Escitalopram & Aripiprazole for psychiatric disorders in youth

December 2020

Dr. Ladan Adibeshgh
pharmacist

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Psychiatric Diseases in Children and Adolescents

- Pharmacotherapy of psychiatric illnesses in children and adolescents has grown significantly over the last few decades.

- However, the body of research examining pharmacological treatments for psychiatric illnesses is much smaller in children and adolescents than it is in adults.

- As most treatments for psychiatric disorders are more effective if started early in the course of illness, treatment options for youth are especially important in order to ensure better treatment outcomes.

- Childhood depression has been shown to lead to an increased risk of poor academic performance, impaired social functioning, suicidal behavior, homicidal ideation, and alcohol/substance abuse.

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Pharmacological treatment options

❖Antidepressants

➢Antidepressants are used to treat depression and anxiety disorders in children.

➢ SSRIs are the most commonly used antidepressants in pediatric populations due to their demonstrated efficacy, low side effect profile, and good tolerability.

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ESCITOVER
ESCITALOPRAM Tablet 10mg

Escitalopram (Escitover®)

Antidepressant, Selective Serotonin Reuptake Inhibitor

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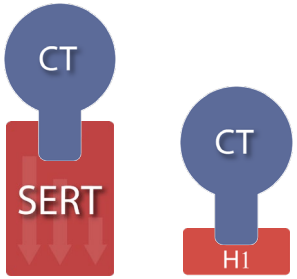
Pharmacodynamics

- **The S(+)-enantiomer of citalopram**
- **Inhibitor of serotonin reuptake with no effects on norepinephrine or dopamine**
- **In addition to SERT inhibition, citalopram is a mild antagonist at histamine 1 receptors. Escitalopram is also a SERT inhibitor, but doesn't block H1 receptors.**

Citalopram



Escitalopram

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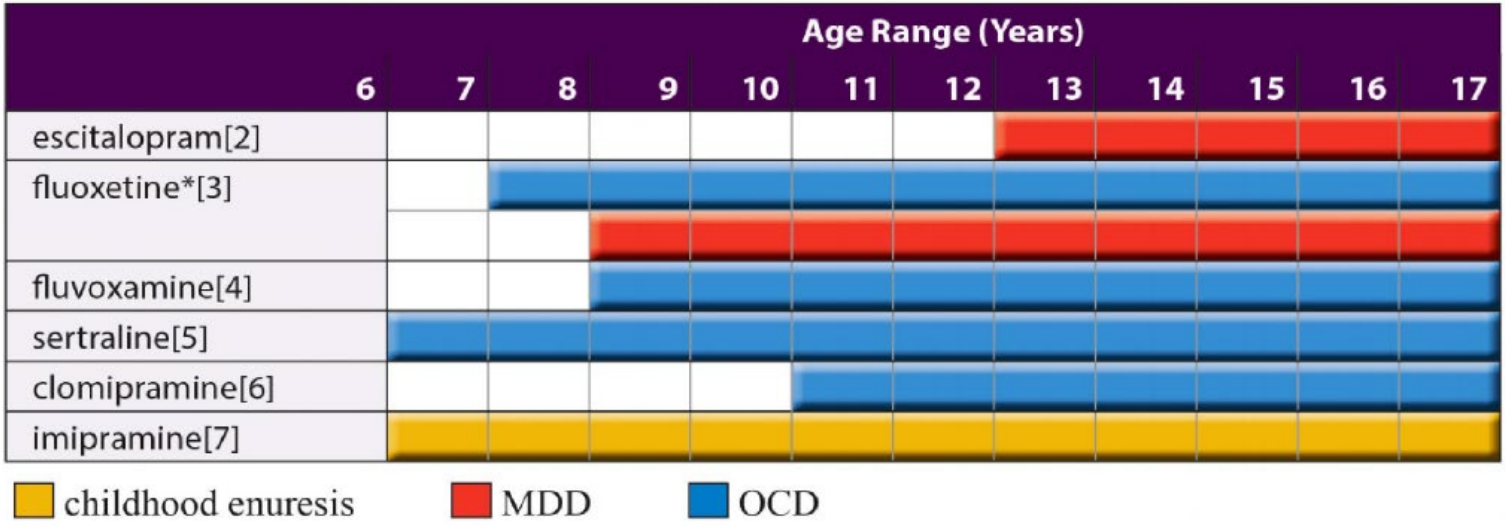
FDA-Approved Indications

Indication	Citalopram	Escitalopram
Major depressive disorder (unipolar)	√	√
Generalized anxiety disorder		√
Depression (Children and Adolescents ≥12 years)		√

Figure 1. FDA-Approved Pediatric Age Ranges and Indications for Antidepressant Medications



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Dosing - Pediatrics

Depression

- Children and Adolescents ≥12 years
- Initial: 10 mg once daily; may be increased to 20 mg/day after at least 3 weeks

Note: Some experts suggest lower starting doses of 5 mg/day and lower titration increments of 5 mg in patients sensitive to adverse effects, particularly in patients with anxiety who are generally more sensitive to overstimulation effects (eg, anxiety, insomnia) with antidepressants (Hirsch 2018c; WFSBP [Bandelow 2012]).

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General side effects

Most common side effects:

- **CNS: Headache, insomnia, drowsiness**
- **GI: Nausea, diarrhea**
- **Genitourinary: Ejaculatory disorder**

They're usually mild and go away after a couple of weeks.

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Primary Care Clinicians Can Effectively Treat Depression in Children and Adolescents

Original Article: Depression in Children and Adolescents: Evaluation and Treatment

Issue Date: November 15, 2019

See additional reader comments at: https://www.aafp.org/afp/2019/1115/p609.html

- Evidence supports the use of fluoxetine and escitalopram as first-line agents for unipolar depression in children and adolescents without complex medical or psychiatric histories.

Selected Medications for the Treatment of Adolescent Mood Disorders

Medication*	Starting dosage (mg per day)	Dose adjustments† (mg per dose)	Therapeutic range (mg)	Maximum dosage (mg per day)
Selective serotonin reuptake inhibitors				
Citalopram (Celexa)	10	5 to 10	20 to 40	40
Escitalopram (Lexapro)	5 to 10	5	10 to 20	20
Fluoxetine (Prozac)	10	10 to 20	20 to 40	60 to 80
Sertraline (Zoloft)	25 to 50	25 to 50	50 to 200	200

SEDATION and INSOMNIA

Medication	Sedation	Agitation/Insomnia
Selective Serotonin Reuptake Inhibitors		
Fluoxetine	+	++++
Sertraline	+	+++
Paroxetine	+++	++
Citalopram	++	++
Escitalopram	+	++

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QT interval prolongation

	Reuptake Antagonism		Anticholinergic Effects	Sedation	Orthostatic Hypotension	Seizures[a]	Conduction Abnormalities[a]
	Norepinephrine	Serotonin					
Selective Serotonin Reuptake Inhibitors (SSRIs)							
Citalopram	0	+++	0	+	0	++	++
Escitalopram	0	+++	0	0	0	0	0
Fluoxetine	0	+++	0	0	0	++	0
Fluvoxamine	0	+++	0	+	0	++	0
Paroxetine	0	+++	+	+	0	++	0
Sertraline	0	+++	0	0	0	++	0

