

CHILD & ADOLESCENT PSYCHIATRY: selected updates


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PART I
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1

Disclaimer

• NO CONFLICT OF INTEREST



2

Learning Objectives


Utilize Evidence Based Treatment for EOS; and monitor as well as treat metabolic side effects from the antipsychotics

Incorporate the cultural formulation tools as apart of assessment of children and adolescents

3

Early Onset Schizophrenia (EOS)

- onset: before age 18;
- rare before age 12 (VEOS/COS)
- WHO: 8th leading cause of disability (15-44) ;DALYs: rising since 2005
- prevalence world-wide: 0.5%
- COS: 0.04%
- usually associated with chronic morbidity and functional impairment
- effectiveness of antipsychotics : variable
- need for identification of specific neurodevelopmental and genetic factors



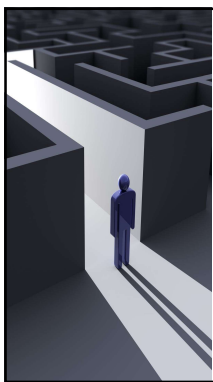
4

Signs and Symptoms (Mayo Clinic)

Thinking : problem w/ thinking and reasoning
 bizarre ideas or speech
 confusing dreams or television for reality

Behavior: withdrawal
 trouble sleeping
 lack of motivation
 ADLs not met
 bizarre or violent behavior
 drug or nicotine use

Emotions: irritability or depressed mood
 lack of emotions
 strange anxiety or fear
 excessive suspicion of others



5

MASTER CLINICIAN REVIEW Check for updates

Psychosis in Children and Adolescents

Jon McClellan, MD

Psychosis is characterized by overt disruptions in thought, perceptions, and behavior. Complex syndromes presenting with psychosis, including schizophrenia spectrum disorders, mood disorders, and medical illnesses, are differentiated by characteristic patterns of symptom presentation and course of illness. Accurate diagnosis is important to guide treatment and to avoid inaccurate labeling, because most youth reporting psychotic-like experiences do not have a true psychotic disorder.

Key words: psychosis, schizophrenia, hallucinations, delusions, antipsychotic medications

J Am Acad Child Adolesc Psychiatry 2018;57(5):308-312. CG CME

6

Challenge in the Youth: is it really psychosis??
Case #1

DJ, 8 y.o boy, poor impulse control, anger problems; mom states child c/o hearing a voice telling him to hurt her after a severe outburst; assessment shows normal growth, thinking and behavior; he drew a picture of demon like face with fiery eyes, "Desperado", who always tells him not to listen to any other voice and not to hurt anyone; DJ not confused nor concerned about the voice; he elaborates with further discussion that explains his behavior; mom's concern of him developing Schizophrenia as her own brother has dx of this condition

7

Challenge in the Youth: is it really psychosis?
Case #2

17 yr girl, in residential treatment for self harm & suicidal behavior; c/o seeing a tall man w/curly brown hair & wearing Wranger-sunglasses; he sometimes talk to her; used to be supportive but recently says "ugly and should commit suicide"; sees more when upset / angry , alone / at night before falling asleep;

Otherwise, organized thoughts, no sign of responding internal stimuli or thought dis;

In therapy, she mentioned that she started seeing this man when her stepfather was sexually abusing her; initially was hopeful of that the man would rescue her later on the images reminded of her of abuse

8


Differential Dx

Psychotic mood d/o(BI-Polar I w/ psychosis ; psychotic depression)	ASD and other developmental d/o	Sec. to general medical conditions	Sz
CNS auto-immune infection	Genetic (vcf syn.)	Meds. (steroids)	Neoplasm
	delirium	Toxins; substance of abuse	


9

Treatment modalities in Youth w/ EOS


- Psycho-pharmacotherapy
- Psycho-education
- Family intervention
- CB strategies
- Social skills training
- Problem solving skills
- Specialized educational program (in some cases)
- Vocational training



10



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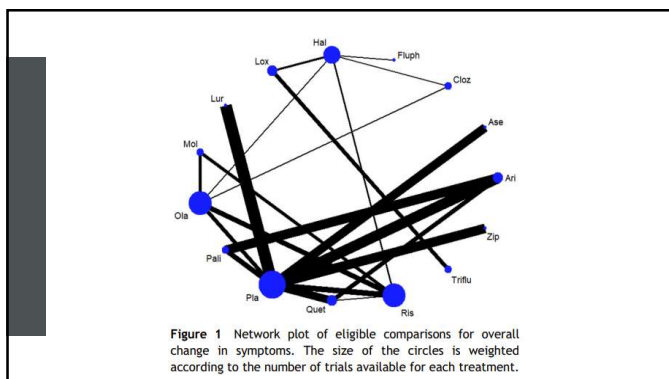


REVIEW

Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis

Marc Krause^{a,f,*}, Yikang Zhu^b, Maximilian Huhn^a, Johannes Schneider-Thoma^a, Irene Bighelli^a, Anna Chaimani^{c,d,e}, Stefan Leucht^a

11



12

Summary of above NMA:

Primary out-come: efficacy as measured by overall change	Secondary out-comes: pos and neg sx response	dropouts
QOL	Soc.functioning	wt gain
sedation	prolactin	EPS

13

European Psychiatry
www.cambridge.org/epa

Review/Meta-analysis

Predicting antipsychotic-induced weight gain in first episode psychosis – A field-wide systematic review and meta-analysis of non-genetic prognostic factors

Ita Fitzgerald^{1,2}, Laura J. Sahn^{2,3}, Amy Byrne⁴, Jean O'Connell^{5,6}, Joie Ensor⁷, Ciara Ni Dhubhlaing^{1,2}, Sarah O'Dwyer⁸ and Erin K. Crowley⁹

