Efficacy and Tolerability of Antipsychotics in Youth with Severe Psychiatric Disorders

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Disclosures: Christoph U. Correll

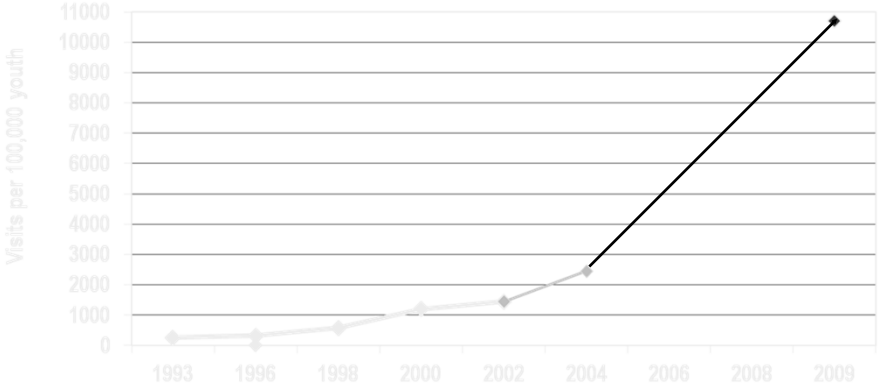
I have an interest in relation with one or more organizations that could be perceived as a possible conflict of interest in the context of this presentation. The relationships are summarized below:

Interest	Name of organization
Grants	Bendheim Foundation, Janssen, National Institute of Mental Health (NIMH), Patient-Centered Outcomes Research Institute, Takeda, Thrasher Foundation
Shares	No share holdings in pharmaceutical companies
Paid positions, honoraria and advisory boards	Alkermes, Angelini, Bristol-Myers Squibb, Forum, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Neurocrine, Otsuka, Pfizer, ProPhase, ROVI, Sunovion, Supernus, Takeda, and Teva

Overview

- Early Onset Schizophrenia
- Autistic Disorder
- Disruptive Behavior Disorders
- Tourette's Disorder
- Adverse Effects
- Adverse Effect Management
- Conclusions

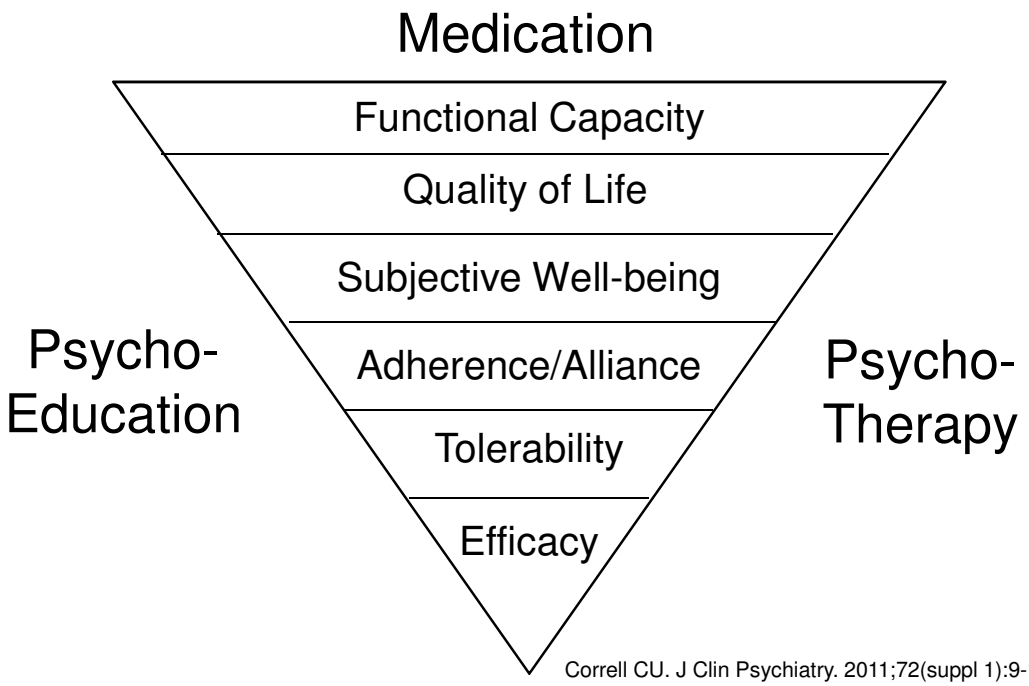
Atypical Antipsychotic Use Increasing Dramatically in Youth



1993-2002: Olfson M et al. Arch Gen Psychiatry. 2006 Jun;63:679-85;
2003-2004 Aparasu R & Bhatara V. Curr Med Res Opin. 2007 Jan;23(1):49-56;
1993-2009 Olfson M et al. Arch Gen Psychiatry. 2012 Dec;69(12):1247-56

- 2002: ~10% of mental health visits involved SGA treatment
- 2005-2009: 31% of psychiatrists visits involved antipsychotic treatment
- 2005-2009: DBDs most common diagnoses in child 63% and adolescent (34%) visits

The Effectiveness Pyramid



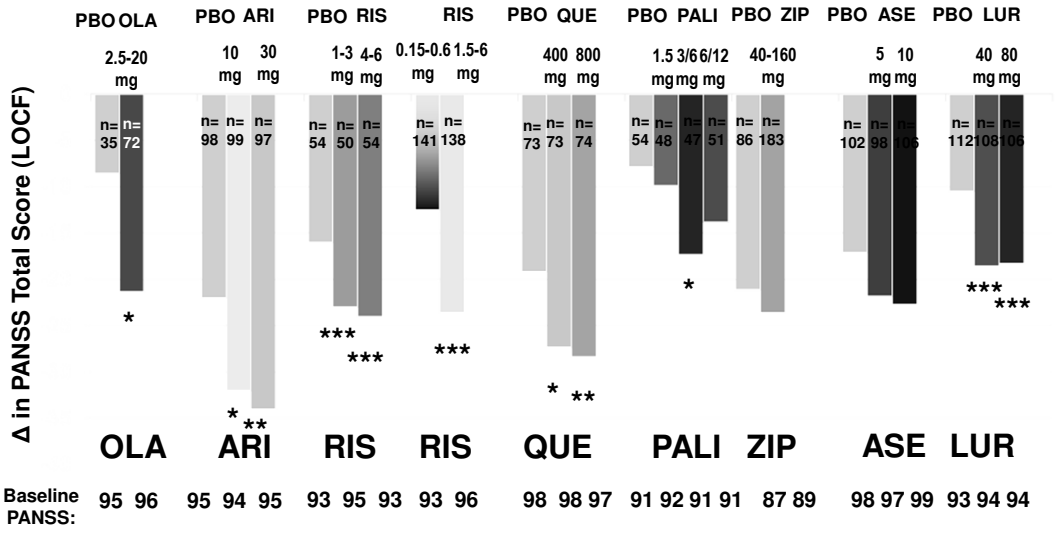
Correll CU. J Clin Psychiatry. 2011;72(suppl 1):9-13.

Non-Pharmacologic Management

- Psycho-education
- Stress management
- Sleep hygiene
- Diet: caffeine, alcohol, illicit drugs
- Support groups
- Psychotherapy
- School / vocational interventions (engage teacher/counselors)
- CBT for compliance (link to desired outcome, routine) and symptoms
- Symptom and adverse effect charting

Early Onset Schizophrenia

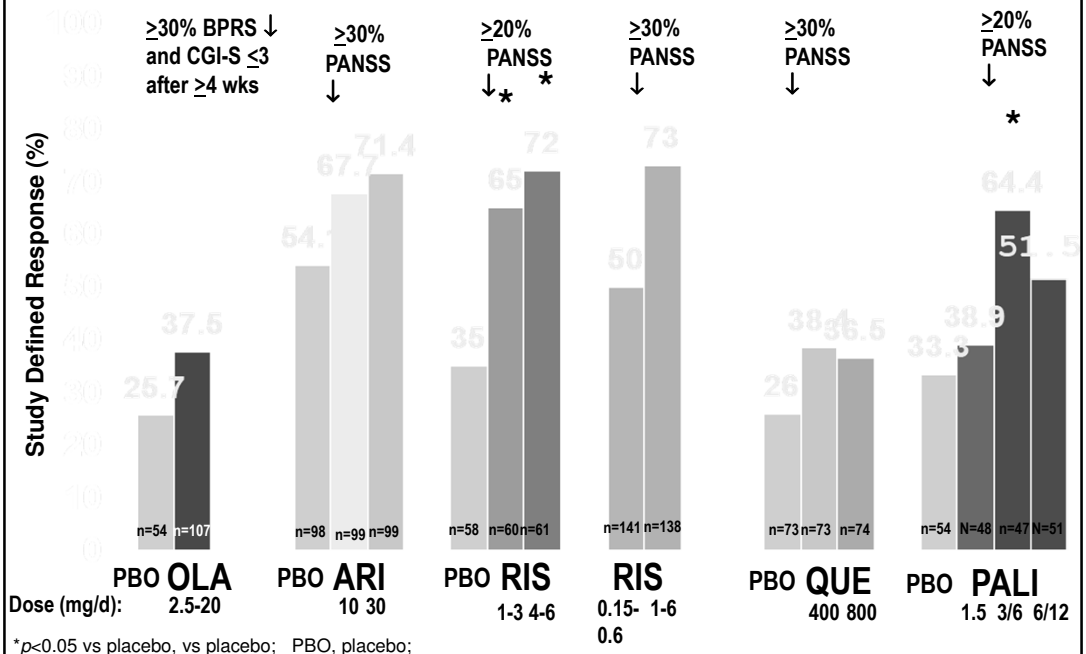
Mean Improvement in PANSS Total Score from 9 6-Wk RCTs in Pediatric Schizophrenia (13-17 Yrs)



*p<0.05 vs placebo, **p<0.01 vs placebo, ***p<0.001 vs placebo;
PBO, placebo; OLA, olanzapine; ARI, aripiprazole; RIS, risperidone; QUE, quetiapine; PALI, paliperidone; ZIP, ziprasidone; ASE, asenapine; LUR, lurasidone

Adapted from: Correll CU et al. J Clin Psychiatry. 2011 May;72(5):655-670.

Study Defined "Response" Rates in Pediatric SCZ: NNTs 3-10

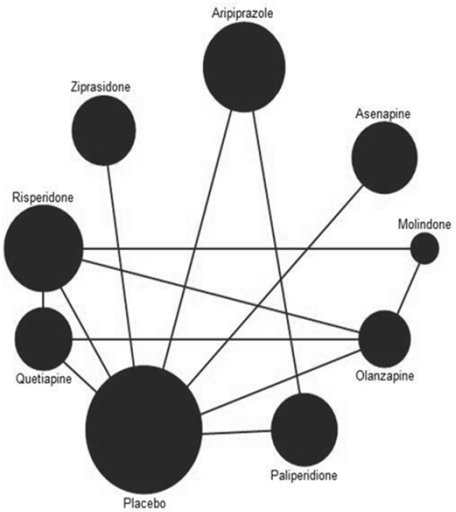


*p<0.05 vs placebo, vs placebo; PBO, placebo;
OLA, olanzapine; ARI, aripiprazole; RIS, risperidone; QUE, quetiapine; PALI, paliperidone

Adapted from Correll CU et al. J Clin Psychiatry. 2011 May;72(5):655-670.

Network Metaanalysis of Non-Clozapine Antipsychotics in Early-Onset Schizophrenia (N=12, n=2157)

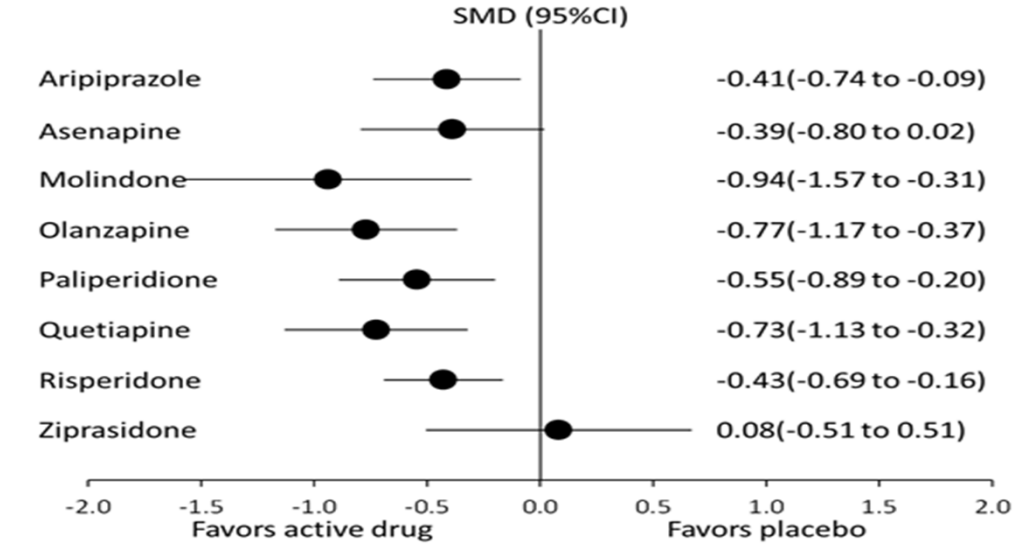
- Random-effects, arm-based network meta-analysis.
- Pairwise meta-analysis was conducted to assess consistency with network meta-analysis.
- The main outcomes were Positive and Negative Syndrome Scale total and positive symptoms; weight; plasma-triglyceride; extra-pyramidal symptoms; akathisia; and all-cause discontinuation.
- Sixteen additional outcomes were also analyzed.



