

Nutzen und Risiken von Antipsychotika bei Kindern und Jugendlichen mit schweren psychiatrischen Erkrankungen



Christoph U. Correll, MD

**Professor of Child and Adolescent Psychiatry
Charité – Universitätsmedizin Berlin
Berlin, Germany**

**Professor of Psychiatry and Molecular Medicine
The Zucker School of Medicine at Hofstra/Northwell
New York, USA**

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Disclosures: Christoph U. Correll, MD

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 covering the last 5 years are summarized below:

Interest	Name of organization
Grants	Bendheim Foundation, Janssen, National Institute of Mental Health (NIMH), Patient-Centered Outcomes Research Institute (PCORI), Takeda, Thrasher Foundation
Share Options	Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax, and Quantic
Consultant, honoraria and advisory boards	AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Saladax, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Tolmar, Vertex, Viatrix and Xenon Pharmaceuticals.

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Overview

- Efficacy
 - Schizophrenia
 - Bipolar Disorder
 - Autism/Aggression
 - Tourette's Disorder
- Safety and Tolerability
 - EPS
 - Endocrine
 - Sedation/Hypersomnia
 - Cardiometabolic
- Adverse Effect Monitoring and Management
- Conclusions

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EDITORS' NOTE Check for updates

The Neuroscience-based Nomenclature Child & Adolescent (NbN C&A) for Psychotropic Medications: Innovation in Progress

To address the issues with the current nomenclature of psychotropic agents, which may be misleading or confusing, the Neuroscience-based Nomenclature (NbN) started being developed in 2009. It was introduced as one approach to the classification of pharmacological treatments based on a medication's putative psychopharmacological mechanisms of action derived from preclinical and clinical studies. In 2018, the NbN-Child & Adolescent (NbN C&A) was released. Since then, the NbN C&A has been refined, and its website and app (<https://nbnc.com/>) have been implemented. *JAACAP* encourages its authors and readers to consider utilizing the NbN C&A and to keep abreast of its developments over time. This is in line with the core missions of the *Journal*: to contribute to the translation and implementation of the most up-to-date science into real-world clinical practice.

Diversity & Inclusion Statement: One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented racial and/or ethnic groups in science.

J Am Acad Child Adolesc Psychiatry 2022;61(11):1317-1318.

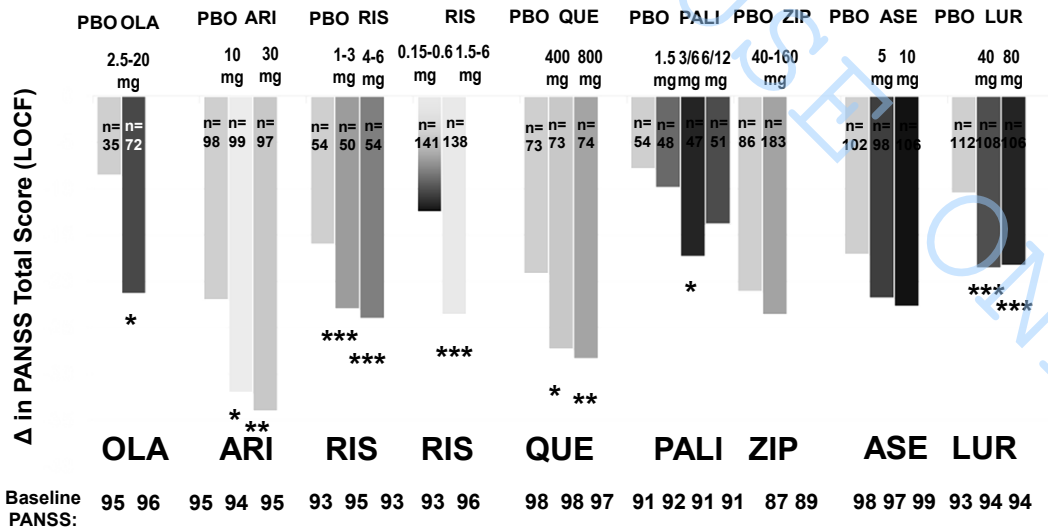
The screenshot displays the NbN app interface. On the left, there is a sidebar menu with the following options: 'The Nomenclature', '4 Additional Dimensions', 'Approved Indication', 'Efficacy & Side Effect', 'Practical Notes', and 'Neurobiology'. The main content area shows a list of medications with their classifications. For example, 'Amphetamine (d) and (d,l)' is classified as 'Nbn' and 'C&A'. 'Chlorpromazine' is classified as 'Nbn' and 'C&A'. 'Diphenhydramine' is classified as 'C&A'. 'Receptor antagonist (2, 5-HT2)' is classified as 'C&A'. The app also includes a 'Check for updates' button in the top right corner.

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Schizophrenia Spectrum Disorders

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

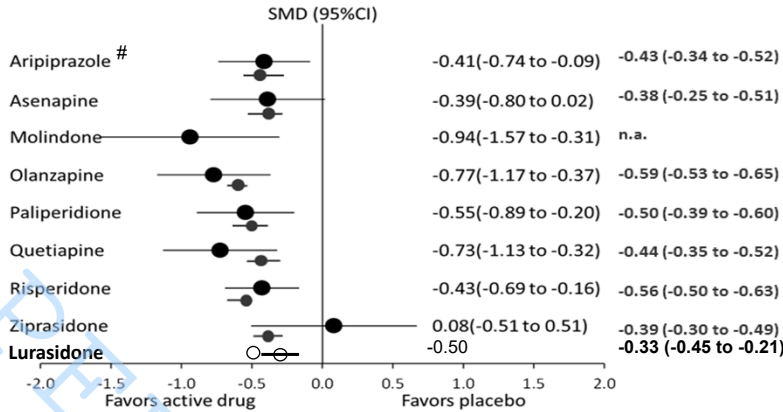


* $p < 0.05$ vs placebo, ** $p < 0.01$ vs placebo, *** $p < 0.001$ vs placebo;
PBO, placebo; OLA, olanzapine; ARI, aripiprazole; RIS, risperidone; QUE, quetiapine; PALI, paliperidone; ZIP, ziprasidone; ASE, asenapine; LUR, lurasidone

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

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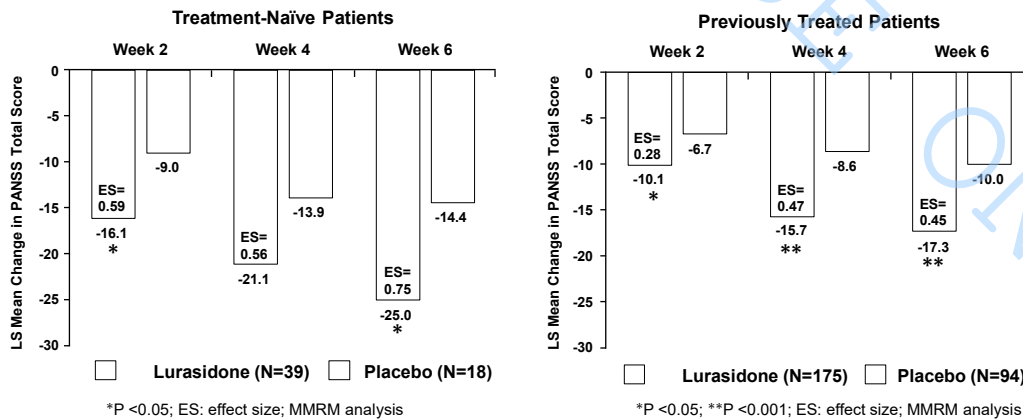
Network Metaanalysis: PANSS Total Score Reduction with 9 Antipsychotics vs. Placebo and vs Adult Data (Leucht et al, Lancet 2013)



Off-Label Einsatz, es sind die Hinweise der aktuellen deutschen Fachinformation zu Aripiprazol zu beachten.
 Pagsberg AK et al J Am Acad Child Adolesc Psychiatry. 2017 Mar;56(3):191-202.
 Goldman R et al J Child Adolesc Psychopharmacol. 2017 Aug;27(6):516-525.
 Leucht S et al. Lancet. 2013 Sep 14;382(9896):951-62.

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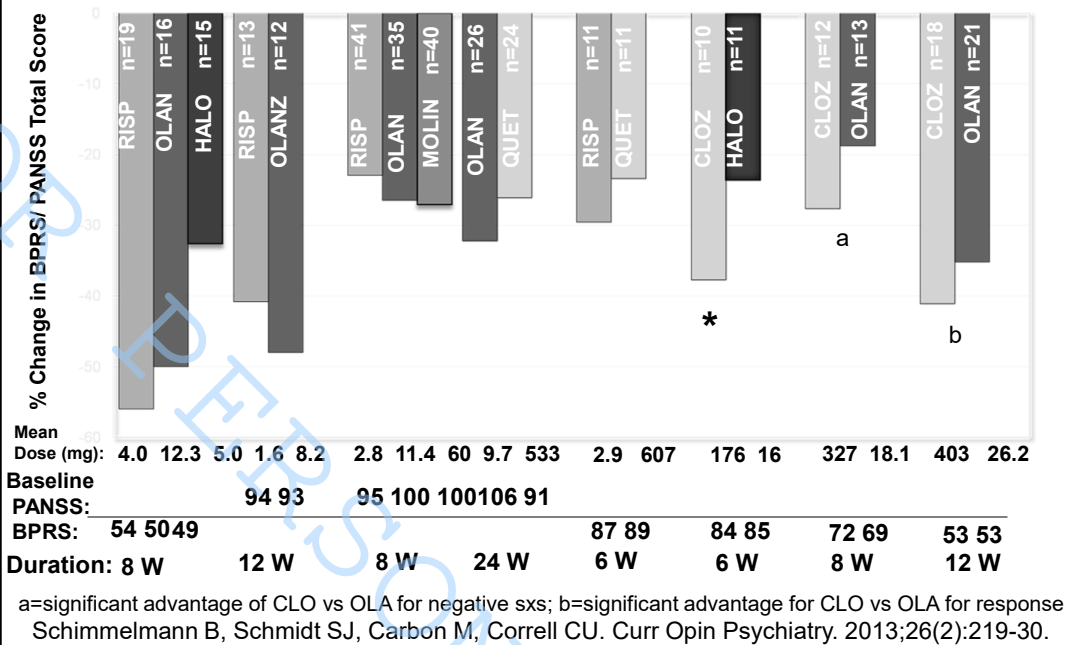
Lurasidone 40 mg and 80 mg vs Placebo for Adolescents with Schizophrenia: Greater PANSS Total Change in Treatment-Naïve (n=57, 17.5%) vs. Previously Treated (n=269, 82.5%) Patients



Correll CU, et al. Eur Psychiatry 2022 Mar 24;65(1):1-35.

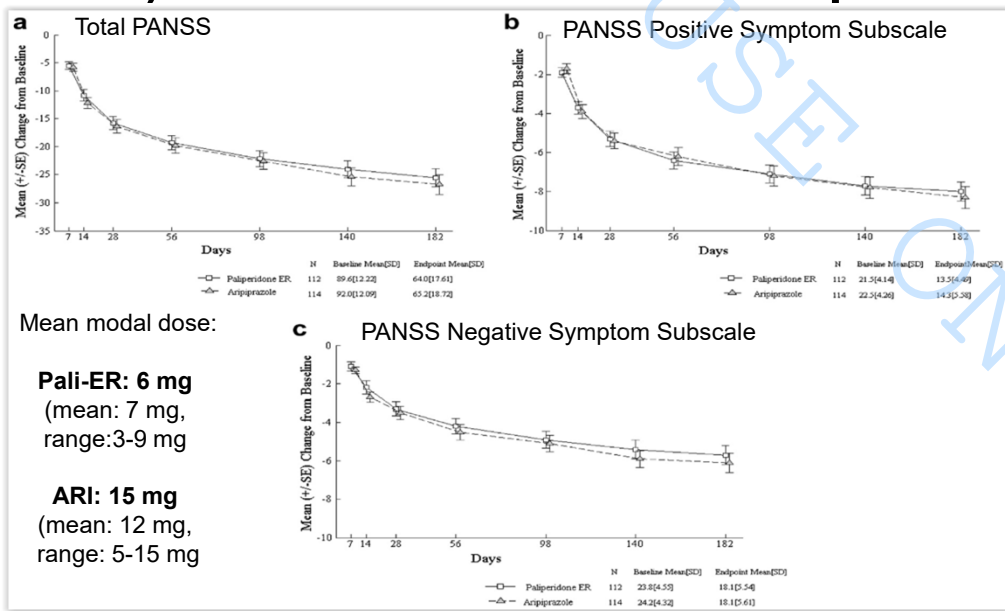
8

No Antipsychotic Efficacy Differences in Pediatric Schizophrenia, Except CLO



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Paliperidone ER (n=113) vs Aripiprazole (n=114) in Adolescents with Schizophrenia



Savitz AJ et al. J Am Acad Child Adolesc Psychiatry. 2015;54(2):126-137.