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14

Summary of review: AIWG

Category	Conclusion
1. Measurement of prognostic factors evaluated prior to medication	Insufficient evidence
2. Clinical variables previously thought to be prognostic influence on AIWG (e.g age and antipsychotic treatment response)	analysis did not provide conclusive evidence significantly impact AIWG
3. Prognostic value of Antipsychotic prescription	The prescribed medication remains the most imp variable but no conclusive evidence dose impacting AIWG prognosis
4. Early increase in BMI	Increase in first 12 weeks by ≥5% in base line body wt. has worse long-term prognosis

15

REVIEW ARTICLE

Comparative Efficacy and Tolerability of Antipsychotics for Juvenile Psychotic Disorders
A Systematic Review and Network Meta-Analysis

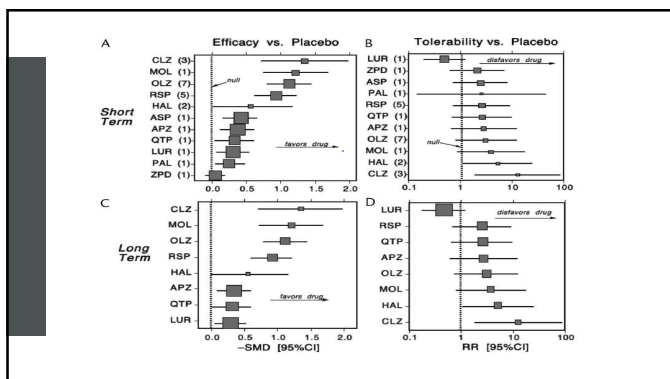
Caitlin S. Yee, MD,^{1,2} Anees Bahji, MD, CISAM, FRCPC,³ Maria Lolich, PhD,⁴
 Gustavo H. Vázquez, MD, PhD, FRCPC,^{1,5} and Ross J. Baldessarini, MD^{5,6}

16

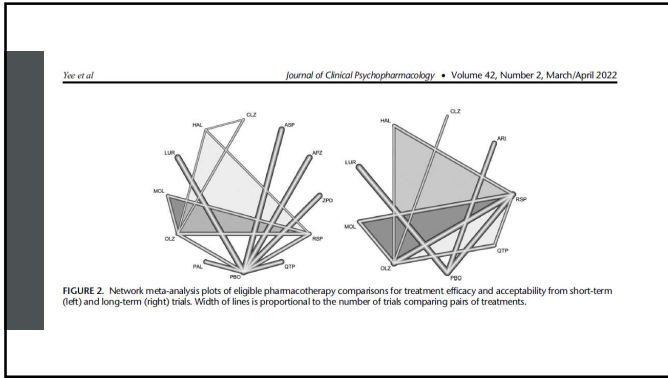
Pairwise Meta-analysis Vs. Network Meta-analysis

- **Pairwise MA** (also known as PW-MA, PMA) involves analysis of RCTs of two agents/treatments
- **Network Metanalysis (NMA)** gives a global estimate of treatment effects for a set of multiple interventions, ≥ 3 , combining direct and indirect evidence, especially when pairwise evidence are available

17



18



19

Psychopharmacologic Treatment of Schizophrenia in Adolescents and Children

Esther S. Lee, MD*, Hal Kronsberg, MD, Robert L. Findling, MD, MBA

20

Table 1
Summary of prescribing information for second-generation antipsychotic agents

Medication	Schizophrenia	Recommended Dosages	Available Strengths	Treatment Considerations for FDA-Approved Agents
Clozapine	No	Initial: 0.5 mg Target: 3 mg Efficacy range: 1.6 mg Maximum: 6 mg/d	Tablets: 0.25, 0.5, 1, 2, 3, 4 mg Oral solution: 1 mg/mL	General warnings/precautions • Neuroleptic malignant syndrome • Tardive dyskinesia • Hyperglycemia and diabetes mellitus • Hyperprolactinemia (higher risk with risperidone)
Risperidone	Yes (13–17 y)	Initial: 2.5–5 mg Target: 10 mg/d Maximum: 20 mg/d	Tablets (not scored): 2.5, 5, 7.5, 10, 15, 20 mg Orally disintegrating tablets: 5, 10, 15, 20 mg Intramuscular injection: 10 mg vial	• Orthostatic hypotension • Leukopenia, neutropenia, and agranulocytosis (elevated risk with clozapine) • Sialorrhea • Hyperlipidemia (higher risk with clozapine, clozapine in adult studies) • Weight gain (higher risk with clozapine, clozapine in adult studies)
Olanzapine	Yes (13–17 y)	Initial: 2.5–5 mg Target: 10 mg/d Maximum: 20 mg/d	Tablets (not scored): 2.5, 5, 7.5, 10, 15, 20 mg Orally disintegrating tablets: 5, 10, 15, 20 mg Intramuscular injection: 10 mg vial	• Cardiovascular changes (higher risk of QTc prolongation with ziprasidone; higher risk of myocarditis with clozapine) • Seizure (clozapine associated with greatest risk increase) • Potential for cognitive and motor impairment • Hypotension (observed with quetiapine use) • Cataracts (observed with long-term quetiapine use) General monitoring recommendations Baseline • Detailed personal, family, and lifestyle history (to be updated regularly) • Parkinsonism, akathisia • Tardive dyskinesia • Weight, weight (every visit) • Blood pressure, pulse
Quetiapine	Yes (13–17 y)	Initial: 25 mg bid Target: 400–800 mg/d Max: 800 mg/d	Tablets: 25, 50, 100, 200, 300, 400 mg	
Aripiprazole	Yes (13–17 y)	Initial: 2 mg Target: 10 mg/d Maximum: 30 mg/d	Tablets: 2, 5, 10, 15, 20, 30 mg Orally disintegrating tablets: 10, 15 mg Oral solution: 1 mg/mL Intramuscular injection: 9.75 mg/1.3 mL, single-dose vial	
Paliperidone	Yes (12–17 y)	Initial: 3 mg Target: 3–6 mg/d (<51 kg), 3–12 mg/d (>51 kg) Maximum: 6 mg/d (<51 kg), 12 mg/d (>51 kg) * Tablet must be swallowed whole	Tablets: 1.5, 3, 6, 9 mg	