Trial duration=6-12 weeks, age=8-19 years; males=61%

Pagsberg AK et al J Am Acad Child Adolesc Psychiatry. 2017 Mar;56(3):191-202.

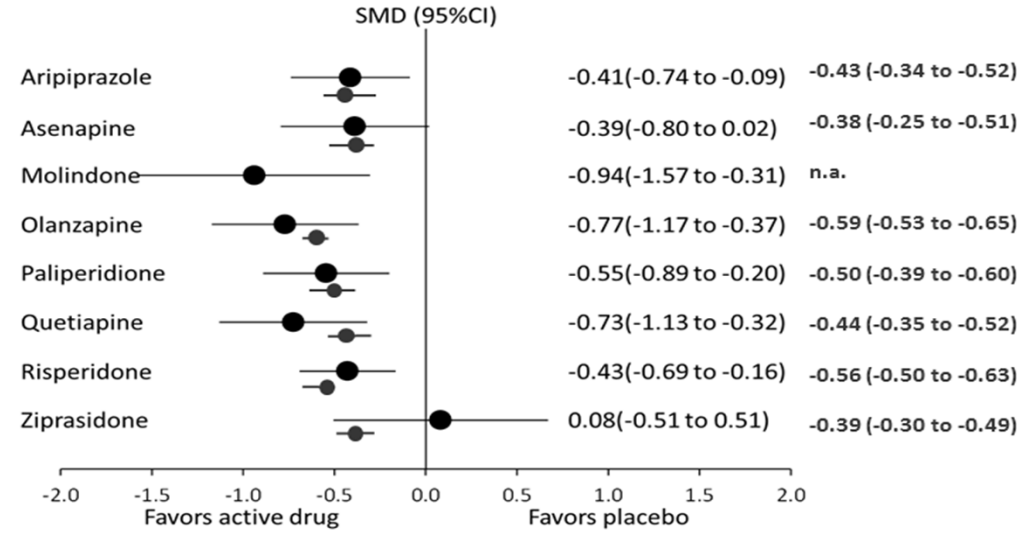
Network Metaanalysis: PANSS Total Score Reduction with 8 Antipsychotics vs. Placebo



Trial duration=6-12 weeks, age=8-19 years; males=61%

Pagsberg AK et al J Am Acad Child Adolesc Psychiatry. 2017 Mar;56(3):191-202.

Network Metaanalysis: PANSS Total Score Reduction with 8 Antipsychotics vs. Placebo and vs Adult Data (Leucht et al, Lancet 2013)



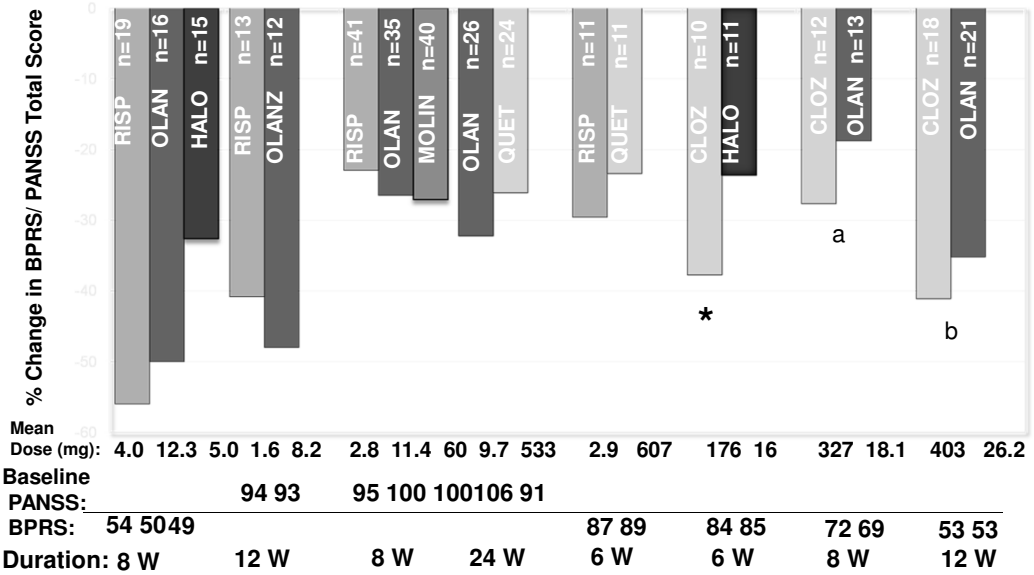
Pagsberg AK et al J Am Acad Child Adolesc Psychiatry. 2017 Mar;56(3):191-202.

Results of the MTA in EOS

- Total and positive symptom changes were comparable among antipsychotics, except ziprasidone (inferior to molindone, olanzapine, paliperidone and risperidone).
- All antipsychotics were superior to placebo regarding total symptoms, except ziprasidone and asenapine.
- Olanzapine was superior to aripiprazole, asenapine, paliperidone, quetiapine, risperidone and ziprasidone on Clinical Global Impression-Severity, and to quetiapine on Clinical Global Impression-Improvement.
- There were no efficacy differences among antipsychotics regarding response rates, depressive symptoms, or global/social functioning.
- Weight gain was primarily associated with olanzapine, extra-pyramidal symptoms and akathisia with molindone, and prolactin increase with risperidone and paliperidone.

Pagsberg AK et al J Am Acad Child Adolesc Psychiatry. 2017 Mar;56(3):191-202.

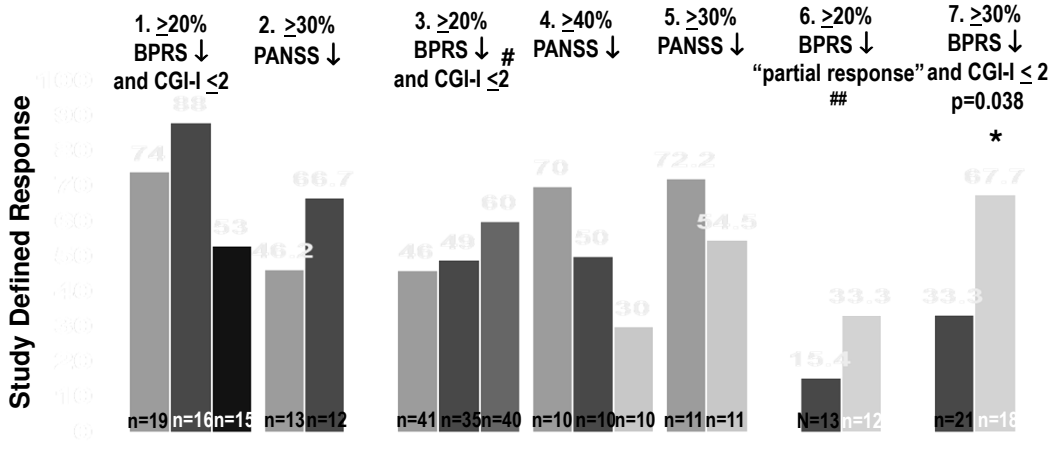
No Antipsychotic Efficacy Differences in Pediatric Schizophrenia, Except CLO



a=significant advantage of CLO vs OLA for negative sxs; b=significant advantage for CLO vs OLA for response

Schimmelmann B, Schmidt SJ, Carbon M, Correll CU. Curr Opin Psychiatry. 2013;26(2):219-30.

No Antipsychotic Response Differences, Except CLO

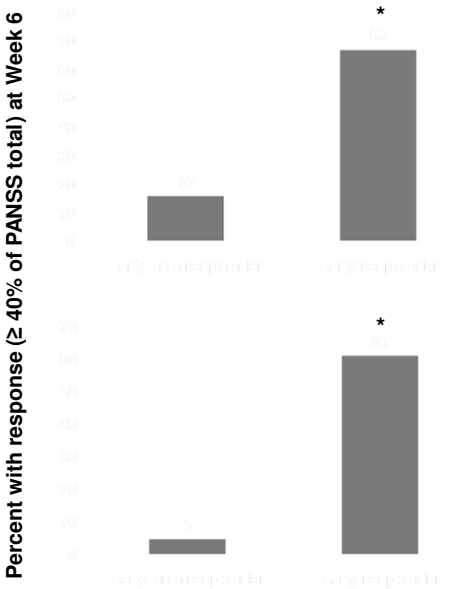


#"Strict" response: ≥20% BPRS ↓ and CGI-S < 3 PLUS persistence until week 8: Mol: 50%, RIS: 46%, OLA: 34%
##"Full" response: ≥20% BPRS ↓ and CGI-S < 3 or BPRS ≤35: OLA: 7.7%, CLO: 0%

1. Sikich et al. Neuropsychopharmacol 2004; 2. Mozes et al. JCAP 2005; 3. Sikich et al. AJP 2008; 4. Jensen et al. JCAP 2008; 5.Swadi et al. Int Clin Psychopharmacol 2010; 6. Kumra S et al. Biol Psychiatry 2008; 7. Shaw P et al. Arch Gen Psychiatry 2006

Correll CU et al – in Preparation

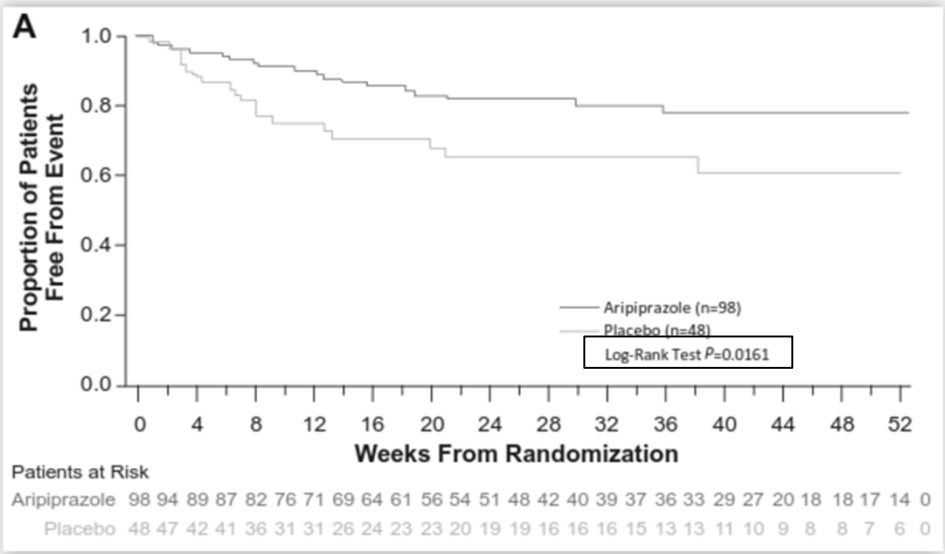
Early response at Week 2 and 3 predictive of Week 6 response



- **Early response at Week 2 predicts response at Week 6**
  - **Odds ratio = 10.8**
  - ***p<0.0001**
  - **Aripiprazole arms combined**
- **Week 3 response more predictive of 6-week outcome**
  - **Odds ratio = 30.3**
  - ***p<0.0001**
  - **Aripiprazole arms combined**

Correll CU et al. J Am Acad Child Adolesc Psychiatry. 2013 Jul;52(7):689-698.

52-week ARI vs PBO for Relapse Prevention
Time to Impending Relapse



Age: 15.4 (13-17) years, 65% male with schizophrenia, PANMSS-total: 64, CGI-S=3.1

Correll CU et al. J Am Acad Child Adolesc Psychiatry. 2017 Sep;56(9):784-792.

52-week ARI vs PBO for Relapse Prevention
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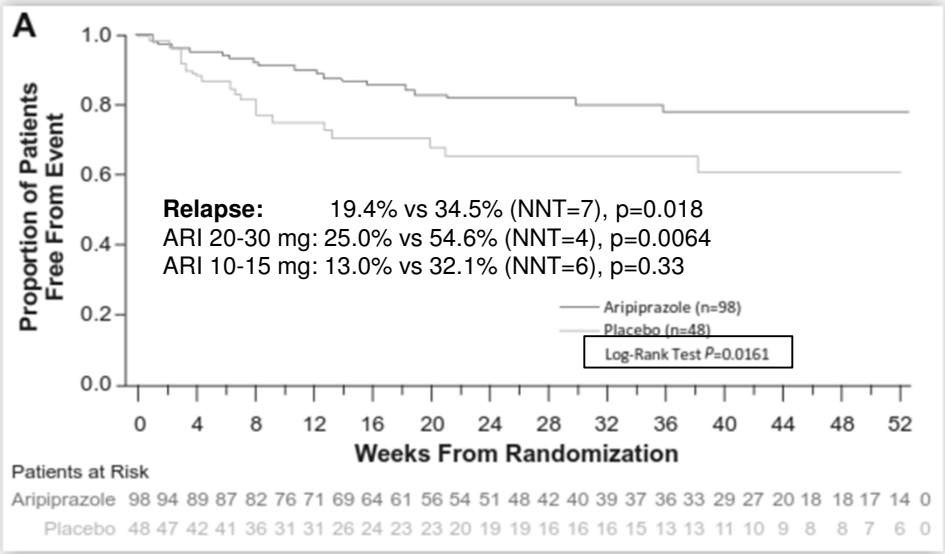

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Correll CU et al. J Am Acad Child Adolesc Psychiatry. 2017 Sep;56(9):784-792.

