Algorithm for Management of Irritability in Children and Adolescents with ASD: Pharmacotherapy

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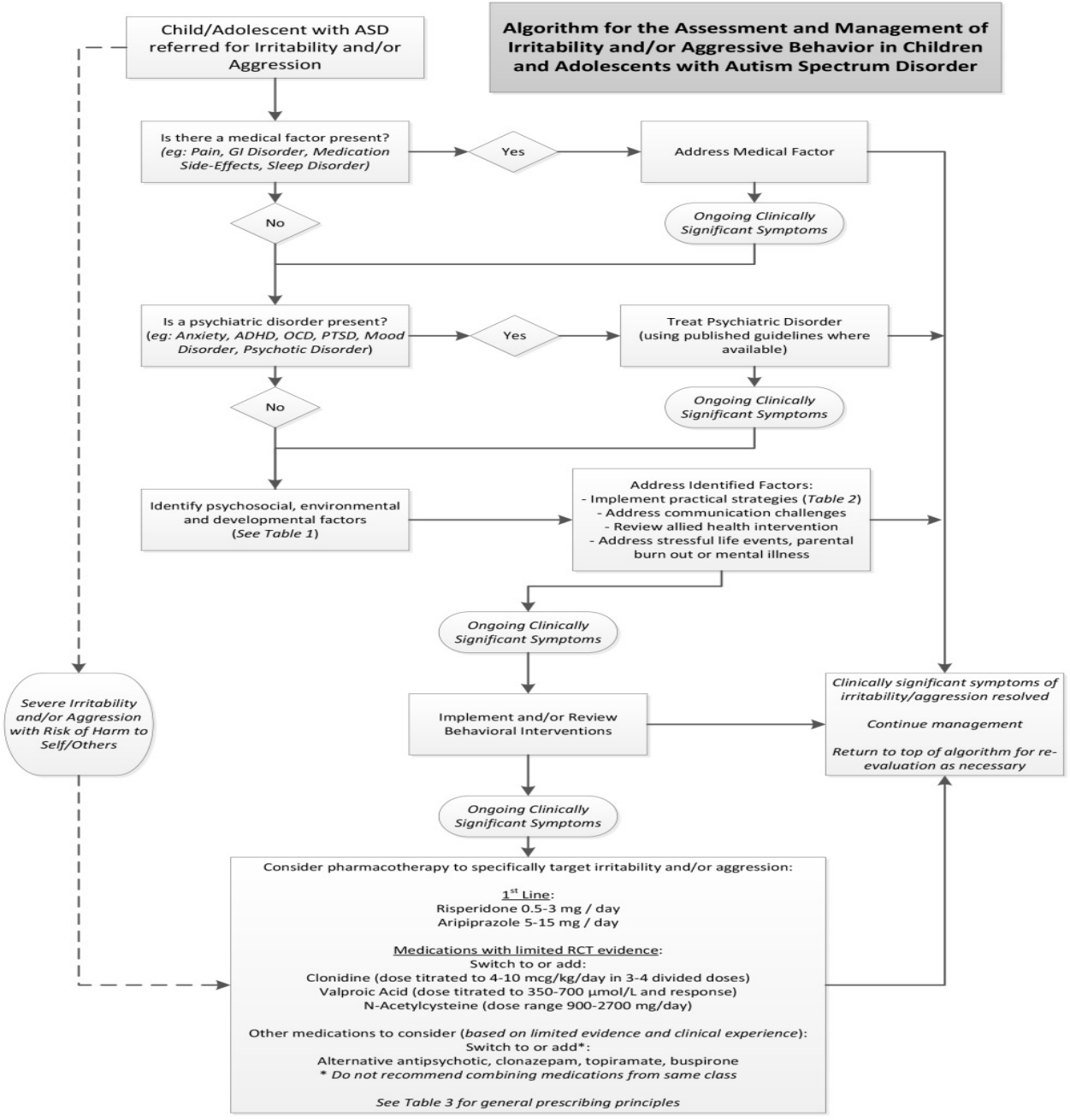
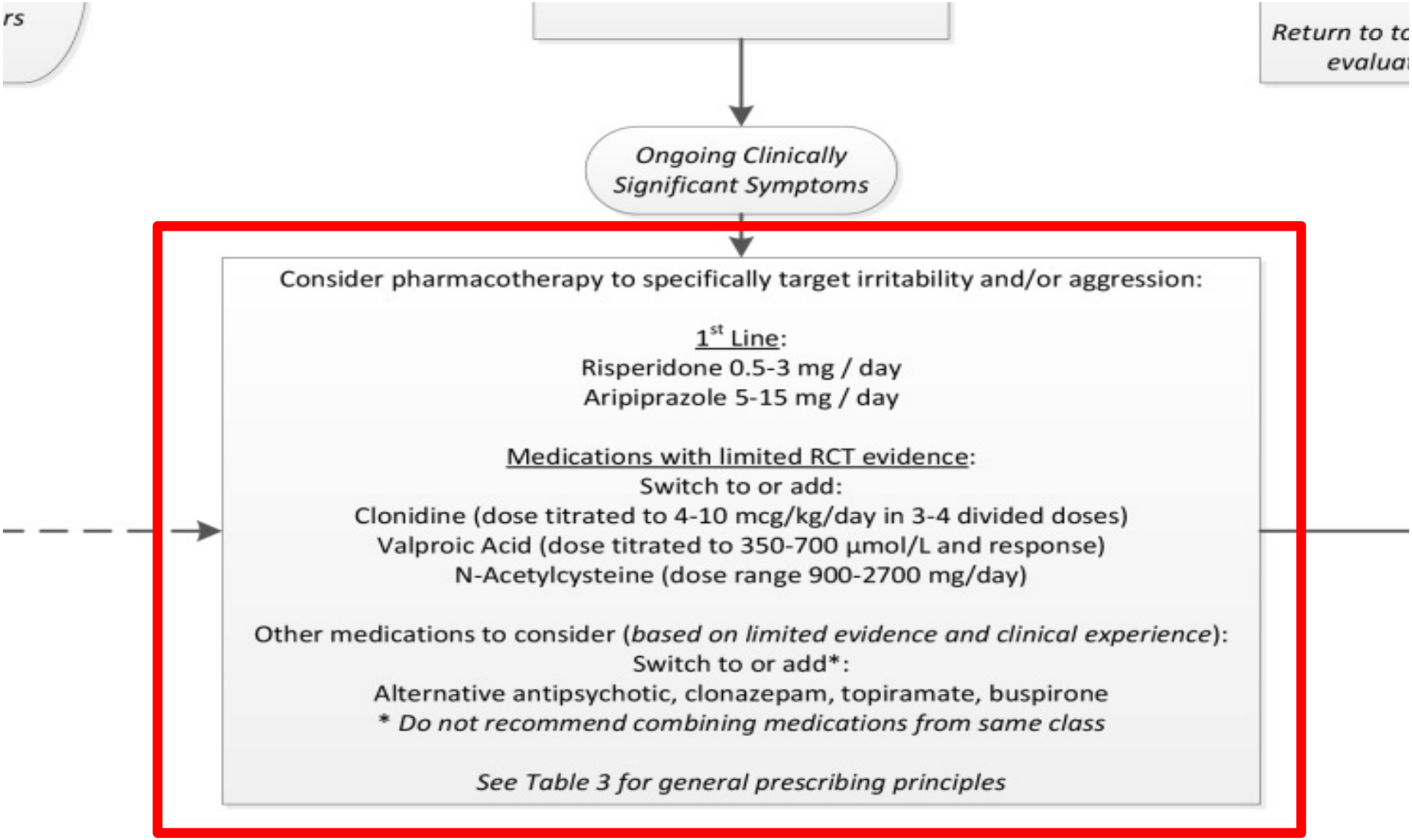
Disclosure Statement