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Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: the multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial

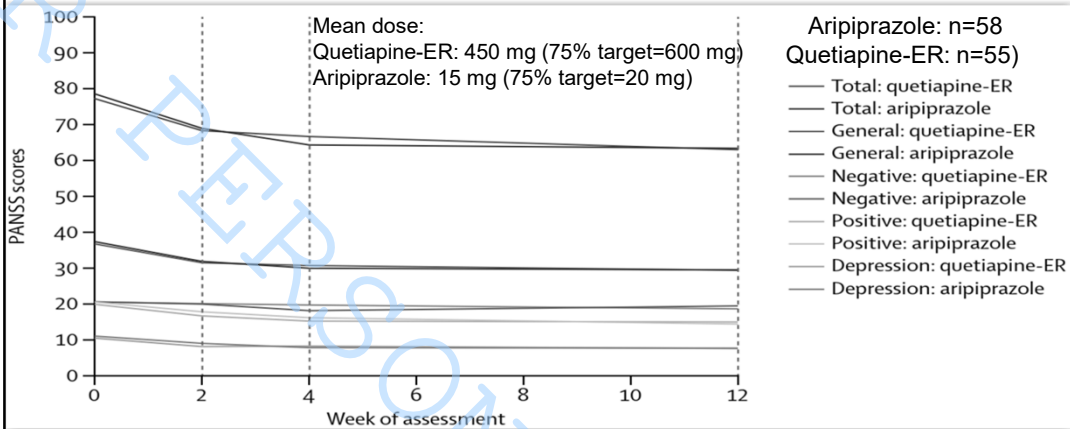
Anne Katrine Pagsberg, Pia Jeppesen, Dea Gowers Klauber, Karsten Gjessing Jensen, Ditte Rudd, Marie Stentebjerg-Olesen, Peter Jantzen, Simone Rasmussen, Eva Ann-Sofie Saldeen, Maj-Britt Glenn Lauritsen, Niels Bilenberg, Anne Dorte Stenström, Louise Nyvang, Sarah Madsen, Thomas M Werge, Theis Lange, Christian Gluud, Maria Skoog, Per Winkel, Jens Richardt M Jepsen, Birgitte Fagerlund, Christoph U Correll, Anders Fink-Jensen

Summary

Background Head-to-head trials to guide antipsychotic treatment choices for paediatric psychosis are urgently needed because extrapolations from adult studies might not be implementable. In this superiority trial with two-sided

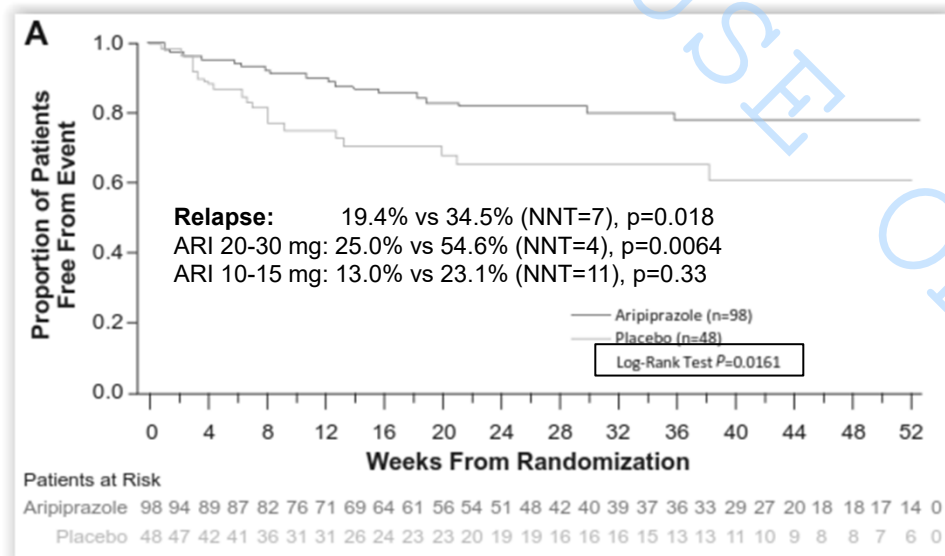
Lancet Psychiatry 2017; 4: 605-18

PANSS Total and Subscale Score Changes



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



Age: 15.4 (13-17) years, 65% male with schizophrenia, PANSS-total: 64, CGI-S=3.1
 Correll CU et al. J Am Acad Child Adolesc Psychiatry. 2017 Sep;56(9):784-792.

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Regulatory approval status of second-generation antipsychotics in youth with schizophrenia based on randomized controlled trials

Oral Second-generation Antipsychotics	USA: Age Group	Europe: Age Group
Aripiprazole	≥ 13 years	≥ 15 years
Clozapine		≥ 16 years
Lurasidone	≥ 13 years	≥ 13 years
Olanzapine	≥ 13 years	
Paliperidone	≥ 13 years	≥ 15 years
Quetiapine	≥ 13 years	
Risperidone	≥ 13 years	

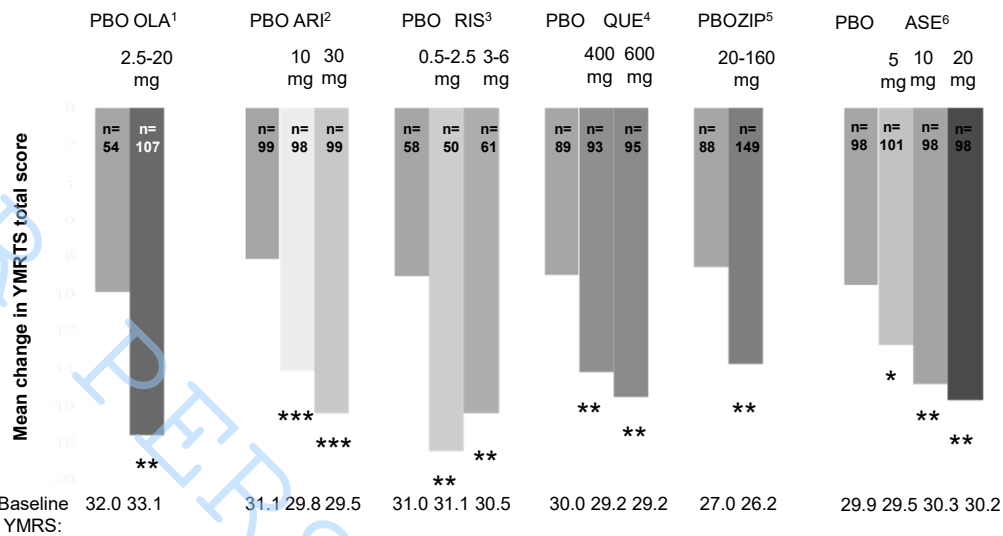
ABILIFY (aripiprazole) Prescribing Information FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023bl.pdf; CLOZARIL (clozapine) Prescribing Information FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/019758s095bl.pdf; LATUDA (lurasidone hydrochloride) Prescribing Information FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/200603bls10s11.pdf; ZYPREXA (olanzapine) Prescribing Information FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020592s051,021086s030,021253s036bl.pdf; INVEGA (paliperidone) Prescribing Information FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021999s018bl.pdf; SEROQUEL (quetiapine fumarate) Prescribing Information FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020639s064bl.pdf; RISPERDAL (risperidone) Prescribing Information FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020272s056%2C020588s044%2C021346s033%2C021444s03bl.pdf.

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Treatment of Pediatric Bipolar Disorder

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SGAs: YMRS Total Improvement from 6 PBO-Controlled RCTs in Pediatric BPD (10–17 yrs)



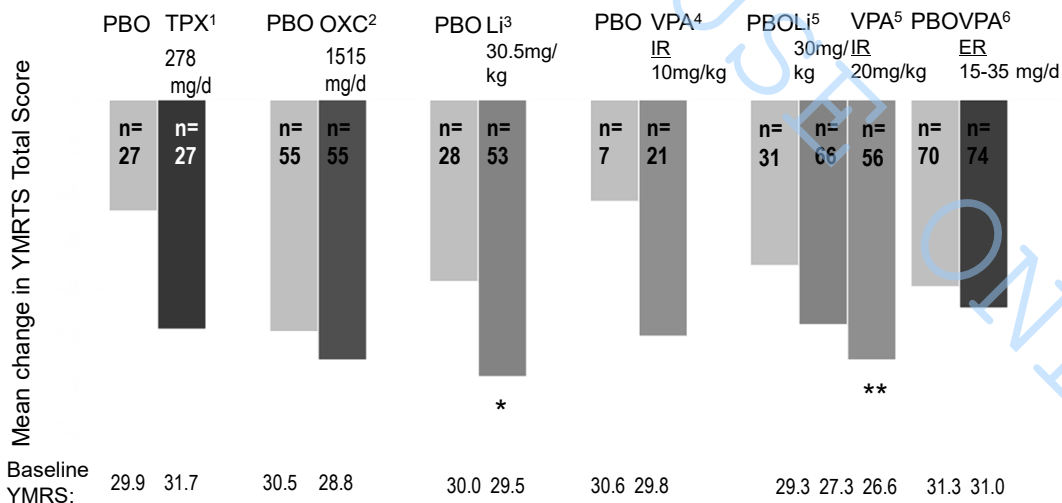
Baseline YMRS: *p<0.01 vs placebo; **p<0.001 vs placebo; ***p<0.0001 vs placebo

1. Tohen M, et al. *Am J Psychiatry* 2007;164:1547–1556 2. Findling RL et al. *J Clin Psychiatry* 2009;70:1441–1451.
 3. Haas M et al. *Bipolar Disord* 2009;11:687–700. 4. Pathak RL et al. *J Clin Psychiatry*. 2013 Jan;74(1):e100-9.
 5. Findling RL et al. *J Child Adolesc Psychoph.* 2013;23(8):545-57. 6. Findling RL et al. *J Am Acad Child Adolesc Psychiatry*. 2015 Dec;54(12):1032-41.

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

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Mood Stabilizers: YMRS Total Improvement from 5 PBO-Controlled RCTs in Pediatric BPD (6-17 Yrs)



Baseline YMRS: *p<0.05 vs placebo; **p<0.01 vs placebo

1. DelBello MP et al *J Am Acad Child Adolesc Psychiatry*. 2005 Jun;44(6):539-47;
 2. Wagner KD et al. *Am J Psychiatry*. 2006 Jul;163(7):1179-86;
 3. Findling RL, et al. *Pediatrics*. 2015 Nov;136(5):885-94.
 4. Kowatch RA et al. *J Child Adolesc Psychopharmacol*. 2015 May;25(4):306-13.
 5. Kowatch R et al. AACAP Annual Meeting, October 27, 2007;
 6. Wagner KD et al *J Am Acad Child Adolesc Psychiatry*. 2009 May;48(5):519-32.

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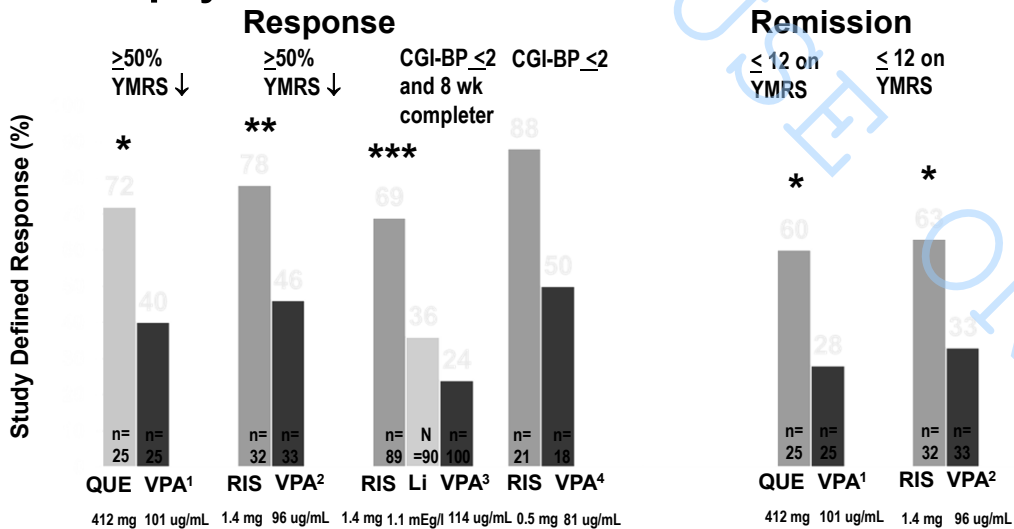
Antipsychotics-PBO vs. Mood Stabilizer-PBO Differences in Efficacy

Outcome	Children and Adolescents				Significant Difference SGA vs MS in Youth
	Second- Generation Antipsychotics N = 1,118		Mood Stabilizers N = 494		
<i>Continuous Outcome</i>	Effect Size	95% CI	Effect Size	95% CI	
YMRS (including TPX among MS)	0.65	0.53– 0.78	0.24	0.06– 0.41	SGA > MS
YMRS (excluding TPX among MS)			0.20	0.02– 0.39	
CGI-BP Overall Illness (including TPX among MS)	0.63	0.50– 0.76	0.47 ¹	-	N/A
<i>Categorical Outcome</i>	NNT	95% CI	NNT	95% CI	
Response: ≥ 50% ↓YMRS	4.0	3.3– 5.3	7.81	4.7– 24.4	NS
Remission: YMRS ≤/ = 12	3.7	3.1– 4.7	-33.3 ^{**}	-6.8– 10.0	NS
All-cause Discontinuation	12.7	7.5– 41.2	15.6 ^{**}	-7.9– 4.3	NS

*N = patients on medication or placebo
 ** = 95% confidence interval crosses 0, which indicates that the difference between treatment group and placebo is not statistically significant
 Correll CU et al. Bipolar Disorders 2010;12(2):116-41.

