Concurrent Mental Health

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Learning Objectives

- Learn the principles of good concurrent mental health and addiction care.
- Apply them to the more common mood and anxiety disorders.
- Appreciate that Borderline Personality Disorder management is not an oxymoron.
- Understand the challenges in prescribing methylphenidate or benzodiazepines to this population.
- Explore case examples.

Epidemiology

- 1 in 7 North Americans meet criteria for a substance use disorder (abuse or dependence) in their lifetime
  - Alcohol – 13%
  - Drugs – 3%
- 20% of visits to primary care physicians are related to alcohol, tobacco, and other drug problems.
- Psychiatric disorders and substance use disorders have overlapping etiologies resulting in reciprocal causality
- Lifetime prevalence of substance use co-morbidity:
  - Major depressive & dysthymic disorders – 32% - 54%
  - Anxiety disorders – 36%
  - Bipolar disorder – 56.1%
  - Adult ADHD – 15 - 45%
- Annual Cost to Canadian Society
  - $40,000,000,000.00

Reiger DA, et al. *JAMA* 1990;264:2511-2518
Kessler RC, et al. *Arch Gen Psychiatry* 1994;51:8-19
Brook DW, et al. *Arch Gen Psychiatry* 2002;59:1039-1044
Kushner MG, et al. *Am J Psychiatry* 1999;156:723-732
Bradley KA. *Alcohol Health Res World* 1994;18:97-104
Hasin D, et al. *Arch Gen Psychiatry* 2002;59:375-380
Farone SV, et al. Am J Addict 2007;16:24-32
Davis LL, et al. Compr Psychiatry 2005;46:81-89

Most Common Substances

- Caffeine
- Alcohol - >90% drink, 13% lifetime abuse or dependence
- Nicotine – 18% of Canadians current daily smokers
- Drugs – 3% lifetime abuse or dependence
  - Cannabis
  - Opioids – prescription opioids #1 abused drug in Canada
  - Sedative-Hypnotics – benzodiazepines and barbiturates
  - Stimulants – cocaine, amphetamines, designer drugs
  - Hallucinogens – LSD, psilocybin
  - NMDA Antagonists – PCP, Ketamine
  - Inhalants – gas, nitrous oxide, amyl nitrate, paint

DSM-5 Criteria for Substance Use Disorder

- **12 month period of maladaptive substance use leading to:**

SUD	CRITERIA
+	Use in Physically Hazardous Situations
+	Failure to Fulfill Major Role Obligations
+	Use Despite Social/Interpersonal Problems
+	Tolerance
+	Withdrawal
+	Craving
+	Larger amounts or longer than intended
+	Unable to cut down/control
+	Great deal of time spent
+	Activities given up
+	Continued use despite consequences

- 0-1 = No diagnosis 2-3 = Mild 4-6 = Moderate 7+= Severe
- In early remission, in sustained remission, on maintenance therapy, in a controlled environment

“Dependence” & Change Measures

- Term to be used to describe physiologic dependence only rather than addiction
- Tolerance/withdrawal – neither necessary nor sufficient to define addiction
- Within person change to be determined by:
  - # of criteria met before/after
  - % days used before /after
  - Averages daily amounts used before/after
  - Biological measures, pt report, informant report

Issues & Key Components for Inclusion

- Social Mores vs Neurophysiology
- Key Components:
  - Clinical need
  - Distinction from other disorders
  - Harm or impairment related to behaviour
  - Potential for treatment
- Problem Gambling moved from Impulse Control to Substance-Related and Addictive Disorders, renamed Gambling Disorder or “Disordered Gambling”, legal criterion eliminated and craving added

Management of Concurrent Psychiatric and Substance Use Disorders

- Best outcomes occur when both disorders are treated simultaneously by the primary treating physician
- Treat psychiatric symptoms to full remission
- Tailor pharmacotherapy to target symptoms (sleep, anxiety, cravings, physical complaints)
- Inquire about substance use and utilize brief interventions at each visit
- Consider agents for sleep during withdrawal (e.g.: trazodone, zopiclone)
- Avoid confrontation! Be encouraging and sympathetic
- Accept relapse to substance use, but work towards abstinence (Aim to help them shift one stage of change with each interaction)

Kranzler HR, Van kirk J. Alcohol Clin Exp Res 2001;25:1335-1341
Chick J et al. Br J Psychiatry 1992;161:84-89. Crum RM et al. Am J Psychiatry 2004;161:1197-1203
Le Fauve CE et al. Alcohol Clin Exp Res 2004;28:302-312
Reiff-Hekking S et al. J Gen Intern Med 2005;20:7-13 Paykel ES et al. Psychol Med 1995;25:1171-1180

Management of Concurrent Psychiatric and Substance Use Disorders

- Psychoeducation:
  - Psychosis: Link positive & negative symptoms to use
  - Depression: Link symptoms of sleep disturbance, low mood, amotivation to use
  - Anxiety: Discuss rebound and protracted withdrawal
- Access/utilize cognitive behavioral interventions
- Avoid benzodiazepines
- Increase follow-up care/structure
- Involve family
- Follow urine drug screens
- Facilitate involvement in self-help &/or other specific addiction treatments especially if action oriented

Whooley MA, Simon GE. NEJM 2000;343:1942-50. Brady KT, Sinha R. Am J Psychiatry 2005;162:1483-1493
Brown RA et al. J Consult Clin Psychol 1997;65:715-726 Nunes EV, Levin FR. JAMA 2004;291:1887-96.
Bosternak MA, Mueller TI. Am J Addict 2001;10:48-68 Moos RH & BS. Alcohol Clin Exp res 2005;29:1858-1868

Signs of a Primary Psychiatric Disorder:

- Psychiatric symptoms predate substance use
- Limited quantity of substance use
- Prominent family history of psychiatric disorders
- Persistent psychiatric symptoms with abstinence
- Full Psychiatric disorder criteria met with typical presenting features (e.g.: auditory hallucinations, melancholia)
- Female
- History of good response to psychiatric treatments or substance use treatment failures

Brady KT, Malcolm RJ. Textbook of Substance Abuse Treatment, 3rd Ed, 2004:529-537