- **No disclosures/conflicts of interest**
- **None of the drugs discussed in this presentation/algorithm are officially approved by Health Canada for the treatment of irritability of autism**
- **Therefore, while today's discussion is evidence-based, technically all of it pertains to 'off-label' medication use**

Algorithm for the Assessment and Management of Irritability and/or Aggressive Behavior in Children and Adolescents with Autism Spectrum Disorder

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Return to to
evaluat
Ongoing Clinically Significant Symptoms
Consider pharmacotherapy to specifically target irritability and/or aggression:
1st Line:
Risperidone 0.5-3 mg / day
Aripiprazole 5-15 mg / day
Medications with limited RCT evidence:
Switch to or add:
Clonidine (dose titrated to 4-10 mcg/kg/day in 3-4 divided doses)
Valproic Acid (dose titrated to 350-700 µmol/L and response)
N-Acetylcysteine (dose range 900-2700 mg/day)
Other medications to consider (based on limited evidence and clinical experience):
Switch to or add*:
Alternative antipsychotic, clonazepam, topiramate, buspirone
* Do not recommend combining medications from same class
See Table 3 for general prescribing principles

2012 JCACAP Article

PSYCHOPHARMACOLOGY

Review of the Pharmacotherapy of Irritability of Autism

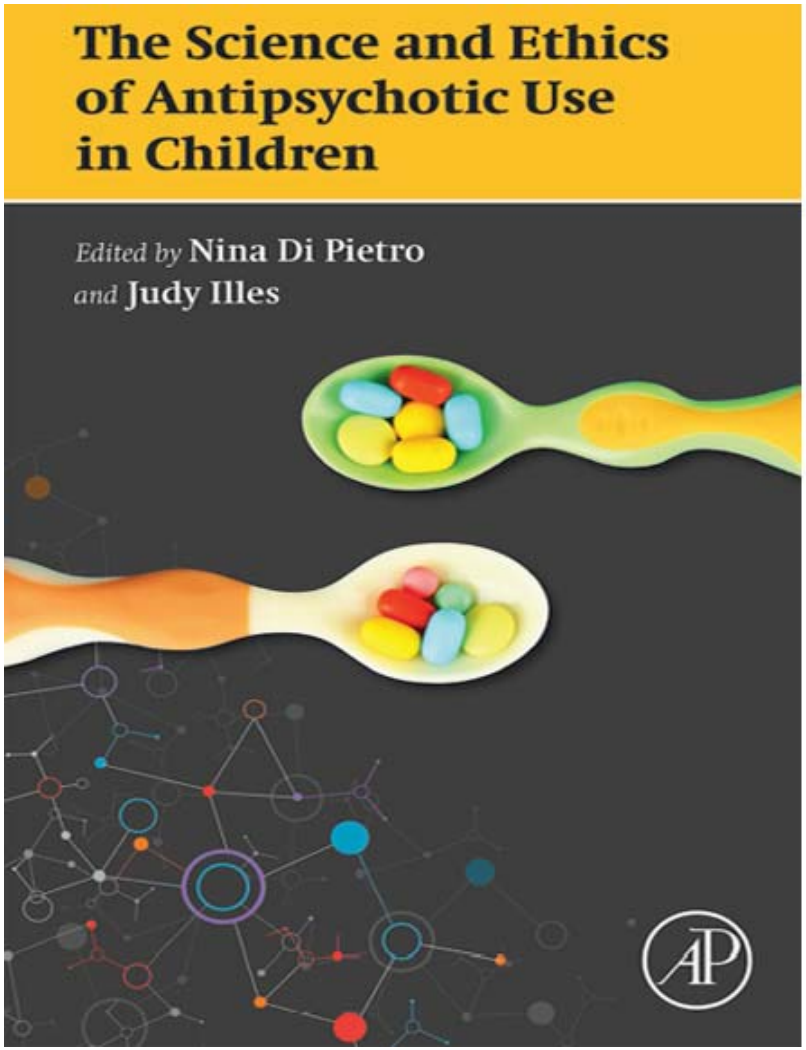
Dean Elbe PharmD, BCPP[1,2]; Zaahira Lalani BSc(Pharm) (cand)[3]

Abstract

Objective: To review the randomized controlled trial data regarding pharmacotherapy of irritability of autism.
Method: A literature review was conducted using the MEDLine search terms: 'autism' OR 'autism spectrum disorder' with the following limits: Randomized Controlled Trials (RCTs), human trials, English language. Additional articles were identified from reference information. Trials involving nutritional supplements, hormones or drugs not approved by either Health Canada or the US Food and Drug Administration (FDA) were excluded from analysis. **Results:** Twenty-three RCTs that met criteria were identified. The greatest number of RCTs involved risperidone, with six of seven placebo-controlled risperidone trials reporting statistically significant improvements on the primary outcome measure. Two aripiprazole RCTs and one olanzapine RCT reported statistically significant improvement in primary outcome measures. Haloperidol was superior to both clomipramine and placebo in a head-to-head crossover trial, while risperidone was superior to haloperidol for treatment of behavioural symptoms in a separate head-to-head trial. Clonidine, methylphenidate, valproate and levocarnitine monotherapy were superior to placebo in single RCTs, while adjunctive treatments cyproheptadine, pentoxifylline and topiramate were superior to placebo in small studies when given in combination with an antipsychotic. Adverse events from RCTs were summarized, including weight gain and metabolic effects, if available. **Conclusion:** The bulk of positive RCT evidence for the pharmacotherapy of irritability of autism pertains to FDA approved antipsychotics risperidone and aripiprazole. RCTs supporting efficacy of several alternative and adjunctive agents may afford additional treatment options when optimal antipsychotic doses fail to control symptoms or cause intolerable adverse effects. Behavioural therapy should be employed where possible either before, or in addition to pharmacotherapy.

