Reviewing Non-Dopaminergic Mechanisms for Positive and Negative Schizophrenia Symptom Management

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Faculty Disclosures

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Educational Objectives

- Outline current medication classes used in the treatment of schizophrenia
- Articulate side effect development and negative symptom control challenges associated with standard-of-care antipsychotics
- Review the latest research describing the biologic rationale of novel non-dopaminergic pathways in schizophrenia
- Analyze emerging clinical trial data for non-dopamine-targeting schizophrenia therapies
Pretest Survey
Understanding Current Unmet Needs in Schizophrenia Management
Overview of Schizophrenia

- Schizophrenia is a chronic and debilitating condition with a global prevalence of approximately 1%, varying by location and diagnostic criterion.

- The average age of onset is in late adolescence to early twenties in men, and slightly later in women.

- However, determining the age of onset depends on the recognized symptom, with changes in personality and cognition often occurring before frank psychosis.

- Schizophrenia is associated with considerable morbidity, and is considered one of the top 20 causes of global disability and the top cause during its acute phase.

Course of Illness

Variable Onset of:
Mood Symptoms, Anxiety, Substance Use

Negative Symptoms
Cognitive Deficits

Positive Symptoms

Course of Illness Over Time

Premorbid  Prodromal  Progressive  Residual

Disability

Illness Severity

Worse
Impact on Function

Physical Comorbidities

Infectious
- HIV
- Hepatitis B/C

Cardiovascular
- Hypertension
- Stroke

Respiratory
- Chronic obstructive pulmonary disease
- Asthma

Metabolic
- Diabetes
- Obesity
- Metabolic syndrome

These physical illnesses and disease categories were consistently reported to be more common compared with the general population.
Mortality Risk

2.52× risk of mortality

10-25 years

Meta-analysis of 135 studies

A 2014 fact sheet from the World Health Organization suggested there is a 10- to 25-year life expectancy reduction in patients with severe mental disorders.

Focus Has Been on Dopamine

- For over a half-century, psychosis, particularly auditory hallucinations and paranoid delusions, have been thought to be the result of hyperactivation of the dopaminergic mesolimbic pathway.
- The mesolimbic pathway projects from the ventral tegmental area (VTA) to the ventral striatum.
- The dorsal striatum is not thought to be affected by this hyperactivity because it is innervated via the nigrostriatal pathway from the substantia nigra and controls motor movements.

The Dopamine Story is Evolving

1. **Mesocortical Pathway**
   - Negative symptoms
   - Cognitive impairment
   - Depression

2. **Mesolimbic Pathway**
   - “Limbic Striatum”
   - Negative symptoms

3. **Nigrostriatal Pathway 1**
   - “Associative Striatum”
   - Psychosis

4. **Nigrostriatal Pathway 2**
   - “Sensorimotor Striatum”
   - Dystonia
   - Akinesia
   - Rigidity
   - Tremor
   - Dyskinesia

5. **Tuberoinfundibular Hypothalamic Pathway**
   - Prolactin elevation
   - Amenorrhea
   - Galactorrhea
   - Sexual dysfunction

1. The **mesocortical pathway** originates from the ventral tegmental area in the midbrain and innervates areas of the frontal cortex.
2. The **mesolimbic pathway** originates from the ventral tegmental area in the midbrain and innervates the ventral striatum, olfactory tubercle, and parts of the limbic system.
3. The **nigrostriatal pathway 1** originates in the substantia nigra and innervates the associative striatum.
4. The **nigrostriatal pathway 2** originates in the substantia nigra and innervates the sensorimotor striatum.
5. The **tuberoinfundibular hypothalamic pathway** projects from the hypothalamus to the anterior pituitary gland.
70 Years of Similar Treatments

Time of FDA Approval


**Typical/first-generation (D₂ antagonism)**

**Atypical/second-generation (D₂/5-HT₂ₐ antagonism)**

Dopamine partial agonists

5-HT₂ₐ = serotonin 2A receptor; D₂ = dopamine D₂ receptor; FDA = US Food and Drug Administration.
**70 Years of Similar Treatments**

**Time of FDA Approval**

- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
- 2020

**Typical/first-generation (D₂ antagonism)**

**Atypical/second-generation (D₂/5-HT₂a antagonism)**

**Dopamine partial agonists**

Despite the large number of available AP treatments:

- All APs work via essentially the same mechanism
- 1 out of every 3 patients do not respond
- Negative and cognitive symptoms may persist
- Varying levels of side effects and long-term risks may contribute to negative outcomes and poor adherence

