

# The Psychopharmacology of Challenging Behaviors

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## Disclosures

- Dr. Tridas is a speaker for:
  - Eli Lilly
  - McNeil
  - Novartis
  - Shire
- Dr. Tridas is a consultant for:
  - Eli Lilly
  - McNeil

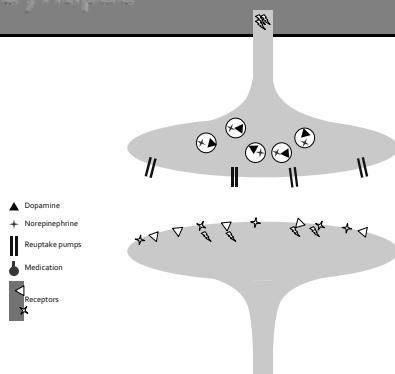
## Neurobiology of Emotions and Behavior

- Limbic structures: Deep Emotions
  - Rage attacks, irritability
  - Associated with Temporal Lobe Epilepsy
- Frontal Lobe: Inhibition
  - Impulsivity
- Striatum: Attention – Reward – Movement
  - Distractibility, drug abuse, dyskinesias, hallucinations

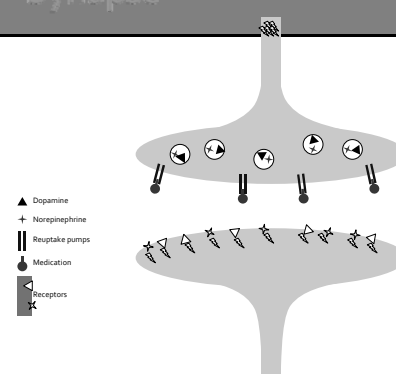
## Synapse

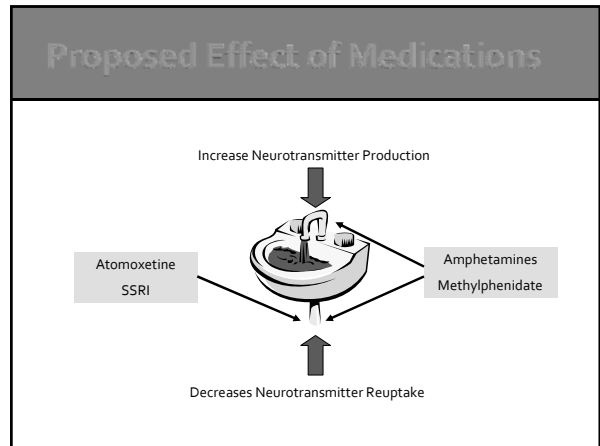
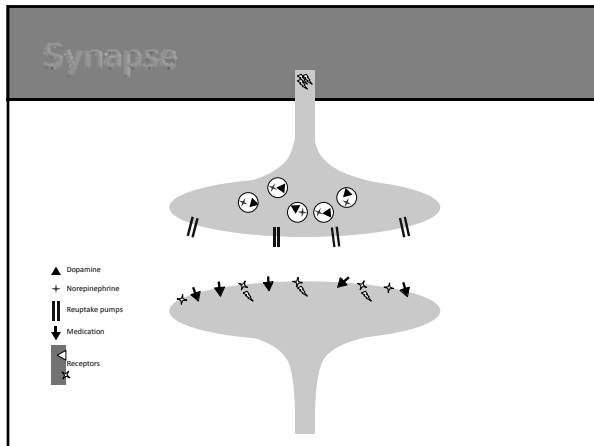
- Communication between neurons is regulated by over 200 neurotransmitters
  - Dopamine, norepinephrine, serotonin, GABA, glutamine, etc.
- Three parts
  - Presynaptic neuron
  - Cleft
  - Postsynaptic neuron
    - Receptors activate the receiving cell

## Synapse



## Synapse





### Neurobiology of Psychiatric Disorders

Disorder	Neurotransmitter	Brain Region
Anxiety	NE, GABA, DA	Global
ADHD	DA, NE	Frontal Lobe, Striatum
Depression	Serotonin, NE	Frontal Lobe, Limbic System
OCD	Serotonin	Striatum, Cingulate
Psychosis	DA, Serotonin	Frontal Lobe, Striatum
Tourette's	DA, serotonin	Basal Ganglia, Frontal Lobe

- ### The Disorders
- Disruptive Behavior Disorders
    - ADHD
  - Anxiety Disorders
    - Separation Anxiety
    - Generalized Anxiety
    - Panic
    - Phobia
    - PTSD
    - OCD