Key words: *pharmacotherapy, autism, irritability, antipsychotic*

2015 Book Chapter



Chapter 3

Do We Know If They Work and If They Are Safe: Second-Generation Antipsychotics for Treatment of Autism Spectrum Disorders and Disruptive Behavior Disorders in Children and Adolescents

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INTRODUCTION

Over the past 20 years, large increases in usage rates of second-generation antipsychotics (SGAs; for the purposes of this chapter also includes aripiprazole, technically a third-generation antipsychotic) by children and adolescents

2014 AACAP Practice Parameter

AACAP OFFICIAL ACTION

Practice Parameter for the Assessment and Treatment of Children and Adolescents With Autism Spectrum Disorder

Fred Volkmar, MD, Matthew Siegel, MD, Marc Woodbury-Smith, MD, Bryan King, MD, James McCracken, MD, Matthew State, MD, PhD, and the American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI)

Fung 2016 Meta-analysis

Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis

Lawrence K. Fung, MD, PhD,[a] Rajneesh Mahajan, MD,[b] Alixandra Nozzolillo, MS,[c] Pilar Bernal, MD,[d] Aaron Krasner, MD,[e] Booil Jo, PhD,[a] Daniel Coury, MD,[f] Agnes Whitaker, MD,[e] Jeremy Veenstra-Vanderweele, MD,[a] Antonio Y. Hardan, MD[a]

abstract

BACKGROUND: Autism spectrum disorder (ASD) is increasingly recognized as a public health issue. Irritability and aggression (IA) often negatively affect the lives of people with ASD and their families. Although many medications have been tested for IA in ASDs in randomized controlled trials (RCTs), critical quantitative analyses of these trials are lacking in the literature.

OBJECTIVES: To systematically review and quantitatively analyze the efficacy and safety of pharmacologic treatments for IA in youth with ASD.

DATA SOURCES: Studies were identified from Medline, PsycINFO, Embase, and review articles.

METHODS: Original articles on placebo-controlled RCTs of pharmacologic treatments of IA in youth age 2 to 17 years with ASD were included. Data items included study design, study goals, details of study participants, details of intervention, study results, statistical methods, side effects, and risks of bias. The primary study outcome measure was the effect size of reduction in the Aberrant Behavioral Checklist–Irritability (ABC-I) scores in the medication group, as compared with placebo, in RCTs using parallel groups design.

RESULTS: Forty-six RCTs were identified. Compared with placebo, 3 compounds resulted in significant improvement in ABC-I at the end of treatment. Risperidone and aripiprazole were found to be the most effective, with the largest effect sizes. Sedation, extrapyramidal sides effects, and weight gain were assessed quantitatively.

CONCLUSIONS: Although risperidone and aripiprazole have the strongest evidence in reducing ABC-I in youth with ASD, a few other compounds also showed significant efficacy with fewer potential side effects and adverse reactions in single studies.

Limits of this Review

- **Scope limited to non-emergency treatment of *irritability of autism***
- **Level 1 evidence only: Randomized Controlled Trials (RCTs)**
- **Excluded trials of hormones, supplements or drugs not currently available in Canada/USA**

Pharmacotherapy

- **May be more effective when medical or behavioural aspect of presentation ruled out**
- **Offers rapid onset of symptom control, especially in severe aggression with risk of harm to self or others**

EDITORIAL

Friends Not Foes: Combined Risperidone and Behavior Therapy for Irritability in Autism

Thomas W. Frazier, Ph.D.

JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY
VOLUME 51 NUMBER 2 FEBRUARY 2012

- **2012 JAACAP editorial: advocates combining pharmacotherapy with behavioural therapy**

Pharmacotherapy - Limitations

- **Potentially serious metabolic and other effects associated with long-term use not truly reflected in short-term 8 week trials**
- **Patients with psychiatric comorbidities usually excluded from RCTs**
- **Presence of intellectual disability not always clearly stated; influences drug response**

Choice of Therapy

- **Treatment choice depends on the qualifications, familiarity and comfort level of the service provider**
- **Psychiatrists more likely to prescribe medication for treatment of irritability**
- **Threshold for prescribing varies widely**

Morgan. BMJ 2007; 334: 1069.

Choice of Therapy

- **Obtain informed consent**
- **Be clear what medication(s) can do: reduce irritability and aggression**
- **And what medication(s) can't do: improve "core" ASD symptoms**
- **Baseline & periodic monitoring**

Morgan. BMJ 2007; 334: 1069.

CAMESAguideline.org

CAMESA helps parents and doctors manage the side effects of second generation antipsychotics in children.

The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guidelines were developed by a group of physicians, health professionals and researchers from across Canada, with the support of the Canadian Institutes of Health Research. The goal of the CAMESA guidelines is to improve the quality of life of children with mental health disorders by promoting antipsychotic drug safety.

There are three CAMESA guidelines:

- How to monitor antipsychotic drug safety
- How to manage or treat metabolic complications of antipsychotic medications if they occur (such as weight gain, or elevated cholesterol)
- How to manage or treat extrapyramidal complications of antipsychotic medications if the occur (involuntary movements)

The guidelines synthesize research findings and provide recommendations on how to perform these tasks.

