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Supplementary Material

Article Title: Antipsychotic Efficacy of KarXT (Xanomeline–Trospium): Post Hoc Analysis of Positive and Negative Syndrome Scale Categorical Response Rates, Time Course of Response, and Symptom Domains of Response in a Phase 2 Study

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Supplementary Material

Supplementary Table 1. Original Positive and Negative Syndrome Scale (PANSS) Based on 3 Factors (Positive Symptoms, Negative Symptoms, General Symptoms)

Item Number (1-30)	Item Number (Positive, Negative, General)	Item Name	What It Measures
Original PANSS Positive Symptom Subscale			
1	P1	Delusion	Delusions
2	P2	Conceptual disorganization	Speech is confusing, hard to follow
3	P3	Hallucinatory behavior	Hallucinations
4	P4	Excitement	Over arousal, outbursts, hyperactivity
5	P5	Grandiosity	Unrealistic beliefs of superiority, abilities, fame, etc
6	P6	Suspiciousness/persecution	Paranoid ideation and experience of persecution
7	P7	Hostility	Anger, resentment, up to assaultive behavior
Original PANSS Negative Symptom Subscale			
8	N1	Blunted affect	Reduced or absent facial expressions
9	N2	Emotional withdrawal	Lack of interest in life
10	N3	Poor rapport	In context, disengaged with interviewer
11	N4	Passive social withdrawal	Reduced or absent social functioning due to apathy and indifference to relationships
12	N5	Difficulty with abstract thinking	Concrete thinking (this is no longer considered a negative symptom; legacy item)
13	N6	Lack of spontaneity and flow of conversation	Conversation stilted, only minimal replies to questions
14	N7	Stereotyped thinking	Little thought content, repetitive or perseverative (also no longer considered a negative symptom)
Original PANSS General Symptom Subscale			
15	G1	Somatic concern	Worry about real or imagined health problems
16	G2	Anxiety	Subjective report of anxiety
17	G3	Guilt feelings	Self-blame, remorse may be accurate or delusional
18	G4	Tension	Physical manifestations of anxiety
19	G5	Mannerisms and posturing	Abnormal movements or postures
20	G6	Depression	Sadness, pessimism, etc
21	G7	Motor retardation	Reduction in general physical movements

22	G8	Uncooperativeness	Lack of cooperation, resentment, etc
23	G9	Unusual thought content	Bizarreness of delusions
24	G10	Disorientation	Unaware of surroundings
25	G11	Poor attention	Poor concentration, distractible
26	G12	Lack of judgment and insight	Not aware of condition or situation
27	G13	Disturbance of volition	Indecision, unable to start anything
28	G14	Poor impulse control	Inappropriate behaviors
29	G15	Preoccupation	Self-absorbed with internal experiences
30	G16	Active social avoidance	Differs from passive social withdrawal because this is caused by paranoia not apathy

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261-276.

Supplementary Table 2. Positive and Negative Syndrome Scale (PANSS) 5 “Marder” Factors (Positive Symptoms, Negative Symptoms, Disorganized Thought, Hostility/Excitement, and Depression/Anxiety)

Original PANSS Item Number (1-30)	Original PANSS Item Number (Positive, Negative, General)	Item Name	What It Measures
Marder Positive Symptom Subscale (8 Items)			
1	P1	Delusion	Delusions
3	P3	Hallucinatory behavior	Hallucinations
5	P5	Grandiosity	Unrealistic beliefs of superiority, abilities, fame, etc
6	P6	Suspiciousness/persecution	Paranoid ideation and experience of persecution
14	N7	Stereotyped thinking	Little thought content, repetitive or perseverative (no longer considered a negative symptom)
15	G1	Somatic concern	Worry about real or imagined health problems
23	G9	Unusual thought content	Bizarreness of delusions
28	G12	Lack of insight	No insight
Marder Negative Symptom Subscale (7 Items)			
8	N1	Blunted affect	Reduced or absent facial expressions
9	N2	Emotional withdrawal	Lack of interest in life
10	N3	Poor rapport	In context, disengaged with interviewer
11	N4	Passive social withdrawal	Reduced or absent social functioning due to apathy and indifference to relationships
13	N6	Lack of spontaneity and flow of conversation	Conversation stilted, only minimal replies to questions
21	G7	Motor retardation	Reduction in general physical movements
30	G16	Active social avoidance	Differs from passive social withdrawal because this is caused by paranoia not apathy
Marder Disorganized Thought (7 Items)			
2	P2	Conceptual disorganization	Speech is confusing, hard to follow
12	N5	Difficulty with abstract thinking	Concrete thinking (no longer considered a negative symptom; legacy item)

19	G5	Mannerisms and posturing	Abnormal movements or postures
24	G10	Disorientation	Unaware of surroundings
25	G11	Poor attention	Poor concentration, distractible
27	G13	Disturbance of volition	Indecision, unable to start anything
29	G15	Preoccupation	Self-absorbed with internal experiences
Marder Uncontrolled Hostility/Excitement (4 Items)			
4	P4	Excitement	Over arousal, outbursts, hyperactivity
7	P7	Hostility	Anger, resentment, up to assaultive behavior
22	G8	Uncooperativeness	Lack of cooperation, resentment, etc
28	G14	Poor impulse control	Inappropriate behaviors
Marder Depression/Anxiety (4 Items)			
16	G2	Anxiety	Subjective report of anxiety
17	G3	Guilt feelings	Self-blame, remorse may be accurate or delusional
18	G4	Tension	Physical manifestations of anxiety
20	G6	Depression	Sadness, pessimism, etc

Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry*. 1997;58(12):538-546.

