Psychopharmacology in Intellectual Disability and Autism Spectrum Disorder

Robert L Findling, MD, MBA

Disclosures

- In the past 12 months, Dr. Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Aevi, Akili, Allergan, American Academy of Child & Adolescent Psychiatry, American Psychiatric Press, Arbor, Bracket, Daiichi-Sankyo, Epharma Solutions, Forest, Genentech, Insys, KemPharm, Lundbeck, NIH, Neurim, Noven, Nuvelution, Otsuka, PCORI, Pfizer, Physicians Postgraduate Press, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Syneurx, TouchPoint, and Validus.

Objectives

- After attending this lecture, the participant will be able to describe:

- The challenges in interpreting the literature regarding the psychopharmacological treatment of intellectual developmental disability
- Which medications have FDA-approval for the treatment of irritability in children with autistic disorder
- Which somatic interventions have promising preliminary data as possible treatments for patients with autism spectrum disorder

Off-Label Use

- All medications, with the exceptions of risperidone and aripiprazole for patients with autistic disorder constitute off-label use in the USA
- FDA-approved use
  - Irritability associated with autistic disorder
    - Risperidone (ages 5-16 years)
    - Aripiprazole (ages 6-17 years)

INTELLECTUAL DISABILITY

An Overview

- There are multiple challenges associated with interpreting the extant intellectual disability literature

Patient Heterogeneity

- Age (pre-school through adult)?
- Presence or absence of syndrome with known genetic underpinnings?
- Presence of autism spectrum disorder?

Primary Outcome

- Which domain(s) are being targeted?
  - Which behavior(s)?
  - Which symptom(s)?
- What primary outcome measure is used?
  - Is the measure validated?
  - Is the outcome focusing on behavior(s)/symptoms?
  - Is the outcome focusing on quality of life?

Study Design

- Case series
- Open-label
- Limited number of double-blind studies

Risperidone

- Placebo-controlled studies of children with ID exist
- Limits exist
  - Patients had sub-average IQ (<85)
  - Somnolence and weight gain

Unwin & Deb, Research in Developmental Disabilities, 2011

Psychostimulants

- Methylphenidate may provide benefit to children with ADHD symptoms
  - Seen in placebo controlled studies
    - More modest efficacy than in typically developing children
    - Less well-tolerated when compared to typically developing children
- Limited amphetamine data

Rowles & Findling, Dev Disabilities Res, 2010;
Thomson, Cochrane Library, 2009

Autism

Autism Nosology

- DSM IV (Autistic Disorder)
  - Impairment in social interaction
  - Impairment in communication
  - Restricted/stereotyped interests and/or behaviors
- DSM V (Autism Spectrum Disorder)
  - Impairment in social interactions + communication
  - Restricted/stereotyped interests and/or behaviors

Differential Diagnosis of Autism

- Selective mutism
- Rett's syndrome
- Language disorders
- Social communication disorder
  - Difficulties in the use of verbal and non-verbal communication
- Stereotypic movement disorder
  - Repetitive, purposeless motoric behaviors
- Intellectual disability

Co-Occurring Conditions in Autism

- Intellectual disability
- Seizures
- Language conditions
- Genetic conditions

Principles to Autism Pharmacotherapy

- There are no established medication treatments for the core symptoms
- Medications to target associated difficulties is the currently accepted approach
- Psychotropic medications are common (27-40%)

Ji & Findling , 2015

Pharmacological Responses in Youths with Autism

- What is true for other patient populations are not necessarily true for youths suffering from autism
  - Efficacy
  - Tolerability
    - Adults
    - Children

Antipsychotics: Target Symptoms and Prevalence

- Irritability* (19.3%)
  - Aggressive behavior (attacks people) 9.9%
  - Tantrums 28.6%
  - Destructive behavior 11.3%
  - Explosive 22.9%
  - Affective lability (changes in mood) 28.0%
  - Self-injurious behavior 11.0%

*Per Parent report
Lecavalier et al. 2006.