Measuring Irritability: ABC-I

- Aberrant Behavior Checklist-Irritability subscale
- Primary outcome measure in most RCTs
- 16-item subscale (scores range 0-48); clinician rates 0-3 for each item severity
- Assesses: SIBs, aggression towards others, screaming, yelling, temper tantrums, demanding behaviours, mood changes, crying in response to minor annoyances

SIBs = self-injurious behaviours

Measuring Irritability: CGI-I

- **Clinical Global Impression-Improvement**
- **Basically answers the question:**
  How are they doing compared to baseline?
- **CGI-I is a Likert-style scale rated from**
  1 (very much improved) to
  7 (very much worse)
- **Scores of $\leq$ 2 typically indicate significant improvement/response in most clinical trials**

Measuring Irritability: CARS

- **Childhood Autism Rating Scale**
- **Primary outcome measure in some RCTs; encompass more 'core' autism symptoms, less specific for irritability**
- **15-item subscale (scores range 15-60); clinician rates 1-4 for each item severity**
- **Assesses: relationships, imitation, emotional response, object use, adaptation to change, sensory response, fear/nervousness, verbal & non-verbal communication, activity level, intellectual level**

Drug Categories

- **Antipsychotic RCTs (14*)**
  - **risperidone (10)**
  - **aripiprazole (3)**
  - **olanzapine (1)**
  - **lurasidone (1)**

***One study is a risperidone-aripiprazole head-to-head trial**

Today's presentation format…

Demographics

Trial Design

Efficacy Outcomes

Adverse Effects
(over & above placebo arm)

NSS=
non-statistically significant

Weight/Metabolic Effects

Effect Size

- **'Effect size' (Cohen's *d*) when reported tells us** *the magnitude of the difference observed between groups*. **Also referred to as the Standardized Mean Difference (SMD)**
- ***d* > 0.8 considered 'large'**

  ***d* = 0.5-0.8 considered 'moderate'**

  ***d* = 0.2-0.5 considered 'small'**

Technically, the formula is $d = \frac{\bar{x}_1 - \bar{x}_2}{s}$

Risperidone RCTs

- **US FDA approved for treatment of irritability of autism in 2006**
- **The bulk of antipsychotic RCTs**
- **Likely a factor of being the first (non-clozapine) 2nd generation antipsychotic drug on the market**
- **Does not appear to impair cognition**

RUPPAN 2002 Risperidone Trial

101 patients (82% male)
8.8 ± 2.7 years old

Flexible Dose risperidone
(0.25-3.5 mg/day (weight))
Monotherapy x 8 weeks

1º Endpoint Efficacy (ABC-I):
risperidone: -14.9
placebo: - 3.6

Responders (CGI-I score ≤ 2):
risperidone: 75.5%
placebo: 11.5%

(very) large effect size (*d*=1.2)

Adverse Effects: drowsiness, fatigue, increased appetite, constipation, dizziness, tremor, nasal congestion, vomiting, tachycardia, dry mouth, EPS

Weight Increase:
risperidone: 2.7 ± 2.9 kg
placebo: 0.8 ± 2.2 kg

No other metabolic tests

RUPP Autism Network. NEJM 2002; 347: 314.

RUPP 2005 Risperidone Extension

- 63 pts entered 4 month open-label continuation
- 81% maintained good response
- ↓ ABC-I score by 59% from start of RCT

- 38 pts entered phase 2 RCT:
  continue vs. discontinue risperidone

Relapse rates:

- 62.5% of pts who discontinued risperidone vs.
  12.5% of pts who continued risperidone

RUPP Autism Network. Am J Psych 2005; 162: 1361.

Shea 2004 Risperidone Trial

79 patients (77% male)
7.5 ± 2.3 years old

Flexible Dose risperidone
(0.02-0.06 mg/kg/day)
***Monotherap-ish* x 8 weeks**

1º Endpoint Efficacy (ABC-I):
risperidone: -12.1
placebo: - 6.5

Responders (CGI-I score ≤ 2):
risperidone: 26%
placebo: 9%

Adverse Effects: somnolence, respiratory infection, apathy, tachycardia, abdominal pain, increased appetite, tremor, constipation, headache

Weight Increase:
risperidone: 2.7 ± 2.0 kg
placebo: 1.0 ± 1.6 kg

No other metabolic tests

Shea et al. Pediatrics 2004; 114: 634.

Hellings 2006 Risperidone Trial

40 patients (58% male)
22 ± 13.1 years old

Low vs. High dose risperidone
Complex Crossover regimen
(1 mg/day vs. 0.05 mg/kg/day)
Monotherapy x 46 weeks

1º Endpoint Efficacy (ABC-I):
Low dose risperidone: -8.05
High dose risperidone: -6.85

Responders
(50% ↓ in ABC-I scores):
All patients: 57.5%

Adverse Effects: drowsiness, weight gain, increased appetite, lack of spontaneity, tremor, nasal congestion.

Severe akathisia (1), recurrent oculogyric crisis (1)

Mean Weight Gain (46 weeks):
Children: 7.9 kg
Adolescents: 8.3 kg, Adults: 6 kg

wt. gain >3 kg in 70% of pts
No other metabolic tests

Hellings et al. J Autism Dev Disord 2006; 36: 401.

Nagaraj 2006 Risperidone Trial

39 patients (87% male)
5.0 ± 1.7 years old

risperidone 1 mg/day
***Monotherap-ish* x 6 months**

1° Endpoint Efficacy (CARS):
risperidone: -7.5
placebo: - 1.0

Secondary Outcome (CGAS):
risperidone: +11.15
placebo: +2.55

Adverse Effects:
sedation, dyskinesias

Weight Increase:
risperidone: 2.81 ± 2.04 kg
placebo: 1.71 ± 1.3 kg

No other metabolic tests

CGAS = Children's Global Assessment Scale (↑ = better)
Nagaraj et al. J Child Neurol 2006; 21: 450.

Pandina 2007 Risperidone Trial

55 patients (78% male)
7.2 ± 2.2 years old

Flexible Dose risperidone
(0.5-4.2 mg/day)
Monotherapy x 8 weeks

1º Endpoint Efficacy (ABC-I):
risperidone: -13.4
placebo: - 7.5

Responders
(CGI-I score ≤ 2 AND
>25% ↓ in ABC-I score):
risperidone: 58.3%
placebo: 21.4%

Adverse Effects:
somnolence, respiratory infection, rhinitis, hypersalivation, fever, increased appetite

Weight Increase:
risperidone: 2.4 ± 2.9 kg
placebo: 1.1 ± 0.7 kg

No other metabolic tests

Pandina et al. J Autism Dev Disord 2007; 37: 367.

