Pharmacology for Autism:
When Can it Help &
When Does it Hurt?

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Support

- Speaker Bureau
  - Astra (Seroquel/Seroquel XR)
  - Bristol Meyers Squibb (Abilify-past)
  - Glaxo Smith Kline (Vyvanse-past)
  - Janssen (Risperdal-past)
  - Lilly (Strattera/Zyprexa-past)
  - Novartis (Focalin XR/Ritalin LA/Focalin/Fanapt)
  - Noven (Daytrana)
  - Pfizer (Zoloft/Geodon-past)
  - Shire (Vyvanse/Daytrana/Adderall (XR)/Intuniv)
Pharmacotherapy of Autism

- Should **NOT** expect that pharmacological agents to cure children with autistic disorder (i.e. eliminate core social & cognitive dysfunction)

- State-of-the-art therapy involves empirical treatment
  - of target symptoms or
  - comorbid disorders
Maladaptive Behavior

- As many as 40% of people with developmental disability experience a period of disturbed behavior/function at some time in their lives, which may signal the onset of a psychiatric disorder.
Causes

- Adaptive dysfunction
- Adjustment issue
- Psychiatric condition
- Medication side effects (new, chronic)
- Medical conditions (new, chronic)

- Often multiple causes/triggers
Adaptive dysfunction

- Mismatch between needs, abilities, goals of individual within his/her environment
  - Move/change of residence
  - Change in daily life schedule
    - Start of school/work, change in work activities, inappropriate expectations to complete tasks or travel independently
Adjustment issues

- Change in staff/co-resident/family/death
  - turnover is very high in some group homes
  - response can be delayed
  - Illness in client or significant other
- Seasonal pattern/anniversary reaction
- Trauma OR abuse OR reminders/triggers of past abuse
Common maladaptive behaviors
(or Reason for Psychiatric Referral)

- Aggression
- Impulsive/Hyperactivity
- Mood lability/irritability
- Low frustration tolerance/tantrums/property destruction
- Noncompliance/oppositional behavior
- Sleep disturbance
- Regression in functioning
- Elopement
Highly deviant behaviors

- Present almost exclusively in severe/profound MR
- Stereotypies
- Repetitive SIB
- Fecal smearing
- Pica
- Rumination
Psychopathology

- Prevalence of mental illness in persons with intellectual disability is 4-5x higher vs gen pop
- Range from 30-70% of the MR population
- Acute-most frequent
  - Adjustment Disorder, Mood Disorder, Anxiety DO, Anxiety Disorder, Post traumatic stress
- Chronic-most frequent co-morbid psychiatric disorder
  - Autism
MR and Psychopathology

- Serious mood DO - 2-10%
  - Dysthymia - 50%
- Anxiety DO - 10-25%
- ADD - 10%
- Schizophrenia - 2-3x > vs general pop
- Stereotyped behavior - 15-50%
- SIB - 10-20%
Medication Side Effects

- Anticonvulsants
  - Cognitive/behavioral side effects
    - Phenobarbital
      - Cognitive impairment, hyperactivity, depression
    - Topomax
      - Word finding/attention difficulties
    - Neurontin
      - Psychosis
Medication Side Effects

● Benzodiazepines
  – Long half-lives
    ● Clonazepam (klonopin)
      – Accumulate > drowsiness & mental clouding
  – Short-acting
    ● Lorazepam (ativan), alprazolam (xanax)
      – Interdose rebound symptoms (marked worsening of anxiety prior to scheduled doses)
  – Ataxia? (autistic individuals)
Medication Side Effects

- Antipsychotic drugs
  - Akathisia (restlessness)
    - Confused with worsening agitation
    - Lead to a counterproductive increase of the dose.
  - Alertness/mental performance
  - Precipitous reduction in dosage
    - Agitation, behavioral deterioration
    - Worsening abnormal involuntary movements (transient withdrawal dyskinesias)
Medical Conditions in MR/DD

- Occult medical illnesses reported as cause of 10% of psychiatric sx’s in general population
- 20-40% of chronically mentally ill have 1 or more medical illness, that may cause/exacerbate psychiatric/behavioral sx’s (Black, et al., 1985; Koran, et al., 1989)
- Persons with MR have more medical problems and prompt treatment is associated with better survival (Carter, Jancar, 1983; McLoughlin, 1988)
Common medical causes

- nervous system (epilepsy)
- metabolic disorders (thyroid disease)
- infections (pneumonia, otitis media, dental infections)
- gastrointestinal disorders (reflux)
- cardiac anomalies (arrhythmia's)
- orthopedic problems (arthritis)
- pain syndrome

http://www.ddhealthinfo.org/
When/why are medications started?

