Antipsychotics in Depression

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AMERICAN PSYCHIATRIC ASSOCIATION
ANNUAL MEETING

1961

First antipsychotic combo for depression with anxiety
Trifluoperazine + MAOI (tranylcypromine)

"Reports on drug research usually follow a pattern:

After extensive and widespread usage of the drug, toxic or allergic side effects are noted, no matter how innocent the chemical may initially have been claimed to be."

–M Stracker, 1960
Introducing Parstelin

Straker M, Can Med Assoc J 1960, 83(25):1306-1310

1980s Use declines due to tardive dyskinesia

Nelson JC et al, Neuropsychiatr Dis Treat 2008 Oct;4(5):937-48

1990s: Atypicals (SGAs) "treat" tardive dyskinesia?

Marked Reduction of Tardive Dyskinesia With Olanzapine

Kimberly H. Littrell, APRN; Craig G. Johnson, MD; Steven Littrell, MA; et al

Arch Gen Psychiatry. 1998;55(3):279-280. doi:

Original Article

Improvement of Debilitating Tardive Dyskinesia with Risperidone

Sunil R. Rangwani, Sanjay Gupta, William J. Burke & Jane Potter

Pages 27-29 | Published online: 04 Dec 2011

Marked improvement in tardive dyskinesia following treatment with olanzapine in an elderly subject

Sir: Clozapine has been reported to improve tardive dyskinesia in some patients (Lieber-

Improvement of tardive dyskinesia following switch from neuroleptics to olanzapine

Schizophrenia and Severe Tardive Dyskinesia Responsive to Risperidone

Improvement in Pisa Syndrome and Tardive Dyskinesia Following Aripiprazole Treatment

International Journal of Neuropsychopharmacology (1999), **2**, 333–334. Copyright © 1999 CINP

Three cases of improvement of tardive dyskinesia following olanzapine treatment

Received 10 March 1999; Reviewed 8 June 1999; Revised 30 June 1999; Accepted 25 July 1999

Review > S D J Med. 2000 Feb;53(2):65-7.

Rapid resolution of antipsychotic-induced tardive dyskinesia with olanzapine

Risperidone treatment of neuroleptic-induced tardive extrapyramidal symptoms

Risperidone for Severe Tardive Dyskinesia: A 12-Week Randomized, Double-Blind, Placebo-Controlled Study

2000s

Atypicals may unleash TD in patients with prior exposure to first-generation antipsychtoics,

or TD on atypicals may be due to *spontaneous dyskinesias*

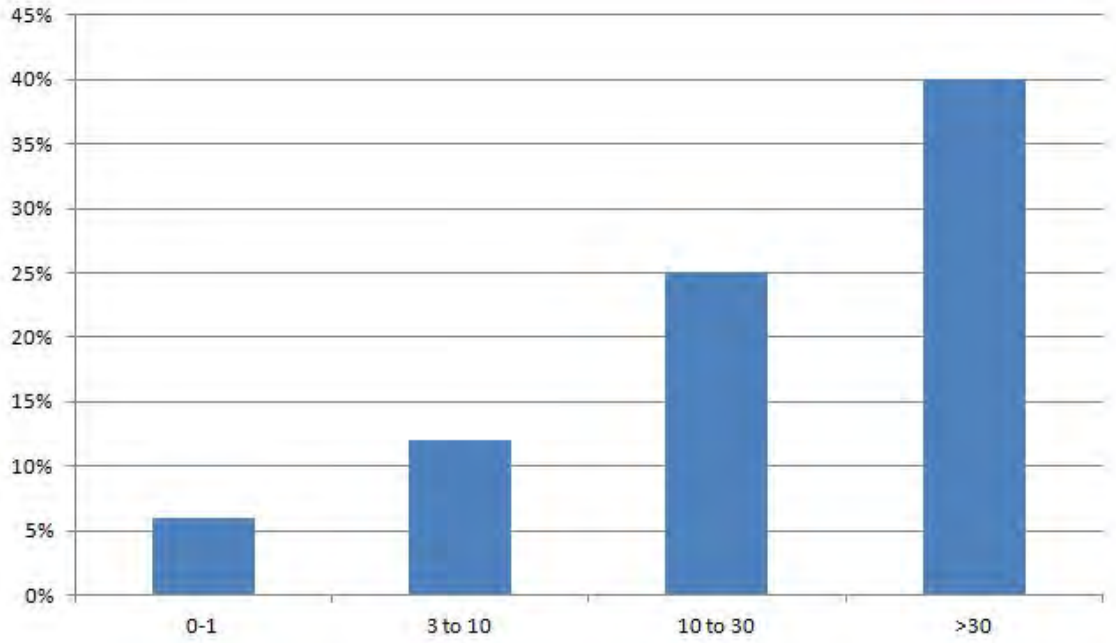
With the exception of clozapine, risperidone has the longest history among the atypical antipsychotics. In most case reports that have documented TD in patients given risperidone, the patients were predisposed to the disorder. For example, they had previous treatment with conventional antipsychotics or there was a potential pharmacokinetic explanation (for exam-