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21

Table 1 (continued)

Medication	VDA Approval for Adolescents	Recommended Dosages	Available Strengths	Treatment Considerations for FDA-Approved Agents
Lurasidone	Yes (13-17 y)	Initial: 40 mg Target: 40-80 mg/d Maximum: 80 mg/d * Tablet should be taken with food (at least 350 calories)	Tablets: 20, 40, 60, 80, 120 mg	<ul style="list-style-type: none"> Electrolytes, complete blood count, renal, and liver function Fasting blood glucose and lipids Liver function tests At 3 mo Parkinsonism, akathisia Tardive dyskinesia Blood pressure, pulse Fasting blood glucose and lipids Liver function tests annually Parkinsonism, akathisia Tardive dyskinesia Blood pressure, pulse Electrolytes, complete blood count, renal and liver function (monitor more frequently with clozapine) Fasting blood glucose and lipids (every 6 mo) Liver function tests Other Proctolin: obtain if symptomatic Electrocardiogram: obtain at baseline for ziprasidone (also during titration and at maximum dose) and clozapine Thyrotropin and free T4: baseline and follow-up measures recommended with quetiapine Eye examination: recommended at baseline and 6 mo intervals with quetiapine
Ziprasidone	No			
Aripiprazole	No			
Risperidone	No			
Cariprazine	No			

* Denotes important med administration considerations.
Data From Refs.^{19,110}

22

Table 2
Summarization of selected second-generation antipsychotic studies

Medication	Publication	Study Design, Duration	N	Age (y)	Target Dose (mg/d)	Primary Efficacy Measure/Purpose	Effectiveness/Findings	Noteworthy AEs
Clozapine	Kumra et al., ¹¹ 1996	Randomized, DB trial against haloperidol & benztropine, 6 wk	21	6-17	Flexible dosing: clozapine up to 325 mg/d (mean 174 mg/d), haloperidol up to 27 mg/d (mean 16 mg/d)	Mean reduction in BPRS, Burney Hamburg Psychosis Rating Scale, Children's Global Assessment Scale, Scale for Assessment of Negative Symptoms, Scale for Assessment of Positive Symptoms	Clozapine had statistically significant improvement over haloperidol on all measures of psychosis	Drowsiness and salivation higher in clozapine, no changes in AIMS for either group. For the clozapine group, 2/10 dropped out from neutropenia (even after stopping and restarting medication), 2/10 had significant seizure activity
Clozapine	Shaw et al., ¹² 2006	Randomized, DB, head-to-head trial against olanzapine, 6 wk	25	7-16	Flexible dosing: clozapine up to 900 mg/d (mean 327 mg/d), olanzapine up to 20 mg/d (mean 16.1 mg/d)	Mean reduction in CGI-S, Scale for the Assessment of Negative Symptoms, Scale for the Assessment of Positive Symptoms, BPRS, Burney Hamburg Psychosis Rating Scale	Moderate to large treatment effects in favor of clozapine, but given sample size only, statistically significant improvement in negative symptoms	Clozapine group had more AEs, especially nocturnal enuresis, tachycardia, and hyperreflexia. Similar weight gain in both groups
Clozapine	Kumra et al., ¹³ 2008	Randomized, DB, head-to-head trial against high-dose olanzapine, 6 wk	39	10-18	Flexible dosing: clozapine up to 900 mg/d (mean 403.1 mg/d), olanzapine up to 30 mg/d (mean 26.2 mg/d)	Response defined as a decrease of >30% in BPRS and a CGI improvement rating of 1 or 2	AE profiles were similar between groups with clozapine compared with 33% taking olanzapine	AE profiles were similar between groups with clozapine compared with 33% taking olanzapine

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23

Table 2 (continued)

Medication	Publication	Study Design, Duration	N	Age (y)	Target Dose (mg/d)	Primary Efficacy Measure/Purpose	Effectiveness/Findings	Noteworthy AEs
Risperidone	Haas et al., ²⁰ 2009	Randomized double-blind controlled trial vs low-dose risperidone, 8 wk	257	13-17	Flexible dosing: standard dose between 1.5 and 6 mg/d (mean 4 mg/d), low-dose between 0.15 and 0.6 mg/d (mean 0.4 mg/d)	Mean improvement in PANSS scores	Statistically significant improvement over low-dose and an average reduction of 22.6 in PANSS score, effect size of 0.49	74.4% in standard-dose group had an AE, most dose adjustments were for somnolence (19%). 33% of this group had EPS-related AEs, and 56% were prescribed an antiparkinsonian agent. 70% of the standard-dose group had prolactin elevations beyond the upper limit of normal
Risperidone	Haas et al., ²¹ 2009	RDBPCT, 6 wk	160	13-17	Flexible dosing: 4-6 mg/d (mode 6 mg) vs 1-3 mg/d (mode 3 mg) vs placebo	Mean improvement in PANSS of greater or equal to 20%	Statistically significant improvement over placebo by both active groups, high dose by 12.8 and low dose by 12.0. Overall improvement by high-dose group was 23.7 and 23.0 in low-dose group	AEs in 75% low-dose and 76% high-dose groups, most often somnolence, and changes in AIMS were minimal in both arms. No glucose-related AEs, weight gain was 1.3 kg in low-dose and 1.5 kg in high-dose groups

