PSYCHOPHARMACOLOGY

Review of the Pharmacotherapy of Irritability of Autism

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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*

Résumé

Objectif: analyser les données expérimentales tirées d'études aléatoires contrôlées (EAC) sur la pharmacothérapie de l'irritabilité associée à l'autisme. **Méthodologie:** analyse d'articles indexés dans *Medline* (mots-clés: autisme, trouble envahissant du développement; limites: étude aléatoire contrôlée, présentation par affiche, étude humaine, anglais). D'autres articles ont été choisis parmi des ouvrages de référence et des présentations par affiche. Les études sur des suppléments alimentaires, des hormones ou des médicaments qui n'ont pas été approuvés par Santé Canada ou par la *Food and Drug Administration* (FDA) américaine ont été exclues de l'analyse. **Résultats:** dix-sept études aléatoires contrôlées répondaient à ces critères. La majorité d'entre elles portaient sur la risperidone: cinq études sur six affichaient des résultats de début d'étude statistiquement significatifs. Deux études sur l'aripiprazole étaient statistiquement significatives, contrairement à celles sur l'olanzapine et le levetiracetam. L'haloperidol s'est avéré supérieur à la clomipramine et au placebo dans une étude tête-à-tête croisée, tandis qu'une étude tête-à-tête distincte indiquait que la risperidone était supérieure à l'haloperidol dans le traitement des symptômes comportementaux. Une seule étude indiquait que la levocarnitine était supérieure au placebo lorsqu'elle était prescrite seule, tandis que des études de moindre envergure montraient que les traitements adjonctifs par cyproheptadine, pentoxifylline et topiramate avaient une plus grande signification statistique que le placebo, lorsque ces molécules étaient administrées avec un antipsychotique. Les

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effets secondaires, comme le gain de poids et les effets métaboliques, étaient résumés lorsqu'ils étaient mentionnés dans les études. **Conclusion:** les résultats positifs de la pharmacothérapie de l'irritabilité associée à l'autisme sont liés, en grande partie, à la risperidone et à l'aripiprazole, antipsychotiques approuvés par la FDA. Les molécules et traitements adjonctifs dont l'efficacité était attestée dans les EAC offrent d'autres possibilités de traitement lorsque les doses optimales d'antipsychotiques ne permettent pas de contrôler les symptômes ou entraînent des effets secondaires intolérables.

Mot clés: *pharmacothérapie, autisme, irritabilité, antipsychotique*

Introduction

Autism is part of a spectrum of pervasive developmental disorders characterized by difficulties with communication and social interaction and unusual behaviors that are restricted or stereotyped and repetitive. A range of disruptive behavioural symptoms may be present, including impulsivity, aggressiveness, self-injurious behaviour, and temper tantrums. In some cases, catastrophic behavioural reactions may occur in response to minor environmental changes (American Psychiatric Association, 2000).

Irritability may be defined as an individual being abnormally sensitive with a disposition or tendency to easily exhibit uncontrolled anger or aggression. While both pharmacotherapy and behavioural treatments are often employed in the treatment of irritability of autism, behavioural treatments are discussed in detail elsewhere (Hanley, Iwata, & McCord, 2003). The treatment modality selected often depends on the qualifications, familiarity and comfort level of the service provider, with psychiatrists more likely to prescribe medications for treatment of irritability. If there is a history of behavioural symptoms that occur in multiple settings and that do not respond to behavioural interventions, pharmacotherapy is often required (Hollander, Phillips, & Yeh, 2003). A recent editorial called for closer integration of behavioural therapy and pharmacotherapy in the treatment of challenging behaviours in autistic patients (Frazier, 2012).

In randomized clinical trials (RCTs), irritability in autistic patients and response to pharmacotherapy is often assessed via the Aberrant Behavior Checklist-Community Irritability subscale (ABC-I) (Aman & Singh, 1994). Symptoms assessed on this 16-item subscale include self-injurious behaviours, physical aggression towards others, screaming, yelling, temper tantrums, demanding behaviours, mood changes, and crying in response to minor annoyances. Other rating scales sometimes used in some trials include the full Aberrant Behavior Checklist-Community (ABC) (Aman & Singh, 1994) and the Childhood Autism Rating Scale (CARS) (Schopler, Reichler, DeVellis, & Daly, 1980). However, the ABC and CARS more broadly encompass the core symptoms of autism, which may be less responsive to pharmacotherapy.

Efficacy Data

A review of the literature was conducted using the search terms: ('autism' OR 'autism spectrum disorder') with limits: RCTs, human trials, English language. Additional articles were identified from reference information. Trials involving drug products (nutritional supplements, hormones or drugs) not available in Canada or the United States were excluded from analysis. Table 1 summarizes the published RCTs for pharmacotherapy of irritability in autism.

We identified 23 RCTs that met criteria. Of these, ten RCTs were with antipsychotic agents (seven with risperidone, two with aripiprazole, one with olanzapine) and 13 RCTs were with miscellaneous agents that included anticonvulsants (lamotrigine, levetiracetam, topiramate, valproate), drugs with central nervous system actions (amantadine, clomipramine, clonidine, cyproheptadine, methylphenidate), nutritional supplements (omega-3 fatty acids (OFA), gingko biloba and levocarnitine) and pentoxifylline, a drug originally marketed for treatment of intermittent claudication, but thought to possess immunosuppressant properties. Haloperidol was an active control in two RCTs.

Antipsychotic Trials

The 2002 Research Units on Pediatric Psychopharmacology Autism Network (RUPPAN, 2002) study was an eight-week trial of 101 patients between 5 to 17 years of age who were randomized to receive flexible-dose risperidone or placebo. The primary outcome measure was change on the ABC-I. Patients who received risperidone (mean: 1.8 ±0.7 mg/day) had a significant reduction in ABC-I (-14.9) compared to placebo (-3.6) at study endpoint (RUPPAN, 2002). Percentage of responders (as denoted by Clinical Global Impression-Improvement (CGI-I) score ≤ 2 at endpoint) was a secondary outcome measure, with 75.5% of patients who received risperidone considered responders, compared to 11.5% of patients who received placebo (RUPPAN, 2002). The effect size (*d=1.2)* of risperidone treatment in this study was large. A secondary analysis (Arnold et al., 2010) found that higher baseline symptom severity, socioeconomic advantage, low prolactin level and absence of co-morbid conditions non-specifically predicted better outcome, while weight gain correlated with negative treatment response.

