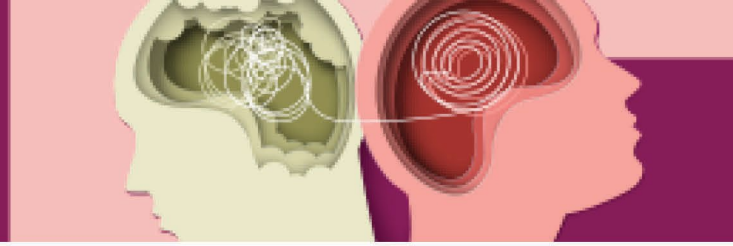
Managing Adverse Effects from Adjunct Atypical Antipsychotics in Inadequately Treated Major Depressive Disorder

Supported by an independent educational grant from Intra-Cellular Therapies, Inc.

Faculty



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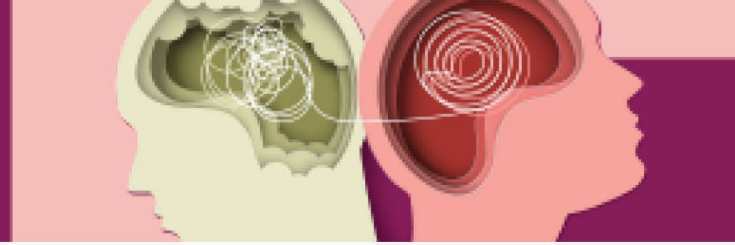
Faculty Disclosures



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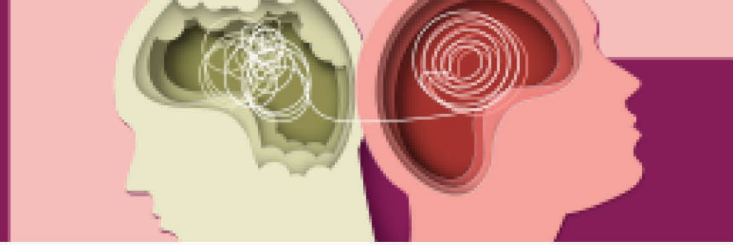

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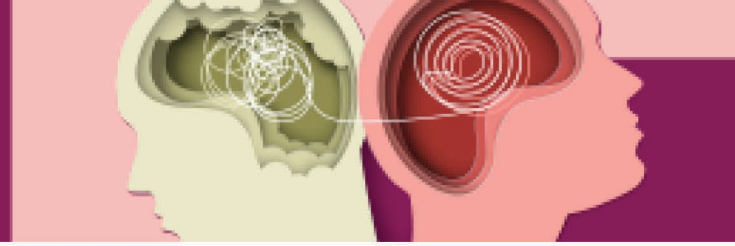
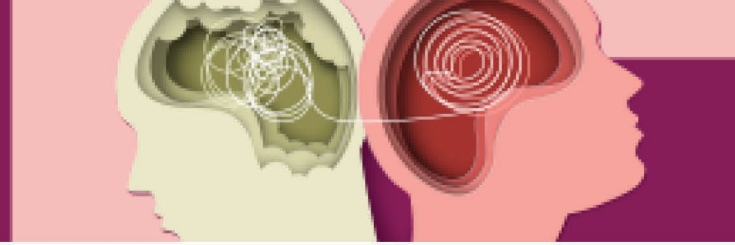
Learning Objectives



- Describe the challenges associated with managing MDD with standard antidepressants, including nonresponse, persistent symptoms, and inability to achieve remission
- Evaluate the MOAs and latest clinical trial data associated with FDA-approved and emerging AAPs for the adjunctive treatment of MDD in patients with inadequate response to standard antidepressants
- Implement strategies for managing adverse effects, particularly DIMDs, associated with FDA approved and emerging AAPs for the adjunctive treatment of MDD

Diagnosis and Initial Treatment of MDD

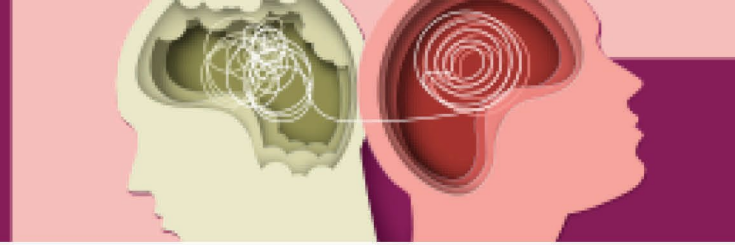
Underdiagnosis of MDD: Screening is KEY



- There are an estimated 21 million adults with MDD in the US
- 59.8% of youth with MDD do not receive any mental health treatment in America
- Depression is about 50% more common among women than among men.
- Economic burden of adults with MDD in the USA in 2019 was estimated at $333.7 billion (equivalent to $382.4 billion in 2023 USD)
- Recent Survey shows that **less than 5%** of adults are screened for depression in the primary care setting

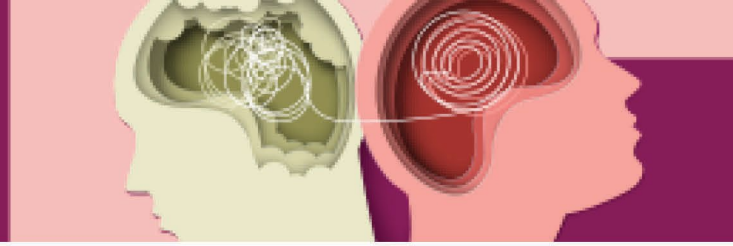
Malhi GS, et al. *Lancet.* 2018;392(10161):2299–2312. Mental Health America. General Mental Health Data. Accessed September 27, 2024. https://mhanational.org/mentalhealthfacts. World Health Organization (WHO). Depressive Disorder (Depression). March 31, 2023. Accessed September 27, 2024. https://www.who.int/newsroom/fact-sheets/detail/depression/?gclid=CjwKCAiAqY6tBhAtEiwAHeRopZuhCJ4FCCEpCmuLEiDqwL6Sdan6hEsdlL5_pQmdP7yvwd_435SHhoCC8cQAvD_BwE. Greenberg, et al. *Advances in Therapy*. 2023;40(10):4460–4479. Anxiety and Depression Association of America. (n.d.). Facts & Statistics. Accessed October 10, 2024, https://adaa.org/understanding-anxiety/depression/facts-statistics

Screening Tools



Screening Instrument	Screening Notes
Patient Health Questionnaire (PHQ-9)	9-question self reported questionnaire that assesses depressive symptoms
Beck Depression Inventory (BDI)	21-questions that assesses the severity of depressive symptoms & observable behaviors
Center for Epidemiologic Studies Depression Scale (CES-D)	20-questions that assess depressive symptoms over a week period
Geriatric Depression Scale (GDS)	15-item questionnaire that identifies symptoms of depression in older adults
Hamilton Depression Rating Scale (HDRS)	17-questions Measures the severity of depression in an inpatient population
Edinburgh Postnatal Depression Scale (EPDS)	10-question scale that rates the presence of depressive symptoms over the prior week

STAR*D Analysis: Antidepressants Don't Work for Everyone



	1st line (n=3,671)	2nd line (n=1,439)	3rd line (n=390)	4th line (n=123)
Remission rate by line of therapy in STAR*D	37%	31%	14%	13%
Response rate by line of therapy in STAR*D	49%	29%	17%	16%

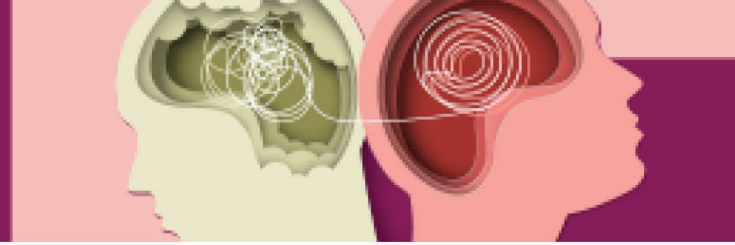
The cumulative remission rate in STAR*D was 67%, leaving over 30% of patients as treatment resistant

Of Note: No Atypical Antipsychotics Were Used in STAR*D

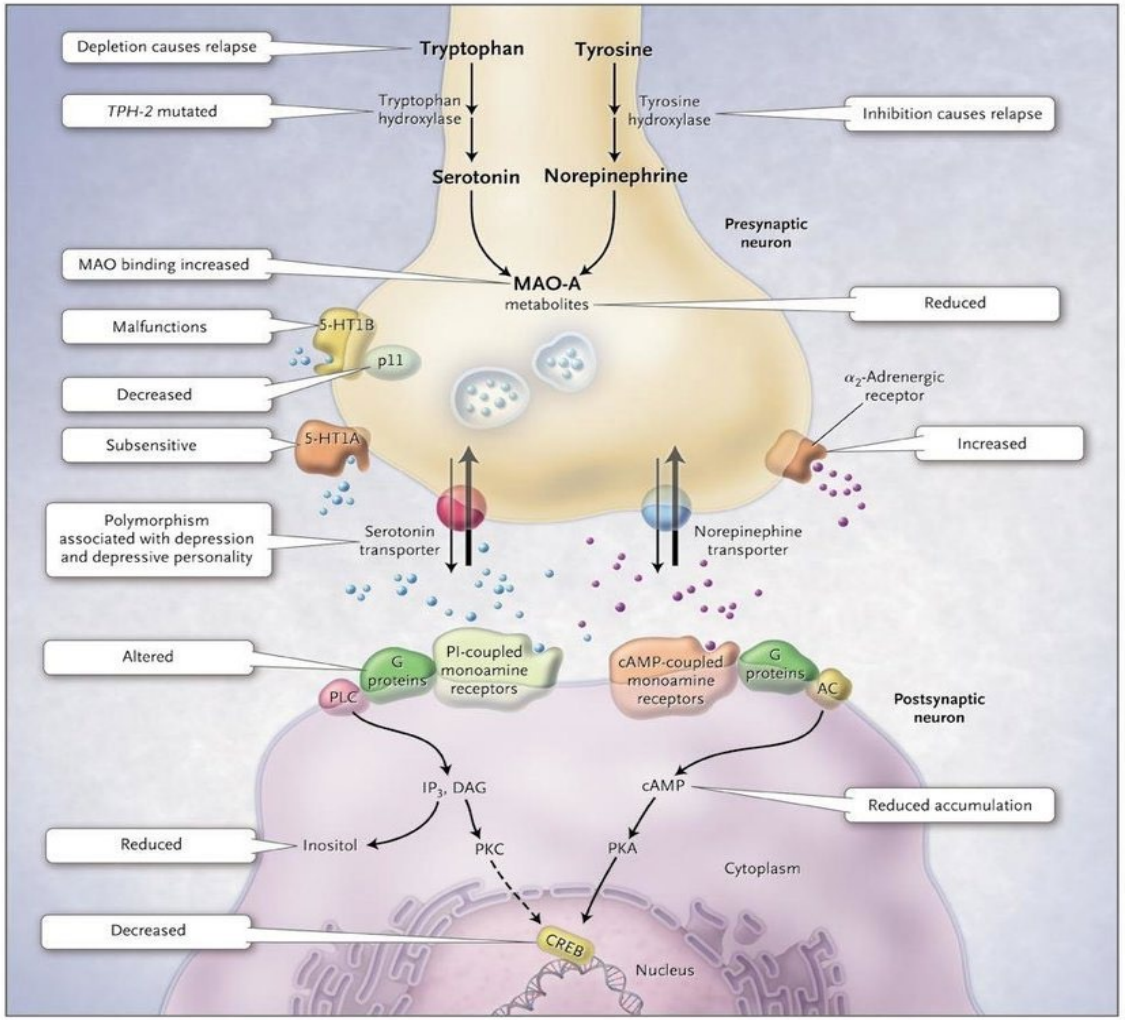
STAR*D = Sequenced Treatment Alternatives to Relieve Depression

Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905.

The Problem with the Monoamine Hypothesis

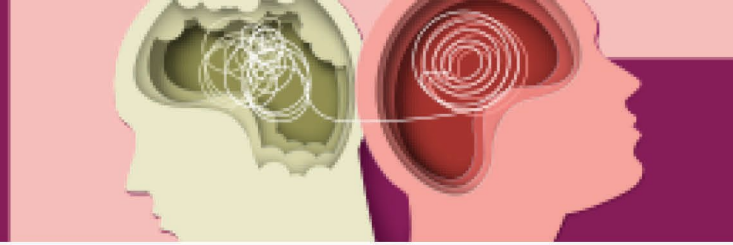


- Main Point: Lowering the levels of monoamines contributes to depression, while raising them lifts depression
- ~60% of patients do not benefit from their first antidepressant, and many do not respond to subsequent trials
- SSRIs, SNRIs, NDRIs take weeks to work



SSRI = selective serotonin reuptake inhibitor; SNRI = Serotonin-Norepinephrine Reuptake Inhibitor; NDRI = Norepinephrine-dopamine reuptake inhibitor.
Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905. Image: Researchgate. Accessed October 15, 2024. https://www.researchgate.net/figure/Monoamine-Hypothesis-of-MDD_fig1_352134689.

