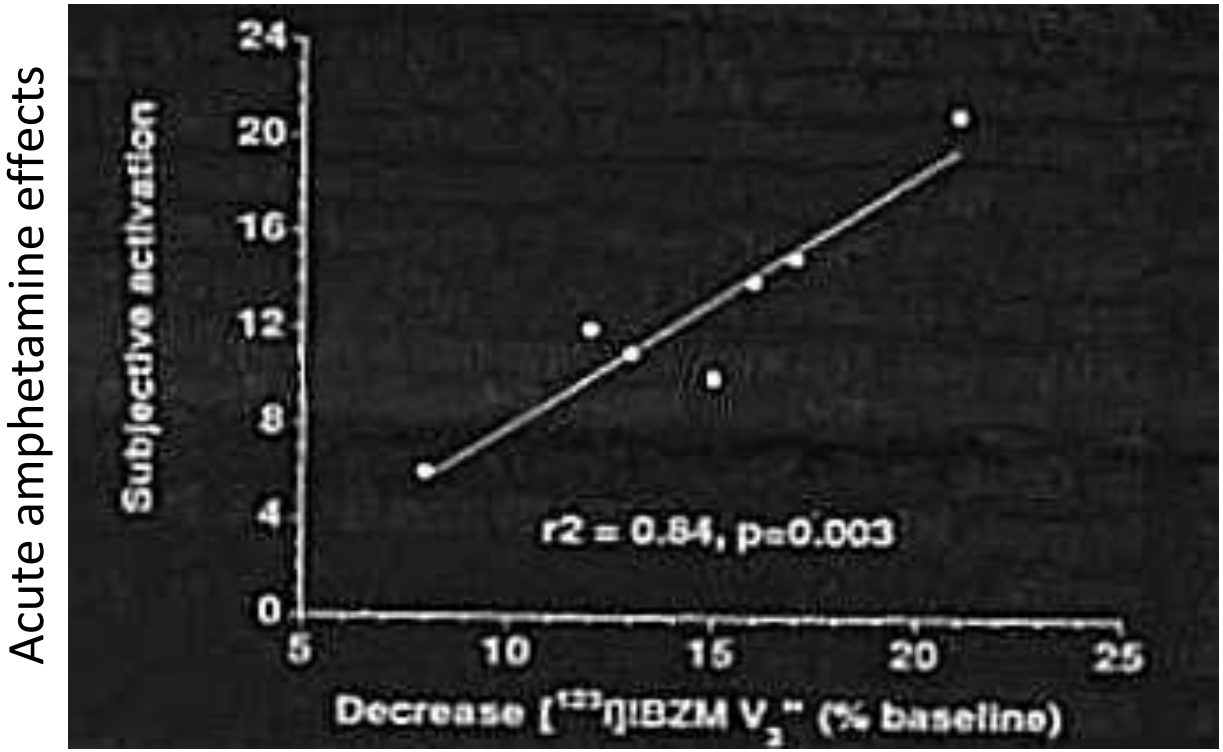
Mechanisms of Action of ATS



World Drug Report 2019 (United Nations publication)