APs = antipsychotics


Lived Experience
Bethany Yeiser
New Presynaptic Antipsychotic Mechanisms: Muscarinic Agonists or PAMS, and TAAR1 Agonism
A Crack in the Postsynaptic Dopamine Edifice: 
The Unexpected Human Findings from LY246708

• **1992:** A novel compound LY246708 is synthesized by Eli Lilly and characterized initially as a selective M₁ agonist (M₄ and M₅ cloned receptors not yet being available). The intent was to develop a procognitive agent for dementia of the Alzheimer type. **It had no D₂ binding.**

• **1997:** Results of a large study (n=343) in mild-moderate Alzheimer’s disease published.
  - **Method:** Patients randomized in a double-blind manner to LY246708 (now called xanomeline) 75 mg/day, 150 mg/day or 225 mg/day or placebo and followed up to 6 months.
  - **Cognitive Results:** Patients in the high dose arm (225 mg/day) had superior endpoint scores on the ADAS-Cog vs placebo (p < 0.05).
  - **Behavioral Results:** Significant dose-dependent reductions in vocal outbursts, suspiciousness, delusions, agitation, and hallucinations.
  - **Tolerability:** 52% discontinued due to dose-dependent adverse events, mostly gastrointestinal. Syncope seen in 12.6% in high-dose group.
Muscarinic Agonism for Psychosis Rediscovered

• 1957: Preclinical evidence that the muscarinic agonist arecoline inhibits conditioned response in rats in a manner comparable to reserpine and chlorpromazine

• 1957: Clinical evidence that arecoline induces 'lucid intervals' in schizophrenia patients

• Limited interest in the cholinergic basis of schizophrenia or related meds through 1990:
  • From 1960-1990: 1299 papers in PubMed on dopamine/schizophrenia
  • From 1960-1990: Only 81 papers in PubMed on acetylcholine/schizophrenia
  • From 1960-1990: Only 22 papers in PubMed with the keywords muscarinic and schizophrenia

• Developments in the 1990s stimulated by the xanomeline findings:
  • Synthesis of muscarinic agonist ligands with antipsychotic effects in animals
  • Recognition that M1 and M4 knockout mice display behavior consistent with psychosis
  • Characterization of norclozapine:
    • Reverses amphetamine induced activity (an effect dependent on M4 agonism)
    • Stimulates M1 receptors, which may potentiate NMDA receptor activity and have procognitive effects
Xanomeline In Vitro Binding and Functional Activity

- Receptor binding is nonselective, functional effects are much more selective with much higher intrinsic activity at $M_1/M_4$ receptors (red arrows)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Affinity Ki (nM) *</th>
<th>PI/cAMP EC$<em>{50}$ nM (% E$</em>{max}$) **</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_1$</td>
<td>6.5</td>
<td>355 (80%) [PI]</td>
</tr>
<tr>
<td>$M_2$</td>
<td>8</td>
<td>2500 (46%) [cAMP]</td>
</tr>
<tr>
<td>$M_3$</td>
<td>7.1</td>
<td>1235 (22%) [PI]</td>
</tr>
<tr>
<td>$M_4$</td>
<td>29</td>
<td>125 (96%) [cAMP]</td>
</tr>
<tr>
<td>$M_5$</td>
<td>9</td>
<td>7500 (59%) [PI]</td>
</tr>
</tbody>
</table>

How $M_1/M_4$ Agonists Control Dopamine Circuits and Modulate Presynaptic VTA Dopamine Release

Concept 1: Bottom-up regulation ($M_4$ Story)

- VTA neurons have muscarinic receptors on their cell bodies. These receptors receive ACh input from the midbrain LDT pathway. **ACh stimulation of VTA neurons increases DA release.**

- LDT ACh release is modulated by the $M_4$ autoreceptor. Stimulation of $M_4$ autoreceptors on the LDT decreases ACh release. **Net effect: decreased VTA neuron firing and less VTA DA release.**

- **Selectivity:** the decreased DA outflow from $M_4$ stimulation occurs selectively in striatal areas related to psychosis, not in motor systems which are controlled more by $M_2$ autoreceptors.


LDT: laterodorsal tegmentum; VTA: ventral tegmental area.
How M₁/M₄ Agonists Control Dopamine Circuits and Modulate Presynaptic VTA Dopamine Release

**Concept 2: Top-down regulation (M₁ Story)**

- GABAergic inhibitory interneurons control glutamate release from excitatory PFC pyramidal neurons. These glutamate neurons have downstream projections to the VTA that stimulate dopamine release.

- **Stimulation of M₁ receptors on GABAergic inhibitory interneurons** inhibits pyramidal cell glutamate release.