- Treat specific symptoms when behavioral interventions only partially or not effective
- Reduce behaviors so that behavioral interventions are possible
- Reduce symptoms so that assessment/learning is possible (hyperactivity, inattention)
- Reduce severe symptoms (impulsivity, agitation, aggression, self injury (SIB))
- Treatment of comorbid psychiatric condition
Pharmacotherapy of Autism

- To date only 2 FDA approved specific agents for treatment of symptoms associated with autism
  - Many agents in child psychiatry do not have FDA approval
- Risperidone (Risperdal)-2006
- Arapiprazole (Abilify)-2009
  - Indicated for the treatment of irritability associated with autistic disorder in children and adolescents
  - Including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods
Target Symptoms

- Hyperactivity, inattention, impulsivity
- Self Injurious behavior (SIB)
- Agitation/tantrums
- Aggression
- Anxiety
- Mood disturbance/low frustration tolerance
- Sleep disturbance
- Impulsivity (elopement, disrobing, sexualized behavior)
- Stereotyped/repetitive behavior/movements
Determine Baseline Behavior

- Define target behaviors
- Determine setting
  - Are symptoms present in only one setting?
    - If yes, then setting (i.e. school) may need to be altered
- Determine frequency, antecedents, consequences
- Collateral sources (care providers, aides, teachers)
- Rating scales
Evidence for efficacy of psychotropics?

- Limited number of properly designed & controlled studies
- Few investigations of monotherapy
- Inherent difficulties studying this population
  - Comorbid neurologic/medical conditions
  - Nonverbal individuals
- Heterogeneity of population studied
  - Inclusion of Autistic spectrum disorders and MR
  - Developmental differences
Pharmacotherapy of Autism

- **Antidepressants**
  - SSRI’s
  - Other antidepressants
- **Anxiolytics**
  - Benzodiazepines
  - Buspirone
- **Antipsychotics**
  - Typical
  - Atypical
- **ADHD & Related Treatments**
  - Stimulants
  - Nonstimulants Atomoxetine (strattera), alpha agonists
  - Other
- **Mood stabilizers**
Serotonin Reuptake Inhibitors (SSRI’s)

- Inhibit serotonin (5-HT) reuptake
  - Prozac (fluoxetine)
  - Paxil (paroxetine)
  - Zoloft (sertraline)
  - Luvox (fluvoxamine)
  - Celexa (citalopram)
  - Lexapro (escitalopram)
Serotonin Reuptake Inhibitors (SSRI’s)

- Potential uses in autistic spectrum
  - Decrease anxiety/depression/irritability/aggression
  - Decreased compulsive/repetitive behaviors, obsessional/perserverative thinking
    - Analogy to obsessive compulsive disorder (OCD)
      - Note-rare for OCD and ASD to co-occur

- Side effects
  - GI upset, headache, sleep disturbance, anxiety/activation/agitation(mania?)
SRI’s-Fluoxetineine (Prozac)

- Open study in adults/adolescents
  - (Cook et al. 1992)
  - n=23; Autism-65%; MR-62%; 7-28 y.o (mean 15.9 y.o)
  - 10mg-80mg/d
  - Improved by CGI (15/23 w/ Aut, 10/16 MR)
  - Improvement in trichotillomania, obsessive compulsive behaviors, ritualistic behavior, mood
  - Side effects - restlessness, insomnia, hyperactivity, anorexia agitation
    - Correlation between dosage & side effects
SRI’s-Fluoxetine (Prozac)

Open in younger children
- Delong et al. 1998
- n=37; 2.25-7.75 y.o.