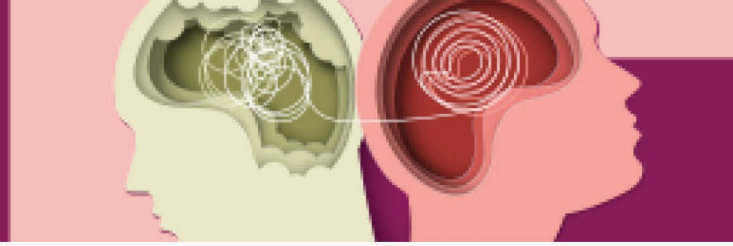
Limitations of Conventional Pharmacologic Management of Depression



- Non-Response
- Persistent Symptoms
- Adverse Effects
- Non-Adherence

Dodd S, et al. A clinical approach to treatment resistance in depressed patients: What to do when the usual treatments don't work well enough?. *The World Journal of Biological Psychiatry : The Official Journal of the World Federation of Societies of Biological Psychiatry.* 2021;*22*(7):483–494. https://doi.org/10.1080/15622975.2020.1851052

Clinical Guidelines for Management of Depression: CANMAT

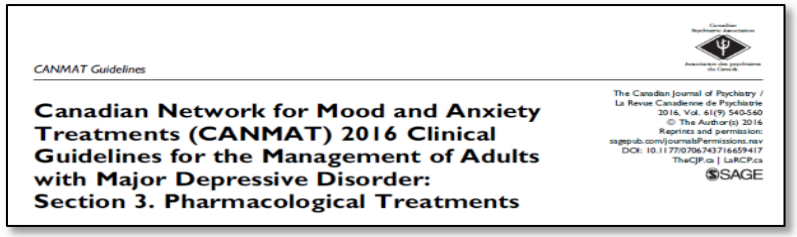


1st Line Treatment

Agomelatine* (MT_1, MT_2, agonist; 5-HT_2 agonist)
Bupropion (NDRI)
Citalopram (SSRI)
Desvenlafaxine (SNRI)
Duloxetine (SNRI)
Escitalopram (SSRI)
Fluvoxamine (SSRI)
Mianserin* (α_2-adrenergic, 5-HT_2 agonist)
Paroxetine (SSRI)
Sertraline (SSRI)
Venlafaxine (SNRI)
Vortioxetine (multimodal)

2nd Line Treatment

Amitriptyline, clomipramine, other (TCAs)
Levomilnacipran (SNRI)
Moclobemide (reversible inhibitor MAO-A)
Quetiapine (AAP)
Selegiline transdermal (irreversible inhibitor MAO-B)
Trazodone (SRI 5-HT_2 agonist)
Viazodone (SRI, 5-HT_{1A} partial agonist)


CANMAT Guidelines

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie 2016, Vol. 61(9) 540-560
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DOI: 10.1177/0706743716659417
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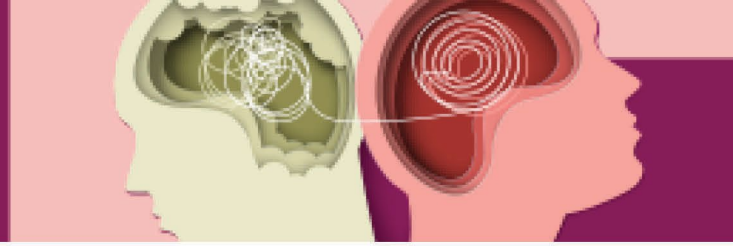
3rd Line Treatment

Phenelzine (irreversible inhibitor MAO)
Tranylcypromine
Reboxetine* (NRI)

*Not FDA approved in the US for MDD.
NDRI=norepinephrine and dopamine reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; MAO=monoamine oxidase; AAP=atypical antipsychotic; SRI= serotonergic reuptake inhibitors; NRI=norepinephrine reuptake inhibitors.

Kennedy SH, et al. *Can J Psychiatry*. 2016;61(9):540-560. Moser G. Pink Sheet Citeline Regulatory. Last updated December 10, 2018.Accessed September 26, 2024. https://pink.pharmaintelligence.informa.com/PS124402/Major-Depressive-Disorder-Patients-Emphasize-Long-Term-Nature-Of-Disease-In-Feedback-Meeting.
Goldberg JF, et al. *Expert Opin Pharmacother*. 2017;18(14):1417-1420.

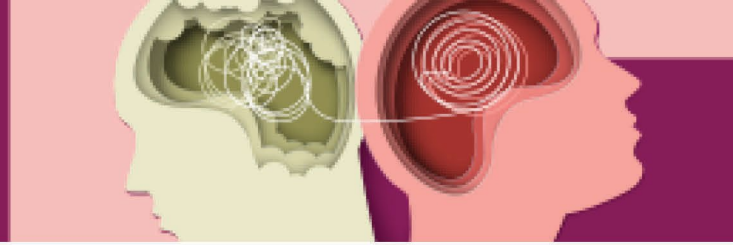
Clinical Guidelines for Management of Depression: *When to Make a Change*?



Consider Adjunctive Medication When:

- There have been **2 or more** antidepressant trials
- There is **partial** response (> 25% improvement) to the initial antidepressant
- There are specific **residual symptoms** or side effects to the initial antidepressant that can be targeted
- There is less time to **wait** for a response (more severe/more functional impairment)
- Patient prefers to **add on** another medication

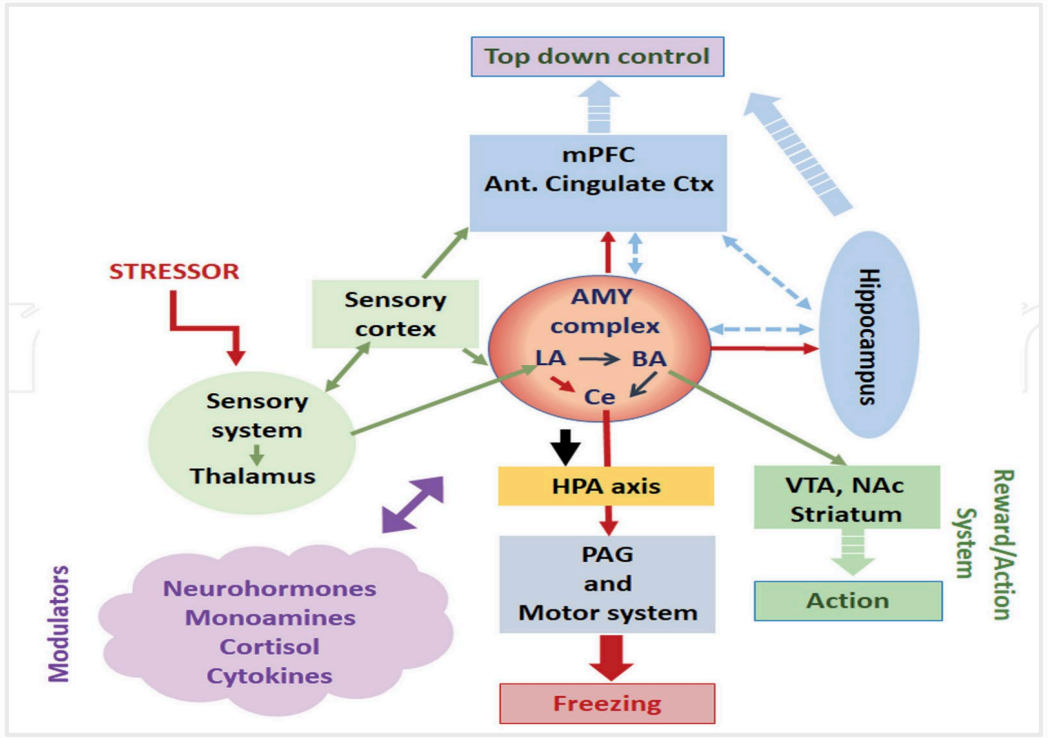
Key Learning Points



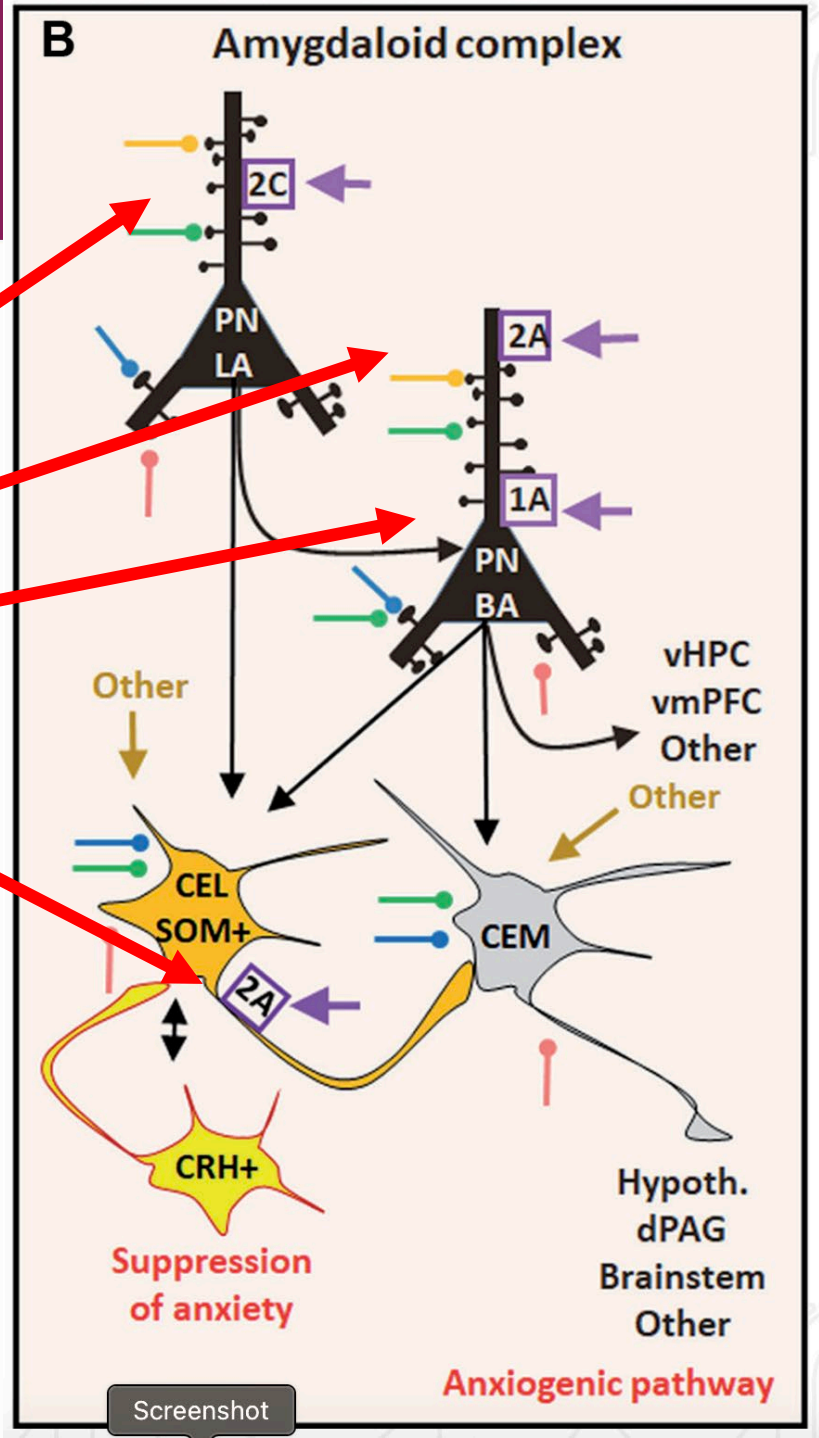
- ~ 21 million adults struggle with Major Depressive Disorder in US
- Roughly 30% individuals with MDD experience treatment resistance
- The Monoamine Hypothesis poses several clinical challenges in treatment
- Conventional Treatment has limited responses including persistent symptoms, non-responses, and adverse reactions which can ultimately lead to non-adherence
- Monitor patients for possibility of using adjunctive treatment options

Why Atypicals Make Sense as Augmentation Agents to Antidepressants When Suboptimum Response Occurs

Atypicals Modulate Receptors on Neurons of Multiple Different Neurotransmitter Families



