A "TEST YOUR KNOWLEDGE" ACTIVITY

A Pathway to
Putting Patients First:

Spotlight on TAAR1 Agonists for Treating Schizophrenia

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Program agenda

Unmet Needs in the Management of Schizophrenia and the Role of Psychiatric Nurses

Amber Hoberg, MSN, APRN, PMHNP-BC; Bethany Yeiser, BS

Where Current Antipsychotic Medications Fall Short

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A Closer Look at TAAR1 Agonists: Efficacy, Safety, and Tolerability

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Unmet Needs in the Management of Schizophrenia and the Role of Psychiatric Nurses

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Bethany Yeiser, BS

What is schizophrenia and how many people have it?

Schizophrenia is a chronic brain disorder that can include **delusions, hallucinations, disorganized speech**, trouble with thinking, and lack of motivation.[1]

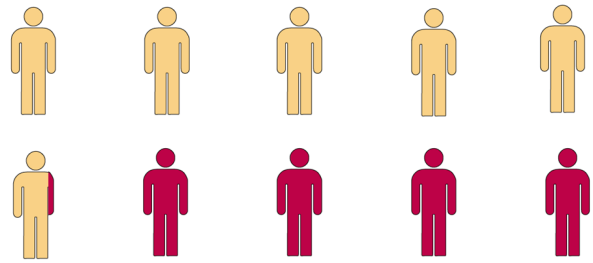
It is typically diagnosed in an individual's **late teens to twenties**, but changes in cognition and social relationships may precede the actual diagnosis by years.[2]

Between **0.25% and 0.64%** of individuals in the United States have schizophrenia or a related psychotic disorder,[2] which translates into roughly 1.5 million Americans.[3]

1. https://www.psychiatry.org/patients-families/schizophrenia/what-is-schizophrenia. 2. https://www.nimh.nih.gov/health/statistics/schizophrenia
3. https://namiwla.org/resources/mental-health-by-the-numbers

Patients with schizophrenia experience poor mental and physical health outcomes

A prospective study of 651 patients receiving treatment for first-episode psychosis found **only 37% to 59% displayed symptomatic remission 7 years later.**

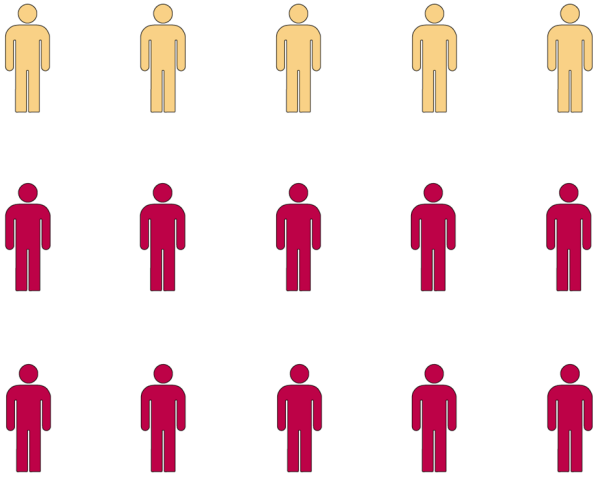


37% to 59%

Henry LP, et al. *J Clin Psychiatry*. 2010;71(6):716-728.

Patients with schizophrenia experience poor mental and physical health outcomes

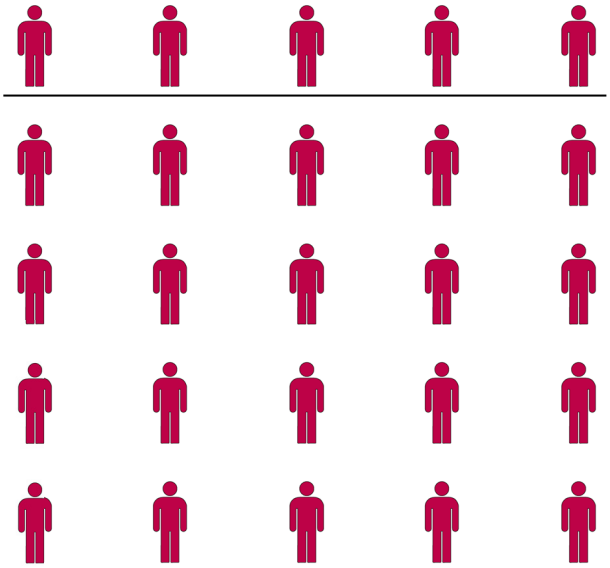
Approximately **two-thirds of patients are partially or fully refractory** to available treatments.