24

Risperidone	Pandina et al. ¹² 2012	Old of the above trials, 6 or 12 mo	390	13-17	Flexible dosing between 2 and 6 mg/d (median dose 3.8 mg/d for 6-mo group and 3.0 mg/d for 12-mo group)	Mean improvement in PANSS scores and response defined as >20% reduction in PANSS total score	PANSS scores decreased 13.6 from baseline at 6 mo, 61.8% response at 6 mo	Serious AEs experienced by 15%, with 80% experiencing any AE. Weight gain was reported as a treatment AE in 15% with a mean gain of 4.0 kg. Prolactin-related AE in 9%. 32.3% of participants dropped out of the study, 31% experienced an EPS-related AE, and 27% reported somnolence.
Olanzapine	Kryzhanovskaya et al. ¹⁷ 2009	RDBPCT, 6 wk	107	13-17	Flexible dosing between 2.5 and 20 mg/d (mean 11.1 mg/d)	Mean change in BPRS-C total score	Significant improvement with olanzapine over placebo (-19.4 vs -9.3) starting at week 2	Significant increases with olanzapine in terms of weight, prolactin levels, fasting triglycerides, uric acid, and alanine aminotransferase
Olanzapine	Kemp et al. ¹⁹ 2013	RDBPCT, 6 wk, post hoc analysis of study by Kryzhanovskaya et al. ¹⁷ 2009	107	13-17	Flexible dosing between 2.5 and 20 mg/d	Study possible association between weight gain and treatment outcome	Significant weight gain appeared to indicate greater treatment efficacy, but effect cancels out once duration is included as a covariate.	

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25

Table 2 (continued)

Medication	Publication	Study Design, Duration	N	Age (y)	Target Dose (mg/d)	Primary Efficacy Measure/Purpose	Effectiveness/Findings	Noteworthy AEs
Quetiapine	Findling et al. ¹⁶ 2012	RDBPCT, 6 wk	222	13-17	400 mg/d or 800 mg/d in divided doses	Mean change in PANSS total score	Both 400-mg/d and 800-mg/d groups demonstrated significant mean improvement compared with placebo, with 15 mean changes from baseline to endpoint being -21.3 and -28.46 vs placebo (-19.15)	Most common TEAEs included somnolence, headache, and dizziness. Active groups also had increased weight (2.2 kg for 400-mg/d, 1.8 mg for 800-mg/d -0.4 kg for placebo), and increases in total cholesterol, LDL cholesterol, and triglycerides. Quetiapine showed a decrease in mean total thyroxine levels (with mean increase in thyroid stimulating hormone in the 400-mg/d group) and greater mean changes in pulse rate.

26

Atipirapazole	Findling et al. ¹⁸ 2008	RDBPCT, phase 3, 6 wk	302	13-17	10 mg/d or 30 mg/d	Mean change in PANSS total score	Atipirapazole statistically superior to placebo at both 10 mg/d (-26.7) and 30 mg/d (-28.6) vs placebo (-21.2)	Extrapyramidal disorder, somnolence, and tremor were most common, with higher incidence in the 30-mg/d group. Both active groups had worsening in Simpson-Angus Scale scores (+1.5 for 10 mg/d, +0.3 for 30 mg/d, -0.2 for placebo). There were reductions in serum prolactin in all groups and minimal weight changes (-0.8 kg for placebo, 0.0 for 10 mg/d, and +0.2 kg for 30 mg/d).
Atipirapazole	Corrall et al. ¹⁷ 2017	RDBPCT, 52 wk	146	13-17	10-30 mg/d	Time from randomization to exacerbation of psychotic symptoms/ impending relapse	Significantly longer time to exacerbation for treatment group (hazard ratio = 0.46) and fewer meeting criteria for exacerbation (19.4% vs 37.5%)	TEAEs reported in a similar proportion in both groups with none being related to neuroleptic malignant syndrome, seizures, orthostatic hypotension, glucose levels, or prolactin levels. There was a comparable incidence of weight gain and somnolence.

(continued on next page)

27

Aripiprazole Finding et al. ¹¹ 2008	RDBPC, phase 3, 6 wk	302	13-17	10 mg/d or 30 mg/d	Mean change in PANSS total score	Aripiprazole significantly superior to placebo at both 10 mg/d (-26.7) and 30 mg/d (-28.6) vs placebo (-21.2)	Extrapyramidal disorder, somnolence, and tremor were most common, with higher incidence in the 30 mg/d group. Both active groups had worsening in Simpson-Angus. Scale scores (+4.5 for 10 mg/d, +4.3 with 30 mg/d, -0.3 for placebo). There were reductions in serum prolactin in all groups and minimal weight changes (-0.8 kg for placebo, 0.0 in 10 mg/d, and +2.2 kg for 30 mg/d).
Aripiprazole Correll et al. ¹² 2017	RDBPC, 52 wk	146	13-17	10-30 mg/d	Time from randomization to exacerbation of psychotic symptoms/impending relapse	Significantly longer time to exacerbation for treatment group (hazard ratio = 0.46) and fewer meeting criteria for relapse (19.4% vs 37.5%)	TEAEs reported in a similar proportion in both groups with none being related to neuroleptic malignant syndrome, seizures, orthostasis, glucose levels, or prolactin levels. There was a comparable incidence of weight gain and somnolence.