- **Net effect:** decreased VTA neuron firing and less VTA DA release but no motor effects.


PFC: prefrontal cortex; VTA: ventral tegmental area.
Managing the Peripheral Pro-Cholinergic Effects of Xanomeline

**Issue:** Xanomeline induces peripheral adverse effects, primarily related to $M_1$ agonism

**The answer:** Find an anticholinergic with limited CNS penetration to mitigate xanomeline's peripheral effects.

**The winner: Trospium!** Found after screening hundreds of compounds.

**What is trospium:** A nonselective muscarinic antagonist available since 1974 for overactive bladder (approved in 2004 in the US).

Trospium is a quaternary ammonium compound. The positively charged ammonium group makes trospium too polar to cross the BBB.

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Other Muscarinic Agonists or PAMS Being Studied

Agents in development include the following mechanisms:

- Positive allosteric modulators of $M_1$ receptors (VU0486846) or $M_1$ receptor agonism
- Positive allosteric modulators of $M_4$ receptors (e.g. emraclidine) or $M_4$ receptor agonism (NBI-1117568)
What’s a TAAR?

**TAAR = Trace-amine associated receptor**
- A class of intracellular receptors discovered in 2001, nomenclature standardized in 2006
- Members of the G-protein-coupled receptor family
- 26 TAARs have been identified in vertebrates; humans express TAAR1, 2, 5, 6, 8, and 9

Where are trace amines?
- Structurally related to classic monoamine neurotransmitters, but found in low concentrations in the CNS
- Trace amines are expressed 2 times lower than DA, NE, and 5-HT
- The trace amines β-phenylethylamine (PEA), p-tyramine (TYR), tryptamine (TRP), and p-octopamine (OCT) have the greatest similarity to monoamine neurotransmitters

The Link Between Trace Amine Receptors and Schizophrenia

- **2001**: TAARs discovered and a unified nomenclature agreed upon in 2005
  - Predominantly intracellular location, members of the G protein-coupled receptor family
  - 26 TAARs identified in vertebrates thus far. Humans express TAAR1, 2, 5, 6, 8, and 9
  - In general, TAAR1 is heterogeneously distributed throughout the CNS, and evidence points to both pre- and postsynaptic TAAR1-mediated effects in animals
- **2004-07**: Early human genetics studies note associations between schizophrenia and TAAR polymorphisms
- **2006-08**: TAAR1 studied in intact and knockout mice, noted heterodimerization with dopamine D2 receptors and the behavioral and molecular impact of KO, dopamine agonists/antagonists
- **2011-13**: TAAR1 agonists dose dependently block cocaine-induced hyperlocomotion, an effect similar to olanzapine, and potentiate the impact of olanzapine on these behaviors. Antidepressant, cognitive & metabolic activities also noted
Lessons from TAAR1 Knockout Mice

1. **Behavioral:**
   - TAAR1-KO are similar to wild type mice in their basal state, but have enhanced behavioral response to amphetamine (e.g., increased hyperlocomotion) and increased striatal dopamine release from amphetamine
   - Worse performance in anxiety and working memory tests
   - Increased propensity for alcohol addiction

2. **Presynaptic Dopamine Function:**
   - TAAR1-KO show increased firing rates of dopamine neurons in the ventral striatum (A10 tract, associated with psychosis related behaviors) but not in the dorsal striatum (A9 tract, associated with motor behaviors)
   - DAT function is normal but decreased dopamine D_{2} autoreceptor function

3. **Postsynaptic Dopamine Function:**
   - Increased expression & supersensitivity of D_{2} receptors (D_{2}R). TAAR1-KO have decreased phosphorylation of Akt (making it less active) and of GSK3β (making it more active). The supersensitivity of postsynaptic D_{2}R is related to higher GSK3β activity.

4. **Prefrontal cortex glutamate function:**
   - TAAR-1 KO have decreased NMDA receptor function, and deficits in prepulse inhibition (a model of cognitive dysfunction)

Preclinical Data on TAAR1 Agonists Show Interactions With Multiple Transmitter and Other Systems

Antipsychotic properties
- TAAR1 agonists block the behavioral effects of stimulants and NMDA antagonists
- TAAR1 agonists potentiate antipsychotic effects on amphetamine-induced hyperactivity, but do not induce catalepsy

**Antidepressant properties** (TAAR1 is expressed in the dorsal raphe and forms heterodimers with the 5-HT$_{1B}$ autoreceptor)
- Dorsal raphe neurons in TAAR1 knockout mice have high firing rates. TAAR1 agonists inhibit this firing rate.
- TAAR1 agonists modify behavioral response in forced swim test

Pro-cognitive properties
- TAAR1 agonists improve attentional set shifting in rodents, and object retrieval in primates

Metabolic properties
- Mitigate olanzapine-related weight gain and fat accumulation in mice
TAAR1 Mediates DA Homeostasis

- TAAR1 agonists decrease the firing rate in midbrain VTA DA neurons
- TAAR1 agonists increase the feedback inhibition from dopamine binding to the presynaptic D2 autoreceptor
- TAAR1 agonists act postsynaptically to reduce DA-driven behaviors

Adapted from Gainetdinov 2018 and Berry 2017.