- 11 “excellent” + 11 “good” clinical response
- Behavioral, affective, cognitive, social benefits
- Family history of major affective illness as predictor
- Hyperactivity, agitation, aggression > discontinuation
Fluoxetine (Prozac) (cont)

- Fluoxetine induced hypomania (Damore et al. 1998)
  - 3 cases in 9-10 y.o. males with Aspergers
    - marked impulsivity, aggressive behavior, mood lability, and irritability
    - pressured speech, marked circumstantiality, sexual inappropriateness, and irritability.
    - irritable, impulsive, and unmanageable
  - Induced by 10-20mg after 1-2mos of treatment
  - Resolved after 3 weeks with discontinuation & treatment with valproic acid (mood stabilizer)
- Thus, caution regarding behavior activation & secondary mania
SRI’s-Fluvoxamine (Luvox)

- Double blind placebo controlled trial in adults
  \( (McDougle \ et \ al. \ 1997) \) \( n=30; \) 12 wks; mean age 30; mean dose 276mg/d
  - 8/15 (53%) responded vs 0/15 placebo by CGI
  - Reduced repetitive thoughts/behavior, aggression
  - 0/15 initial responders responded in replication
  - Minimal side effects-sedation, nausea

- Same methodology in children/adolescents
  \( (McDougle \ et \ al. \ unpublished) \) \( n=34; \) 12 wks; age 5-18; 12 Aut., 3 Asp
  - 1/18 on drug had clinical improvement (mean dose 107mg/d)
  - Side effects-14/18
    - insomnia (9), hyperactivity(5), agitation(5), aggression(5), anxiety (3)

- Developmental differences in medication response
SRI’s-Paroxetine (Paxil)

- **No controlled** studies in autism
- Generally not use because of
  - Withdrawal on discontinuation
  - Drug-drug interactions

- Reports of higher suicidal statements in childhood depression studies?

- Developmental pharmacodynamic issues?
Citalopram (Celexa)

- RUPP study
  - Not found to be effective
- Still useful given broad dosing range
- Liquid form
SRI’s-Escitalapram (Lexapro)

Escitalopram (Lexapro)
- Cousin (single isomer) of above citalopram (Celexa)
- Most purely serotonergic SRI available
- Oral tablets may limit use in sensitive patients
  - 10mg = 20mg of Celexa?
  - Narrower dosing window
  - Liquid form though
- Newer drug
  - Only SRI NOT generic
- No controlled studies in autism
Other Antidepressants

- Tricyclic’s
- Novel
  - Venlafaxine (Effexor)
  - Mirtazapine (Remeron)
  - Bupropion (Wellbutrin, Zyban)
  - Trazodone (Deseryl)
  - Nefazodone (Serzone)
- New
  - Duloxetineine (cymbalta)
  - Symbyax (fluoxetine/olanzapine)
Tricyclic Antidepressants

- Inhibit reuptake of norepinephrine, serotonin, dopamine
- Used to treat depression/anxiety in adults
  - Not effective for childhood depression
  - Anafranil used also for OCD
- Secondary
  - Desipramine (Norpramin)
  - Nortryptyline (Pamelor)
- Tertiary
  - Imipramine (Tofranil)
  - Amitryptyline (Elavil)
  - Clomipramine (Anafranil)
Clomipramine

- While may be effective for older individuals with autism in reducing hyperactivity, stereotypies, compulsive/ritualized behaviors, side effects remain a concern especially in young children.
- Efficacy in young children remains questionable.
- Potential for exacerbating seizure disorders suggests further need for caution.
Venlafaxine (Effexor/Effexor XR)

- Serotonin/Norepinephrine reuptake inhibitor (Dopamine?)
  - Low dose primarily serotonergic agent
  - Higher doses (> 150mg) affect norepinephrine
- **No controlled** studies in children with autism
- Complicated pharmacological profile & side effects limit use in children and those with autism
  - Withdrawal on discontinuation
  - Higher suicidal statements in childhood depression studies?
Mirtazapine (Remeron)

- Mixed serotonergic, adrenergic effect
  - $5HT_{2/3}$ antagonist, $\alpha_2$ antagonist, $H_1$ agonist
- **No controlled** studies in children with autism
- Works well as sleep agent for some
- Not often used in younger people
- Can cause significant weight gain
- Cognitive impact?
Other Antidepressants

- Bupropion (Wellbutrin/Welbutrin SR/Welburtin XL Zyban)
  - NE/DA reuptake inhibitor
  - **No controlled** studies in children with autism
  - May be an option for those who cannot tolerate psychostimulants for ADHD
Other Antidepressants