Luby 2007 Risperidone Trial

23 patients (74% male)
4.0 ± 1.0 years old

Flexible Dose risperidone
(0.5-1.5 mg/day)
Monotherapy x 6 months

1° Endpoint Efficacy (CARS):
risperidone: -4.6 (NSS)
placebo: - 1.8

Adverse Effects:
increased appetite,
sedation, hypersalivation

2° Outcome (GARS):
Non-significant difference

Weight Increase:
risperidone: 2.96 ± 2.53 kg
placebo: 0.61 ± 1.1 kg

No other metabolic tests

GARS=Gilliam Autism Rating Scale
Luby et al. J Child Adolesc Psychopharmacol 2006; 16: 575.

Miral 2008 Risperidone vs. Haloperidol Trial

30 patients (80% male)
10.5 ± 2.8 years old

Flexible Dose
risperidone (1-2.4 mg/day)
vs. haloperidol (1.5-7 mg/day)
Monotherapy x 12 weeks

1º Endpoint Efficacy
(ABC (full-scale)):
risperidone: -48.8
haloperidol: - 21.3

Adverse Effects (risperidone):
respiratory infection,
constipation, enuresis

Adverse Effects (haloperidol):
respiratory infection, blunted
affect, ↑ appetite, constipation,
rigidity, enuresis

Weight Increase:
risperidone: 4.3 ± 0.7 kg
haloperidol: 4.6 ± 0.1 kg

No other metabolic tests

Miral et al. Eur Child Adolesc Psychiatry 2008; 17: 1.

New Data Kent 2013 Risperidone Trial

96 patients (92% male)
9 ± 3.1 years old

Weight-Based Fixed Dose
Low Dose R:0.125 – 0.175 mg/day
High Dose R:1.25-1.75 mg/day
Monotherapy x 6 weeks

1º Endpoint Efficacy (ABC-I):
low dose R: -12.4
high dose R: -7.4 (NSS)
placebo: - 3.5

Responders
(CGI-I score ≤ 2 AND
>25% ↓ in ABC-I score):
low dose R: 83%
high dose R: 52% (NSS)
placebo: 41%

2º Outcome (CY-BOCS):
high dose R>placebo

Adverse Effects:, ↑ appetite, sedation, somnolence, akathisia, nasopharyngitis, thirst, fever, headache, epistaxis, constipation, insomnia

Weight:
high dose R: 2.4±2.1 kg
low dose R:1.2±1.1kg
placebo: 0.7±1.2 kg
↑ prolactin (high dose group)
insulin, TG, LDL, ↓ HDL

Kent et al. J Autism Dev Disord 2013; 43: 1773-83.

Olanzapine RCT

- **Not US FDA approved for treatment of irritability of autism**
- **Significant weight gain (and adverse metabolic effects)**

Hollander 2006 Olanzapine Trial

11 patients (82% male)
9.1 ± 2.5 years old

Flexible Dose olanzapine
(2.5-20 mg/day (weight))
Monotherapy x 8 weeks

1° Endpoint Efficacy (CGI-I):
olanzapine: -2.25
placebo: - 1.1

Adverse Effects:
constipation, sedation, decreased appetite, glazed eyes, insomnia, rhinitis, increased appetite

Weight Increase:
olanzapine: 3.4 ± 2.2 kg
placebo: 0.7 ± 0.7 kg

No other metabolic tests

Hollander et al. J Child Adolesc Psychopharmacol 2006; 16: 541.

Aripiprazole RCTs

- US FDA approved for treatment of irritability of autism in 2009
- The ‘challenger’ to risperidone
- More robust metabolic effects reporting
- Post-hoc ABC-I line item analysis: particularly effective for tantrums and hyperactivity

Aman et al. J Child Adolesc Psychopharmacol 2010; 20: 415.

Owen 2009 Aripiprazole Trial

98 patients (88% male)
9.2 ± 2.9 years old

Flexible Dose aripiprazole
(2-15 mg/day)
Monotherapy x 8 weeks

1º Endpoint Efficacy (ABC-I):
aripiprazole: -12.9
placebo: - 5.0

Responders
(CGI-I score ≤ 2 AND
>25% ↓ in ABC-I score):
aripiprazole: 52.2%
placebo: 14.3%

large effect size (*d*=0.87)

Adverse Effects:
sedation, fatigue, EPS,
tremor, hypersalivation,
vomiting, ↑ or ↓ appetite,
fever, somnolence

Weight/BMI Increase:
aripiprazole: 2 kg / 0.7
placebo: 0.8 kg / 0.3

No significant differences
in metabolic parameters
between groups

Owen et al. Pediatrics 2009; 124; 1533.

Marcus 2009 Aripiprazole Trial

218 patients (89% male)
9.6 ± 3.0 years old

Forced Dose Titration
aripiprazole (5, 10 or 15 mg/day)
***Monotherap-ish* x 8 weeks**

1º Endpoint Efficacy (ABC-I):
A5: -12.4
A10: -13.2
A15: -14.4
placebo: - 8.4

Responders
(CGI-I score ≤ 2 AND
>25% ↓ in ABC-I score):
A5: 55.8%
A10: 49.2% (NSS)
A15: 52.8% (NSS)
placebo: 34.7% (high)

Adverse Effects:
sedation, tremor, cough, fever, lethargy, fatigue, drooling, EPS, decreased appetite, somnolence, nausea/vomiting, increased appetite, hypersalivation, nosebleed, URTI, weight increased, abdominal pain

Weight/BMI Increase:
see next slide

Marcus et al. J Am Acad Child Adolesc Psychiatry 2009; 48: 1110.

Marcus 2009 Aripiprazole Trial

Weight Increase:

A5: 1.3 ± 0.3 kg

A10: 1.3 ± 0.3 kg

A15: 1.5 ± 0.3 kg

placebo: 0.3 ± 0.3 kg

% with > 7% weight gain:

A5: 32.7%

A10: 15.3 %

A15: 30.2%

placebo: 8.2%

BMI Increase:

A5: 0.6 ± 0.2

A10: 0.6 ± 0.2

A15: 0.8 ± 0.2

placebo: 0.2 ± 0.2

No significant differences in metabolic parameters between groups

Ghanizadeh 2015 Risperidone-Aripiprazole Trial

59 patients (% male not stated)
mean 9.6 ± 4 years old

Weight-based Flexible Dose
aripiprazole (10-15 mg/day)
vs. risperidone (2-3 mg/day)
Monotherapy x 8 weeks

1º outcome measure (ABC-I):
aripiprazole: -11.6
risperidone: -9
(difference was NSS,
but higher baseline scores
in aripiprazole group)

Adverse Effects
↑ appetite, hypersalivation,
drowsiness, fatigue, constipation,
tremor, dystonia, rash/itching,
abdominal pain, nervousness,
dry mouth, akathisia

aripiprazole vs. risperidone:
NS differences

2º outcome measures:
NSS differences in other ABC
subscales between groups

Weight/metabolic changes:
not reported

Ghanizadeh et al. Child Psychiatry Hum Dev 2014; 45: 185-92.