Psychosis - ATS and Dopamine

Acute amphetamine effects correlate with binding to D2 receptors

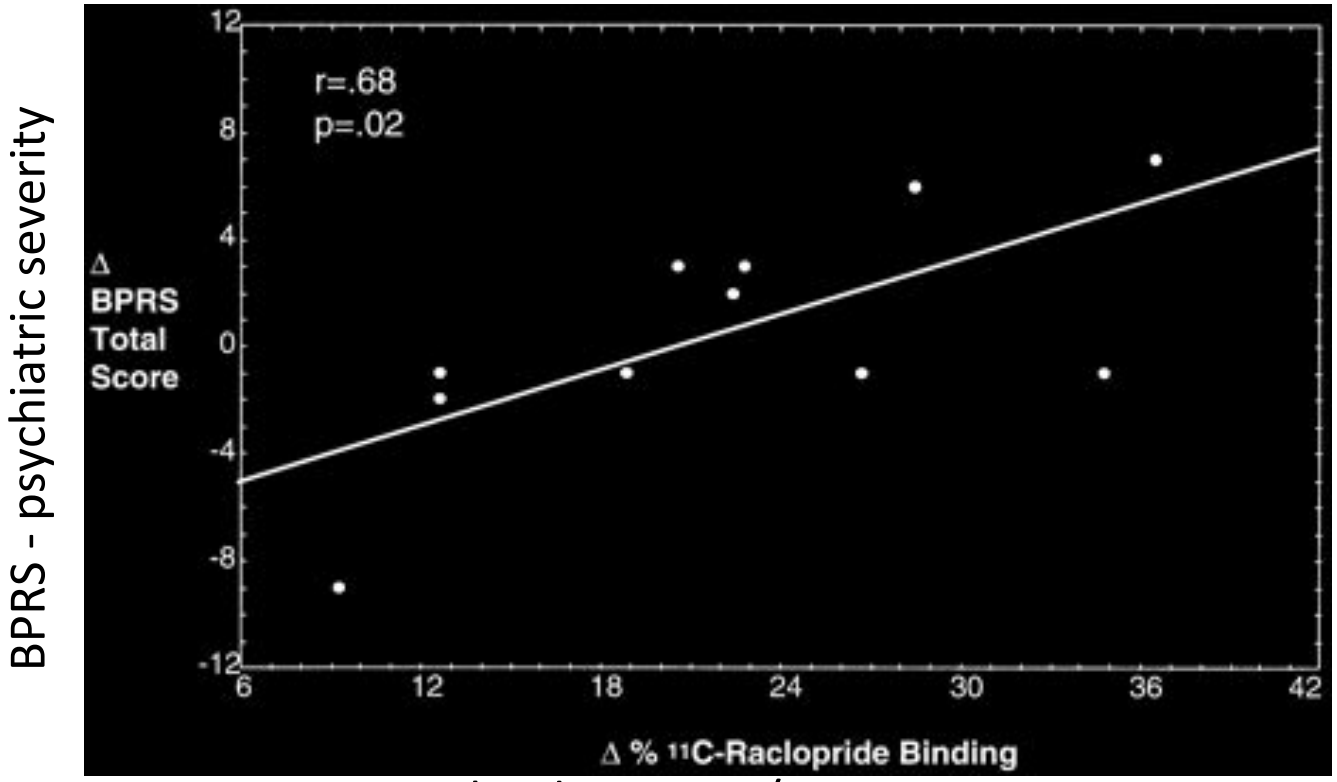


Dopamine binding to D2 receptors

Laruelle et al (1995) Journal of Nuclear Medicine 36: 1182-1190

Psychosis - ATS and Dopamine

DA release correlates with amphetamine-induced psychiatric effects



BPRS - psychiatric severity

Dopamine binding to D2/D3 receptors

Breier et al (1997) Proc.Natl.Acad.Sci. 94: 2569

How long do the effects last?

	Bioavailability	Half Life	Peak Effects
Intravenous	100%	12 hours	17 minutes
Smoking	90%	11 hours	18 minutes
Oral	67%	10 hours	90 minutes
Intranasal	No reliable pharmacokinetic data		

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Harms Associated with ATS Use 1

- Psychiatric - psychosis, withdrawal, neurotoxicity
- Hyperthermic syndrome - inability of body to cool itself
- Overdose - hyperstimulation, hyperpyrexia, intracerebral haemorrhage, systemic toxicity, cardiac arrest, seizures
- Long term - malnutrition, profound weight loss, increased infections because of immune susceptibility, blood born viruses, sexually transmitted illnesses including HIV

Harms Associated with ATS Use 2

- Other drugs for ATS withdrawal - cannabis, benzodiazepines, heroin, alcohol
- Maternal-infant effects - intra-cerebral haemorrhage, cardiovascular collapse, seizures, amniotic fluid embolism, cleft palate, cardiac anomalies
- Aggression, violence, criminal activity, suicides, homicides, accidents, toxic waste, laboratory explosions

Deaths Due to ATS Use in Australia

- Average Age – 36.9 years
- Gender – 78.4% male
- Crude Mortality Rate – 1.03/100,000 and rising. In 2015, the mortality rate was 1.8 [(CI) = 1.2–2.4] times that of 2009
- Deaths due to accidental drug toxicity (43.2%), natural disease (22.3%), suicide (18.2%), other accident (14.9%) and homicide (1.5%)