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Guideline Recommendations

❖NICE

- Compared to the 2010 guideline, the 2018 guideline included a new section on Escitalopram specifically.
- **More effective than citalopram** and at least as effective as other SSRIs
- **Better tolerability**, except as compared to sertraline

❖CANMAT

- Escitalopram as a "first line" treatment, along with all others
- Escitalopram, mirtazapine, sertraline, and venlafaxine: as "some antidepressants have modest superiority for treatment response, particularly."
- "**Minimal or low potential" for drug-drug interactions**

❖APA

- Slight superiority of Escitalopram over other SSRIs and venlafaxine
- Favorable drug-drug interaction profile over that fluoxetine, fluvoxamine, and paroxetine

❖RANZP

- Reasonable efficacy and tolerability profile

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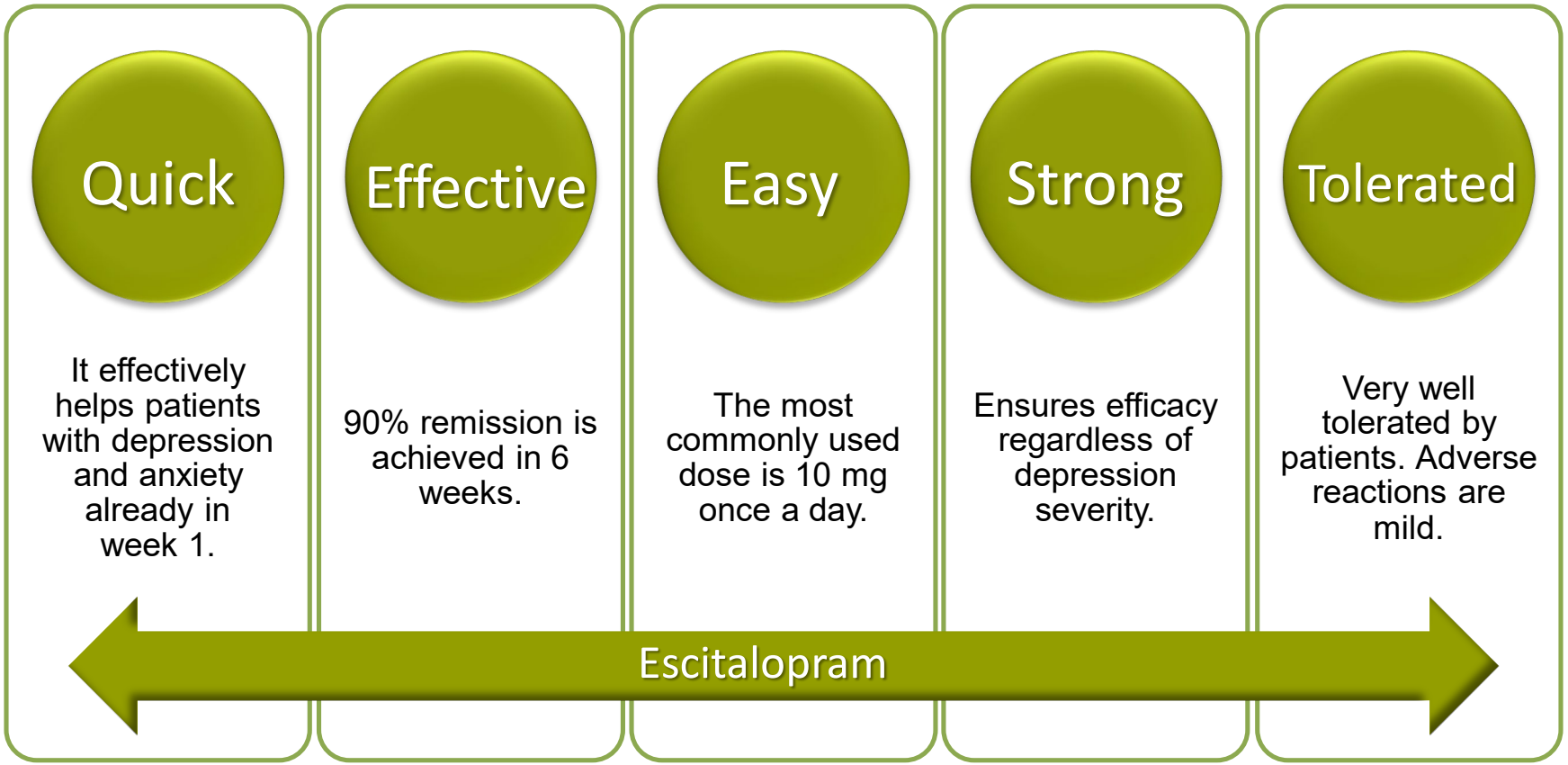
Quick solution for active patients



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Easy to be administered, safe in overdose

ONCE DAILY

ANY TIME A DAY

WITH OR WITHOUT FOOD

PATIENTS ARE MORE WILLING TO TAKE IT REGULARLY

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Meta-analysis published in February 2018

