## Amphetamine vs. Methylphenidate



## Learning Objectives

After the webinar, clinicians should understand how the two stimulant classes differ in respect to their:

- 1. Mechanism of action
- 2. Efficacy
- 3. Tolerability
- 4. Psychiatric risks
- 5. Neurotoxic and neuroprotective properties



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## **Conflicts and Disclosures**

None

# Diagnosis

Childhood onset (before 12)? Not better explained by another disorder? Meet full DSM-5 criteria?





"Do you often fail to give close attention to details, or do you make careless mistakes in your work... And how was that during childhood?"

www.divacenter.eu



# ADD/ADHD subtype does not influence response to either stimulant



## Stimulants

**Ritalin** Methylin **Ritalin SR** Methylin ER Metadate ER **Ritalin LA** Metadate CD Aptensio XR Adhansia XR Concerta QuilliChew ER Quillivant XR Cotempla XR-ODT Daytrana Jornay PM Azstarys Focalin **Focalin XR** 

## Amphetamine

Adderall Adderall XR Adzenys XR-ODT Adzenys ER liquid **Dyanavel XR liquid Mydayis** Evekeo **Evekeo ODT** Dexedrine Zenzedi **Dexedrine Spansules** Vyvanse

## Amphetamine

Increases dopamine release

## Methylphenidate

Blocks dopamine reuptake



## In children... About half respond to either (43%) About half respond to only one (41%) The rest respond to neither (16%)



## **Expert Consensus**

	Methylphenidate	Amphetamine
Child and Adolescent		
USA AACAP	1	1
England NICE	1	2 (as Vyvanse)
Canada	1	1
Adults		
USA Psychopharm Algorithm	1	2
England NICE	1	1 (as Vyvanse)
Scotland Royal College	1	2



Lower effect size

## Amphetamine

#### **Higher effect size**



## **Stimulant Side Effects**

Physical	Psychiatric
Headaches	Anxiety
GI Distress	Depression
Dry mouth	"Like a zombie"
Anorexia	Insomnia
Tics	Compulsivity (nail biting, skin picking)
Growth delay (in children)	Mania
QTc Prolongation	Psychosis
Cardiac arrest (in Congenital Long QT Syndrome)	Stimulant abuse

Lower effect size Better tolerated

## Amphetamine

Higher effect size Poorer tolerability





## Only two drugs had better acceptability than placebo:

### Methylphenidate in children/adolescents Amphetamine in adults



# Psychosis

A single stimulant dose caused psychosis in Acute schizophrenia: 50–70% Remitted schizophrenia: 30%

Children given stimulants had earlier age of psychosis onset (20 vs 25)

Moran LV, J Psychiatr Res 2015 Curran C, Br J Psychiatry 2004 The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

#### Psychosis with Methylphenidate or Amphetamine in Patients with ADHD

Lauren V. Moran, M.D., Dost Ongur, M.D., Ph.D., John Hsu, M.D., M.S.C.E., Victor M. Castro, M.S., Roy H. Perlis, M.D., and Sebastian Schneeweiss, M.D., Sc.D.

### 221,000 patients with ADHD Age 13-25 Treated with stimulants



### Rate of psychosis: 1 in 660

### Rate was double for amphetamine vs. methylphenidate.



## Mania

# Amphetamine is often used as an animal model for mania





# Associated with 7-fold risk of mania when used without a mood stabilizer

Mirror image "before/after" study (n=2,307 w/ bipolar)



Viktorin A, Am J Psychiatry 2017

### Associated with 30% lower risk of developing bipolar disorder with long-term use in children treated for ADHD

Atomoxetine had no effect (n=289,000)



Wang LJ, J Psychiatr Res 2016

## No worsening of mania on methylphenidate

RCT, dose 20-40 mg/d, duration 2.5 days





Hegerl H, Eur Neuropsychopharmacol 2018

Lower effect size Better tolerated Lower risk of psychosis Risk of mania is likely lower

## Amphetamine

Higher effect size Poorer tolerability Higher risk of psychosis (2-fold) Higher risk of mania

## **Complex Comorbidities**

## 1935 Amphetamine released as Benzedrine1955 Methylphenidate released as Ritalin



#### "... if the individual is depressed...."

".... if the individual is depressed or anhedonic ... you can change his attitude ... by physical means just as surely as you can change his digestion by distressing thought ... In other words, drugs and physical therapeutics are just as much psychic agents as good advice and analysis and must be used together with these latter agents of cure."

> Myerson, A.— Anhedonia— Am. J. Psychiat., July, 1922,

When this was written—in 1922—the only stimulant drugs employed in the treatment of simple depression were of limited effectiveness. Only in the last decade has there been available—in Benzedrine Sulfate—a therapeutic weapon capable of alleviating depression, overcoming "chronic fatigue" and breaking the vicious circle of anhedonia.