Consequences of Co-Morbidity

- Decreased treatment adherence
- Decreased response & remission rates
- Increased risk of relapse to both disorders
- Increased suicide risk
- Increased risky drug use practices (IV)
- Worse overall social function
- Increased health care utilization
- Problematic diagnosis
- Exclusion from treatment

Brady KT, Sinha R. Am J Psychiatry 2005;162:1483-1493
Davis LL, et al. *Comprehensive Psychiatry* 2005;46:81-89
Sullivan LE, et al. Am J Med 2005;118:330-341
Fisher B, et al. Can J Psychiatry 2006;51:624-634

Goals of Treatment:

- Full Remission of Psychiatric Disorder (if present)
- Progressive Reduction of Substance Use Aiming for Abstinence (Behaviour Change!)
- Functional Improvement
- Retention in Treatment
  - Engagement & Persuasion
  - Active Intervention
  - Relapse Prevention

Choice of Treatment Setting:

- Initial reviews → treatment setting unrelated to outcome
- ASAM patient placement criteria
- Patients with greatest substance use &/or co-morbidity severity benefit most inpatient/residential treatment
- Stimulant dependent patients have better outcomes with initial residential treatment
- Prior suicide attempts or current suicidal ideation should suggest inpatient/residential treatment rather than outpatient treatment at least initially

Ilgen MA et al. Alcohol Clin Exp Res 2005;29:1664-1671

Moos RH et al. Addiction 2000;95:833-846

McKay JR et al. Am J Drug Alcohol Abuse 2002;28:307-338

Timko C, Moos RH. Adm Policy Ment Health 2002;30:35-54

Rational Pharmacotherapy for Addiction?

Few evidence based pharmacotherapy options! (* = clinical indication)

- ***Naltrexone:** opioid antagonism blocking high
- *Acamprosate: GABA, glutamate modulation
- ***Disulfiram:** inhibits aldehyde dehydrogenase
- **Modafanil:** 2 positive RCTs for cocaine dependence
- D2 Antagonists, SSRIs & other antidepressants: primarily negative trials
- *Bupropion: partially blocks dopamine uptake (methamphetamine, nicotine)
- ***Varenicline** (nicotine)
- Anticonvulsants: withdrawal, GABA modulation of DA activity (topiramate: alcohol, cocaine)
- Baclofen (cocaine, smoking)
- ***Methadone, *Buprenorphine** (opioids)

Tihonen J et al. Am J Psychiatry 2007;164:160-2.
Vocci FJ, Appel NM. Addiction 2007;102:96-106
Barr AM et al. J Psychiatry Neurosci 2006;31:301-313
Elkashef A et al. Addiction 2007;102:107-113.
Ling W et al. Curr Psychiatr Reports 2006;8:345-354

Neurobiological Overlap Between Substance Use and Depressive/Anxiety Disorders

- Decreased prefrontal cortex and increased amygdala activity
  - Present in panic disorder, depression, and with abstinence from substance dependence
- Negative affect states & emotional stress
  - Predispose to substance craving
  - Increase subjective reinforcing effects of substance use
- Common dysfunction of limbic-cortical network
- Decreased dopamine receptor availability with dependence during initial abstinence may predispose to dysphoria

Brady KT, Sinha R. *Am J Psychiatry* 2005;162:1483-1493
Tremblay LK, et al. *Arch Gen Psychiatry* 2005;62:1228-1236
Drevets WC. *Ann NY Acad Sci* 2003;985:420-444
Goldapple K, et al. *Arch Gen Psychiatry* 2004;61:34-41
Seminowicz DA, et al. *Neuroimage* 2004;22:409-418

Does Concurrent Substance Abuse/Dependence Alter Treatment Outcome of Depression?

- Current recommendations emphasize that concurrent substance abuse/dependence NOT be a barrier to depression treatment
- Ideally, a period of abstinence (2 weeks minimum) should be sought to aid diagnosis and for best treatment outcome
- Efficacy of antidepressants for depressive symptoms similar for depressed outpatients with or without alcohol dependence (0.38 and 0.43, respectively), but worse in those with drug dependence
- Substance use minimally changed with depression treatment, emphasizing importance of concommitant treatment

Nunes EV, Levin FR. *JAMA* 2004;291:1887-1896
Torrens M, et al. *Drug Alcohol Depend* 2005;78:1-22
Walsh BT, et al. JAMA 2002;287:1840-1847

Bipolar Disorder - Management

- DDx: Stimulant induced mania vs. Bipolar I disorder – manic
  - Clues:
    - FH
    - Lack of insight
    - Timing of use
    - Persistence
    - Prior Rx
- Treatment:
    - Hospitalization / detoxification
    - Lithium vs. DVP
    - Timing of substance treatment

Psychosis - Management

- **Differential Diagnosis Clues:**
  - **Hallucinations / Thought disorder**
  - **Orientation**
  - **FH**
  - **Timing of use**
  - **Persistence of symptoms**
- **Treatment:**
  - **Hospitalization / detoxification**
  - **Initiation of 2nd generation antipsychotic**
  - **Time intervention to improvement and base on stage of change**
  - **Compliance**
  - **Psychoeducation / monitoring**
  - **Nicotine - ↓ EPS, ↓ negative sx, ↑ med dose, ↑ postive sx.**

Can Cannabis Use Cause Schizophrenia?

- Psychosis in context of clear sensorium well described:
  - Abrupt onset; hypomania and agitation
  - Less incoherence of speech, affective flattening, and auditory hallucinations
  - Clears with abstinence
- Cannabis use aggravates the severity of positive symptoms in schizophrenics and worsens the prognosis
- Onset of schizophrenia 6.9 years earlier in regular users
- Role of endocannabinoids (anandamide)?
  - Elevated with arousal exercise
  - Not altered with treatment of psychosis

Linszman Dit et al. Arch Gen Psychiatry 1994
Negrete JC et al. Psychological Med 1986
Zammit et al. BMJ 2002;325:1199.
Johns A. Br J Psychiatry 2000
Macleod et al. Lancet 2004;363:1579-88,
Arsenault L et al. BMJ 2002;325:1212-3.
Degenhardt L & Hall W. Can J Psychiatry 2006;51:556-565. Moore THM et al. Lancet 2007;370:319-28.
Potvin S et al. J Psychopharm 2008;22:262-9
Can J Psychiatry 2005 Clinical Practice Guidelines

Can Cannabis Use Cause Schizophrenia?