Antipsychotics and Autism

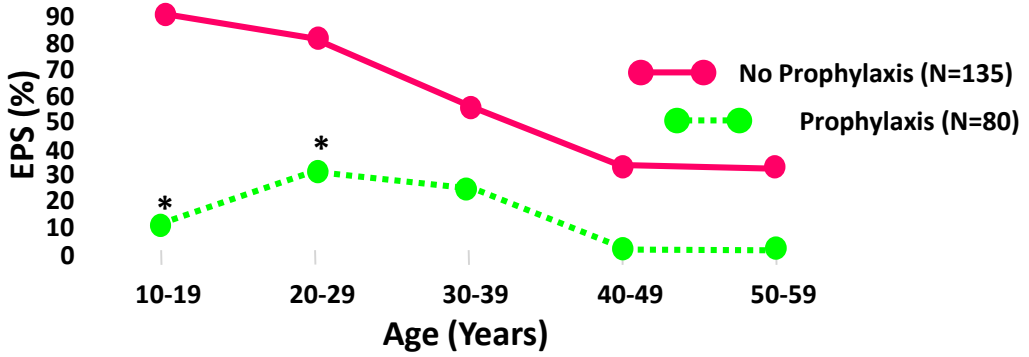
- Target symptoms of antipsychotics are common in this population
- Rates at which antipsychotics are being prescribed to children and adolescents has increased

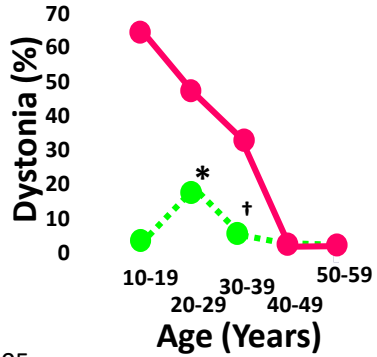
Lecavalier. *J Autism Dev Disord* 2006;36(8):1101-14.
Olfson et al. *Arch Gen Psychiatry* 2006;63:679-685.

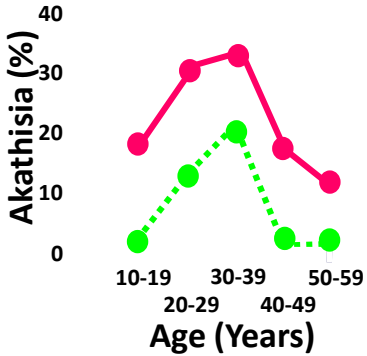
Typical Antipsychotics

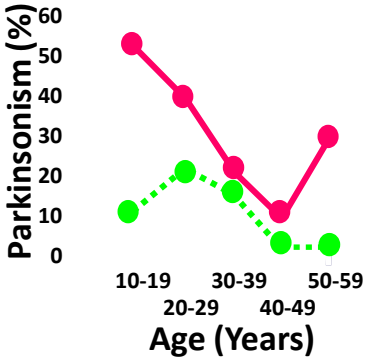
- Potential benefits
- Risks
  - Neurological side effects

Incidence of EPS as a Function of Age









*p<0.001; †p<0.05

Keepers GA et al. (1983).

Risperidone

- Acute 8 week trial
  - Double the magnitude of symptom reduction with active treatment v. placebo
- Acute 8 week trial
  - Response 69% vs 12% placebo
- 8 Week Discontinuation Study
  - 62.5% placebo vs. 12.5% risperidone
- Increased weight/appetite; sedation

RUPP Autism Network, NEJM 2002; Shea et al., Pediatrics, 2004; RUPP Autism Network Am J Psychiatry 2005

Aripiprazole

- Superior to placebo in 2 8-week acute randomized trials
  - One Fixed Dose (5; 10; 15; Placebo)
    - All doses superior to placebo
  - One Flexible Dose (2-15; Placebo)
    - Response rate (67% vs 16%)
  - Long-term 52-week study
    - Sustained effectiveness
      - Weight gain; EPS