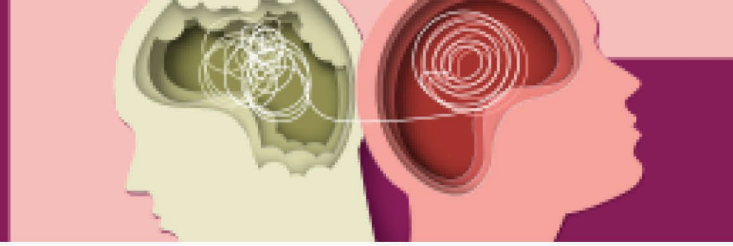
Serotonin Receptors



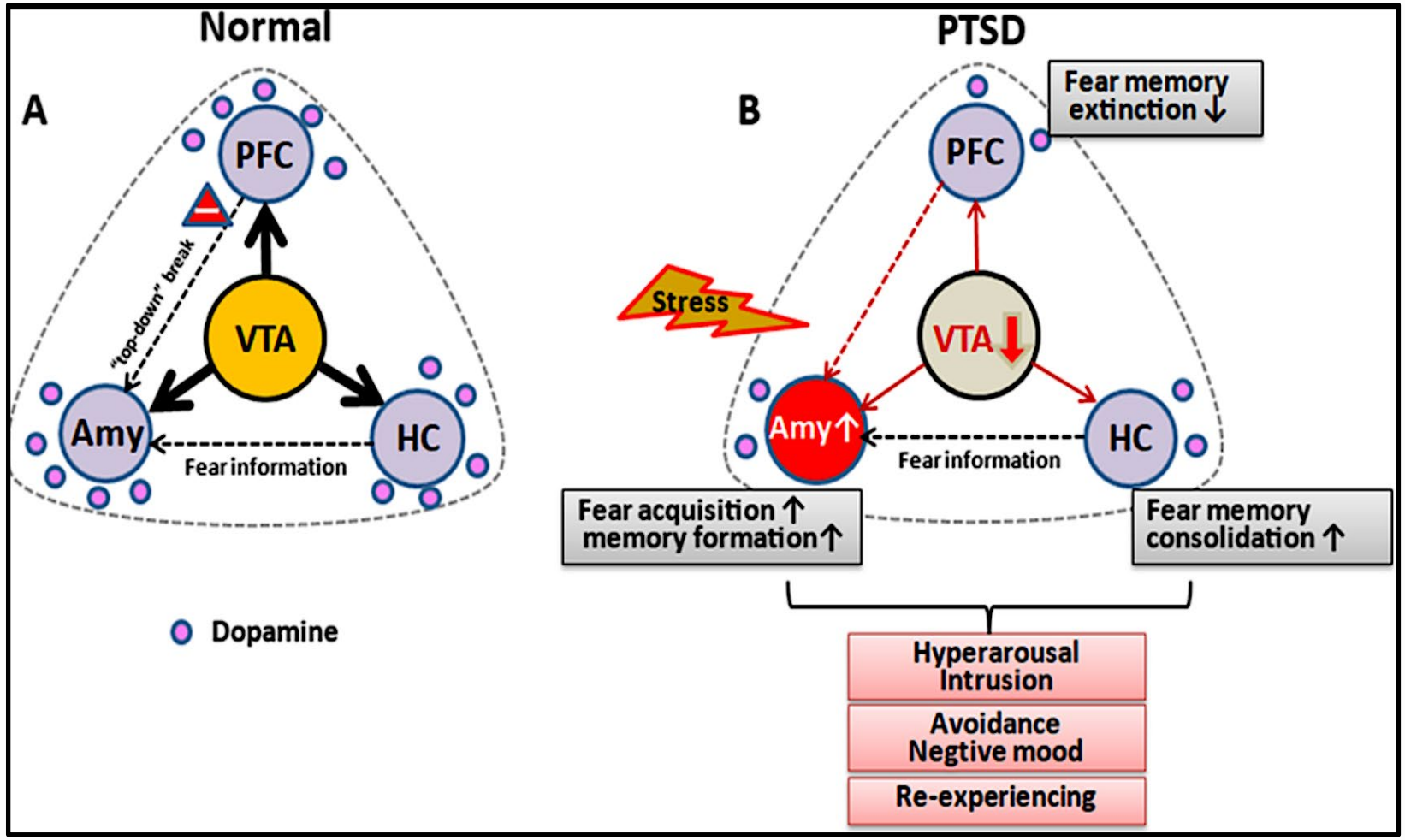
Vitalis T, Verney C. Roles of the Serotoninergic System in Coping with Traumatic Stress DOI: http://dx.doi.org/10.5772/intechopen.97221

Screenshot

Dopamine Is Also Deeply Connected to the Pathophysiology of Major Depression



Dopamine (from the Ventral Tegmental Area – VTA) project to the depression core circuit



Liu M-N, et al. *Mol Neurobiol.* 2023 Jul;60(7):3708-3723.

Atypical Medications Are Vastly Different from Each Other in Terms of Receptor Affinity

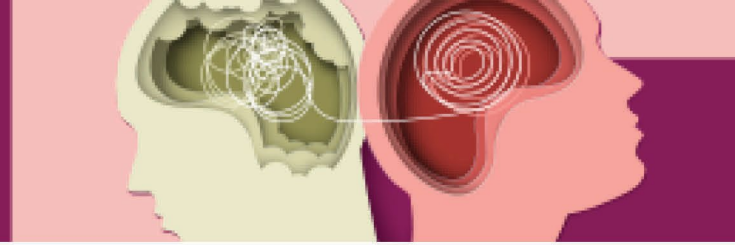
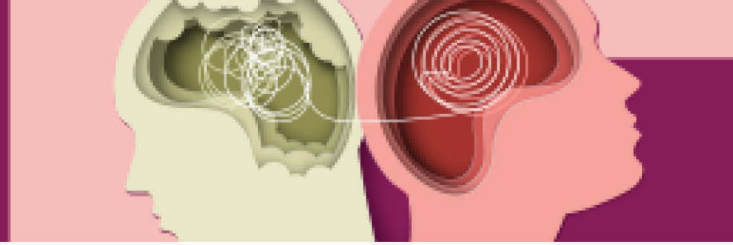


TABLE 1. Receptor Affinity Values (Ki) for Atypical and Typical Antipsychotic Drugs[a]

	Receptor								
Drug Name	D1	D2	D3	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	α2	H–1	M–1
Amisulpride	>10K	3	2.4	>10K	8,304	>10K	1,114	>10K	>10K
Aripiprazole	387	0.95	5.35	5.6	4.6	181	74	29	>6K
Asenapine	NA	2	NA	15	0.8	0.3	16.1	9.3	24.3
Brexpiprazole	NA	0.3	1.1	0.1	0.5		0.6	19	negligible
Cariprazine	NA	9.2	0.085	8.6	7.7	6.9	<6.0	7.6	negligible
Chlorpromazine	112	2	4.65	>3K	3.2	26	184	0.18	47
Clozapine	189	431	240	105	13	29	142	2	14
Fluphenazine	21	0.54	1.75	145	7.4	418	314	7.3	>1K
Haloperidol	83	2	8.5	>1K	73	>10K	>1K	>3K	>10K
Iloperidone	129	3.3	7.1	33	0.2	14	3	12.3	>1K
Loxapine	54	10	22	>2K	3.9	21	151	2.8	175
Lumateperone	52	32	NA	NA	0.5	173	NA	>1K	NA
Lurasidone	NA	1.7	NA	6.8	2		40.7	>1K	>1K
Olanzapine	58	72	49	>2K	3	24	314	4.9	24
Paliperidone	41	9.4	0.5	637.8	1.9	100.3	4.7	5.6	>10K
Perphenazine	28.2	1.4	2.1	421	5.6	132	810.5	8	NA
Pimavanserin	NA	NA	NA	NA	0.4	16	NA	NA	NA
Pimozide	5,495	0.65	0.25	650	19	>3K	>1K	692	800
Quetiapine	900	567	940	431	366	>1K	>3K	7.5	858
Risperidone	60.6	4.9	9.6	427	0.19	94.9	151	5.2	>10K
Thioridazine	89	10	7.4	108	11	69	134	14	33
Thiothixene	51	1.4	0.4	410	111	>1K	80	12	>10K
Trifluoperazine	NA	1.3	NA	950	13	378	653.7	63	NA
Ziprasidone	30	4	7.2	76	2.8	68	160	130	>10K

Meltzer H, Gadaleta E. *Focus.* Winter 2021; 19(1).

Let's Take a Deeper Dive into Receptor Pharmacology of Select Medications

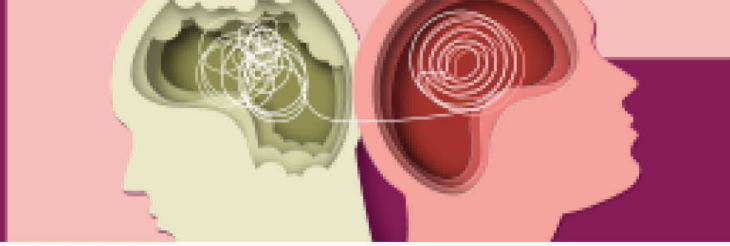


Name od Drug	Aripiprazole	Brexpiprazole	Cariprazine	Lurasidone	Asenapine	Lumateperone
Mechanism of action	D_2 partial agonist 5-HT_{1A} partial agonist 5-HT_{2A} antagonist	D_2/D_3 partial agonist 5-HT_{1A} partial agonist 5-HT_{2A} antagonist $\alpha_{1B/2C}$ antagonist low affinity for H_1 and M_1 receptors	D_2/D_3 partial agonist 5-HT_{1A} partial agonist low affinity for H_1 and 5-HT_{2A} receptors lack of affinity for M receptors	D_2, 5-HT_{2A} and 5-HT_7 antagonist 5-HT_{1A} partial agonist an affinity for adrenergic receptors–higher for α_{2C} and slightly lower for α_1 and α_{2A} very low affinity for D_1, 5-HT_{2C}, H_1 and M_1 receptors	D_2, 5-HT_{2A}, 5-HT_{2C} and 5-HT_7 antagonist an affinity for adrenergic receptors –α_1 and α_2 lack of affinity for M receptors	full postsynaptic D_2 antagonist D_2 partial presynaptic agonist 5-HT_{2A} antagonist D_1 agonist SERT inhibitor

Take Home Message: Our treatment options are not created equal. And this is good news!
This allows the provider and client to potentially optimize both efficacy and tolerability
For individual patients.

Orzelska-Górka, J. et al. Int. J. Mol. Sci. 2022, 23, 10624.

Some Atypicals Have Both the FDA Indication, as Well as Solid Evidence to Support Their Use in MDD



Systematic review and network meta-analysis suggest that Adjuvant AAPs significantly improved response rates and reduced the score of depressive rating scales compared with PBO

Depression symptom scores(SMD[95%,CI]) | Comparison | Response rate(RR[95%,CI])

BRE	0.92 (0.77,1.08)	1.12 (0.92,1.37)	0.85 (0.72,1.01)	***0.72 (0.61,0.84)***
0.11 (-0.19,0.40)	OLA	***1.22 (1.07,1.40)***	0.93 (0.85,1.02)	***0.79 (0.74,0.83)***
0.04 (-0.22,0.30)	-0.07 (-0.38,0.24)	ARI	***0.76 (0.66,0.88)***	***0.64 (0.57,0.73)***
0.15 (-0.15,0.46)	0.05 (-0.31,0.40)	0.12 (-0.23,0.46)	QTP	***0.85 (0.79,0.91)***
-0.25 (-0.42,-0.07)	***-0.35 (-0.59,-0.11)***	***-0.28 (-0.47,-0.09)***	***-0.40 (-0.68,-0.12)***	PBO

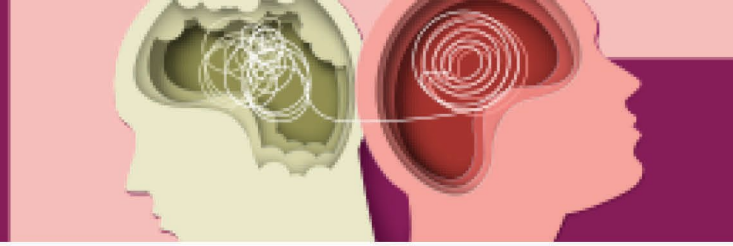
All-cause discontinuation(RR[95%,CI]) | Comparison | Side-effect discontinuation(RR[95%,CI])

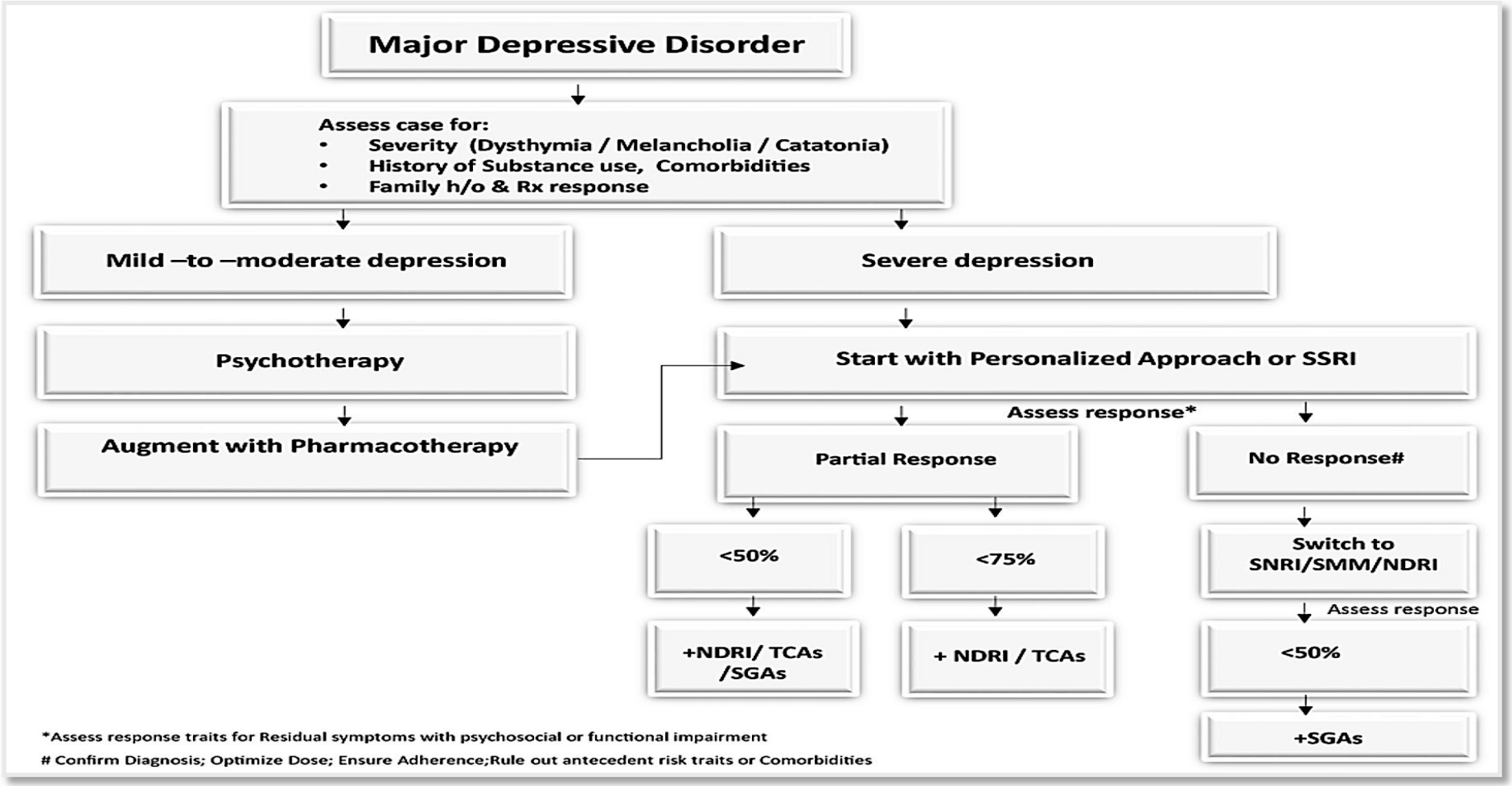
BRE	1.22 (0.48,3.14)	0.94 (0.37,2.37)	1.52 (0.57,4.05)	***0.37 (0.18,0.75)***
0.83 (0.39,1.79)	OLA	0.77 (0.33,1.78)	1.24 (0.46,3.38)	***0.30 (0.16,0.55)***
0.83 (0.44,1.58)	1.00 (0.49,2.05)	ARI	1.61 (0.60,4.31)	***0.39 (0.22,0.69)***
0.82 (0.42,1.59)	0.99 (0.41,2.39)	0.99 (0.45,2.15)	QTP	***0.24 (0.11,0.53)***
0.92 (0.56,1.51)	1.10 (0.61,1.99)	1.10 (0.73,1.67)	*1.12 (0.58,2.16)*	PBO

- "In terms of tolerability, compared with the PBO, all AAPs were significantly less well tolerated."
- "Adverse events caused by combination therapy cannot be ignored, such as akathisia and weight gain"

Wang J, et al. *Medicine.* 2023;102:38(e34670).