Loebel 2015 Lurasidone Trial

148 patients (82% male)
mean 10.7 ± 3 years old

Fixed Dose
lurasidone 20 mg/day (L20)
or lurasidone 60 mg/day (L60)
monotherapy x 6 weeks

1° outcome measure (ABC-I):
L20: -9.4 (NSS)
L60: -8.8 (NSS)
placebo: - 7.5

Responders (↓ ABC-I ≥50%)
L20: 31.3%
L60: 35.3%
placebo: 22.4%

Responders (CGI-I ≤ 2)
L20: 33.4%
L60: 35.3%
placebo: 30.6%

CYBOCS/other ABC subscales: NSS

Adverse Effects:

nausea, vomiting, irritability, suicidal ideation, somnolence, nasopharyngitis, akathisia, fatigue, cough, constipation

Weight Changes:
L20: 1.2 ± 0.2 kg
L60: 0.5 ± 0.2 kg (NS)
placebo: 0.4 ± 0.2 kg

↑ cholesterol, prolactin & TGs in L60 group

Loebel et al. J Autism Dev Disord 2015; Epub Ahead of Print.

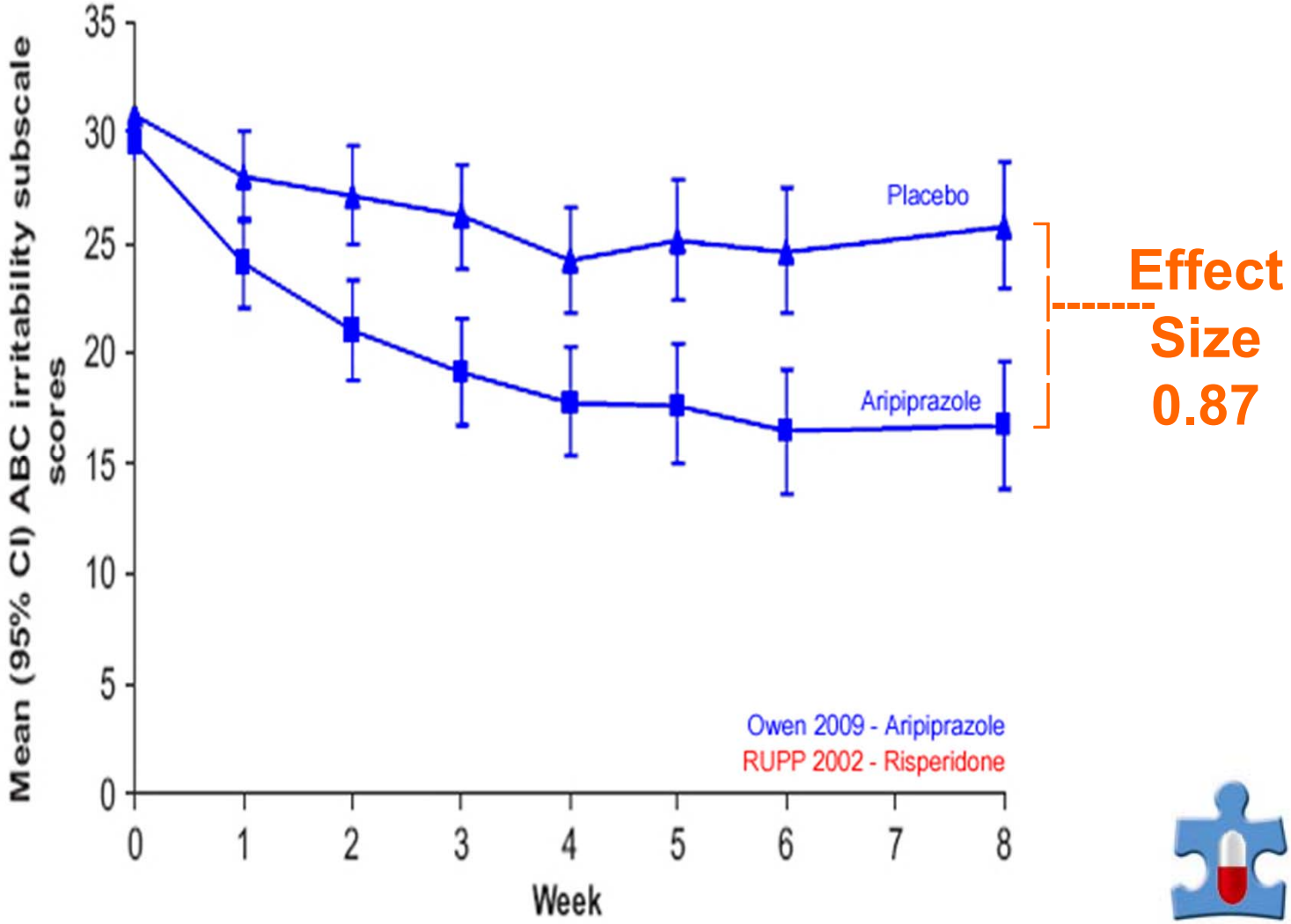
Efficacy Summary

- **Antipsychotics the most studied category**
- **The most positive RCTs with risperidone**
- **(very) large effect size in RUPP 2002**
- **large effect size in Owen 2009 (similar design to RUPP risperidone trial)**