Kantrowitz JT. *CNS Drugs*. 2020;34(9):947-959.

Patients with schizophrenia experience poor mental and physical health outcomes

The prevalence of **obesity, type 2 diabetes, and hypercholesterolemia** in people with schizophrenia is estimated to be **3–5 times higher** than in the general population.

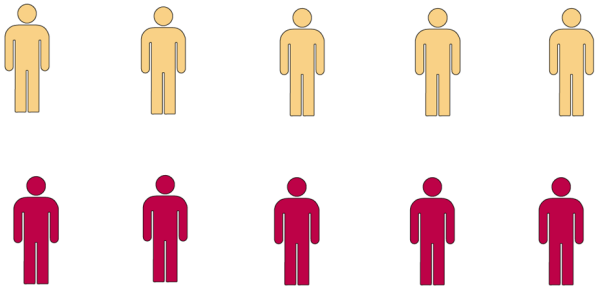


3X to 5X

Pillinger T, et al. *Lancet Psychiatry*. 2020;7(1):64-77.

Patients with schizophrenia experience poor mental and physical health outcomes

As few as **14% to 50%** of patients with schizophrenia **achieve recovery**, depending on the definition used.



14% to 50%

Vita A, Barlati S. *Curr Opin Psychiatry*. 2018;31(3):246-255.

Burden of schizophrenia on patients and their families

In the United States, the average lifespan for a patient with schizophrenia is **35% shorter** (29 years) than that of the general population.[1]

About **10%** of individuals experiencing **homelessness**[4] and **3%** of individuals in one state **prison** system have schizophrenia.[5]

As many as **15%** of patients experiencing **first-episode psychosis attempt suicide**.[2,3]

Caregivers report that their loved one's schizophrenia **affects their own emotional health**, ability to have a satisfying personal life, and family life.[6]

1. https://www.nimh.nih.gov/health/statistics/schizophrenia. 2. Barrett EA, et al. *Schizophr Res*. 2010;119(1-3):11-17. 3. Cohen S, et al. *Acta Psychiatr Scand*. 1994;90(3):167-171. 4. Ayano G, et al. *BMC Psych*. 2019;19:370. 5. Al-Rousan, T. *BMC Public Health*. 2017;17:342. 6. Citrome L, et al. *Patient Pref Adher*. 2022;16:159-168.

Patients are unhappy with currently available medications for schizophrenia

Findings from a recent qualitative study of unmet needs in individuals with schizophrenia

- 27% reported gaining between 50-100 pounds.
- 53% reported they had switched medications because of side effects.
- 87% reported discontinuing their antipsychotic at some point.

"You have a big appetite. A way big appetite."
"It had me walking [in] slow motion, like I felt like I was a zombie or something."
"I didn't say anything until I ended up with diabetes. Because I was wondering why my hands were always so numb and my toes. So, then I went for a physical and they was like, 'Oh you have diabetes.'"
"With every medicine I've been on, like, they're affecting me sexually, too. I hate that side effect."

Qualitative focus group study of patients with schizophrenia (3 groups of 5 patients).

Doane MJ, et al. *BMC Psychiatr*. 2023;23:245.

Antipsychotic discontinuation causes relapse, with permanent ramifications

- Each episode of psychosis can be thought of as a "brain attack."[1]
- During patients' first episode of psychosis, they lose an average of 1% of their brain volume, including millions of glial cells and billions of synapses.[1,2]
- Each subsequent relapse causes additional irreversible loss of brain tissue, making it more difficult for a patient to function in everyday life and also narrowing their future treatment options.[1,3,4]

1. Nasrallah H. *Current Psychiatr.* 2017;16(8):4-7. 2. Cahn W, et al. *Arch Gen Psychiatry*. 2002;59(11):1002-1010. 3. Takeuchi H, et al. *Neuropsychopharmacol*. 2019;44(6):1036-1042. 4. Emsley R, et al. *J Clin Psychopharmacol*. 2013;33(1):80-83.

Summary: Unmet needs in schizophrenia

- Schizophrenia remains a devastating disease for patients, their loved ones, and society.
- Patients are unhappy with current treatment options, especially the side effects.
- Psychiatric nurses can help ensure patients receive optimal treatment using the therapies currently available.