This study continued as a four-month open-label risperidone phase to further analyze safety and efficacy. Of the

Table 1. Review of irritability of autism randomized controlled trials involving children and adolescents

Lead Author/ Year/Journal	# of pts; % ♂; Age (years)	Drug/Dose; Duration	Monotherapy?	Efficacy results (bold=1° outcome(s))
Risperidone Trials				
RUPPAN 2002; New Engl J Med	n=101; 82% ♂; 8.8 ± 2.7; (range: 5-17)	Flexible Dose R:(< 20 kg):0.25-2.5 mg/day (20-45 kg): 0.5-2.5 mg/day (> 45 kg): 0.5-3.5 mg/day (mean: 1.8 ± 0.7 mg/day) vs PBO; 8 weeks duration	Yes (anticonvulsants OK for seizures - 2% in each group on unspecified anticonvulsant(s))	**†ABC-I: R: -14.9** PBO: -3.6** % with CGI-I ≤ 2 at endpoint: R: 75.5% vs PBO: 11.5%
Shea 2004; Pediatrics	n=79; 77% ♂; R: 7.6 ± 2.3 PBO: 7.3 ± 2.3	Flexible Dose (at investigator's discretion) R: 0.02 - 0.06 mg/kg/day (mean: 1.17 mg/day) vs PBO; 8 weeks duration	Yes - 62% receieved concomitant medications including: analgesics, anti-asthmatics, antibiotics, anticholinergics, cough and cold preparations and sedative/hypnotics	**†ABC-I: R: -12.1** PBO: -6.5** % with CGI-I ≤ 2 at endpoint: R: 26% vs PBO: 9% †N-CBRF conduct problem: R: -10.4 PBO: -6.6 †VAS-MS (aggression): R: -38.4 PBO: -26.2
Hellings 2006; J Autism Dev Disord	n=40; 58% ♂; mean: 22 ± 13.1 (range: 8-56)	Complex Crossover Design Low dose R: 1 mg/day High dose R: 0.05 mg/kg/day (mean high dose 2 mg/day, in children and adolescents (range 1.2-2.9 mg/day)) vs PBO; 46 weeks duration‡	Yes	**†ABC-I:** (acute phase results, comparison vs first PBO phase) **R low dose: -8.05** R high dose: -6.85**** Responders (≥ 50% reduction in ABC-I): 57.5% (groups not differentiated)
Nagaraj 2006; J Child Neurol	n=39; 87% ♂; R: 4.8 ± 1.7 PBO: 5.25 ± 1.67	R: 1 mg/day vs PBO; 6 months duration	Yes (antipsychotic use OK - 10% of patients received unspecified antipsychotic agent(s))	**†CARS: R: -7.5** PBO: -1.0 CGAS: R: 11.15** PBO: 2.55**
Luby 2006; J Child Adolescent Psychopharmacol	n=23; 74% ♂: R: 4.1 ± 0.9 PBO: 4.0 ± 1.1	Flexible Dose R: range 0.5-1.5 mg/day (mean dose: 1.14 ± 0.32 mg/day) vs PBO; 6 months duration	Yes (implied)	**†CARS: R: -4.6 PBO: -1.8** GARS: non-significant difference, unspecified results
Pandina 2007; J Autism Dev Disord	n=55; 78% ♂; R: 7.4 ± 2.4 PBO: 7.1 ± 2.1	Flexible Dose R: 0.5-4.2 mg/day (mean: 1.37 ± 0.7 mg/day) vs PBO; 8 weeks duration	Yes	**†ABC-I: R: -13.4** PBO: -7.5** % with CGI-C ≤ 2 at endpoint and ≥ 25% ABC-I improvement: R: 58.3% vs PBO: 21.4% †N-CBRF conduct problem: R: -9.0 PBO: -6.0 †VAS-MS (aggression): R: -41.1 PBO: -24.9
Miral 2008; Eur Child Adolesc Psychopharmacol	n=30; 80% ♂; R: 10 ± 2.7 H: 10.9 ± 2.9	Flexible Dose R: 1.2-4 mg/day (mean: 2.6 ± 0.8 mg/day) vs H: 1-5.7 mg/day (mean: 2.6 ± 1.3 mg/day); 12 weeks duration	Yes (implied)	**†ABC: R: -48.8 H: -21.3**

Adverse effects	Weight gain/ metabolic effects
% above PBO: drowsiness (37%), fatigue (32%), increased appetite (24%), constipation (17%), dizziness (12%), nasal congestion (12%), tremor (12%), tachycardia (10%), vomiting (9%), dry mouth (8%), muscle rigidity (8%), sore throat (8%), drooling (6%), URTI (6%)	R: 2.7 ± 2.9 kg; PBO: 0.8 ± 2.2 kg
% above PBO: somnolence (64.8%), URTI (22.2%), rhinitis (17.2%), apathy (12.5%), tachycardia (12.5%), abdominal pain (12.3%) increased appetite (12.2%), tremor (10%), constipation (9.9%), fatigue (7.5%), headache (7.4%), increased saliva (7.4%), increased weight (7.4%)	R: 2.7 ± 2.0 kg; PBO: 1.0 ± 1.6 kg
(Incidence not specified) drowsiness, weight gain, increased appetite, lack of spontaneity, tremor, nasal congestion. Severe akathisia in 1 pt, recurrent oculogyric crisis in 1 pt.	at 46 weeks: children: 7.9 kg adolescents: 8.3 kg adults: 6 kg weight gain of ≥ 3 kg observed in 70% of pts
% above PBO: sedation (10%), dyskinesia (7.6%)	R: 2.81 ± 2.04 kg; PBO: 1.71 ± 1.3 kg
% above PBO: increased appetite (26%), sedation (22%), hypersalivation (8%)	R: 2.96 ± 2.53 kg; PBO: 0.61 ± 1.10 kg
% above PBO: somnolence (67%), URTI (23%), rhinitis (19%), increased saliva (9%), fever (8%), anorexia (7%), increased appetite (7%), influenza-like symptoms (7%)	R: 2.4 ± 2.9 kg; PBO: 1.1 ± 0.7 kg
R: URTI (53.1%), constipation (23.1%), nocturnal enuresis (23.1%) H: URTI (53.3%), blunted affect (26.7%), increased appetite (26.7%), constipation (20%), difficulty sleeping (20%), nocturnal enuresis (20%), rigidity (20%)	R: 4.3 ± 0.7 kg; H: 4.6 ± 0.1 kg

Table 1. Review of irritability of autism randomized controlled trials involving children and adolescents (continued)

Lead Author/ Year/Journal	# of pts; % ♂; Age (years)	Drug/Dose; Duration	Monotherapy?	Efficacy results (bold=1º outcome(s))
Aripiprazole Trials				
Owen 2009; Pediatrics	n=98; 88% ♂; A: 9.7 ± 3.2 PBO: 8.8 ± 2.6	Flexible Dose A: 2-15 mg (mean: 10 mg/day) vs PBO; 8 weeks duration	Yes (implied)	**†ABC-I: A: -12.9** PBO: -5.0** % with CGI-I ≤ 2 and ≥ 25% ABC-I improvement: A: 52.2% PBO: 14.3%
Marcus 2009; J Am Acad Child Adolesc Psychiatry	n=218; 89% ♂; A5: 9 ± 2.8 A10: 10 ± 3.2 A15: 9.5 ± 3.1 PBO: 10.2 ± 3.1	A: 5, 10 or 15 mg vs PBO; 8 weeks duration	Yes - 33% received concomittent medications which included: analgesics, antipyretics, anticholinergics, anxiolytics, and hypnotics/sedatives	**†ABC-I: A5: -12.4**; A10: -13.2**; A15: -14.4**; PBO : -8.4** % with CGI-I ≤ 2 and ≥ 25% ABC-I improvement: A5: 55.8% A10: 49.2% A15: 52.8% PBO: 34.7%
Olanzapine Trial				
Hollander 2006; J Child Adolesc Psychopharmacol	n=11; (82% male); O: 9.25 ± 2.9 PBO: 8.9 ± 2.1	Flexible Dose O: < 40 kg: 2.5-20 mg/day > 40 kg: 5-20 mg/day (mean: 10 ± 2.04 mg/day) vs PBO; 8 weeks duration	Yes (implied)	**†CGI-I: O: -2.25 PBO: -1.1** CY-BOCS, OAS-M: findings non-significant, unspecified results
Miscellaneous Trials - monotherapy				
Jaselskis 1992; J Clin Psychopharmacol	n=8; 100% ♂; mean: 8.1 ± 2.8; (range: 5-13.4)	CLD: 4-10 mcg/kg/day (tapered on and off) vs PBO; Crossover design; 14 weeks duration‡	Yes	†ABC-I: ^CLD: -5.3** †CPTQ: ^CLD: -2.8** †CGI-I: ^CLD: -0.1
Quintana 1995; J Autism Dev Disord	n=10; 60% ♂; mean: 8.5 ± 1.3; (range: 7-11)	MPH: 10 mg BID x 1 week then 20 mg BID x 1 week vs PBO; Crossover design; 4 weeks duration‡	Yes	†ABC: MPH: -28.2** PBO: -17.8 †ABC-I: MPH: -7.8** PBO: - 4.6 significant, modest reduction in hyperactivity symptoms
Remington 2001; J Clin Psychiatry	n=36; 83% ♂; mean: 16.3 (range: 10-36)	Flexible Dose CMP: 100-150 mg/day (mean: 128.4 mg/day) vs H: 1-1.5 mg/day (mean: 1.3 mg/day) vs PBO; 7 weeks duration	Yes (benztropine use OK - unspecified number of patients)	**†CARS: CMP: -4.0 H: -5.1** PBO: -2.4 †ABC-I: CMP: -3.0 H: -7.0** PBO: -2.0**