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*

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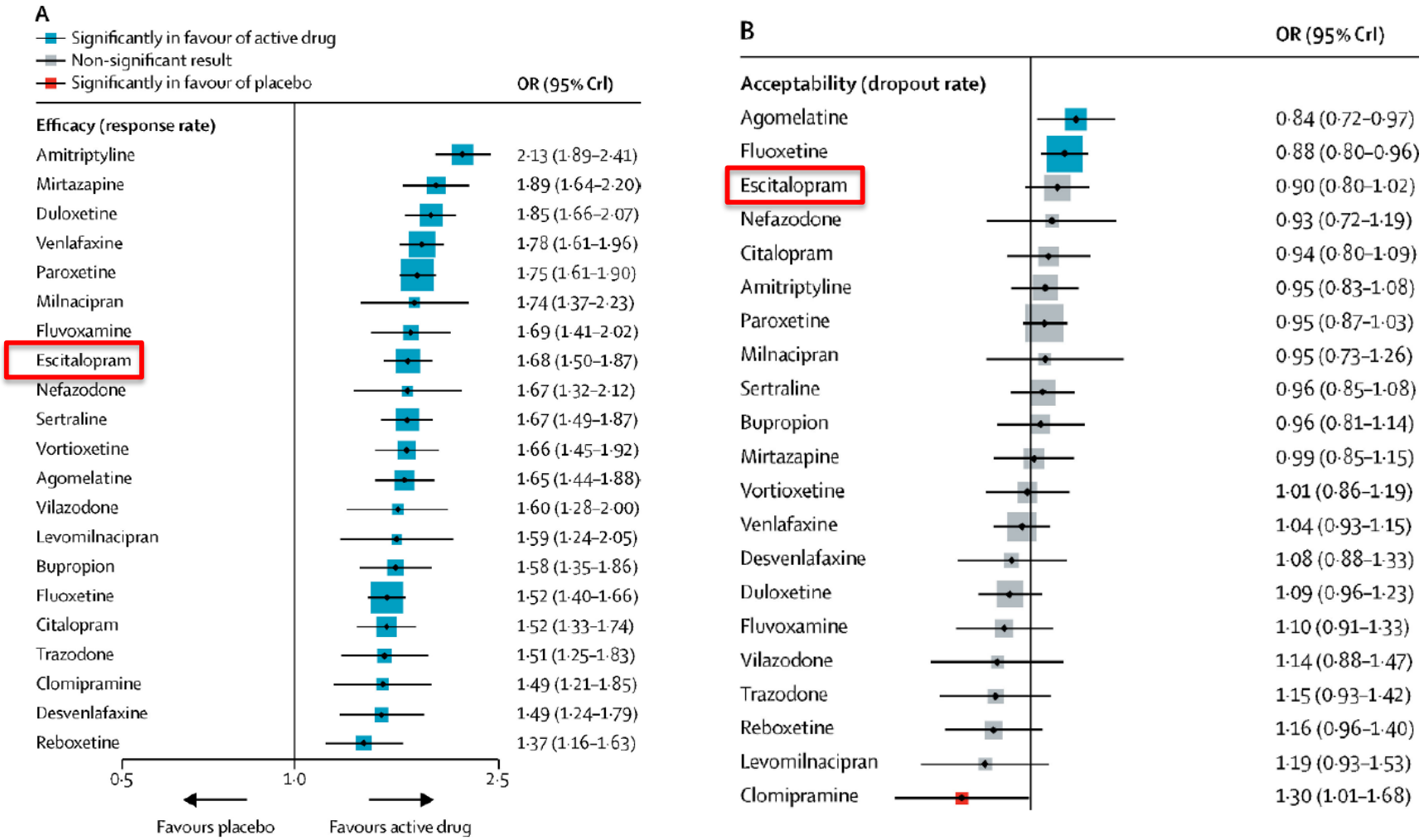
Efficacy (A) and acceptability (B)



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International Journal of Neuropsychopharmacology (2011), **14**, 261–268. © CINP 2010
doi:10.1017/S146114571000115X

Efficacy of escitalopram compared to citalopram: a meta-analysis

Stuart Montgomery[1], Thomas Hansen[2] and Siegfried Kasper[3]

[1] *University of London, UK*
[2] *H. Lundbeck A/S, Denmark*
[3] *Department of Psychiatry and Psychotherapy, Medical University Vienna, Austria*

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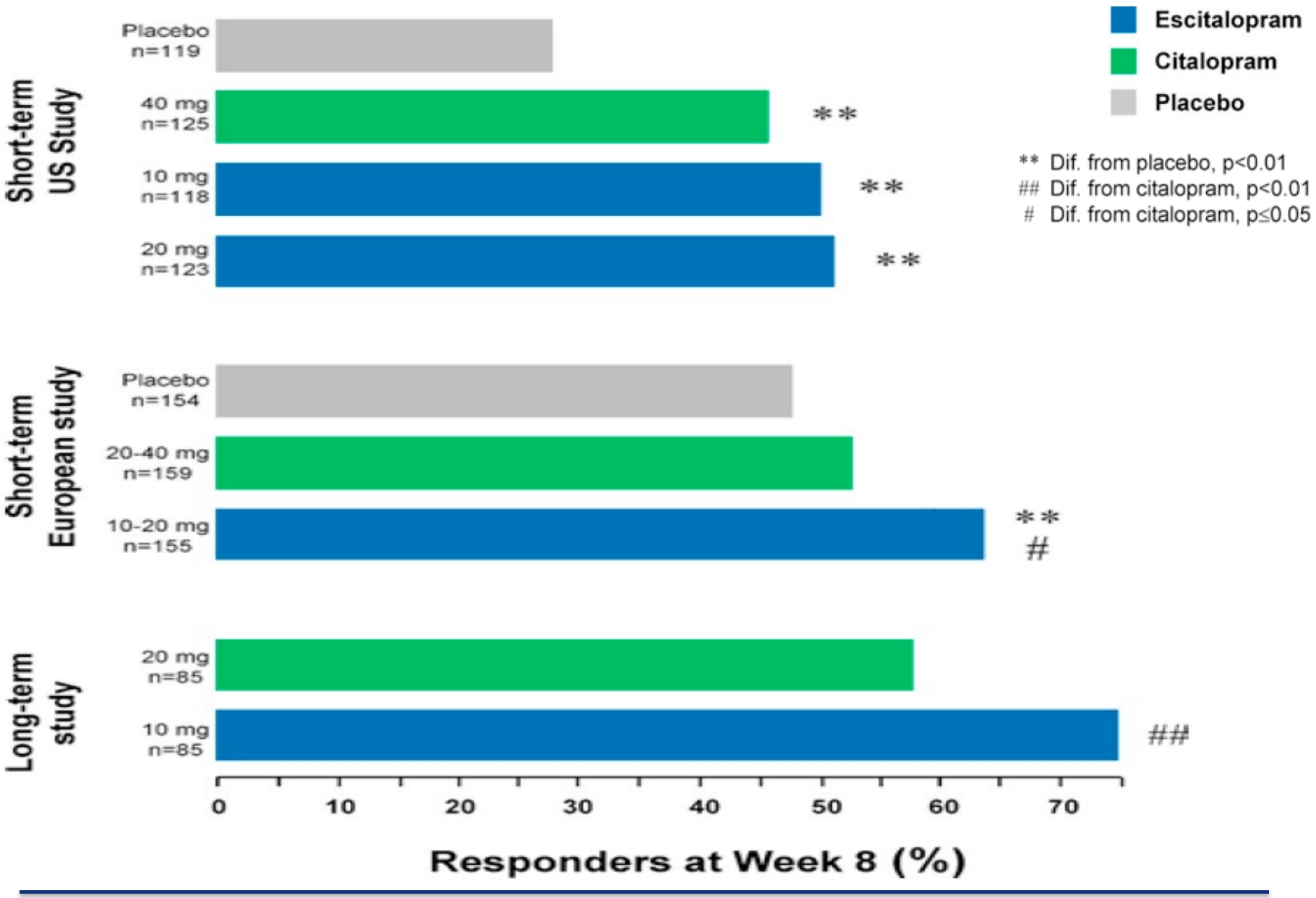