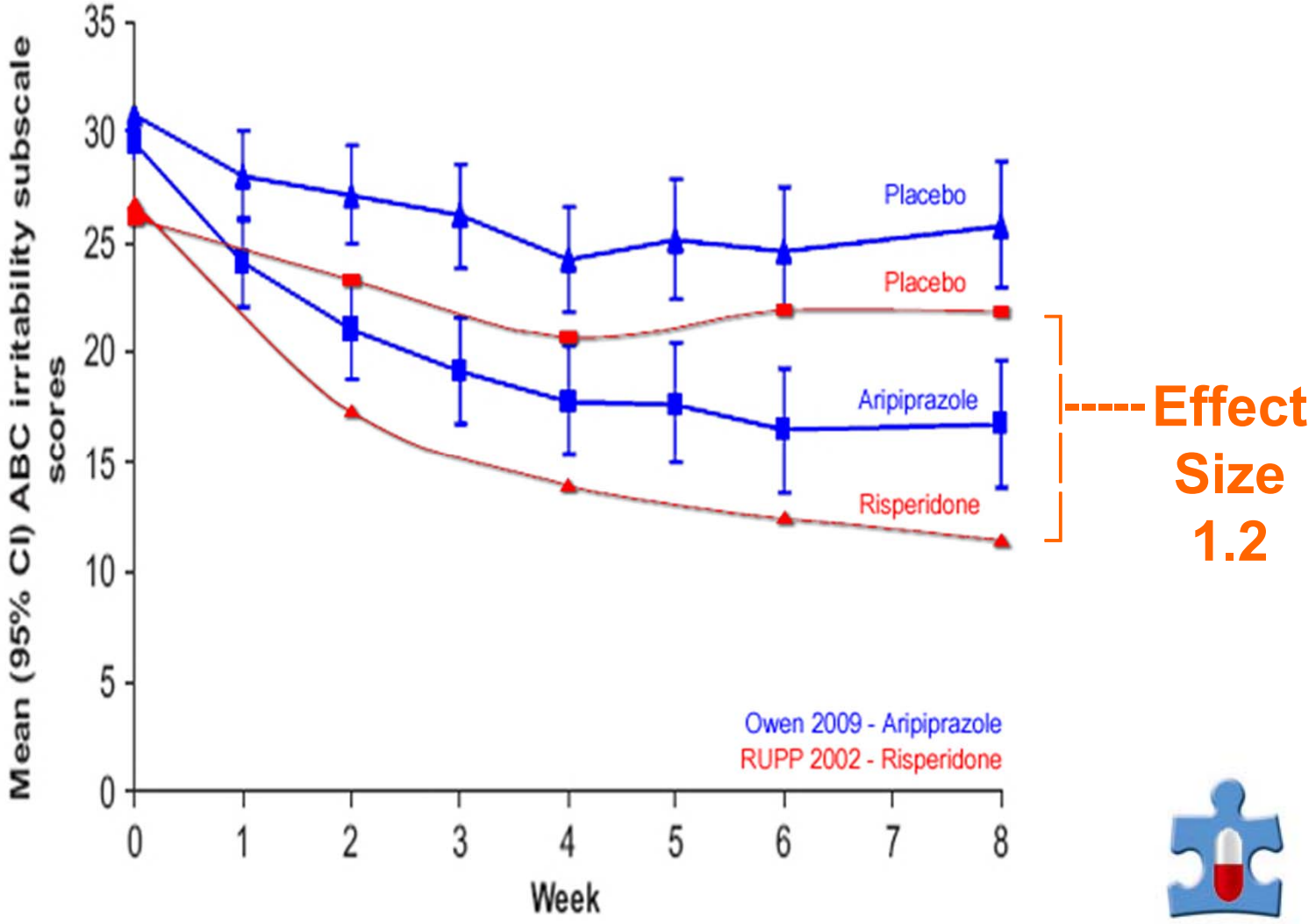
Efficacy Summary

- **Risperidone and aripiprazole achieved US FDA approval for irritability of autism**
- **Olanzapine – positive pilot RCT; significant weight gain, metabolic effects**
- **Recent negative trial with lurasidone**
- **No RCTs for quetiapine, ziprasidone (open label data only)**

Owen 2009 – aripiprazole vs RUPP 2002 – risperidone



Owen 2009 – aripiprazole vs RUPP 2002 – risperidone



Adverse Effects Summary

- **Fairly characteristic adverse effect pattern in antipsychotic RCTs**
- **Sedation, EPS, tremor, tachycardia, hypersalivation, increased appetite, respiratory infection/rhinitis, ↑ prolactin**
- **A mixed bag with non-neuroleptics: typical to their pharmacological class**

Metabolic Effects Summary

- *Only* **Body Weight changes reported in most risperidone/olanzapine RCTs**
- **Metabolic effects of antipsychotics only realized in children/adolescents ~2008**
- **Minimal metabolic changes in lurasidone trial but NSS re: efficacy**
- **Aripiprazole caused some weight gain; but fewer metabolic abnormalities**

Metabolic Effects Summary

- **Antipsychotic pre-treatment not usually reported; can affect interpretation of weight change data**
- **No attempt to account for expected growth in weight/BMI during trial**
- **Desirable to report *z-scores* in children to account for growth, but usually not done**
- **Kent 2013 risperidone trial provided better information on metabolic effects**

Algorithm - Pharmacotherapy

Consider pharmacotherapy to specifically target irritability and/or aggression:

1st Line:
Risperidone 0.5-3 mg / day
Aripiprazole 5-15 mg / day

Medications with limited RCT evidence:
Switch to or add:
Clonidine (dose titrated to 4-10 mcg/kg/day in 3-4 divided doses)
Valproic Acid (dose titrated to 350-700 µmol/L and response)
N-Acetylcysteine (dose range 900-2700 mg/day)

Other medications to consider (*based on limited evidence and clinical experience*):
Switch to or add*:
Alternative antipsychotic, clonazepam, topiramate, buspirone
** Do not recommend combining medications from same class*

See Table 3 for general prescribing principles

Non-neuroleptics

Negative RCTs:

- **lamotrigine** *monotherapy*
- **levetiracetam monotherapy**
- **clomipramine** *monotherapy*
- **amantadine** *monotherap-ish*
- **Omega-3 fatty acids** *monotherap-ish*
- **ginkgo biloba** *adjunctively*

Belsito 2001; Wasserman 2006; King 2001; Hasanzadeh 2012; Amminger 2007; Remington 2001;

Non-neuroleptics

Positive RCTs:

- **carnitine** *monotherapy*
- **pentoxifylline** *monotherapy*
- **cyproheptadine** *adjunctively*
- **memantine** *adjunctively*
- **celecoxib** *adjunctively*
- **galantamine** *adjunctively*
- **riluzole** *adjunctively*

Akhondzadeh 2004; Ghaleiha 2012; Asadabadi 2012; Ghaleiha 2013; Ghaleiha 2013(2); Akhondzadeh 2010

Non-neuroleptics

Positive RCTs with drugs we actually would consider prescribing:

- **clonidine** *monotherapy*
- **methylphenidate** *monotherapy*
- **valproate** *monotherapy*
- **topiramate** *adjunctive*
- **n-acetylcysteine (NAC)** *adjunctive*
- **buspirone** *adjunctive*