Table 2 TD associated with olanzapine, quetiapine, and ziprasidone

Study	Number of patients	Medication	dosage (mg daily)	Duration of treatment (months)	Previous antipsychotic therapy
Herran and Vazquez-Barquero (38)	2	Olanzapine	10, 20	2,10	Yes
Ananth and Kenan (39)	1	Olanzapine	20	57	Yes
Snoddgrass and Labbate (20)	1	Olanzapine	5	1	Yes (first had TD with risperidone, see Table 4)
Benazzi (40)	1	Olanzapine	5	2	Yes
Bella and Piccoli (41)	1	Olanzapine	10	18	No
Ghelber and Belmaker (45)	1	Quetiapine	150 to 300	6	Yes
Ghaemi and Ko (46)	1	Quetiapine	125	3	Yes (only risperidone and olanzapine)
Rosenquist (50)	1	Ziprasidone	100	4	Yes (risperidone and olanzapine)
Keck (51)	1	Ziprasidone	100	2.25	Yes (haloperidol 6 days; quetiapine 12 months)

Reports in Schizophrenia Confuse TD

spontaneous dyskinesias are part of illness, increasing toward 40% with time

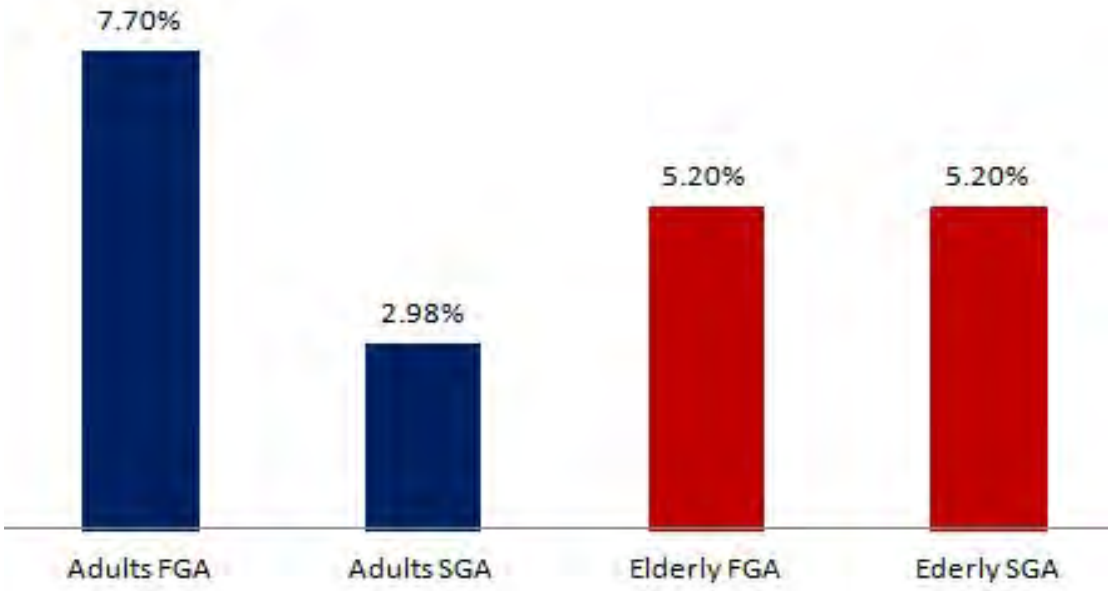


Duration of schizophrenia illness (years, no antipsychotic treatment)