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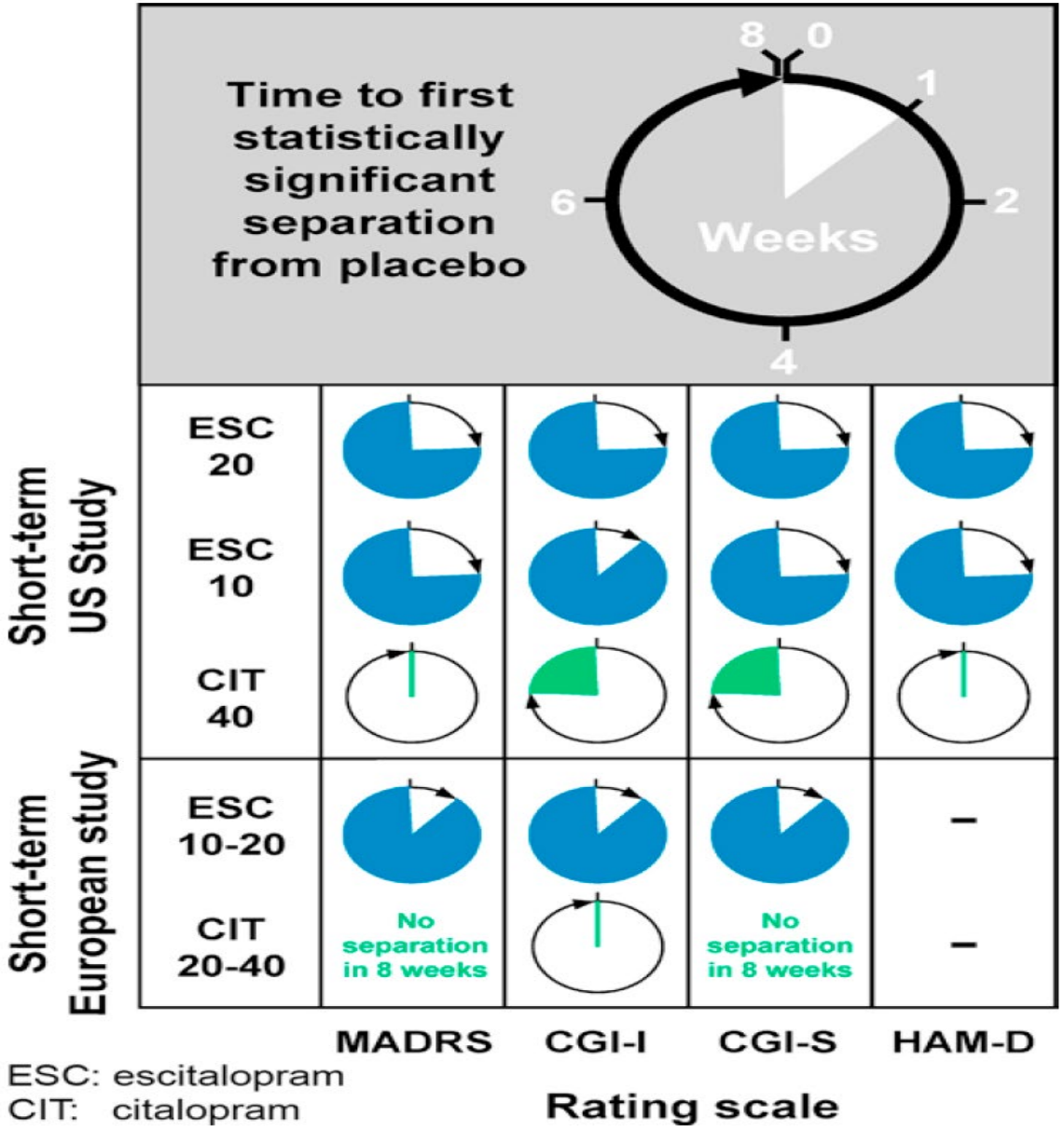

The week at which the mean scores of escitalopram-treated or citalopram-treated patients on various rating scales were first statistically significantly different from placebo-treated patients is shown as a clock display in which the size of the white wedge corresponds to the time required to achieve separation from placebo.

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Children and adolescents

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume XX, Number XX, 2018
© Mary Ann Liebert, Inc.
Pp. 1–8
DOI: 10.1089/cap.2017.0174

Update on Randomized Placebo-Controlled Trials in the Past Decade for Treatment of Major Depressive Disorder in Child and Adolescent Patients: A Systematic Review

Martha J. Ignaszewski, MD,[1,2] and Bruce Waslick, MD,[3,4]

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Children and adolescents

- The totality of available evidence support the use of fluoxetine and **Escitalopram** as **first-line** medication treatment for youth with depressive disorders and demonstrated effect to prevent relapse.

- There were no statistically significant **suicidal signal** increases in acute **Escitalopram** treatment compared with placebo.

- **Discontinuation rates** of **Escitalopram** were low generally due to adverse effects compared with placebo.

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Comorbid anxiety disorders

❖Anxiety disorders or anxiety symptoms are frequent comorbid conditions among children and adolescents with depressive disorders

An Open-Label Trial of Escitalopram in Children and Adolescents with Social Anxiety Disorder

Luciano Isolan M.D., Gabriel Pheula M.D., Giovanni Abrahão Salum, Jr., Sylvia Oswald, Ph.D., Luis Augusto Rohde, M.D., Ph.D., and Gisele Gus Manfro, M.D., Ph.D.

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 17, Number 6, 2007
© Mary Ann Liebert, Inc.
Pp. 751–759
DOI: 10.1089/cap.2007.0007

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Comorbid anxiety disorders

- All symptomatic and quality of life measures showed improvements from baseline to week 12.
- Escitalopram was generally well-tolerated.
- All adverse events ranged from mild to moderate in intensity.
- There were no clinically significant changes in vital signs or weight.
- These results suggest that escitalopram may be an effective and safe treatment for **pediatric SAD**.

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Archives of Psychiatry and Psychotherapy, 2018; 3: 42–54

Pharmacotherapy for treatment-respondent vs. refractory obsessive–compulsive disorder in children and adults: strategies, meta-analyses and clinical guidelines

Mehdi Sayyah, Fakher Rahim

- Obsessive–compulsive disorder (OCD) is a common mental health disorder that occurs at all ages, but more commonly in younger people.
- In children with OCD the greatest incremental treatment gains occur early in treatment with SSRIs.
- In treatment-resistant OCD augmentation of SRIs can be regarded as an evidence-based measure in pharmacological therapy.
- Antipsychotics combination/augmentation of SSRIs should be used in comorbid psychosis, a frequent comorbidity in OCD