VTA, ventral tegmental area; DA, dopamine; AADC, aromatic L-amino acid decarboxylase; 3-MT, 3-methoxytyramine; COMT, catechol-o-methyltransferase; D2R, D2-like dopamine receptor; DAT, dopamine transporter; DOPAC, 3,4-dihydroxyphenylacetic acid; MAO A/B, monoamine oxidase; L-Phe, l-phenylalanine; l-Tyr, l-tyrosine; OCT2, organic cation transporter; PAA, phenylacetic acid/4-hydroxyphenylacetic acid; PEA, β-phenylethylamine; TH, tyrosine hydroxylase; TYR, p-tyramine; VMAT2, vesicular monoamine transporter.
Novel Muscarinic and TAAR1 Mechanisms: Summary

1. Neither mechanism involves binding to dopamine D$_2$ receptors

2. Both modulate presynaptic dopamine release
   - Importantly both mechanisms act SELECTIVELY in the area of the striatum associated with the positive symptoms of psychosis and spare striatal motor and hypothalamic dopamine circuits
   - **Implications:** no D$_2$ antagonism related adverse effects (motor, endocrine)

3. Preclinical studies also indicate possible benefits on cognition, and no adverse effects on metabolic parameters, with data suggesting that TAAR1 agonism may improve metabolic functioning
Latest Clinical Data for Muscarinic Agonists or PAMS
EMERGENT-1 Phase 2b Clinical Trial Design

- 5 week double-blind, placebo-controlled inpatient trial
- Adults ages 18–60 with an acute exacerbation of schizophrenia
- Mean age 42.5 years, 70% male, 76% nonwhite, mean baseline PANSS 97.1

91% were able to tolerate titration the highest dose of xanomeline-trospium
Xanomeline/Trospium (XT) Phase 2b Results: PANSS Total Score

XT: -17.4 ± 1.8 pts
Placebo: -5.9 ± 1.7 pts
(p < 0.001)

Effect size: 0.75

Please see source for original image: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7610870/pdf/EMS123174.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7610870/pdf/EMS123174.pdf)
Xanomeline/Trospium (XT) Phase 2 Tolerability Data

Adverse effects (AEs) occurring in > 2% of XT and greater than placebo

<table>
<thead>
<tr>
<th></th>
<th>XT (n = 89)</th>
<th>Placebo (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>48 (54%)</td>
<td>39 (43%)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Severe AE</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>18 (20%)</td>
<td>19 (21%)</td>
</tr>
<tr>
<td>AE leading to D/C</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Weight Changes

<table>
<thead>
<tr>
<th></th>
<th>XT (n = 89)</th>
<th>Placebo (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in weight</td>
<td>3.3 lb ± 6.2</td>
<td>2.4 lb ± 7.7</td>
</tr>
<tr>
<td>≥7% increase in weight</td>
<td>2 (2.2%)</td>
<td>5 (5.6%)</td>
</tr>
</tbody>
</table>

- There were no discontinuations due to cholinergic or anticholinergic AEs
- Incidence of movement disorders and QT<sub>C</sub> changes similar for XT vs placebo

EMERGENT-2 and EMERGENT-3 Phase 3 Trial Results: PANSS Total Score

- 5 week, double-blind, placebo-controlled, inpatient trial, adults 18-65 yrs with acute exacerbation of schizophrenia
- Mean age 45.6 (E-2), 43.1 (E-3); 75% male (E-2, E-3), % nonwhite 77.4% (E-2), 61.8% (E-3); baseline PANSS 98.1 (E-2), 97.0 (E-3)

*P<0.05; **P<0.01; ****P<0.0001.
LS, least squares; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

Brannan SK. Poster presented 2023 Annual Conference of the Schizophrenia International Research Society (SIRS), May 11-15, 2023, Toronto, Canada
EMERGENT-2 and EMERGENT-3 Phase 3 Trial Results: Tolerability