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28

Table 2 (continued)

Medication	Publication	Study Design, Duration	N	Age (y)	Target Dose (mg/d)	Primary Efficacy Measure/Purpose	Effectiveness/Findings	Noteworthy AEs
Paliperidone	Singh et al. ¹³ 2011	RDBPC, 6 wk	201	12-17	Weight-based, fixed doses ranging from low (1.5 mg/d), medium (3 or 6 mg/d), and high (6 or 12 mg/d)	Mean change in PANSS total score	Significant for the medium-treatment group (-17.3; P = .006) vs the high (-13.8; P = .09) and low-treatment (-9.8; P = .51) groups as well as placebo (-7.9)	Most common TEAEs included somnolence, akathisia, tremor, isometria, and headache, many of which were dose related
Paliperidone	Savitz et al. ¹⁴ 2015	OLE trial (Singh et al. ¹³ , 2 y) (36 patients involved in a 6-mo study)	220	12-17	Flexible dosing between 1.5 and 12 mg/d (6 mg/d most common dose)	Primary objective was to evaluate long-term safety parameters; secondary objective was efficacy per PANSS, CGI-5, and Children's Global Assessment Scale scales	Improvement in PANSS total score observed within 3 mo of treatment initiation and continued to endpoint, with the mean change in score being 19.1%, and 41.7% of patients achieving remission. Safety profile consistent with that of paliperidone in adults, and risperidone in adolescents	TEAEs experienced by 83.3% of patients, with somnolence and weight gain being most common (18.3% each). 4.3% participants showed a shift to high glucose levels, 9.3% suicidality-related TEAEs, and 9.3% a potentially prolactin-related event (18.5% in girls, 2.3% in boys). EPS-related events were most commonly related to Parkinsonism (15.5%) and hyperkinesia (13.8%)

29

Lurasidone Goldman et al. ¹⁵ 2017	RDBPC, 6 wk	326	13-17	40 mg/d or 80 mg/d	Mean change in PANSS total score	LS mean change significant for both 40 mg/d and 80 mg/d groups (-18.6, -18.3) vs placebo (-10.5), with separation apparent starting at week 1. A greater proportion of 40 mg/d and 80 mg/d participants also met criteria for response (63.9% and 65.1% vs 42.0% placebo)	Lower overall incidence of serious AEs with treatment (3.6% at 40 mg/d, 1.9% at 80 mg/d) vs placebo (0.0%), and no clinically significant difference for body weight, lipid parameters, glycemic indices, and prolactin levels. Higher incidence of akathisia (9.1% for 40 mg/d, 8.7% for 80 mg/d, and 1.8% for placebo) and other EPS-related AE (6.4% at 40 mg/d, 3.8% in 80 mg/d, 1.8% with placebo)
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30

Table 2 (continued)

Medication	Publication	Study Design, Duration	N	Age (y)	Target Dose (mg/d)	Primary Efficacy Measure/Purpose	Effectiveness/Findings	Noteworthy AEs
Ziprasidone	Findling et al. ¹⁰ 2015	RDBCT, 8 wk followed by 26 wk open extension	283	13-17	Flexible dosing: 40-160 mg/d (mean modal dose 129.9 mg/d)	Mean change in BPRS-A, PANSS, CGI-S scores	In the RCT, no significant separation in BPRS-A or other measures, statistically significant improvement in PANSS-positive subscale	In the RCT, somnolence (19.7%) and EPS (11.4%) were the most common AEs. No differences in AMS and small increase in QT interval corrected by Fridericia's formula (3.9 ms to 10.8 ms). ziprasidone was generally well tolerated with minimal associated changes in body mass index and no differences in metabolic AEs.
Asenapine	Findling et al. ¹¹ 2015	RDBCT, 8 wk followed by 26 wk open extension	306	12-17	Fixed doses, either 5 mg/d or 10 mg/d	Mean change in PANSS scores	In the RCT, PANSS score did not separate from placebo despite numerical improvement. In OLE, 46% had a 30% decrease in PANSS total.	In the RCT, somnolence, sedation, hypersomnia, and gastrointestinal disorders were most common AEs. In the RCT, 10% had >7% weight gain, and in the OLE, 14.3% had >7% gain.

31

Table 3 Summarization of selected head-to-head antipsychotic studies

Medications	Publication	Study Design, Duration	N	Age (y)	Target Dose (mg/d)	Primary Efficacy Measure/Purpose	Effectiveness/Findings	Noteworthy AE
Haloperidol Olanzapine Risperidone	Skitch et al. ¹² 2004	Randomized double-blind controlled trial, 8 wk	50	8-19	Flexible dosing: olanzapine 2.5-20 mg/d (mean 12.3 mg/d), haloperidol 1.8 mg/d (mean 5 mg/d), risperidone 1.6 mg/d (mean 4 mg/d)	Mean change in BPRS-C	74% of risperidone, 88% of olanzapine, 53% of haloperidol had significant symptom reduction; between-group overall comparisons failed to show statistical improvement differences.	Risperidone and olanzapine had higher rates of AEs than in adults and more than half of those on atypicals had mild to moderate EPS; severe EPS was even higher on haloperidol; significant weight gain across all groups.
Risperidone Olanzapine Quetiapine	Jensen et al. ¹³ 2008	Randomized open-label, 12 wk	30	10-18	Flexible dosing: olanzapine 5-20 mg/d (mean 11.4 mg/d), risperidone 0.5-6 mg/d (mean 2.8 mg/d), quetiapine 100-800 mg/d (mean 611 mg/d)	Mean reduction in PANSS	No statistically significant differences between treatment arms, although differences between risperidone > quetiapine approached significance.	No significant differences in PANSS. Significant weight gain across all groups.
Molindone (with benzazepine) Olanzapine Risperidone	Skitch et al. ¹⁴ 2008	Randomized double-blind controlled trial, 8 wk	116	8-19	Flexible dosing: olanzapine 2.5-20 mg/d (mean 11.4 mg/d), risperidone 0.5-6 mg/d (mean 2.8 mg/d), molindone 10-140 mg/d (mean 59.9 mg/d)	Response defined as CGI improvement score of 1 or 2 and >20% reduction in PANSS	Molindone achieved 50% response, olanzapine achieved 38% response, and risperidone achieved 46% response. No statistically significant differences.	Weight gain in olanzapine > risperidone > molindone. Randomization to olanzapine stopped due to weight gain. More changes in lipids and liver function tests in olanzapine group, more akathisia in molindone group.