Where Current Antipsychotic Medications Fall Short

Amber Hoberg, MSN, APRN, PMHNP-BC

Eric Achtyes, MD

Bethany Yeiser, BS

Treating schizophrenia: Where are we now?

- For the past 70 years, the treatment of schizophrenia has relied on antipsychotic drugs whose primary mechanism of action is via blockade of the dopamine type 2 (D2) receptor.
- Second-generation antipsychotics, introduced almost 30 years after the original first-generation antipsychotics, offer a better safety and tolerability profile, but their efficacy is not significantly higher, except for clozapine.
- One-third of patients taking second-generation antipsychotics do not achieve remission, the majority achieve partial response, and many experience intolerable side effects

Achtyes ED, et al. *Europ Arch Psychiatr Clin Neurosci.* 2023;273(7):1543-1556.

Overview: Limitations of current treatments

Treatment Resistance

- ~30% of patients with schizophrenia are refractory to antipsychotics.[1]
- ~60% have a partial response.[2]
- Only ~14% achieve sustained recovery (definition: long-term remission plus good functional outcome).[3]

Comorbidities

- Can exacerbate preexisting medical comorbidities, such as diabetes or cardiovascular disease.
- May inadequately address the psychiatric comorbidities experienced by >50% of patients with schizophrenia.[4]

Negative & Cognitive Symptoms

- Low efficacy for addressing negative and cognitive symptoms.[1]

Adverse Effects of Medications

- Discontinuation rates in the CATIE trial due to side effects varied from 10%-19%.[5]
- Side effects can contribute to nonadherence, reduced life expectancy, and stigma (eg, involuntary movements of tardive dyskinesia).[4,6]

1. Achtyes ED, et al. *Europ Arch Psychiatr Clin Neurosci*. 2023;273(7):1543-1556. 2. Samara MT, et al. *Schizophr Bull*. 2019 Apr 25;45(3):639-646. 3. Yeomans D, et al. *Advances in Psychiatric Treatment*. 2010;16(2):86-95. 4. Dedic N, et al. *Int. J. Mol. Sci*. 2021;22(13185). 5. Lieberman JA, et al. *N Engl J Med*. 2005;353(12):1209-1223. 6. Doane MJ, et al. *BMC Psychiatr*. 2023;23:245.

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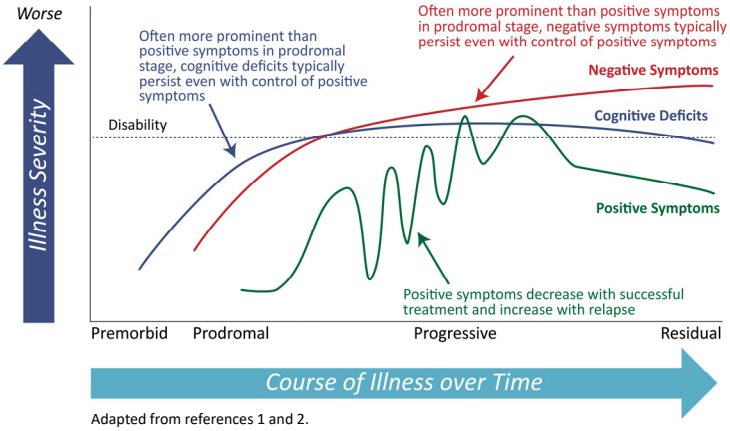
Schizophrenia: Course of illness



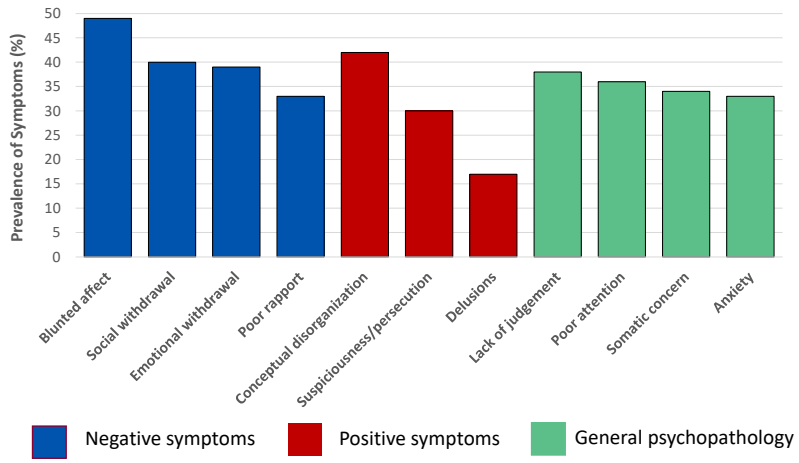
Adapted from references 1 and 2.