Autistic Disorder

Subtypes of Aggression

Predatory

Goal-oriented, planned, controlled

- Hides aggressive acts
- Can control own behavior when aggressive
- Very careful to protect self when aggressive
- Tries to benefit from being aggressive
- Plans aggressive acts
- Is proud of being aggressive
- Steals

Impulsive/Affective

Reactive, unplanned, and uncontrolled

- Nonprofitable damaging of own property
- Aggressive in front of people
- Loss of control in front of people
- Exposes self to physical harm
- Fights with stronger children
- Aggressive without purpose
- Aggression is unplanned
- May express remorse after aggression

Vitiello B et al. *J Neuropsychiatry.* 1990;2:189-192.

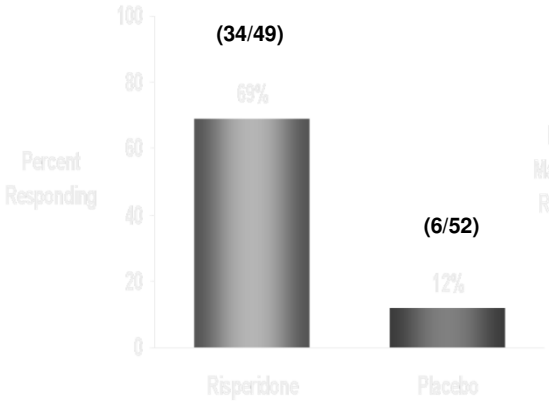
Pharmacologic Treatment of Autism Spectrum Disorder: Level of the Evidence for Specific Targets

Class	Agent	Primary target symptom(s)	Level of evidence
Alpha 2 Agonist	Clonidine	Hyperactivity	Insufficient evidence
	Guanfacine	Hyperactivity	Insufficient evidence
Antipsychotics	Aripiprazole	Irritability, hyperactivity, stereotypy	Established evidence
	Haloperidol	Behavioral symptoms	Established evidence
	Risperidone	Irritability, hyperactivity	Established evidence
	Risperidone	Repetitive behavior, stereotypy	Preliminary evidence
	Olanzapine	Global functioning	Insufficient evidence
Mood Stabilizers	Divalproex sodium/ valproic acid	Irritability	Insufficient evidence (conflicting results)
	Divalproex sodium/ valproic acid	Repetitive behavior	Insufficient evidence
	Lamotrigine	Irritability, social behavior	Insufficient evidence
	Levitiracetam	Irritability	Insufficient evidence
Norepinephrine reuptake inhibitor	Atomoxetine HCI	Hyperactivity	Preliminary evidence
Serotonin reuptake inhibitor	Citalopram	Repetitive behavior	Insufficient evidence
	Fluoxetine	Repetitive behavior	Insufficient evidence
	Clomipramine	Repetitive behavior, stereotypy, irritability, hyperactivity	Insufficient evidence
Stimulants	Methylphenidate	Hyperactivity	Promising evidence
Miscellaneous	Amantadine	Hyperactivity, irritability	Insufficient evidence
	Naltrexone	Social behavior, communication, indiscriminant learning, SIB	Insufficient evidence
	Naltrexone	Hyperactivity	Preliminary evidence
	Pentoxifylline	Irritability, social withdrawal	Preliminary evidence

Siegel M & Beaulieu AA. J Autism Dev Disord 2012;42:1592-1605.

RUPP Trial: Risperidone in Autism

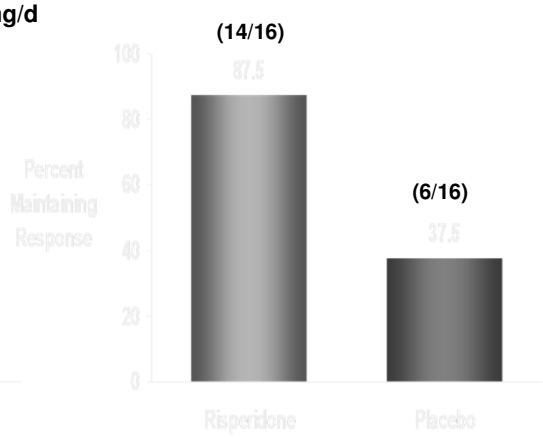
8-Week Acute Trial: n=101
Mean age: 8.8 yrs, mean dose: 1.8 mg/d



Response criteria: ≥25% improvement in the ABC Irritability score, and a rating of "much improved" or very much improved" on the CGI-I

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

8-Week Relapse Prevention Trial: n=32

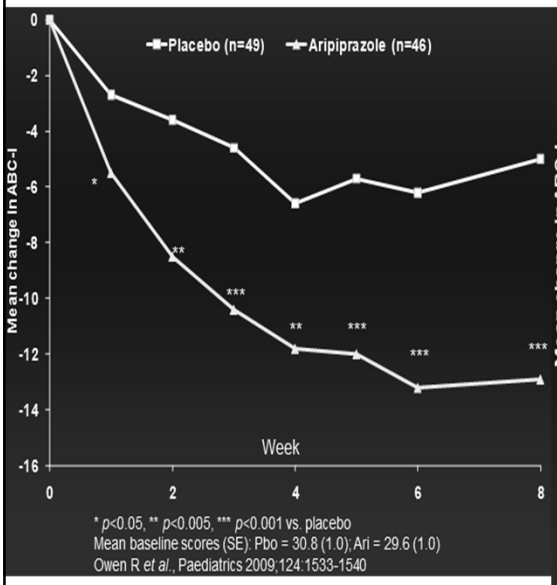


Maintenance of response criteria

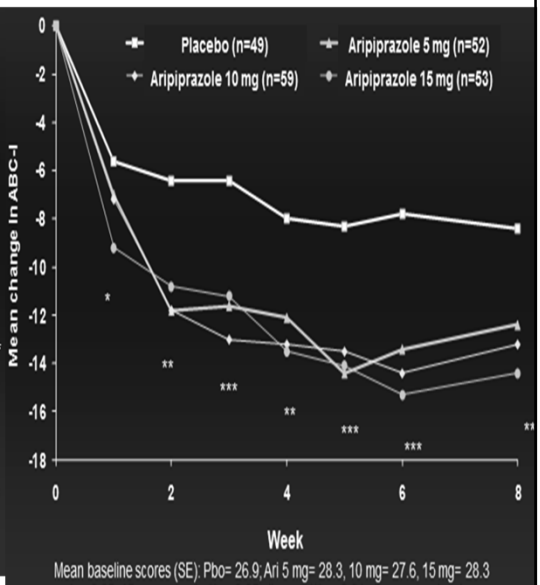
Median time to relapse 34 days on PBO vs 52 days on risperidone

RUPP Autism Network. *Am J Psychiatry.* 2005;162:1361-69

Aripiprazole in autistic disorder: mean change in the aberrant behaviour checklist - irritability subscale by week

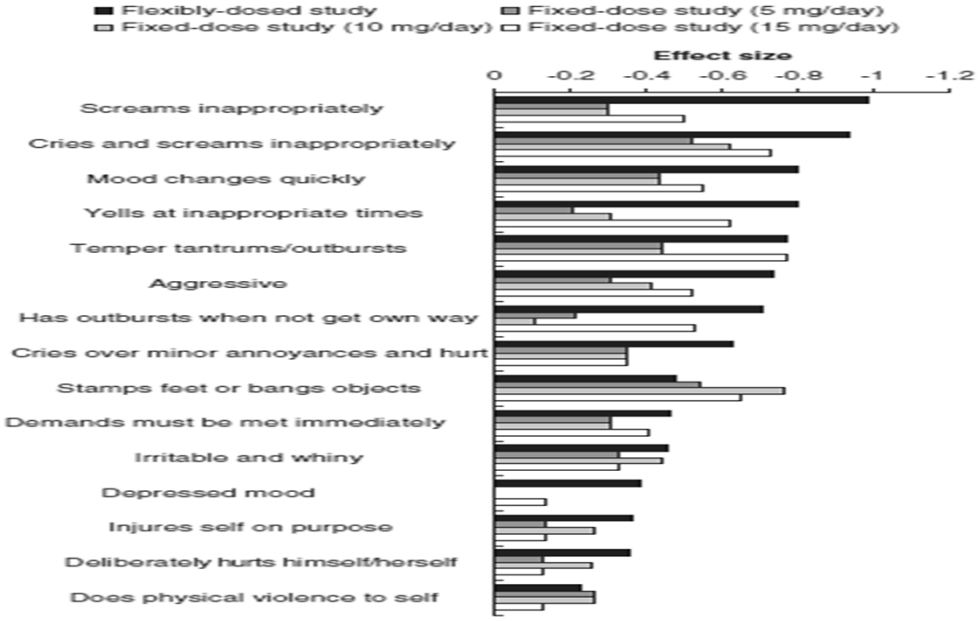


* $p<0.05$, ** $p<0.005$, *** $p<0.001$ vs. placebo
Mean baseline scores (SE): Pbo = 30.8 (1.0); Ari = 29.6 (1.0)
Owen R *et al*., Paediatrics 2009;124:1533-1540



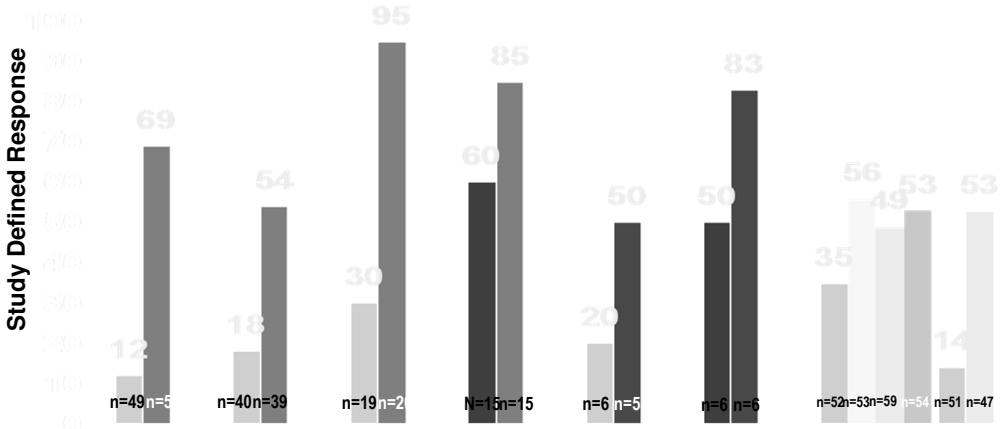
Mean baseline scores (SE): Pbo= 26.9; Ari 5 mg= 28.3, 10 mg= 27.6, 15 mg= 28.3
* $p<0.05$, 15 mg arm only, ** $p<0.05$ all arms, *** $p<0.01$ all arms vs. placebo
Marcus RN et al. *J Am Acad Child Adolesc Psychiatry* 2009;48:1110–1119

Aripiprazole in Autistic Disorder: Line Item Analysis of 2 Pooled Registration Trials



Aman MJ et al. J Child Adolesc Psychopharmacol. 2010 Oct;20(5):415-22

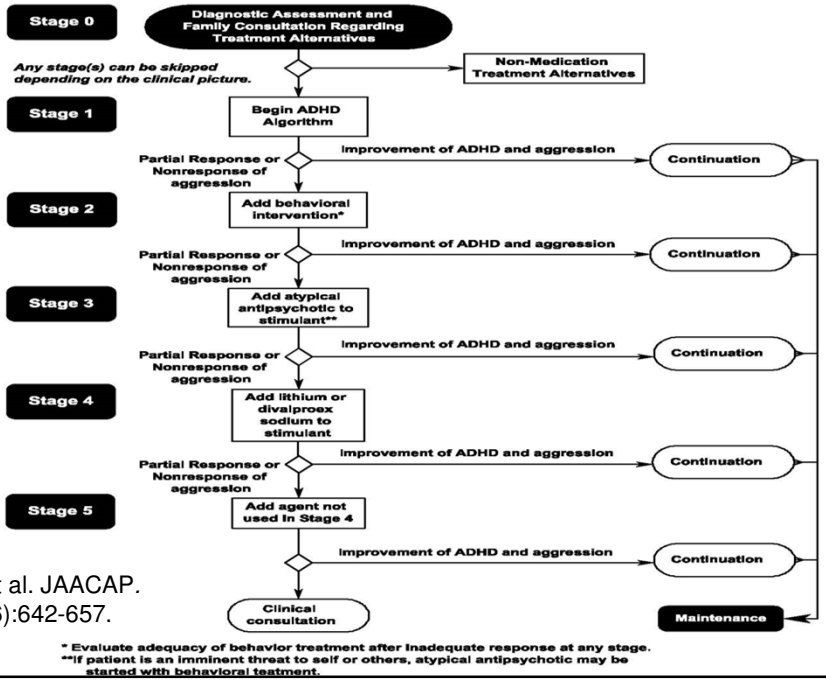
Study Defined "Response" in Pediatric Autism: NNT= 2-7



1. RUPP NEJM 2002; 2. Shea et al. 2004; 3. Nagaraj et al. 2006; 4. Miral et al. 2008; 5. Hollander et al. 2006; 6. Malone et al. 2001; 7. Marcus R et al. 2009; 8. Owen R et al. 2009

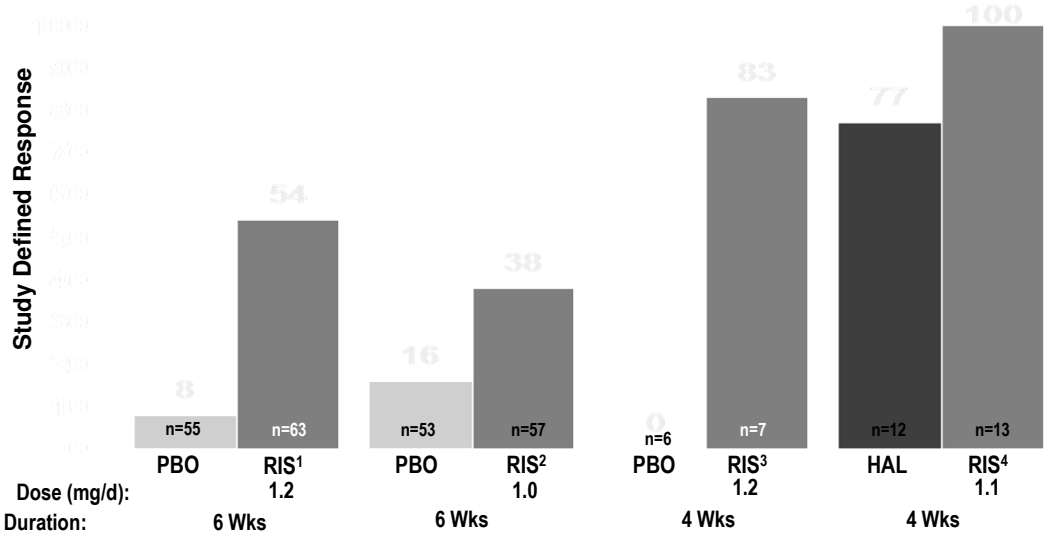
Efficacy in Disruptive Behavior Disorders

Algorithm for ADHD + Aggression



Pliszka SR et al. JAACAP. 2006;45(6):642-657.