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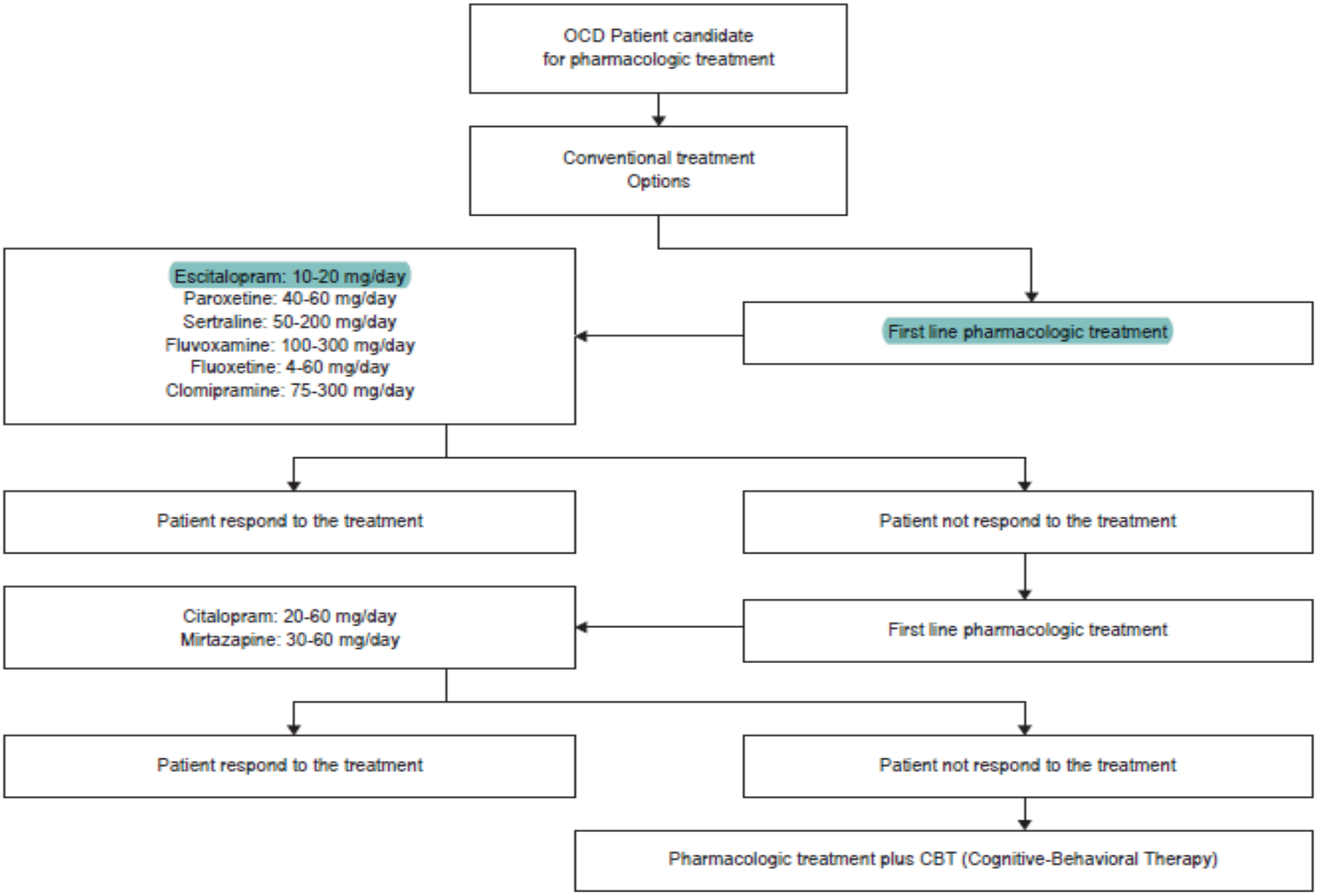

Figure 1. Conventional treatment options usually considered in Obsessive-Compulsive Disorder (OCD)

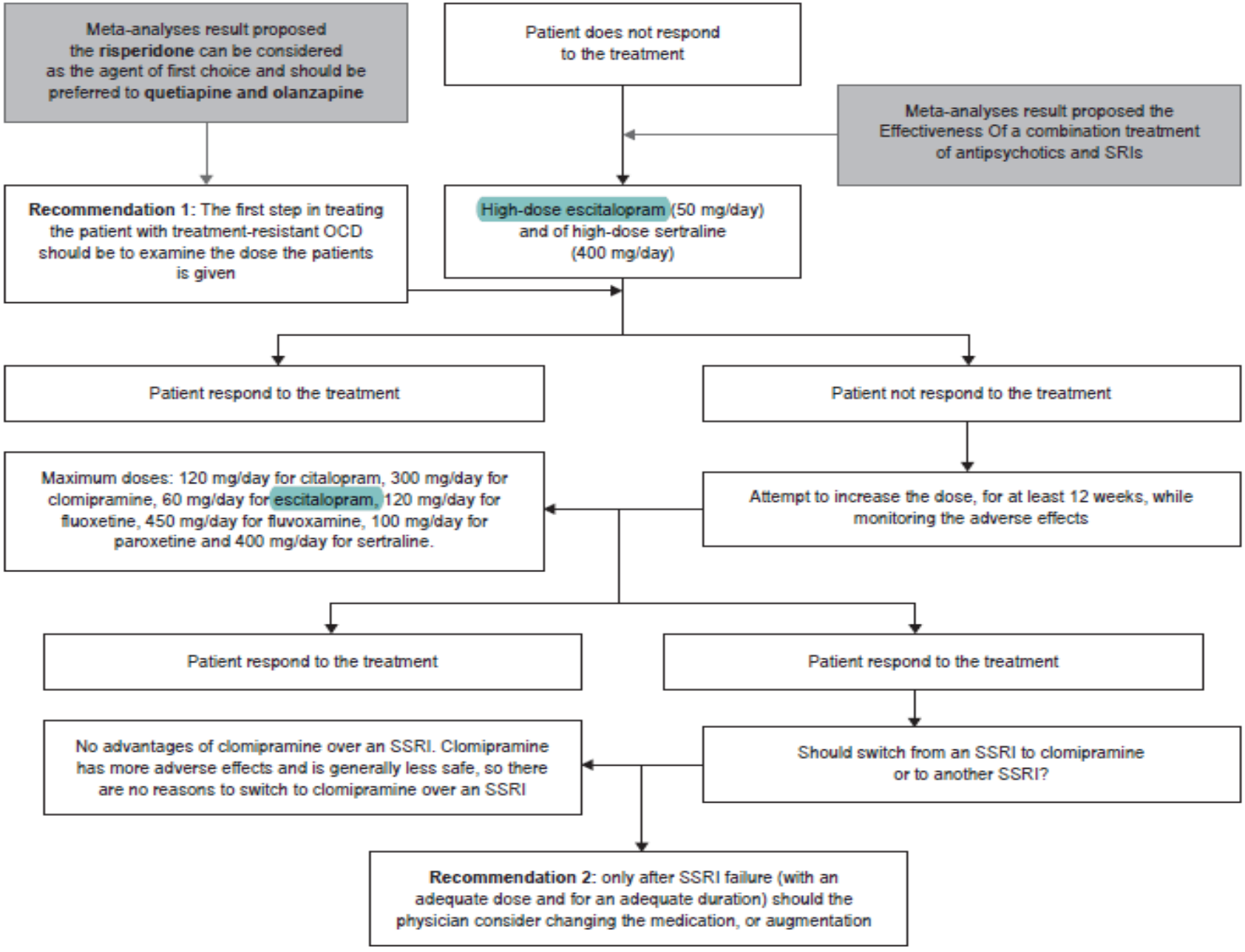

Fig. 2. Pharmacological management of treatment-resistant OCD

Safe choice

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No potent effect on hepatic cytochrome enzymes