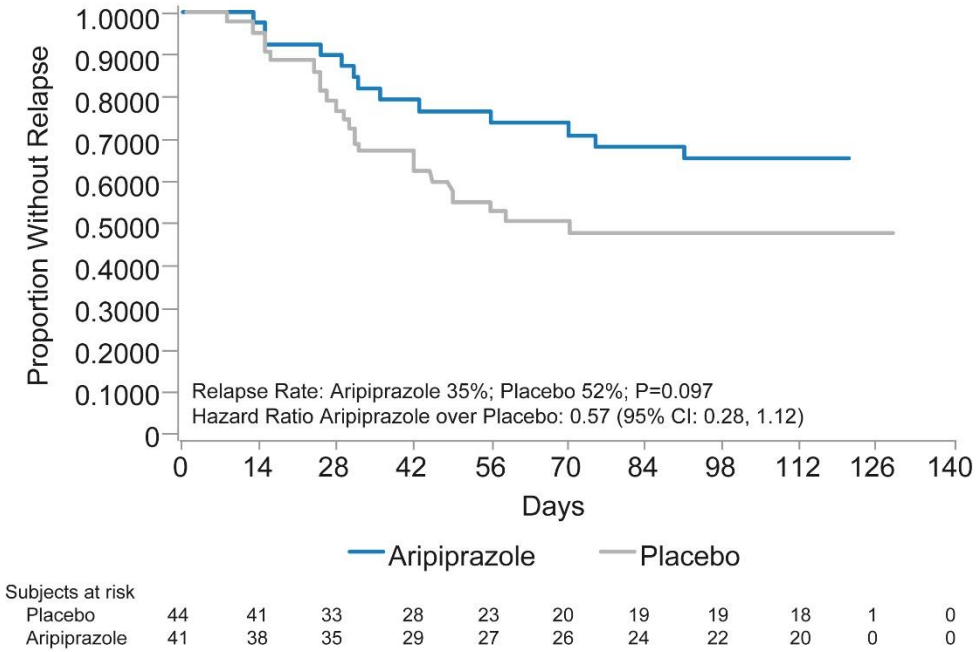
Marcus, JAACAP 2009; Owen, Pediatrics 2009;
Marcus, J Clin Psych 2011

Relapse Definition in Maintenance Study

- ABC-I score increase of ≥ 25% and CGI-I rating of "much worse" or "very much worse"
  - For 2 consecutive visits
  - For 1 visit + and a "lost to follow up" at the next visit
  - For 1 visit and starting an adjunctive medication
- Hospitalization

Findling et al., 2014

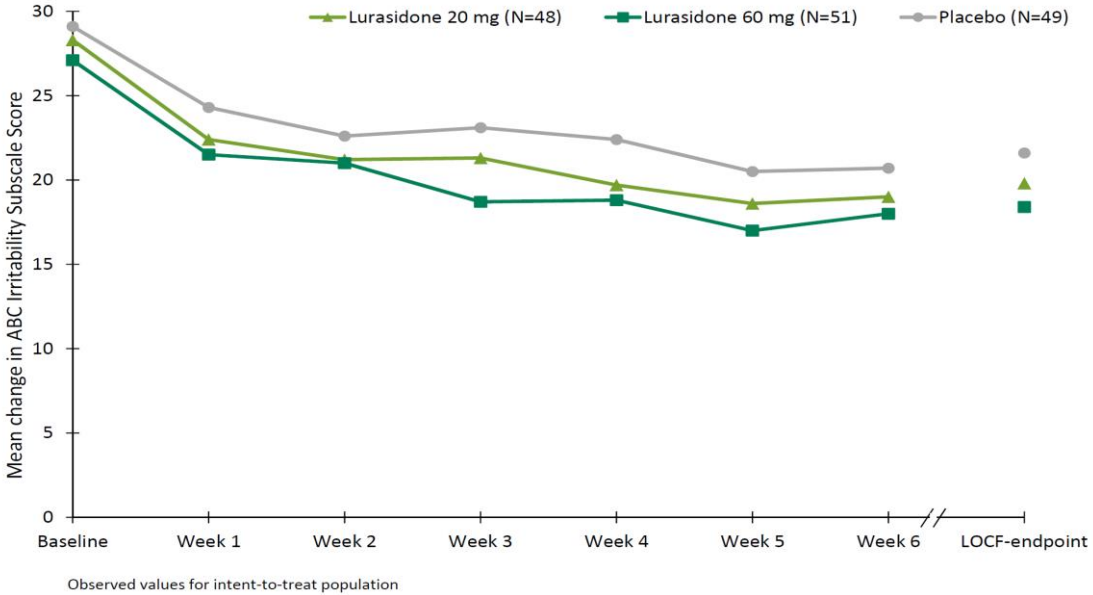
Aripiprazole Maintenance



Findling et al., J Clin Psych 2014

Lurasidone

Mean Change From Baseline in the ABC Irritability Subscale Score (ITT population)