- Trazodone (Deseryl)
  - 5HT agonist/antagonist
  - No controlled studies in children with autism
  - Primary use is as a sleep agent

- Nefazodone (Serzone)
  - 5HT$_2$ antagonist, 5HT reuptake inhibitor
  - No longer available in US due to hepatotoxicity
New Antidepressants

- **Duloxetine (cymbalta)**
  - Similar to Venlafaxine (Effexor)
  - 5HT/NE reuptake inhibitor,…DA?
  - Better tolerated

- **Symbyax (fluoxetine/olanzapine)**
  - Combination agent
  - Indication for Major Depression
  - Good when pill number matters
Anxiolytics

- Benzodiazepines
  - Lorazepam (Ativan)
  - Clonazepam (Klonopin)
  - Alprazolam (Xanax)
  - Diazepam (Valium)

- Buspar (Buspirone)
Anxiolytics

- Benzodiazepines
  - Often NOT effective for anxiety in children
  - Often cause more sedation than anxiety reduction
  - Disinhibition limits use especially in vulnerable populations and in the context of sedation (*MR*-Barron, Sandman, 1985)
    - Patients seem “intoxicated”
Buspirone

- 5HT$_{1A}$ partial agonist
- **No double blind, placebo controlled** studies
- Open study in PDD/MR adults *(King, Davanzo, 1996)*
  - n=26; MR(servere to profound); 9 PDD’s
  - Not effective for symptoms of SIB, aggression, (30-60mg)
- Open study in children/adolescents with PDD *(Buitelaar et al. 1989)* n=22; 20 PDDNOS, 2 Autism;15-45mg/d; 6-8wks
  - 9/22 improvement by CGI
  - Target symptoms (anxiety, irritability) reduced
  - Orofacial lingual dyskinesia in 1 child after 10mos treatment
Antipsychotics

- Also called neuroleptics or major tranquilizers
- Typical agents
  - Haloperidol (haldol)
  - Thioridazine (Mellaril)
  - Others-minimal use currently
- Atypical agents
  - Risperidone (risperdal)
  - Olanzapine (zyprexa)
  - Clozapine (clozaril)
  - Quetiapine (seroquel)
  - Ziprasidone (geodon)
  - Arapiprazole (abilify)
Conventional Antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Brand Name</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>1958</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine</td>
<td>1958</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon</td>
<td>1958</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Mellaril</td>
<td>1959</td>
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<tr>
<td>Fluphenazine</td>
<td>Prolixin</td>
<td>1959</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Navane</td>
<td>1967</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>1967</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>Serentil</td>
<td>1970</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxitane</td>
<td>1973</td>
</tr>
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# Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Clozaril</td>
<td>1989</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>1993</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa/Zydis</td>
<td>1996</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>1997</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>2001</td>
</tr>
<tr>
<td>Abilify (ODT)</td>
<td>Arapiprazole</td>
<td>2003</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega</td>
<td>2007</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Consta (IM)</td>
<td>2007</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel XR</td>
<td>2008</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega Sustena (IM)</td>
<td>2010</td>
</tr>
<tr>
<td>Fananpt</td>
<td>Iloperidone</td>
<td>2010</td>
</tr>
<tr>
<td>Asenepine</td>
<td>Saphris</td>
<td>2010</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda</td>
<td>2010</td>
</tr>
</tbody>
</table>
Antipsychotics/Neuroleptics

- Uses in Medicine
  - Antiemtic (anti nausea)
  - Movement Disorders
    - Tics/Tourette’s
    - Huntington’s
  - Preoperative anesthesiA
  - Delirium (confusional state)
Antipsychotics/Neuroleptics

- **Uses in Psychiatry**
  - Schizophrenia & other psychotic disorders
    - Atypical Psychosis
    - Brief Psychotic Disorder
    - Schizotypal Disorder
    - Schizoaffective Disorder (SAD)
    - Delusional Disorder
    - Borderline PD
    - Dementia associated psychosis
  - Mood Disorders
    - Bipolar Disorder (acute mania)
    - Depression with Psychosis
Antipsychotics/Neuroleptics