Low potential for drug-drug interactions

Improved side-effect profile

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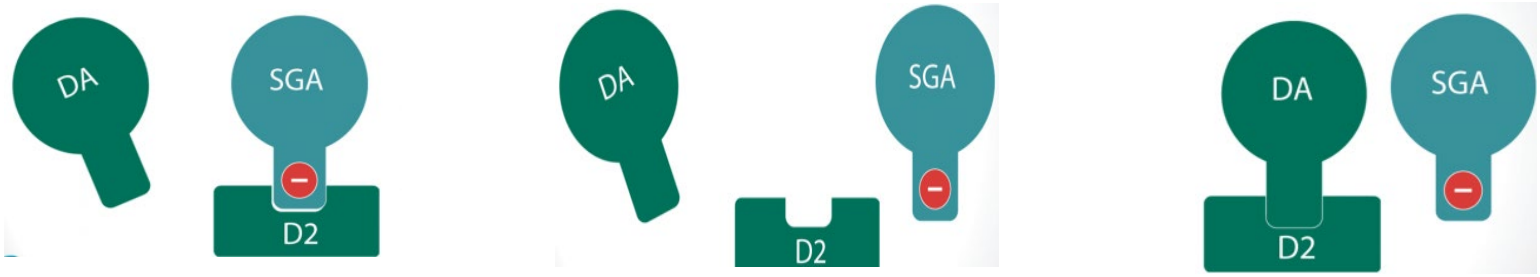
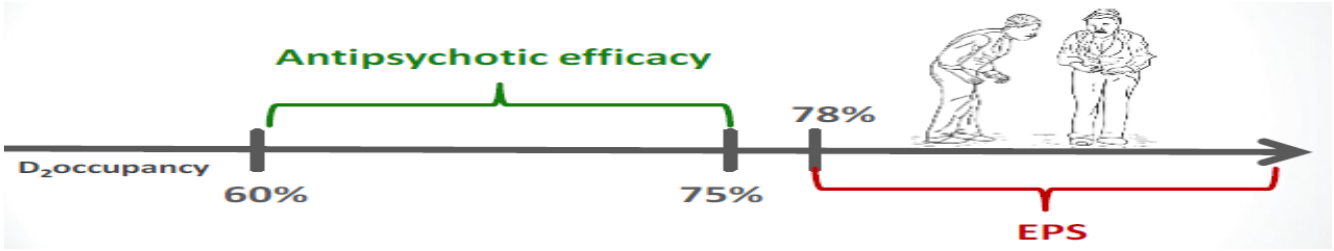
Pharmacological treatment options

❖Antipsychotic

- There is less evidence for the use of first-generation antipsychotics (FGA), such as haloperidol, molindone, and pimozide, in the pediatric population.
- Compared to the second generation antipsychotics (SGA), including risperidone, Aripiprazole, quetiapine, olanzapine, and others.





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Aripiprazole (Arizover®)

Second Generation (Atypical) Antipsychotic

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Medication	FDA-approved indication	Age range, years	Recommended dose range, mg
Risperidone	Schizophrenia	13–17	1–6
	BD (mixed/manic episode)	10–17	1–6
	Irritability, associated with ASD	5–18	0.5–3
Aripiprazole	Schizophrenia	13–17	10–30
	BD (mixed/manic episode)	10–17	10–30
	Irritability, associated with ASD	6–17	5–15
	Tourette's disorder	6–18	<50 kg – 5 to 10 ≥50 kg – 10 to 20
Olanzapine	Schizophrenia	13–17	10
	BD (mixed/manic episode)	13–17	10
Asenapine	BD (mixed/manic episode)	10–17	2.5–10 twice daily
Quetiapine	Schizophrenia	13–17	400–800
	BD (mixed/manic episode)	10–17	400–600
Lurasidone	Schizophrenia	13–17	40–80
	BD (depressive episode)	10–17	20–80
Paliperidone	Schizophrenia	12–17	<51 kg – 3 to 6 ≥51 kg – 3 to 12
Olanzapine/fluoxetine combination	BD (depressive episode)	10–17	3/25–12/50

TABLE 1. ARIPIPRAZOLE IN CHILDREN AND ADOLESCENTS: WORLDWIDE AGENCIES' AUTHORIZATION (UNTIL APRIL 2019)

Country	*Year of first approval*	*SCZ*	*Bipolar disorder*	*Behavior impairments associated with autism or intellectual disability*	*Tourette's syndrome*
United States	2007	>13 Years	>10 Years	>6 Years	>6 Years
UE	2012		>13 Years		
Canada	2013	>15 Years	>13 Years		
France	2009 SCZ and 2016 BP	>15 Years	>13 Years		
Suisse	2018	>13 Years	>13 Years		
Indonesia	2018	Children	Children		
Philippines	2018				>6 Years

Modified from Perraudin et al. (2018).
BP, bipolar disorder; SCZ, schizophrenia.

- ❖ Aripiprazole is one of the most widely prescribed atypical antipsychotics, due to a:
- ✓ Well-established efficacy profile
- ✓ Safety profile
- ❖ Adverse effects are more important in children and adolescents, (weight gain, drowsiness, extrapyramidal effects, and metabolic effects)

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Dosing - Pediatric

❖***Autistic disorder ; 6 to 17 Years***

Initial: 2 mg daily, for 7 days, followed by 5 mg daily

Dose increase: 5 mg/day increments every ≥7 days

Maximum: 15 mg/day

❖***Bipolar I disorder, Acute treatment of manic or mixed episodes; 10 to 17 years***

- Manic and mixed episodes associated with Bipolar I Disorder
  - ➢ Monotherapy
  - ➢ Adjunctive to lithium or valproate
- Maintenance treatment of Bipolar I Disorder
- Agitation associated with bipolar mania

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Dosing - Pediatric

❖*Tourette's syndrome; ≥8 years*

Less than 50 kg

Initial: 2 mg/d for 2 days, then increase to 5 mg/day

Maximum dose: 10 mg/d

50 kg or Greater

Initial: 2 mg/d for 2 days, then increase to 5 mg/d for 5 days, and then to target dose of 10 mg/d on day 8

Maximum dose: 20 mg/d

❖*Schizophrenia: 13 to 17 Years*

Initial: 2 mg/d , then increase to 5 mg after 2 days and then to 10 mg after an additional 2 days

Maintenance dosage: 10 mg/d

subsequent dose increases may be made in 5 mg increments up to a maximum daily dose of 30 mg/day