Darke et al. Rates, characteristics and circumstances of methamphetamine-related death in Australia: a national 7-year study. Addiction. doi:10.1111/add.13897

Psychiatric Assessment of a Patient Using ATS 1

- Presenting complaint – psychosis, withdrawal, risk of harm to self or others
- Form of ATS and method of administration
- Amount used and money spent each week
- Number of hours per day spent using, being intoxicated and recovering from use
- Activities undertaken whilst intoxicated

Psychiatric Assessment of a Patient Using ATS 2

- Age when first tried and started to use regularly
- Past withdrawal symptoms
- Other substances used
- Co-morbid – physical and mental health
- Psychosocial functioning
- Insight and motivation to change
- Treatment goals

ATS & Psychosis - Differential Diagnosis

- ATS-induced psychosis
- Primary psychotic disorders with ATS use
- Acute psychosis that persists beyond the period of acute intoxication but is not a primary psychotic disorder???

Prevalence of Psychotic Symptoms Among Methamphetamine Users

- 309 Sydney methamphetamine users surveyed
- Prevalence of psychosis: 13% versus 1.2% (normal)
- Prevalence of schizophrenia: 10% versus 1%
- 18% without schizophrenia had experienced a significant symptom of psychosis in the past year
- Dependent users x3 more likely to experience psychotic symptoms than non-dependent users

McKetin et al. Addiction 2006;101:1473-8

Factors Increasing the Risk of Psychosis

- Genes – psychosis, cluster A traits, ASPD
- Quantity used
- Age of onset of ATS use
- Polydrug use
- Methamphetamine worse than amphetamine

Glasner-Edwards S & Mooney LJ. CNS Drugs 2014;28:1115-1126

ATS-induced Psychosis

- Psychosis onset is 30 to 120 minutes after use
- ATS induced psychosis resolves within 1-7 days in >50% of cases
- If >3 months (approximately 15 % of cases) more likely to be schizophrenia or other primary psychotic disorder

McKetin et al. Addiction 2006;Oct;101(10):1473-8

Schizophrenia and ATS-induced Psychosis - Similarities

- Persecutory delusions
- Increased motor activity
- Anxiety
- Suspicion
- Auditory hallucinations (69.8% Vs 68.7%)
- Lack of insight

Janowsky DS, Risch C. Psychopharmacology (Berl). 1979, 65 (1): 73-77. 10.1007/BF00491982.
Bramness JG, Gundersen ØH, et al. 2012 BMC psychiatry, vol. 12, no. 1, pp. 221-221.

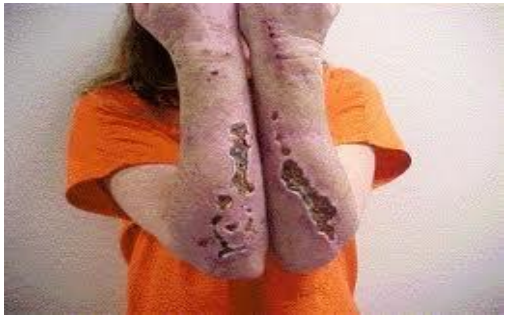
Schizophrenia and ATS-induced Psychosis - Differences

Schizophrenia

- More pronounced thought disorder
- More negative symptoms

ATS-induced Psychosis

- Visual hallucinations - 50%
- Ideas of reference - 90%
- Grandiosity
- Tactile hallucinations - 30%



Harris D, Batki SL. Am J Addiction. 2000, 9 (1): 28-37

McKetin et al. Addiction. 2006;Oct;101(10):1473-8

Treatment of ATS-induced Psychosis 1

- Encourage abstinence from ATS
  - Low stimulus environment
  - Allow personal space
  - De-escalation techniques

- Psychosis and agitation – antipsychotics and/or benzodiazepines until acute symptoms settle

- Hypertension and tachycardia – Beta blockers (9 studies), calcium channel blockers (3 studies)

References – next slide

Treatment of ATS-induced Psychosis 2

- Treat other psychiatric disorders especially post-traumatic stress disorder, mood disorders

- Treat other substance use disorders especially withdrawal

Nick O'Connor & John Corish. Pharmacological management of acute severe behavioural disturbance: a survey of current protocols. Australasian Psychiatry 2017, Vol 25(4) 395-398

