Comparative Clinical Effectiveness of KarXT and Selective Second-Generation Antipsychotics for the Treatment of Schizophrenia: Literature Review and Network Meta-Analysis

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Introduction

- KarXT (Karuna Therapeutics) is an oral therapy taken twice daily in development for the treatment of schizophrenia.
- It combines xanomeline, which targets CNS muscarinic receptors (M1 and M4 receptor agonists), with trospium, which reduces the peripheral side effects of muscarinic receptor activation.

Objective

- To evaluate the comparative effectiveness of KarXT compared to three second-generation oral antipsychotics (aripiprazole, risperidone, and olanzapine) for the treatment of schizophrenia.

Methods

- We systematically identified 33 RCTs of KarXT, aripiprazole, risperidone, and olanzapine that enrolled individuals for treatment of acute exacerbations of schizophrenia.
- We conducted random-effects Bayesian NMAs, and results are presented as relative risk or mean difference.
- Main outcomes were PANSS response [defined as >30% improvement PANSS score], weight gain, and all-cause discontinuation. All outcomes were evaluated between three and eight weeks.
- Long-term comparative data on KarXT was not available at the time of our review.

Results

- All antipsychotics had significant changes in PANSS response compared to placebo, but no statistically significant differences between the active treatments were found.
- KarXT had significantly less weight gain compared to olanzapine and risperidone.
- KarXT had numerically higher all-cause discontinuation than the three comparators and placebo, but the differences were only statistically significant compared with olanzapine and risperidone.

Figure 1. Overall Network Diagram (33 trials)

A thicker line signifies more trials for each comparison.

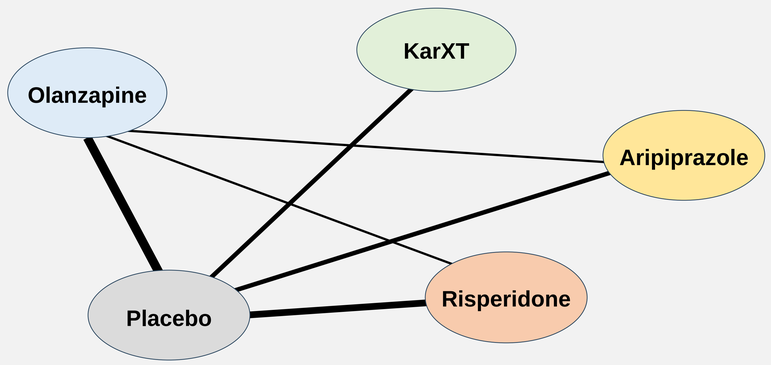

Table 1. PANSS Response (>30% improvement)

KarXT				
1.48 (0.91, 2.47)	Aripiprazole			
1.22 (0.78, 1.98)	0.83 (0.55, 1.24)	Olanzapine		
1.03 (0.62, 1.8)	0.7 (0.44, 1.14)	0.85 (0.56, 1.29)	Risperidone	
2.03 (1.4, 3.06)	**1.37 (1.01, 1.88)**	**1.66 (1.28, 2.17)**	**1.96 (1.36, 2.83)**	Placebo

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1.

Table 2. Change from Baseline in Weight, kg

KarXT				
-0.64 (-1.88, 0.59)	Aripiprazole			
-2.86 (-3.97, -1.82)	**-2.23 (-3.12, -1.39)**	Olanzapine		
-2.06 (-3.29, -0.87)	**-1.43 (-2.51, -0.36)**	0.8 (-0.06, 1.7)	Risperidone	
-0.37 (-1.34, 0.58)	0.26 (-0.52, 1.04)	**2.49 (2.02, 3)**	**1.69 (0.96, 2.43)**	Placebo

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0.

Table 3. All-cause Discontinuation

KarXT				
1.39 (1, 1.94)	Aripiprazole			
1.67 (1.21, 2.29)	1.2 (0.99, 1.44)	Olanzapine		
1.58 (1.14, 2.2)	1.14 (0.91, 1.42)	0.95 (0.78, 1.15)	Risperidone	
1.19 (0.89, 1.59)	0.86 (0.72, 1.01)	**0.71 (0.63, 0.81)**	**0.75 (0.65, 0.88)**	Placebo

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1.

Key Takeaways

- KarXT provides similar clinical benefits to other second-generation antipsychotics commonly used in clinical practice with the potential for less weight gain.
- There is uncertainty around the long-term use of KarXT in an outpatient setting as only short-term inpatient trials with limited data on tardive dyskinesia or metabolic syndrome are available.

Acronyms

CNS: central nervous system, kg: Kilogram, NMA: Network meta-analysis, PANSS: Positive and negative syndrome scale, RCT: Randomized controlled trial.

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