- Con: Later use predicts psychosis > earlier use
- Con: Decreased D2 receptor availability with regular use
- Evidence suggesting cannabis use leads to psychotic illness persisting with abstinence confounded, but users should be advised of increased risk.
- Cannabis use is likely a marker, rather than a cause, of future psychosocial problems / mental illness
- Increased risk in those predisposed/vulnerable

Linszman Dit et al. Arch Gen Psychiatry 1994

Negrete JC et al. Psychological Med 1986

Zammit et al. BMJ 2002;325:1199.

Johns A. Br J Psychiatry 2000

Macleod et al. Lancet 2004;363:1579-88,

Arsenault L et al. BMJ 2002;325:1212-3.

Degenhardt L & Hall W. Can J Psychiatry 2006;51:556-565.

Can J Psychiatry 2005 Clinical Practice Guidelines

Schizophrenia And Tobacco

- Mortality: 50% of regular users.
- Leading cause of preventable mortality and morbidity.
- Increased cancer risk in schizophrenia, increased vulnerability for subsequent alcohol use.
- Smoking increases the metabolism of antipsychotic medications by inducing hepatic cytochrome P450 enzymes (especially 1A2); clozapine levels increased by 57.4% upon smoking cessation in one study (Meyer, 2001).
- However, nicotine has been shown to temporarily normalize auditory evoked potential deficits in some schizophrenics (via the alpha 7 subunit of the nicotinic acetylcholine receptor), possibly accounting for the high rate of nicotine dependence (Adler et al, 1998).

Personality Disorders And Addictive Disorders I

- Personality disorders and substance use disorders have a high comorbidity. A study in which 200 patients referred for treatment of personality disorders were assessed for substance use disorders found a lifetime prevalence of 50%; 34.5% for alcohol, 24.5% for cannabis, 9.5% for cocaine, and 8% for polysubstance abuse (Skodol et al, 1999).
- 70% of cocaine dependent individuals were comorbid for at least one Axis II diagnosis (majority with a Cluster B diagnosis) and 44% of alcohol dependent individuals were comorbid for an Axis II diagnosis in one European study (Verheul et al, 1995).

Personality Disorders And Addictive Disorders II

- The most common personality disorders comorbid with substance abuse are borderline and antisocial personality disorders (Widiger & Trull, 1993); avoidant and dependent personality disorders are also common.
- A diagnosis of antisocial personality disorder is a poor prognostic indicator in the treatment of alcoholism or opiate addiction.
- Substance abusers with borderline personality disorder (BPD) are more disturbed than other substance abusers; the prevalence of current substance use disorders in patients receiving treatment for BPD ranged from 25% (Miller et al, 1994) to 67% (Dulit et al, 1990).

Personality Disorders And Addictive Disorders III

- Dialectical behaviour therapy (an accepted treatment for chronically suicidal patients with BPD) has been shown to be effective for substance-dependent patients with BPD. In one study where DBT was compared to TAU ("treatment as usual") the DBT group showed greater reduction in drug use, longer retention in treatment, and greater social global gains (Linehan et al, 1999).

Benzo Basics

- BZs are one of our oldest classes of pharmacotherapeutic agents
- First discovered by Sternbach in 1955
- Reportedly the most frequently prescribed psychotropic medication
- In a recent study of a Canadian general population cohort (12 year follow-up), at each interview the frequency of BZ/sedative-hypnotic use was 2% to 3%

Benzodiazepines – Mechanisms of Action

- Large family of compounds; act as agonists on specific receptors on cell membranes
- Two subtypes of BZ receptors (BZ-1 and BZ-2) are part of the GABA-A receptor
- GABA is a major inhibitor inhibitory neurotransmitter in the brain; stimulating BZ receptors increases the affinity of GABA receptors for GABA, increasing the amount of time the chloride channel stays open
- Benzodiazepines potentiate GABA's inhibitory control over nerve impulse conduction

Benzodiazepines – Mechanisms of Action

- Reinforcing effects of BZ may be mediated via an opioid mechanism as well as GABA receptors
- This may explain the high level of co-occurrence of BZ and opioid dependence
- BZ are the only major class of drug with abuse potential that decrease dopamine levels in the mesolimbic system

Benzodiazepine Indications

- Anxiety Disorders
- Sleep Disorders
- Seizure Disorders
- Movement Disorders
- Muscle Spasticity
- Anaesthesiology
- Agitation (Psychotic, Mood, Cognitive Disorders)
- Withdrawal (Alcohol & Sedative-Hypnotics, Agitation from Stimulants)

Physiologic Dependence

- Dose and duration of exposure to BZ determines the development of physiological dependence; continued exposure of a receptor to its agonist results in a reduction in the number of those receptors
- Almost never seen in patients treated for less than 2 weeks
- Occurs in about 50% of patients treated daily for more than 4 months

Physiologic Dependence

- Short- and long-acting BZs produce comparable severity of withdrawal
- Dependence is reduced with intermittent versus continuous exposure to BZs
- Tolerance to sedative effects usually develops among patients prescribed a stable dose of BZs; however, memory impairment can persist after several years of daily administration

Loss of Control....

- Most patients treated chronically with BZs do not develop compulsive substance use
- A small subset (likely those who have abused other substances) develop compulsive drug-seeking behaviour with loss of control; often there is a positive family history of drug or alcohol dependence
- BZs as the primary substance of abuse in patients admitted for addiction treatment make up < 1% of admissions; most report abuse of alcohol or opioids as well
- Comorbidity: co-occurring mood, anxiety and Cluster C personality disorder in up to 50% of these admissions

What concerns do you have regarding long-term use of benzodiazepines?

- Sedation
- Potential for cognitive impairment / ataxia (especially in the elderly); BZs may have negative effects on cognitive performance and functioning in the community
- Increased risk of falls
- Increased frequency of motor vehicle accidents
- Dependence / withdrawal issues
- Benzodiazepines are generally recommended only for short-term use
- Some patients may require long-term adjunctive treatment

Canadian Psychiatric Association Guidelines. *Can J Psychiatry* 2006.