<table>
<thead>
<tr>
<th>Variable</th>
<th>EMERGENT-2</th>
<th></th>
<th>EMERGENT-3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KarXT (n=126)</td>
<td>Placebo (n=125)</td>
<td>KarXT (n=125)</td>
<td>Placebo (n=128)</td>
</tr>
<tr>
<td>Any TEAE, n (%)</td>
<td>95 (75.4)</td>
<td>73 (58.4)</td>
<td>88 (70.4)</td>
<td>64 (50.0)</td>
</tr>
<tr>
<td>Serious TEAE, n (%)</td>
<td>2 (1.6)</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>TEAE leading to discontinuation, n (%)</td>
<td>9 (7.1)</td>
<td>7 (5.6)</td>
<td>8 (6.4)</td>
<td>7 (5.5)</td>
</tr>
<tr>
<td>TEAE occurring in ≥5% of people in the KarXT group in either trial, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>27 (21.4)</td>
<td>13 (10.4)</td>
<td>16 (12.8)</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>24 (19.0)</td>
<td>10 (8.0)</td>
<td>20 (16.0)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (19.0)</td>
<td>7 (5.6)</td>
<td>24 (19.2)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (14.3)</td>
<td>1 (0.8)</td>
<td>20 (16.0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>17 (13.5)</td>
<td>15 (12.0)</td>
<td>14 (11.2)</td>
<td>15 (11.7)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>12 (9.5)</td>
<td>1 (0.8)</td>
<td>8 (6.4)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (8.7)</td>
<td>4 (3.2)</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>8 (6.3)</td>
<td>0</td>
<td>5 (4.0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>7 (5.6)</td>
<td>4 (3.2)</td>
<td>2 (1.6)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (5.6)</td>
<td>4 (3.2)</td>
<td>7 (5.6)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (2.4)</td>
<td>6 (4.8)</td>
<td>7 (5.6)</td>
<td>10 (7.8)</td>
</tr>
<tr>
<td>Body weight: mean change from baseline to week 5, kg±SD</td>
<td>1.36±3.31</td>
<td>2.49±6.92</td>
<td>1.41±3.37</td>
<td>2.04±3.08</td>
</tr>
<tr>
<td>Body weight: ≥7% increase from baseline to week 5, n/N (%)</td>
<td>6/94 (6.4)</td>
<td>13/100 (13.0)</td>
<td>5/78 (6.4)</td>
<td>12/92 (13.0)</td>
</tr>
<tr>
<td>Simpson-Angus Scale score: mean change from baseline to week 5, ±SD</td>
<td>0.0±0.61</td>
<td>-0.1±0.70</td>
<td>-0.1±0.55</td>
<td>-0.1±0.36</td>
</tr>
<tr>
<td>Barnes Akathisia Rating Scale score: mean change from baseline to week 5, ±SD</td>
<td>-0.1±1.09</td>
<td>-0.2±0.98</td>
<td>-0.1±0.75</td>
<td>-0.1±0.88</td>
</tr>
</tbody>
</table>

*In EMERGENT-2, 2 serious TEAEs were 2 cases of suicidal ideation in the KarXT group, 1 case of appendicitis in the placebo group, and 1 case of worsening of schizophrenia in the placebo group. *In EMERGENT-3, 3 serious TEAEs of gastroesophageal reflux disease occurred in the KarXT group. Hypertension is the MedDRA preferred term and is not necessarily reflective of clinical hypertension. MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation; TEAE, treatment-emergent adverse event.

Comments:
1. AEs leading to drop-out low and close to PBO
2. Procholinergic (N/V) and anticholinergic AEs seen (constipation) but were not significant causes of drop-out
3. No significant change in mean wt, the % of subjects gaining ≥ 7% of weight, or D₂ related side effects
4. No significant change in serum prolactin (not shown in table, E-2 poster Correll et al.)

Emraclidine, an $M_4$ Positive Allosteric Modulator: Phase 1B Results

**Symptom Reduction**

- Emraclidine 30 mg QD: -19.5 pts
- Emraclidine 20 mg BID: -17.9 pts
- Placebo: -11.1 pts

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**PANSS Total Score**

Week

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo (n=27)</th>
<th>Emraclidine 30 mg QD (n=27)</th>
<th>Emraclidine 20 mg BID (n=27)</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>14 (52)</td>
<td>14 (52)</td>
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<td>1</td>
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<td>14 (52)</td>
<td>15 (56)</td>
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<td>4</td>
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<td>7 (26)</td>
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<td>6</td>
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<td></td>
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</tbody>
</table>

---

**AEs, n (%)**

<table>
<thead>
<tr>
<th>AEs</th>
<th>Placebo (n=27)</th>
<th>Emraclidine 30 mg QD (n=27)</th>
<th>Emraclidine 20 mg BID (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>14 (52)</td>
<td>14 (52)</td>
<td>15 (56)</td>
</tr>
<tr>
<td>AEs related to study drug</td>
<td>10 (37)</td>
<td>7 (26)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>AEs leading to D/C</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