Loebel et al., 2016

Pervasive Developmental Disorders- Antipsychotics

- FDA-approval for risperidone and aripiprazole
- Clozapine
  - Efficacious in case reports
- Olanzapine
  - Superior to placebo in pilot study of 11 patients (ages 6-14)
    - Mean 7.5 lb weight gain over 8 weeks with active treatment (1.5 lbs with placebo)
- Quetiapine
  - Mixed effectiveness in retrospective/prospective studies
- Ziprasidone
  - Efficacious in case series
- Paliperidone
  - Efficacious during open label treatment
- Others

*Hollander et al., J Child Adolesc Psychopharm, 2006

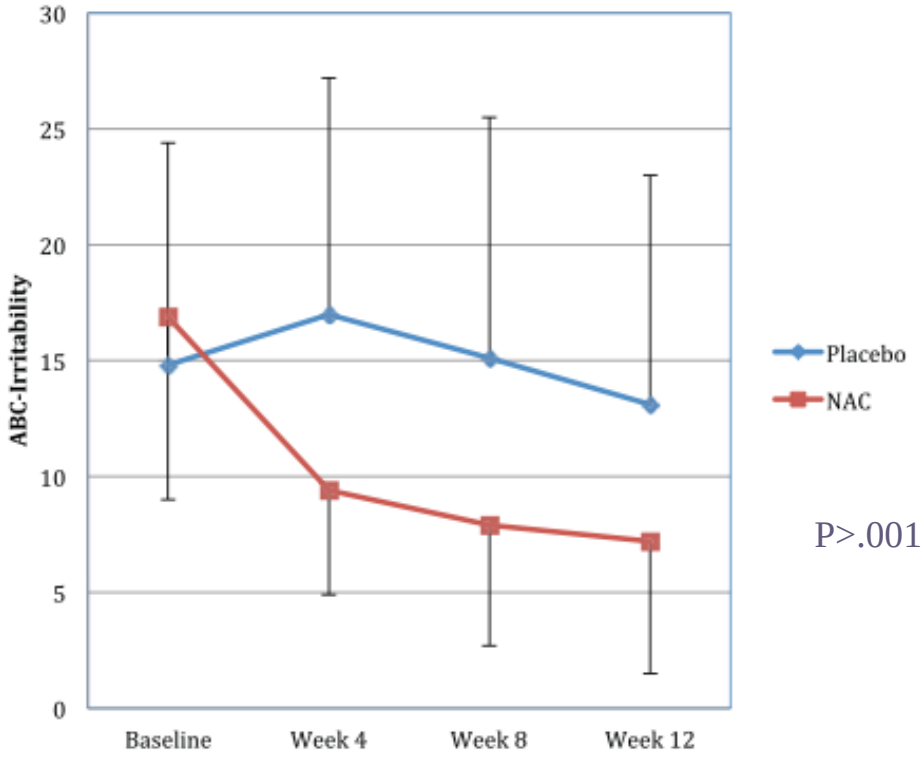
Atypical Antipsychotic Limitations

- Side effects
  - Common
    - Increased appetite
    - Weight gain
      - Multiple sequelae of weight gain
    - Sedation
  - Others

Pilot Trial of N-acetylcysteine (NAC) in Children with Autism

33 patients
Ages 3.2-10.7

Dose at End of Study= 900 mg TID



P>.001

Hardan et al. *Biol Psychiatry*; 2012

Methylphenidate and ADHD Symptoms

- 49% response rate
- 18% discontinued due to adverse events
  - Irritability was the most common cause
- Anorexia, initial insomnia, irritability more common with active treatment