Adverse effects	Weight gain/ metabolic effects
% above PBO: fatigue (17%), somnolence (13%), vomiting (11%), sedation (9%), tremor (9%), drooling (9%), fever (7%), EPS (7%), increased appetite (5%)	Mean weight change: A: +2.0 kg; PBO: +0.8 kg Mean BMI change: A: +0.7; PBO: +0.3 pts with ≥ 7% weight gain: A: 28.9% PBO: 6.1% No significant differences in changes for FBG, TG, LDL, HDL, TChol
% above PBO (range for all A dosage levels): sedation (11-18%), tremor (8-12%), cough (7-11%), fever (6-12%), lethargy (5-8%), fatigue (4-18%), drooling (4-14%), EPS (4-11%), decreased appetite (4-8%), somnolence (4-6%), vomiting (2-13%), increased appetite (1-16%), hypersalivation (0-9%), epistaxis (0-7%), URTI (0-6%), weight increased (0-6%), abdominal pain (0-5%), nausea (0-5%)	Mean weight change: A5: +1.3 ± 0.3 kg; A10: +1.3 ± 0.3 kg; A15: + 1.5 ± 0.3 kg; PBO: +0.3 ± 0.3 kg Mean BMI change: A5: +0.6 ± 0.2; A10: +0.6 ± 0.2; A15: +0.8 ± 0.2; PBO :+0.2 ± 0.2 pts with ≥ 7% weight gain: A5: 32.7% A10: 15.3% A15: 30.2% PBO: 8.2% No significant differences in changes for FBG, TG, LDL, HDL, TChol
% above PBO: constipation (50%), sedation (47%), decreased appetite (17%), glazed eyes (17%), insomnia (17%), rhinitis (17%), increased appetite (10%)	O: 3.4 ± 2.2 kg; PBO: 0.7 ± 0.7 kg
hypotension (38%), drowsiness, irritability	N/A
Incidence compared to PBO not specified: decreased appetite, increased irritability, insomnia, stomachache, headache	N/A
CMP: fatigue/lethargy (31%), tremors (15%), tachycardia (7%), insomnia (7%), diaphoresis (7%), nausea and vomiting (7%), decreased appetite (7%) H: fatigue/lethargy (38%), dystonia (7%), depression (7%)	N/A

Table 1. Review of irritability of autism randomized controlled trials involving children and adolescents (continued)

Lead Author/ Year/Journal	# of pts; % ♂; Age (years)	Drug/Dose; Duration	Monotherapy?	Efficacy results (bold=1° outcome(s))
Miscellaneous Trials - monotherapy				
King 2001; J Am Acad Child Adolesc Pyschiatry	n=39; 87% ♂; mean: 7 (range 5-15)	AM: 5 mg/kg/day vs PBO; 4 weeks duration	Yes (psychopharmacological agents OK - including use of serotonin reuptake inhibitors)	**% ABC responders (≥ 25% reduction in irritability and/or hyperactivity subscales) AM: 47% PBO: 37%** **% CGI-I responders (CGI-I ≤ 2) AM: 53% PBO: 25%**
Belsito 2001; J Autism Dev Disord	n=28; 96% ♂; mean: 5.8; (range: 3-11)	LAM: 5 mg/kg/day vs PBO; 18 weeks duration‡	Yes	†AUBC: LAM: -25.7 PBO: -24.1 †ABC: LAM: no significant differences vs PBO in total score or any subscale score †CARS: LAM: +0.1 PBO: -0.6 VABS: LAM: no significant differences vs PBO on any subscale score
Wasserman 2006; International Clin Psychopharmacol	n=20 85% ♂	Flexible Dose LVT: 20-30 mg/kg/day (mean: 862.50 ± 279.29 mg) vs PBO; 10 weeks duration	Yes (implied)	**†ABC-I: LVT: -3.55 PBO: -2.65** **CGI-I: findings non-significant, unspecified results**
Amminger 2007; Biol Psychiatry	n=13 100% ♂; OFA: 10.5 ± 3.2 PBO: 12.1 ± 2.7	OFA: 7 capsules/day (120 mg EPA and 100 mg DHA/capsule) vs PBO (contained 1 mg fish oil to mimic taste); 6 weeks duration	Yes (anticonvulsants OK for patients with seizure disorders)	**†ABC-I: OFA: -4.7 PBO: -4.6**
Hollander 2010; Neuropsychopharmacol	n=27; 84% ♂; VPA: 9.66 ± 2.64 PBO: 8.97 ± 2.8	VPA: weight based dose titrated to achieve clinical response with VPA level above 350 µmol/L vs PBO; 12 weeks duration	Yes (implied)	**†ABC-I VPA -7.5** PBO: -3.6** **% with CGI-I ≤ 2 at endpoint VPA: 63%** PBO: 9%** No statistically significant improvement in cY-BOCS, OAS-M Irritability scores
Geier 2011: Med Sci Monit	n=30; 85% ♂; LCAR: 6.3 ± 2.4 PBO: 6.7 ± 1.6	LCAR: 50 mg/kg/day vs PBO; 3 months duration	Yes (implied)	†CARS: LCAR: -1.94** PBO: +0.09 †modified CGI-I: LCAR: -0.5** PBO: + 0.09

Adverse effects	Weight gain/ metabolic effects
% above PBO: insomnia (11%), somnolence (5%)	N/A
insomnia, hyperactivity (incidence not specified). None of the children were withdrawn from this trial due to rash.	N/A
% above PBO: Hyperactivity (10%), impulsivity (10%), aggression (10%), weight gain (10%), weight loss (10%), loss of appetite (10%), self injurious behaviour (10%)	N/A
reported adverse effects, incidence not stated: OFA: fever PBO: headache, insomnia	N/A
incidence above PBO: rash (2), polyuria (2), headache (1), severe agitation (1)	VPA: 1.37 ± 2.91 kg; PBO: 1.34 ± 1.53 kg
(incidence not specified) irritability, stomach discomfort	N/A

Table 1. Review of irritability of autism randomized controlled trials involving children and adolescents (continued)