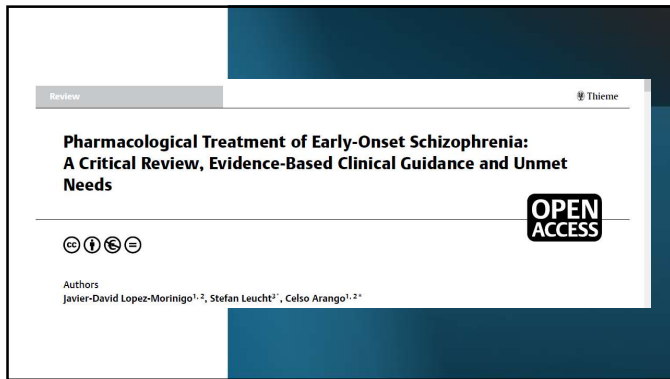
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32

Table 3 (continued)

Molindone (with benzazepine) Olanzapine Risperidone	Findling et al. ¹⁵ 2010	DB extension of Skitch et al. ¹⁴ 2008 study, up to 44 wk	54	8-19	Flexible dosing (as above): olanzapine mean 9.8 mg/d, risperidone mean 3.9 mg/d, molindone mean 76.5 mg/d	Response defined as CGI improvement score of 1 or 2 and >20% reduction in PANSS	PANSS score varied little during the maintenance period.	All groups had statistically significant weight gains but olanzapine > molindone for several weight measures. Only 12% of participants completed the study on the same medication they started and only 55% completed the extension trial.
Quetiapine Risperidone	Swaid et al. ¹⁶ 2010	Open label, 6 wk	22	<19	Flexible dosing: quetiapine 100-800 mg/d (mean 607 mg/d), risperidone 1.5-5 mg/d (mean 2.9 mg/d)	Response defined as 30% or more reduction in PANSS, BPRS, and CGI-S scores	No significant differences in reduction of symptoms, but risperidone performed better on most outcome measures.	Although not statistically significant, greater weight gain was seen with quetiapine and more anticholinergic coadministration for management of EPS with risperidone.
Paliperidone Aripiprazole	Savitz et al. ¹⁷ 2015	RDBT against aripiprazole, 26 wk	228	12-17	Flexible dosing for paliperidone (5, 6, or 9 mg/d) and aripiprazole (5, 10, or 15 mg/d)	Mean change in PANSS total score	Similar improvement for paliperidone ER and aripiprazole at day 56 (-19.3 vs -19.8) and day 182 (-25.6 vs -26.8). Paliperidone ER and aripiprazole also showed similar rates of response (67.9% and 76.3% at day 56, 76.8% and 81.6% at day 182).	Higher frequency of TEAEs for paliperidone ER compared with aripiprazole (77.0% vs 66.7%); most common TEAEs were somnolence, headache, tremor, and weight gain. Incidence of dystonia and hyperkinesia for paliperidone ER was higher (>2%) and also demonstrated more frequent TEAEs related to prolactin (6.4% vs 0.9%).

33



34

First Author	Publication year	Article type	Number of studies	N	Average follow-up (weeks)	Primary outcome(s)	Secondary outcome(s)
Pagsberg	2017	NMA	12	2158	7	Efficacy: 1. ARI, PAL, RIS, QUIET, OLZ, MOL 2. ASE, ZIPRA	Safety - WG: 1. MOL > ARI > ZIPRA > 2. PAL > RIS, OLZ Safety - EPS: 1. ASE, OLZ > 2. ZIPRA, PAL, RIS, ARI, PAL, RIS, QUIET > 3. MOL Acceptability: 1. OLZ, PAL, QUE, RIS > all others
Druyts	2016	SR	11	1772	6	-	Safety - PRL: 1. ARI, CLOZ, QUIET 2. RIS, OLZ, PAL
Harvey	2016	NMA	11	1714	6	Efficacy: 1. HAL and MOL > 2. OLZ, ARI, RIS, PAL QUIET > ZIPRA	Safety - WG: 1. HAL, MOL, ZIPRA 2. RIS, PAL, ARI 3. QUE 4. OLZ Acceptability: 1. HAL 2. QUIET 3. MOL, ZIPRA, RIS, PAL, OLZ, ARI

35

Krause	2018	NMA	28	3303	6	Efficacy: 1. CLZ 2. RIS, OLZ, ARIP, LUR, ASE 3. HAL, ZIPRA	Acceptability: 1. PAL, MOL, RIS, OLZ 2. ARI Safety - WG: 1. MOL > ZIPRA > LUR > ARI > ASE > QUIET, RIS, PAL 2. CLZ, OLZ, QUE Safety - sedation: QUE > LUR, ASE, CLZ Safety - PRL: 1. ARI 2. ASE 3. LUR 4. QUE, RIS, HAL and PAL Safety - EPS: HAL, MOL, LUR and RIS worse than the others. Social functioning: 1. RIS, ARI, LUR QoL: NMA not feasible due to data unavailability.
Arango	2020	NMA	13	2210	6	Efficacy: 1. LUR > CLZ, OLZ, QUIET, ZIPRA, ARIP, ASE	Safety - WG: 1. LUR > 2. LUR > PAL > ASE > RIS > QUE > OLZ Safety - Motor symptoms: No differences Safety - Dyslipidemia and Glucose: 1. ZIPRA 2. LUR 3. OLZ AE discontinuation: 1. LUR > all others Somnolence/sedation: No differences