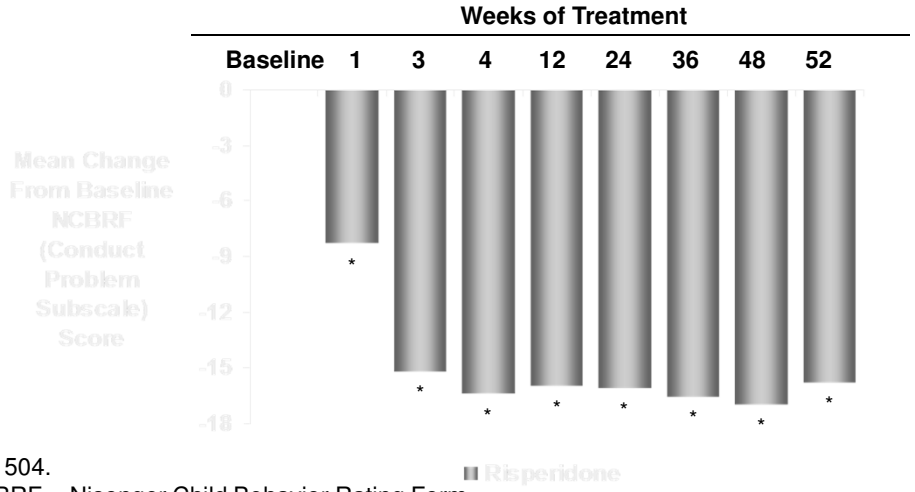
Study Defined "Response" in Pediatric DBDs: NNT= 2-5



1. Aman et al. 2002; 2. Snyder et al. 2002; 3. Van Bellinghen et al. 2006; 4. Armenteros et al. 2007;
Four additional RCTs without categorical response data

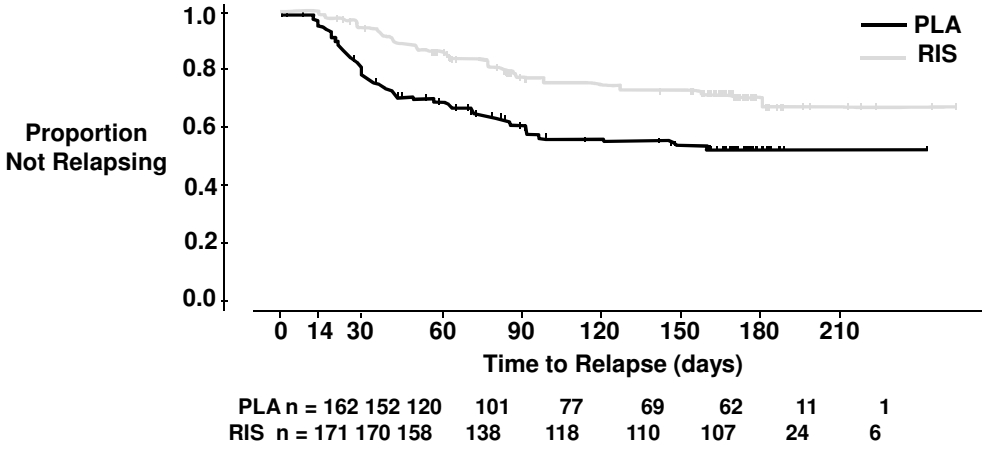
Risperidone in DBD/Subaverage IQ: Results of a 52-Week, Open-Label Study

504 children, age = 9.7 years (5–14 y)
RIS: 1.5 mg/d (0.1–4.3 mg/d)



N = 504.
NCBRF = Nisonger Child Behavior Rating Form.
*$P < 0.001$ versus baseline at each time point (two-sided paired *t*-test).
Croonenberghs J et al. *J Am Acad Child Adolesc Psychiatry*. 2005;44:64-72.

Relapse Prevention of DBD in Children and Adolescents: Time to Relapse*

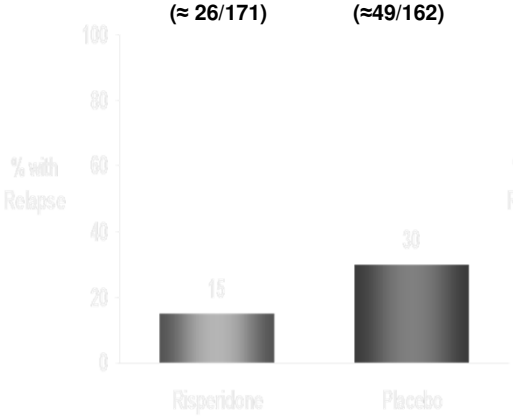


RIS = risperidone-treated subjects; PLA = placebo subjects.
*Kaplan-Meier estimates of time (days) from initiation of maintenance treatment to relapse. Relapse defined as deterioration (compared with the end of the continuation treatment phase) at 2 consecutive weekly visits as measured by an increase ≥2 points on CGI-S or an increase by ≥7 points on N-CBRF Conduct subscale.
Reyes M et al. Am J Psychiatry 2006; 163:402-410

Relapse Prevention with RIS Vs. PBO in Youth with DBDs and with Autism

DBD patients with relapse at 8 weeks

(≈ 26/171) **(≈49/162)**



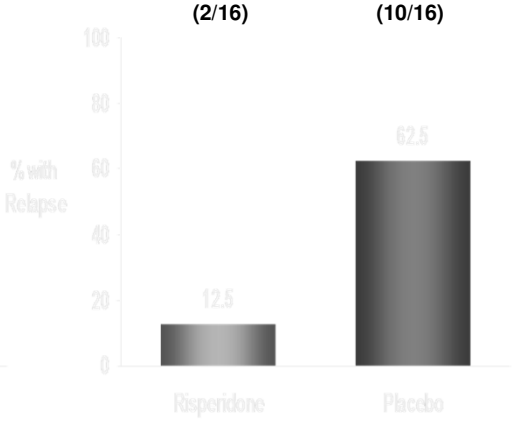
26-Week trial in youth with DBDs (n=233)

Approximate survival curve estimated relapse at 6 months: 30% vs 50%

Reyes M et al. Am J Psychiatry 2006; 163:402-410

Autism patients with relapse at 8 Weeks

(2/16) **(10/16)**



8-Week trial in youth with Autism (n=32)

Median time to relapse 34 days on PBO vs 52 days on risperidone

RUPP Autism Network. *Am J Psychiatry.* 2005;162:1361-69

Mean Effect Sizes of Psychotherapeutic Interventions for Aggression in Outpatient Youth: 8-16 y/o

- Integrative Family Therapy: ES= 0.98
- Brief Strategic Family Therapy: ES= 0.66
- Cognitive Behavior Therapy: ES= 0.58
- Multidimensional Treatment: ES= 0.56
- Group treatment: ES= 0.35
- Multisystemic Therapy: ES= 0.25
- Multimodal Psychoeducation: ES= 0.23
- Problem Solving Skills Mgmt: ES= 0.14
- [Inpatient: Problem Solving Skills/Mgmt: ES= 0.81]

Scotto Rosato N, Correll CU, …The T-MAY Steering Group. Pediatrics. 2012;129(6):e1577-e1586.

Mean Effect Sizes of Psychopharmacologic Interventions for Aggression in Outpatient Youth

- RIS Acute (N=10, n=698, 8.3 wks): ES= .72
- ARI Acute (N=2, n=308, 8 wks): ES= .41- .79
- HAL (N=1, n= 40 inpatients, 4 wks): ES= .83
- Stimulants (N=6, n=907, 6.2 wks: ES= .60
  - MPH (N=5, n=579, 6.6 wks: ES= .63
  - AMPH (N=2, n=346, 3.5 wks): ES= .42
- Mood Stabilizers (N=6 (5 IP), n=208, 5.3 wks): ES= .47
  - VPA in Outpatients: ES= -.13
  - Lithium (N=4 (IP), n=164, 4.5 wks: ES= .63
  - CBZ (N=1 (IP), n=24, 6 weeks: ES= .06

[ES= effect size (0.2 =small, 0.5=medium, 0.8=large]

Scotto Rosato N, Correll CU, …The T-MAY Steering Group. Pediatrics. 2012;129(6):e1577-e1586.

CERTs Pocket Reference Guide for Primary Care Clinicians and Mental Health Specialists

Assessment and Diagnosis: PRESTO

P What is the **PROBLEM**? Why is treatment sought?

R **REFERRAL**: Who wants what to change?

E **ENVIRONMENT**: the context (s) in which the symptoms have developed

S **SEVERITY**: Severity: What are the stakes?
(e.g. does child's aggression threaten family crisis, school expulsion, probation, child protective services involvement)

T **TARGET SYMPTOMS**:
(a) Aggression type (e.g. verbal, physical, interpersonal, toward property)
(b) Other symptoms (e.g. depression, psychosis, etc

O **OUTCOMES** or Goals: What specific change would be required for treatment to be successful?

Knapp P, Chait A, …The T-MAY Steering Group. Pediatrics. 2012 Jun;129(6):e1562-e1576;
http://www.chainonline.org/CHAINOnline/assets/File/TMAY%20final_120926.pdf

CERTs Pocket Reference Guide for Primary Care Clinicians and Mental Health Specialists

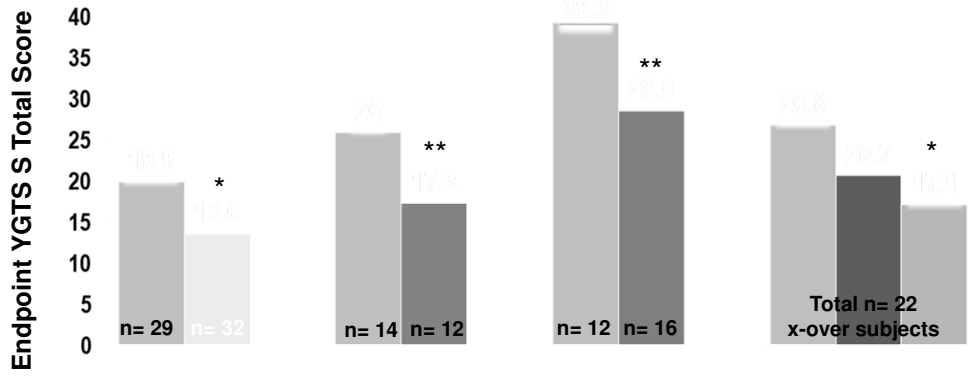
Description of target symptom(s): BOLDER

- B **Behavior** of the child in the presence of the target symptom & the characteristic of the symptom. – e.g., is the aggression impulsive? Directed toward others?
- O **Onset** of the target symptom – when does it appear? what are the triggers?
- L **Location/context** of target symptom- where does it take place? At school? At home?
- D **Duration** of the target symptom – how long does the symptom last?
- E **Exacerbation** of the target problem – what makes it worse?
- R **Relief** and resolving the target problem – what relieves t he target problem?

Knapp P, Chait A, …The T-MAY Steering Group. Pediatrics. 2012 Jun;129(6):e1562-e1576; http://www.chainonline.org/CHAINOnline/assets/File/TMAY%20final_120926.pdf

Tourette's Disorder

Endpoint Yale Global Tic Severity Total Scores



	PBO	ARI[1]	PBO	RIS[2]	PBO	ZIP[3]	PBO	HAL	PIM[4]
Dose (mg/d):		2-20		0.5-4		5-40		3.5	3.4
Baseline YGTSS:	29.5	28.3	28.6	27.0	46.9	46.9	28.5		
Duration:	10 Weeks		8 Weeks		4 Weeks		6 Weeks [3-way x-over study]		

* p<0.05; ** p<0.001

1. Yoo HK *et al. J Clin Psychiatry*. 2013 Aug;74(8):e772-80; 2. Scahill L *et al. Neurology*. 2003 Apr 8;60(7):1130-5; 3. Sallee FR *et al. J Am Acad Child Adolesc Psychiatry*. 2000;39(3):292-9; 4. Sallee FR *et al. Am J Psychiatry* 1997;154:1057-1062.