Curran et al. Brit J Psych 2004;185:196-204

Glasner-Edwards S & Mooney LJ. CNS Drugs 2014;28:1115-1126

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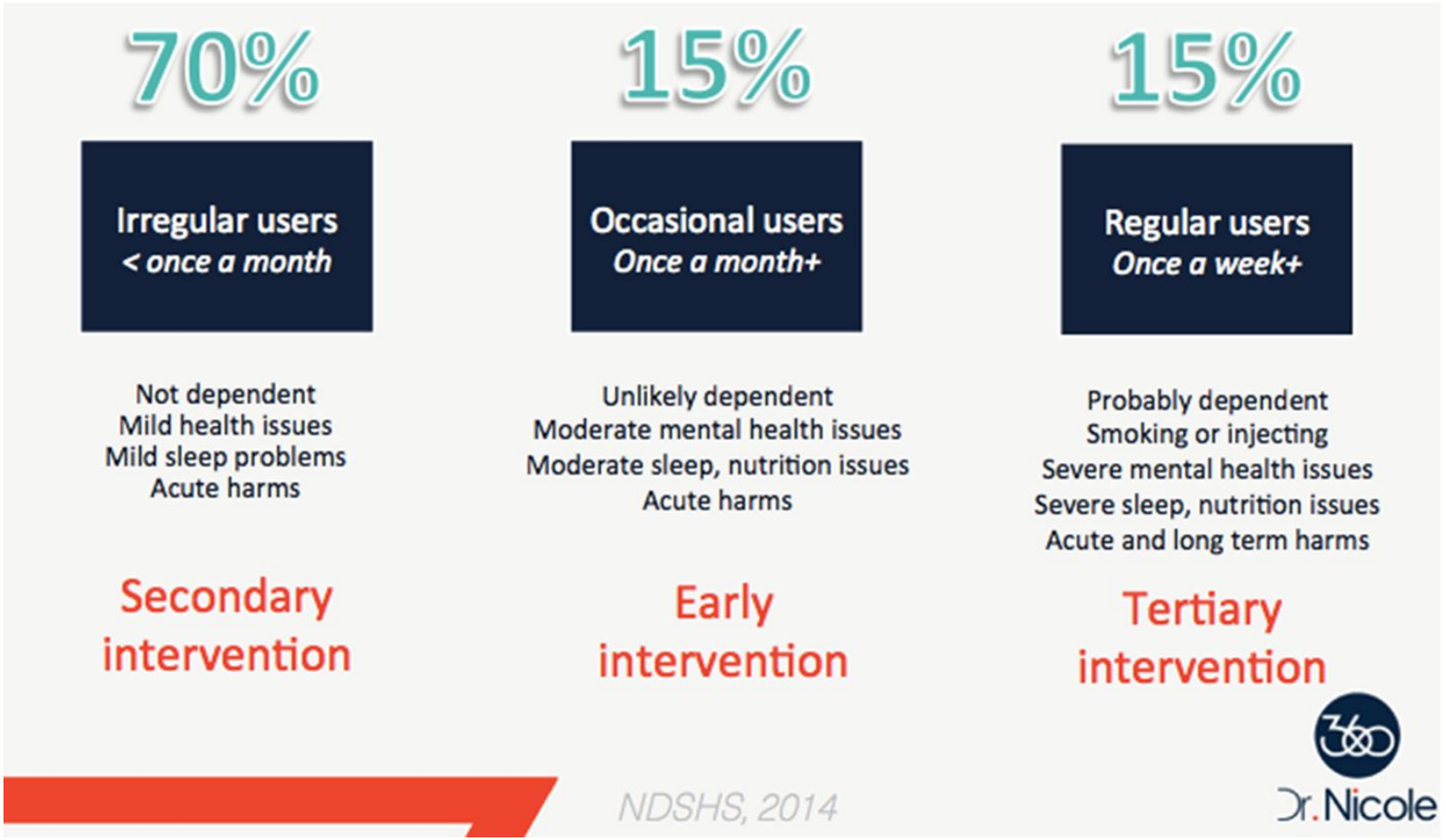
ATS - Intervention vs Treatment



ATS Withdrawal

Effects peak in first week after use but can last for months -

- Restless, irritable, depressed, anxious
- Exhaustion, lethargy, fatigue
- Increased need but poor quality sleep
- Poor concentration
- Increased appetite
- Lack of motivation

http://www.racgp.org.au/download/Documents/Good%20Practice/2016/April/GP2016Apr-ice.pdf