studies published around that time (54) indicating a lower risk of TD with newer antipsychotics. However, a subsequent update on TD risk for atypical antipsychotics in 2008, which was identified as the most important publication, showed that the incidence of TD with atypical antipsychotics was higher than previously reported. Despite this evidence, interest in TD continued to decline until 2014. Another reason for the dwindling interest in TD may be the shift of focus from motor side effects to metabolic side effects of antipsychotics, a

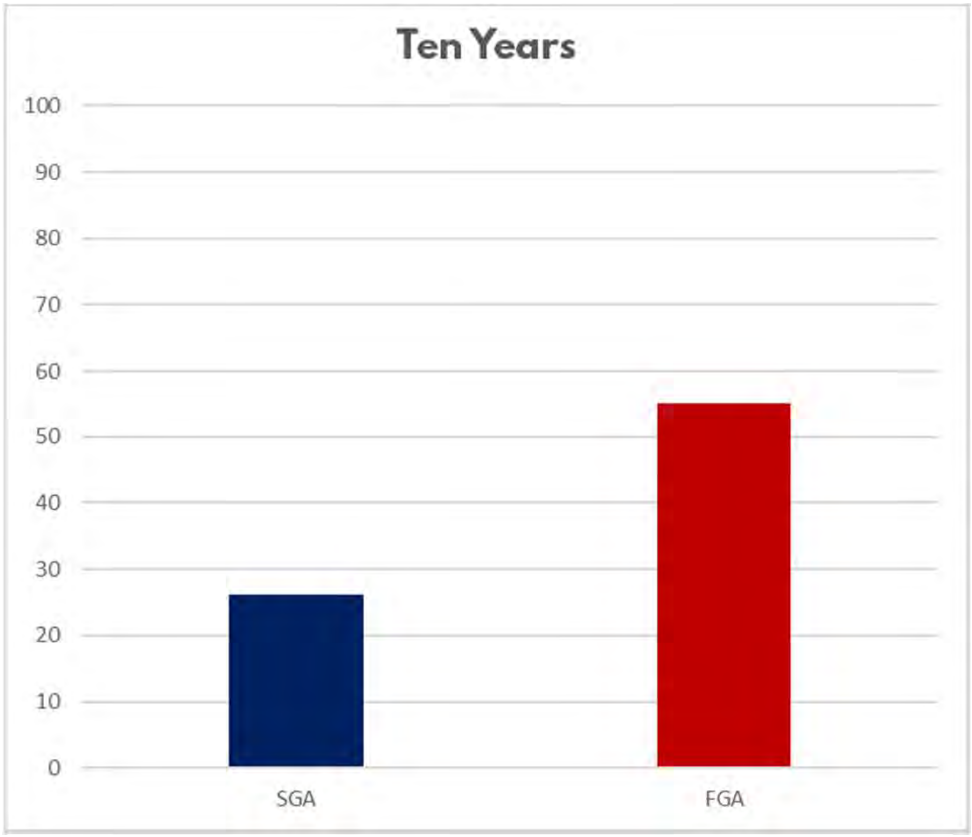
2008: Proof comes from bipolar

- Spontaneous dyskenisas *do not* occur in mood disorders
- In bipolar, TD rate: Typicals > Atypicals > No antipsychotic



Annualized TD rate across 12 trials, 500,000 person years

Correll CU, Schenk EM, Curr Opin Psychiatry. 2008;21(2):151-156



Estimated Rate of Tardive Dyskinesia on Second Generation Antipsychotics in Bipolar Disorder