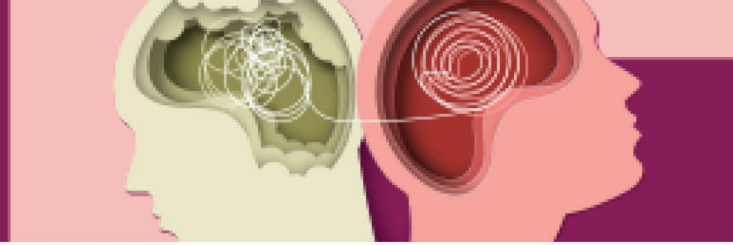
A Clinical Paradigm for the Appropriate Use of Atypicals in Major Depression





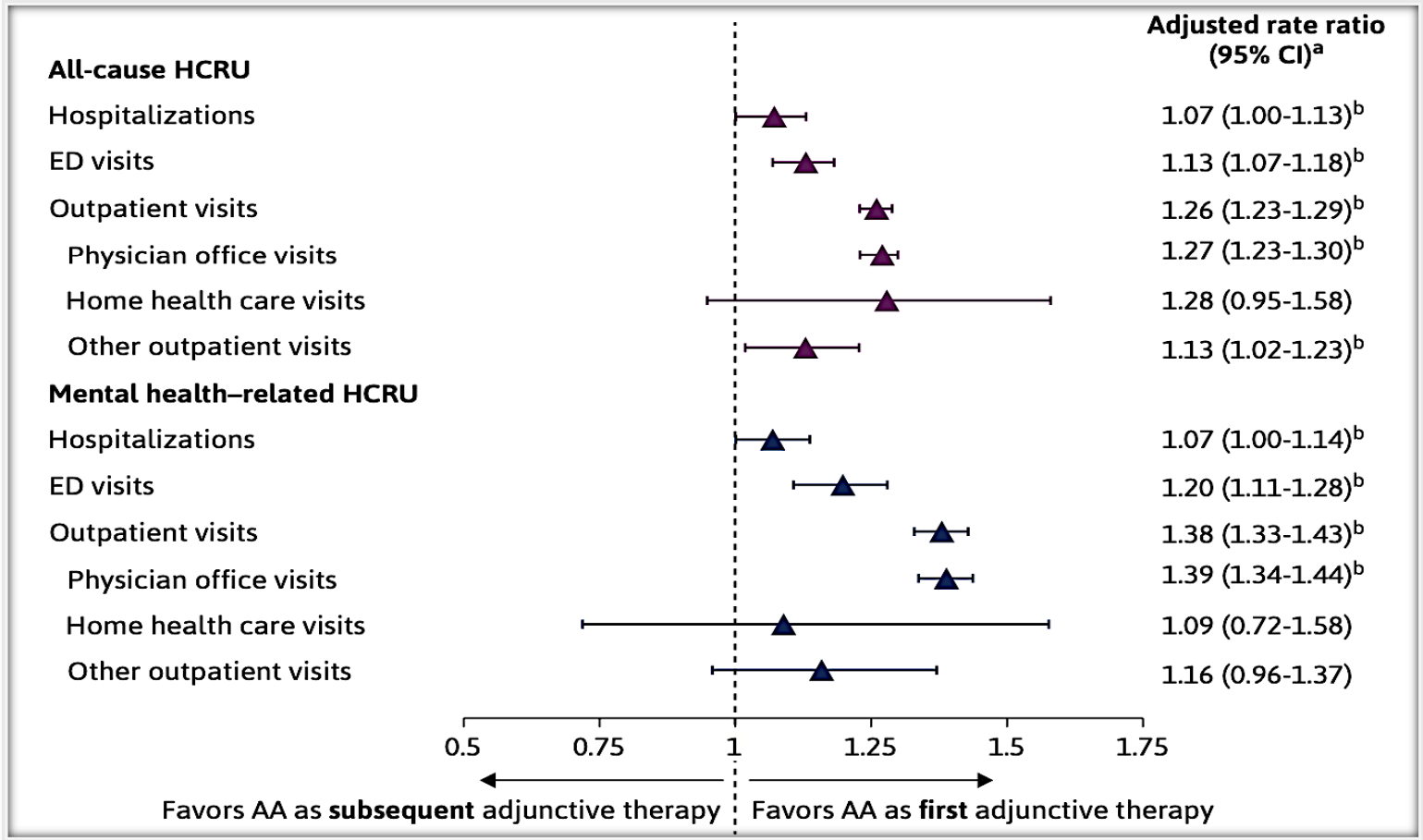
Bhachech H, et al. *Cureus*. 2024;16(1):e52878.

Certain Adjunctive Atypicals Also Help Patients with Health Cost Related Issues



Delay in starting an adjunctive AA was associated with negative impacts on HCRU and health care costs

Health Care Resource Utilization (HCRU)



[a]Rate rations for AAs as subsequent vs first adjunctive therapy were calculated from Poisson regression models adjusted for baseline characteristic differences.
[b]P<0.05

Jain R, et al. *J Manag Care Spec Pharm*. 2023;29(8):896-906.

Treatment Guidelines and FDA Recommendations Are Both Important

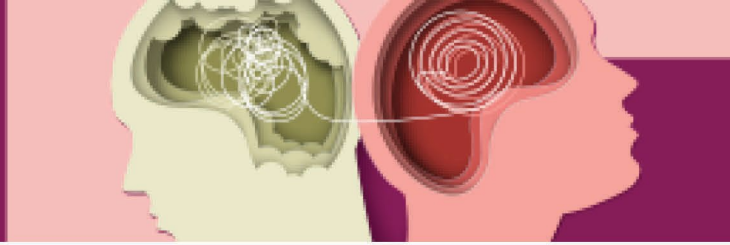


Table 4. Summary of Pharmacological Augmentation Recommendations by Guideline

	APA	BAP	CANMAT	CPGS	ICSI	NICE	MPG	RANZCP	TMAP	WFSBP
AAPs[1]	2nd	1st	1st	1st	✔	1st	1st	1st	2nd	1st
Lithium	2nd	1st	2nd	1st	✔	✔	1st	1st	✔	1st
Other mood stabilisers	✔	2nd 1	✘	✘	–	✘	2nd 1	–	✔[a]	–
Thyroid hormones	2nd	2nd	2nd	✘	✔	✘	2nd	1st	1st	2nd
Stimulants	✔	✔	2nd[b]	–	✔	✘	✔	✘	–	–
Bupropion	✔	✔	2nd	✘	✔	✘	1st	✘	1st	✘
Buspirone	✔	✔	✘	✘	✔	✘	2nd	✘	1st	✘
Ketamine	–	✘	✔	–	✔	–	2nd	✘	–	✘

We clinicians need to know FDA indications and Treatment Guidelines for various treatment options in adjunctive use of Atypicals in MDD

Table 5. General Side Effects for AAPs

Side effect
Weight gain
Other metabolic complications/metabolic syndrome
Glucose dysregulation/diabetes mellitus
Dyslipidaemia
Hyperprolactinemia
QTc prolongation
Coronary heart disease/risk of sudden cardiac death
Extrapyramidal side effects (including tardive dyskinesia and neuroleptic malignant syndrome)[a]
Acute kidney injury
Sedation
Postural hypotension
Anticholinergic effects
Hyponatraemia
Sexual dysfunction
Increased risk of pneumonia
Increased risk of thromboembolism

Taylor RW et al. *International Journal of Neuropsychopharmacology.* 2020;23(9):587–625.

Akathisia Is an Important Side Effect to Keep in Mind

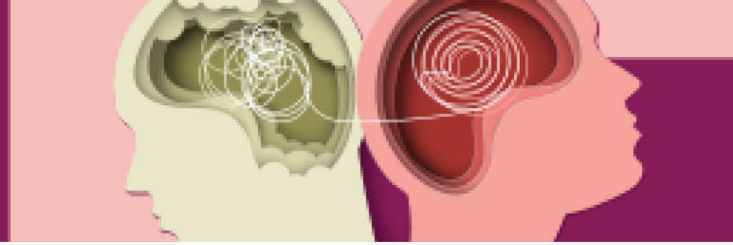


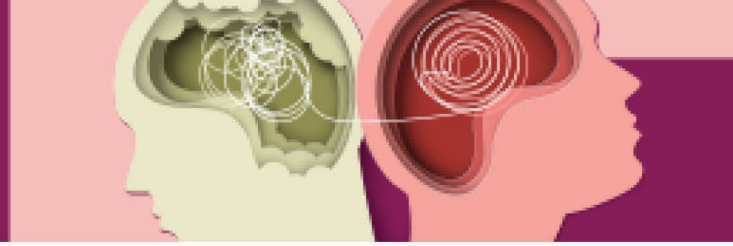
Table 4. Composite Akathisia Rates by Diagnosis in Individual SGAs and Placebo

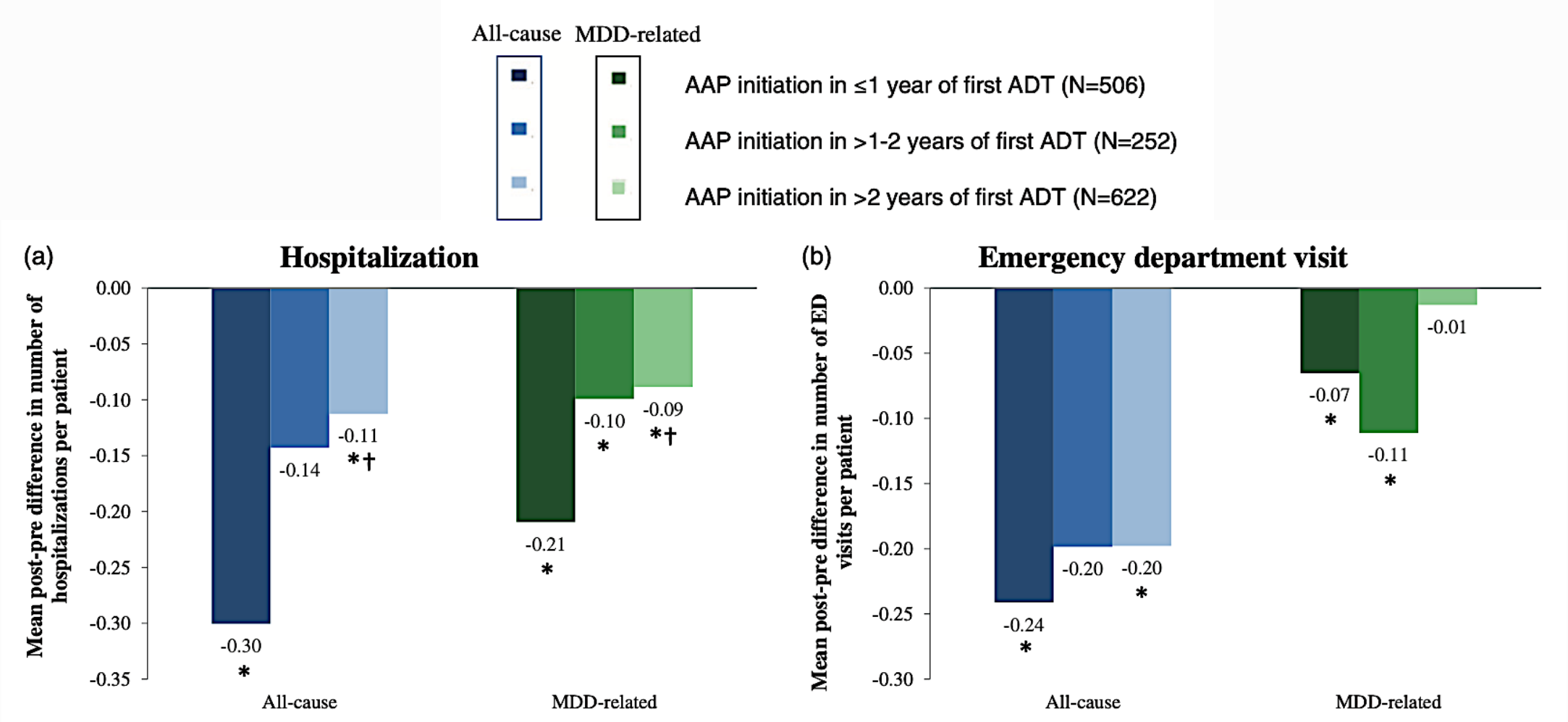
	Schizophrenia, %	Bipolar disorder, %	MDD, %	Total composite, %
Aripiprazole	8.71	–	–	8.71
Aripiprazole LAI	8.27	–	–	8.27
Aripiprazole lauroxil	4.48	–	–	4.48
Asenapine	5.98	7.02	–	6.31
Brexpiprazole	5.74	–	8.55	6.25
Cariprazine	12.09	14.35	14.47	13.04
Iloperidone	2.94	–	–	2.94
Lurasidone	12.31	8.58	–	11.16
Paliperidone ER	6.57	–	–	6.57
Paliperidone palmitate	4.40	–	–	4.40
Risperidone	13.03	–	–	13.03
Risperidone LAI	8.93	–	–	8.93
Ziprasidone	8.10	10.45	–	9.03
Placebo	4.03	3.01	1.92	3.69

- Second-generation antipsychotics as a class are associated with akathisia
- Clinicians should monitor for akathisia in all patients beginning therapy with any of these agents or following a dose increase of the SGA

Chow CL, et al. *International Journal of Neuropsychopharmacology*. 2020;23(9):587–625.