---

**AEs in ≥5% of all emraclidine**

<table>
<thead>
<tr>
<th>AEs</th>
<th>Placebo (n=27)</th>
<th>Emraclidine 30 mg QD (n=27)</th>
<th>Emraclidine 20 mg BID (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7 (26)</td>
<td>8 (30)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4)</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>CPK increased</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0)</td>
<td>3 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

---

* QD = once daily; BID = twice daily

Krystal et al. Presented at the American College of Neuropsychopharmacology Annual Meeting December 5-8, 2021, San Juan, Puerto Rico.
Muscarinic Mechanisms: Clinical Implications

**Advantages (efficacy):** The effect sizes of xanomeline-trospium (XT) for symptom reduction are as high or higher than agents approved for schizophrenia in the past 25 years, and have been replicated in 3 clinical trials.

XT is being studied adjunctively for schizophrenia

**Advantages (tolerability):** no metabolic, endocrine or motor adverse effects

XT requires titration in the first week to mitigate its procholinergic adverse effects.

**Practical issues:** Concurrent use of centrally acting anticholinergics (e.g. benztropine, trihexyphenidyl, diphenhydramine) and possibly strongly anticholinergic antipsychotics (e.g. olanzapine, high dose quetiapine) can interfere with the mechanism of action for muscarinic agonists or PAMS

**Future:** awaiting data for emraclidine and other muscarinic agents
Latest Clinical Data for TAAR1 Agonism
Investigational TAAR1 Agonists

One TAAR1 compound is in clinical development for the treatment of schizophrenia

**Ulotaront**: TAAR1 agonist with 5-HT_{1A} agonist activity

- Ralmitaront: A TAAR1 partial agonist that was evaluated in two Phase 2 studies that were terminated because of inadequate efficacy
- TAAR1 antagonists have been studied preclinically, but none have reached clinical trials
Ulotaront Phase 2

4-week RCT
- 1:1 randomization
  - Ulotaront 50 or 75 mg/d (flexible dosing) n=120
  - Placebo n=125

26-week OLE
- Open-label extension or follow-up visit* (n=156)
  - Ulotaront 50 mg/d
  - Ulotaront 25, 50, or 75 mg/d (flexible dosing)

≤ 2 weeks
- Hospitalization required

4 weeks
- Hospitalization required

1 week
- Hospitalization (optional)

26 weeks
- Hospitalization (optional for ≤ 7 days upon termination)

7 ± 2 days

Half not continuing into open-label extension, follow-up visit to occur 7 ± 2 days after last dose.

DBPC = double-blind, placebo-controlled; RCT = randomized clinical trial.

Ulotaront Phase 2: Key Info

**PRIMARY ENDPOINT**
PANSS total score

**SECONDARY ENDPOINTS**
CGI-S scale; PANSS subscales; BNSS; MADRS; PANSS responders; UPSM-transformed PANSS factor severity scores

**PRIMARY ENDPOINT**
Safety

**SECONDARY EFFICACY ENDPOINTS**
Relapse, time to relapse, PANSS total and subscales, CGI-S; BNSS total score; MADRS total score, PANSS responders

**KEY PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS**
- Subjects were between 18-40 years old—mean age 30.6 (placebo), 30.0 (ulotaront)
- Mostly male (63.2% placebo, 64.2% ulotaront) and white (83.2% placebo, 80.0% ulotaront)
- PANSS total score at baseline 99.7 (placebo), 101.4 (ulotaront)

*Not inclusive of all endpoints and analyses.*
BNSS = brief negative symptom scale; CGI-S = clinical global impression-severity scale; MADRS = The Montgomery-Åsberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; UPSM = uncorrelated PANSS score matrix.
Primary Endpoint: Phase 2 RCT

**Response rate** (total PANSS improvement ≥20%):
- 64.6% ulotaront vs 44.0% placebo

NNT = 5 (95% CI 3-12)*

By the end of the flexible dosing period (week 3),
- 27.5% were on 50 mg and 72.5% on 75 mg

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*P<0.05. **P<0.01. *NNT calculations performed by Dr. Citrome.
LS = least squares; NNT = number needed to treat.