- Anxiety
  - OCD
  - Acute Stress Disorder
  - Post Traumatic Stress Disorder

- Personality Disorders

- Autism
  - Anxiety, agitation, aggression, SIB

- Acute aggression/violence/agitation
  - Not diagnostic specific
Antipsychotics

- Oral dissolving tabs (melt on tongue)
  - Risperidone, Olanzapine, Arapiprazole
- Liquid
  - Risperidone, Arapiprazole
- IM Short acting-relevance?
  - Arapiprazole
- IM Long acting (‘‘depo’’)- not relevant for most
  - Haloperidol, Prolixin, Risperdal, Invega, Zyprexa
- BID
  - Fanapt, Geodon
Antipsychotic Medications: Side Effects

- Weight gain
- ↑ Glucose levels
- ↑ Lipid levels
- ↑ Prolactin levels
- Sedation
- Cardiovascular effects

Abilify is indicated for the treatment of schizophrenia. Please see important safety information on slides 35 & 36. Please see accompanying full prescribing information.
Antipsychotic Medications: Side Effects

- Extrapyramidal symptoms (EPS)
  - Acute dystonia, Parkinsonism, Akathesia

- Tardive dyskinesia (TD)
  - Develops after 3 mos
  - Choreoathetoid movements-oral, limbs, trunk
  - Lower incidence with new agents
  - Risk- >40 yrs, higher dose, duration
Haloperidol (Haldol)

- Extensively studied potent D2 antagonist
- **Double blind placebo controlled** *(Campbell 1978)*
  - n=40 children; 2.6-7.2yo; optimal dose 1.65mg/d
  - Decreased stereotypies, repetitive behavior (Children’s Psychiatric Rating Scale (CPRS)) & increased attention
  - Sedation (12/20), acute dystonia (2/20)
- **Double blind placebo controlled** *(Anderson 1984, 89)*
  - n=40 children; 2.3-6.9yo; optimal dose=1.11mg/d
  - Improved withdrawal, stereotypies, hyperactivity, anger (CPRS)
  - Improved learning?/increased attention
  - Not due to decrease of maladaptive behaviors
  - Irritability, sedation, acute dystonia(11)
RUPP Risperdal Study: ABC-Irritability

After 8 weeks of treatment, the RISPERDAL® (risperidone) group had a 56.9% improvement compared with a 14.1% improvement in the placebo group.

- RISPERDAL (n=49)
- Placebo (n=52)

BL = baseline; RIS = Risperdal®; LOCF = last observation carried forward. PBO = Placebo LOCF analysis; *P<0.001 vs placebo.

# RUPP Risperdal Study: Significant Adverse Events*

<table>
<thead>
<tr>
<th>Adverse Event (AE)†</th>
<th>RISPERDAL® (risperidone) n=49, n (%)</th>
<th>Placebo n=52, n (%)</th>
<th>(P) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>24 (49)</td>
<td>13 (25)</td>
<td>0.03</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (24)</td>
<td>2 (4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29 (59)</td>
<td>14 (27)</td>
<td>0.003</td>
</tr>
<tr>
<td>Drowsines</td>
<td>24 (49)</td>
<td>6 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drooling</td>
<td>13 (27)</td>
<td>3 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Tremor</td>
<td>7 (14)</td>
<td>1 (2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (16)</td>
<td>2 (4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (29)</td>
<td>6 (12)</td>
<td>0.06</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6 (12)</td>
<td>1 (2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>2.7 ± 2.9</td>
<td>0.8 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*One child withdrew from trial at baseline and thus was not included in AE analysis.
†Other AEs reported, but were considered not statistically significant (\(P\)≥0.1).
‡All AE’s were in the mild to moderate range.

During the 8-week study:

- **RISPERDAL®** (risperidone) therapy was associated with an average weight gain of $2.7 \pm 2.9$ kg (5.94 lbs) compared with $0.8 \pm 2.2$ kg (1.76 lbs) with placebo ($P<0.001$)

- Drowsiness was reported at a higher rate for the RISPERDAL group ($n=24$), but was generally mild ($n=16$) to moderate and diminished by week 4

- Severity of EPS as measured by the AIMS and SAS was similar between the RISPERDAL and placebo groups
  - Change in median scores for both treatment groups = 0

EPS = extrapyramidal symptom.
Aripiprazole (Abilify)