36

First Author	Publication year	Article type	Number of studies	N	Average follow-up (weeks)	Primary outcome(s)	Secondary outcome(s)
Sarkar & Grover	2013	MA	15	995	6	Efficacy: 1. CLZ 2. PAL, OLZ, RIS, QUE, ARI, HAL, MOL, FLU	Tolerability: FGA-EPS SGA (Olanzapine and clozapine) – weight gain and glucose
Kumar	2013	MA	13	1112	6-8	Efficacy: FGA=SGA, with no differences FGA: PER, MOL, HAL, CHOR. SGA: RIS, OLZ, QUE, ZIPRA, ARI, AMI, PAL, LUR, CLZ	Safety – WC: To avoid: OLZ, RIS, CLZ Safety – GIU and PRL: 1. To use ARI
Cohen	2012	MA	41	4015	3-12	Safety – WC: ARI>QUE>RIS>CLZ>OLZ GIU: OLZ>RIS Dyslipidaemia: OLZ>QUE PRL: ZIPRA>OLZ>RIS EPS: RIS>ARI>OLZ>ZIPRA	
Xia	2018	MA	8	457	8.5	Efficacy: RIS=OLZ	Safety – WC: RIS=OLZ Safety – Sedation: RIS>OLZ Safety – Insomnia: OLZ>RIS Safety – PRL: OLZ>RIS Safety – EPS: OLZ>RIS

37

Pfingsthelm	2011	MA	35	2667	6-12	Safety – WC: ARI>QUE>RIS>OLZ Safety – Dyslipidaemia: CLZ and OLZ worse than the others Safety – GIU: OLZ worse Safety – EPS: RIS worse than all others	
Solmi	2020	UR	17	51108	NA	Safety – any EPS: RIS>ARI>PAL>OLZ>AMI>MOL>ZIPRA>HAL>LOX Safety – Asthenia: RIS>HAL Safety – anorexia: ARI Safety – Sedation: ARI>HAL>LOX>CLZ>MOL>PAL>RIS>ZIPRA>OLZ Safety – Anxieties: ARI>OLZ>RIS>PAL>MOL Safety – Cholesterol: ARI>QUE>OLZ Safety – PRL: QUE>HAL>OLZ>PAL Safety – WC: PAL>ARI>QUE>CLZ>OLZ Safety – GIU: ASE>RIS>OLZ	
Correll	2021	UR	28	9778	6-8	Acceptability: 1. PAL, RIS, OLZ 2. LUR, ZIPRA, QUE, ASE, ARI	Efficacy: 1. OLZ>RIS>LUR>ARI>QUE>PAL>ASE Tolerability: LUR>ZIPRA>RIS>ARI>ASE>QUE>OLZ>PAL

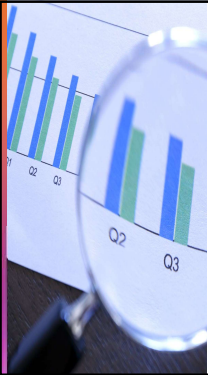
ARI: Aripiprazole; ARI: Aripiprazole; ASE: Aripiprazole; CLZ: Clozapine; EPS: Extrapyramidal symptoms; HAL: Haloperidol; LOX: Loxapine; LUR: Lurasidone; MOL: Molidindone; MA: Pairwise meta-analysis; MA: Network Meta-analysis; OLZ: Olanzapine; PAL: Paliperidone; PRL: Protractin; QUE: Quetiapine; RIS: Risperidone; GIU: Glucose; SR: Systematic review; UR: Umbrella review; ZIPRA: Ziprasidone.

38

Continent	Country	Title	Author	Publication date	Abbreviation and reference	Pharmacological treatment Recommendations
Europe	Germany	S3 Guideline for Schizophrenia	German Association for Psychiatry, Psychotherapy and Psychosomatics	2019	DGPPN (German Association for Psychiatry, Psychotherapy and Psychosomatics, 2019)	1. ARI, QUE, PAL, RIS, CLZ (TR) 2. HAL, OLZ.
	UK	The Maudsley Prescribing Guidelines in Psychiatry, 13th Edition.	Editors: Taylor, Barnes, Young	2018	Maudsley (Taylor et al., 2019)	1. ARI, QUE, PAL, RIS, OLZ, CLZ (only for TR, OLZ should be tried first). 2. ASE, ZIPRA (less efficacious than the above drugs) 3. FCAs should be avoided due to extrapyramidal adverse effects
Oceania	Australia	Australian Clinical Guidelines for Early Psychosis	Orygen, The National Centre of Excellence in Youth Mental Health	2016	Orygen (Australion Clinical Guidelines for Early Psychosis, 2016)	1. ARI, OLZ, RIS, QUE 2. CLZ (TR)
North America	US	Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia	American Academy of Child and Adolescent Psychiatry	2013	AACAP (McClellan et al., 2013)	1. RIS, ARI, QUE, PAL, 2. OLZ, ZIPRA, HAL, 3. CLZ (TR)
	Canada	Canadian Guidelines for Schizophrenia	Abadi, et al.	2017	CSG (Abadi et al., 2017)	No clear recommendations, but: 1. SGA (rather than FCAs). 2. OLZ, only as second line option due to metabolic side effects. 3. CLZ (only TR cases)

ARI: Aripiprazole; PAL: Paliperidone; RIS: Risperidone; QUE: Quetiapine; OLZ: Olanzapine; MOL: Molidindone; ASE: Aripiprazole; ZIPRA: Ziprasidone; CLZ: Clozapine; HAL: Haloperidol; LOX: Loxapine; LUR: Lurasidone; AMI: Amisulpride.