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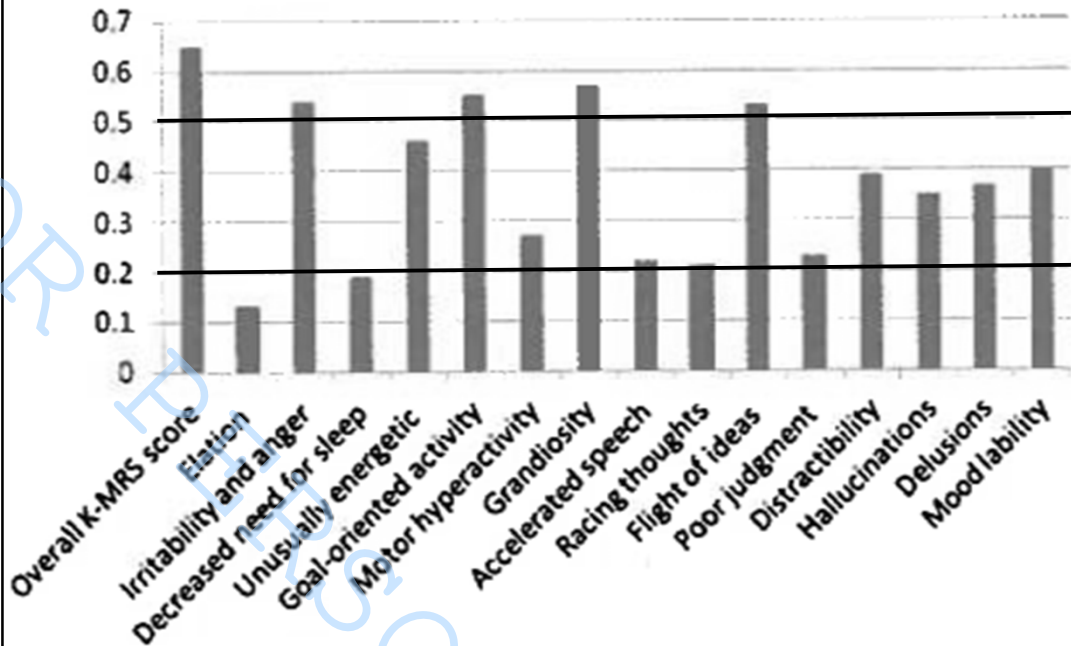
Response and Remission in 4 Trials Comparing Antipsychotics with Mood Stabilizers in PBD



1. DelBello MP, et al. JAACAP 2006;54(3):305-13 – mean age: 15.0 years; 46% with psychosis
2. Pavuluri MN et al. Bipolar Disord 2010;12:593-605 – mean age: 10.9 years; 20% with psychosis
3. Geller B et al. Arch Gen Psychiatry 2012;69:515-28 – mean age: 10.1 years; 77% with psychosis
4. Kowatch RA et al. J Child Adolesc Psychopharmacol. 2015 May;25(4):306-13.

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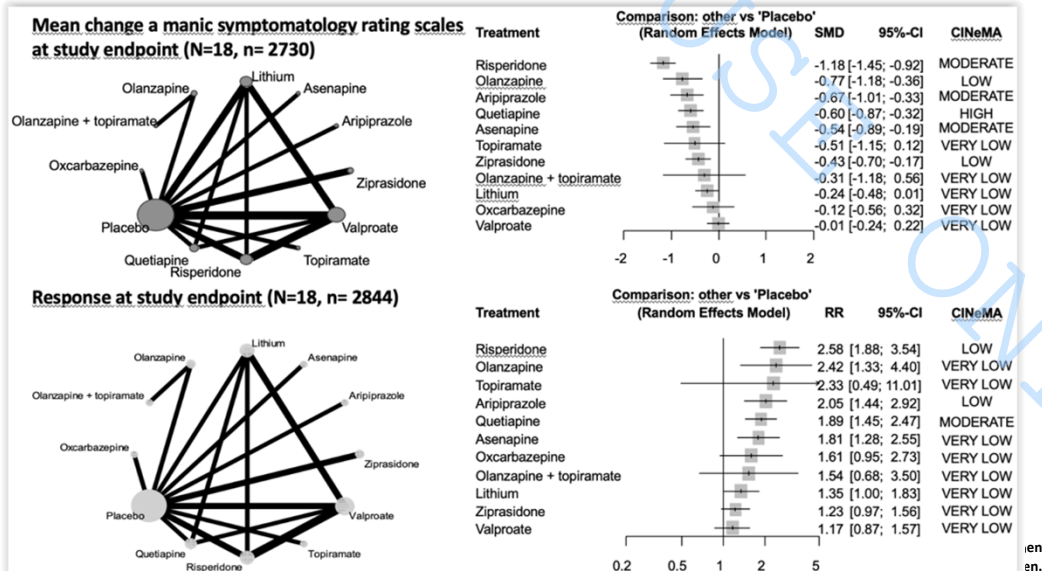
TEAM Study: Effect Sizes of Risperidone vs. Lithium *



* On KSADS-Mania Rating Scale Vitiello B et al. J Am Acad Child Adolesc Psychiatry. 2012;51(9):867-78.

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Network Meta-analysis of 6 Antipsychotics and 4 Mood Stabilizer for Acute or Mixed Mania Sx Reduction or Response

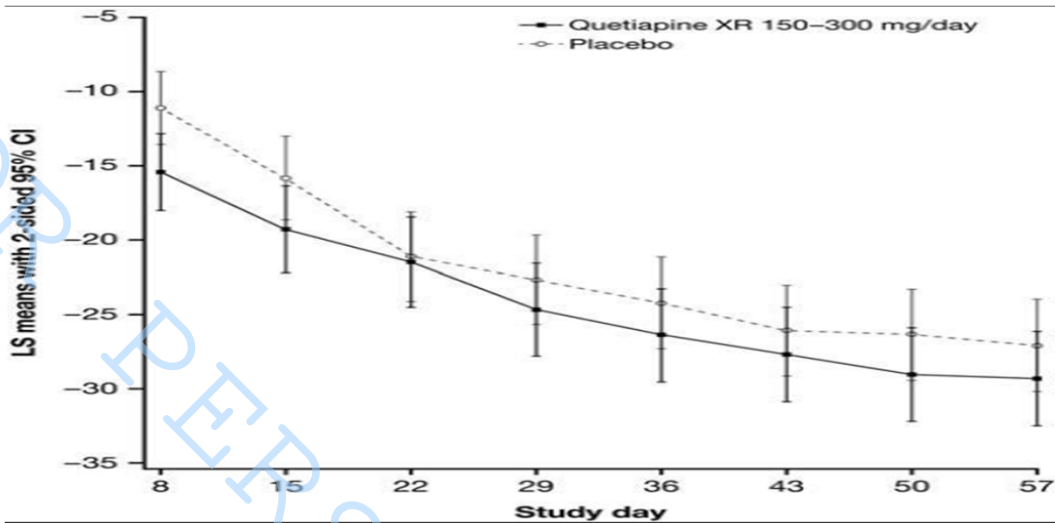


n=2844, mean age=11.76, females=47.3%, mean study duration=5.2 weeks

Vita G et al. JAACAP – in revision.

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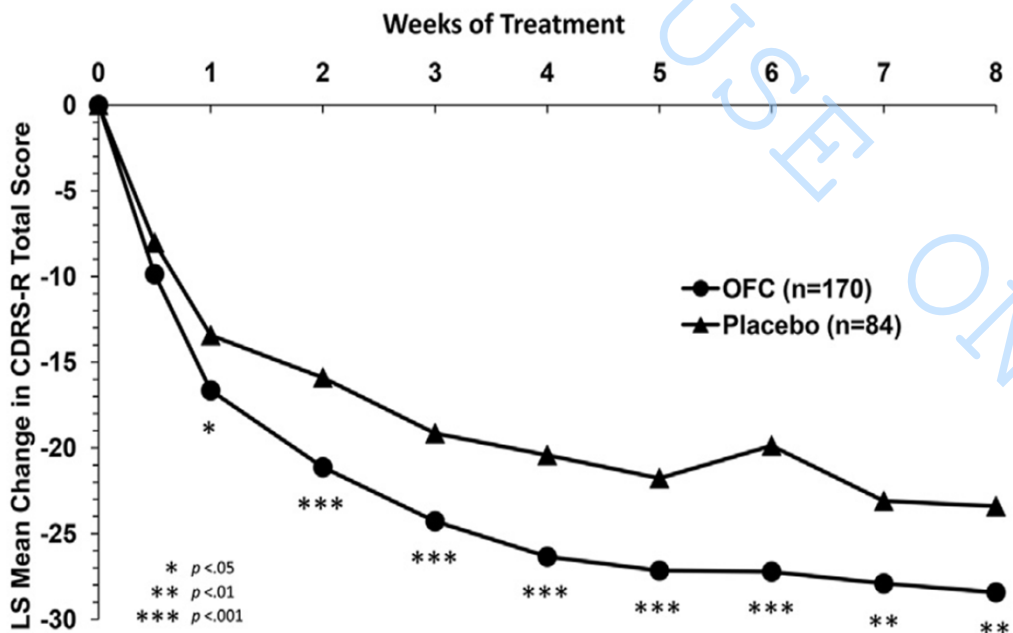
Quetiapine (n=93) vs. Placebo (n=100): CDRS-R Change



Age: 10-17 years (mean=14.0), females: 49.5%
 Response: PBO=55.0% vs QUE: 63.0%; Remission: PBO: 34.0% vs QUE: 45.7%
 Findling RL et al. J Child Adolesc Psychopharmacol. 2014 Aug;24(6):325-35.

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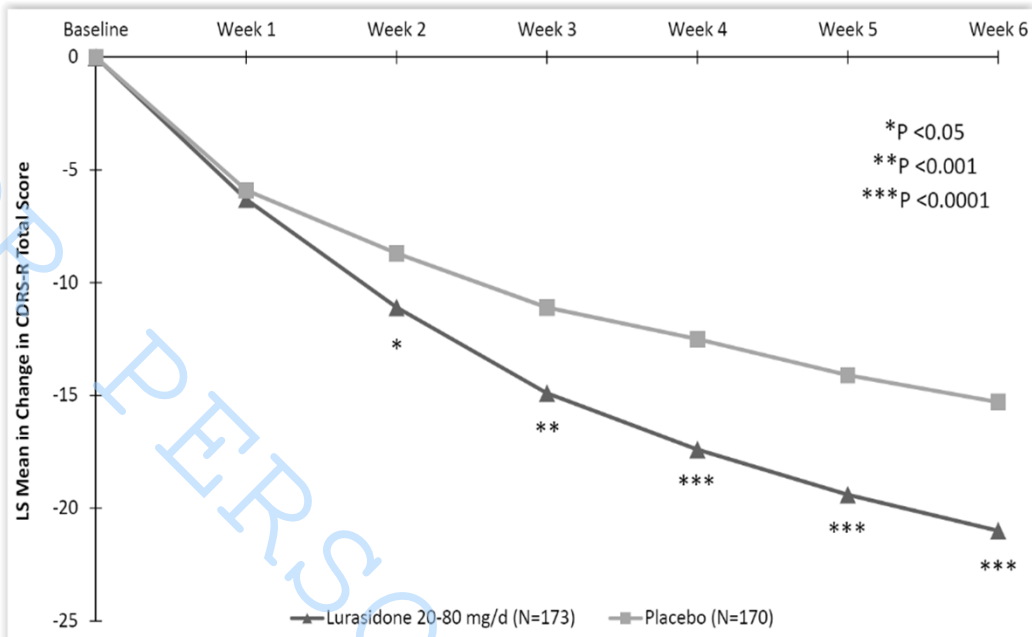
8-Week RCT of OLA/FLU vs PBO



Detke H et al. J Am Acad Child Adolesc Psychiatry. 2015 Mar;54(3):217-24.