- 8 wk multisite DB PCO fixed dose study (5, 10, 15 mg) children with ASD (n=218/6-17 years)
  - All doses significantly better versus placebo at 8 wks by ABC
  - Side effects-sedation, drilling, tremor, akathisia, waking
    - Marcus et al. 2009

- 8 wk multisite DB PCO flexible dose study (5, 10, 15 mg) children with ASD (n=98/6-17 years)
  - Abilify better versus placebo at 8 wks by ABC-Irr + CGI
  - Side affect-fatigue, Somnulin, EPS, waking
    - Owen et al. 2009

- Basis of FDA approval
**Olanzepine (zyprexa)**

- Open label studies suggest effectiveness in children, adolescent, & adults with PDD *Potenza et al. 1998, Malone et al. 2001, Kenmer et al. 2000*
  - Significant improvements in hyperactivity, social relatedness, affectual reactions, sensory responses, language usage, SIB, aggression, irritably, anxiety, and depression
- Small placebo-controlled study *Hunter, Wasserman et al. 2006*
- Increased appetite/ weight gain
  - Mean weight gain =4.8kg, Max= 16 lbs
- No/limited evidence of EPS
- Few side effects (VS, EKG, labs) except sedation
Quetiapine (Seroquel)

- 4 published studies targeting disruptive behavior in autism
- Small (N = 6) open label study (100-350 mg/day/mean age = 10.9 years) report “much improved” or very much improved.” by CGI
  - Withdraw-sedation, lack of efficacy  
    Martin et al. 1999
- Another open label study (n=14 C/A/mean age 12/477 mg/day) in ASD/MR significant improvement and inattention and hyperactivity. Based upon the Connors scale
  - Side effects –sedation, sialorrhea
    Hardan et al. 2003
Other agents

- All are basically continued to have sufficient data with this population
  - Invega
  - Fanapt
  - Saphris
  - Lutada
Psychostimulants

- Enhance CNS release of norepinephrine & dopamine
- Need to distinguish between poor sustained attention vs poor joint attention or other core symptoms
- Potential uses in autism
  - Analogy to ADHD
  - Decreased aggression, impulsivity/increased attention
- Side effects may limit use
  - stereotypties, tics (new)
  - irritability/agitation
  - decreased appetite
  - sleep disturbance
  - psychosis
<table>
<thead>
<tr>
<th>Stimulants</th>
<th>Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>(d,l)-methylphenidate</td>
<td>Ritalin®, Ritalin-SR®, Ritalin LA®, Concerta®,</td>
</tr>
<tr>
<td></td>
<td>Metadate® CD, Methylin® ER, Daytrana™</td>
</tr>
<tr>
<td>(d)-methylphenidate</td>
<td>Focalin™, Focalin™ XR</td>
</tr>
<tr>
<td>Mixed amphetamine salts</td>
<td>Adderall®, Adderall XR®</td>
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<tr>
<td>(d)-amphetamine</td>
<td>Dexedrine®, Dexedrine Spansule®</td>
</tr>
<tr>
<td>Nonstimulant</td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Strattera®</td>
</tr>
</tbody>
</table>

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Psychostimulants
Sprinkle forms

- Methylphenidate
  - Focalin XR, Ritalin LA, Metadate CD
- Amphetamine
  - Adderall XR
- Can be sprinkled on applesauce (also yogurt, ice cream, etc)

Non-stimulant treatments

- Atomoxetine (strattera)
- Alpha 2 Agonists
  - Clonidine (catapres)
    - Capvay
    - Guanfacine (tenex)
      - Intuniv
- Modafinil (provigil)
  - Was not approved for ADHD
- Pemoline (cylert)
  - No longer available in US
Non-Stimulants-Strattera

- Block re-uptake of norepinephrine in synapse
  - Ultimately also affect dopamine
  - Similar action as stimulants but takes time (2-3 weeks) to have effect

- Once a day dosing (usual) with sustained effect

- Lower overall rate of side effects
  - Better tolerability especially for those who had problems with stimulants (too activating, anxiety, anorexia, insomnia, tics etc)
Alpha Agonists