Responsible Prescribing

- APA guidelines and NICE guidelines for Panic Disorder and GAD recommend SSRIs and not BZs as the principle choice of medication, along with CBT and self-help approaches
- BZs associated with poorer long-term outcomes, and are not recommended beyond 2 to 4 weeks in GAD

Responsible Prescribing

- In the short-term, prescription of high-potency BZs may be helpful to reduce anticipatory anxiety and the severity of panic attacks; non-BZ anti-anxiety medication and CBT often take weeks before there is any beneficial effect
- With comorbid anxiety and depression, SSRIs and SNRIs are first-line medications; in GAD antidepressants should be started earlier as earlier treatment leads to better prognosis. BZs as an adjunct may lead to better speed of response and overall response

Targeting High-Risk Patients

- Reduction of physiological dependence

  - use of adequate doses over only a few weeks

  - drug holidays
- Differentiate physiological dependence (common) versus iatrogenic addiction (rare)

Some General Advice

- BZs with a rapid entry into the CNS and a more potent effect on CNS receptors will have a greater psychoactive effect and therefore a greater risk for dependence
- Higher Risk

  diazepam, lorazepam, alprazolam, triazolam
- Lower Risk

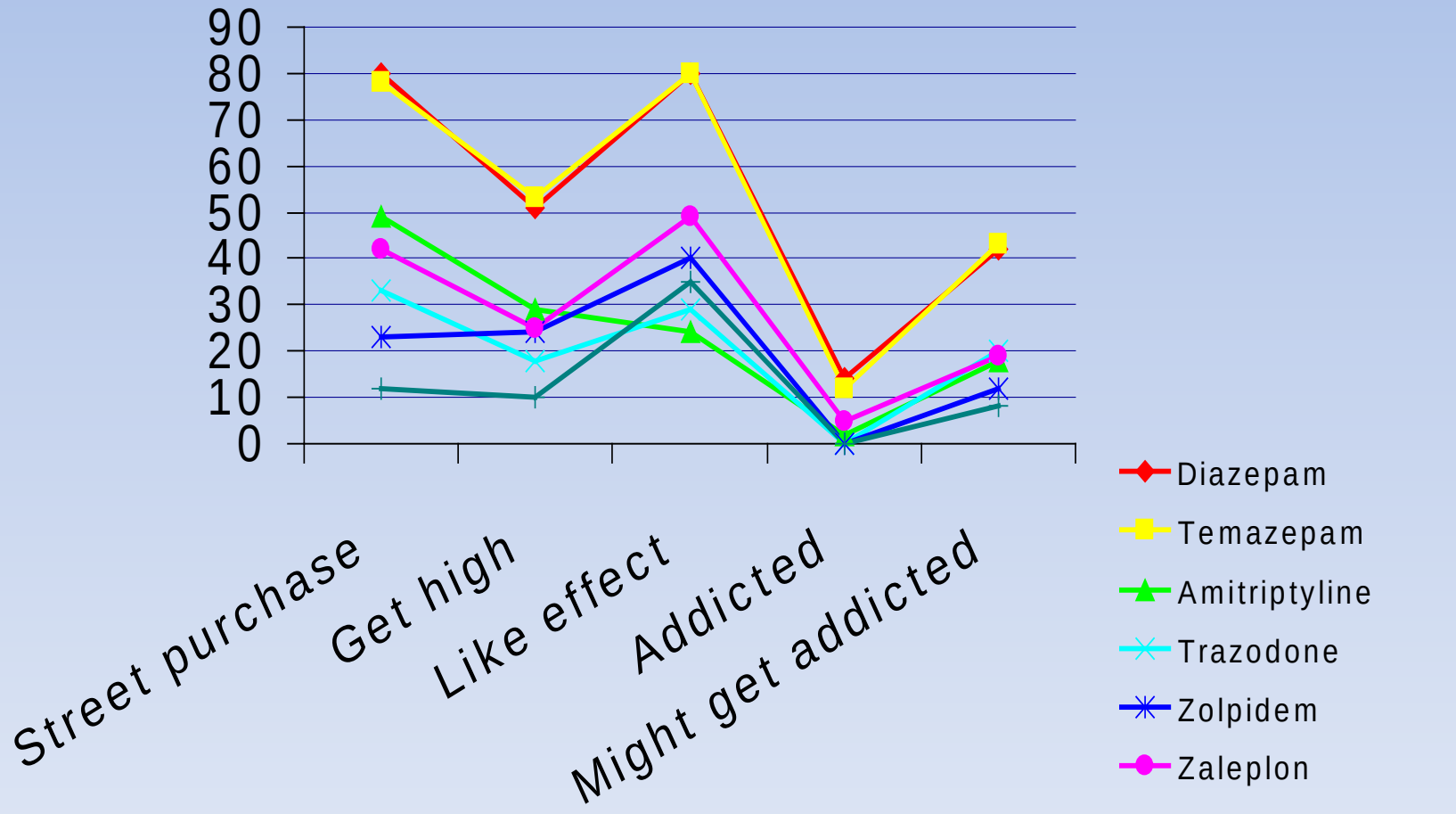
  oxazepam, chlordiazepoxide, clonazepam

What About Benzodiazepines?

- Safe: Overdoses rarely fatal
- Low addiction potential: BZDs are primary substance of abuse in less than 1% of all admissions
- Look it up: BZD use debated in The Canadian Journal of Psychiatry, Vol 55, No 11, November 2010

el-Guebaly N et al. *Can J Psychiatry* 2010;55(11):709-714.
Substance Abuse and Mental Health Services Administration (SAMHSA).
Treatment Episode Data Set (TEDS): 1995-2005; national admissions to substance abuse treatment services; 2007.