Aripiprazole vs PBO: Subject Characteristics

Table 1 Descriptive data and medication information for 61 children and adolescents with Tourette's disorders

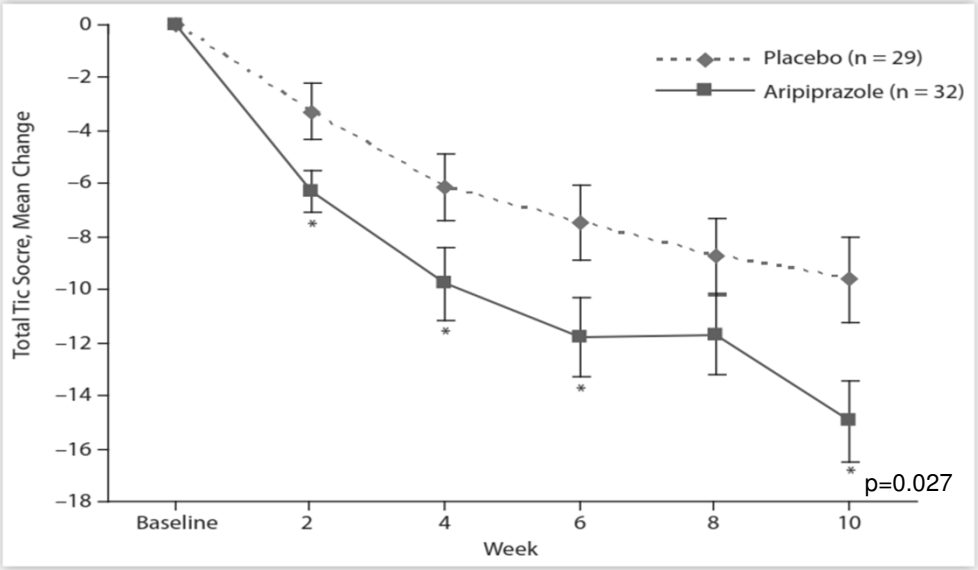
Demographics and baseline characteristics (ITT population)	Aripiprazole (n = 32)	Placebo (n = 29)
Male, n (%)	30 (93.75)	23 (79.31)
Age (years), mean (SD)	10.97 (2.49) (range: 6 to 18)	10.93 (3.00) (range: 6 to 17)
Type of tic disorders		
Tourette's disorder, n (%)	32 (100.00)	29 (100.00)
Comorbidities		
Attention deficit hyperactivity disorder, n (%)	5 (15.63)	1 (3.45)
Oppositional defiant disorder, n (%)	3 (9.38)	0 (0.00)
Anxiety disorder, n (%)	0 (0.00)	1 (3.45)
Body weight (kg), mean (SD)	46.15 (16.96)	41.46 (14.71)
Height (cm), mean (SD)	149.37 (15.06)	144.25 (15.24)
Body mass index (kg/m^2), mean (SD)	20.20 (4.35)	19.24 (3.40)
Waist circumference (cm), mean (SD)	69.65 (11.60)	67.84 (9.69)

Medication information (Safety population[#1])	Aripiprazole (n = 32)	Placebo (n = 28)
Final dose/day (mg), mean (SD)[#2]	10.97 (6.09) (range: 2 to 20)	16.13 (5.27) (range: 2 to 20)
Duration of study medication (days), mean (SD)	68.63 (10.02) (range: 20 to 77)	63.75 (19.09) (range:7 to 78)

Note :
#1 : One subject who was randomized to Aripiprazole group but not took study drug was not included in safety population.
One subject who was randomized to Placebo group but took Aripiprazole was included in Aripiprazole group for the safety analysis.
#2 : Only for the subjects who completed the study (Aripiprazole group n=30, Placebo group n=24).

Yoo HK *et al. J Clin Psychiatry*. 2013 Aug;74(8):e772-80.

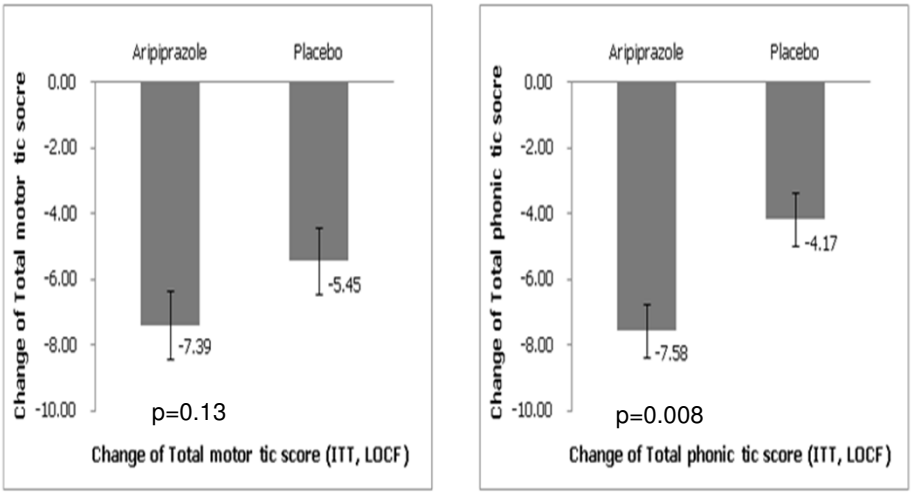
Significant Superiority on the Yale Global Tic Severity Score with Aripiprazole (n=29) vs. Placebo (n=32)



*p<0.05; mean dose 11+/-6 mg (range: 2-20)
Yoo HK *et al. J Clin Psychiatry*. 2013 Aug;74(8):e772-80.

Aripiprazole vs PBO: Efficacy by Tic Type

Figure 2. Changes of total motor and vocal tic score from baseline to endpoint



Yoo HK *et al. J Clin Psychiatry*. 2013 Aug;74(8):e772-80.

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(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2498

Aripiprazole for Tourette's syndrome: a systematic review and meta-analysis

Wei Zheng[1,2], Xian-Bin Li[1,2], Ying-Qiang Xiang[1,2]*, Bao-Liang Zhong[3], Helen F. K. Chiu[3], Gabor S. Ungvari[4,5], Chee H. Ng[6], Grace K. I. Lok[7] and Yu-Tao Xiang[8]*

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Objective To review the efficacy and safety of aripiprazole (ARI) for Tourette's syndrome (TS).
Methods This review included randomized controlled trials (RCTs) of children and adolescents (6–18 years) with TS comparing ARI monotherapy with another monotherapies in relation to clinical improvement and adverse events.
Results Six RCTs with a total of 528 subjects (ARI treatment group: n = 253; control group: n = 275) met the inclusion criteria. These included two RCTs (n = 255) that compared ARI monotherapy with tiapride (TIA). Tic symptoms control assessed by Yale Global Tic Severity Scale (Standard Mean Difference (SMD) = −0.38 (Confidence Interval (CI) = −1.32 to 0.56); I^2 = 90%, P = 0.42) revealed no significant differences between the two groups. Extrapyramidal symptoms were significantly different when ARI (1.5%) was compared with haloperidol (HAL) (43.5%). No significant group differences were found in the rates of nausea/vomiting, dizziness, and dry mouth between ARI and TIA (RR = 0.57 to 1.00 (95%CI = 0.14–4.20); I^2 = 0% to 69%, P = 0.35 to 1.00).
Conclusion This review found that ARI has similar efficacy to TIA and HAL for TS, while extrapyramidal symptoms were significantly less with ARI than with HAL. ARI can be considered as an alternative treatment option for TS.

Aripiprazole low dose (N=44) vs. high dose (N=45) vs. Placebo (44)

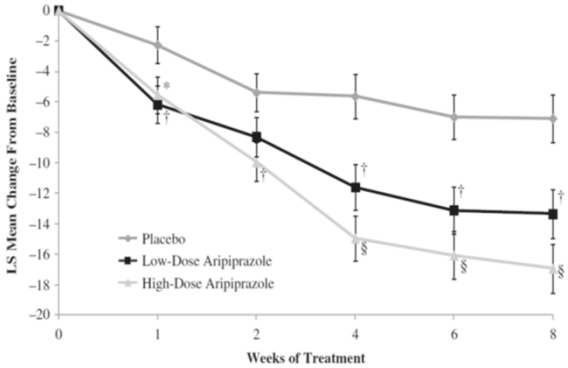


FIG. 3. LS mean (SE) change from baseline in YGTSS-TTS (ITT population). Shown are the LS mean changes from baseline in the YGTSS-TTS by week calculated by using MMRM. Error bars represent the LS mean ± 1 SE. *$p < 0.05$; †$p < 0.01$; §$p < 0.0001$ versus placebo. ITT, intent-to-treat; LS, least squares; MMRM, mixed-model repeated measures; SE, standard error; YGTSS-TTS, Yale Global Tic Severity Scale Total Tic Score.

Low-dose aripiprazole (5 mg/day if <50 kg; 10 mg/day if ≥50 kg),
high-dose aripiprazole (10 mg/day if <50 kg; 20 mg/day if ≥50 kg)
Sallee F, et al. J Child Adolesc Psychopharmacol. 2017 Nov; 27 (9): 771-781.

Adverse Effects

Time Course of Antipsychotic Adverse Effects

Receptor	Acute ≤1 wk	Consequence	Early <3 mo	Consequence	Late: ≥3 mo	Consequence
α 1	Hypotension*	Falls non-adherence	Hypotension *	Falls non-adherence	Hypotension	Falls non-adherence
D 2	Dystonia * Parkinsonism*	Pain non-adherence	Parkinsonism* Akathisia *	↓ cognition non-adherence	TD	Stigma ↓ socialization ↓ quality of life
	↑ Prolactin (*)	Sexual Dysfunction non-adherence	↑ Prolactin (*)	Sexual Dysfunction Hypogonadism non-adherence	↑ Prolactin	Osteoporosis ? CHD ? breast cancer
H 1	Sedation *	↓ cognition ↓ functioning non-adherence	Sedation *	↓ cognition ↓ functioning non-adherence	Sedation	↓ cognition ↓ functioning non-adherence
	↑ Weight	↑ lipids/ glucose	↑ Weight	↑ lipids/glucose non-adherence	Diabetes dyslipidemia CHD	↓ functioning ↓ quality of life early death
M 1-4	Blurry vision* dry mouth *	Discomfort non-adherence	↓ cognition Blurry vision * dry mouth * constipation *	↓ functioning discomfort non-adherence	↓ cognition Blurry vision * dry mouth * constipation *	↓ functioning discomfort non-adherence

Acute (<1 week) Early (<3 months) Late

*= Tolerance may develop; CHD= Coronary heart disease Correll CU. CNS Spectr. 2007;12(12) (Suppl 21):10-14.

Psychotropic Adverse Events In Children and Adolescents vs. Adults

Increased risk for acute and intermediate adverse effects:

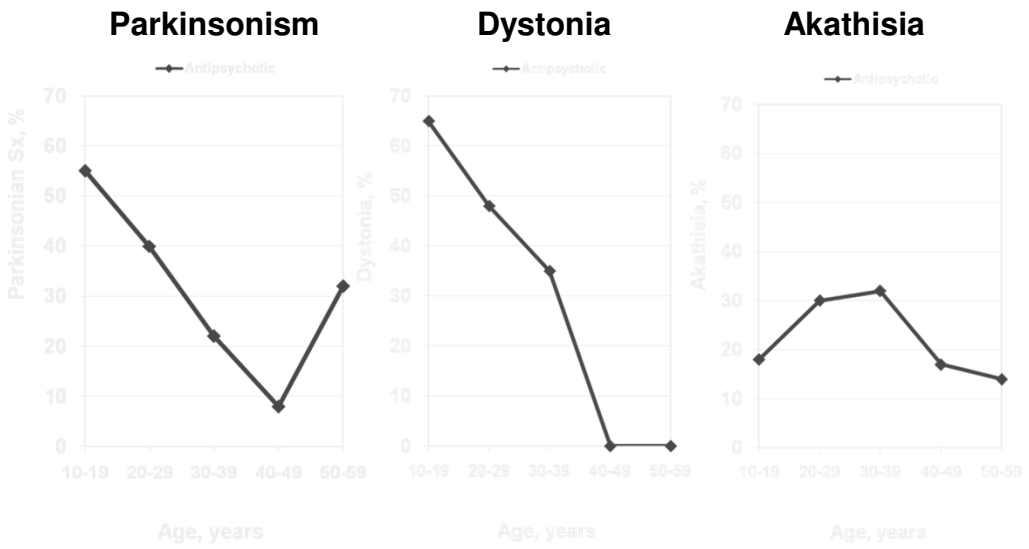
- Sedation
- Parkinsonism (possibly not for SGAs if titrated slowly
- Withdrawal dyskinesia
- Prolactin-related AEs (especially postpubertal females)
- Weight gain and dyslipidemia

Decreased (delayed?) risk for:

- Persistent TD
- Diabetes mellitus

Adapted from: Correll CU et al. Child Adolesc Psychiatr Clin N Am. 2006;15(1):177-206.