- 90% of patients experiencing their first psychotic episode have negative symptoms.[1]
- 80% of patients with schizophrenia experience cognitive symptoms.[2]
- Negative and cognitive symptoms have an even greater impact on patients' lives than positive symptoms.[1,3,4]

1. Correll CU, et al. *Neuropsychiatr Dis Treat*. 2020;16:519-534. 2. Carbon M, et al. *CNS Spectr*. 2014;19(Suppl 1):38-52. 3. Millan MJ, et al. *Eur Neuropsychopharmacol*. 2014;24(5):645-692. 4. Jones MT, et al. *Expert Opin Emerg Drugs*. 2020;25(2):189-200.

Residual symptoms are common, even in remitted patients with schizophrenia

Residual symptoms in 236 patients with schizophrenia in remission at time of discharge



- 94% had at least 1 residual symptom
- One-third to one-half of patients (n=94) with a residual symptom at discharge experienced the same symptom at 1-year follow-up
- Residual symptoms were significantly associated with diminished functioning ($P < .001$)

Schennach R, et al. *Eur Arch Psychiatry Clin Neurosci.* 2015;265(2):107-116.

Second-generation (atypical) antipsychotics: Select side effects

Acute Dystonias[1]

- Occurs first few days of antipsychotic initiation
- Young men at highest risk
- Sudden onset of abnormal postures
  - Tongue protrusion
  - Oculogyric crisis
  - Trismus
  - Torticollis

Akathisia[1]

- Subjective: feelings of anxiousness and restlessness
- Objective: pacing, rocking
- Adrenergic dysregulation may be involved
- Develops days after antipsychotic initiated

Pseudoparkinsonism[1]

- Tremor, rigidity, bradykinesia
- High-potency antipsychotics greatest risk
- Typically develops within days
- Due to postsynaptic dopamine blockade in striatum

Tardive Dyskinesia[1,2,3]

- Risk 1% per year with second-generation antipsychotics, 5% per year with first-generation antipsychotics
- Involuntary abnormal movements
  - Persistent & hyperkinetic
  - Oral/tongue movements
  - Choreiform quick movements of extremities
- Older women at highest risk

1. Mathews M, et al. *Psychiatry*. 2005 Mar;2(3):36-41. 2. Correll C, et al. *Am J Psychiatry*. 2004 Mar;161(3):414-25. 3. Caroff SN. *Neuropsychiatr Dis Treat.* 2019;15:785-794.

Monitoring protocol for patients on second-generation antipsychotics

	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Every 5 years
Personal/Family History	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circumference	X					X	
Blood Pressure	X			X		X	
Fasting Plasma Glucose	X			X		X	
Fasting Lipid Profile	X			X			X

Kiraly B, et al. *Am Fam Physician.* 2008;78(3):355-362.

Summary: Limitations of antipsychotics

- Available antipsychotics primarily target the positive symptoms of schizophrenia, leaving other types of symptoms (eg, negative, cognitive) unaddressed
- Available antipsychotics have a variety of side effects that negatively affect patients' health and quality of life
- These side effects, which result from dopamine blockade or other off-target receptor binding, cause many patients to stop taking their medications
- Treatments for schizophrenia that do not rely on dopamine blockade are urgently needed
- Nurses play an essential role in detecting and managing side effects associated with antipsychotics

A Closer Look at TAAR1 Agonists: Efficacy, Safety, and Tolerability

Eric Achtyes, MD

Bethany Yeiser, BS

The case for a new type of schizophrenia treatment

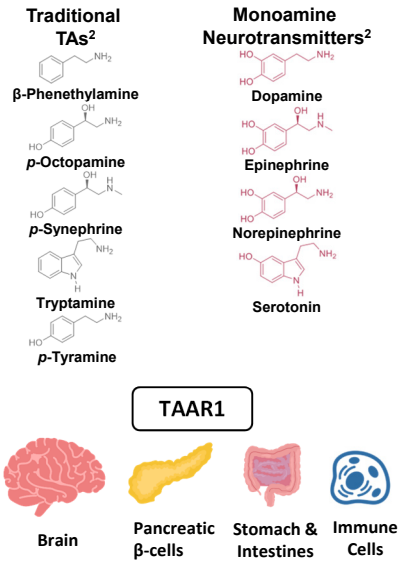
- Schizophrenia is a multifaceted disorder that affects numerous biological pathways, including those involving dopaminergic, serotonergic, glutamatergic, and gamma-aminobutyric acid (GABAergic) neurotransmitters.[1-3]
- All currently available antipsychotics work primarily by antagonizing dopamine D2 receptors.[2] This may help explain why available antipsychotics
  - Only work for some patients[4]
  - Are not effective in treating many types of schizophrenia symptoms (eg, negative, cognitive)[3]
- Many side effects associated with antipsychotics are caused by excessive D2 receptor occupancy.[5]
- Alternative treatments for schizophrenia that do not rely on dopamine blockade are urgently needed.[6]