Relative Abuse Liability of Hypnotic Drugs



Attention-Deficit/Hyperactivity Disorder And Addictive Disorders

- 23% (averaged number) of adults and adolescents with a substance use disorder had a comorbid diagnosis of ADHD (Wilens et al, 1994).
- Diagnosis can be difficult, as problems with attention are common during substance intoxication and withdrawal. Symptoms of ADHD are best assessed during a period of abstinence, with questioning about clear childhood symptoms of ADHD (Gallanter, 1999).
- Stimulants are the first-line treatment for ADHD, but in a dual diagnosis population the abuse potential is problematic.

Attention-Deficit/Hyperactivity Disorder And Addictive Disorders

- Other options include TCAs and bupropion (treat ADHD, comorbid depression), and antihypertensives such as clonidine and propranolol (decrease impulsivity and aggression).
- Behavioural therapies can help with increasing focus and attention. Psychotherapy can be used as part of a psychoeducational approach.

Case 1 The Good Patient

- 36 year-old police officer
- Major Depressive Disorder, Generalized Anxiety Disorder, Post-Traumatic Stress Disorder
- Symptoms improved with Cipralex 20mg QD, Sublinox 10mg QHS, counselling with Dr. Carverhill, RTW planning
- Nephew diagnosed with ADHD/being treated, identifies strongly with his symptoms, wife says “you’re just like him”
- Reviews ADHD symptoms checklist in waiting room, endorses inattention, impulsiveness, legs bounce/”vibrating with energy”

Case 1 The Good Patient

- Completes Adult ADHD Self-Report Scale (ASRS), scores most symptoms “often” or “very often”
- Completes Conners’ Continuous Performance Test II (CPT II), scores 70% Clinical versus 30% Non-Clinical profile; high inattention and impulsivity scores, poor vigilance (reaction times slower and less consistent as test progressed)
- Scores normalize with trial of methylphenidate
- Started on trial of Concerta 36 mg QD, reports significant symptom improvement at home and work

Case 2 The Difficult Patient

- 19 year-old HIV positive male, significant learning disability/FASD, polysubstance dependence history, stabilizing on methadone but no carries as not providing clean urine drug screens (UDS)
- Urines consistently positive for stimulants, methadone physician agrees to trial of methylphenidate (Ritalin SR) with patient, but consults psychiatry as he is uncomfortable with treating patient without clear diagnosis
- Patient seen in consultation at West Side Community Clinic

Case 2 The Difficult Patient

- Patient identifies clear history of attention problems at home and at school, persisting into adulthood. Now wishes to complete Grade 12 studies at SIAST, struggles in the classroom and with homework
- Books appointment at downtown office, completes ASRS, CPT II pre- and post-medication
- Significant improvement in impulsivity, inattention, and vigilance symptoms after Ritalin SR 20mg tablet

Case 2 The Difficult Patient

- In past year, patient has married girlfriend, attending SIAST to complete Grade 12 studies, working part-time for a moving company
- Stabilized on methadone, now dispensed weekly with Ritalin SR 20mg BID (wished to remain on medication started previously), on Citalopram 40mg QD for mood/anxiety symptoms, providing clean UDS to methadone clinic
- Reports improved attention and concentration, functioning better at home and at school

Misuse and Abuse Liability of ADHD and Medications

- Among individuals with ADHD, what percentage misuse their medication?
  a. 5%
  b. 10%
  c. 20%
  d. 30%

Faraone and Upadhyaya, 2007

Stimulant Abuse and Diversion in Canada

- *Canadian Medical Association Journal*, Oct 2001[1]
- 13,549 randomly selected students in Atlantic Canada in grades 7, 9, 10 and 12 were surveyed in 1998.
  - ~ 15% who were prescribed stimulants have given away some of their pills
  - ~ 7 % had sold some of their pills

- Students with ADHD asked to trade, give, or sell their prescriptions[2]
  - 16-29%

[1]Poulin. CMAJ 2001

[2] Wilens et al JACAP 2008

Evolution of Amphetamine Abuse / Misuse

- From 1969 – 1971 the US Government:
  - Markedly reduced the production of Amphetamines by 80%
  - Alerted physicians to possibility of dependence
  - FDA reschedules Amphetamines to Schedule II
  - **The pendulum has swung back to the point that potentially important clinical uses are being avoided by physicians**

* The Substance Abuse – Handbook, Ruiz, 2007

Definitions

Therapeutic Use: Clinical indication(s)

Misuse: used other than as prescribed

Diversion: Process of redirection to someone else for whom it was not prescribed

Abuse: used for the purpose of intoxication

***Dependence: the pleasurable effects of a drug and its propensity to produce dependent behavior (psychological and/or physical)**

*** Physical dependence involves increasing tolerance, intense craving, and withdrawal reaction when drug use is stopped.**

Wilens et al., J Am Acad Child Adolesc Psychiatry 2008; 47(1):21-31.
APA - Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision (DSM-IV TR), 2000.

Stimulant Class

Low Abuse Potential → **High Abuse Potential**

Commonly Used Stimulants
- Caffeine
- Red Bull
- Nicotine
- Chocolate
- Decongestants

Pseudoephedrine

Prescription Stimulants
- Mixed Amphetamine salts
- Dextroamphetamine
- Methylphenidate

Illegal Stimulants
- Cocaine
- MDMA
- Methamphetamine

Stimulants

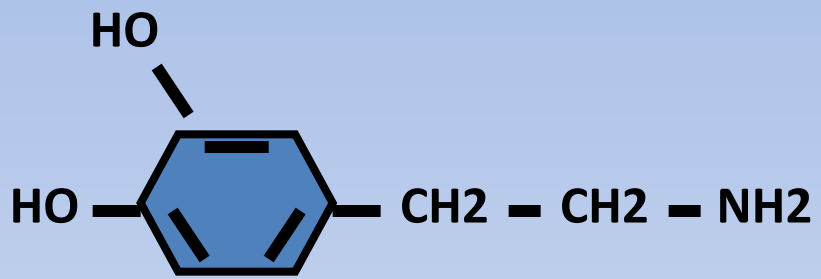
- Cocaine – catecholamine re-uptake inhibitor
  - Crack = cocaine HCl + Na bicarbonate → able to be smoked
  - Free base → IV
  - Cocaine powder → insufflated
- Amphetamines – promote catecholamine release from the vesicle at VMAT2 receptor
  - Methamphetamine → smoked
  - Prescription amphetamines → oral, snorted
- Designer amphetamines (MDMA, MDA, etc)
  - Mix of hallucinogen (serotonin release promoter) and amphetamine
- Direct effect on DA pathway = highest dependence liability