22

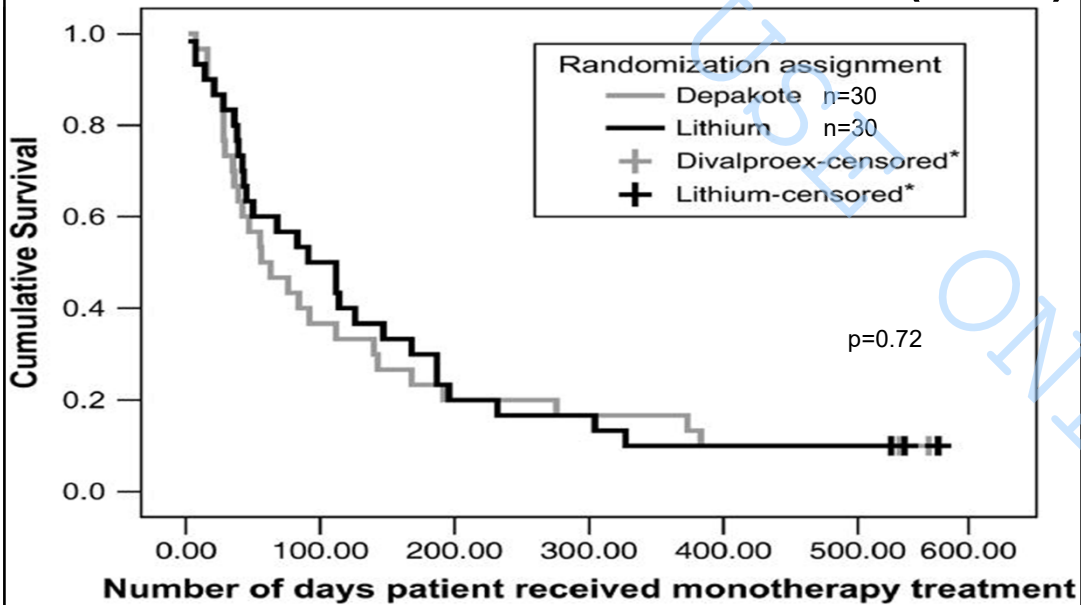
6-Week RCT of Lurasidone vs PBO: CDRS-R



DelBello M et al. J Am Acad Child Adolesc Psychiatry. 2017. Dec;56(12):1015–25.

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18 Mo Maintenance VPA or Li Trial (N=60)

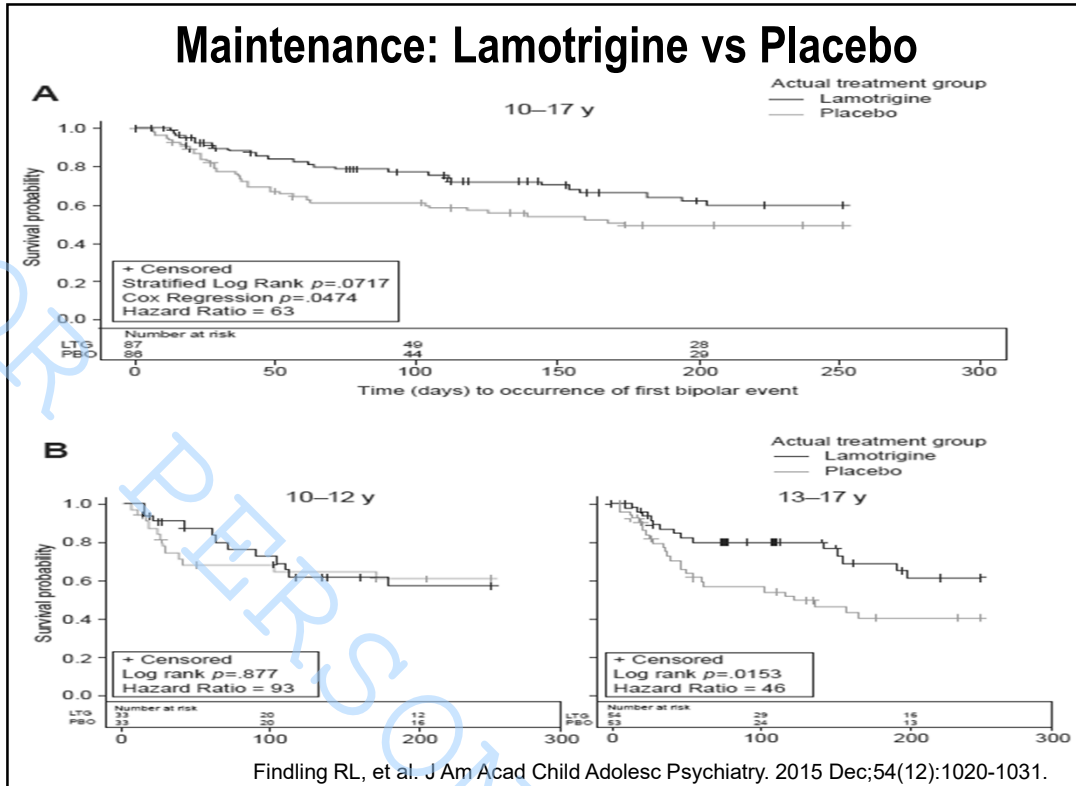


139 youths (10.8±3.5 yrs) initially treated with Li+/DVPX for 10.7±5.4 weeks. Li+ and DVPX did not differ in survival time until emerging relapse (p=0.55) or all-cause discontinuation (p=0.72).

Findling et al., J Am Acad Child Adolesc Psychiatry. 2005 May;44(5):409-17.

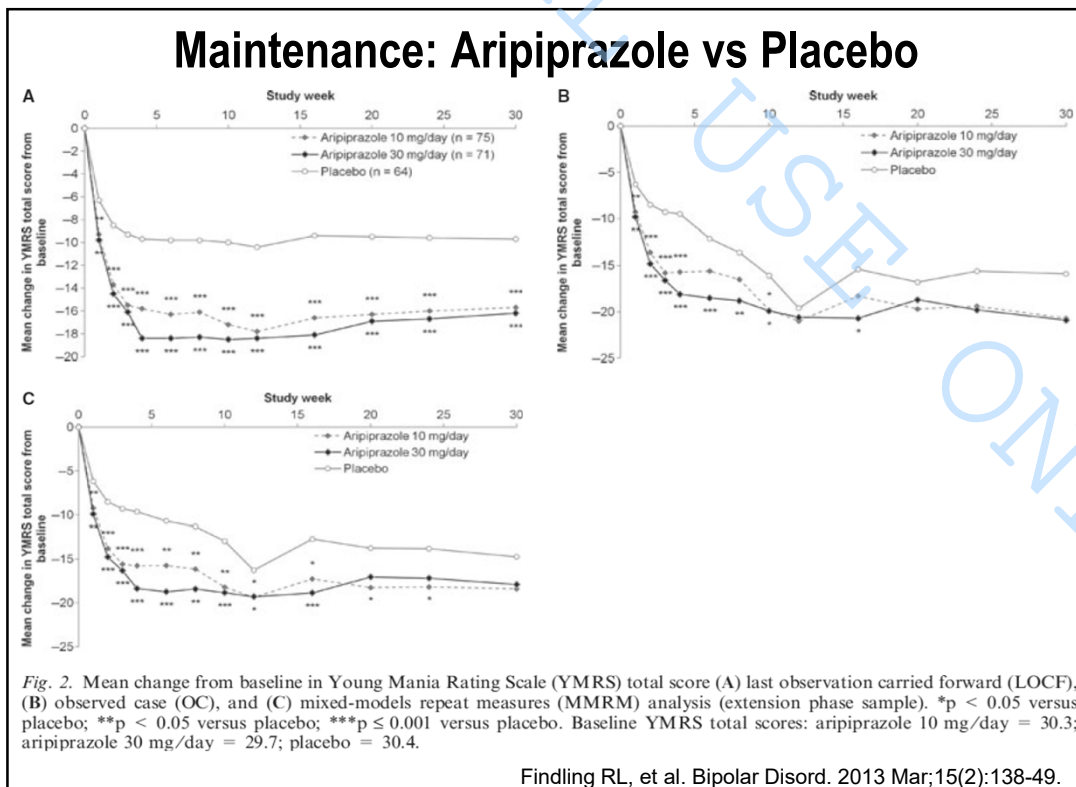
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Maintenance: Lamotrigine vs Placebo



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Maintenance: Aripiprazole vs Placebo



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Double-Blind Trials For Pediatric Bipolar Disorder

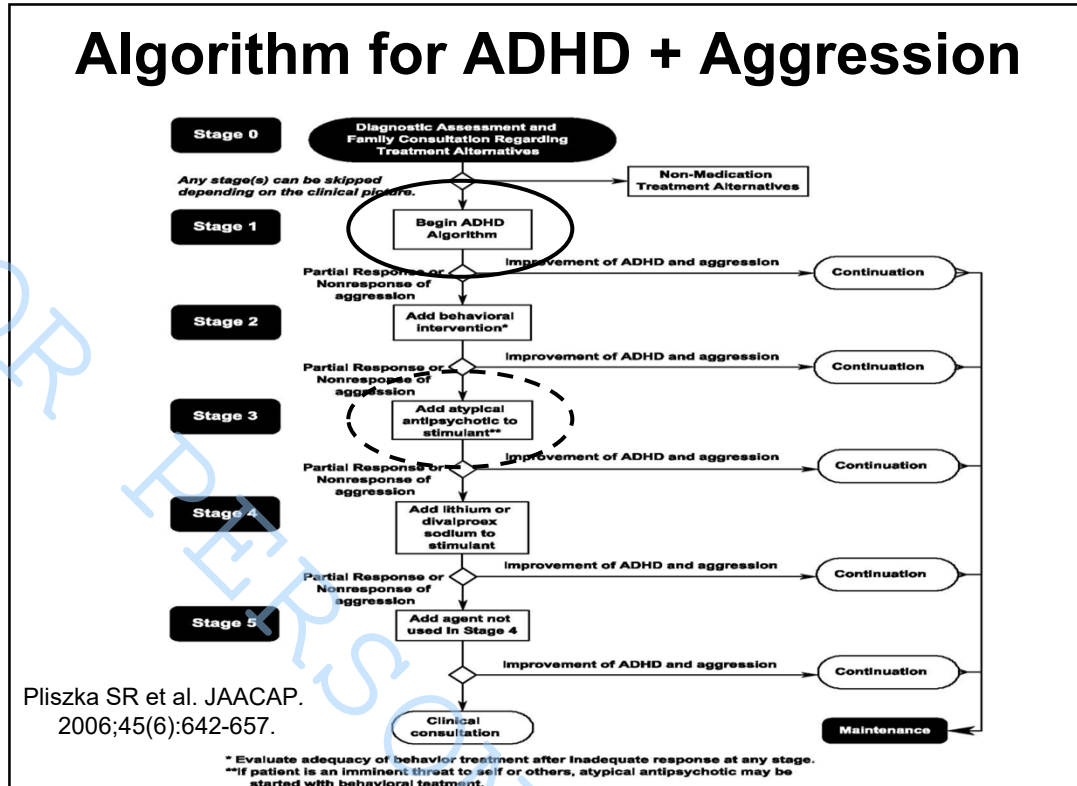
Medication	Manic/Mixed	Depressed	Maintenance
Mood Stabilizers			
Lithium (FDA approved)	+		
Divalproex	- (ER) (+?, DVP)		
Lamotrigine			+/-
Oxcarbazepine	-		
Topiramate	- (+/-)		
Second-Generation Antipsychotics			
Aripiprazole (FDA approved)	+		+
Asenapine (FDA approved)	+		
Lurasidone		+	
Olanzapine (FDA approved)	+		
Olanzapine/Fluoxetine (FDA approved)		+	
Quetiapine (FDA approved)	+	-	
Risperidone (FDA approved)	+		
Ziprasidone	+		

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Efficacy in Autism/Disruptive Behavior Disorders

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Algorithm for ADHD + Aggression