39



Unmet needs: (Research-Gaps)

- Long term efficacy
- Efficacy on neg. sx
- Cognition
- Functioning
- QOL
- Suicide behavior
- Mortality
- Service use
- Cost effectiveness: long term
- Dosing (age- dosing in EOS)

46



CHANGE

47

Tools to Craft a Cultural Formulation

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48

Table 1 Outline for cultural formulation elements		
OCF Elements DSM-IV (APA 1994)	OCF Elements DSM-5-TR (APA 2022)	Comments
Cultural identity of the individual	Cultural identity of the individual	This emphasizes the need to include <i>any</i> "socially and culturally defined characteristics that may influence interpersonal relationships, access to resources, and developmental and current challenges, conflicts, or predicaments" (p. 861), including the aspects prioritized by the individual and the impact of intersectionality.
Cultural explanations of the individual's illness	Cultural concepts of distress	Further normalizes the potential for differences between cultures by changing the phrasing from "cultural reference groups" to "cultural background."

49

Cultural factors related to the psychosocial environment and functioning	Psychosocial stressors and cultural features of vulnerability and resilience	Specifically identifies the need to identify social determinants of mental health, such as access to resources and opportunities such as housing, transportation, education, employment, and exposure to individual or structural racism and structural violence. Online interactions are included as stressors or supports.
Cultural elements of the relationship between the individual and the clinician.	Cultural features of the relationship between the individual and the clinician, <i>treatment team and institution</i> (text in italics is new in DSM-5-TR)	Continues to expand the understanding of the potential for previous experiences of discrimination to impact the clinical encounter, affecting rapport, and development of an effective clinical alliance (p. 862)

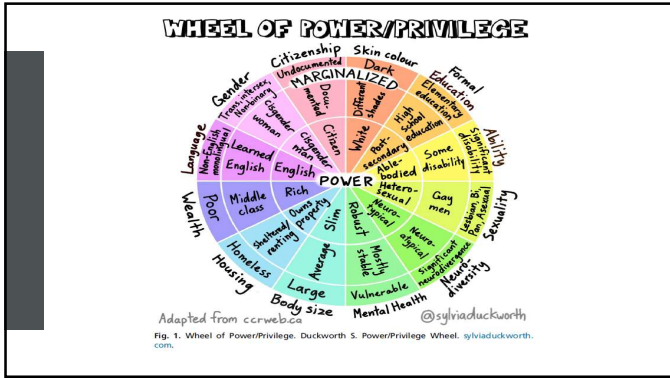
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50

Table 1 <i>(continued)</i>		
OCF Elements DSM-IV (APA 1994)	OCF Elements DSM-5-TR (APA 2022)	Comments
Overall cultural assessment for diagnosis and care	Overall cultural assessment	Essentially unchanged, this summarizes the implications of the four elements for differential diagnosis, management, and treatment.

Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association; 1994 (p.843-844); American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. American Psychiatric Association; 2022.p.861.

51



52

Table 3
Use of ADDRESSING for Christian (case 2)

Cultural Influences (ADDRESSING Framework)	Clinical Information
Age and generational influences	Christian was an adolescent who appeared easily distracted and active on two electronic devices in addition to his PlayStation
Developmental disabilities	There may have been a concern for distractibility and inattention as Christian was not fully engaged and had noticeable difficulty sitting still, but he had no formal diagnoses
Disabilities acquired later in life	Christian was diagnosed with cystic fibrosis in childhood, including subsequent hepatic Failure
Religion and spiritual orientation	Uncertain
Ethnic and racial identity	Christian is an African American, who appeared to engender subsequent implicit bias by the primary team that he would be "difficult"
Socioeconomic status	Christian was raised by a single African American mother with little financial means and limited support
Sexual orientation	Christian identifies himself as heterosexual
Indigenous heritage	Uncertain
National origin	US citizen
Gender	Male

Data from Hays PA. Connecting Across Cultures: The Helper's Toolkit. In: Connecting Across Cultures: The Helper's Toolkit. Sage Publications; 2013:123. <https://doi.org/10.1037/14801-000>.

53

Table 4
Use of RESPECTFUL for Andrew (Case 1)

Cultural Influences (RESPECTFUL Framework)	Clinical Information
Religion/spiritual identity	Atheist
Economic class background	Middle class; two-parent household
Sexual identity	Previously gay male; exploring gender identity
Psychological maturity	Appropriate for age
Ethnic/racial identity	Caucasian, Irish, and Scandinavian origins
Chronologic/developmental challenges	None
Trauma and threats to well-being	Experienced bullying for small stature throughout middle school that resulted in physical abuse
Family background	Fourth-generation Irish immigrant family; within the United States; the Mormon faith
Unique physical characteristics	Thin, petite, ruddy skin with freckles, blue eyes, and dark brown hair; wears glasses
Location of residence and language differences	Resides in Virginia; English-speaking

Data from D'Andrea M, Daniels J. Before You Get Started. In: Ivey AE, D'Andrea M, Ivey MB, Simek-Morgan L, eds. Theories of Counseling and Psychotherapy - A Multicultural Perspective. Fifth Edit. Allyn & Bacon; 2002:456; pages xvii-xxv.

54

CLINICS CARE POINTS

- Cultural assessment should be used in all encounters but can be especially helpful in difficult diagnostic assessments, limited engagement and adherence, or disagreement between clinician and patient
- Cultural formulation is a dynamic process and should continue as a clinician longitudinally works with a patient, including gathering information from appropriate collateral sources
- Use tools such as the Outline for Cultural Formulation and Cultural Formulation Interview, including its Supplementary Modules
- There are also frameworks in psychology literature, such as *ADDRESSING* and *RESPECTFUL*, to help guide clinicians in their cultural formulations
- Aim to be patient centered and allow the patient to narrate their own symptoms in their own experiential, cultural context
- Interdisciplinary case discussions can be helpful in crafting a more nuanced cultural formulation

55



56



57