Methamphetamine Use

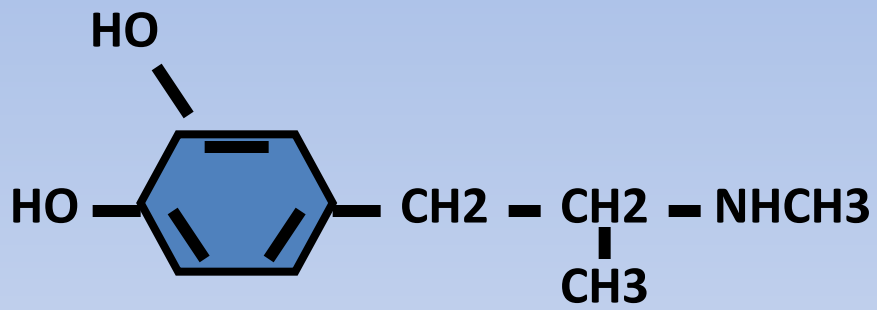
- Canadian Addiction Survey (2004) – 15 & over:
  - 6.4% used at least once in lifetime
  - Less than 1% reported use in last year
- Peak use during late adolescence/early adulthood (15-30 yrs)
- West >> East
- 1 in 10 who use become dependent
- Use more common in street involved youth, gay men and homeless populations
  - 71% of a convenience sample of street involved youth in Vancouver had used
  - 37% of homeless youth in Toronto used at least once a month
- Few dependent users present for treatment

CCSA 2006

How are Prescription Amphetamines Different from Illegal Amphetamines?



Amphetamine

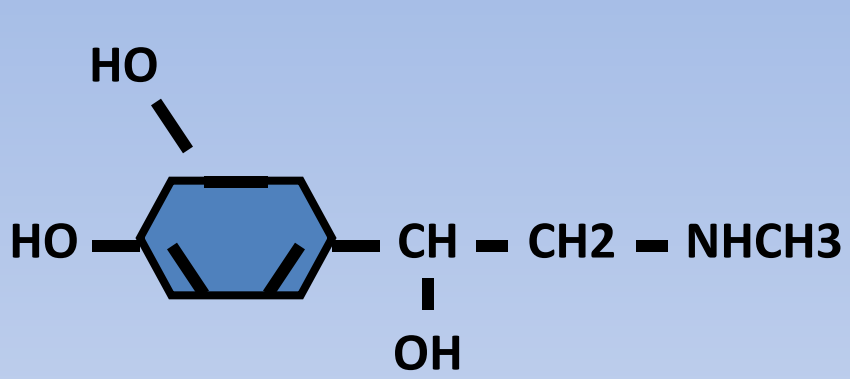


Methamphetamine

Although illegal and prescription amphetamines come from the same class of drugs, they have completely different chemical structures and therefore do not have the same effects on the brain

Westfall & Westfall, 2006

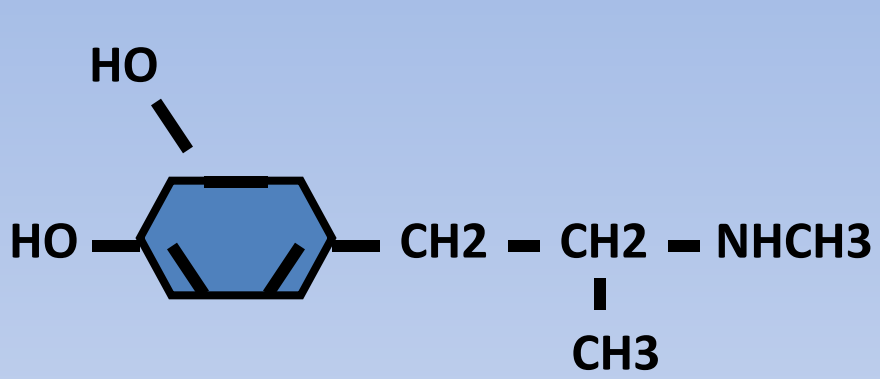
Similar Structures – Very Different Effects