Inverse Relationship Between Age and Incidence of EPS



Keepers GA et al. Arch Gen Psychiatry. 1983;40:1113-7.

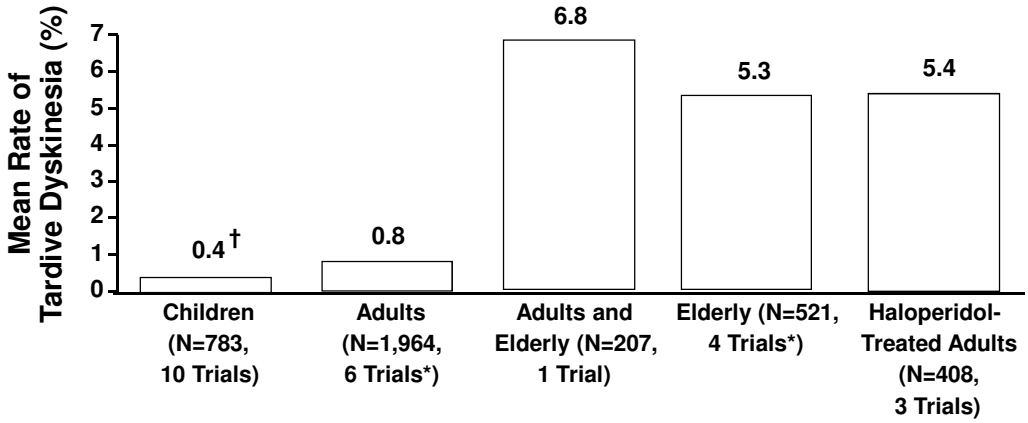
Neuromotor Side Effects in Youth Naturalistically Treated with 5 SGAs for 3 Months (n=342)

	Total	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone	
3-mo Frequencies (LOCF)	N = 342	n = 66	n = 58	n = 66	n = 137	n = 15	
Drug-induced parkinsonism, n (%)	52 (15.20)	18 (27.27)	8 (13.79)	1 (1.52)	22 (16.06)	3 (20.00)	.002*
Anticholinergic medication, n (%)	17 (5.03)	3 (4.76)	0 (0.0)	0 (0.0)	14 (10.22)	0 (0.0)	.0004*
Highest single SAS item score, mean ± SD	0.88 ± 1.00	1.14 ± 0.99	0.91 ± 0.85	0.55 ± 0.66	0.86 ± 1.08	1.13 ± 1.50	.01*
Significant, treatment-emergent dyskinesia, n (%)	28 (8.28)	3 (4.55)	9 (15.52)	6 (9.5)	6 (4.41)	4 (26.67)	.005*
Highest AIMS item during 3 mo, mean ± SD	0.91 ± 0.91	1.19 ± 0.84	0.80 ± 1.04	0.96 ± 0.98	0.84 ± 0.83	1.0 ± 1.0	.11
Akathisia, n (%)	16 (4.83)	5 (8.06)	3 (5.36)	1 (1.59)	7 (5.15)	0 (0.0)	.45
Neuroleptic malignant syndrome, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Discontinuation due to extrapyramidal side effect, n (%)	11 (3.27)	4 (6.15)	1 (1.72)	0 (0.0)	6 (4.48)	0 (0)	.008*

13.6 years; male=58.2% ; AP-naïve=65.8%

Carbon M et al. J Am Acad Child Adolesc Psychiatry. 2015 Sep;54(9):718-727.

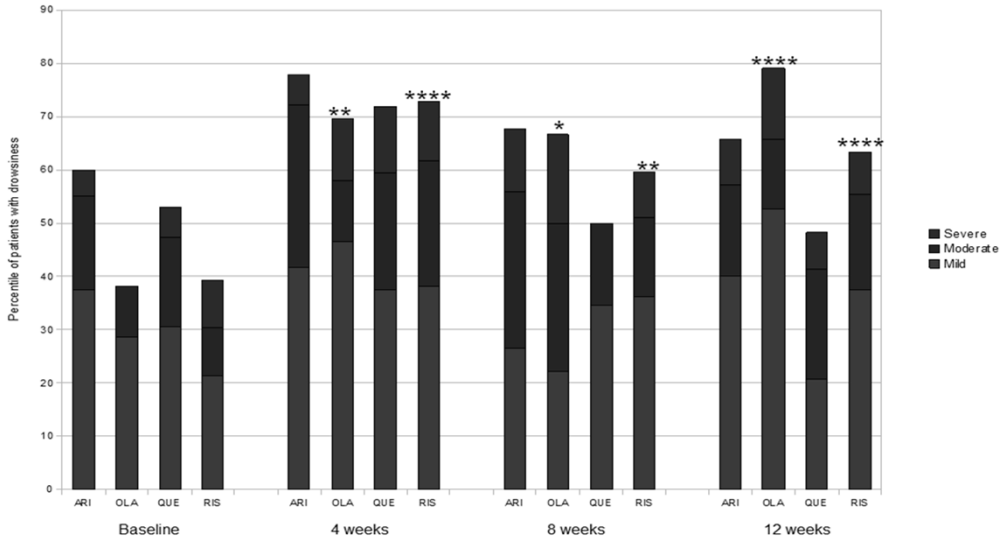
6 times lower 1-Year Incidence Rates of TD with Atypical Antipsychotics vs. Haloperidol in Adults and 50% lower Risk in Youth



Participants Treated With 2nd-Generation Antipsychotics

***1 study reported separate rates for TD in adults and in the elderly; Correll CU et al. (2004), Am J Psychiatry 161(3):414; †Correll CU & Kane JM (2007), J Child Adolesc Psychiatry;15(5):647-655.**

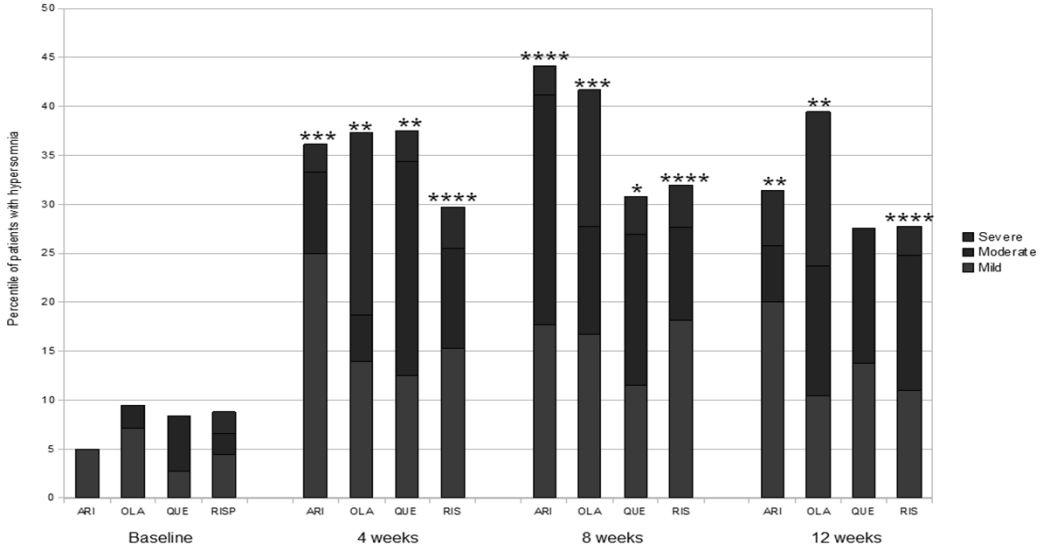
Naturalistic Comparison of Aripiprazole, Olanzapine, Quetiapine and Risperidone: 3-Month Rates of Drowsiness in 257 AP-Naïve Youth (SATIETY Study)



257 antipsychotic-naïve youth (13.8±3.6 years, male=57.8%) initiated aripiprazole (n=40), olanzapine (n=45), quetiapine (n=36), or risperidone (n=135)

Al Dhaher Z et al. – under review

Naturalistic Comparison of Aripiprazole, Olanzapine, Quetiapine and Risperidone: 3-Month Rates of Hypersomnia in 257 AP-Naïve Youth (SATIETY Study)



257 antipsychotic-naïve youth (13.8±3.6 years, male=57.8%) initiated aripiprazole (n=40), olanzapine (n=45), quetiapine (n=36), or risperidone (n=135)

Al Dhaher Z et al. – under review

Relative Potency of Antipsychotics in Elevating Serum PRL Prolactin in Youth

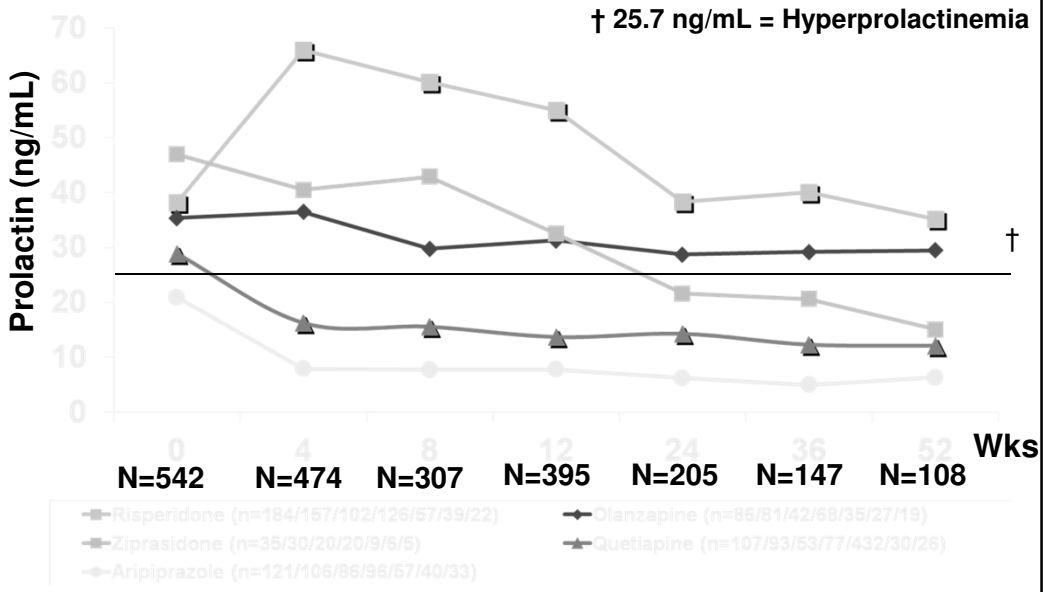
- Paliperidone ≥ Risperidone > Haloperidol
- > Olanzapine > Ziprasidone
- > Quetiapine > Clozapine > Aripiprazole

- Aripiprazole has partial D2-DA agonist activity, and may suppress PRL below baseline levels