RUPP Autism Network, Arch Gen Psychiatry, 2005

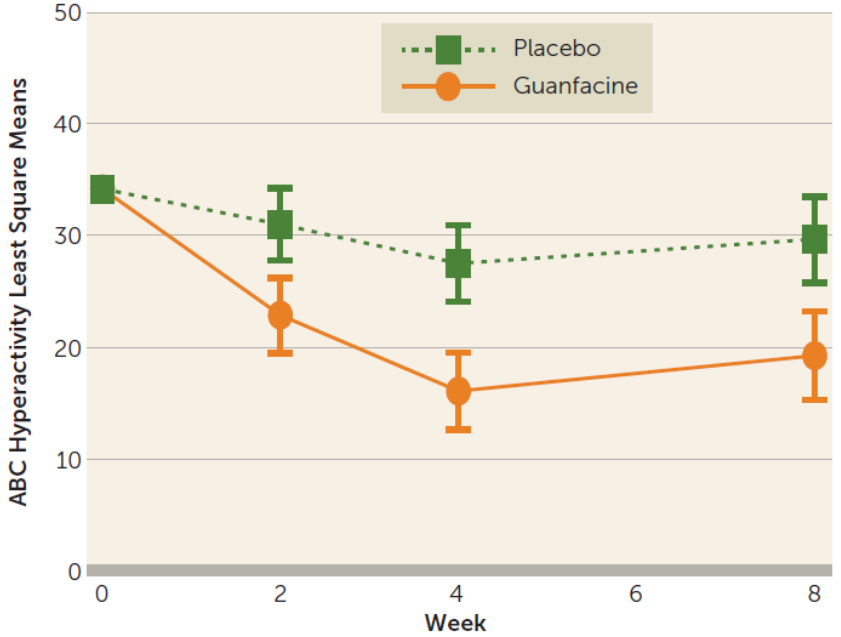
Guanfacine-Extended release

N=32 placebo, 30 GXR

-Ages 5-14 years

-Most common side effects- sedation, fatigue

Modal dose – 3 mg/d
ES= 1.67
4 PCB and 4 GXR
did not complete the study



Scahill et al., 2015

Other ADHD Treatments

- Alpha-2 agonists
  - Clonidine
    - 1 placebo-controlled study in 8 children
- Atomoxetine
  - Placebo-controlled studies exist
    - Possible benefit and “holds promise”
- Amphetamine
  - Limited data

Reichow et al., J Aut Dev Dis, 2013; Aman et al., Res Dev Dis, 2014;
Handen et al., J Dev Behav Pediatrics, 2008

SSRI's- Differences in Response

Effective in the treatment of dysfunctional repetitive behavior in multiple populations

Serotonin Reuptake Inhibitors

- Clomipramine better than placebo and desipramine in children and young adults with autism, but risk of AEs[1]

- Fluvoxamine superior to placebo in adults with autism[2]
- Fluvoxamine no better than placebo and poorly tolerated in youth with PDDs[3]

[1]Gordon et al. *Arch Gen* Psychiatry 1992; 149(3):363-6.; [2]McDougle et al. *Arch Gen Psychiatry* 1996;53:1001-8.; [3]McDougle CJ. Unpublished data.

Fluoxetine

- Double-blind, placebo-controlled
- 158 patients, ages 5-17 years with autism
- Fluoxetine not superior to placebo for repetitive behaviors

ACTN = Autism Clinical Trials Network
Autism Speaks, press release 2009

Citalopram in PDDs

- 12-week, double-blind, placebo-controlled study
- N=149; mean age 9.4 y (range, 5-17 y)
-Mean dose=16.5 mg/d
-Citalopram not superior to placebo for repetitive behaviors
-Citalopram side effects: increased energy level, impulsiveness, decreased concentration, hyperactivity