1. Tsegay EW, et al. *Neuropsychiatr Dis Treat*. 2020;16:2499-2509. 2. Kruse AO, et al. *Transl Psychiatry*. 2022;12(1):500. 3. Xu MY, et al. *Acta Pharmacol Sin*. 2018;39(5):733-753. 4. Howes OD, et al. *Br J Psychiatry*. 2014;205(1):1-3. 5. Findlay LJ, et al. *Perspect Psychiatr Care*. 2017;53(3):148-155. 6. Correll CU, et al. *Neuropsychiatr Dis Treat*. 2020;16:519-534.

What are TAAR1 agonists and how do they work?

- Trace amines (TAs) are endogenous chemical messengers with structures similar to the monoamine neurotransmitters (dopamine, norepinephrine, serotonin) that play a key role in schizophrenia.[1-3]
- In humans, trace amine–associated receptor 1 (TAAR1) is expressed in the brain, pancreas, stomach & intestines, and immune cells.[2,4]
- TAAR1 appears to modulate the presynaptic dopamine dysfunction and glutamatergic alterations observed in psychosis **without blockade of the postsynaptic dopamine receptor.**[1-3,5]
- TAAR1 agonists may treat schizophrenia in an entirely new way, **without the side effects associated with currently available antipsychotics.**[3]

1. Nair PC, et al. *Mol Psychiatry*. 2022;(27):88-94. 2. Gainetdinov RR, et al. *Pharmacol Rev*. 2018;70(3):549-620. 3. Dedic N, et al. *Int J Mol Sci*. 2021;22(24):13185. 4. Andersen G, Krautwurst D. Chapter 7: Trace Amine-Associated Receptors in the Cellular Immune System. In: Farooqui AA, Foruuqui T, eds. *Trace Amines and Neurological Disorders.* Elsevier; 2016:97-103. 5. Achtyes ED, et al. *Europ Arch Psychiatr Clin Neurosci*. 2023;273(7):1543-1556.



Ralmitaront: TAAR1 partial agonist

Phase 2 trial[1]

Intervention: Ralmitaront vs placebo monotherapy

Participants: Acute exacerbation of schizophrenia or schizoaffective disorder

Length of study: 4 weeks

Primary outcome: Change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score

In a preliminary analysis, the primary endpoint was negative, and ongoing portions of the study have been discontinued.

Phase 2 trial[2]

Intervention: Ralmitaront vs placebo monotherapy or add-on therapy

Participants: Medically stable schizophrenia or schizoaffective disorder with PANSS negative symptom factor score ≥18

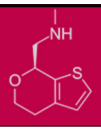
Length of study: 12 weeks

Primary outcome: Change from baseline in Brief Negative Symptoms Scale (BNSS) Avolition/Apathy Subscore

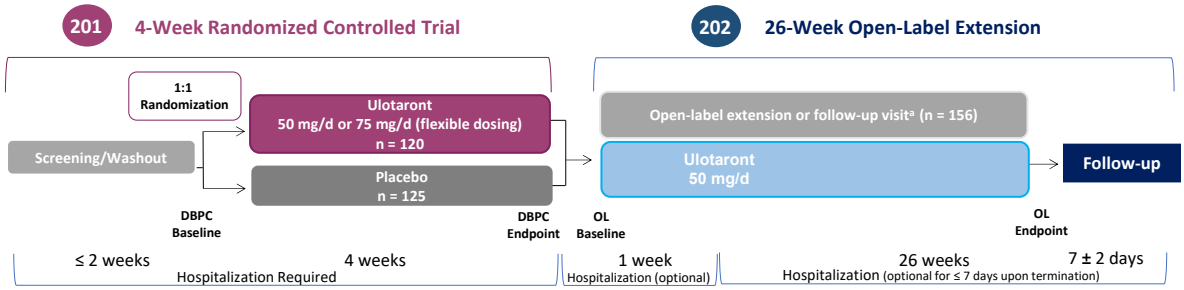
Terminated due to an interim analysis that indicated ralmitaront was unlikely to meet primary endpoint

1. ClinicalTrials.gov. Identifier: NCT04512066. 2. ClinicalTrials.gov. Identifier: NCT03669640. 3. Chemical structure: Kuvarzin - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=108308649.