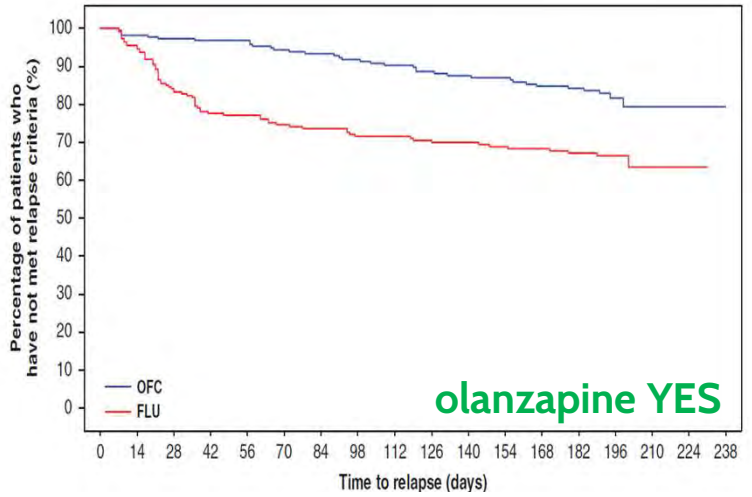
FDA Approvals

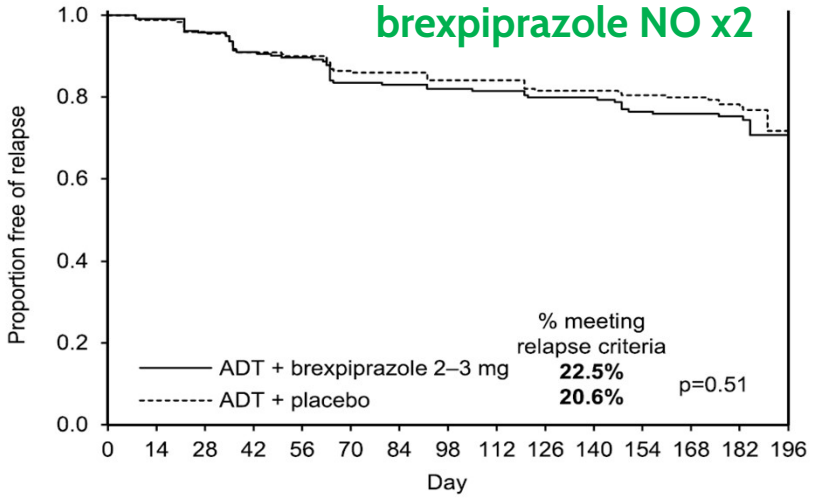
Antidepressant Augmentation

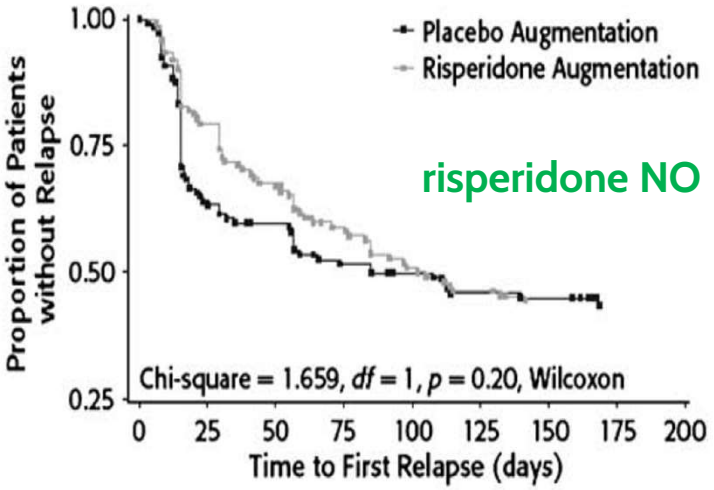
2007	**Aripiprazole**
2009	**Olanzapine-Fluoxetine** **Quetiapine**
2015	**Brexpiprazole**
~~**2017**~~	~~**Lurasidone rejected**~~ (monotherapy for mixed feat)
2022	**Cariprazine**
[in review]	*Lumateperone*

Does antipsychotic continuation prevent depression?