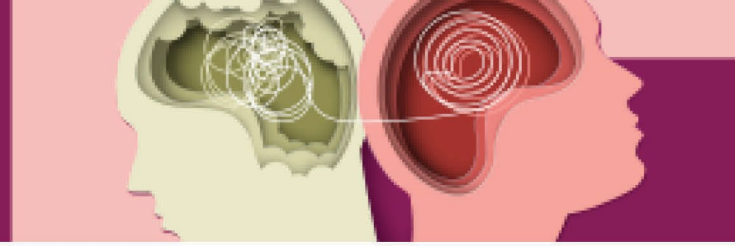
Clear Advantages of Starting Atypical Antipsychotic (AAP) Augmentation Therapy Earlier

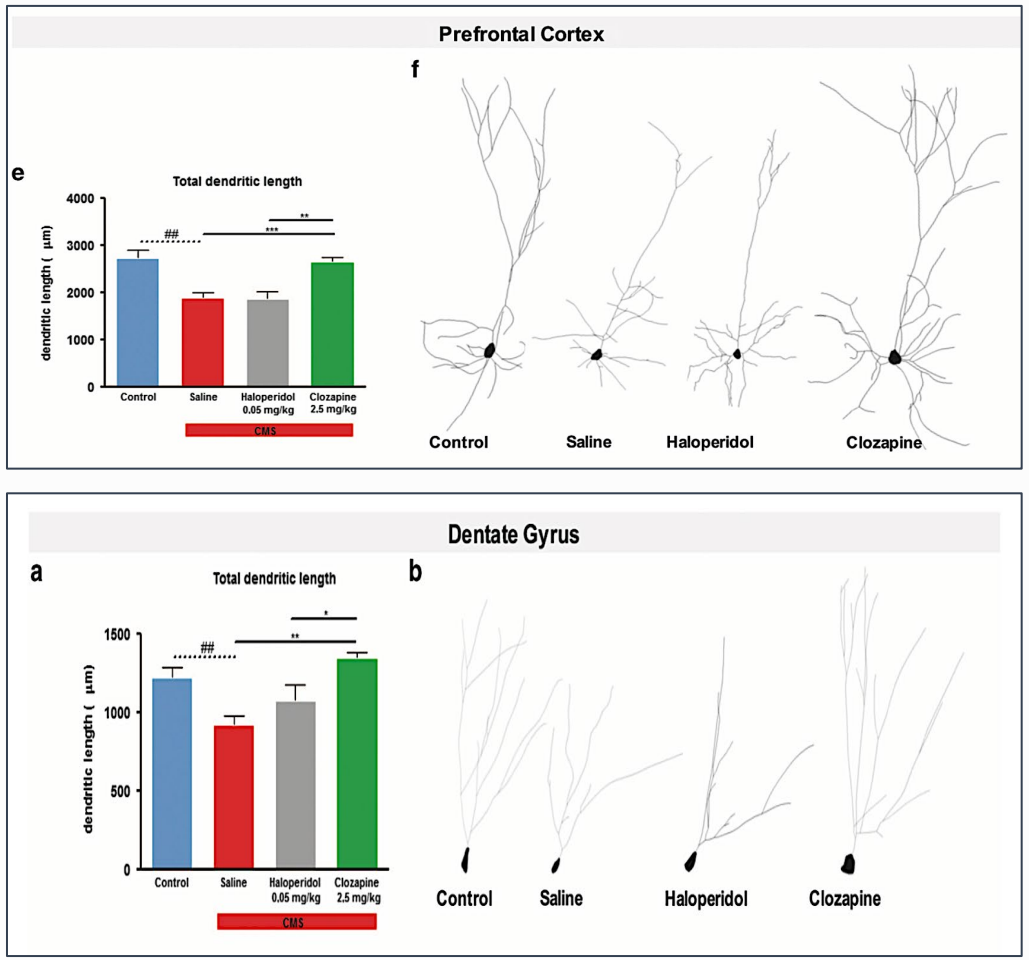




Arpamas S, et al. *Journal of Medical Economics*. 2018;21(9):888-901.

Neuroplasticity May Be Involved in the Mechanism of Action of AAP in Major Depression





Neuroplasticity is the brain's ability to make functional or structural changes in response to experiences

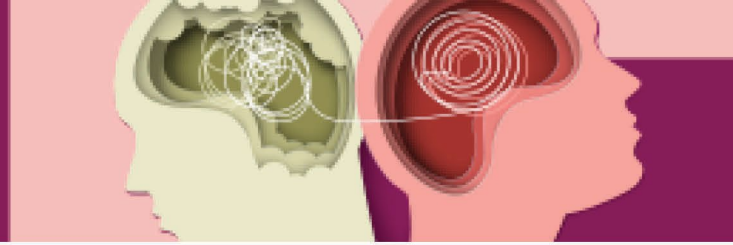
- In this study, an unpredictable chronic mild stress protocol was used to induce a depressive-like phenotype in rats.
- In the last 3 weeks of stress exposure, animals were treated with two different antipsychotics: haloperidol (a classical antipsychotic) and clozapine (an atypical antipsychotic).

Morais M, et al. *Transl Psychiatry.* 2017;7:e1146. doi:10.1038/tp.2017.120.

Let’s Go on a Deeper Dive into AAP Options in Major Depression

Focus on:
Aripiprazole in MDD

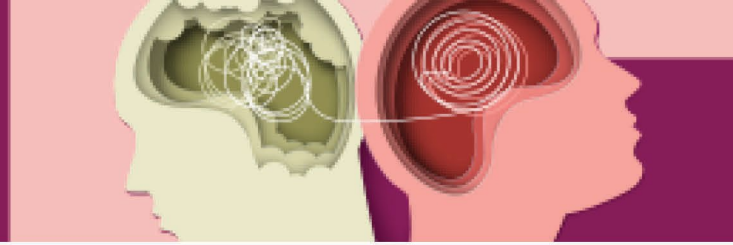
Examining Aripiprazole in More Detail



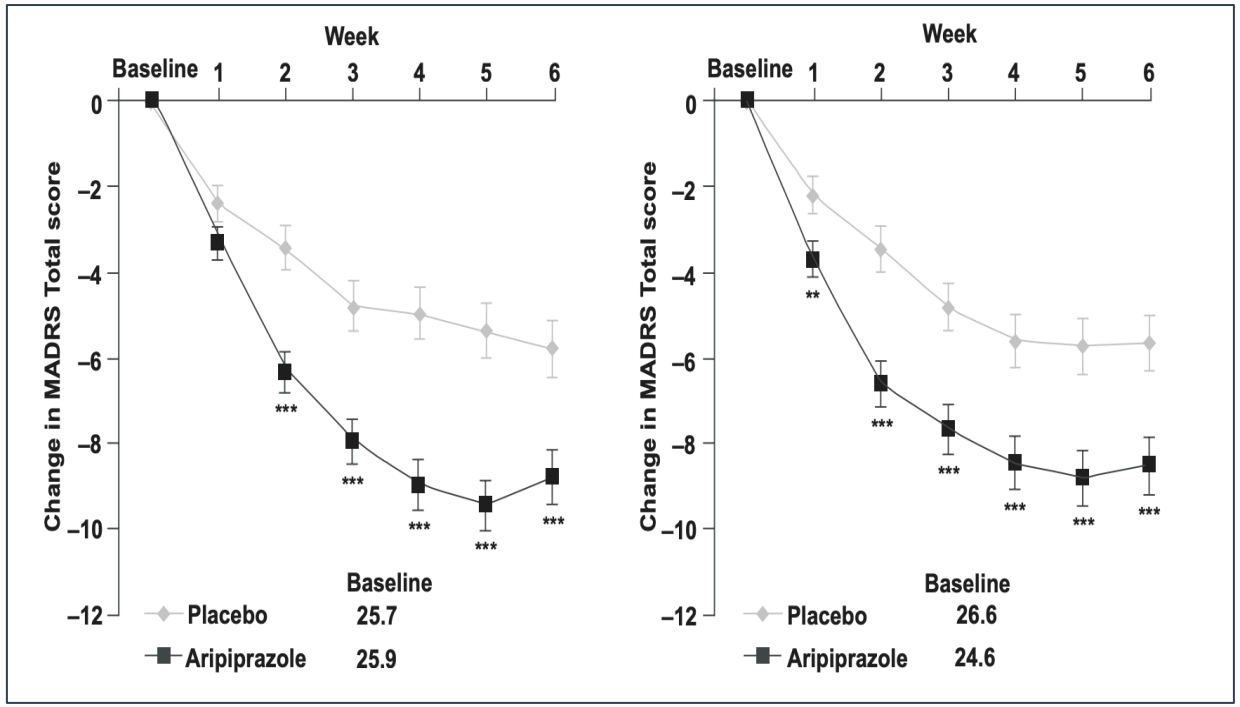
Aripiprazole	
Indication	Major Depressive Disorder – Adults Adjunct to antidepressants
Doses approved	Initial dose = 2-5mg/day, Recommended dose = 5-10 mg, Maximum dose = 15mg/day
Can be used with any anti-depressant	Yes
FDA Indication year	2007

Aripiprazole Prescribing Information. Accessed October 15, 2024.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf

Data on Efficacy and Side-effects with Aripiprazole



Two separate trials of aripiprazole in MDD augmentation treatment were positive



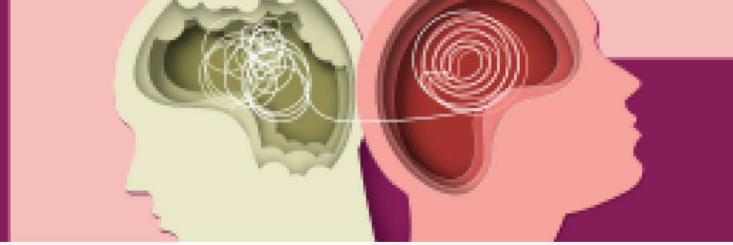
Incidence of side-effects with aripiprazole in Major depression augmentation

Table 23: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction[a] ABILIFY + ADT* (n=371)	 Placebo + ADT* (n=366)
Eye Disorders		
Blurred Vision	6	1
Gastrointestinal Disorders		
Constipation	5	2
General Disorders and Administration Site Conditions		
Fatigue	8	4
Feeling Jittery	3	1
Infections and Infestations		
Upper Respiratory Tract Infection	6	4
Investigations		
Weight Increased	3	2
Metabolism and Nutrition Disorders		
Increased Appetite	3	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	4	3
Myalgia	3	1
Nervous System Disorders		
Akathisia	25	4
Somnolence	6	4
Tremor	5	4

Nelson JC, et al. Neuropsychiatric Disease and Treatment. 2008:4(5) 937–948. Aripiprazole Prescribing Information. Accessed October 15, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf

Aripiprazole: Risk of Weight Gain and Akathisia in this Study



Akathisia Risk

Akathisia was the most common AE reported with adjunctive aripiprazole in the two samples occurring in 24.8% of the patients.

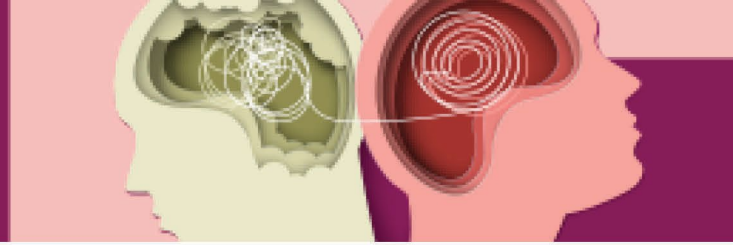
Weight Gain Risk

Mean weight gain with adjunctive aripiprazole was higher than adjunctive placebo in both studies (+2.01 ± 0.17 kg vs +0.34 ± 0.18 kg, p 0.001]; +1.47 ± 0.16 kg s +0.42 ± 0.17 kg, p 0.001 over a 6-week treatment period.