Lead Author/ Year/Journal	# of pts; % ♂; Age (years)	Drug/Dose; Duration	Monotherapy?	Efficacy results (bold=1º outcome(s))
Miscellaneous Trials - adjunctive therapy				
Akhondzadeh 2004; J Clin Pharmacol Ther	n=40; 60% ♂; CYP: 6.04 ± 0.48 PBO: 6.90 ± 0.42	Flexible Dose: CYP: 0.2 mg/kg/day; 8 weeks duration	No H: 0.05 mg/kg/day and biperiden: 0.04 mg/kg/day	**†ABC: CYP: -10.9** PBO: -3.7** †CARS CYP: -1.85 PBO: -0.37
Akhondzadeh 2010; Prog Neuropsychopharmacol Biol Psychiatry	n=40; 70% ♂; PTF: 8.05 ± 2.01 PBO: 7.37 ± 2.41	Flexible Dose PTF add-on: (10-40 kg): 400 mg/day (> 40 kg): 600 mg/day vs PBO; 10 weeks duration	No R: (10-40 kg): 2 mg/day (> 40 kg): 3 mg/day	**†ABC-I: PTF: -9.53** PBO: -4.41**
Rezaei 2010; Prog Neuropshychopharmacol Biol Psychiatry	n=40; 68% ♂; TOP: 8.17 ± 1.85 PBO: 7.85 ± 1.82	TOP: (< 30 kg/age 3-6): 100 mg/day (> 30 kg/age 7-12): 200 mg/day vs PBO; 8 weeks duration	No R: (10-40 kg): 2 mg/day (> 40 kg): 3 mg/day	**†ABC-I: TOP: -9.05** PBO: -1.5**
Hasanzadeh 2012; Child Psych Hum Dev	n=47; 83% ♂; GB: 6.04 ± 1.61 PBO: 6.76 ± 2.6	GB: (<30 kg): 80 mg/day (> 30 kg): 120 mg/day vs PBO; 10 weeks duration	No R: (10-30 kg): 2 mg/day (> 30 kg): 3 mg/day	†ABC-I: GB: -4.41 PBO: -4.2

Abbreviations

A=aripiprazole; AM=amantadine; BID=twice daily; BMI=Body Mass Index; CLD=clonidine; CMP=clomipramine; CYP=cyproheptadine; EPS=extrapyramidal symtpoms; FBG=fasting blood glucose; GB=gingko biloba; H=haloperidol; HDL=high-density lipoprotein; LAM=lamotrigine; LCAR=levocarnitine; LDL=low-density lipoprotein; LVT=levetiracetam; MPH=methylphenidate; N/A=not available; O=olanzapine; OFA=omega-3 fatty acids; PBO=placebo; pt=patient

Abbreviations of Rating Scales used: ABC: Aberrant Behavior Checklist (Complete scale); ABC-I: Aberrant Behavior Checklist (Irritability subscale); AUBC: Autism Behavior Checklist; CARS: Childhood Autism Rating Scale; CGI-C: Clinical Global Impresssion - Change; CGI-I: Clinical Global Impresssion - Improvement; CGAS: Children's Global Assessment Scale; CGSQ: Caregiver Strain

initial 101 subjects enrolled in the RCT, 63 patients who were responders consented to enrollment in the open-label continuation phase (RUPPAN, 2005). Following four months of open-label risperidone treatment (mean dose 1.96 mg/day), ABC-I scores increased from the RCT endpoint by 2.2. This was deemed clinically insignificant by the authors (RUPPAN, 2005). Following this open-label phase, an eight-week randomized, double-blind, placebo-substitution study of risperidone withdrawal in 32 patients was conducted. Of placebo-substituted patients, 62.5% experienced relapse (defined as an increase of >25% on ABC-I and CGI-I score of ≥6 (much worse or very much worse) compared to 12.5% of patients who continued to receive risperidone (RUPPAN, 2005).

Shea and colleagues (Shea et al., 2004) conducted an eight-week trial of 79 patients between 5 to 12 years of age with pervasive developmental disorders, including autistic disorder (68% of patients). Patients were randomized to receive a flexible risperidone dose of 0.02-0.06 mg/kg/day or placebo. The primary outcome measure was change on the ABC-I. Patients who received risperidone (mean 1.17 mg/day) had a statistically significant reduction in ABC-I score (-12.5) compared to patients who received placebo (-6.1) (Shea et al., 2004). A secondary analysis conducted amongst the 54 patients with autistic disorder also showed a statistically significant reduction in ABC-I score for risperidone patients (-13.5) compared to placebo (-7.5) (Shea et al., 2004). A secondary outcome measure was percentage of responders (defined as CGI-I ≤2 at study endpoint) with 26% of risperidone patients considered responders versus 9% of placebo patients (Shea et al., 2004).

Hellings and colleagues (Hellings et al., 2006) conducted a 22-week trial with a complex crossover design of 40 patients 8 to 56 years of age (mean: 22 ±13.1 years) with intellectual disability (90% of which had autism spectrum disorders) who were randomized to receive either low-dose risperidone (1 mg/day), high-dose risperidone (0.05 mg/kg/day) (children and adolescents: mean 2 mg/day, range 1.2-2.9 mg/day) or placebo. Each of the active treatment periods were maintained for a four-week period prior to evaluating outcome measures. Patients who received low-dose risperidone had a reduction in ABC-I score of -8.05 (compared to observed scores during the first placebo phase), while patients who received high-dose risperidone had a reduction

	Adverse effects	Weight gain/ metabolic effects
	% above PBO: increased appetite (25%), constipation (10%)	non-significant difference in fasting glucose compared to PBO
	% above PBO: increased appetite (15%), daytime drowsiness (10%), flatulence (10%), constipation (5%), weight gain (5%)	N/A
	% above PBO: somnolence (30%), decreased appetite (30%), paresthesia (20%), insomnia (20%), nausea (20%), dizziness (15%)	Mean weight change: TOP: 0.43 kg PBO: 0.52 kg
	% above PBO: nervousness (17.6%), fatigue (13.4%), morning drowsiness (8.7%)	N/A

PTF=pentoxifylline; R=risperidone; Tchol=total cholesterol; TG=triglyceride; TOP=topiramate; URTI=Upper Respiratory Tract Infection VPA=divalproex/valproate; vs=versus; ♂ = male; ‡=see body text for trial durations details; †=negative score denotes improvement; ^=net difference compared to placebo reported since baseline values not specified; **=statistically significant result for primary outcome/ implied primary outcome measure

Questionnaire; cY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale; GARS: Gilliam Autism Rating Scale; NCBF: Nisonger Child Behavior Rating Form; OAS-M: Overt Aggression Scale-Modified; PedsQL: Pediatric Quality of Life Inventory; VABS: Vineland Adaptive Behavior Scale; VAS-MS: Visual Analog Scale for Most Troublesome symptom

in ABC-I score of -6.65 (Hellings et al., 2006). Statistical comparisons for both active risperidone treatment phases were made with the first placebo phase, and results for both risperidone groups were statistically significant (Hellings et al., 2006). During the acute phase of the study, 57.5% of patients were considered full responders (defined *a priori* as a ≥50% reduction in ABC-I score) (Hellings et al., 2006). A 24-week open label phase involving 32 patients followed the acute phase study. While detailed results were not reported, mean irritability scores were considered relatively stable during this phase (Hellings et al., 2006). The authors concluded that low-dose risperidone was equally effective but better tolerated than high-dose risperidone (Hellings et al., 2006).