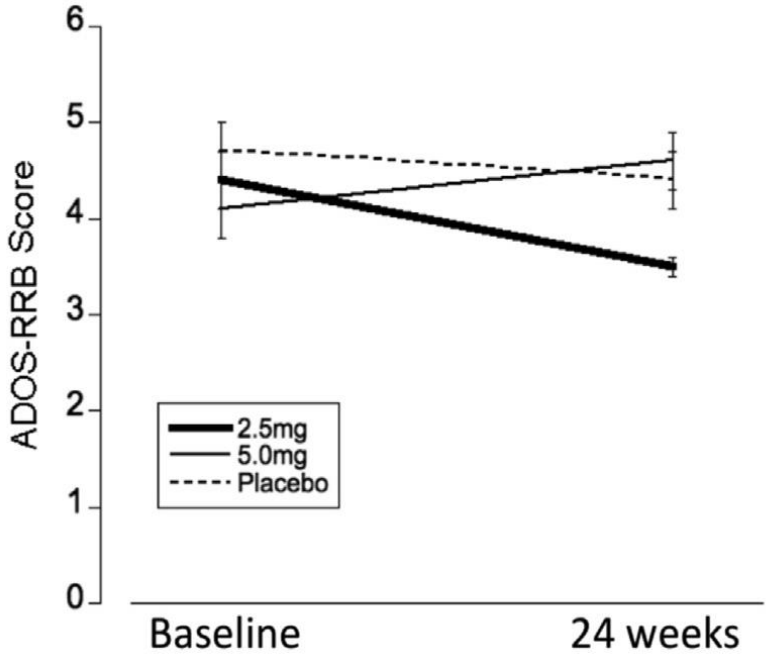
King et al. *Arch Gen Psychiatry* 2009;66(6):583-90.

Buspirone in Young Children with ASD

- 2- < 6 years-old with DSM-IV-TR ASD
- Placebo, 2.5mg BID, 5 mg BID
- 24-week long trial
- Primary Outcome- Autism Diagnostic Observation Schedule (ADOS) Composite Score
  - No between-group differences (p=.400)
- No differences between groups in adverse events

Chugani et al., 2016

ADOS Restricted and Repetitive Behavior Score



P=.003 for 2.5 mg BID group

Chugani et al., 2016

Anticonvulsants

- Divalproex- inconsistent results relating to efficacy in randomized controlled trials
- Other anticonvulsants do not separate from placebo or are untested

Ji & Findling, 2015

Other Pharmacological Agents

- None with consistent safety or efficacy in controlled clinical trials

Sulforaphane-1

- Derived from broccoli sprouts
- Up-regulates genes that protect against oxidative stress
- 40 patients aged 13-27 (all males)
- 18-weeks, placebo-controlled

Singh et al., PNAS 2014

Sulforaphane-2

- Aberrant Behavior Checklist Improvement ($p < 0.001$)
- Clinical Global Impressions –Improvement ($p<0.015$)
- Social Responsiveness Scale ($p=0.02$)
- Efficacy diminished after discontinuation
- “Negligible toxicity”

Singh et al., PNAS 2014

Melatonin

- Sleep difficulties are common
- Improvements reported in
  - Sleep latency
  - Sleep duration
- Limited improvement in night-time awakenings

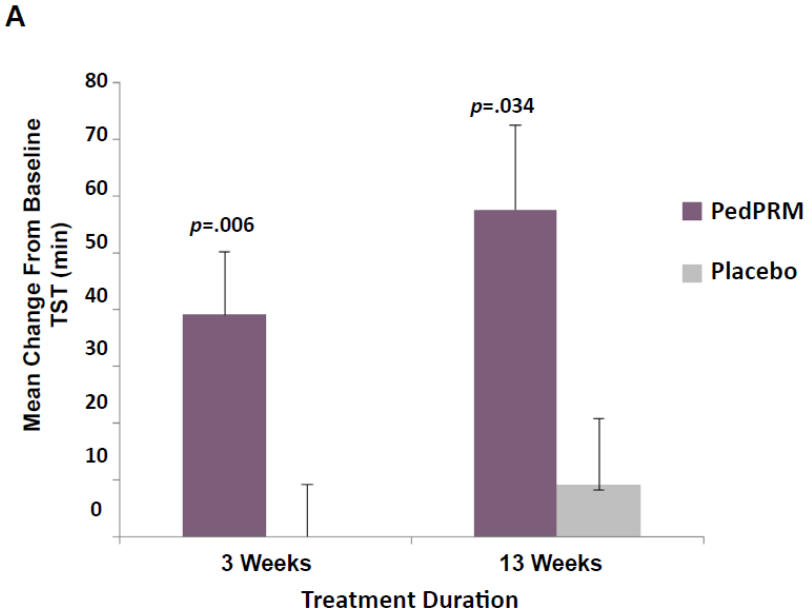
Rossignol & Frye, Dev Med & Child Neurology; 2011