#### BENZEDRINE SULFATE TABLETS

(racemic amphetamine sulfate)



#### Brighten the day

depression, fatigue, lethergy

spirits and performance

morover



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- the depressed
- . the psychically fatigued
- · the apathetic
- . the oversedated
- the moody.
- CIBA manities

### Do stimulants help comorbidities?

	Methylphenidate	Amphetamine
Depression	<b>Yes</b> (in geriatrics)	No (2 large RCTs)
Suicide and Self-harm	Yes	No
Borderline personality d/o with ADHD	Yes	May worsen
OCD	Yes	Unknown
Fatigue in medical illness	Yes	Few studies

Lavretsky H, Am J Psychiatry 2015 Richards C, J Psychopharmacol 2017 Richards C, J Affect Disord 2016 Gvirts HZ, Int Clin Psychopharmacol 2018 Schulz C, Psychiatry Res 1985 Zheng H, Eur Neuropsychopharmacol 2019 Shakeri J, Drug Alcohol Depend 2016 Pederson L, J Pain Symptom Manage 2020

## Methylphenidate associated with half the risk of suicide/self-harm in... **ADHD** Depression **Personality disorder Possibly bipolar with ADHD But not in schizophrenia** And not with amphetamine (mirror-image studies comparing rates 2 years before/after starting stimulants, n=8,500)

What happens at high doses?

Going above 120 mg/day of either stimulant associated with higher risk of...

Psychosis (12x) Psychiatric hospitalization (3x) Substance abuse (4x) Possibly suicide (5x)

In <u>narcolepsy</u> (n=112)



Lower effect size Better tolerated Lower risk of psychosis Risk of mania is likely lower May lower suicide risk May help comorbidities

## Amphetamine

Higher effect size Poorer tolerability Higher risk of psychosis (2-fold) Higher risk of mania No reduction in suicide risk Ineffective/harmful in comorbities

## Addiction

## Amphetamine use (includes prescribed)





### **Amphetamine dependence**





## Is it Rewarding?

Do you like the drug? Willing to take it again? Willing to pay for it?





Lower effect size Better tolerated Lower risk of psychosis May lower suicide risk May help comorbidities Risk of mania is likely lower Slightly less rewarding

## Amphetamine

Higher effect size Poorer tolerability Higher risk of psychosis (2-fold) No reduction in suicide risk Ineffective/harmful in comorbities Higher risk of mania Slightly more rewarding



# 5-34% of college students use a stimulant without a prescription

Korn L, Med Sci Monit 2019



## Similar rates of diversion



#### 1960's Amphetamine abuse peaks



#### 1971 Stimulants restricted as schedule-II controls



#### 1970-1980 Amphetamine prescriptions fall from 1969 peak





Lower effect size Better tolerated Lower risk of psychosis May lower suicide risk May help comorbidities Risk of mania is likely lower Slightly less rewarding Similar drug diversion

## Amphetamine

Higher effect size Poorer tolerability Higher risk of psychosis (2-fold) No reduction in suicide risk Ineffective/harmful in comorbities Higher risk of mania Slightly more rewarding Similar drug diversion

## Neuroprotection

## Are they Neuroprotective?



Stress has caused brain cells in the picture above to shrink back



The brain cells pictured above have more connections - like a tree with more branches - due to the effects of medication. High dose amphetamine → High dopamine in cytoplasm → Oxidative stress and inflammation → Damaged dopamine nerve terminals in hippocampus and cerebral cortex

Berman SM, Mol Psychiatry 2009

## **Dopamime depletion in clinical doses**



Primates after 2-4 weeks Adderall 40-60 mg/d equivalent

Ricaurte GA, J Pharmacol Exp Ther 2005 Melega WP, Brain Res 1997 Older brains have...

More toxicity from <u>meth</u>amphetamine

Higher <u>amphetamine</u> levels in CNS (2-fold higher compared to younger)

[in animal studies]



Methylphenidate has some evidence of toxicity, but is neuroprotective in animal models of...

Stroke
Parkinson's disease
Methamphetamine abuse

Lower effect size Better tolerated Lower risk of psychosis May lower suicide risk May help comorbidities Risk of mania is likely lower Slightly less rewarding Similar drug diversion Less neurotoxic, ? neuroprotective

## Amphetamine

Higher effect size Poorer tolerability Higher risk of psychosis (2-fold) Slightly more rewarding Similar drug diversion No reduction in suicide risk Ineffective/harmful in comorbities Higher risk of mania Neurotoxic

#### **Bottom Line**

Safer, particularly with complex comorbidities

Better tolerated

Less effective in some patients



## Amphetamine

#### **Bottom Line**

Riskier, particularly in the young, elderly, and those at risk for abuse, mania, or psychosis

More effective in some patients



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## Join us next time for... How to Select a Stimulant Formulation From isomer mixes to extended release