Pseudoephedrine / Sudafed ®

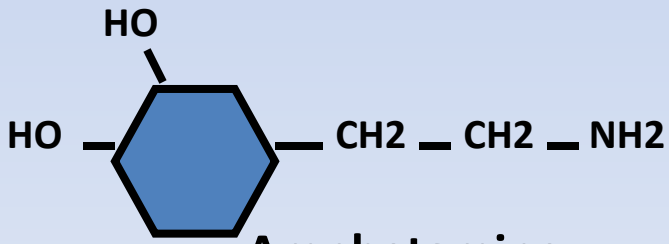
Reduction

Red Phosphorus + Iodine



Desoxyephedrine / Methylamphetamine

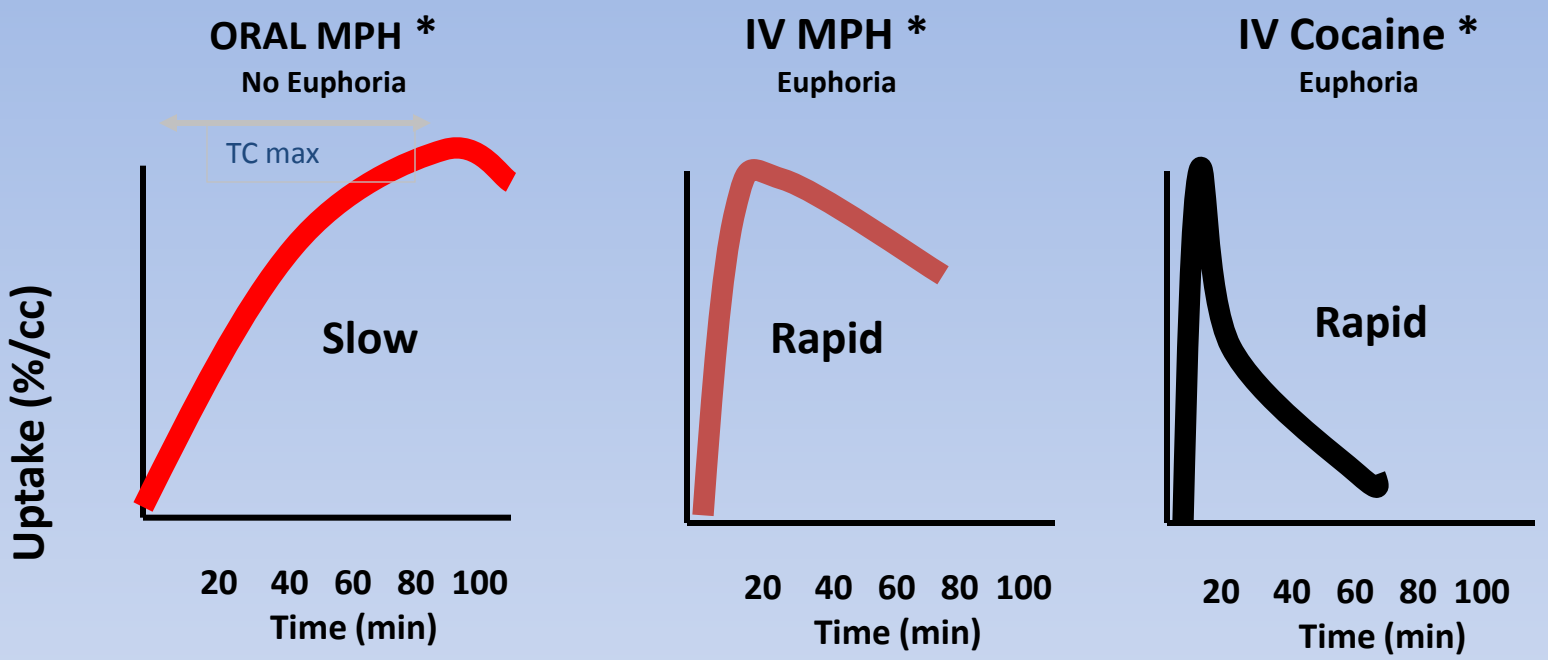
- Methamphetamine has a methyl group substituted on the terminal amine portion of the amphetamine molecule.
- This substitution may be responsible for methamphetamine entering the brain rapidly and producing more CNS effects.



Amphetamine

Westfall & Westfall, 2006

Route of Administration is Everything



Slow	Absorption Peak (TC max)	Fast
Low	Dosage	High
Low	Risk of Abuse/Misuse / Dependency	High

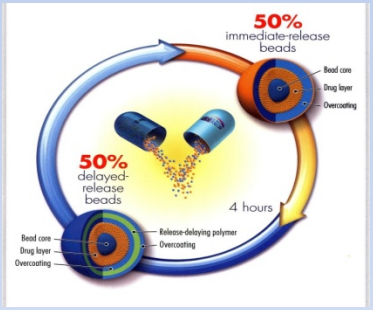
* Volkow et al., J Neurosci, 2001

Do all Oral Medications Share the Same Risk?

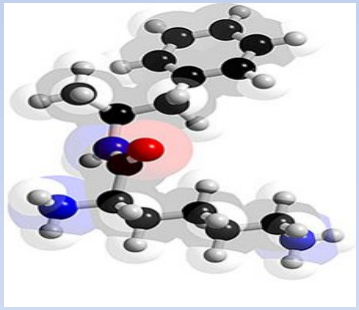
High-Tech Delivery Systems

Immediate Release Formulations

Low ← **Risk of Abuse / Dependence** → **High**



Microtrol Delivery System



Pro-Drug Technology

Releasing Mechanism lowers the Potential for Psychostimulant Abuse

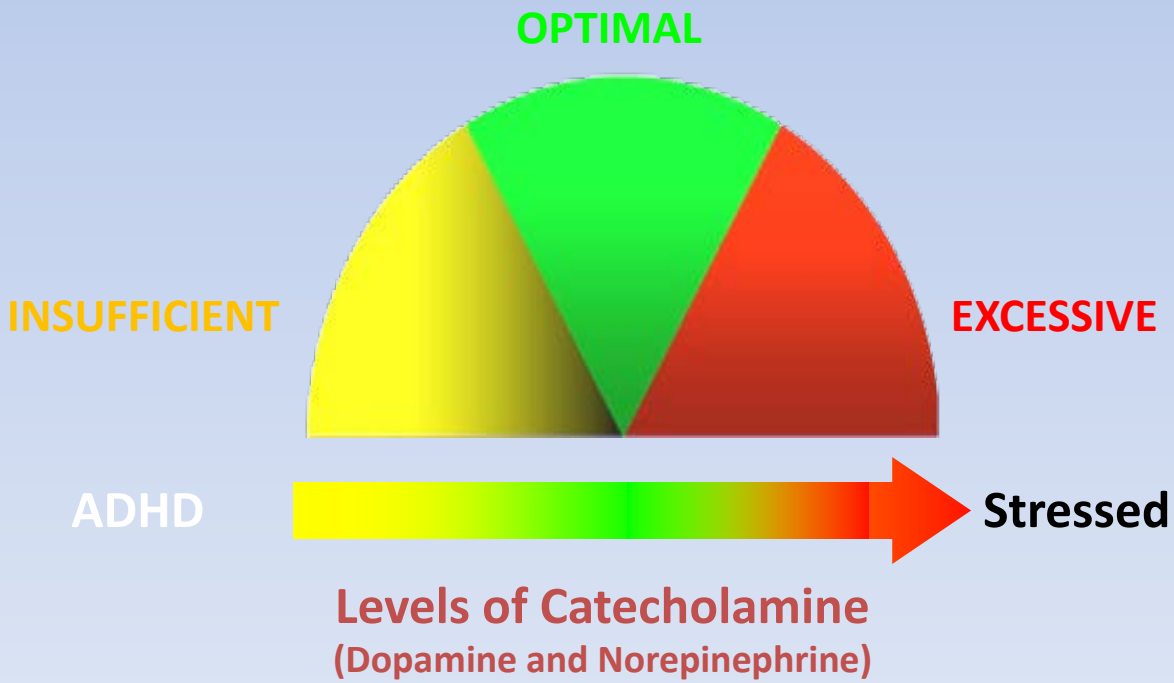
Short acting formulations can be crushed, snorted or injected having rapid effects on the brain that produce a 'high'

Wilens, Gignac et al., J Am Acad Child Adolesc Psychiatry 2006; 45(4):408-414.
Wilens et al., J Am Acad Child Adolesc Psychiatry 2008; 47(1):21-31.