- ### The Disorders
- Mood Disorders
    - Depression
    - Manic-Depressive
  - Autistic Spectrum Disorders
    - PDD-NOS
    - Autism
    - Asperger
  - Schizophrenia and Psychotic Disorders
    - Psychosis

### ADHD

## Definition of ADHD

- Inattention
- Impulsivity
- Overactivity

## Inattention

- Inability to pay attention...
  - to the right thing (selectivity),
  - at the right time (timing),
  - for the appropriate amount of time (duration),
    - Requires inhibition of distractions
  - as in depth as needed (intensity)

## Impulsivity

- Inability to sustain inhibition
  - Stop to...
    - Think about consequences
    - Formulate a plan
    - Think about previous experiences or rules
  - Wait for...
    - Question to be finished
    - Turn

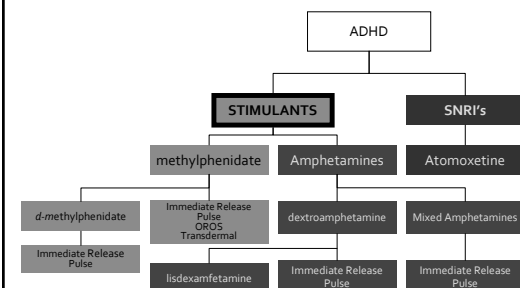
## Hyperactivity

- Overactive
  - Can't stay seated
  - Runs rather than walking
  - Can't stay on line
  - Driven by a motor
  - Can't keep hands to self
- Fidgety
  - Can't sit still
- Talkative

## Clinical impact of ADHD

- Educational/Occupational
  - Decreased production and accuracy
- Behavioral
  - Disruptive behavior and non-compliance
- Social
  - Decreased social awareness, inappropriate behavior

## Types of Medications Used In Managing ADHD



## Medications: Clinical Impact

- Increase control of attention
- Increase impulse control
- Decrease activity
- Decrease disruptive behavior
- Improve handwriting (in 50%)

## Medications: Target Outcomes

- Academic
- Behavior
- Socialization
- Increase Production
- Increase Compliance  
Decrease Disruption
- Increase Awareness

## Stimulant Medications

- Side Effects
  - Insomnia (50-60%)
  - Anorexia (50-60%)
  - Irritability (30%)
  - Headache
  - Stomachache
  - Nausea
  - Tics

## Atomoxetine: Side Effects

- Anorexia
- Dizziness - Sleepiness
- Dyspepsia
- Dermatitis
- Constipation
- Mood Swings
- *Transient elevation of liver enzymes*
- *Increased suicidality*

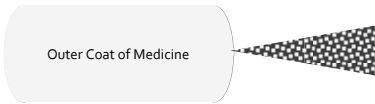
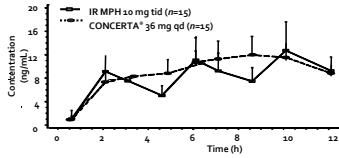
## Medications: Duration of Action

- Short Acting: 4 hours
- Intermediate Acting: 6 – 8 hours
- Long Acting: 8 – 12 hours  
24 hours

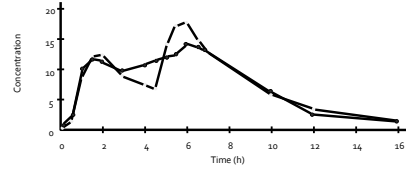
## Medications

- Short-Acting
  - Ritalin, Dexedrine, DextroStat, Focalin Methylin (Tablet, Chewable & Liquid)
- Intermediate-Acting
  - Ritalin SR, Metadate ER, Adderall, Ritalin LA, Metadate-CD, Methylin ER, Focalin XR
- Long-Acting
  - Dexedrine Spansules, Cylert, Adderall-XR, Concerta, Daytrana, Vyvanse
- 24 hours
  - Strattera

## MPH OROS (Concerta®)

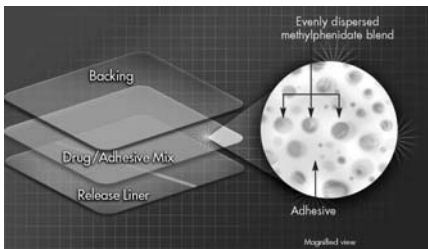


## Pulse Delivery System (SODAS, Difucaps)



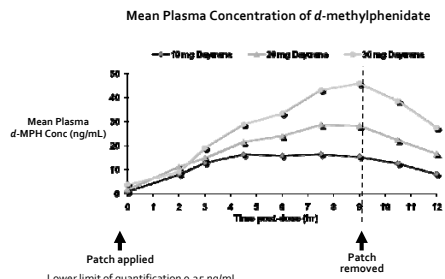
## Daytrana DOT Matrix™ Transdermal Technology

- Methylphenidate is mixed with adhesive



DOT Matrix is a trademark of Noven Pharmaceuticals, Inc.