PANSS: Phase 2 OLE

## Adverse Events: Phase 2 RCT

<table>
<thead>
<tr>
<th>Frequency ≥ 2% in ulotaront group and &gt; placebo group</th>
<th>Placebo (n=125)</th>
<th>Ulotaront (n=120)</th>
<th>NNH (all ns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any AE, n (%)</td>
<td>63 (50.4)</td>
<td>55 (45.8)</td>
<td>-22</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (4.8)</td>
<td>8 (6.7)</td>
<td>54</td>
</tr>
<tr>
<td>Agitation</td>
<td>6 (4.8)</td>
<td>6 (5.0)</td>
<td>500</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (3.2)</td>
<td>6 (5.0)</td>
<td>56</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (0.8)</td>
<td>3 (2.5)</td>
<td>59</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0 (0.0)</td>
<td>3 (2.5)</td>
<td>40</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening of schizophrenia</td>
<td>3 (2.4)</td>
<td>1 (0.8)</td>
<td>-64</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>0</td>
<td>1 (0.8)</td>
<td>120</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>1 (0.8)</td>
<td>0</td>
<td>-125</td>
</tr>
</tbody>
</table>

Table lists most common AEs vs placebo (≥ 2% and more frequent than placebo)

- Discontinuation due to an AE = 8.3% (ulotaront) vs 6.4% (placebo); NNH=52 (ns)
- No significant differences observed in potential movement disorders between ulotaront and placebo patients, as measured by SAS, BARS, and AIMS scales
- Percentage of patients experiencing any EPS (including akathisia, restlessness, musculoskeletal/joint stiffness, tremor, or nuchal rigidity) was 3.3% for ulotaront and 3.2% for placebo; NNH = 750 (ns)

**NNH calculations performed by Dr. Citrome**

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; EPS = extrapyramidal symptoms; NNH = number needed to harm; ns = not significant; SAS = Simpson-Angus Scale.

Adverse Events: Phase 2 OLE

Overall, 56% of patients treated with ulotaront in the 26-week OLE experienced an AE

- Schizophrenia (worsening or exacerbation of), headache, insomnia, and anxiety occurred at an incidence greater than 5%
- Rates of severe AEs in patients treated with ulotaront was 5.1%
- The only severe AE observed in more than 1 patient was schizophrenia (n=5)
- Overall incidence of EPS-related AEs (parkinsonism, dyskinesia, tremor, and restlessness) was 3.2%
- Study completion rates were 66.9%
- Over the 26 weeks, rate of AEs leading to discontinuation was 11.5% in patients treated with ulotaront

<table>
<thead>
<tr>
<th>Safety parameter, n (%)a</th>
<th>Ulotaront (n =156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one adverse event</td>
<td>88 (56.5)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>19 (12.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (11.5)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13 (8.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8 (5.1)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7 (4.5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7 (4.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>Irritability</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Influenza</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Blood prolactin increased</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Serious AE, n (%)</td>
<td>15 (9.6)</td>
</tr>
<tr>
<td>AEs leading to discontinuation, n(%)</td>
<td>18 (11.5)</td>
</tr>
</tbody>
</table>

aIndicates any event with a reported frequency ≥ 2%

## Weight, Labs, Sleep: Phase 2 RCT

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=125)</th>
<th>Ulotaront (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight/BMI, mean (SD) change at week 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>-0.1 (2.3)</td>
<td>+0.3 (1.9)</td>
</tr>
<tr>
<td>BMI, (kg/m²)</td>
<td>0.0 (0.8)</td>
<td>+0.1 (0.6)</td>
</tr>
<tr>
<td><strong>Laboratory values (fasting), median change at week 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>0.0</td>
<td>-0.2</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>0.0</td>
<td>-0.1</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>-0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>+0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>HbA1c (% change)</td>
<td>-0.03</td>
<td>+0.04</td>
</tr>
<tr>
<td>Prolactin, male/female capmol/L</td>
<td>-36/-101</td>
<td>-37/-175</td>
</tr>
<tr>
<td><strong>PSQI global score, LS mean (SE) change at week 4</strong></td>
<td>-1.7 (0.4)</td>
<td>-2.5 (0.4)</td>
</tr>
</tbody>
</table>

*ₐn=120 for ulotaront and n=125 for placebo. ᵇn=117 for ulotaront and n=124 for placebo. ᶜₙ=74 (males) and n=40 (females) for ulotaront and n=71 (males) and n=42 (females) for placebo. ᵈₙ=115 for ulotaront and n=113 for placebo.

Endpoints were not controlled for multiplicity and were obtained as part of the safety evaluation.