Nagaraj and colleagues (Nagaraj, Singhi, & Malhi, 2006) conducted a six-month trial of 39 autistic patients between 2 to 9 years of age who were randomized to receive risperidone 1 mg/day or placebo. The CARS and the Children's Global Assessment Scale (CGAS) were co-primary outcome measures. Patients who received risperidone had a mean decrease in CARS score of -7.5 while patients who received placebo had a mean decrease in CARS score of -1.0 (Nagaraj et al., 2006). Improvement was defined as a 20% or greater reduction in CARS score from baseline. For patients in the risperidone group, 63% were considered improved, compared to none of the patients in the placebo group (Nagaraj et al., 2006). Patients who received risperidone had a mean increase in CGAS score of 11.15 while patients who received placebo had a mean increase in CGAS score of 2.55. Improvement was defined as an increase of 20% or greater from baseline CGAS score. In the risperidone group, 89% of patients were deemed to have improved, compared to only 10% of patients in the placebo group (Nagaraj et al., 2006). The differences favoring risperidone were statistically significant for both outcome measures (Nagaraj et al., 2006).

Luby and colleagues (Luby et al., 2006) conducted a six-month trial in a group of 23 pre-school children between 2.5 to 6 years of age with autism spectrum disorders. Patients were randomized to receive flexible dose risperidone (0.5-1.5 mg/day) or placebo. The primary outcome measure was the CARS scale. Patients who received risperidone (mean: 1.14 ±0.32 mg/day) had a statistically non-significant reduction in CARS score (-4.6) compared to patients who

received placebo (-1.8) (Luby et al., 2006). Analysis was complicated by a significant difference in baseline symptom scores between groups, despite standard randomization procedures being employed (Luby et al., 2006). Detailed results regarding secondary rating scales and outcome measures of interest were not provided, though a statement was included that there were no statistically significant differences between groups for these measures (Luby et al., 2006).

Pandina and colleagues (Pandina, Bossie, Youssef, Zhu, & Dunbar, 2007) conducted an eight-week trial of 55 patients with autistic disorder between 5 to 12 years of age who were randomized to receive flexible-dose risperidone or placebo. The primary outcome measure was change in ABC-I scores. Patients who received risperidone (mean: 1.37 ±0.7 mg/day) had a statistically significant mean decrease on the ABC-I scale (-13.4) compared to patients who received placebo (-7.5) (Pandina et al., 2007). Percentage of responders was a secondary outcome measure, with response defined as a ≥25% improvement in ABC-I and a CGI-I score ≤2 at endpoint. For patients who received risperidone, 58.3% were deemed responders compared to 21.4% of patients who received placebo (Pandina et al., 2007).

Miral and colleagues (Miral et al., 2008) conducted a 12-week trial of 30 patients with autistic disorder between 8 to 18 years of age who were randomized to receive flexible-dose risperidone or haloperidol. The full ABC scale was used as a primary outcome measure and no subscale values were reported. Patients who received risperidone (mean: 2.6 ±0.8 mg/day) had a mean change in ABC score at endpoint of -48.8 while patients who received haloperidol (2.6 ±1.3 mg/day) had a mean change in ABC score at endpoint of -21.3 (Miral et al., 2008). The Ritvo-Freeman Real Life Rating Scale that includes five subscales (social, sensorimotor, affect, sensory and language) was the secondary outcome measure. All subscale scores showed statistically significant improvement for risperidone compared to baseline, however only three subscales (social, sensorimotor and affect) showed statistically significant improvement with haloperidol compared to baseline (Miral et al., 2008).

Two aripiprazole RCTs were identified. Owen and colleagues (Owen et al., 2009) conducted an eight-week trial of 98 patients with autistic disorder between 6 to 17 years of age who were randomly assigned to receive flexible-dose aripiprazole (2-15 mg/day) or placebo. The primary outcome measure was change in ABC-I. Statistically significant improvement over placebo was noted in the aripiprazole group after one week of treatment. Due to the dose titration schedule, the aripiprazole dosage was 2 mg/day at this time point. At study endpoint, patients who received aripiprazole (mean: 10 mg/day) had a mean decrease in ABC-I score (-12.9) compared to patients who received placebo (-5.0) (Owen et al., 2009). A secondary outcome measure was percentage of responders (defined as ≥25% ABC-I improvement and a CGI-I score ≤2 at endpoint). Of patients who received aripiprazole, 52.2% were responders compared to 14.3% of patients who received placebo (Owen et al., 2009). The effect size (*d=0.87)* of aripiprazole treatment in this study was large (Owen et al., 2009).

Marcus and colleagues (Marcus et al., 2009) studied 218 patients with autistic disorder between 6 to 17 years of age who were randomized to receive aripiprazole at a fixed dose of 5, 10, or 15 mg/day or placebo during an eight-week trial in a forced dose-titration design. The primary outcome measure was change in ABC-I. Improvement compared to placebo was seen by week two in all aripiprazole treated patients. Due to the dose titration schedule, all aripiprazole treated patients were receiving a dosage of 5 mg/day at this time point. At study endpoint, statistically significant reductions in ABC-I were seen in all active treatment groups (5 mg/day: -12.4, 10 mg/day: -13.2, 15 mg/day: -14.4) compared to placebo (-8.4) (Marcus et al., 2009). A secondary outcome measure was percentage of responders (defined as ≥25% ABC-I improvement and a CGI-I score ≤2 at endpoint). Response rates for aripiprazole treated patients (5 mg/day: 55.8%, 10 mg/day: 49.2%, 15 mg/day: 52.8%) were superior to the 34.7% of responders in patients who received placebo (Marcus et al., 2009). At endpoint the percentage of responders was statistically significant compared to placebo for the aripiprazole 5 mg/day group, but not in the aripiprazole 10 or 15 mg/day groups (Marcus et al., 2009).

A single RCT for olanzapine was identified. Hollander and colleagues (Hollander et al., 2006) conducted an eight-week trial that studied 11 patients 6 to 17 years of age with pervasive developmental disorders (six of whom met criteria for autistic disorder). Patients were randomized to receive olanzapine at a flexible dose of 2.5-20 mg/day or placebo. Patients receiving olanzapine (mean: 10 ±2.04 mg/day) had a statistically significant mean change in CGI-I score (the primary outcome measure) of -1.75, while patients receiving placebo had a mean change in CGI-I score of -0.5 (Hollander et al., 2006). Secondary outcome measures included the Children's Yale-Brown Obsessive-Compulsive scale (cY-BOCS) and Overt Aggression Scale-Modified. Detailed scores were not specified for these measures but differences between treatment groups at endpoint were reported as statistically non-significant (Hollander et al., 2006).

Non-antipsychotic Trials

Thirteen RCTs involving miscellaneous other agents were identified. Jaselskis and colleagues (Jaselskis, Cook, Fletcher, & Leventhal, 1992) conducted a 14-week trial of eight patients between 5 to 13.4 years of age with autistic disorder. Patients were randomized to receive clonidine 4-10 micrograms/kg/day in divided doses or placebo in a crossover design. Clonidine dosage was titrated up over two weeks,

and then maintained for a four-week period prior to patients being evaluated for outcome measures. At endpoint for the clonidine group, patients had a statistically significant net change (compared to patients receiving placebo) in ABC-I score of -5.3 (Jaselskis et al., 1992). However, on the CGI-I, the net change (compared to placebo) was -0.1 (Jaselskis et al., 1992). A statistically significant net change on the Conners' Parent-Teacher Questionnaire score of -2.8 was also reported (Jaselskis et al., 1992).