## Pharmacokinetics with Daytrana

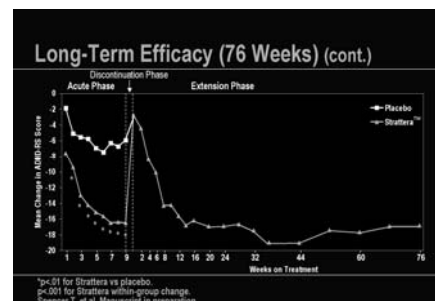


Pierce et al. Poster presented at the AACAP Annual Meeting, Toronto, October 20, 2005.

## Vyvanse™

- Is a pro-drug
  - Inactive until the body breaks it down
- Combines an amphetamine and an amino acid
  - Dextroamphetamine and lysine
- It lasts 12+ hrs
- Not affected by GI transit time or pH

## Atomoxetine (Strattera™) Efficacy



\*p < .01 for Strattera vs placebo.  
 <math>p < .001</math> for Strattera within-group change.  
 Spencer T, et al. Manuscript in preparation.

## Internalizing Behaviors

- Overcontrol symptoms
  - Inappropriate control of internal emotions or cognitive style
  - The way they think about the way they feel
- Behaviors are directed inward
  - Developed and maintained within the individual
- Common internalizing diagnoses
  - Depression
  - Anxiety
  - Social Withdrawal
  - Somatic

## Anxiety Disorders

## Anxiety

- Excessive anxiety or worry that is difficult to control
- Restless, keyed up, on edge, physiological arousal
- Difficulty concentrating, mind goes blank
- Irritability
- Sleep disturbances
- Hypersensitivity to physical cues
- Negative and unrealistic thoughts
- Misinterpretation of symptoms and events
- Panic attacks
- Obsessive and/or compulsive behaviors
- Phobias

## Anxiety Disorders

- Generalized Anxiety Disorder
- Panic Attack
- Agoraphobia
- Specific Phobia
- Social Phobia
- Obsessive-Compulsive Disorder
- Posttraumatic stress disorder
- Separation disorder
- Acute stress disorder
- Anxiety disorder due to medical condition or drug induced

## Separation Anxiety

- Excessive anxiety about separation from caregiver
- Concerns about something bad happening to parents

## Generalized Anxiety

- Excessive anxiety or worry
- Restless, keyed up, on edge
- Difficulty concentrating, mind goes blank
- Irritability
- Sleep disturbance
  - Onset and maintenance

## Obsessive Compulsive Disorder

- Obsessions
  - Recurrent and persistent thoughts, impulses and images that cause marked anxiety or distress
  - The person attempts to neutralize or suppress thoughts through actions
  - The person recognizes the obsessional thoughts as the product of their own mind

## Obsessive Compulsive Disorder

- Compulsions
  - Repetitive behaviors or mental acts in response to an obsession or rigid rules with the goal or minimizing distress
  - The actions may be excessive in nature

## Social Phobia

- Considered a component of many disorders and a separate disorder
- Unrealistic self-appraisal of social performance
- Lack of interest in social interaction
  - Excessive shyness
- Complicated by excessive fear
  - Fear of humiliation in social situations

## Panic Disorders

- Attacks of excessive fear
- Racing heart
- Rapid breathing
- Anger attacks when feeling trapped
- Agoraphobia
  - Fear of being in a place where escape is limited

## Somatic Problems

- Physical discomfort, pain or illness that have no medical basis.
- Usually caused by psychological distress
- Often a key component of depression and anxiety

## Anxiolytics

- Improve
  - Anxiety
  - Agitation
  - Insomnia

## Anxiolytics

- Benzodiazepines\*
  - alprazolam (Xanax)
  - diazepam (Valium)
  - lorazepam (Ativan)
  - clorazepate (Tranxene)
  - clonazepam (Klonopin)
  - oxazepam (Serax)
- Side Effects
  - Sedation
  - Drowsiness
  - Decreased mental acuity
  - Paradoxical agitation
  - Disinhibition

*\*Potential for physiological and psychological dependency*

## Anxiolytics

- Antihistamines
  - diphenhydramine (Benadryl)
  - hydroxyzine (Vistaril, Atarax)
  - chlorpheniramine maleate (Chlor-Trimeton)
- Atypical
  - buspirone (BuSpar)

## Antidepressants / Anti obsessive

- Effective in treatment of:
  - Obsessions
  - Anxiety
  - Depression
    - In children TCAs are not as effective in the management of depression.