Correll and Carlson, JAACAP 2006;45: 771-791

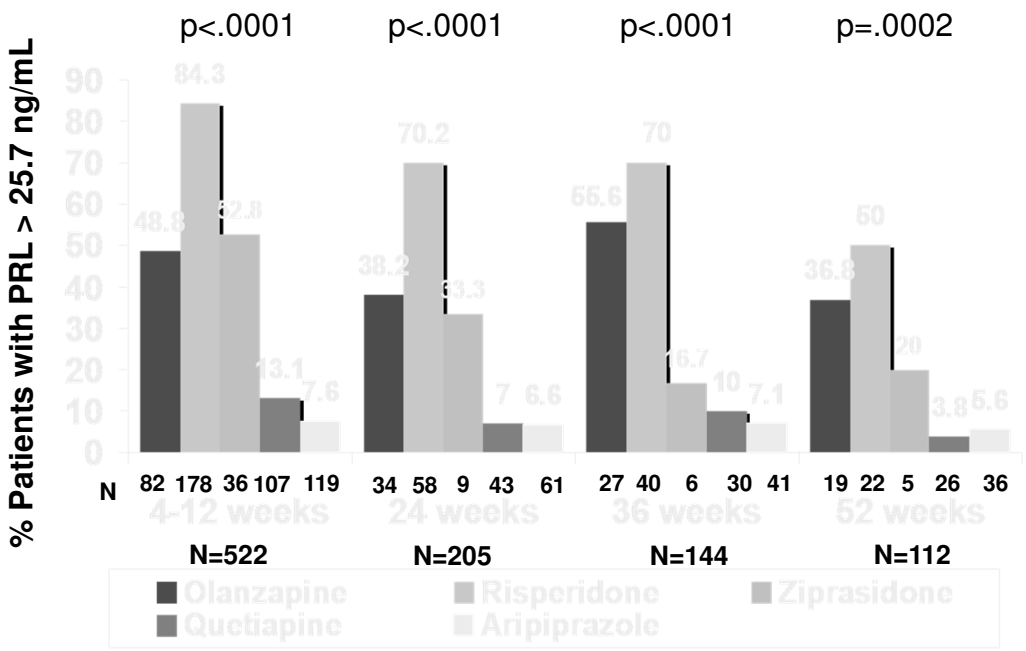
1 Year Prolactin Change

Overall group comparison p<0.0001 at all time points



Correll CU et al. ICOSR 2007

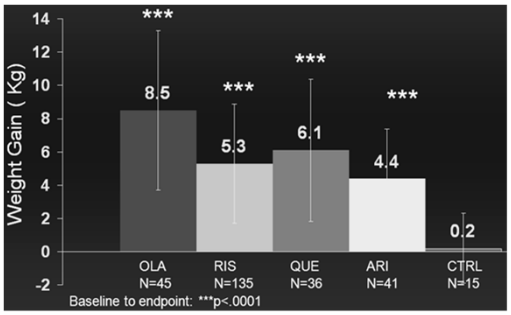
% Of Youth With Hyper-Prolactinemia



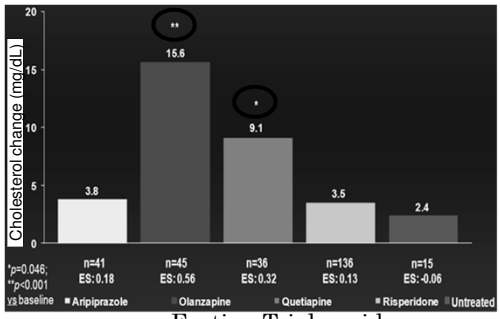
Correll CU et al. ICOSR 2007

12-week Cardiometabolic Effects of SGAs in AP-Naïve Youth

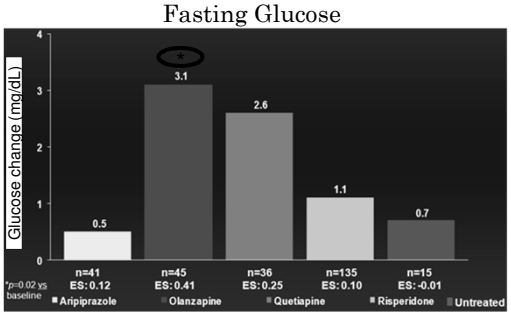
Body Weight



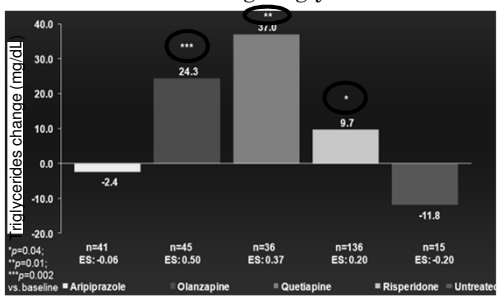
Fasting Total Cholesterol



Fasting Glucose



Fasting Triglycerides

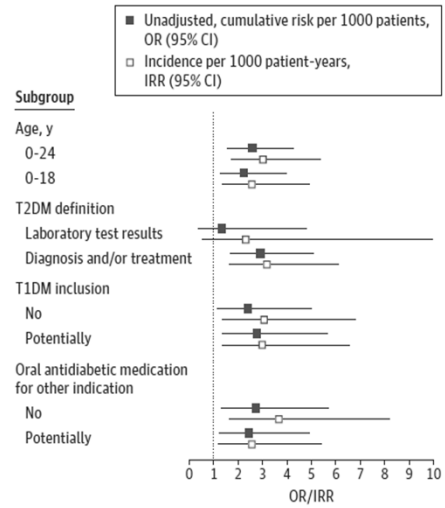


Correll CU *et al. JAMA* 2009;302:1765–1773

2.6-3-fold higher Incidence of Type 2 Diabetes in Youth Exposed to Antipsychotics than in Healthy Control Youth

Healthy Controls vs Antipsychotic-Treated Youth

Healthy Controls			Antipsychotic-Treated Youth				
No.	Patient-Years	T2DM Cases	No.	Patient-Years	T2DM Cases	OR (95% CI)	IRR (95% CI)
298803	463084	504	37999	68028	292	2.58 (1.56-4.24)	3.02 (1.71-5.35)
268923	403615	487	35011	63438	284	2.25 (1.28-3.95)	2.56 (1.34-4.92)
38559	43161	26	9915	3846	13	1.33 (0.37-4.79)	2.31 (0.54-9.93)
260244	428922	478	28084	64182	279	2.92 (1.67-5.09)	3.18 (1.66-6.10)
56460	126961	139	13364	49224	160	2.75 (1.34-5.66)	2.99 (1.36-6.55)
242343	336123	365	24635	18803	132	2.40 (1.16-4.99)	3.06 (1.37-6.82)
56475	126967	139	13643	49361	161	2.45 (1.22-4.91)	2.56 (1.20-5.43)
242328	336117	365	24356	18667	131	2.72 (1.31-5.67)	3.67 (1.64-8.21)



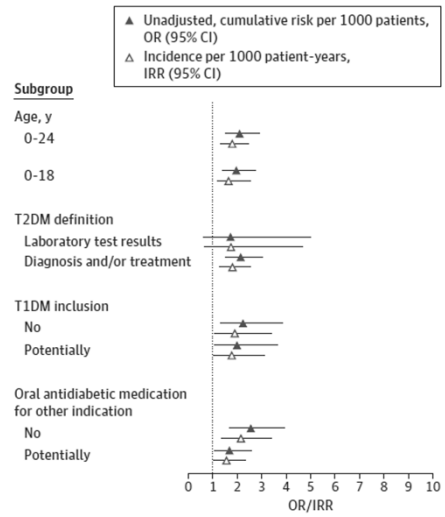
Studies=8, 298,803 patients and 463 084 patient-years; cumulative T2DM risk (odds ratio [OR], 2.58; 95%CI, 1.56-4.24; P < .0001) and incidence rate ratio (IRR) (IRR, 3.02; 95%CI, 1.71-5.35; P < .0001)

Galling B et al. JAMA Psychiatry. 2016 Mar 1;73(3):247-59.

1.8-2-fold higher Incidence of Type 2 Diabetes in Youth Exposed to Antipsychotics than in Psychiatrically Ill Youth

Psychiatric Controls vs Antipsychotic-Treated Youth

Psychiatric Controls			Antipsychotic-Treated Youth				
No.	Patient-Years	T2DM Cases	No.	Patient-Years	T2DM Cases	OR (95% CI)	IRR (95% CI)
1342121	2071135	3235 (3198)	169840	294347	74 (753)	2.09 (1.50-2.90)	1.79 (1.31-2.44)
1327692	2053172	3221 (3184)	140982	256325	682 (661)	2.00 (1.39-2.76)	1.64 (1.20-2.55)
26265	10231	19	9636	3710	12	1.72 (0.60-4.98)	1.74 (0.65-4.68)
1315856	2060904	3216 (3179)	160204	290637	762 (741)	2.14 (1.50-3.05)	1.80 (1.29-2.53)
71213	300574	594	13417	107143	269	1.99 (1.08-3.65)	1.77 (1.01-3.11)
1270908	1770561	2641 (2604)	129589	187204	505 (484)	2.23 (1.29-3.86)	1.90 (1.06-3.40)
1251601	1903757	3046	140549	245681	618	1.68 (1.08-2.59)	1.56 (1.04-2.34)
90520	167378	189 (152)	29291	48666	156 (135)	2.55 (1.66-3.92)	2.15 (1.35-3.42)



Studies=7, 1,342,121 patients and 2,071,135 patient-years; cumulative T2DM risk (OR, 2.09; 95%CI, 1.50-5 2.90; P < .0001) and IRR (IRR, 1.79; 95%CI, 1.31-2.44; P < .0001).

Galling B et al. JAMA Psychiatry. 2016 Mar 1;73(3):247-59.

Monitoring and Management of Adverse Effects

Psychotropic Side Effect Monitoring in Youths

Assessments	Frequency
Personal and family history	Baseline and Annually
Lifestyle monitoring	Every visit
Height, weight, BMI percentile / z-score	Every visit
Somnolence/sedation	Every visit
Sexual symptoms/signs	Baseline, during titration and q 3 mo
Blood pressure, pulse	Baseline, 3-months and 6-monthly
Fasting glucose, HbA1C, lipids	Baseline, at 3 mo and (6-)12monthly
Liver function tests (if on APs)	Baseline, at 3 mo and (6-)12 monthly
EPS, akathisia	Baseline, titration, 3 mo and annually
Dyskinesia / TD	Baseline, 3 mo and annually
Electrolytes, blood count, renal f'ction	On per case basis (except if on CLO)
Prolactin	Only when symptomatic
EKG	If on ZIP: during titration, at max. dose If abnormal exam/Hx prior to stimulants

Adapted from: Correll CU. *J Am Acad Child Adolesc Psychiatry*. 2008;47(1):9-20.

Assessment : Body Composition

- **Weight change: dependent on baseline weight and growth**
- **BMI: only useful within 3 months of follow up**
- **BMI %ile (sex- and age adjusted standard: 50th %ile) and BMI z-score (adjusted standard: z score of 0):**
- Growth charts: www.cdc.gov/growthcharts/
- Web-based calculators:
  http://www.bcm.edu/cnrc/bodycomp/bmiz2.html
- **BMI percentile: Definition of weight categories**
- **Underweight: < 5th %ile; Normal: 5-<85th %ile;**
- **Overweight: 85-<95th %ile; Obese: ≥95th %ile**
- **BMI z-score: Tracking of change over time (>3 months)**
- **Age adjusted BMI: (BMI - 50th BMI %ile) / 50th BMI %ile**
- **Waist circumference: not recommended by AMA (difficult to asses, age dependent cut-offs uncertain)**

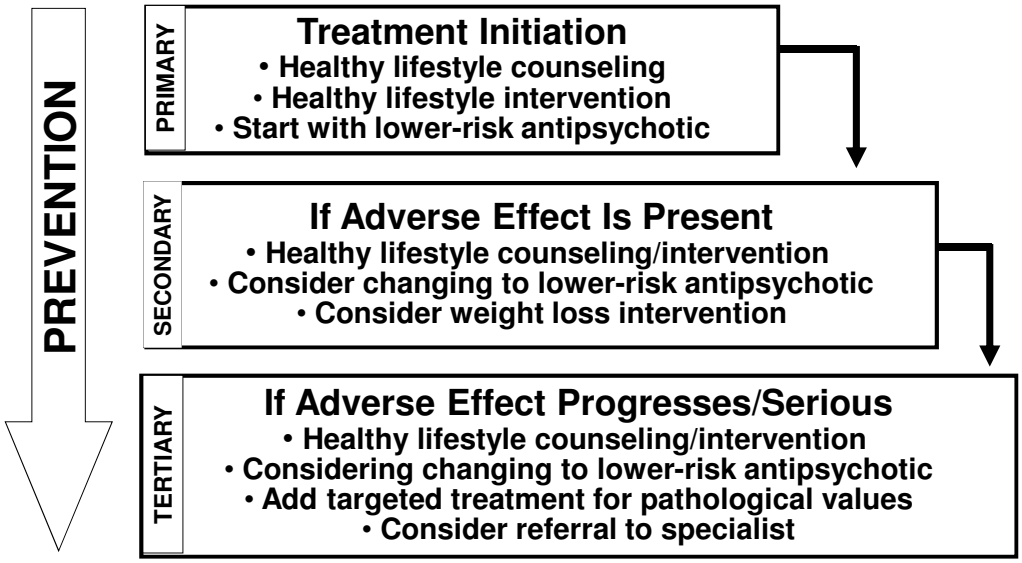
Correll CU. *J Am Acad Child Adolesc Psychiatry*. 2008;47(1):9-20.

Assessment : Blood Pressure and Labs

- **Blood Pressure (cuff should cover >80% of the upper arm)**
  - **Hypertension: >90th percentile for sex and age (Calculate height %ile (https://www.nutropin.com/patient/3_5_3_growth_charts.jsp) and compare blood pressure with population norms**
- **Hyperglycemia: ≥100 mg/dL**
- **Diabetes: ≥126 mg/dL (two fasting measures)**
- **Insulin resistance:**
  - **HOMA-IR [insulin (mg/dL) x glucose (mg/dL)/405]: >4.4 (adolescent)**
  - **TG/HDL ratio: >3.5**
- **Hypertriglyceridemia: ≥110 mg/dL**
- **Hypercholesterolemia: ≥170 mg/dL**
- **High LDL: >130 mg/dL**
- **Low HDL: <40 mg/dL**

Correll CU. *J Am Acad Child Adolesc Psychiatry*. 2008;47(1):9-20.

Medical Risk Management Strategies in Antipsychotic-Treated Patients



Correll CU. CNS Spectr. Vol 12. No 10 (Suppl 17), 2007: 12-20,35.

Adverse Effect Management in Children and Adolescents

Adverse Event	Selected Interventions
Suicidality	Careful monitoring, frequent visits, safety precautions, involvement of support system
Sedation/ Somnolence	Wait if tolerance develops, ↓ dose (↑ if on quetiapine <300 mg/d); switch to lower-risk drug; add modafinil
Parkinsonism	Slow titration, ↓ dose; switch to lower-risk drug; add anticholinergic, antihistamine, benzodiazepine, etc
Akathisia	Slow titration, ↓ dose; switch to lower-risk drug; add benzodiazepine, beta-blocker, antihistamine, anticholinergic, etc
Tardive dyskinesia	↓ dose; ↑ dose (masking); replace with nonantipsychotic (if possible); switch to clozapine; add vitamin E

Adapted from: Correll CU. *J Am Acad Child Adolesc Psychiatry.* 2008;47:9-20.