Prolonged-release melatonin

- 125 patients with ASD randomized
  - Dose of 2mg (which could be increased to 5mg) vs placebo
- Age range was 2-17 years (mean age 9.0 +/- 4.08) for PRM group
- PRM was “generally safe”

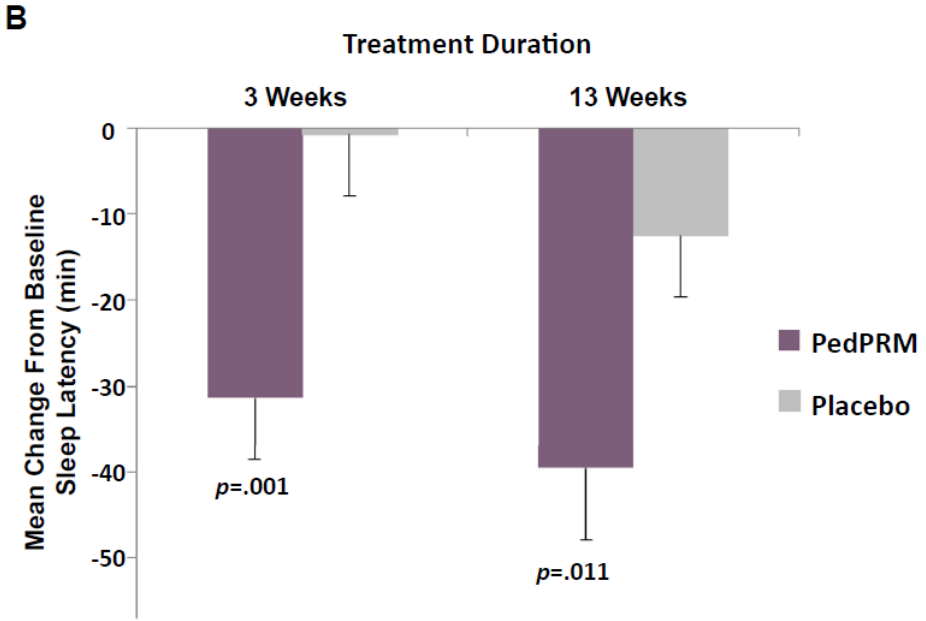
Gringras et al., 2017

Prolonged-release melatonin-Total Sleep Time



Gringras et al., 2017

Prolonged-release melatonin-Sleep Latency



Gringras et al., 2017

PRM Open-Label Extension

- 39-week study
  - Up to 52 weeks of PRM exposure
- 95 participants
- “No evidence of decreased efficacy”
- “Generally safe” with most common side effects “fatigue” or “mood swings”

Maras et al., 2018

Pharmacologic Management

- Target Symptom Approach
  - Irritability
    - Outward aggression
    - Self-injurious behavior
    - Tantrums
    - Mood lability
  - Restlessness and/or Hyperactivity
  - Repetitive Behavior
  - Insomnia

Conclusions

- Medications may be used to treat some associated symptoms of autism
- Clinical trials are necessary to confirm or refute experience
- Medicines have side effects
- Treatment options might improve the lives of youths with autism suffering from disabling “irritability”

OTHER PATIENT POPULATIONS

What to do the absence of data?

- PubMed
- Clinicaltrials.gov
- Seek consultation
- Rely on your own experience
- Extrapolate from other populations

Extrapolation

- Limits of extrapolation
- That still may be the best you can do

Unmet Needs

- Self-injurious behavior
  - No effective treatments proven to be effective

QUESTIONS?