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

Derek Ott, M.D., M.S.
Assistant Clinical Professor of Psychiatry
Director Pediatric Neuropsychiatry Clinic
Division of Child Psychiatry
David Geffen School of Medicine at UCLA

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
  - NonstimulatnsAtomoxetine (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 (citolapram)
  - Lexapro (escitolapram)

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-Fluoxetine(Prozac)

- Open study in adults/adolescents
  - *(Cook et al. 1992)*
  - n=23; Autism-65%; MR-62%;7-28y.o (mean 15.9yo)
  - 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" clinicial 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 9-10y.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?

SRI's-Citalapram (Celexa)

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
  - Duloxetine (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, α_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)
  - o NE/DA reuptake inhibitor
  - o **No controlled** studies in children with autism
  - o 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 hepatoxicity

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

Chlorpromazine	Thorazine	1958
Trifluoperazine	Stelazine	1958
Perphenazine	Trilafon	1958
Thioridazine	Mellaril	1959
Fluphenazine	Prolixin	1959
Thiothixene	Navane	1967
Haloperidol	Haldol	1967
Mesoridazine	Serentil	1970
Loxapine	Loxitane	1973

Atypical Antipsychotics

Clozapine	Clozaril	1989
Risperidone	Risperdal	1993
Olanzapine	Zyprexa/Zydis	1996
Quetiapine	Seroquel	1997
Ziprasidone	Geodon	2001
Abilify (ODT)	Arapiprazole	2003
Paliperidone	Invega	2007
Risperidone	Consta (IM)	2007
Quetiapine	Seroquel XR	2008
Paliperidone	Invega Sustena (IM)	2010
Fananpt	Iloperidone	2010
Asenepine	Saphris	2010
Lurasidone	Latuda	2010

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

Antipsychotic Medications: Side Effects

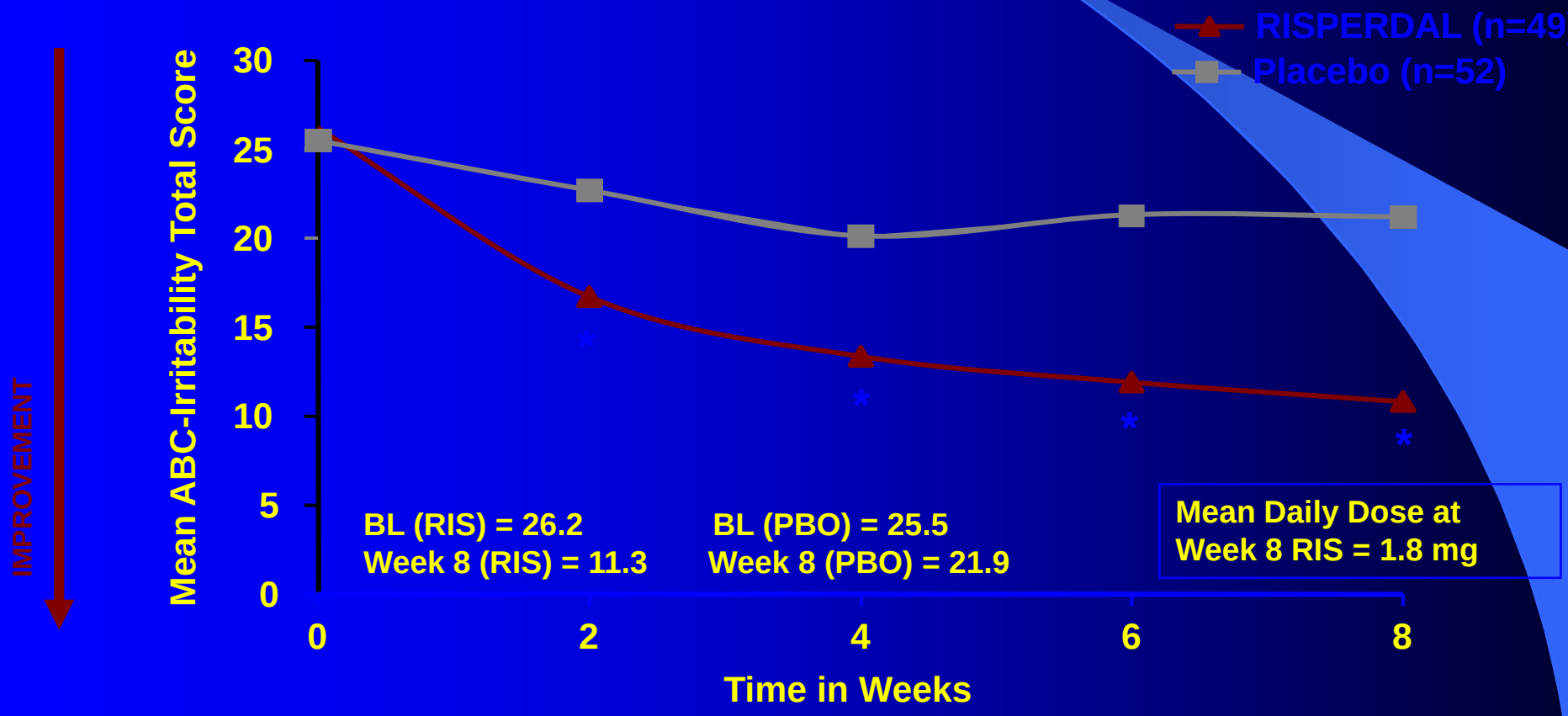
- Extrapyramidal symptoms (EPS)
  - Acute dystonia, Parkinsonism, Akathesia
- Tardive dyskinesia (TD)
  - Develops after 3 mos
  - Choreoathetoid movements-oral, limbs, trunk
  - Lower incidence with new agents
  - Risk- >40 yrs, higher dose, duration