- Can be used alone or in combination with stimulants
  - Often useful in young/medication sensitive patients
- Useful for hyperactivity, insomnia, symptoms of aggression, lability/irritability, impulsivity, anxiety and tics
  - Does not trigger anxiety as some stimulants can
- Side effects: dry mouth, drowsiness, cognitive dulling, lower BP
  - Side effect profile often cleaner as compared to stimulants
  - Low BP not usually an issue for most
  - Watch mood if significant FH of mood disorders
Alpha Agonists

- Clonidine (Catapres)
  - (0.1 - 0.3 mg/day)
  - Patch form
- Clonidine (Kapvay)
- Guanfacine (Tenex)
  - (1 – 3 mg/day)
- Guanfacine (Intuniv)

Dosage: Typically start with evening doses and titrate toward the morning
Clonidine (Catapress)

- Alpha-2 (adrenergic) receptor agonist
- Reduces a sympathetic discharge and lowers level of catecholamine production
- Studies reveal improved attention, hyperactivity, impulsivity in ADHD children
- Smaller studies in ASD improved parent/teacher ratings of hyperactivity, irritability and oppositional behavior

- Side effects include sedation and hypotension
Clonidine (Kapvay)

- New “long acting” version
  - Still bid (2x) dosing
  - Short acting 2-3 x per day

- Better tolerability?
Guanfacine (Tenex)

- Alpha-2a (adrenergic) receptor agonist
  - More specific receptor effect vs clonidine
  - Selectively target prefrontal cortex (attention benefit?)
  - Less sedation/BP impact
- Similar target symptoms in ASD patients but lacks effect for sleep
  - Can activate in some/disturb sleep
  - No concern about secondary mood effects
- Studies in a ASD reveal positive impact on parent/teacher ratings of inattention and hyperactivity
Guanfacine XR (Intuniv)

- Long acting form of guanfacine
  - Guanfacine/Tenex typically dosed 2x – 3x /day
  - This form allows once a day dosing
- Sedation can be problematic in some

### PK Parameters in Adults

<table>
<thead>
<tr>
<th>Parameter</th>
<th>INTUNIV 1 mg qd (n = 52)</th>
<th>Guanfacine 1 mg qd (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1.0 ± 0.3</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>6.0 (4.0 – 8.0)</td>
<td>3.0 (1.5 – 4.0)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng.h/mL)</td>
<td>32 ± 9</td>
<td>56 ± 15</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>18 ± 4</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>Relative bioavailability</td>
<td>58</td>
<td>100</td>
</tr>
</tbody>
</table>
Nonstimulants

- **Modafinil (Provigil)**
- **Armodafinil (Nuvigil)**
  - Not a stimulant
    - Affects histamine and possibly dopamine (much less as compared to stimulants)
    - Promotes alertness > concentration
  - Not approved by FDA in children
    - Approved for narcolepsy, shift phase work
    - Studies demonstrated effect at 400mg in ADHD
    - “safety” concerns regarding rash prevented approval
    - Cost limits use for many
Alternative/New Medications

- Omega 3 Fatty Acids

- Memory/Dementia Medications
  - Aricept (donepezil)
  - Exelon (rivistigmine)
  - Namenda (memantine)

- Nicotine analogues
Alternative/New Medications

- **Omega 3 Fatty Acids**
  - Support the neuronal support cells (glia)
  - Work well adjunctively
    - Probably not sufficient for most by themselves
  - Have mood/anti-anxiety properties
  - Also affect attention, memory, language (?)
  - Very few side effects
    - GI upset can happen
    - Activation especially if FH of Mood D/O
  - Dosing still to be determined
Alternative/New Medications

- Memory/Dementia Medications
  - Aricept (donepezil)
  - Exelon (rivastigmine)
  - Namenda (memantine)

- Small number of studies (mostly for Aricept)
  - Namenda also studies for Autism
- Helpful when other medications not tolerated
Amantadine

• Noncompetitive N-methyl-O-aspartate (NMDA) antagonist
• Indicated for the treatment of Parkinson’s
• Some studies indicate benefit for behavioral symptoms in ASD
  • Benefit on clinician rated measures of hyperactivity, but not parent
• Most common side effects include insomnia and somnolence
Naltrexone

- Opiate antagonist
  - Generally used to block the effects of opiates in the body (i.e. overdose)
- Open label studies in ASD demonstrate impact on hyperactivity and attention, but results are mixed
- Generally well tolerated, but liver function in times need to be tracked over time
Mood Stabilizers