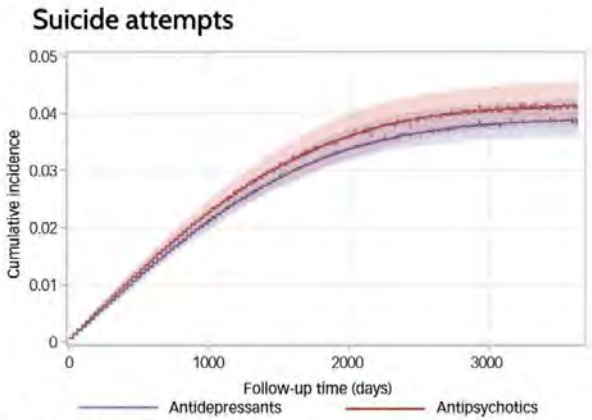
Not in 3/4 trials (6 months, n=2,308)

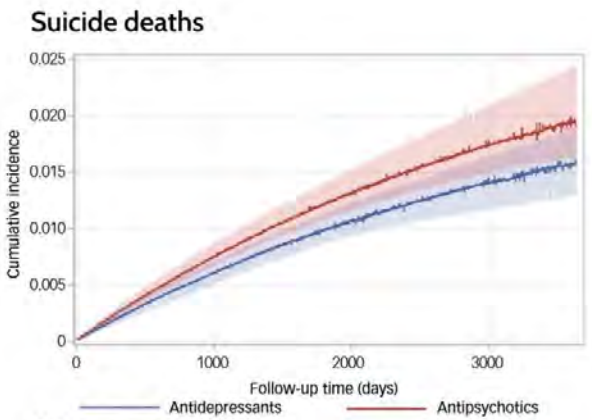


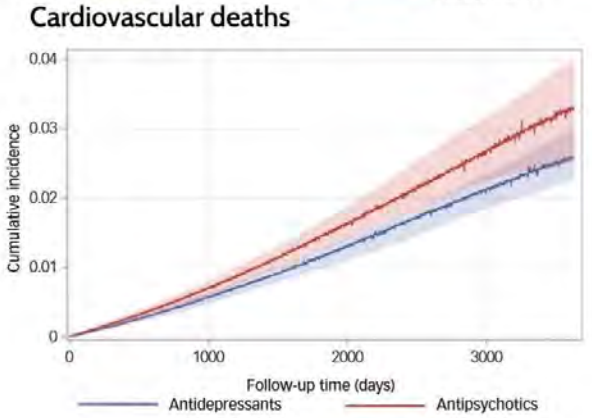


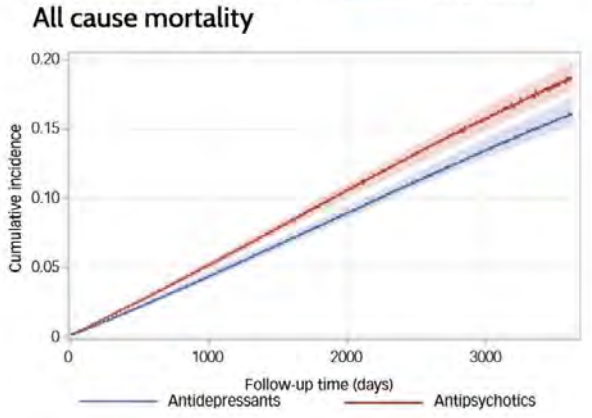


No Suicide Reduction, Higher Cardiac Mortality









Comparative cohort study of 79,898 patients with TRD.