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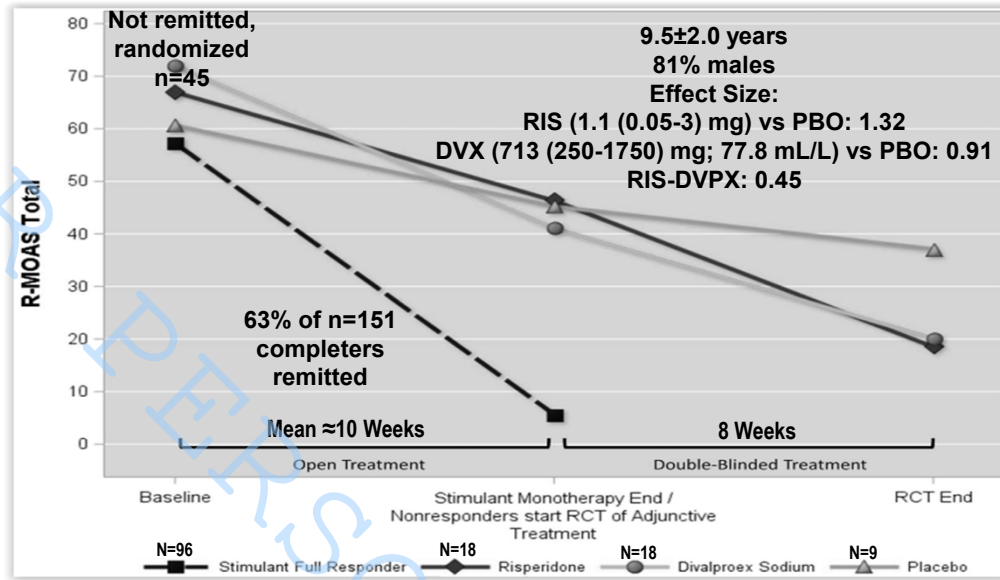
Psychopharmacologic Rx of Aggression in Youth

- RIS Acute (N=10, n=698, 8.3 wks): ES= .72
- RIS Maintenance (N=3, n=391, 13.3 wks): ES= .40
- ARI Acute (N=2, n=308, 8 wks): ES= .41, .49, .62 & .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 OPs: ES=-.13
 - Lithium (N=4 (IP), n=164, 4.5 wks: ES= .63
 - CBZ (N=1 (IP), n=24, 6 weeks: ES= .06
- SGAs: NNT=3; Lithium: NNT=4; STIM: NNT=4

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

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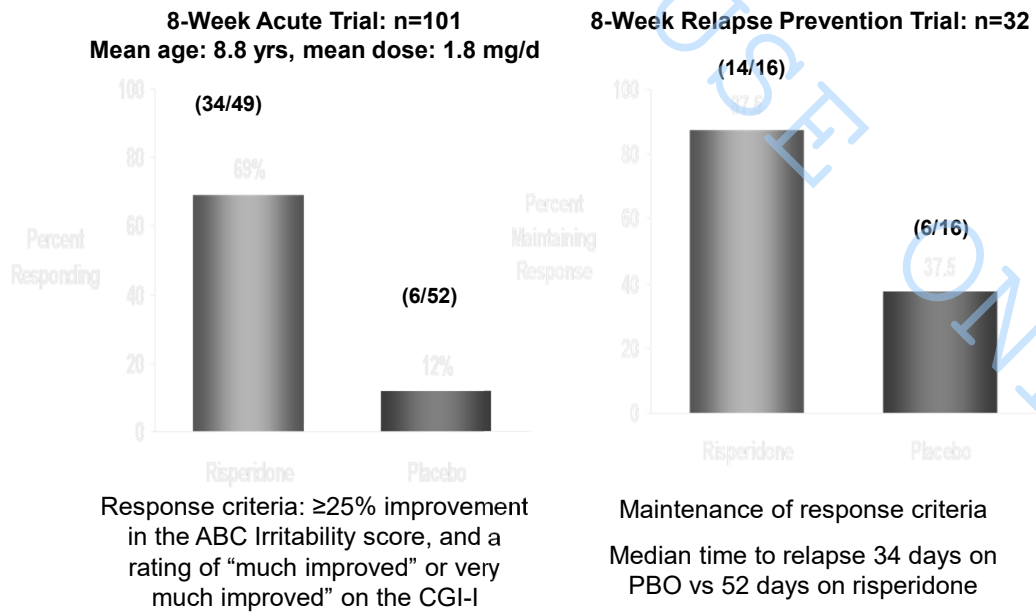
RIS vs DVPX vs PBO for ADHD (6-12 Years) + Aggression After Stimulant Optimization



Patients/families received family based behavioral therapy throughout open and RCT phase
Blader JC et al. J Am Acad Child Adolesc Psychiatry. 2021 Feb;60(2):236-251

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RUPP Trial: Risperidone in Autism

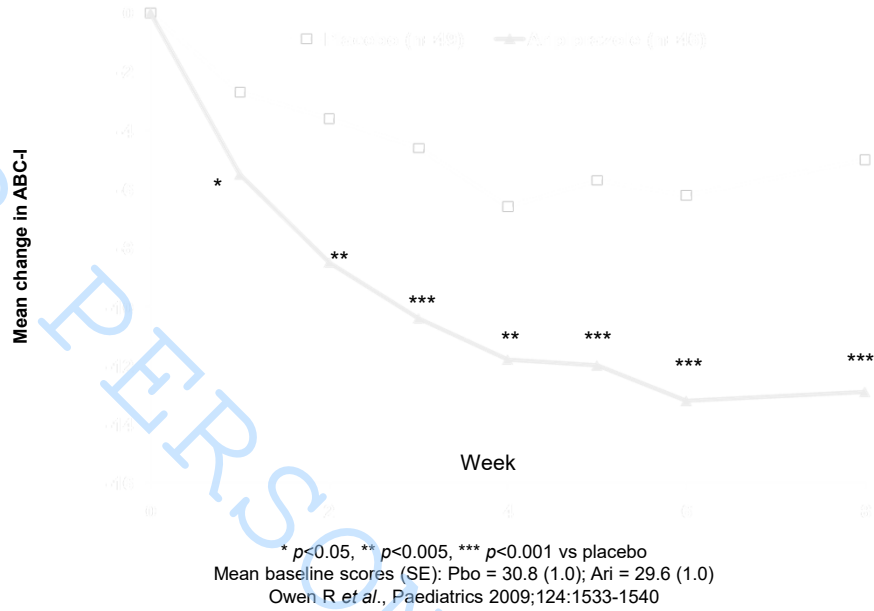


RUPP Autism Network. N Engl J Med. 2002;347:314-321.

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

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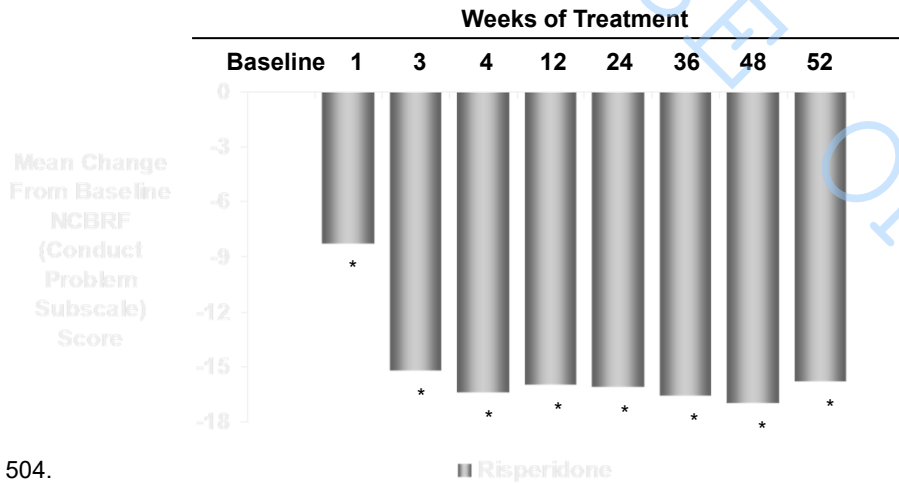
Aripiprazole in autistic disorder: mean change in the aberrant behaviour checklist - irritability subscale by week



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

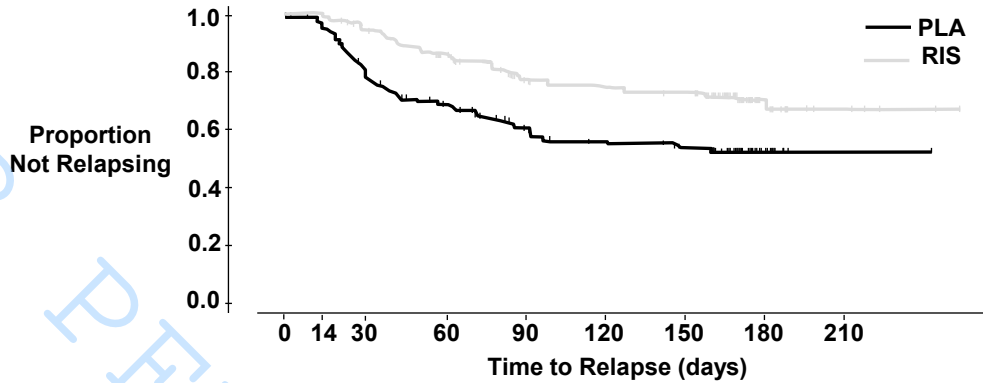
504 children, age = 9.7 years (5–14 y)
 RIS: 1.5 mg/d (0.1–4.3 mg/d)



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.

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



PLA n =	162	152	120	101	77	69	62	11	1
RIS n =	171	170	158	138	118	110	107	24	6

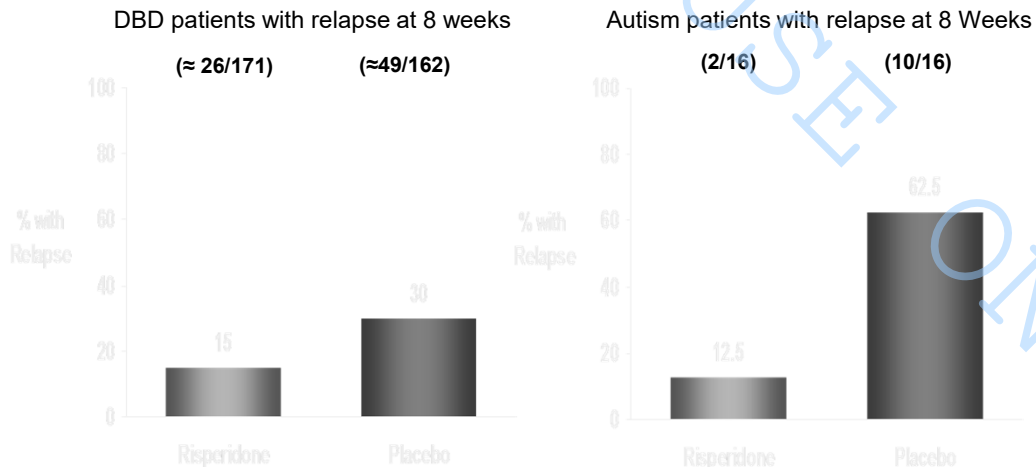
RIS = risperidone-treated subjects; PLA = placebo subjects.

*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

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



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

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

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

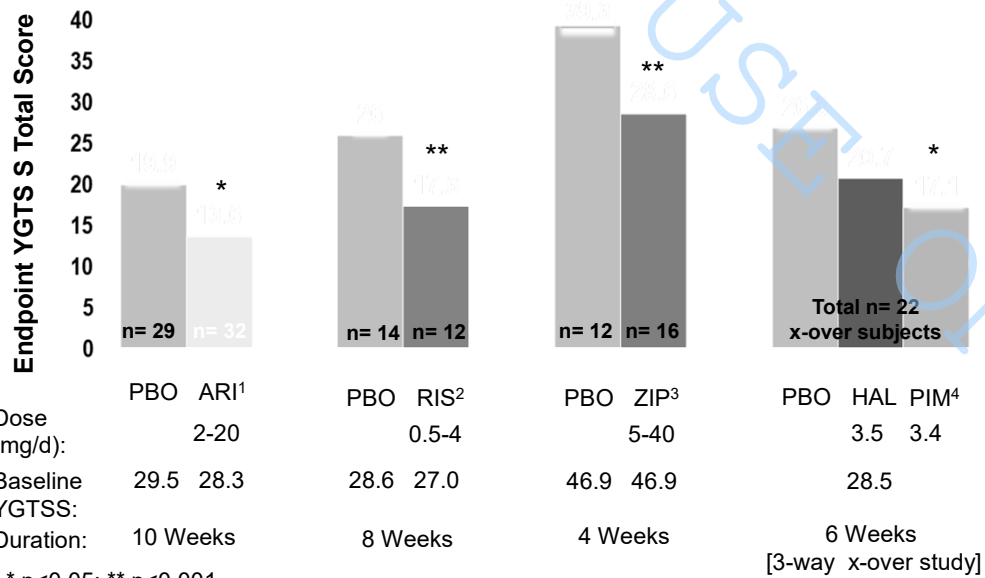
RUPP Autism Network. *Am J Psychiatry*. 2005;162:1361-69

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Tourette's Disorder

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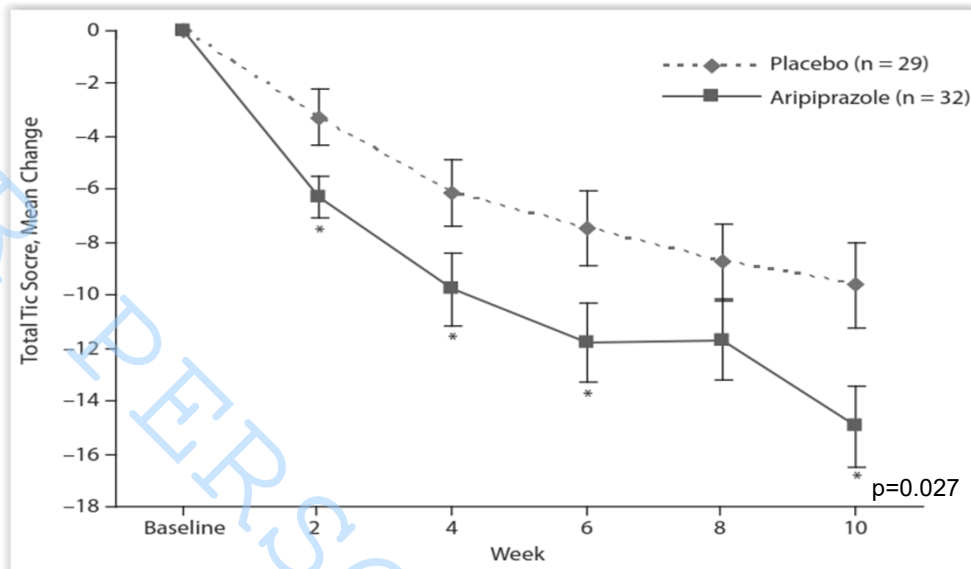
Endpoint Yale Global Tic Severity Total Scores



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.