Nelson JC, et al. *Neuropsychiatric Disease and Treatment*. 2008;4(5):937–948.

Focus on:
Quetiapine in MDD

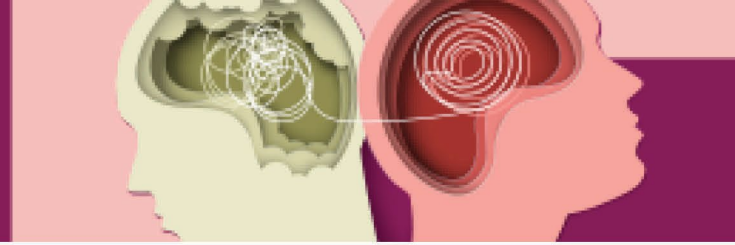
Examining Quetiapine XR in More Detail



Quetiapine XR	
Indication	Major depressive disorder, adjunctive therapy with antidepressants - adults
Doses approved	50mg/day =initial dose, dose range = 150mg-300mg/d, maximum dose = 300mg/day
Can be used with any anti-depressant	yes
FDA Indication year	2009

Quetiapine Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022047Orig1s042lbl.pdf

Quetiapine: Risk of Weight Gain and Akathisia in this Study



Akathisia Risk

"The incidence of AEs potentially related to EPS (MedDRA-preferred terms akathisia, restlessness, tremor, extrapyramidal disorder, psychomotor hyperactivity, hypertonia, drooling, and cogwheel rigidity) was 3.4% in the placebo and quetiapine XR 150 mg/d groups, and 8.1% in the quetiapine XR 300 mg/d group. The two most commonly reported AEs related to EPS were akathisia (0.7%, 1.4%, and 2.7%) and restlessness (1.4%, 0.7%, and 2.7%) in the placebo, quetiapine XR 150 mg/d, and 300 mg/d groups, respectively."

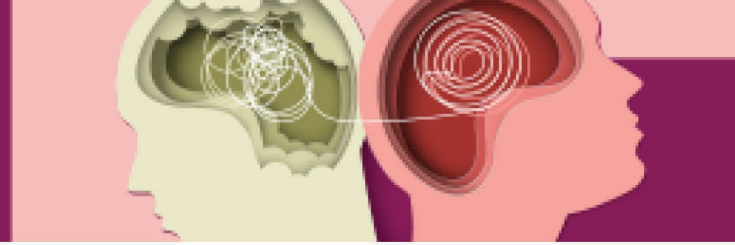
Weight Gain Risk

	Placebo + AD (n = 148)	Quetiapine XR 150 mg/d + AD (n = 148)	Quetiapine XR 300 mg/d + AD (n = 149)
Weight (kg)			
Mean (S.D.) at randomization	83.5 (21.5)	87.7 (23.0)	83.5 (20.1)
Mean (S.D.) change	0.3 (2.5)	0.8 (2.3)	1.6 (2.4)
Patients with a ⩾7% increase in body weight, n (%)	3 (2.1)	2 (1.4)	11 (7.6)

El-Khalili N, et al. *International Journal of Neuropsychopharmacology.* 2010;13:917–932.

Focus on:
Brexpiprazole in MDD

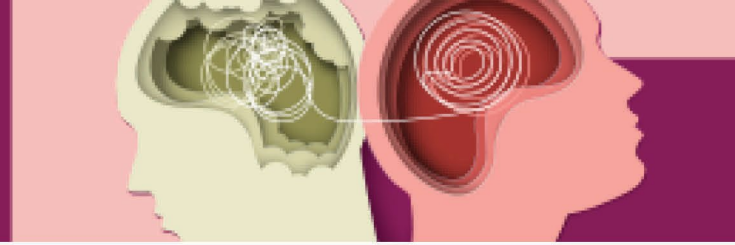
Examining Brexpiprazole in More Detail

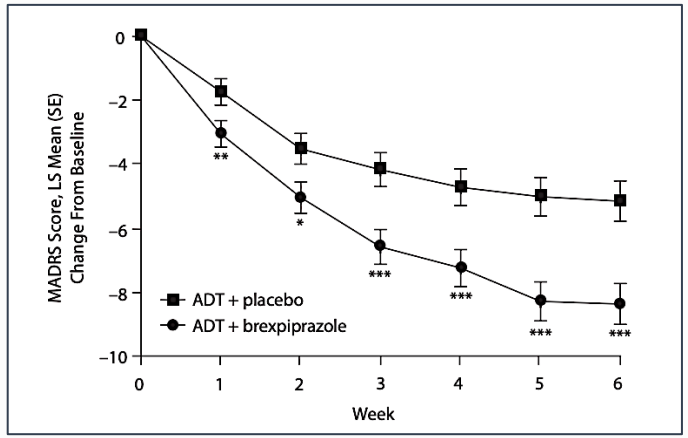


Brexpiprazole	
Indication	Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults
Doses approved	0.5 to 1.0 mg/d =initial dose, dose range = 2-3 mg/d maximum dose = 3 mg/day
Can be used with any anti-depressant	yes
FDA Indication year	2015

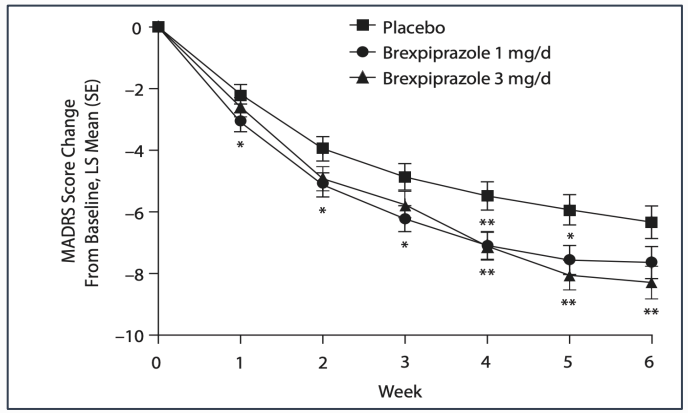
Brexpiprazole Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2024. www.accessdata.fda.gov/scripts/cder/daf/

Brexpiprazole – An Effective, FDA Approved Treatment Option





2 mg/day brexpiprazole vs placebo



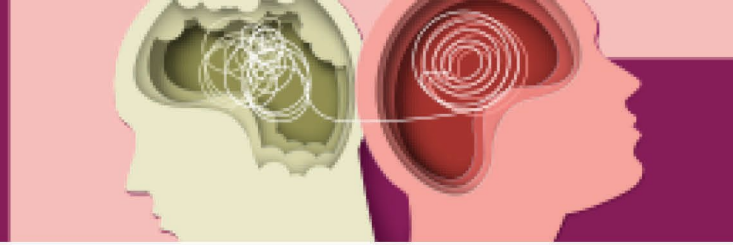
1 mg/day and 3 mg/ day brexpiprazole vs placebo

Table 3. TEAEs, Body Weight Changes, and Laboratory Assessments (safety population)[a]

Variable	ADT + Placebo (n = 220)	ADT + Brexpiprazole 1 mg (n = 226)	ADT + Brexpiprazole 3 mg (n = 229)
At least 1 TEAE	103 (46.8)	124 (54.9)	145 (63.3)
Serious AE	0	1 (0.4)	1 (0.4)
Discontinuation due to TEAE	3 (1.4)	3 (1.3)	8 (3.5)
TEAEs occurring in ≥ 5% of patients in any group			
Headache	17 (7.7)	21 (9.3)	14 (6.1)
Nasopharyngitis	4 (1.8)	15 (6.6)	7 (3.1)
Weight gain	2 (0.9)	15 (6.6)	13 (5.7)
Akathisia	5 (2.3)	10 (4.4)	31 (13.5)
Somnolence	1 (0.5)	9 (4.0)	13 (5.7)
Tremor	7 (3.2)	9 (4.0)	12 (5.2)
Activating TEAEs			
Restlessness	0 (0)	4 (1.8)	10 (4.4)
Anxiety	1 (0.5)	5 (2.2)	8 (3.5)
Insomnia	7 (3.2)	5 (2.2)	6 (2.6)
Sedating TEAEs			
Somnolence	1 (0.5)	9 (4.0)	13 (5.7)
Fatigue	4 (1.8)	7 (3.1)	11 (4.8)
Sedation	0 (0)	0 (0)	0 (0)
Body weight			
Change from baseline at week 6, mean, kg	0.24	1.40	1.57
Increase ≥ 7% from baseline at any visit	2 (0.9)	11 (4.9)	4 (1.8)
Laboratory assessments[b]			
ALT, mean change, U/L	1.32	1.02	2.73
AST, mean change, U/L	−0.04	1.00	2.34
LDL-C, mean change, mg/dL	−1.41	−0.51	−0.92
HDL-C, mean change, mg/dL	0.34	1.13	2.07
Triglycerides, mean change, mg/dL	−1.31	3.31	2.20
Prolactin, mean change, ng/dL			
Male	0.4	1.0	2.1
Female	−0.5	4.0	10.2
Prolactin > 3 × upper limit of normal			
Male	1 (1.3)	0	1 (1.4)
Female	2 (1.4)	0	0

Thase ME, et al. *J Clin Psychiatry.* 2015;76(9):1232-1240. Thase ME, et al. *J Clin Psychiatry.* 2015.;76(9):1224-1231.

Brexpiprazole – Examining Akathisia and Weight Gain *(Thase ME, et al.)*



Akathisia Risk

The most frequent adverse event was akathisia.

- Placebo = 2.3 %
- Brexpiprazole 1 mg/day = 4.4 %
- Brexpiprazole 3 mg/day = 9.3 %

Weight Gain Risk

Weight gain risk was:

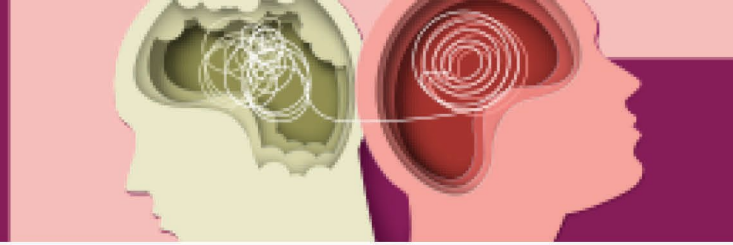
- Placebo = 0.9 %
- Brexpiprazole 1 mg/day = 6.6 %
- Brexpiprazole 3 mg/day = 5.7 %

Variable	ADT + Placebo (n = 220)	ADT + Brexpiprazole 1 mg (n = 226)	ADT + Brexpiprazole 3 mg (n = 229)
Body weight			
Change from baseline at week 6, mean, kg	0.24	1.40	1.57
Increase ≥ 7% from baseline at any visit	2 (0.9)	11 (4.9)	4 (1.8)

Thase ME, et al. J Clin Psychiatry. 2015;76(9):1232-1240.

Focus on:
Cariprazine in MDD

Examining Cariprazine in More Detail



Cariprazine	
Indication	Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults
Doses approved	Starting dose = 1.5mg/day. Recommended doses = 1.5 mg or 3 mg per day
Can be used with any anti-depressant	yes
FDA Indication year	2022

Cariprazine Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2023. www.accessdata.fda.gov/scripts/cder/daf/

Cariprazine - The FDA Package Insert Offers Evidence for Efficacy and Adverse Event Profile in MDD Patients

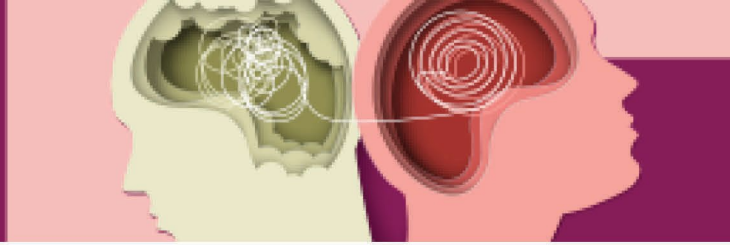
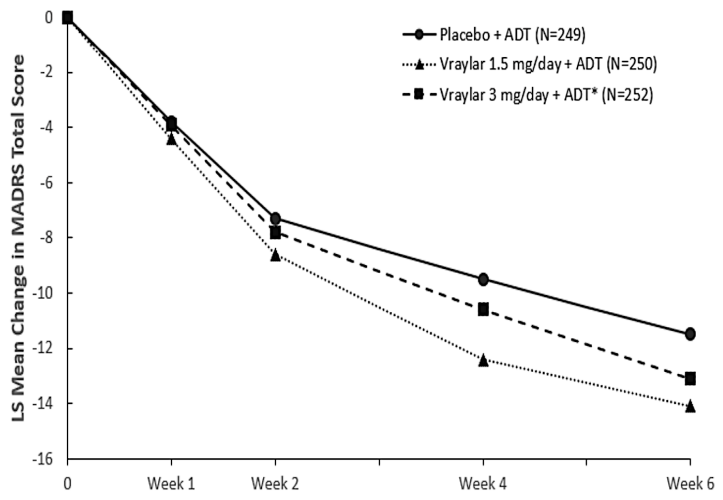


Figure 6. LS Mean‡ Change from Baseline to Week 6 in MADRS Total Score in Adjunctive Treatment of Major Depressive Disorder (Study 10)