Antipsychotic augmentation vs. matched controls who received third-line antidepressants

Tsai DH et al, Brit J Psychiatry 2025;1-9

Lithium prevents unipolar depression

- 21 controlled trials, average duration 2 years
- Also prevents depression after ECT
- Prevents suicide and hospitalization more than antidepressants and antipsychotics in unipolar
- Acute benefits similar to antipsychotics (12 trials, NNT=5)

Undurraga J et al, J Psychopharmacol 2019;33(2):167-176
Lambrichts S et al, Acta Psychiatr Scand 2021;143(4):294-306
Tiihonen J et al, Lancet Psychiatry. 2017;4(7):547-553
Pompili M et al, J Affect Disord 2023, 340:245-249

Antipsychotic effect size = 0.3-0.4

Risks

Tardive dyskinesia

Metabolic syndrome

Hyperprolactinemia

Orthostatic hypotension

Arrhythmias

Hyperthermia

Neuroleptic Malignant Syndrome

Priapism

Neutropenia

Elevated LFTs

Mortality in dementia

Tolerability

Akathisia

Dystonia

Muscle stiffness (EPS)

Weight gain

Sedation

Sexual dysfunction

Anticholinergic effects

Methylfolate effect size = 0.4-0.9*

Risks

None

Tolerability

None

Cost

15 mg/day, $7.50/month

Recommended Products:

chrisaikenmd.com/supplements

*0.9 in large RCT of depression with MTHFR genotype abnormalities, as monotherapy in vitamin-complex Enlyte:

Mech AW and Farah A, J Clin Psychiatry 2016;77(5):668-71

0.4 in metaanalysis of depression augmentation trials:

Maruf AA et al, Pharmacopsychiatry 2022;55(3):139-147

Light Therapy effect size = 0.5-0.8

Risks

Photosensitivity. Caution in eye disease.

Tolerability

Headache, eye strain.

Cost

$120-200 (one time)

Recommended Products:

chrisaikenmd.com/lighttherapy

*0.5 in non-seasonal depression, 0.5-0.8 in winter seasonal depression, 0.4 in bipolar depression

Mårtensson B et al, J Affect Disord 2015;182:1-7
Tao L et al, Psychiatry Res 2020, 291:113247
Lam RW et al, Can J Psychiatry 2020;65(5):290-300

Light Therapy effect size = 0.4-0.9*

Risks

None

Tolerability

None

Cost

15 mg/day, $7.50/month

Recommended Products:

chrisaikenmd.com/supplements

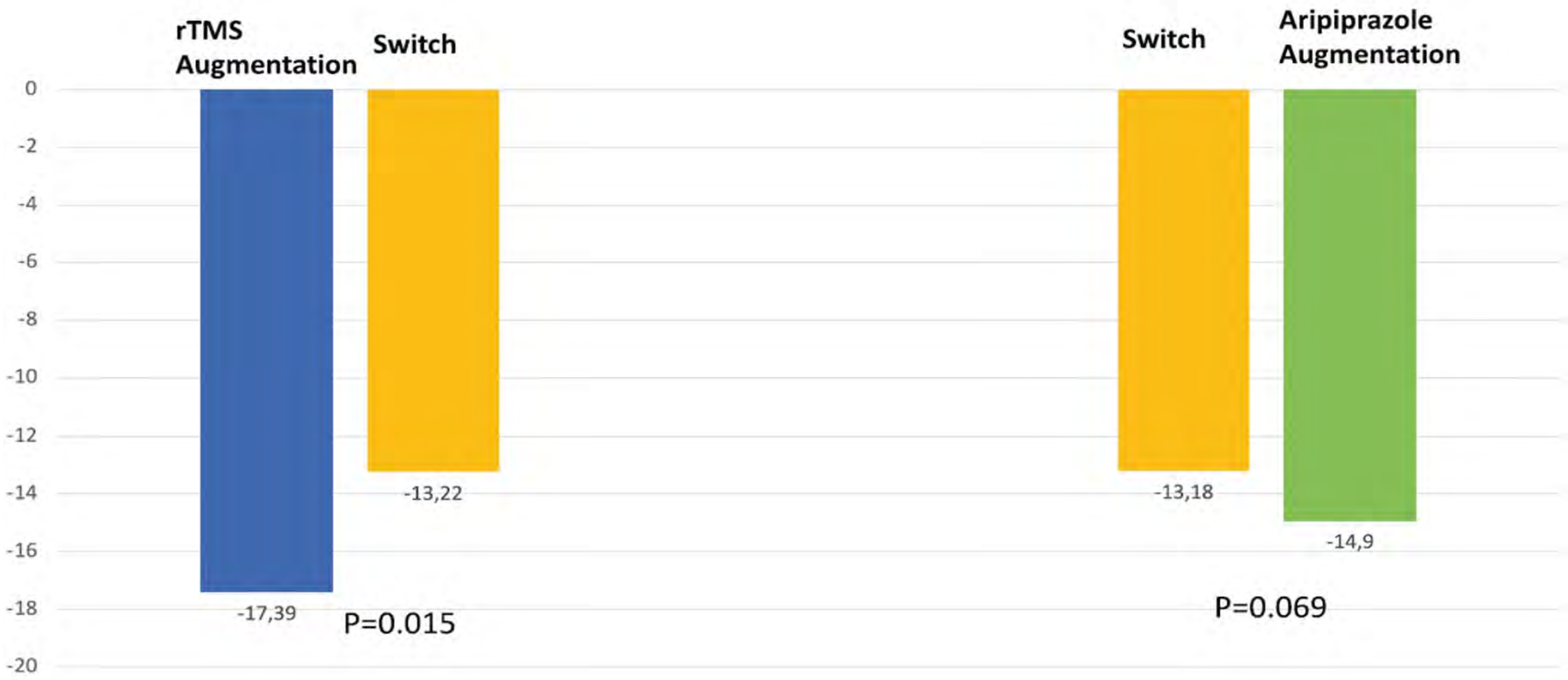
*0.9 in large RCT of depression with MTHFR genotype abnormalities, as monotherapy in vitamin-complex Enlyte:

Mech AW and Farah A, J Clin Psychiatry 2016;77(5):668-71

0.4 in metaanalysis of depression augmentation trials:

Maruf AA et al, Pharmacopsychiatry 2022;55(3):139-147

TMS More Effective than Aripiprazole Aug in TRD



Papakostas GI et al, Mol Psychiatry. March 7, 2024.

Antipsychotics in Bipolar

Antipsychotics = Faster onset

Lithium = Better long-term functioning and prevention

Atypicals:

Conditions they treat in RCTs

	Unipolar Depression	Bipolar Depression	Mania & Mixed	Schizo-phrenia	Irritability due to Autism	OCD	Borderline Personality	Tourette's	Akathisia	Weight Gain	Fatigue
Risperidone (Risperdal)	◊		■	■	■	□	□	□	↑↑↑	↑	↑↑
Olanzapine (Zyprexa, Symbyax)	♦	♦	■	■		□	□	□	↑↑	↑↑↑	↑↑↑
Quetiapine (Seroquel)	♦	■	■	■		□	□		—	↑↑↑	↑↑↑
Ziprasidone (Geodon)	◊		■	■				□	↑	—	↑↑↑
Aripiprazole (Abilify)	♦		■	■	■	□	□	□	↑↑	↑	↑↑
Paliperidone (Invega)				■		□			↑↑	↑	↑
Asenapine (Saphris)			■	■					↑↑	↑	↑↑
Cariprazine (Vraylar)	♦	■	■	■					↑↑	↑	↑
Lurasidone (Latuda)	◊	■		■					↑↑↑	↑	↑↑
Brexpiprazole (Rexulti)	♦		NO	■		(PTSD)			↑	↑	↑
Lumateperone (Caplyta)	◊	■	?	■					—	—	↑↑
Iloperidone (Fanapt)			■	■					↑	↑↑	↑

■ = FDA-approved ♦ = FDA-approved w/ antidepressant □ = Effective but not FDA-approved NO = tested, did not work

Side effects: ↑↑↑ major, ↑↑ moderate, ↑ mild, — rare