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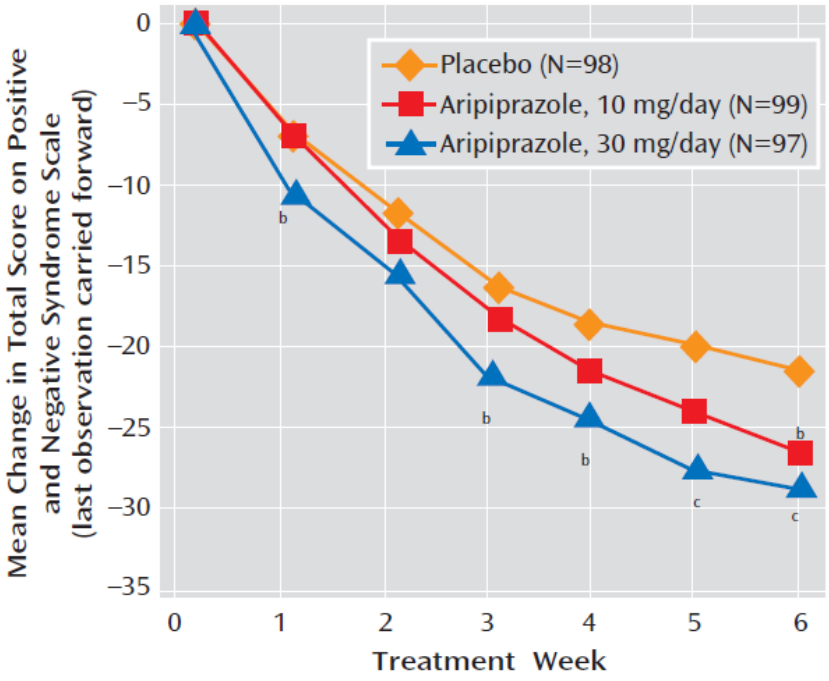
Adolescent schizophrenia

Article *(Am J Psychiatry 2008; 165:1432–1441)*

A Multiple-Center, Randomized, Double-Blind, Placebo-Controlled Study of Oral Aripiprazole for Treatment of Adolescents With Schizophrenia



Conclusion: Both 10- and 30-mg/day doses of aripiprazole were superior to placebo in the acute treatment of adolescents with schizophrenia. Aripiprazole was generally well tolerated.

Adverse events:
Aripiprazole treatment was generally well tolerated and not dose limiting.

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Wider spectrum of psychiatric disorders in children and adolescents

Eur Child Adolesc Psychiatry (2012) 21:361–368
DOI 10.1007/s00787-012-0270-0

25 March 2012

REVIEW

Efficacy and safety of aripiprazole in child and adolescent patients

Eiji Kirino

- **Body weight and metabolic parameters**
- **Serum prolactin significantly lower after APZ administration than at baseline:** growth and sexual maturation
- **Cardiovascular problem:** no changes evident in blood pressure, heart rates, ECG, or the QTc interval in trials
- **Low sedation:** learning ability

➢ **Few side effects (such as EPS, hyperprolactinemia, weight gain, metabolic disorders, and sedation)**

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Overall safety and tolerability

- Aripiprazole has demonstrated a relatively favorable tolerability profile.

➢Lower potential for weight gain or metabolic changes

➢Lower liability for extrapyramidal symptoms (compared to many FGA)

➢Lower Sedation (compared to more other antipsychotics)

➢Lower hyperprolactinemia (compared to risperidone, paliperidone or amisulpride)

➢Lower QTc prolongation (compared to the older, FGA)

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Autism Spectrum Disorder

- In a comparison study, aripiprazole and risperidone similarly reduced irritability scores in children with ASD, but aripiprazole showed effects more quickly

A Head-to-Head Comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial

Running title: comparing aripiprazole and risperidone for treating autism

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OCD

Aripiprazole Treatment for Obsessive Compulsive Disorder in 2 Young Subjects Who Could Not Tolerate Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are the mainstay pharmacological treatment of obsessive compulsive disorder (OCD) in young subjects.[1–3] Despite that they are generally safe and well tolerated in young subjects with OCD, some subjects may develop adverse effects that may limit or discourage the use of SSRIs.[3–7] Here, we present 2 pediatric cases who could not tolerate fluoxetine or sertraline for the treatment of OCD. Fluoxetine or sertraline were discontinued in these subjects, and they were treated successfully without any significant adverse effects with using low dose of aripiprazole.

Aripiprazole Monotherapy Was Effective in Treating Obsessive-Compulsive Disorder in a Preschool Boy

Aripiprazole augmentation has been reported effective in the treatment of obsessive-compulsive disorder (OCD) in young and adult subjects.[1–3] Here, a case of a pre-school boy with multiple psychiatric diagnoses whose primary complaint was distressing symptoms of OCD is reported. He developed manic reaction with escitalopram-risperidone combination treatment. Then he was switched to aripiprazole monotherapy for his OCD and other behavioral symptoms. Clinical picture of the subject and successful treatment with aripiprazole monotherapy are discussed in this very young subject.

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Aripiprazole in the Treatment of Pediatric Bipolar Disorder: A Systematic Chart Review

By Joseph Biederman, MD, Mary Ann McDonnell, APRN, BC, Janet Wozniak, MD, Thomas Spencer, MD, Megan Aleardi, BA, Richard Falzone, MD, and Eric Mick, ScD

FOCUS POINTS

- Bipolar and bipolar spectrum disorder are common in children.
- Atypical neuroleptics have been found to be efficacious in the management of youth with bipolar and bipolar spectrum disorder.
- Aripiprazole appears to be a promising and well-tolerated agent in the treatment of children and adolescents with bipolar disorder.

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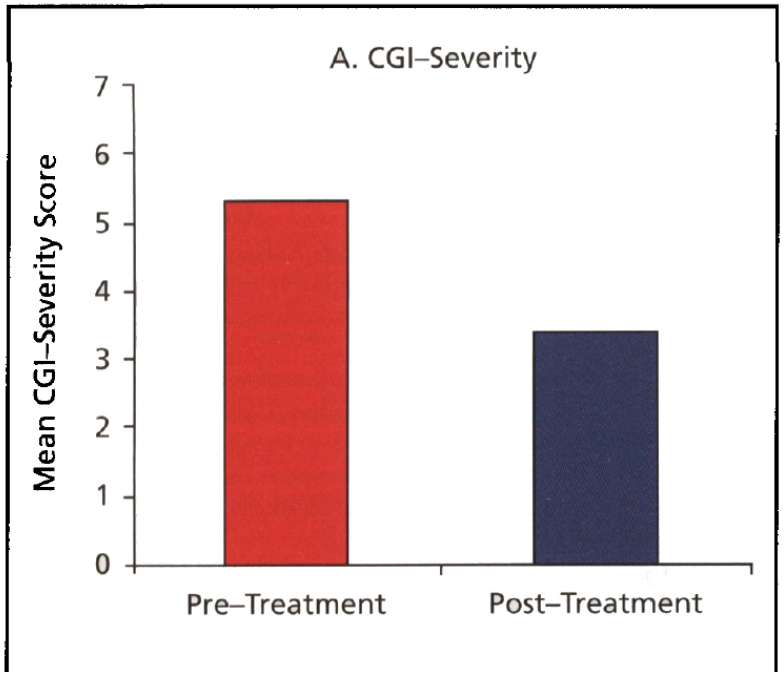