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.



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

RUPP Autism Network. *N Engl J Med.* 2002;347:314-321; Data on file. Janssen Medical Affairs, LLC.

RUPP Risperdal Study: Significant Adverse Events*

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

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

RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

RUPP Autism Phase I: Adverse Events

- During the 8-week study:
  - RISPERDAL® (risperidone) therapy was associated with an average weight gain of 2.7 ± 2.9 kg (5.94 lbs) compared with 0.8 ± 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.

RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

Arapiprazole (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 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

FDA-Approved Medications Indicated for ADHD in Children or Adolescents

Stimulants	Brand Names
d,l-methylphenidate	Ritalin®, Ritalin-SR®, Ritalin LA®, Concerta®, Metadate® CD, Methylin® ER, Daytrana™
d-methylphenidate	Focalin™, Focalin™ XR
Mixed amphetamine salts	Adderall®, Adderall XR®
d-amphetamine	Dexedrine®, Dexedrine Spansule®
Nonstimulant	
Atomoxetine	Strattera®

Ritalin®, Ritalin SR®, and Ritalin LA® are trademarks of Novartis Pharmaceuticals Corporation; Concerta® is a trademark of ALZA Corporation; Metadate® CD is a trademark of Celltech Pharma Limited; Methylin® ER is a trademark of Mallinckrodt Inc; Daytrana™ is a trademark of Shire Pharmaceuticals Ireland Limited; Adderall®, and Adderall XR® are trademarks of Shire US Inc.; Dexedrine® and Dexedrine Spansule® are trademarks of GlaxoSmithKline; Strattera® is a trademark of Eli Lilly and Company.

Psychostimulants Sprinkle forms

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

Focalin XR [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2006.

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, impulsivitiy, 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

Parameter	INTUNIV 1 mg qd (n = 52)	Guanfacine 1 mg qd (n = 12)
C_{max} (ng/mL)	1.0 ± 0.3	2.5 ± 0.6
T_{max} (h)	6.0 (4.0 – 8.0)	3.0 (1.5 – 4.0)
$AUC_{0-\infty}$ (ng.h/mL)	32 ± 9	56 ± 15
$T_{1/2}$ (h)	18 ± 4	16 ± 3
Relative bioavailability	58	100

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 (memantime)
- 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 (rivistigmine)
  - Namenda (memantime)
  - 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 stablizer 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

Treatment

- 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

Treatment

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