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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.

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

ORAL ARIPIPRAZOLE FOR TOURETTE'S DISORDER

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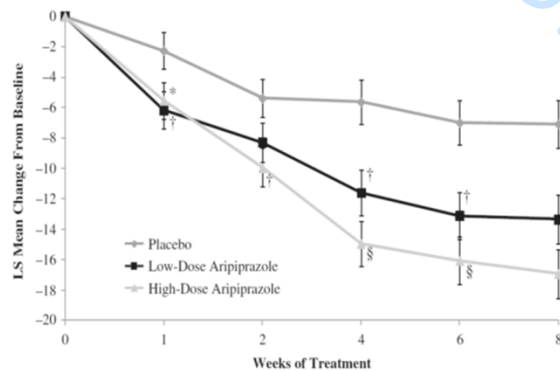


FIG. 3. LS mean (SE) change from baseline in YGTSS-TTS (ITT population). Shown are the LS mean changes from baseline in the YGTSS-TTS by week calculated by using MMRM. Error bars represent the LS mean \pm 1 SE. *p<0.05; †p<0.01; ‡p<0.0001 versus placebo. ITT, intent-to-treat; LS, least squares; MMRM,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

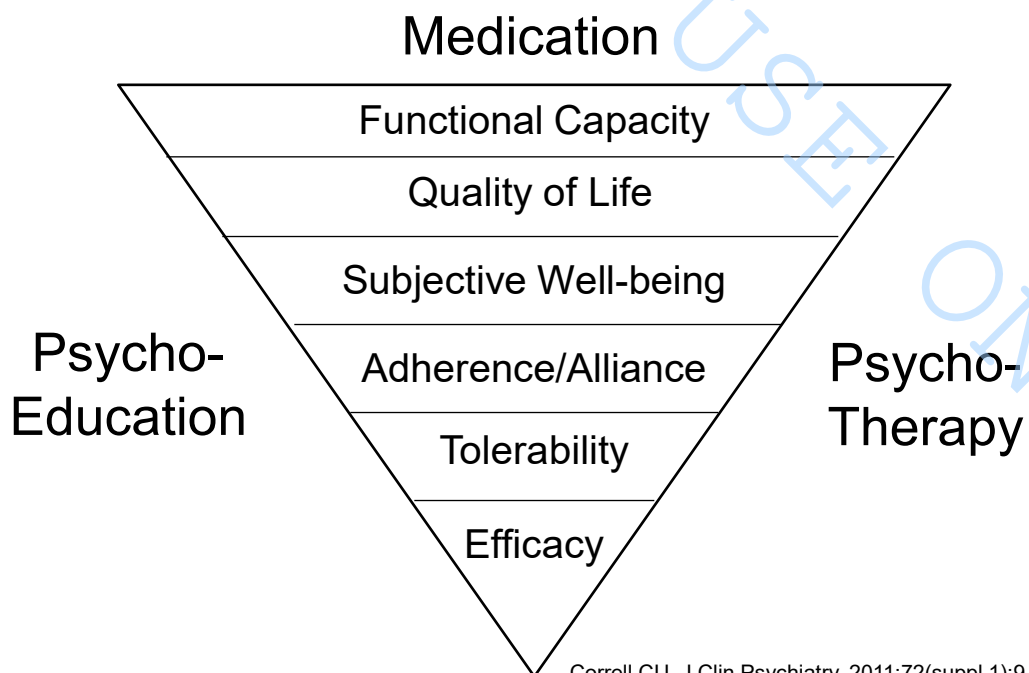
Low-dose aripiprazole (5 mg/day if <50 kg; 10 mg/day if \geq 50 kg),
high-dose aripiprazole (10 mg/day if <50 kg; 20 mg/day if \geq 50 kg)
Sallee F, et al. *J Child Adolesc Psychopharmacol*. 2017 Nov; 27 (9): 771-781.

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Adverse Effects

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The Effectiveness Pyramid

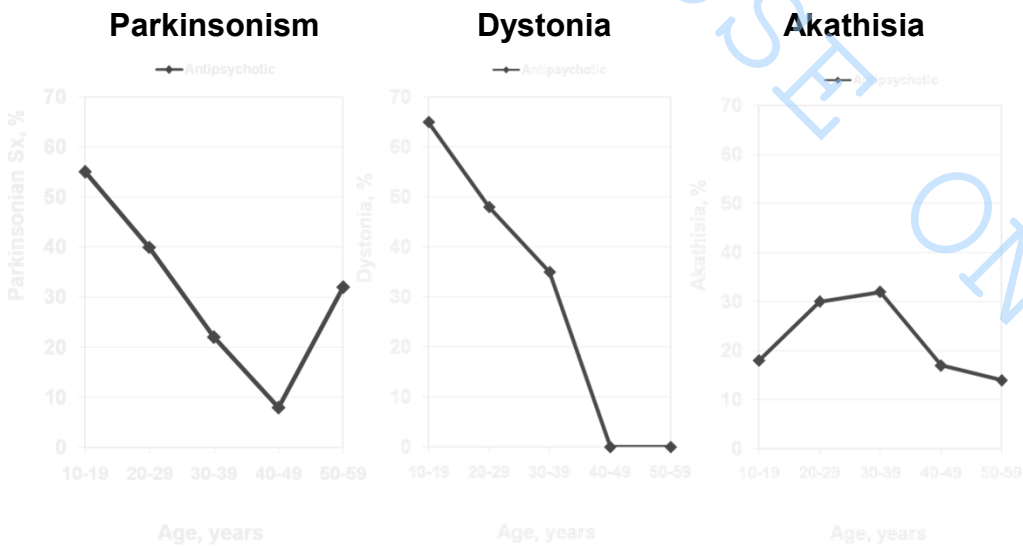


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Extrapyramidal Effects

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Inverse Relationship Between Age and Incidence of EPS



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

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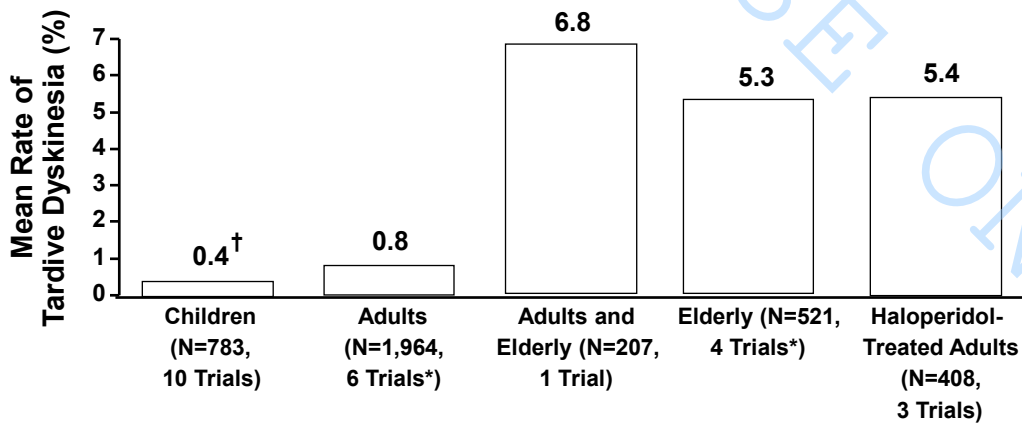
Neuromotor Adverse Effects in 342 Youth During 12 Weeks of Naturalistic Treatment With 5 Second-Generation Antipsychotics

Maren Carbon, MD, Sandeep Kapoor, MD, Eva Sheridan, MD, Aseel Al-Jadiri, MD, Sally Azzo, MD, Tania Sarkaria, MD, John M. Kane, MD, Ema Saito, MD, Christoph U. Correll, MD

	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*
n=342, age: 13.6 years; male=58.2%; antipsychotic-naïve=65.8%							
J Am Acad Child Adolesc Psychiatry 2015;54(9):718-727.							

45

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.

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Endocrine Adverse Effects

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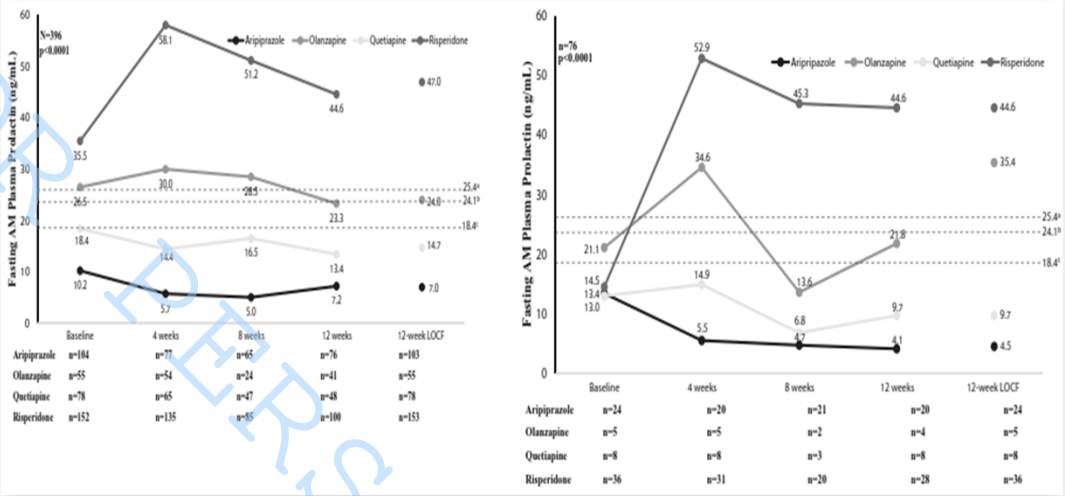
Relative Potency of Antipsychotics in Elevating Serum PRL Prolactin in Youth

- Paliperidone \geq 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

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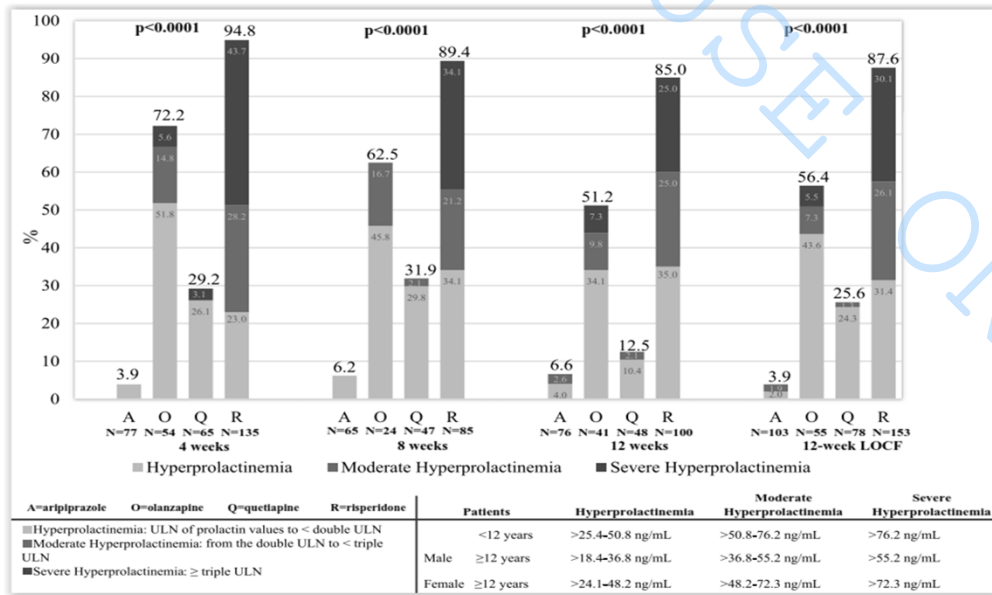
Prolactin Values During 12 Weeks of Antipsychotic Treatment in Youth (n=396)



Koch MT, et al. J Am Acad Child Adolesc Psychiatry. 2023 Sep;62(9):1021-1050.