Quintana and colleagues (Quintana et al., 1995) conducted a four-week trial of ten patients with autistic disorder between 7 to 11 years of age. Patients were randomized to receive methylphenidate immediate-release (IR) 10 mg twice daily for one week, followed by methylphenidate IR 20 mg twice daily for one week, or placebo in a crossover design. At endpoint, patients receiving methylphenidate had a statistically significant reduction in ABC and ABC-I scores (-28.2, -7.8 respectively) compared to patients receiving placebo (-17.8, -4.6 respectively) (Quintana et al., 1995). A statistically significant moderate reduction in hyperactivity symptoms was also observed (Quintana et al., 1995).

King and colleagues (King et al., 2001) conducted a four-week study of 39 patients with autistic disorder between 5 to 19 years of age who were randomized to receive amantadine 5 mg/kg/day or placebo. Primary outcome measures were the percentage of ABC responders (defined as a 25% or greater reduction in irritability and/or hyperactivity subscale scores at endpoint) and percentage of CGI-I responders (defined as a CGI-I score of 2 or less at endpoint). Of patients who received amantadine, 47% were ABC responders and 53% were CGI-I responders respectively, compared to patients who received placebo with 37% ABC responders and 25% CGI-I responders respectively (King et al., 2001). Differences between groups were not statistically significant (King et al., 2001).

Remington and colleagues (Remington, Sloman, Konstantareas, Parker, & Gow, 2001) conducted a seven-week study of 36 patients with autistic disorder between 10 to 36 years of age who were randomized to receive flexible doses of clomipramine 100-150 mg/day, haloperidol 1-1.5 mg/day or placebo. The primary outcome measure was change in CARS score. Patients who received clomipramine had a change in CARS score of -5.1, patients receiving haloperidol had a change in CARS score of -4.0, and patients receiving placebo had a change in CARS score of -2.4 (Remington et al., 2001). The secondary outcome measure was change in ABC-I score. Patients receiving haloperidol had a mean decrease of -7.0 in the ABC-I scale (a statistically significant reduction compared to baseline) compared to patients receiving clomipramine who had a mean decrease of -3.0 and patients receiving placebo who had a mean decrease of -2.0 (Remington et al., 2001).

Belsito and colleagues (Belsito, Law, Kirk, Landa, & Zimmerman, 2001) conducted a 12-week trial of 28 patients with autistic disorder between 3 to 11 years of age who were randomized to receive lamotrigine 5 mg/kg/day (titrated up over an eight-week period, followed by a four-week maintenance period) or placebo. A primary outcome measure was not specified. However, no significant differences were observed on any outcome measure between patients who received lamotrigine and patients who received placebo at the end of the four-week maintenance phase (Belsito et al., 2001).

Wasserman and colleagues (Wasserman et al., 2006) conducted a ten-week trial of 20 patients with autistic disorder between 5 to 17 years of age who were randomized to receive levetiracetam (at a flexible dose of 20-30 mg/kg/day) or placebo. The co-primary outcome measures were change on the CGI-I and the complete ABC score. Patients who received levetiracetam (mean maximum dosage: 862.5 ±279.19 mg/day) did not show statistically significant differences compared to patients who received placebo on either the CGI-I or ABC score (Wasserman et al., 2006). Secondary outcome measures included the CY-BOCS and the Conners' Rating Scale-Revised: Long Version (parent and teacher) that also did not show statistically significant differences compared to placebo (Wasserman et al., 2006).

Amminger and colleagues (Amminger et al., 2007) conducted a six-week trial of 13 patients with autistic disorder between 5 to 17 years of age who were randomized to receive a combination OFA supplement (containing 840 mg of eicosapentaenoic acid and 700 mg of docosahexaenoic acid) once daily or placebo. The authors theorized that fatty acid deficiencies may contribute to or exacerbate neurodevelopmental disorders such as autism. Seizure control with anticonvulsant medication was allowed during this trial. Patients who received OFA had a non-significant reduction of ABC-I scores (-4.7) compared to patients who received placebo (-4.6). Non-significant differences in the other four ABC subscale measures were observed (Amminger et al., 2007).

Hollander and colleagues (Hollander et al., 2010) conducted a 12-week trial of 27 patients with autistic spectrum disorders between 4.8 to 14.9 years of age who were randomized to receive divalproex at a weight-based dose titrated to achieve clinical response and a serum valproate level above 350 μmol/L (the customary lower limit of the valproate therapeutic range). The primary outcome measure was change in ABC-I score. Patients who received divalproex had a statistically significant reduction in ABC-I scores (-7.5) compared to patients who received placebo (-4.6) (Hollander et al., 2010). The percentage of patients who were considered responders (CGI-I scores of $\leq$2) was 63% for patients who received divalproex, compared to 9% for patients who received placebo (Hollander et al., 2010). No statistically significant differences between groups were observed for scores on the cY-BOCS or the Overt

Aggression Scale-Modified Irritability subscale (Hollander et al., 2010).

Geier and colleagues (Geier et al., 2011) conducted a three-month trial of 30 patients with autism spectrum disorders between 3 to 10 years of age who were randomized to receive either levocarnitine (50 mg/kg/day) or placebo. Outcome measures included changes in CARS score, modified CGI-I score (a 3-point scale encompassing ratings of improved, same, worse) and the parent-rated Autism Treatment Evaluation Checklist (ATEC) score. Patients who received levocarnitine had a statistically significant change in CARS score (-1.94) compared to patients who received placebo (+0.09) (Geier et al., 2011). A statistically significant reduction in modified CGI-I score was observed with levocarnitine treatment compared to placebo, while a non-statistically significant reduction in ATEC score was observed with levocarnitine compared to placebo (Geier et al., 2011).

Akhondzadeh and colleagues (Akhondzadeh et al., 2004) conducted an eight-week study of 40 patients with autistic disorder between 3 to 11 years of age. Patients were randomized to receive adjunctive cyproheptadine (0.2 mg/kg/day) or placebo in addition to haloperidol (0.05 mg/kg/day). The primary outcome measure was change in the complete ABC scale. Patients receiving adjunctive cyproheptadine had a statistically significant mean decrease in ABC score of -10.9 compared to a mean decrease of -3.7 in patients receiving placebo (Akhondzadeh et al., 2004).

Akhondzadeh and colleagues (Akhondzadeh et al., 2010) conducted a ten-week study of 40 patients with autistic disorder between 4 to 12 years of age. Patients were randomized to receive adjunctive pentoxifylline (400-600 mg/day) or placebo in addition to risperidone (2-3 mg/day) treatment. Pentoxifylline had previously been marketed as a blood viscosity reducing agent (Lexi-Comp Online, 2012) for treatment of intermittent claudication and has previously been tested for autism in open-label trials due to its possible effects on the immune system (Gupta, Rimland, & Shilling, 1996). The primary outcome measure was change in ABC-I score. Patients who received pentoxifylline had a statistically significant mean decrease in ABC-I score (-9.53) compared to patients who received placebo (-4.1) (Akhondzadeh et al., 2010).