**BMI = body mass index; HbA1c = glycolated hemoglobin A1c; LDL = low-density lipoprotein;**

**PSQI = Pittsburgh Sleep Quality Index;**

**SE = standard error.**

## Weight, Labs, Sleep: Phase 2 OLE

### Table: Ulotaront Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ulotaront (n =156)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)(^a)</strong></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>-0.3 (3.7)</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>-0.1 (1.2)</td>
</tr>
<tr>
<td><strong>Laboratory values, median</strong></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L(^b)</td>
<td>-2.0</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L(^b)</td>
<td>0</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L(^b)</td>
<td>-9.0</td>
</tr>
<tr>
<td>Triglycerides, mmol/L(^b)</td>
<td>-5.0</td>
</tr>
<tr>
<td>Glucose, mmol/L(^c)</td>
<td>+2.0</td>
</tr>
<tr>
<td>HbA1c (%)(^c)</td>
<td>0.0</td>
</tr>
<tr>
<td>Prolactin, male/female (ng/mL)(^d)</td>
<td>-2.7/-3.4</td>
</tr>
<tr>
<td>PSQI global score LS mean (SD)</td>
<td>-2.0 (3.0)</td>
</tr>
</tbody>
</table>

\(^a\)n=104. \(^b\)n=117 for ulotaront and n=111. \(^c\)n=109. \(^d\)n=73 (males) and n=39 (females).  

Endpoints were not controlled for multiplicity and were obtained as part of the safety evaluation.

Ulotaront data are shown for all extension phase patients.

Ulotaront Summary

**Phase 2 Results**

- Change from baseline in PANSS total score was -17.2 for ulotaront and -9.7 for placebo ($P=0.001$) at week 4
- Incidence of AEs for ulotaront was 45.8% and 50.4% for placebo with a difference of 2.5% or less for each event; discontinuation due to an AE was 8.3% for ulotaront and 6.4% for placebo
- 56.5% of patients experienced an AE; 66.9% of patients completed 26 weeks of open-label treatment with ulotaront
- On average, patients showed a mean PANSS total score reduction of -22.6 from open-label baseline to week 26
- FDA granted breakthrough therapy designation to ulotaront for the treatment of schizophrenia
- Ulotaront is currently in phase 3 clinical trials in patients with schizophrenia
# Ulotaront Phase 3 Development Program

## Phase 3 Clinical Development for Schizophrenia

<table>
<thead>
<tr>
<th>STUDY ELEMENT</th>
<th>SEP361-301 (Acute Study)</th>
<th>SEP361-302 (Acute Study)</th>
<th>SEP361-303 (Open-Label Extension)</th>
<th>SEP361-304 (Long-Term Safety Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicaltrials.gov identifier</td>
<td>NCT04072354</td>
<td>NCT04092686</td>
<td>NCT04109950</td>
<td>NCT04115319</td>
</tr>
<tr>
<td>Study duration</td>
<td>6 weeks</td>
<td>6 weeks</td>
<td>52 weeks</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Setting</td>
<td>Inpatient</td>
<td>Inpatient</td>
<td>Outpatient</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Dosing type</td>
<td>Fixed</td>
<td>Fixed</td>
<td>Flexible</td>
<td>Flexible</td>
</tr>
<tr>
<td>Ulotaront dosing</td>
<td>50 mg, 75 mg</td>
<td>75 mg, 100 mg</td>
<td>25-100 mg</td>
<td>50-100 mg</td>
</tr>
<tr>
<td>Comparators</td>
<td>Placebo</td>
<td>Placebo</td>
<td>None (open-label)</td>
<td>Quetiapine XR 400-800 mg</td>
</tr>
<tr>
<td>Population</td>
<td>Acutely psychotic</td>
<td>Acutely psychotic</td>
<td>Rollover patients from 301 &amp; 302</td>
<td>Stable patients</td>
</tr>
<tr>
<td>Age</td>
<td>13-65 years</td>
<td>18-65 years</td>
<td></td>
<td>18-65 years</td>
</tr>
<tr>
<td>Randomization ratio</td>
<td>1:1:1</td>
<td>1:1:1</td>
<td></td>
<td>2:1 (ulotaront:QXR)</td>
</tr>
<tr>
<td>Sample size</td>
<td>525</td>
<td>462</td>
<td>555</td>
<td>300</td>
</tr>
</tbody>
</table>

OLE = open-label extension; QXR = quetiapine extended release.
Clinical Implications

- TAAR1 agonists appear to be free of motoric adverse effects, do not adversely impact weight/metabolic variables, do not increase prolactin, do not prolong the ECG QTc interval, and are largely devoid of sedation.
- Should they be proven to work in reducing symptoms, they will be a compelling choice.
- Will they be used first-line? Later-line? Monotherapy? Combination therapy?
- How do we explain this new class of anti-schizophrenia medication?

Panel Q&A
Posttest Survey