Ulotaront: TAAR1 agonist with serotonin 5-HT$_{1A}$ agonist activity



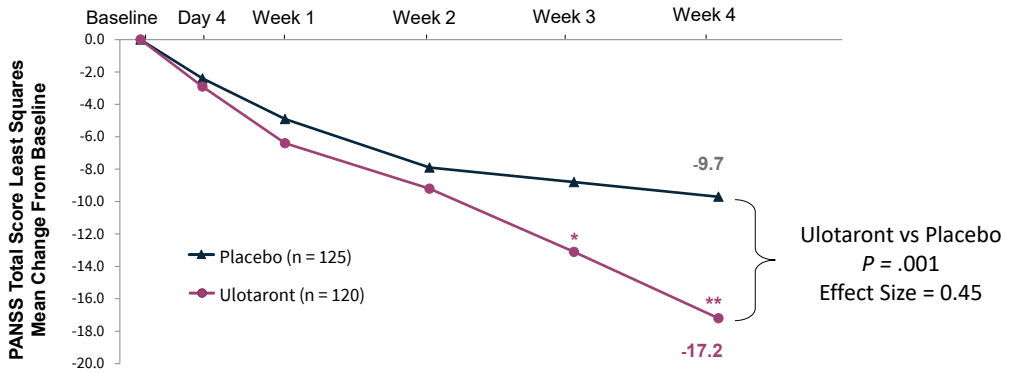
Phase 2 trial of ulotaront vs placebo monotherapy with 26-week open-label extension



DBPC = double-blind, placebo-controlled; OL = open-label.
[a]If not continuing into open-label extension, follow-up visit to occur 7 ± 2 days after last dose.

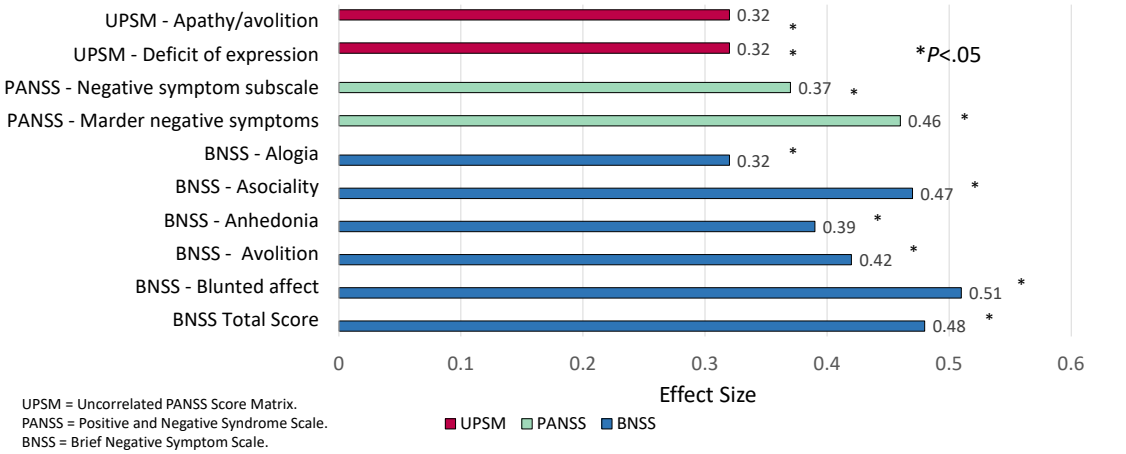
1. Koblan KS, et al. *N Engl J Med.* 2020;382:1497-1506. 2. Correll CU, et al. *NPJ Schizophr.* 2021;7:63.

Ulotaront primary end point: Phase 2 trial



PANSS = Positive and Negative Syndrome Scale.
*P < .05.
**P < .01.
Koblan KS, et al. *N Engl J Med.* 2020;382:1497-1506.