49

Prevalence of Hyperprolactinemia During Antipsychotic Treatment in Youth (n=396)

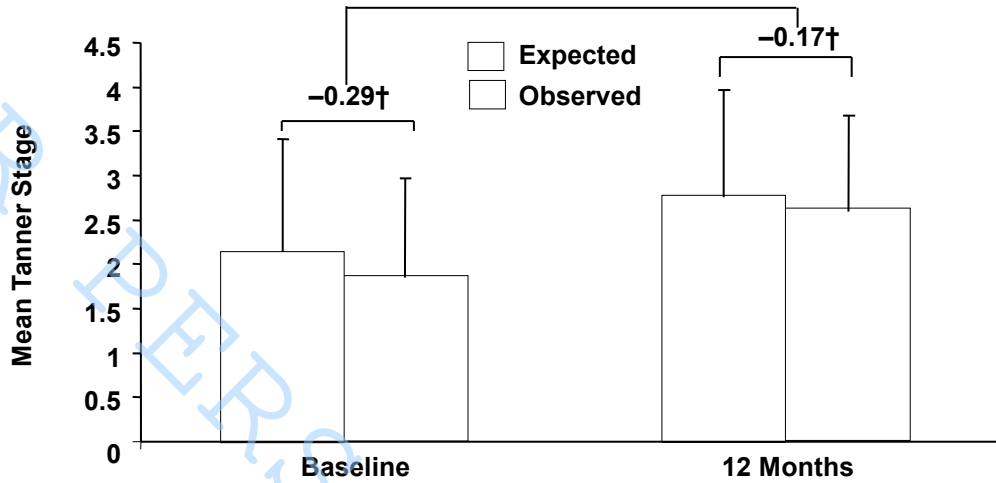


Koch MT, et al. J Am Acad Child Adolesc Psychiatry. 2023 Sep;62(9):1021-1050.

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Observed vs. Expected Tanner Stage in Youth ≥ 9 years Treated with Risperidone (N=222)

Deviation from expected maturation at year 1 was 0.12 ± 0.77



Mean age: 11.9 ± 1.4 years; Boys (≥ 10 years): 80%; Girls (≥ 9 years): 20%; Caucasian: 88%

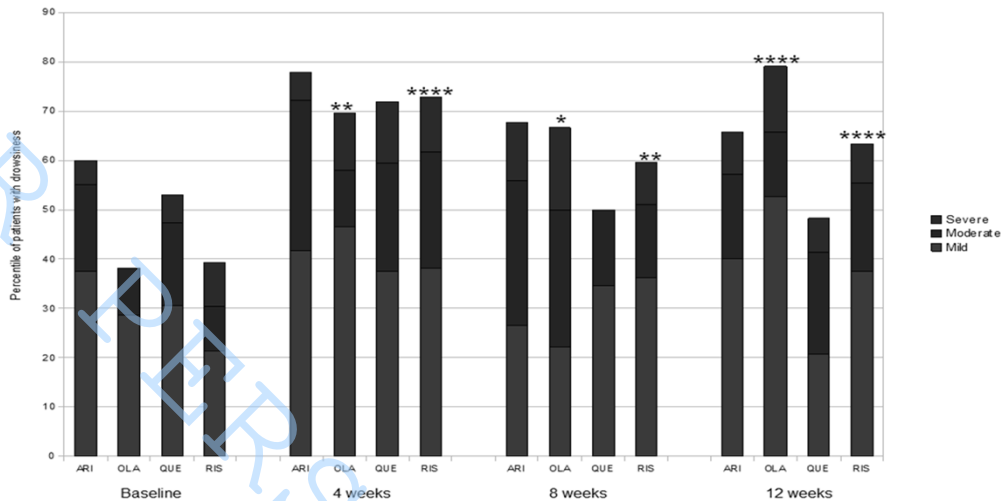
Dunbar et al. Am J Psychiatry 2004 May;161(5):918-20.

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Sedation/Hypersomnia

52

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

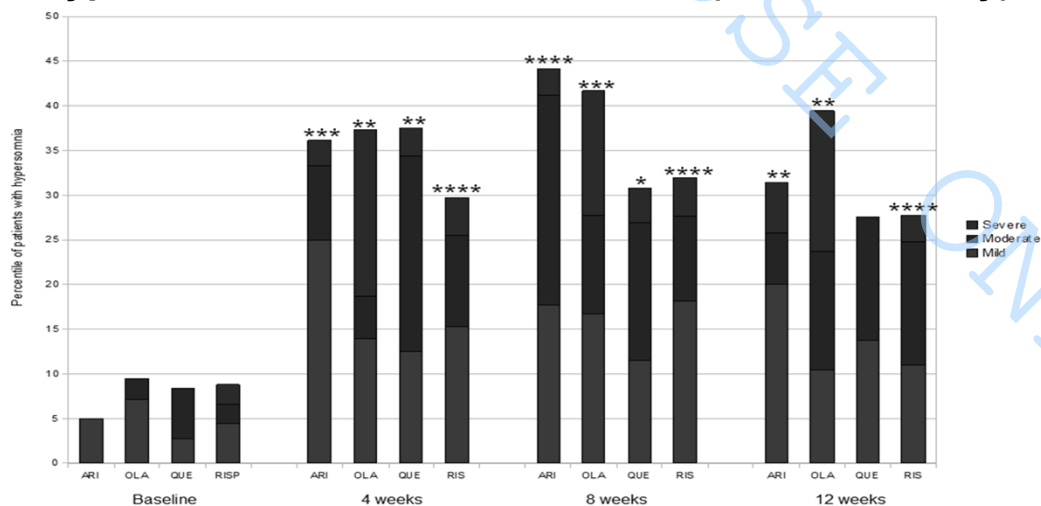


257 antipsychotic-naïve youth (13.8 ± 3.6 years, male=57.8%) initiated aripiprazole (n=40), olanzapine (n=45), quetiapine (n=36), or risperidone (n=135)

Al Dhaher Z et al. J Child Adolesc Psychopharmacol. 2016 Jun;26(5):458-70.

53

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



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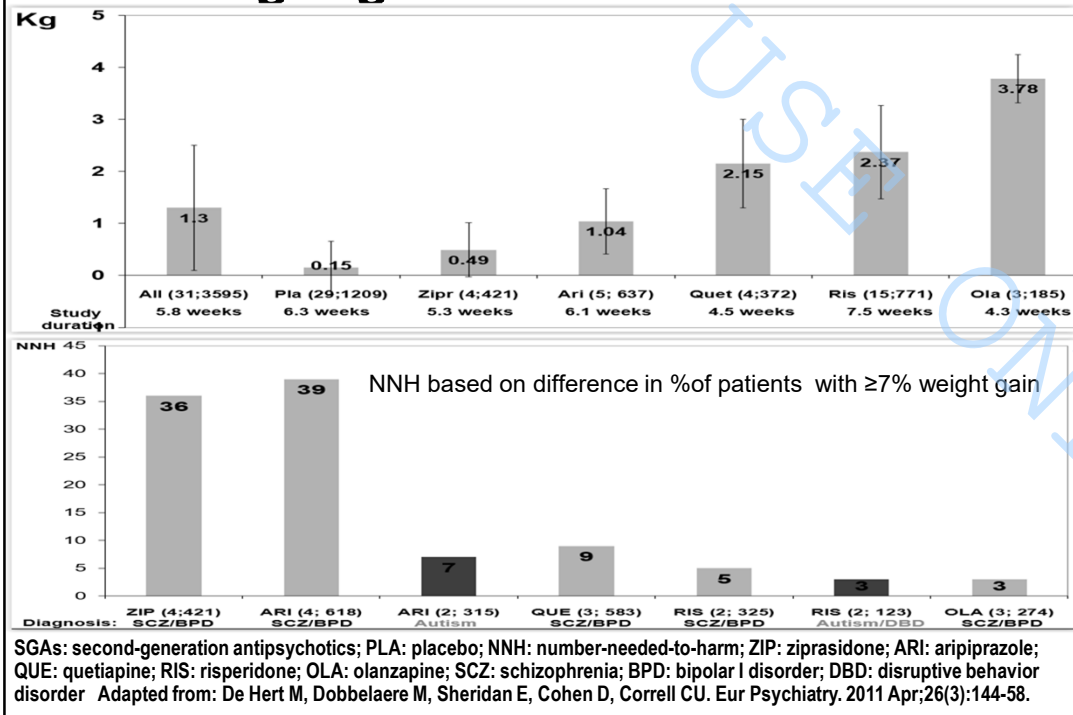
Al Dhaher Z et al. J Child Adolesc Psychopharmacol. 2016 Jun;26(5):458-70.

54

Cardiometabolic Adverse Effects

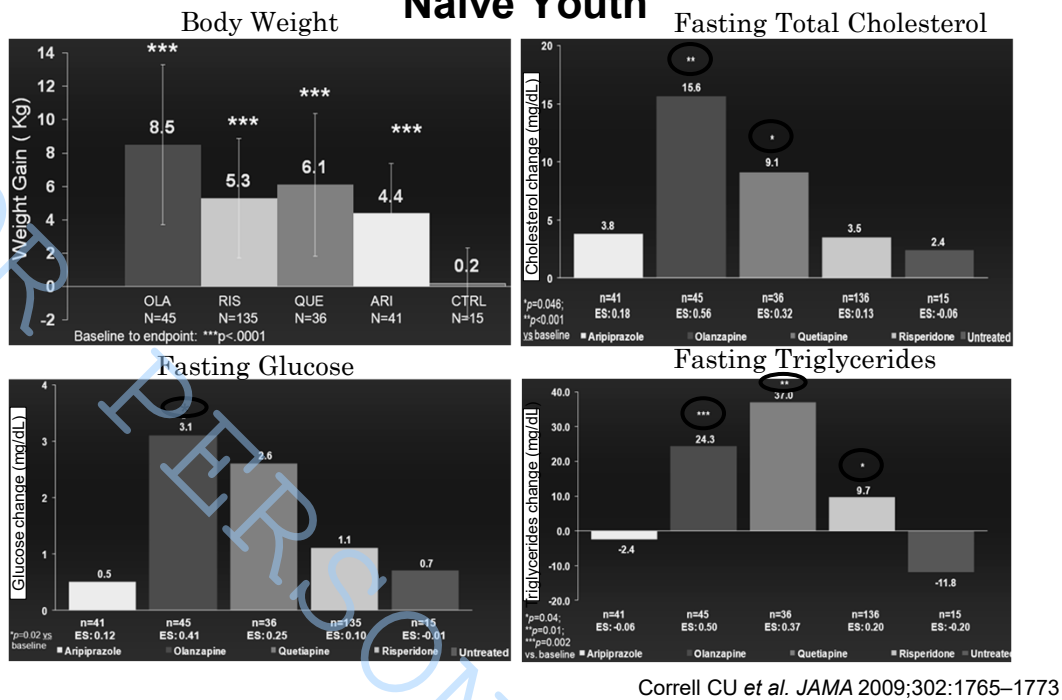
55

Weight gain on SGAs vs. PLA



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



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Number needed to harm (NNH) for adverse body composition outcomes

Antipsychotic-naïve sample. Total n=272*

Outcome variable	Aripiprazole (n=41)	Olanzapine (n=45)	Quetiapine (n=36)	Risperidone (n=135)
Weight gain $\geq 7\%$	2 (1-3)	1 (1-2)	2 (1-3)	2 (1-3)
Weight gain $\geq 14\%$	6 (3- ∞)	2 (1-4)	3 (2-14)	4 (2-31)
Weight gain $\geq 21\%$	20 (6- ∞)	4 (2-38)	18 (6- ∞)	15 (5- ∞)

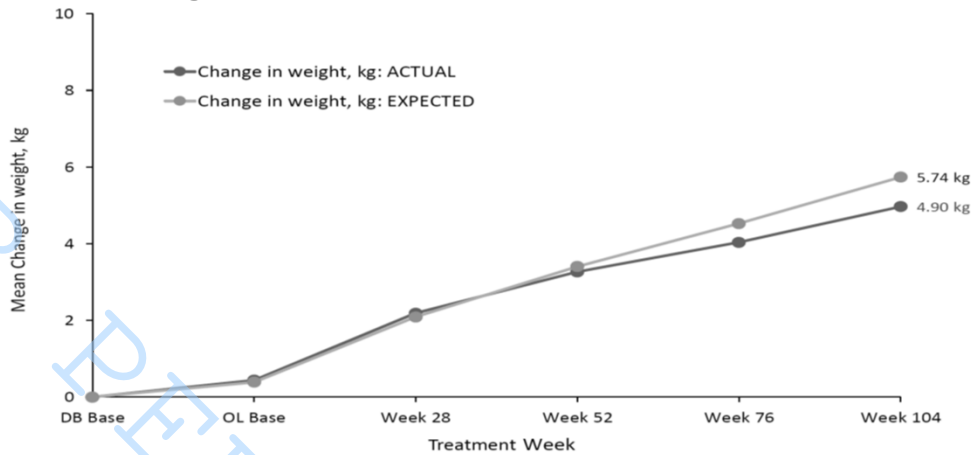
*Includes 15 untreated comparison patients

Data are presented as NNT +/- 95% Confidence Interval

Calculated from data in Correll CU et al. JAMA 2009;302:1765-1773

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Change From Double-blind Baseline in Body Weight and BMI: Actual vs. Expected



	DB Base	OL Base	Week 28	Week 52	Week 76	Week 104
BMI-change: ACTUAL		+0.10	+0.47	+0.64	+0.70	+0.84
BMI-change: EXPECTED		+0.07	+0.39	+0.64	+0.84	+1.02
Sample size:	N=271	N=271	N=215	N=189	N=174	N=156

Expected weight values are based on CDC growth charts, and expected BMI values (in kg/m²) are based on WHO reference growth charts
 Note: the x-axis (DB to OL Baseline) is not proportional to the number of weeks between each assessment time-point

Correll CU et al. CNS Spectr. 2022 Feb;27(1):118-128.