## Antidepressants / Anti obsessive

- |                          |                         |
|--------------------------|-------------------------|
| <u>SSRI's</u>            | <u>Side effects</u>     |
| ▪ fluoxetine (Prozac)    | ▪ Agitation             |
| ▪ sertraline (Zoloft)    | ▪ Stomach aches         |
| ▪ paroxetine (Paxil)     | ▪ Irritability          |
| ▪ fluvoxamine (Luvox)    | ▪ Behavioral activation |
| ▪ escitalopram (Lexapro) | ▪ Headaches             |
| ▪ citalopram (Celexa)    | ▪ Insomnia              |
|                          | ▪ Sedation              |

*Long duration of action*

*Do not stop abruptly*

## Antidepressants / Anti obsessive

- |                           |                     |
|---------------------------|---------------------|
| <u>TCA's</u>              | <u>Side Effects</u> |
| ▪ desipramin (Norpramin)  | ▪ Dry mouth         |
| ▪ imipramin (Tofranil)    | ▪ Constipation      |
| ▪ clomipramin (Anafranil) | ▪ Sedation          |
| ▪ amitriptyline (Elavil)  | ▪ Vivid dreams      |
|                           | ▪ Headaches         |
|                           | ▪ Stomachaches      |
|                           | ▪ Blurred vision    |
|                           | ▪ Prolonged QTc     |

## Antidepressants / Anti obsessive

- |                           |  |
|---------------------------|--|
| <u>Atypical</u>           | <u>Side Effects</u>  |
| 1. venlafaxine (Effexor)  | 1. Nausea, agitation, S/A, H/A, hypertension (at high doses) |
| 2. bupropion (Wellbutrin) | 2. Irritability, anorexia, insomnia, tics, seizures          |
| 3. trazadone (Desyrel)    | 3. Priapism, sedation  |
| 4. mirtazapine (Remeron)  | 4. Sedation, upset stomach, increased appetite               |

## Mood Disorders

## Depression

- Depressed mood or excessive sadness\*
- Anhedonia – lost of interest in activities\*
- Change in weight or appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue, loss of energy
- Problems with concentration or decision making
- Recurrent thoughts of death or suicide
- Feelings of hopelessness or excessive guilt
- Somatic complaints
- Irritability

\* Hallmark of depression

## Disorders with Depression

- Major depressive disorder
- Dysthymic disorder
- Depressive disorder, NOS
- Bipolar disorders
- Cyclothymic disorder
- Mood disorder due to medical condition or substance abuse
- Adjustment disorder with depressive mood

## Antidepressants / Anti obsessive

- Effective in treatment of:
  - Obsessions
  - Anxiety
  - Depression
    - In children TCAs are not as effective in the management of depression.

## Antidepressants / Anti obsessive

### SSRI's

- fluoxetine (Prozac)
- sertraline (Zoloft)
- paroxetine (Paxil)
- fluvoxamine (Luvox)
- escitalopam (Lexapro)
- citalopram (Celexa)

## Antidepressants / Anti obsessive

### TCA's

- desipramin (Norpramin)
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- amitriptyline (Elavil)

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### Atypical

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4. mirtazapine (Remeron)

## Manic Depressive Disorder

- Agitation
- Grandiosity (Disdainful defiance)
- Explosive mood
- Excess energy
- Insomnia
- Pressured speech
- Poor judgment/reckless behavior
  - Hypersexual
  - Overspending

## Antipsychotics

- AKA antipsychotics, major tranquilizers
- Grouped
  - High potency
  - Intermediate potency
  - Atypical (less extrapyramidal side effects)
- Dopamine and Serotonin antagonists

## Antipsychotics

- Reduce
  - Stereotyped Behaviors
  - Hyperactivity
  - Inattention
  - Tantrums
  - Negative-labile affect
  - Aggressiveness, SIB
  - Oppositionality
  - Mania