Why are Extended-Release Formulations Recommended for Adults with ADHD?

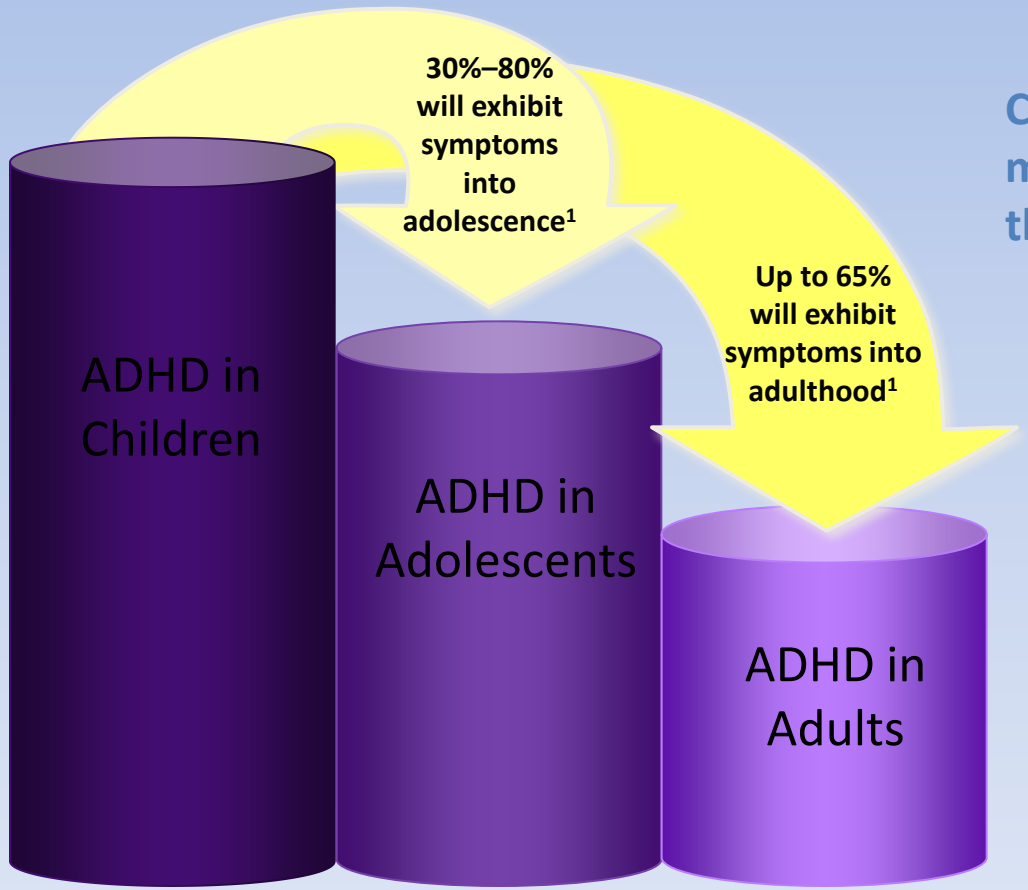
- No stigma of taking medication during the day
- Better adherence[1,2]
- Some research shows better effectiveness[2] and higher rates of remission[1]

Prefrontal cortex requires proper "tuning" of catecholamine levels for optimal function[3]



Hosenbocus S and Chahal R. *Can Acad Child Adolesc Psychiatry.* 2009;18(4):331-39; Ramos-Quiroga JA, et al. *CNS Drugs.* 2008;22(7):603-11; Stahl MS. Stahl's essential psychopharmacology (3rd ed). 2008.

ADHD Persists from Childhood to Adulthood



Co-morbidities (sleep, mood and anxiety) fill in the gaps

*According to results from the National Comorbidity Survey Replication in 3199 respondents aged 18 to 44 years.

Dulcan M, et al. *J Am Acad Child Adolesc Psychiatry*. 1997;36(10, suppl):85S-121S; Kessler RC, et al. *Am J Psychiatry*. 2006;163:716-23.

Diagnosing ADHD in Adults Is Complex

DSM-IV has child bias for ADHD to begin with

- Symptoms seen in other disorders or in normals

Patients often undiagnosed

- 1. Co-morbidity is caught, (Depression) but ADHD is missed
- 2. ADHD correctly diagnosed but primary co-morbidity is missed (bipolar/anxiety)
- 3. Both are missed and written off to substance abuse/personality disorder

Prejudice of the ADHD diagnosis

- Negative: Physician more than patient
- Positive: patient may be more willing to admit ADHD than mood/anxiety disorder
- Coping strategies can "cover up" the true extent of the impairment more than other illnesses

ADHD And Substance Use Disorder

- ADHD and SUD Comorbidity
- Self medication?
- Shared risk factors?
- Potential effect of stimulants?
  - Brain alteration in children with ADHD via reward system
  - Symptom diversion

Prevention of Substance Abuse in Youth With ADHD

- Reasons for Discrepant Results
- Risk reduction was greater in studies that followed children into adolescence than into adulthood
  - Older studies used medications that were not routinely used as children transitioned into adulthood
  - Lack of medication coverage in adulthood may have made it difficult to resist using substances
- Children with severe ADHD were more likely to be treated
  - Studies that did not factor in baseline severity were more likely to find no protective effect

Prevention of Substance Abuse in Youth With ADHD

- General Conclusions on Pharmacotherapy for ADHD and SUD Risk
- Pharmacotherapy for ADHD
  - Reduces the risk of SUD
  - Does not immunize patients against SUD
- Controlling ADHD and the biological effects of ADHD in the brain can control the incremental effect of substance use