Pharmacotherapies for ATS Withdrawal

- Mirtazapine up to 60mg nocte for 2 weeks
- Modafinil up to 400mg daily for 7-14 days

- Very limited evidence for benzodiazepines, antipsychotics or other sedatives

http://www.atoda.org.au/wp-content/uploads/rp29-medication-treatment-options.pdf

Psychotherapies for Relapse Prevention

- Cognitive-Behavioural Therapy
- SMART - Self Management and Recovery Training
- CrystalMeth Anonymous - www.crystalmeth.org

- Inpatient Drug & Alcohol Treatment Units including Residential Rehabilitation programs

Pharmacotherapies for Relapse Prevention

- Modafinil up to 400mg daily
- Limited evidence for dexamphetmine
- Very limited evidence for benzodiazepines, antipsychotics or other sedatives

http://www.atoda.org.au/wp-content/uploads/rp29-medication-treatment-options.pdf

Other Pharmacotherapies for ATS Withdrawal and Relapse Prevention

- Lisdexamphetamine - up to 250mg/d, ongoing RCTs
- N-acetylcysteine - ongoing RCTs
- Baclofen - NS on abstinence in 2xRCTs
- Gabapentin - NS on abstinence in 2xRCTs
- Topiramate - 2xRCTs, 1 effective, 1 NS
- Varenicline - may improve cognition in WD and RP but no phase II studies
- Perindopril - may decrease anxiety in WD but no phase II studies
- Bupropion - 4xRCTs, 2 effective, 2 NS
- Naltrexone - NS in 1 RCT but decreases cue induced cravings during WD

- "Mixed results across all studies, and as a result no one agent has come out with consistent efficacy"

Pharmacotherapeutic agents in the treatment of methamphetamine dependence. Kirsten C. Morley et al. Expert Opinion on Investigational Drugs. Volume 26, 2017 - Issue 5

Why are ATS Use Disorders Difficult to Treat?

- Difficult to identify who is using
- Difficult to provide early intervention
- Limited pharmacotherapy options for withdrawal and relapse prevention

Co-morbidity Treatment

- Co-morbidity = a patient has co-occurring psychiatric and substance use disorders
- Efficacious treatments for reducing psychiatric symptoms also work in co-morbid patients
- Efficacious treatment for reducing substance use also work in co-morbid patients
- Best of model(s) of integrated treatment unclear

Conclusions

- Methamphetamine use in Vietnam is increasing
- Limited evidence for medications for ATS-induced psychosis, withdrawal and relapse prevention
- ATS Use Disorders are difficult to treat because of difficulties in identifying who is using, providing early intervention and limited pharmacotherapies

Thanks for your attention – any questions?

Additional Slides

Modafinil

- Wakefulness-promoting agent approved for:
  - narcolepsy
  - sleep disorder associated with shift work
  - excessive daytime sleepiness associated with obstructive sleep apnoea
- Actions on:
  - hypocretin and orexin system
  - glutamate and GABA system
  - some dopamine-mediated effects
  - some alpha-adrenergic effects

Modafinil

- Anderson, et al (2012)
  - RCT, n=210, modafinil 200mg, 400mg or placebo
  - Participants who were compliant with modafinil dosing had a longer duration of consecutive non-using days than less compliant participants and showed better study retention
- Shearer, et al (2009)
  - RCT, n=80, modafinil 200mg or placebo
  - Trend towards significance in treatment group p=0.07
  - Outcomes were better for methamphetamine-dependent subjects with no other substance dependence and those who accessed counselling
- Heinzerling, et al (2010)
  - RCT, n=71, modafinil 200mg, 400mg or placebo
  - High dropout rates 65%
  - No significance other than trends in those who used less amounts at commencement

Dexamphetamine

- Approved for Attention Deficit Hyperactivity Disorder (ADHD)
- Functional agonist and stereoisomer of amphetamine molecule - substitution treatment
- Dosing is three (or more) times per day
- MA vs dexamphetamine doses are not bioequivalent
- Two studies (dose 60-110mg) showed:
  - Some benefit in withdrawal
  - Better retention in treatment
  - Less MA used generally led to better outcomes