Ulotaront: Effect size (vs placebo) on negative symptoms at Week 4



UPSM = Uncorrelated PANSS Score Matrix.
PANSS = Positive and Negative Syndrome Scale.
BNSS = Brief Negative Symptom Scale.
Effect sizes based on observed case Analysis of Covariance (ANCOVA), except Mixed Models for Repeat Measures (MMRM) for PANSS-Negative & Marder, and BNSS total.

Achtyes ED, et al. *Europ Arch Psychiatr Clin Neurosci.* 2023;273(7):1543-1556.

Ulotaront: Adverse events

201

	Placebo (n = 125)	Ulotaront (n = 120)
Patients with any adverse event, n (%)[a]	63 (50.4)	55 (45.8)
Somnolence	6 (4.8)	8 (6.7)
Agitation	6 (4.8)	6 (5.0)
Nausea	4 (3.2)	6 (5.0)
Diarrhea	1 (0.8)	3 (2.5)
Dyspepsia	0 (0.0)	3 (2.5)
Serious adverse events[b]		
Worsening of schizophrenia	3 (2.4)	1 (0.8)
Sudden cardiac death	0 (0.0)	1 (0.8)
Suicide attempt	1 (0.8)	0 (0.0)

- Ulotaront has a relatively mild adverse event profile relative to current antipsychotics.
- Discontinuation due to adverse event was 8.3% for ulotaront vs 6.4% for placebo.
- The percentage of patients experiencing extrapyramidal symptoms (including akathisia, restlessness, musculoskeletal/joint stiffness, tremor, nuchal rigidity) was 3.3% for ulotaront and 3.2% for placebo.

[a]Indicates any event with a reported frequency ≥ 2% and more frequent in the ulotaront group compared to placebo group.
[b]Adverse events that occurred during the 4-week study and 7-day follow-up periods.

Koblan KS, et al. *N Engl J Med.* 2020;382:1497-1506.

Ulotaront: Weight, labs, sleep

201

	Placebo (n = 125)	Ulotaront (n = 120)
Weight/BMI, mean (SD) change at Week 4		
Weight, kg	-0.1 (2.3)	+0.3 (1.9)
BMI, (kg/m^2)	0.0 (0.8)	+0.1 (0.6)
Laboratory values (fasting), median change at Week 4		
Total cholesterol, mmol/L	0.0	-0.2
LDL cholesterol, mmol/L	0.0	-0.1
Triglycerides, mmol/L	-0.1	0.0
Glucose, mmol/L	+0.1	0.0
HbA_{1c}, % change	0.0	0.0
Prolactin, male/female pmol/L	-36/-101	-37/-175
PSQI global score, least squares mean change at Week 4 (standard error)	-1.7 (0.4)	-2.5 (0.4)

- Treatment with ulotaront resulted in minimal changes in weight, lipid levels, and glycemic measures.
- Effect of ulotaront on prolactin levels was minimal, comparable to placebo.
- Improvement in sleep quality.

BMI = body mass index; HbA_{1c} = glycated hemoglobin A_{1c}; LDL = low-density lipoprotein; PSQI = Pittsburgh Sleep Quality Index.

Koblan KS, et al. *N Engl J Med.* 2020;382:1497-1506.

Ulotaront: Phase 3 trials

DIAMOND 1[1,2]

Intervention: Ulotaront (50 mg or 75 mg daily) vs placebo monotherapy

Participants: 435 patients with acute exacerbation of schizophrenia

Length of study: 6 weeks

Primary outcome: Change from baseline in Positive and Negative Syndrome Scale (PANSS) total score

All groups showed a reduction from baseline. PANSS at week 6 was –16.9 and –19.6 in the ulotaront 50 mg/d and 75 mg/d groups, respectively, compared with –19.3 in the placebo group. The difference between the treatment effect and placebo did not reach statistical significance.

DIAMOND 2[2,3]

Intervention: Ulotaront (75 mg or 100 mg daily) vs placebo monotherapy

Participants: 462 patients with acute exacerbation of schizophrenia

Length of study: 6 weeks

Primary outcome: Change from baseline in Brief Negative Symptoms Scale (BNSS) Avolition/Apathy Subscore

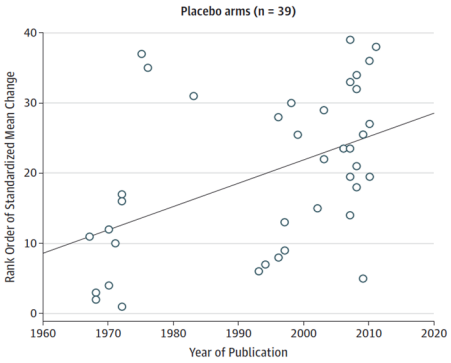
All groups showed a reduction from baseline. PANSS at week 6 was –16.4 and –18.1 in the ulotaront 75 mg/d and 100 mg/d groups, respectively, compared with –14.3 in the placebo group. The difference between the treatment effect and placebo did not reach statistical significance.