- Approved for bipolar disorder (mania)
- Used intermittent explosive disorder & symptoms of aggression, impulsivity, irritability
- True traditional mood stabilizers
  - Lithium
  - Valproic acid (depakote)
  - Carbamazepine (tegretol)
  - Lamotrigine (lamictal)
- Limited data
  - Gabapentin (neurontin)
  - Trileptal (oxcarbazepine)
  - Topiramate (topomax)
Mood Stabilizers

- Side Effects (vary by drug)
  - Nausea, vomiting, GI upset - Lithium, Valproic
  - Sedation - Valproic
  - Tremor - Lithium, Valproic acid
  - Cognitive
    - Topiramate (topomax) - word finding difficulties/memory
    - Phenobarb - decrease IQ
  - Psychiatric
    - Gabapentin (neurontin) - psychosis
    - Topiramate (topomax) - psychosis
- Some require blood tests
  - Lithium, Valproic acid (depakote), Carbamazepine (tegretol)
Lithium

- In general, lithium has not proven efficacious in individuals with autism
- Lithium may be helpful if strong family history of Bipolar disorder or if additional diagnosis of Bipolar disorder (Campbell, et al., 72; Delong, 94)
- Uncontrolled studies that suggest lithium may have an anti-aggressive effect in children with mental retardation
- Low therapeutic index, side effects limit use
Mood Stabilizers

- Frequent use for aggression, irritability, lability but paucity of literature
- Side effects, especially in combination with other medications
- Limitations—blood draws for levels
Valproic acid (Depakote)

- **NO** double blind, placebo *controlled* studies
  - Frequent use for aggression, irritability, lability
  - Side effects, especially in combination with other medications
- Limitations—blood draws for levels
- **Retrospective review** *(Hollander et al., 2001)*
  - n=14; 5-40 y.o.; PDD NOS; mean 768 mg
  - 10/14 improved in terms of affective stability, aggression, repetitive behaviors
  - Adverse effects included sedation, behavioral activation & weight gain
Carbamazepine (tegretol)

- **NO** double blind, placebo controlled studies
- May help ADHD, aggression in conduct disorder
  
  (Kafantaris et al., 92; Silva et al., 96)

- Limitations - blood draws for levels
- Generally do NOT use as if need mood stabilizer will often use other agent first
Lamotrigine (Lamictal)

- Much less information
- **NO** double blind, placebo controlled studies
- No need for blood draws for levels
- Naturalistic study of lamictal *(Uvebrant et al., 94)*
  - Children/adolescents with intractable epilepsy
  - 13/50 decrease of “autistic symptoms”
Thank You
Treatment

- Primary symptoms:
  - Hyperactivity
  - Short attention
  - Impulsivity

- Consider:
  - Stimulants
    - Knowing higher functioning autistics respond better
  - Alpha agonist
  - Naltrexone
  - Atypical neuroleptics
    - Realizing AIMS tracking is important
Treatment

- Primary symptoms:
  - resistance to change
  - repetitive thoughts
  - perseverative talking
  - compulsive behaviors

- Consider:
  - SSRI
  - clomipramine
    - remembering exacerbation of seizure d/o can be a problem and no data to support treatment in younger children
  - atypical neuroleptics
Primary symptoms:
- stereotyped movements
- tics
- Tourette’s disorder

Consider:
- atypical neuroleptics
- alpha agonist
Treatment

- Primary symptoms:
  - excessive fear
  - worry
  - anxiety

- Consider:
  - SSRI
  - Buspar
Treatment

- Primary symptoms:
  - irritability
  - labile mood
  - sleep disturbance

- Consider:
  - mood stabilizers
  - atypical neuroleptics
Treatment

- Primary symptoms
  - delusions
  - hallucinations
  - bizarre behavior
  - schizophrenia

- Consider:
  - atypical neuroleptics
Treatment

- Primary symptoms:
  - depressed mood
  - crying spells
  - irritability

- Consider:
  - SSRI
Treat Trea

Primary symptoms:
- SIB
- aggression

Consider:
- SSRI
- mood stabilizer
- atypical neuroleptics
- naltrexone
  - Severe/frequent SIB
  - Head banging, biting