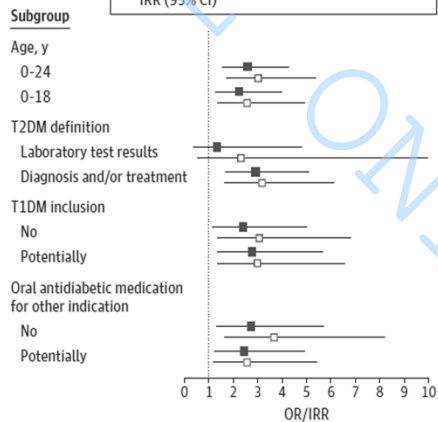
59

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)		
Subgroup									
Age, y									
0-24									
0-18									
T2DM definition									
Laboratory test results									
Diagnosis and/or treatment									
T1DM inclusion									
No									
Potentially									
Oral antidiabetic medication for other indication									
No									
Potentially									

■ Unadjusted, cumulative risk per 1000 patients, OR (95% CI)
 □ Incidence per 1000 patient-years, IRR (95% CI)



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.

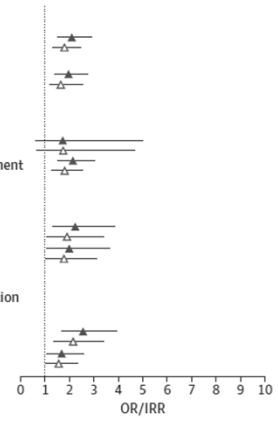
60

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			OR (95% CI)	IRR (95% CI)	Subgroup
No.	Patient-Years	T2DM Cases	No.	Patient-Years	T2DM Cases			
1342121	2071135	3235 (3198)	169840	294347	74 (753)	2.09 (1.50-2.90)	1.79 (1.31-2.44)	Age, y
1327692	2053172	3221 (3184)	140982	256325	682 (661)	2.00 (1.39-2.76)	1.64 (1.20-2.55)	0-18
26265	10231	19	9636	3710	12	1.72 (0.60-4.98)	1.74 (0.65-4.68)	T2DM definition
1315856	2060904	3216 (3179)	160204	290637	762 (741)	2.14 (1.50-3.05)	1.80 (1.29-2.53)	Laboratory test results
71213	300574	594	13417	107143	269	1.99 (1.08-3.65)	1.77 (1.01-3.11)	Diagnosis and/or treatment
1270908	1770561	2641 (2604)	129589	187204	505 (484)	2.23 (1.29-3.86)	1.90 (1.06-3.40)	T1DM inclusion
1251601	1903757	3046	140549	245681	618	1.68 (1.08-2.59)	1.56 (1.04-2.34)	No
90520	167378	189 (152)	29291	48666	156 (135)	2.55 (1.66-3.92)	2.15 (1.35-3.42)	Potentially
								Oral antidiabetic medication for other indication
								No
								Potentially

▲ Unadjusted, cumulative risk per 1000 patients, OR (95% CI)
 △ Incidence per 1000 patient-years, IRR (95% CI)

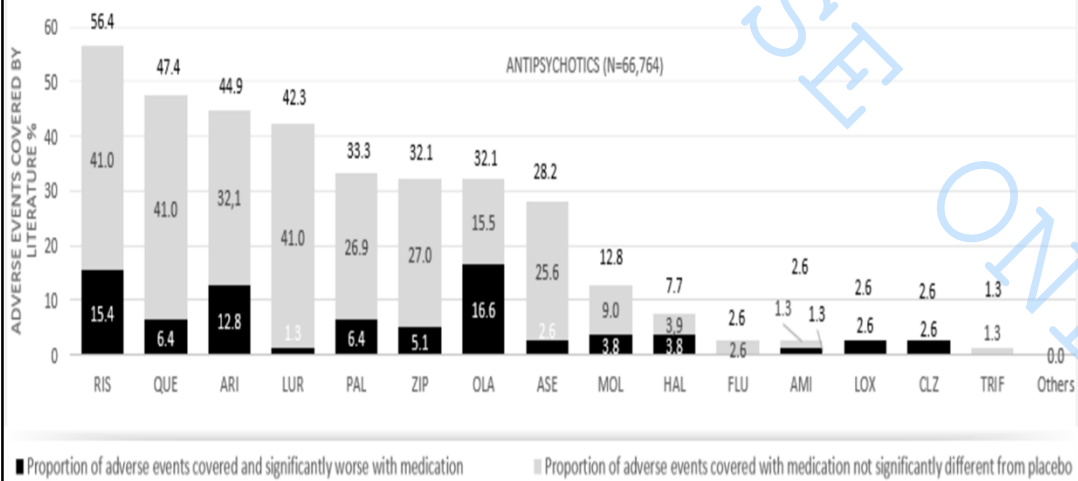


Studies=7, 1,342,121 patients and 2,071,135 patient-years; cumulative T2DM risk (OR, 2.09; 95%CI, 1.50-2.90; P < .0001) and IRR (IRR, 1.79; 95%CI, 1.31-2.44; P < .0001).

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

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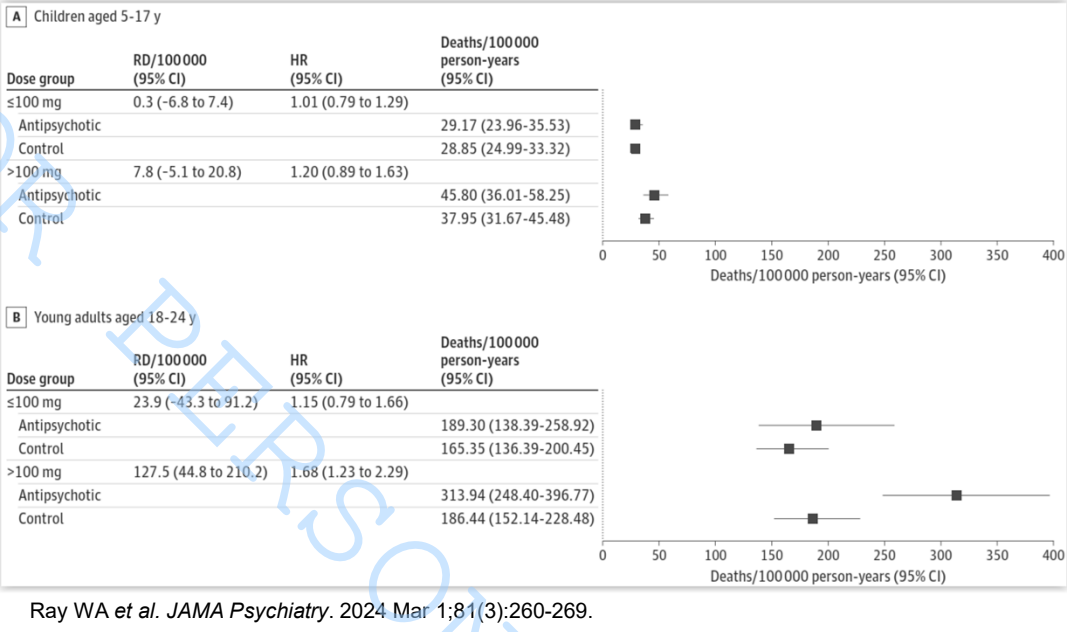
Proportion of 78 Reported Adverse Events of 80 Psychotropic Drugs in Youth Either Worse / not Different from PBO



Solmi M et al. World Psychiatry 2020;19:214-232.

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Adjusted Incidence of Mortality According to Antipsychotic Treatment and Dose in CPZ Equivalents for Children and Young Adults



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Adverse Effect Monitoring and Management

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Antipsychotic 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, blood lipids	Baseline, at 3 mo and (6-)12monthly
Liver function tests	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	When symptomatic or PRL-raising AP
EKG	If on ZIP: during titration, at max. dose If on CLO: baseline and if cardiac sx

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

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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.

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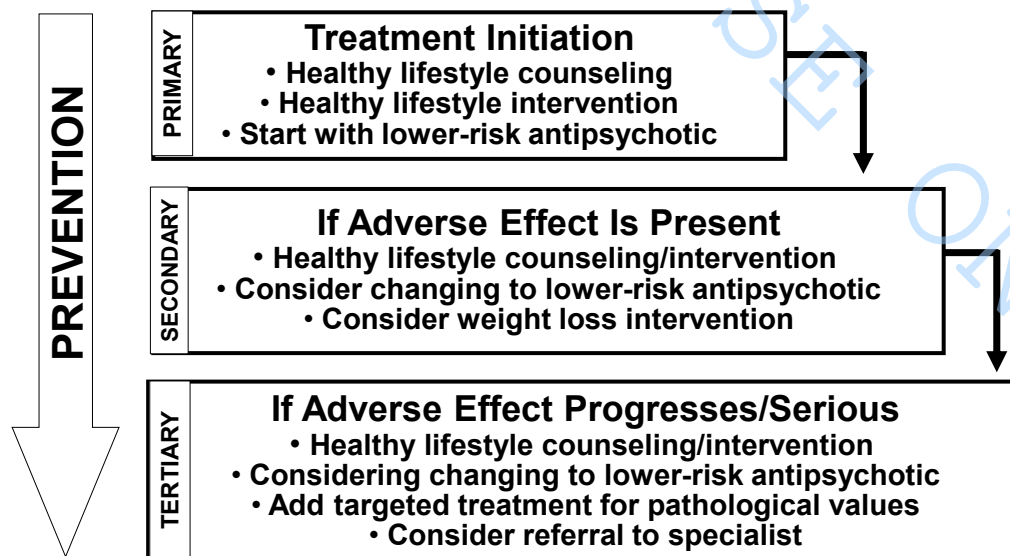
Assessment : Blood Pressure and Labs

- **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.

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Medical Risk Management Strategies in Antipsychotic-Treated Patients



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

68

12-Step Healthy Lifestyle Program

Do's	Do Not's
<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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.

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Summary

- **Second-generation antipsychotics have proven efficacy in pediatric schizophrenia, bipolar disorder, irritability associated with autistic disorder, aggression and Tourette's disorder.**
- **Like in adults, the relative efficacy of antipsychotics seems to be roughly similar, except for clozapine**
- **Additional efficacy based on open studies/ extrapolation from adult data exist for antidepressant augmentation for OCD and MDD, physical hyperactivity/narrow body focus in anorexia nervosa, focus on traumatic event/insomnia/anxiety with PTSD.**
- **A careful risk-to-benefit evaluation is needed and lowest risk agents and non-pharmacologic treatment options ought to be tried first**

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Summary (2)

- Pediatric patients are at greater risk than adults for prolactin elevation, sedation, weight gain and metabolic side effects
- Ranking order of adverse effects are roughly similar to adults with possible exceptions of:
 - RIS more and ? CLZ less relative weight gain
 - OLA and ZIP greater relative prolactin effects
 - All APs associated with relevant rates of sedation
- Although diabetes and metabolic syndrome are rare, the marked increase in insulin resistance and incidence of dyslipidemia in youth are of great concern

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Recommendations

- Patients and families should be included in a careful risk-benefit assessment when choosing a specific psychotropic medication
- Consideration of adverse effects and dietary/life style counseling should be part of any psychotropic treatment initiation
- Routine, proactive monitoring of side effects is essential to optimize outcomes
- In case of severe early side effects, consider switching to a lower risk medication
- Mechanisms and risk/protective factors for specific adverse effects require further study
- Interventions to reverse or, even, prevent specific adverse effects need to be developed and tested

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