Jaselskis 1992; Quintana 1995; Hollander 2010; Rezaei 2010; Nikoo 2015; Ghanizadeh 2015

Jaselskis 1992 Clonidine Trial

8 patients (100% male)
mean 8.1 ± 2.8 years old

clonidine
(titrated up to 4-10 mcg/kg/day)
Monotherapy x 6 weeks**
Crossover design

ABC-I:
clonidine: -5.3
(net difference c/w placebo)

CPTQ (full scale):
clonidine: -2.8
(net difference c/w placebo)

CGI-I:
clonidine: -0.1
(net difference c/w placebo)

Adverse Effects:
hypotension (38%), sedation, increased irritability

No pts had rebound hypertension on tapering

Weight/metabolic changes:
not reported

Jaselski et al. J Autism Dev Disord 1992; 31: 175.
CPTQ = Conners' Parent-Teacher Questionnaire

Quintana 1995 Methylphenidate Trial

10 patients (60% male)
mean 8.5 ± 1.3 years old

methylphenidate (IR)
(10-20 mg BID vs placebo)
Monotherapy x 2 weeks**
Crossover design

ABC (full scale):
methylphenidate: -28.2
placebo: -17.8

ABC-I:
methylphenidate: -7.8
placebo: -4.6

significant, modest reduction
in hyperactivity symptoms

Adverse Effects:
reduced appetite, insomnia,
increased irritability,
stomachache, headache

Weight/metabolic changes:
not reported

Quintana et al. J Autism Dev Disord 1995; 25: 283.

Hollander 2010 Valproate Trial

27 patients (84% male)
mean 9.46 ± 2.65 years old

valproate (divalproex)
(titrated to effect & minimum level of 350 µmol/L)*
Monotherapy x 12 weeks

1º Endpoint Efficacy (ABC-I):
valproate: -7.5
placebo: -3.6

Responders (CGI-I score ≤ 2):
valproate: 63%
placebo: 9%

moderate effect size (*d*=0.44)

No differences in secondary measures (cY-BOCS, OAS-M)

Adverse Effects:
Rash, polyuria,
headache, severe agitation (1)

Weight Increase:
valproate: 1.37 ± 2.91 kg
placebo: 1.34 ± 1.53 kg

No other metabolic tests

Hollander et al. Neuropsychopharmacol 2010; 35: 990.

Rezaei 2010 Topiramate Trial

40 patients (68% male)
mean 8 ± 1.8 years old

topiramate
(100-200 mg/day (weight/age))
***adjunct* to risperidone (R)**
2-3 mg/day x 10 weeks

1º Endpoint Efficacy (ABC-I):
topiramate + R: -9.05
placebo+ R: -1.5

Adverse Effects:
Somnolence, decreased appetite, paresthesia, insomnia, nausea, dizziness

Weight Increase:
topiramate + R: 0.43 kg
placebo + R: 0.52 kg

No other metabolic tests

Rezaei et al. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34: 1269.

Nikoo 2015 N-Acetylcysteine (NAC) Trial

40 patients (83% male)
mean 7.5 ± 2.6 years old

Weight-based Fixed Dose
NAC (600-900 mg/day)
***adjunct* to risperidone (R)**
1-2 mg/day x 10 weeks

1° Endpoint Efficacy (ABC-I):
NAC + R: -9.25
placebo + R: -5.35

Adverse Effects
vomiting, nausea, headache, diarrhea, abdominal pain

2° outcome measures
(ABC-hyperactivity): p<0.001
(ABC-speech, stereotypy, withdrawal): NS

Weight/metabolic changes: not reported

Nikoo et al. Clin Neuropharm 2015; 38: 11-7.

Ghanizadeh 2015 Buspirone Trial

40 patients (83% male)
mean 7.3 ± 2.5 years old

Weight-based Flexible Dose
buspirone (10-20 mg/day)
***adjunct* to risperidone (R)**
2-3 mg/day x 8 weeks

1° Endpoint Efficacy (ABC-I):
buspirone + R: -9.1
placebo + R: -6.5

Responders (≥30% ↓ ABC-I):
buspirone + R: 81%
placebo + R: 39%

2° outcome measures
not reported

Adverse Effects
↑ appetite, drowsiness, fatigue

Weight/metabolic changes:
not reported

Ghanizadeh et al. Pediatr Neurol 2015; 52: 77-81.

Non-neuroleptic Efficacy

- **Intriguing, but less robust effects**
- **Ideas for adjunctive treatment when neuroleptics alone aren't enough**

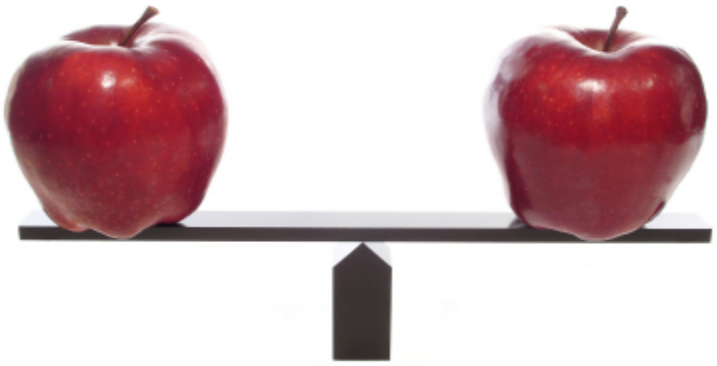
BC Pharmacare Considerations

- **risperidone is a full benefit drug**
- **aripiprazole only covered for *psychosis* in age 15+ via Special Authority Application**
- **Exception requests may be possible; more likely to be successful if evidence of metabolic abnormalities**
- **Clonidine, valproate are full benefit drugs**

Drug Costs

- **(generic) risperidone 1 mg: $0.34**
- **aripiprazole 5 mg: $3.94**

an approximate ‘apples to apples’ comparison



Algorithm - Prescribing principles

Table 3 – General Prescribing Principles

1. Obtain informed consent
2. Identify specific target(s) of treatment (e.g. anxiety, irritability)
3. Use objective measure/tool to monitor treatment (e.g. rating scale, Likert scale)
4. Start medications at low dose, use lowest effective dose
5. Discontinue treatments that are ineffective
6. Monitor closely for side-effects, using guidelines where applicable (e.g. CAMESA)
7. Avoid polypharmacy as much as possible
8. Consider treatment discontinuation or reduction in dose after 6-12 months