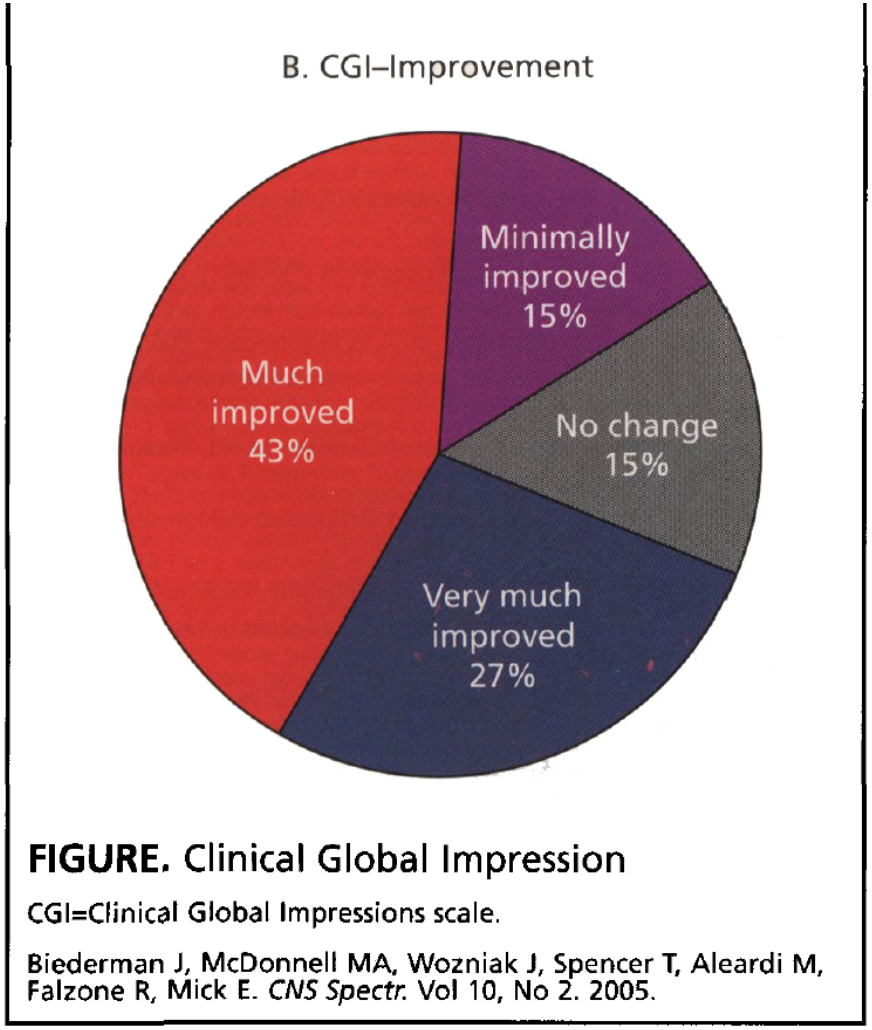

FIGURE. Clinical Global Impression

CGI=Clinical Global Impressions scale.

Biederman J, McDonnell MA, Wozniak J, Spencer T, Aleardi M, Falzone R, Mick E. *CNS Spectr.* Vol 10, No 2. 2005.

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Double-Blind, Randomized, Placebo-Controlled Long-Term Maintenance Study of Aripiprazole in Children With Bipolar Disorder

Robert L. Findling, MD, MBA; Eric A. Youngstrom, PhD; Nora K. McNamara, MD; Robert J. Stansbrey, MD; Jaime L. Wynbrandt, MA; Clara Adegbite, BA; Brieana M. Rowles, MA; Christine A. Demeter, MA; Thomas W. Frazier, PhD; and Joseph R. Calabrese, MD

A growing body of research has documented the validity, chronicity, and seriousness of a bipolar diagnosis in patients under 10 years of age.[4–18] Owing to the severity and persistence of bipolarity in this patient group, safe and effective long-term intervention strategies are needed. This study tested the maintenance efficacy of aripiprazole in children with a bipolar disorder.

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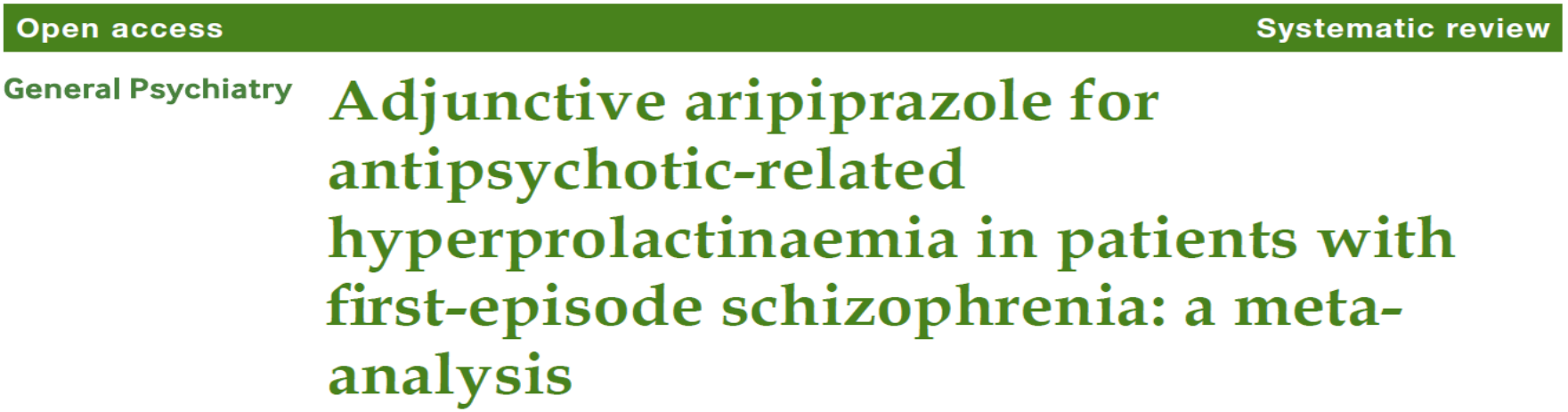
Hyperprolactinemia

❖Antipsychotics cause hyperprolactinemia through their primary mechanism of dopamine (D2) receptor antagonism.



❖ This meta-analysis of RCTs showed that adjunctive aripiprazole appears to be associated with reduced hyperprolactinemia induced by AP and improved prolactin-related symptoms in first-episode schizophrenia.

Zheng W, Cai DB, Yang XH, Ungvari GS, Ng CH, Shi ZM, Hu ML, Ning YP, Xiang YT. Adjunctive aripiprazole for antipsychotic-related hyperprolactinaemia in patients with first-episode schizophrenia: a meta-analysis. General Psychiatry. 2019;32(5).

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Thanks for your attention

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