Rezaei and colleagues (Rezaei et al., 2010) conducted an eight-week study of 40 patients with autistic disorder between 4 to 12 years of age randomized to receive adjunctive topiramate (100-200 mg/day) or placebo in addition to risperidone treatment (2-3 mg/day). The outcome measures reported were change in each of the five ABC subscales. Patients who received adjunctive topiramate had a statistically significant mean decrease in ABC-I score of -9.25 compared to a mean decrease in ABC-I score of -1.5 in patients who received placebo (Rezaei et al., 2010). Statistically significant differences were also seen for the topiramate group compared to the placebo group for the stereotypic behaviour and hyperactivity/noncompliance subscales, but not for the lethargy/social withdrawal and inappropriate speech subscales (Rezaei et al., 2010).

Hasanzadeh and colleagues (Hasanzadeh et al., 2012) conducted a ten-week study of 47 patients with autistic disorder between 4 to 12 years of age randomized to receive adjunctive gingko biloba (80-120 mg/day) or placebo in addition to risperidone treatment (2-3 mg/day). It was theorized by the researchers that the antioxidant properties of gingko biloba may be helpful for treatment of autism. Patients who received adjunctive gingko biloba had a non-significant mean decrease in ABC-I score of -4.41 compared to a mean decrease in ABC-I of -4.2 for patients who received placebo (Hasanzadeh et al., 2012). Non-significant differences in the other four ABC subscale scores were reported (Hasanzadeh et al., 2012).

Safety Data

In the risperidone RCTs, sedation and somnolence were the most commonly reported adverse events, though these appeared to occur more commonly during the early portion of trials (especially during the dose titration phase) and diminish over time. In the study by Shea and colleagues (Shea et al., 2004) somnolence was reduced by the administration of risperidone in the evening, by dividing the dosage to be given twice daily instead of once daily or by risperidone dose reduction. Other common adverse events in patients receiving risperidone in all studies included upper respiratory tract infection (URTI), increased appetite, hypersalivation, nasal congestion (rhinitis), and constipation. Tachycardia and tremor were also observed at an incidence greater than in the placebo group in several studies. Nagaraj and colleagues (Nagaraj et al., 2006) reported three incidents of dyskinesia (two orolingual, one involving the lower extremity) with risperidone treatment. Systematic monitoring of prolactin levels was not performed in any of the risperidone RCTs.

In the aripiprazole RCTs, commonly reported adverse events included sedation, somnolence, fatigue, hypersalivation, vomiting, diarrhea, increased appetite and fever. In the study comparing three fixed dosage levels of aripiprazole, statistical analysis of adverse events was not performed, though numerically there was little difference between groups, with the exception of fatigue (5 mg/day: 3.8%, 10 mg/day: 22%, 15 mg/day: 18.5%) (Marcus et al., 2009). Extrapyramidal symptoms (EPS) including tremor were reported at rates greater than placebo in both trials. Owen and colleagues (Owen et al., 2009) reported a significant decrease in serum prolactin levels from baseline for patients receiving aripiprazole (-6.3 ng/mL) compared to patients receiving placebo (+1.6 ng/mL). Marcus and colleagues (Marcus et al., 2009) also showed decreases in serum prolactin levels from baseline in patients receiving aripiprazole

(5 mg/day: -5.4 ng/mL, 10mg/day: -5.2 ng/mL, 15 mg/day: -5.8 ng/mL) compared to placebo (+0.9 ng/mL).

In the olanzapine RCT (Hollander et al., 2006) no patients reported dyskinesias or EPS. Common adverse events were sedation and weight gain. Rhinitis, "glazed eyes", constipation and insomnia were also reported.

In patients who received haloperidol, the most commonly reported adverse events were constipation, blunted affect, rigidity, difficulty sleeping, increased appetite and URTI. Adverse events of dystonia, depression and fatigue were also reported (Miral et al., 2008). Miral and colleagues reported a significant change from baseline to endpoint in prolactin levels in the patients receiving haloperidol, however this was stated to not be as large as the change in prolactin levels for risperidone-treated patients though actual prolactin values were not reported (Miral et al., 2008).

In the clomipramine RCT (Remington et al., 2001) the adverse events reported in patients who had received clomipramine were fatigue, tachycardia, tremors, insomnia, nausea and vomiting, decreased appetite and diaphoresis.

In the clonidine RCT (Jaselskis et al., 1992) significant hypotension was reported in three out of eight patients during clonidine treatment, in addition to drowsiness and irritability at unspecified incidences.

In the methylphenidate RCT (Quintana et al., 1995) adverse effects of decreased appetite, irritability, insomnia, stomachache and headache were reported at unspecified incidences.

In the amantadine RCT (King et al., 2001) patients who received amantadine reported adverse effects of insomnia and somnolence more often than in patients who received placebo.

In the lamotrigine RCT (Belsito et al., 2001) insomnia and hyperactivity were commonly reported adverse events, though there were no significant differences between groups. None of the children enrolled in the trial were withdrawn due to skin rash (a potentially serious adverse effect of lamotrigine treatment).

In the levetiracetam RCT (Wasserman et al., 2006), patients who received levetiracetam experienced increased irritability (two of ten patients had increased aggression and one of ten patients each became agitated, hyperactive, impulsive, and self-injurious) compared to patients who received placebo that became less irritable during the trial.

In the RCT involving OFA (Amminger et al., 2007) patients who received OFA treatment reported the adverse effect of fever at an unspecified incidence.

In the valproate RCT (Hollander et al., 2010) patients who received valproate treatment reported adverse effects of rash, polyuria, headache and severe agitation more often than in patients who received placebo.

In the levocarnitine trial (Geier et al., 2011) levocarnitine was generally well tolerated with adverse effects of irritability and stomach discomfort occurring at unspecified incidences for patients who received levocarnitine (Geier et al., 2011).

The RCT of adjunctive cyproheptadine (Akhondzadeh et al., 2004) reported adverse events of increased appetite and constipation in patients who had received cyproheptadine. There was no statistically significant increase in frequency of adverse events above placebo. EPS occurred in patients receiving cyproheptadine, though specific symptoms were not reported (Akhondzadeh et al., 2004). The observed EPS are attributable to the concomitant haloperidol treatment all patients received. Prophylactic treatment for EPS with the anticholinergic drug biperiden (0.04 mg/kg/day) was given to all patients in the study (Akhondzadeh et al., 2004). There was no significant difference in the rate of adverse events observed between the two groups (Akhondzadeh et al., 2004).

In the RCT of adjunctive pentoxifylline (Akhondzadeh et al., 2010) common adverse events reported in patients who received pentoxifylline were constipation, daytime drowsiness, increased appetite and flatulence (reported as "gassing"). There was no statistically significant increase in frequency of adverse events above placebo, including EPS (Akhondzadeh et al., 2010).

In the RCT of adjunctive topiramate (Rezaei et al., 2010) the reported adverse events included somnolence, decreased appetite, paresthesia, dizziness, insomnia and nausea. There was a notably lower incidence of increased appetite in the patients who received topiramate (20% below placebo) (Rezaei et al., 2010). EPS occurred in patients who received adjunctive topiramate, however specific symptoms were not reported. The observed EPS are attributable to the concomitant risperidone all patients received. There was no significant difference in the rate of adverse events observed between the two groups (Rezaei et al., 2010).

In the gingko biloba RCT (Hasanzadeh et al., 2012) patients who received ginkgo biloba treatment reported adverse effects of nervousness, fatigue and morning drowsiness more often than in patients who received placebo.