1. ClinicalTrials.gov. Identifier: NCT04072354. 2. O'Brien E. *Psychiatric Times*. July 31, 2023. https://www.psychiatrictimes.com/view/schizophrenia-treatment-fails-to-meet-primary-endpoint-in-phase-3-clinical-studies. 3. ClinicalTrials.gov. Identifier: NCT04092686.

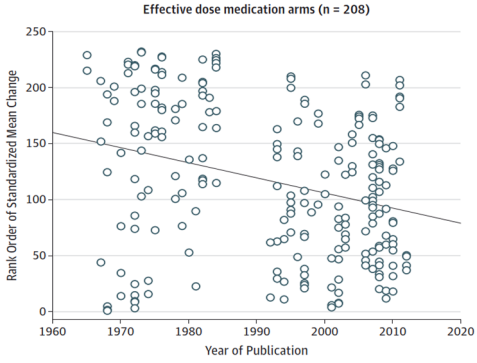
Placebo effect has increased while effective dose has decreased

Meta-analysis of 105 antipsychotic clinical trials from 1960 to 2013

The mean change in placebo arms has increased significantly (n = 39, r = –0.52, P = .001).



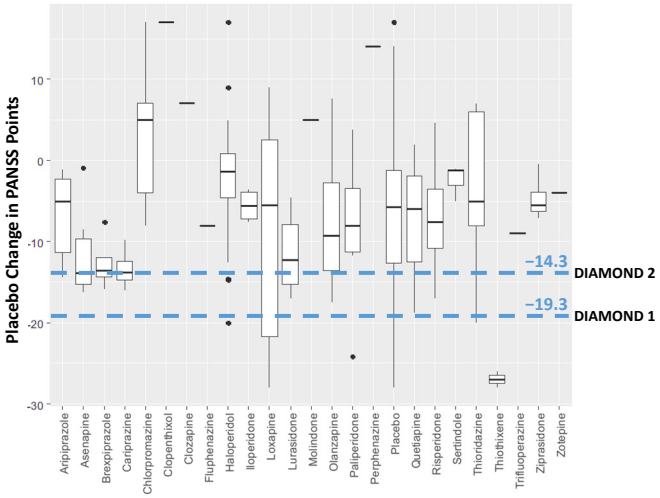
The mean change in effective dose medication arms decreased significantly (n = 208, r = –0.26, P < .001).



Rutherford BR, et al. *JAMA Psychiatry*. 2014;71(12):1409-1421.

Placebo response in phase 3 ulotaront trials compared with 32 antipsychotic trials

- The large placebo responses in DIAMOND 1 and DIAMOND 2 may have masked the substantial therapeutic response to ulotaront.[1]
- Placebo responses in DIAMOND 1 and DIAMOND 2 were greater than the placebo response in 32 controlled antipsychotic trials.[2]



Box plot distribution of placebo response is the change in PANSS points from baseline. Dashed blue lines are from preliminary endpoint analysis at week 6 for ulotaront in the DIAMOND 1 and DIAMOND 2 studies.[1]

1. O'Brien E. *Psychiatric Times.* July 31, 2023. https://www.psychiatrictimes.com/view/schizophrenia-treatment-fails-to-meet-primary-endpoint-in-phase-3-clinical-studies.
2. Huhn M, et al. *Lancet*. 2019;394:939-951.

Summary: TAAR1 agonists

- Targeting TAAR1 is a promising approach to treating schizophrenia with an entirely new mechanism of action.
- Phase 2 trial data for ulotaront suggested that this agent
  - Can ameliorate negative symptoms as well as positive symptoms.
  - Has a more favorable side effect profile than currently available antipsychotics.
- In two phase 3 trials, therapeutic effects may have been masked by a larger-than-normal placebo effect.
- The increase in placebo response in antipsychotic trials over several decades is a documented trend.
- Additional phase 3 trials of ulotaront are underway and may clarify the utility of this agent.

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Thank you for your participation.

Please complete your evaluation and posttest to receive credit for this activity.