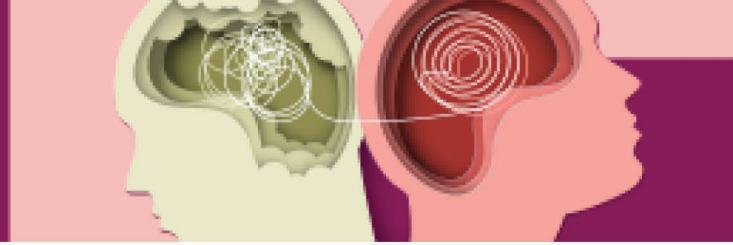
Study Number	Treatment Group (# ITT patients)	Primary Efficacy Endpoint: MADRS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 10	VRAYLAR (1.5 mg/day) + ADT* (n=250)	32.8 (5.0)	-14.1 (0.7)	-2.5(-4.2, -0.9)
	VRAYLAR (3 mg/day) + ADT (n=252)	32.7 (4.9)	-13.1 (0.7)	-1.5 (-3.2, 0.1)
	Placebo + ADT (n=249)	31.9 (5.7)	-11.5 (0.7)	
Study 11	VRAYLAR (1 to 2 mg/day) + ADT (n=273)	29.0 (4.3)	-13.4 (0.5)	-0.9 (-2.4, 0.6)
	VRAYLAR (2 to 4.5 mg/day) + ADT* (n=271)	29.3 (4.1)	-14.6 (0.6)	-2.2 (-3.7, -0.6)
	Placebo + ADT (n=264)	28.9 (4.3)	-12.5 (0.5)	

Table 10. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-Treated Patients and > Placebo-Treated Adult Patients in a Flexible-dose 8-Week Placebo-Controlled Trial of Adjunctive Treatment of Major Depressive Disorder

System Organ Class/ Preferred Term	Placebo + ADT (N=266) (%)	VRAYLAR 1 to 2 mg/day + ADT (N=273) (%)	VRAYLAR 2 to 4.5 mg/day + ADT (N=273) (%)
Cardiac disorders			
Palpitations	1	2	<1
Eye disorders			
Vision blurred	1	1	4
Gastrointestinal disorders			
Nausea	5	7	13
Constipation	2	2	5
Dry mouth	3	5	4
Vomiting	<1	1	3
General disorders			
Fatigue	4	7	10
Edema	<1	2	1
Infections			
Nasopharyngitis	2	4	1

Cariprazine Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204370s009lbl.pdf

Cariprazine – Focus on Weight Gain and Akathisia



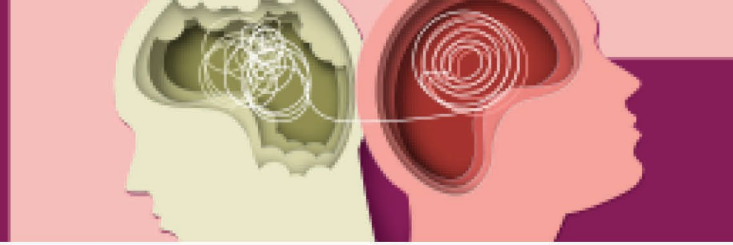
Trial of Adjunctive Treatment of Major Depressive Disorder

System Organ Class / Preferred Term	Placebo + ADT (N = 266) (%)	VRAYLAR (cariprazine) 1 -2 mg/day + ADT (N = 273) (%)	VRAYLAR (cariprazine) 2 – 4.5 mg/day + ADT (N = 273) (%)
Increased Appetite	2	2	5
Weight Increased	1	2	3
Nervous System Disorders			
Akathisia	3	8	23
Extrapyramidal Symptoms	5	12	18

Table adapted from Table 10, Cariprazine Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204370s009lbl.pdf

Emerging AAP Treatment Option in MDD — Lumateperone

Examining Lumateperone in More Detail



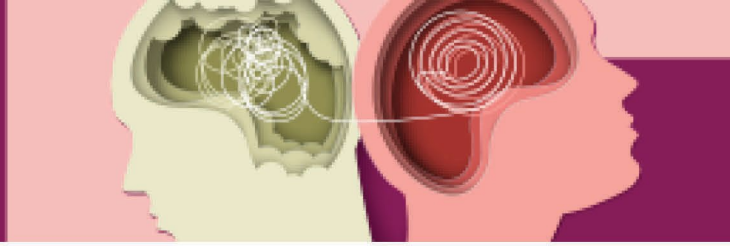
Lumateperone*	
Indication	Potentially - Major depressive disorder, adjunctive therapy with antidepressants - adults
Doses approved	Potentially - 42 mg/day
Can be used with any anti-depressant	Potentially - yes
FDA Indication year	Potentially 2025

*** Not currently approved for the treatment of MDD.**

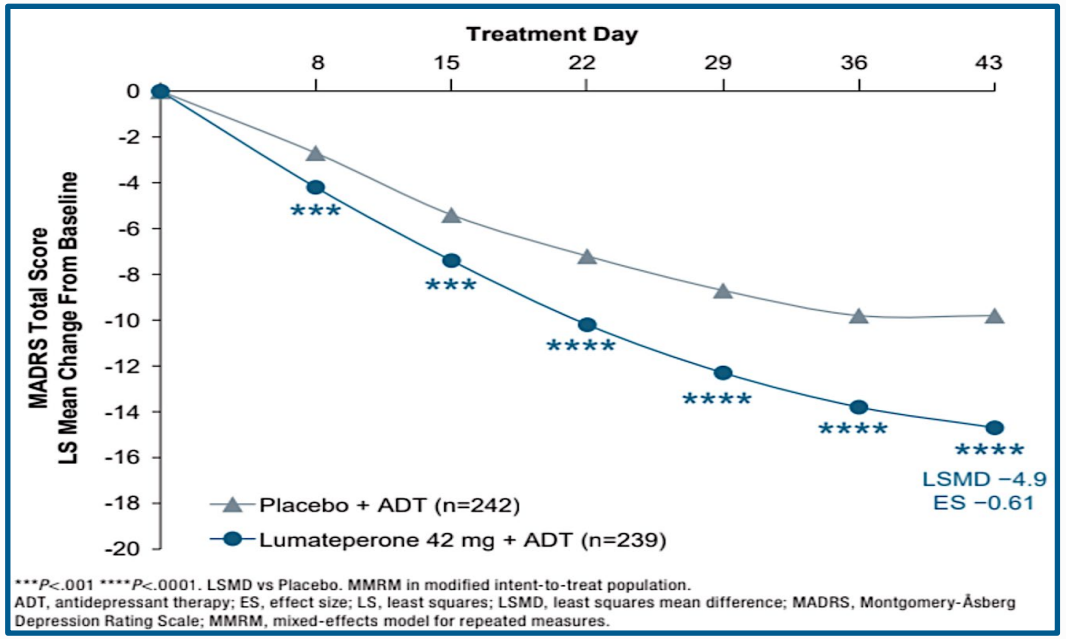
Kuntz L. New Phase 3 Study Results on Lumateperone, An Adjunctive Therapy to Antidepressants. Psychiatric Times. April 16, 2024. Accessed October 17, 2024. https://www.psychiatrictimes.com/view/new-phase-3-study-results-on-lumateperone-an-adjunctive-therapy-to-antidepressants

Lumateperone prescribing Information. Accessed October 15, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022047Orig1s042lbl.pdf.

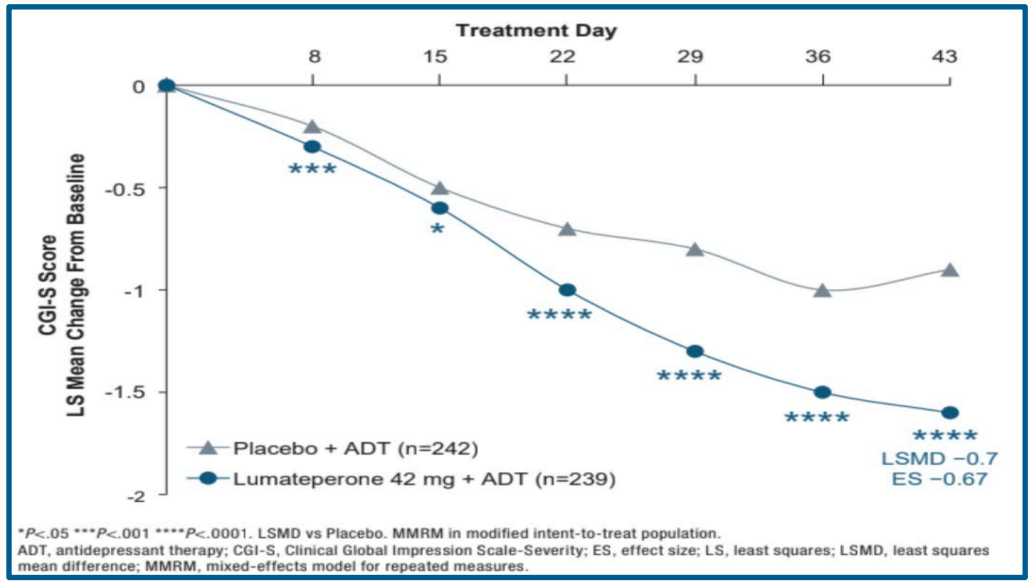
Lumateperone – Two Positive Studies in Adjunctive Treatment of Major Depression (Study 501 and 502)



- Inadequate response to ADT was defined as <50% improvement with ≥6 weeks ADT monotherapy
- Patients were randomized 1:1 to 6-week oral placebo + ADT or Lumateperone 42 mg + ADT



***P<.001 ****P<.0001. LSMD vs Placebo. MMRM in modified intent-to-treat population.
ADT, antidepressant therapy; ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

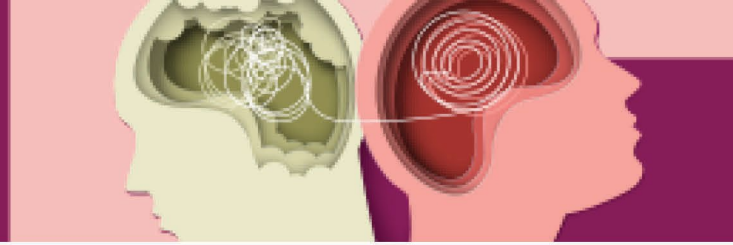


*P<.05 ***P<.001 ****P<.0001. LSMD vs Placebo. MMRM in modified intent-to-treat population.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression Scale-Severity; ES, effect size; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures.

In an additional, similarly designed trial (Study 502; NCT05061706), lumateperone 42 mg + ADT met primary and key secondary efficacy endpoints and was generally safe and well tolerated in patients with MDD with inadequate ADT response.

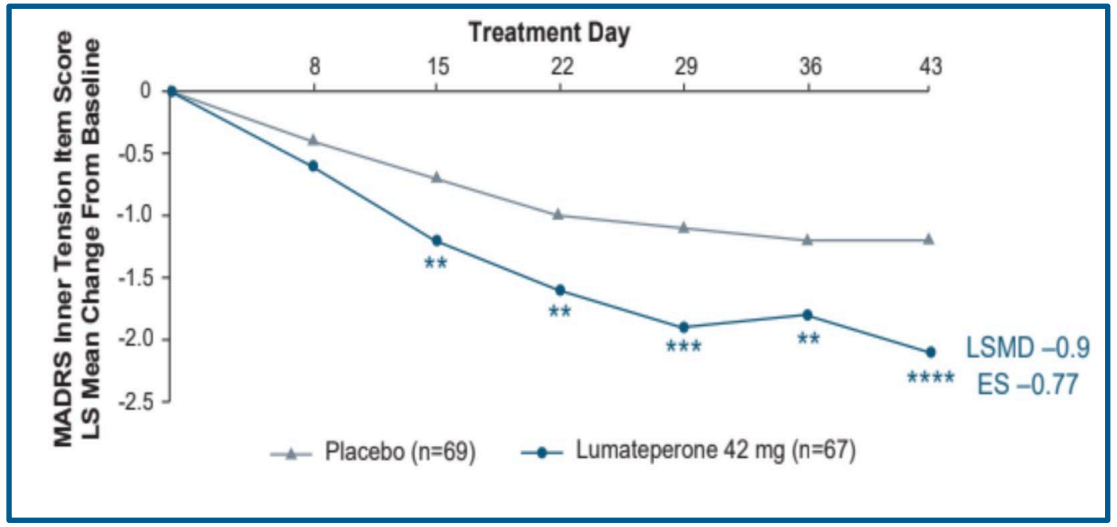
Durgam S, et al. Presented at the 37th European College of Neuropsychopharmacology (ECNP) Annual Congress. Milan, Italy, September 2024.