Changes in Body Weight/Metabolic Parameters

In the risperidone RCTs, mean weight increase of approximately 1-2 kg over the placebo groups were consistently observed at study endpoints (RUPPAN, 2002; Shea et al., 2004; Nagaraj et al., 2006; Luby et al., 2006; Pandina et al., 2007). Reported weight increases for the risperidone treated patients were statistically significant compared to placebo in all trials. In the four-month RUPPAN open-label risperidone follow-up study, a mean weight gain of 5.1 kg

was observed (RUPPAN, 2005). Hellings and colleagues (Hellings et al., 2006) reported a weight gain of greater than 3 kg in 70% of risperidone-treated patients. Other details regarding body weight and metabolic parameters were not reported in any of the risperidone RCTs.

In the two RCTs conducted with aripiprazole, mean weight increase of approximately 1.2 kg over the placebo groups were observed (Marcus et al., 2009; Owen et al., 2009). However, 7-24% of aripiprazole patients (depending on treatment dosage assignment) experienced weight gain of ≥7% in these studies. Mean body mass index (BMI) change was reported in both aripiprazole trials. There was a mean increase in BMI of approximately 0.6 kg/m^2 above placebo at endpoint in the aripiprazole RCTs (Marcus et al., 2009; Owen et al., 2009).

In the olanzapine RCT, 66% of patients who received olanzapine had a weight increase of ≥7%, compared to 20% of patients who received placebo (Hollander et al., 2006). In the risperidone/haloperidol head-to-head trial, weight gain with haloperidol at trial endpoint was a mean 4.6 ±0.1 kg, compared to the weight gain observed with risperidone (4.3 ±0.7 kg), a statistically non-significant difference (Miral et al., 2008).

For the RCTs involving miscellaneous agents, the majority did not report changes in weight or metabolic parameters. In the levetiracetam RCT, detailed weight and metabolic parameters were not reported, but two of ten patients in the levetiracetam group reported weight change (one report each of weight loss and weight gain) (Wasserman et al., 2006). There were no reports of weight change in the placebo group (Wasserman et al., 2006). In the valproate RCT (Hollander et al., 2010) weight gain with valproate at trial endpoint was a mean of 1.37 ±2.91 kg, compared to weight gain in patients who received placebo of 1.34 ±1.53 kg. One patient who received valproate experienced weight gain ≥7% (Hollander et al., 2010). In the adjunctive topiramate RCT (Rezaei et al., 2010) there was no significant difference in weight change between the groups who received risperidone plus topiramate (+0.65 kg) compared to those who received risperidone alone (+1.6 kg) (Rezaei et al., 2010).

Discussion

Currently, no medications have Health Canada approval for treatment of irritability of autism, while risperidone and aripiprazole have been FDA approved for the treatment of irritability of autism since 2006 and 2009 respectively. A large portion of the RCT literature for treatment of irritability of autism involves risperidone, which may in part reflect its earlier marketing availability date compared to other agents.

Six of the seven risperidone RCTs had a positive result on the primary outcome measure(s). Patients who received risperidone in the RUPPAN study showed the greatest response rates and reduction in symptoms of all available risperidone RCTs (RUPPAN 2002). Baseline ABC-I scores of 25-26 in the RUPPAN study (RUPPAN, 2002) indicated a higher symptom severity in this trial compared to other risperidone RCTs which used ABC-I as a primary outcome measure, (Shea et al., 2004; Hellings et al., 2006; Pandina et al., 2007) most of which had baseline ABC-I scores in the 18-21 range. In clinical trials, higher symptom severity at baseline affords greater opportunity for improvement with treatment, and this phenomenon may have led to the higher response rate and large effect size observed in the RUPPAN study.

Both aripiprazole RCTs were positive for the stated primary outcome measures, and demonstrated mean reductions in ABC-I scores comparable to those observed in the risperidone RCTs. Baseline ABC-I scores in these trials were in the 28-30 range (Marcus et al., 2009; Owen et al., 2009).

No trials involving a direct head-to-head comparison of risperidone and aripiprazole were identified. The risperidone RCT by RUPPAN (RUPPAN, 2002) and the flexible dose aripiprazole RCT by Owen and colleagues (Owen et al., 2009) compared most favorably in terms of methodology (Erickson, Stigler, Posey, & McDougle, 2010). Effect sizes in both the risperidone (effect size $d=1.2$) and aripiprazole (effect size $d=0.87$) trials are considered to be large (RUPPAN, 2002; Owen et al., 2009). While both drugs are FDA approved for treatment of irritability of autism, from the point of view of efficacy, the larger effect size in favour of risperidone in this comparison combined with a greater number of published positive risperidone RCTs indicates risperidone remains the first-line pharmacological treatment for irritability of autism.

Several intriguing options as alternative (clonidine, methylphenidate, valproate and levocarnitine) or adjunctive treatment (cyproheptadine, pentoxifylline and topiramate) to antipsychotics have data from a single positive RCT to support their efficacy. However, the number of patients enrolled in each of these trials was small, and the reduction in primary outcome measure(s) are modest compared to approved treatments. These treatments are all currently available in Canada, and may be considered for use on an off-label basis when FDA approved medications are not effective in reducing symptoms, or cause intolerable adverse effects.

Generally, treatment with antipsychotic agents in these RCTs was well tolerated with low rates of EPS and serious adverse effects. Adverse metabolic effects of second- and third-generation antipsychotics in children and adolescents have become increasingly evident in recent years (Correll et al., 2009; Panagiotopoulos, Ronsley, Elbe, Davidson, & Smith, 2010). As many clinicians have observed, there is evidence that autistic children and adolescents may be even more prone to weight gain with antipsychotic treatment

than patients with general psychiatric conditions (De Hert, Dobbelaere, Sheridan, Cohen, & Correll, 2011). This may occur because these individuals often have less autonomy and ability to take control of appetite, food intake and exercise levels to prevent weight gain (Hellings et al., 2006).

Metabolic data other than weight gain was not reported from any of the available risperidone RCTs. This may be due to the era in which these studies were conducted, since the severity of the metabolic adverse effects in children and adolescents from antipsychotic treatment have only recently become well documented (Correll et al., 2009; Panagiotopoulos et al., 2010; DeHert et al., 2011). By contrast, weight and metabolic parameter reporting are more robust in the more recently conducted aripiprazole trials, though this may be somewhat expected with a treatment purported to cause less weight gain and fewer adverse metabolic effects than other antipsychotic agents. For patients at high risk of metabolic adverse effects from second-generation antipsychotics, or when significant weight gain/metabolic abnormalities have developed during risperidone treatment, aripiprazole may be a reasonable alternative. Trials of aripiprazole longer than eight weeks duration that demonstrate minimal effects on weight over the long term and an ongoing lack of metabolic abnormalities would be helpful. The approximate four-fold differential in cost in Canada between comparable doses of generically available risperidone and the still-patented aripiprazole, and provincial/territorial formulary/coverage must also be factored into the prescribing decision.

When a decision to start an antipsychotic medication for treatment of irritability of autism is made, appropriate baseline and periodic monitoring of height, weight, waist and hip circumference, blood pressure, and metabolic parameters (fasting glucose and lipids) should be carried out (Panagiotopoulos et al., 2010). It should be recognized that for many children the venipuncture and blood collection process may be traumatic, but for some children with autism spectrum disorder, attempts at blood collection can lead to severe behavioural outbursts and intervention may be required to complete appropriate monitoring (Davit, Hundley, Bacic, & Hanson, 2011).

Acknowledgements / Conflicts of Interest

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