Adverse Effect Management in Children and Adolescents

Adverse Event	Selected Interventions
Weight loss / growth retardation	Lower dose, drug holidays, larger evening meals, etc
Cardiac risk	Physical examination and history, EKGs in high risk patients
Weight gain, hyperglycemia, dyslipidemia, hypertension	Switch to lower-risk drug; healthy lifestyle intervention; add weight-loss agent (metformin, orlistat, amantadine, topiramate, bupropion, etc), statin/fibrate, antihyperglycemic, antihypertensive
Hyper-prolactinemia sexual/ reproductive dysfunction	If asymptomatic: may wait. If symptomatic: ↓ dose; switch to lower-risk drug. If symptomatic despite switch to low-risk drug: MRI; add full (bromocriptine, amantadine, cabergoline) or partial dopamine agonist (aripiprazole); for performance: add bupropion, sildenafil, etc

Adapted from: Correll CU. *J Am Acad Child Adolesc Psychiatry.* 2008;47:9-20.

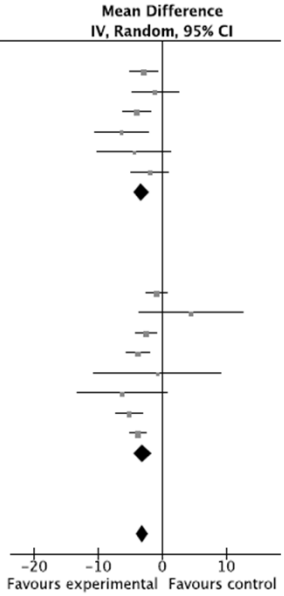
12-Step Healthy Lifestyle Program

Do's	Do Not's
• Replace sugar-containing drinks with water • Eat 4 to <6 meals, with <2 meals in the evening or night • Serve small meal portions • Eat slowly, drink water, take seconds only after delay • Eat food with a low glycemic index (<55) • Consume >25–30 grams of soluble fiber per day • Snack only when hungry and use fruit or vegetables • Perform moderate physical activity for >30–60 min/day	• Skip breakfast • Consume fast food >1 per wk • Consume saturated or processed fat-free food • Watch TV, play computer games ≥2 hours/day  

Correll CU, Carlson HE. *J Am Acad Child Adolesc Psychiatry.* 2006;45: 771-791.

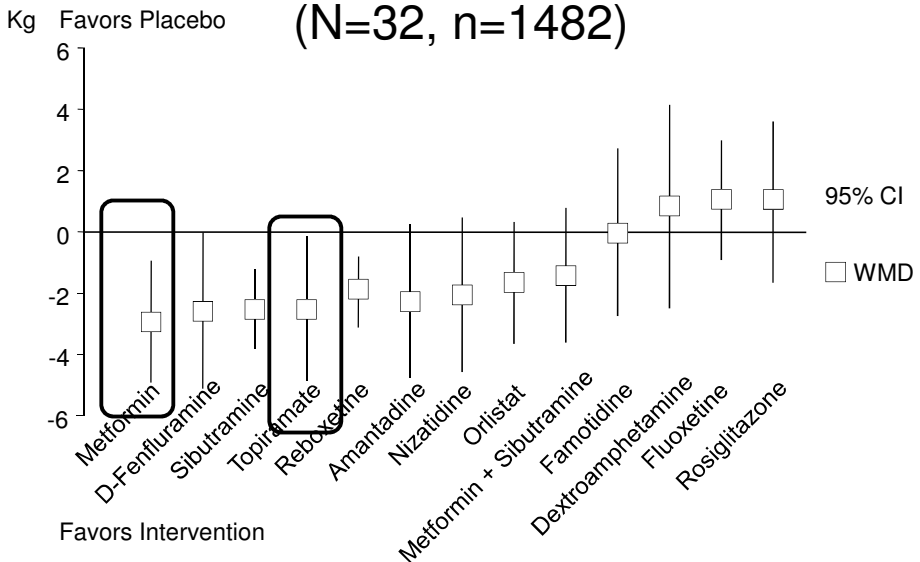
Weight Loss (kg) with Behavioral Interventions vs Control Condition in AP-treated Patients (N=17, n=810)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.59.1 Prevention trials								
Alvarez-Jimenez 2006	4.1	3.99	28	6.98	4.5	33	9.6%	-2.88 [-5.01, -0.75]
Cordes et al 2011	3.4	4.2	13	4.5	6.1	18	4.8%	-1.10 [-4.73, 2.53]
Evans 2005	2	3.6	23	6	2.6	11	9.7%	-4.00 [-6.13, -1.87]
Littrell 2003	0.81	8.97	35	7.17	9.16	35	3.8%	-6.36 [-10.61, -2.11]
Poulin 2007	84.4	18.2	59	88.8	12.3	51	2.3%	-4.40 [-10.14, 1.34]
Scocco 2005	0.99	3.34	10	2.96	3.08	8	6.4%	-1.97 [-4.94, 1.00]
Subtotal (95% CI)			**168**			**156**	**36.6%**	**-3.23 [-4.41, -2.04]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.87$, df = 5 (P = 0.43); $I^2 = 0\%$								
Test for overall effect: Z = 5.35 (P < 0.00001)								
1.59.2 Intervention trials								
Brar 2005	-2	3.79	34	-1.1	3.11	37	12.4%	-0.90 [-2.52, 0.72]
Khazaal 2007	88	14.9	31	83.5	17.2	30	1.2%	4.50 [-3.59, 12.59]
Kwon 2006	-3.94	3.63	29	-1.48	1.88	14	12.2%	-2.46 [-4.11, -0.81]
Mauri 2008	-3.6	2.6	15	0.2	2.9	18	10.9%	-3.80 [-5.68, -1.92]
McKibbin 2006	98.5213	21.228	28	99.2924	16.919	29	0.8%	-0.77 [-10.76, 9.22]
Weber 2006	84.1848	6.54236	8	90.4667	7.35393	7	1.5%	-6.28 [-13.37, 0.81]
Wu 2007	-4.2	4.4	28	1	3.4	25	9.8%	-5.20 [-7.31, -3.09]
Wu 2008	63.4	2.6	32	67.2	2.6	32	14.5%	-3.80 [-5.07, -2.53]
Subtotal (95% CI)			**205**			**192**	**63.4%**	**-3.04 [-4.39, -1.68]**
Heterogeneity: $Tau^2 = 1.82$; $Chi^2 = 17.54$, df = 7 (P = 0.01); $I^2 = 60\%$								
Test for overall effect: Z = 4.40 (P < 0.0001)								
Total (95% CI)			**373**			**348**	**100.0%**	**-3.12 [-4.03, -2.21]**
Heterogeneity: $Tau^2 = 1.08$; $Chi^2 = 22.46$, df = 13 (P = 0.05); $I^2 = 42\%$								
Test for overall effect: Z = 6.69 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $I^2 = 0\%$								



Mean age: 38.8 years, 52.7% male, 40.8% White, 85.6% with schizophrenia-spectrum d/o's
Caemmerer J, Correll CU, Maayan L. Schizophr Res. 2012 Sep;140(1-3):159-68.

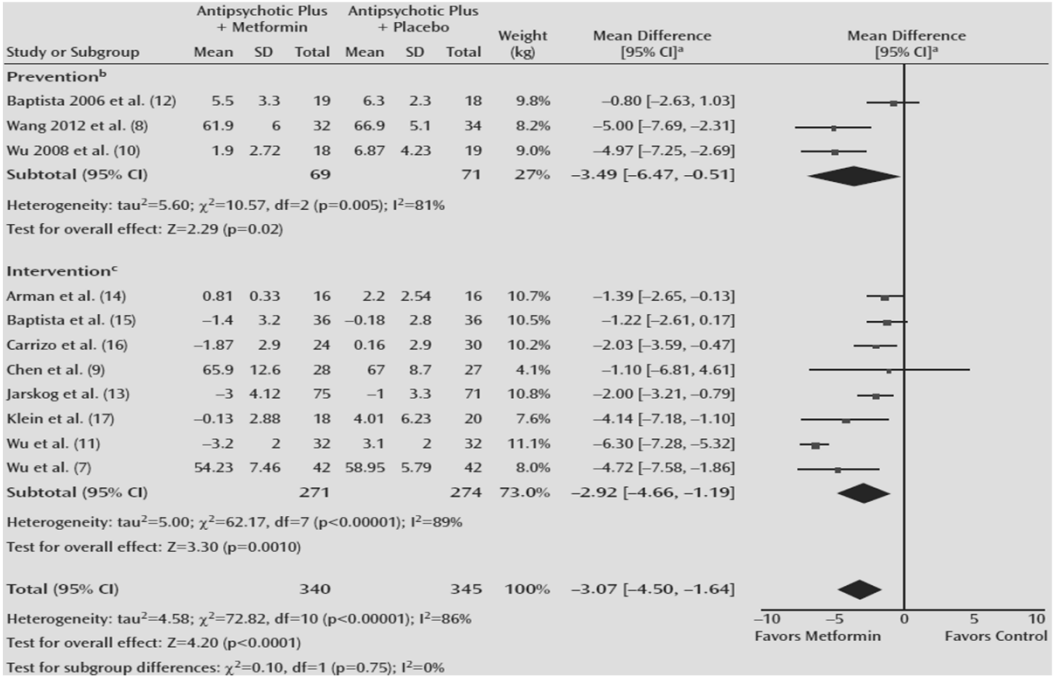
Pharmacologic Weight Loss (kg) Compared to Placebo in Antipsychotic-treated Patients (N=32, n=1482)



Grey squares: significant difference

Maayan L, Vakhrusheva J, Correll CU. Neuropsychopharmacology. 2010 Jun;35:1520-30.

Metformin vs. PBO for AP-Related Weight Gain



Study or Subgroup	Antipsychotic Plus + Metformin Mean	SD	Total	Antipsychotic Plus + Placebo Mean	SD	Total	Weight (kg)	Mean Difference [95% CI][a]
Prevention[b]								
Baptista 2006 et al. (12)	5.5	3.3	19	6.3	2.3	18	9.8%	−0.80 [−2.63, 1.03]
Wang 2012 et al. (8)	61.9	6	32	66.9	5.1	34	8.2%	−5.00 [−7.69, −2.31]
Wu 2008 et al. (10)	1.9	2.72	18	6.87	4.23	19	9.0%	−4.97 [−7.25, −2.69]
Subtotal (95% CI)			69			71	27%	−3.49 [−6.47, −0.51]
Heterogeneity: tau²=5.60; χ²=10.57, df=2 (p=0.005); I²=81%								
Test for overall effect: Z=2.29 (p=0.02)								
Intervention[c]								
Arman et al. (14)	0.81	0.33	16	2.2	2.54	16	10.7%	−1.39 [−2.65, −0.13]
Baptista et al. (15)	−1.4	3.2	36	−0.18	2.8	36	10.5%	−1.22 [−2.61, 0.17]
Carrizo et al. (16)	−1.87	2.9	24	0.16	2.9	30	10.2%	−2.03 [−3.59, −0.47]
Chen et al. (9)	65.9	12.6	28	67	8.7	27	4.1%	−1.10 [−6.81, 4.61]
Jarskog et al. (13)	−3	4.12	75	−1	3.3	71	10.8%	−2.00 [−3.21, −0.79]
Klein et al. (17)	−0.13	2.88	18	4.01	6.23	20	7.6%	−4.14 [−7.18, −1.10]
Wu et al. (11)	−3.2	2	32	3.1	2	32	11.1%	−6.30 [−7.28, −5.32]
Wu et al. (7)	54.23	7.46	42	58.95	5.79	42	8.0%	−4.72 [−7.58, −1.86]
Subtotal (95% CI)			271			274	73.0%	−2.92 [−4.66, −1.19]
Heterogeneity: tau²=5.00; χ²=62.17, df=7 (p<0.00001); I²=89%								
Test for overall effect: Z=3.30 (p=0.0010)								
Total (95% CI)			340			345	100%	−3.07 [−4.50, −1.64]
Heterogeneity: tau²=4.58; χ²=72.82, df=10 (p<0.00001); I²=86%								
Test for overall effect: Z=4.20 (p<0.0001)								
Test for subgroup differences: χ²=0.10, df=1 (p=0.75); I²=0%								

Correll CU et al. Am J Psychiatr. 2013 Sep;170(9):947-52.

Options to Improve Outcomes

- **General**
  - **Education and monitoring**
  - **Rule out medical or psychiatric (co)morbidity**
  - **Healthy lifestyle counseling / intervention**
- **Efficacy**
  - **Optimize the dose**
  - **Switch to more effective agent**
  - **Augment**
- **Adverse Effects**
  - **Optimize the dose**
  - **Switch to lower-risk agent**
  - **Augment**
  - **Refer to specialist**

Correll CU et al. - in preparation

Summary

- Severe psychiatric disorders not infrequently start before age 18
- While some symptom presentations may differ across the age range, the diagnostic criteria are identical for youth and adults
- Treatment guidelines are identical for youth and adults, except that dosing may have to be slower and (potentially somewhat) lower, and youth are more sensitive to adverse events
- Atypical antipsychotics have proven efficacy in pediatric schizophrenia, bipolar disorder, irritability associated with autistic disorder, aggression and Tourette's disorder

Summary cont'd

- Like in adults, the relative efficacy of antipsychotics seems to be roughly similar, at least at group levels, except for clozapine
- Pediatric patients are at greater risk than adults for prolactin elevation, sedation, weight gain and metabolic effects
- A careful risk-to-benefit evaluation is needed when deciding to start or continue individual agents and lowest risk agents and non-pharmacologic treatment options ought to be tried first
- Future drug development will need to pay attention to effects of antipsychotics on brain development and long-term efficacy and tolerability
- Stratified and personalized treatment is needed

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