Lumateperone in MDD, with Anxious Distress Specifier – Notable High Effect Size



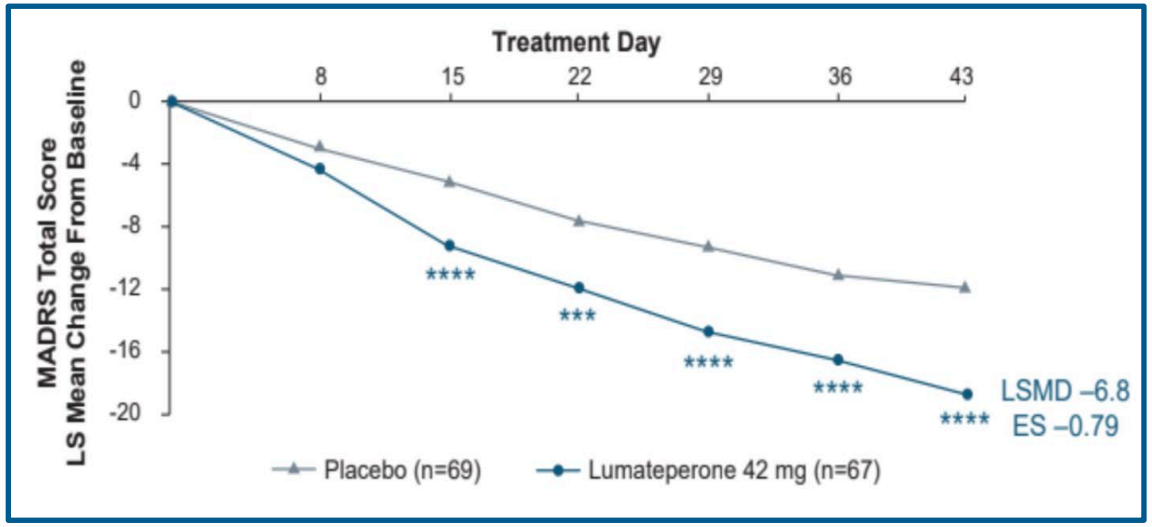
Randomized, double-blind, placebo-controlled, multicenter trial, post hoc analysis of Study 403 investigated the efficacy of Lumateperone 42 mg in the prespecified patient population with MDD or bipolar depression with mixed features who also met the DSM-5 criteria for anxious distress

MDD Population



Mean Change From Baseline in MADRS Inner Tension Item Score in Patients With Anxious Distress

MDD Population

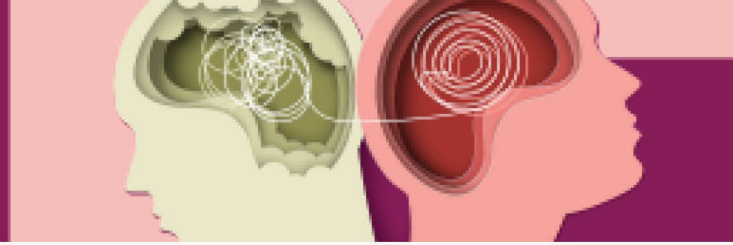


Mean Change From Baseline in MADRS Total Score in Patients With Anxious Distress

MADRS = Montgomery–Åsberg Depression Rating Scale.

Earley W, et al. Poster Presented at the 37th European College of Neuropsychopharmacology (ECNP) Annual Congress

Lumateperone – Focus on Side Effects from Study 501



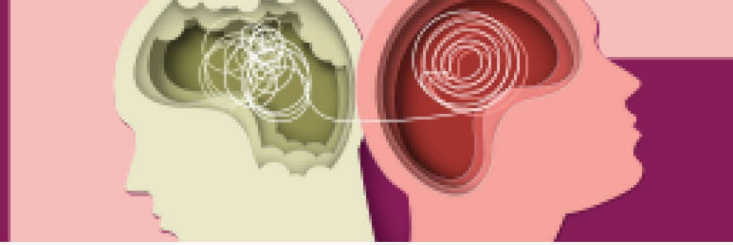
Inadequate response to ADT was defined as <50% improvement with ≥6 weeks ADT monotherapy

- Patients were randomized 1:1 to 6-week oral placebo + ADT or lumateperone 42 mg + ADT

	Placebo + ADT (n=243)		Lumateperone 42 mg + ADT (n=241)	
	Baseline Mean (SD)	Mean Change (SE)	Baseline Mean (SD)	Mean Change (SE)
Prolactin, ng/mL	9.6 (8.83)	0.6 (0.48)	11.0 (14.57)	1.6 (0.76)
Cholesterol, mg/dL				
Total	199.1 (45.89)	–1.3 (2.01)	197.7 (41.38)	–10.3 (2.08)
HDL	57.5 (17.05)	–0.4 (0.64)	54.7 (17.53)	–0.4 (0.77)
LDL	136.2 (46.29)	–0.9 (1.99)	136.0 (39.50)	–9.4 (1.91)
Triglycerides, mg/dL	131.3 (77.24)	1.7 (3.98)	138.8 (85.89)	–4.7 (5.13)
Glucose, mg/dL	93.8 (16.45)	0.8 (1.12)	91.3 (15.19)	0.9 (0.98)
Insulin, mIU/L	13.5 (16.81)	1.4 (1.37)	15.7 (28.79)	–1.5 (1.98)

Durgam S, et al. Presented at the 37th European College of Neuropsychopharmacology (ECNP) Annual Congress. Milan, Italy, September 2024.

Lumateperone: Focus on EPS and Weight Gain



EPS Risk

EPS-related TEAEs occurred in:

- 0.8% of the placebo + ADT group
- 1.7% of the lumateperone + ADT

Weight Gain Risk

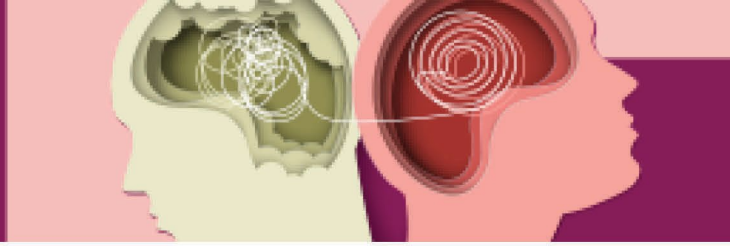
In the lumateperone + ADT group, no clinically relevant increases in prolactin or cardiometabolic parameters occurred at the end of the double-blind treatment period

Weight and body mass index remained stable in both groups

Durgam S, et al. Presented at the 37th European College of Neuropsychopharmacology (ECNP) Annual Congress. Milan, Italy, September 2024.

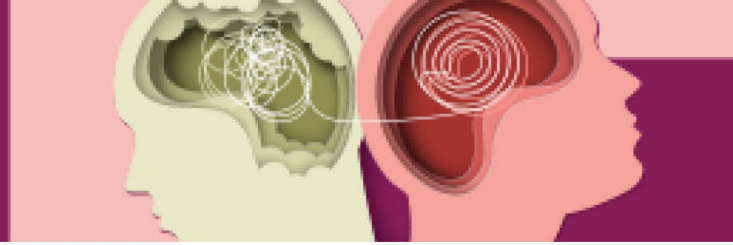
Strategies for Optimal MDD Treatment

Managing Adverse Effects Associated with Adjunctive AAPs in Patients with MDD



- Weight Gain
- Diabetes Mellitus
- Sexual Side Effects
- Hyperlipidemia
- Movement Disorders
- QTc Prolongation

Strategies for Optimal MDD Treatment

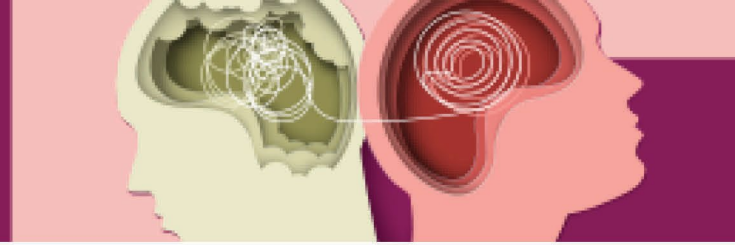


Use of clinical judgement and individualized care guide our treatment selection when using antipsychotics for depression.

1. Indication
2. Efficacy
3. Avoidance of metabolic adverse effects and sedation
4. Ease of titration
5. Movement disorder risk
6. Patient specific

Yildiz A, et al. Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults: a systematic review and network meta-analysis. *The Lancet Psychiatry*. 2023;*10*(9):693–705. Yan Y, et al. Efficacy and acceptability of second-generation antipsychotics with antidepressants in unipolar depression augmentation: a systematic review and network meta-analysis. *Psychological Medicine*. 2022;52(12):2224–2231.

The Power of Motivational Interviewing in Treatment Decisions



Open Questions

Open ended questions allow patient to give more information including their feelings, attitudes, and understanding.

Affirmations

To help overcome self-sabotaging or negative thoughts.

Reflections

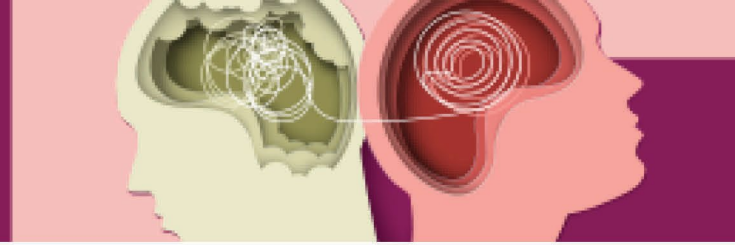
As a way to express ambivalence.

Summarize

To let your patient know they are being heard.

Lundahl B, et al. Motivational interviewing adherence tools: A scoping review investigating content validity. Pa*tient Educ Couns.* 2019;102(12):2145-2155.

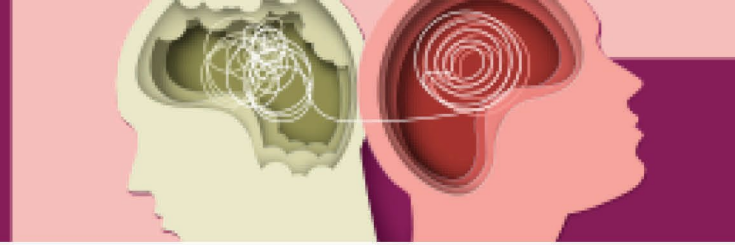
Understanding Potential Receptor Effects Implicated in Weight Gain



Receptor Activity	Potential Effects
H_1 antagonism	Appetite/weight increase (especially when paired with 5-HT_{2C} antagonism)
M_3 antagonism	May interfere with cholinergic actions on insulin secretion
5-HT_{2C} antagonism	Appetite/weight increase (especially when paired with H_1 antagonism)
5-HT_{2A} antagonism	May interfere with serotonergic actions on insulin secretion
α1 antagonism	May decrease insulin secretion
D_2 antagonism	Facilitates pancreatic insulin release, leading to insulin resistance

Raben AT, et al. *Frontiers in Neuroscience.* 2018:741. Hahn M, et al. *Schiz Research*. 2011;131(1-3):90-5. Matsui-Sakata A, et. al. *Drug Metabolism and Pharmacokinetics.* 2005;20(5): 368-378.

Off-Label Strategies to Address Weight Gain

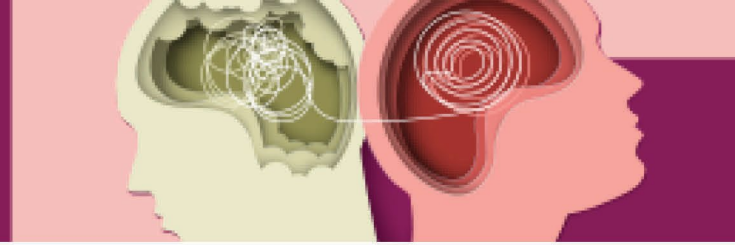


Intervention	Outcomes	Limitations
Diet, exercise, lifestyle management	9 lb. weight loss @ 6 mos. in STRIDE study	Adherence and access challenges
Metformin	Meta-analysis of 12 randomized trials in schizophrenia: mean weight reduction = 7.2 lb.	GI side effects, lactic acidosis risk, works better for prevention than weight loss
Topiramate or Zonisamide	Modest reported mean weight loss (~3-6 lb.) across agents over several months	Frequent CNS side effects, including cognitive dulling
Naltrexone/bupropion combination	7–8 lb. weight loss in schizophrenia patients with antipsychotic-associated weight gain	GI side effects common, coverage challenges
GLP-1 (±GIP) Receptor Agonists	liraglutide: 11.7 kg weight loss in schizophrenia; little data for semaglutide or tirzepatide in AIWG	Daily or weekly subcutaneous injections, coverage limited without T2DM diagnosis

GI=gastrointestinal; GLP-1=glucagon-like peptide-1; SC=subcutaneous.

Green CA, et al. *Am J Psychiatry*. 2015;172(1):71-81. de Silva VA, et al. *BMC Psychiatry*. 2016;16(1):341. Larsen JR, et al. *JAMA Psychiatry*. 2017;74(7):719-728. Zheng W, et al. *J Clin Psychopharmacol*. 2017;37(3):341-346. Tek C, et al. *J Clin Psychopharmacol*. 2014;34(5):608-612.

Considerations for Monitoring Throughout Treatment



	Olanzapine/ Fluoxetine	Quetiapine (IR and XR)	Lurasidone	Cariprazine	Lumateperone
Weight & Metabolic Risks	**High**	**High**	**Low**	**Low**	**Low**
Movement Disorder Risks	**Low**	**Low**	**Moderate**	**Moderate**	**Low**

Early onset of weight gain or metabolic changes are usually a harbinger of further problems

Early movement disorders (akathisia, dystonia, DIP) are risk factors for later development of TD

Both must be monitored closely in the short and long term!

As patients transition from acute treatment to long-term maintenance, treatment satisfaction is a key factor in adherence!

DIP = drug-induced Parkinsonism; TD = tardive dyskinesia.

Olanzapine/fluoxetine, quetiapine, quetiapine XR PI, lurasidone, cariprazine, and lumateperone PI. Drugs@FDA: FDAApproved Drugs. Accessed January 10, 2023. www.accessdata.fda.gov/scripts/cder/daf/.

Bates JA, et al. *The Primary Care Companion for CNS Disorders.* 2010;12(5):26157

Practical Take-Aways

- ✓ Inadequate response to anti-depressants is common and Atypicals are useful agents in such clinical scenarios
- ✓ FDA indications, as well las support from treatment guidelines are important
- ✓ Effect size is one means through which we can compare the degree of effect of a medication
- ✓ Side-effects of an individual treatment option are as important as efficacy. Two side effects in particular need deep thought on our part – EPS and akathisia, and weight gain. Minimizing risk for both is critical