Supplementary Table 3. Patient Baseline Demographics¹

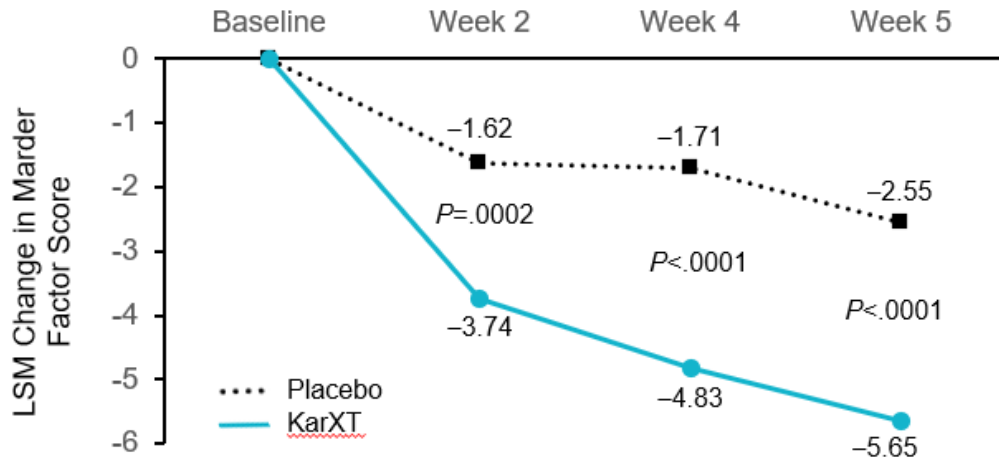
Characteristic	KarXT (n=83)	Placebo (n=87)
Age (y), mean ± SD	43.7 ± 10.0	41.8 ± 10.0
Male sex, n (%)	67 (81)	64 (74)
PANSS total score, mean ± SD	97.3 ± 9.34	96.6 ± 8.39
PANSS Marder 5-factor baseline scores, mean ± SD		
Positive symptom factor	30.8 ± 3.8	30.6 ± 3.5
Negative symptom factor	22.3 ± 4.6	22.4 ± 5.1
Disorganized thought factor	22.1 ± 4.0	22.3 ± 4.1
Hostility/excitement factor	9.7 ± 2.9	9.5 ± 2.5
Depression/anxiety factor	12.4 ± 2.8	11.9 ± 3.1
CGI-S score, mean ± SD	5.0 ± 0.6	4.9 ± 0.6

Abbreviations: CGI-S=Clinical Global Improvement–Severity, PANSS=Positive and Negative Syndrome Scale, SD=standard deviation.

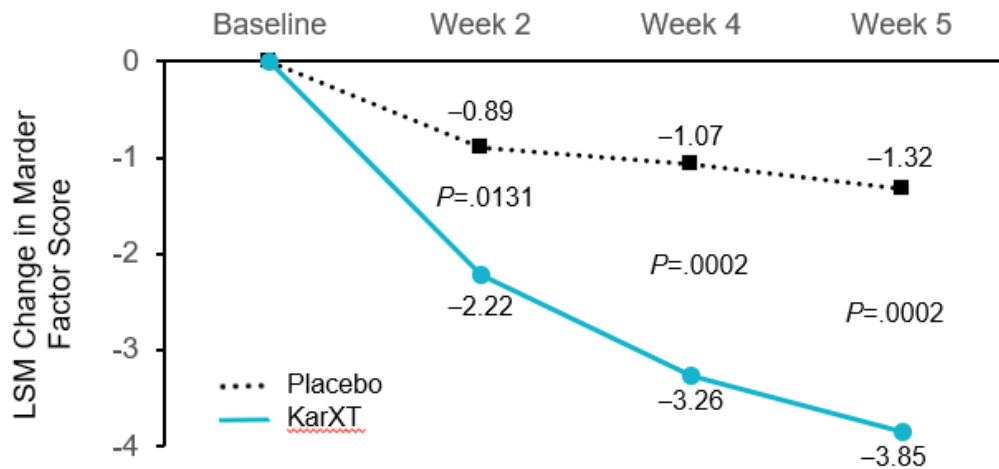
1. Brannan S, Breier A, Weiden PJ, Paul S, Miller A. The M1/M4 agonist xanomeline in combination with trospium is effective for acute treatment of schizophrenia: PANSS responder and PANSS 5-factor analyses of a phase 2 placebo-controlled inpatient trial. Presented at: Schizophrenia International Research Society Virtual Congress; pril 17-21, 2021.

Supplementary Figure 1. Effect of KarXT on the Symptom Domains of (A) Marder Positive Symptom factor and (B) Marder Negative Symptom factor*

A. Positive Symptoms



B. Negative Symptoms



Abbreviation: LSM=least squares means.

*Disorganized thought, uncontrolled hostility, and depression/anxiety factors are published in the manuscript (Figure 3).