## Antipsychotics

- Improve
  - Some aspects of social relatedness
  - May improve some aspects of discrimination learning

## Antipsychotics

- haloperidal (Haldol)\*
- thioridazine (Mellaril)\*
- chlorpromazine (Thorazine)
- risperidone (Risperdal)\*
- olanzepine (Zyprexa)\*
- aripipazole (Abilify)\*
- Side Effects
  - Sedation
  - Constipation
  - \*Tardive Dyskinesia
  - \*Neuroleptic Malignant Syndrome
  - \*Weight Gain

## Anticonvulsants

- Reduce
  - Mania
  - Rapid cycling
  - Aggression-SIB
- Improve
  - Language
  - Social skills

## Anticonvulsants

- carbamazepine (Tegretal)
- valproic acid (Depakene)
- phenytoin (Dilantin)
- lamotrigine (Lamictal)
- oxcarbazepine (Trileptal)

## Anticonvulsants Side Effects

- Depakote
  - Hepatic Failure ( $\leq 2$  yrs)
  - Pancreatitis
  - Thrombocytopenia
  - Leukopenia
  - Weight gain
  - Sedation (elderly)

## Anticonvulsants Side Effects

- Trileptal
  - Diplopia, nystagmus, abnormal vision
  - Irritability
  - Dyspepsia
  - Fatigue
  - Sedation
  - Vertigo
  - Hyponatremia
  - Stevens-Johnson

## Anticonvulsants Side Effects

- Lamictal
  - Dizziness
  - Headache
  - Blurred or double vision
  - Lack of coordination
  - Sleepiness
  - Nausea/vomiting
  - Insomnia
  - Tremor
  - Stevens-Johnson
    - Rapid titration, concurrent with Depakote, overdose

## Anticonvulsants Side Effects

- Tegretal
  - Sedation
  - Confusion
  - Elevated LFT's
  - Dizziness
  - Nausea
  - Aplastic anemia (very rare)
  - Photosensitive rash
  - Stevens Johnson

## Autistic Spectrum Disorders

## PDD - DSM IV Definition

- Behaviorally defined neurological disorder
- Severely incapacitating
- Life-long
- Appears during the first 3 years of life
- Areas of impact
  - Qualitative impairment in *social interaction*
  - Qualitative impairment in *communication*
  - *Restricted repetitive and stereotyped* patterns of behavior, interests and activities (Perseveration)

## Social Interaction (2 or more)

- Impairment in use of non verbal behaviors (eye contact, gestures) to regulate social interaction.
- Failure to develop peer relationships appropriate for developmental level.
- Lack of spontaneous seeking to share enjoyment, interests or achievements (Joint Attention).
- Lack of social or emotional reciprocity.

## Communication (1 or more)

- Delay / total lack of development of language (not compensated by gestures)
  - 50% are non-verbal
  - 20-30% regress between 1-2 years
- Inability to initiate or sustain conversation in spite of adequate language
  - Lack of reciprocal interchange
  - Fails to attend to social cues, body language (pragmatics)

## Repetitive Behavior (1 or more)

- Restricted pattern of interest that is abnormal in intensity or focus
- Inflexible adherence to nonfunctional routines and rituals
- Stereotyped / repetitive motor mannerisms
- Persistent preoccupation with parts of objects

## Pervasive Developmental Disorders

- Autism
- Rett Syndrome
- Disintegrative Disorder
- Asperger Disorder
- PDD-NOS

## Management of Autism

- No specific pharmacotherapy for the disorder
- Manage the symptoms
  - Repetitive behaviors
  - Aggression, SIB
  - Sleep disturbances

## Indications for Medical Intervention

- Severe symptoms of:
  - Sleep disturbance
  - Self-injurious behavior
  - Aggression
  - Hyperactivity
  - Stereotypes and perseveration
  - Withdrawal

## Antihypertensives

- clonidine (Catapres)
- guanfacine (Tenex)
- propranolol (Inderal)
- naldolol (Corgard)

## Antihypertensives

Effective in treatment of:

- Aggression
- Over-reactivity
- Sleep problems
- Hyperactivity
- Impulsivity
- Inattention
- Great "chill pills"

## Medication for Sleep Problems

- clonidine (Catapres)
- diphenhydramine (Benadryl)
- hydroxyzine (Vistaril / Atarax)
- trazadone (Desyrel)
- mirtazapine (Remeron)
- chloral hydrate
- TCA's
- Antipsychotics
- melatonin

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