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ZUCKER SCHOOL *of* MEDICINE
AT HOFSTRA/NORTHWELL

From Inertia to Action: Integrating Muscarinic Therapies into Schizophrenia Practice

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Disclosures

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I am an advisor to TEVA, have received honoraria from Jannsen (relationship has ended), have received consulting fees from Bristol-Myers Squibb (relationship has ended), I have been independent contractor to Neurocrine (relationship has ended), I am co-Principal Investigator in an investigator initiated study sponsored by Bristol-Myers Squibb, I have received research awards from Neurocrine (relationship has ended).

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Outline

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Section 1: D2 No More? From Trials to Treatment: The Evidence Behind Muscarinic Therapies

Section 2: Breaking Clinical Inertia: Integrating Muscarinic Agents into Care Pathways

Section 3: Clinical Pearls for Optimizing Muscarinic Therapy Outcomes

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D2 receptor antagonism

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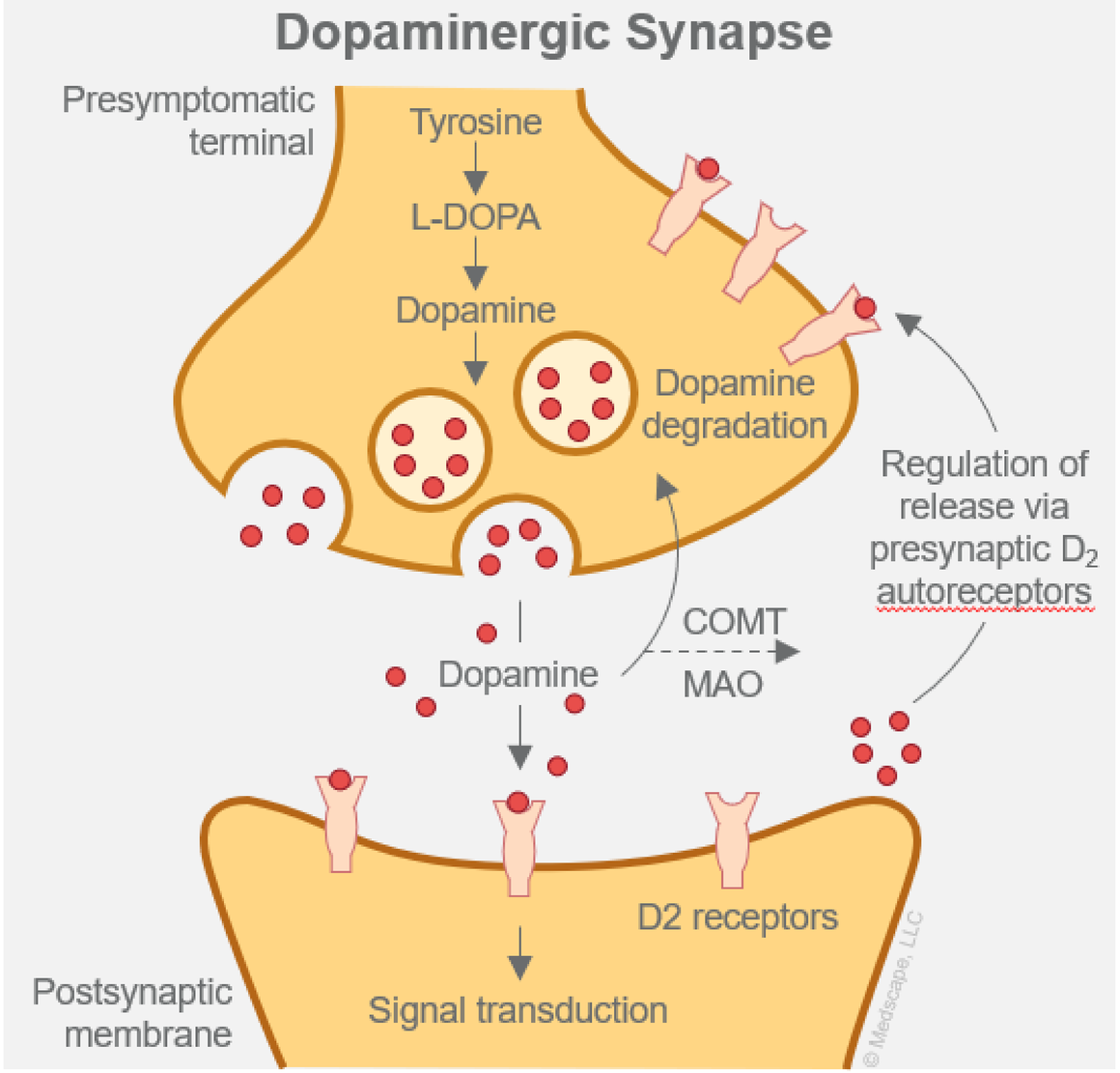

Positive symptoms associated with excessive striatal dopamine release

D2 receptors present on presynaptic AND postsynaptic neurons

Presynaptic D2 receptors are inhibitory autoreceptors

D2 receptor antagonists "release the brake" when they block presynaptic D2 receptors

Disinhibiting presynaptic dopamine release

D2 receptor antagonist antipsychotics must occupy 65% to 80% of postsynaptic receptors

To compensate for increased presynaptic dopamine release

Meyer JM. In: Brunton LL, et. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill; 2022:357-384.

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Conventional and atypical antipsychotics

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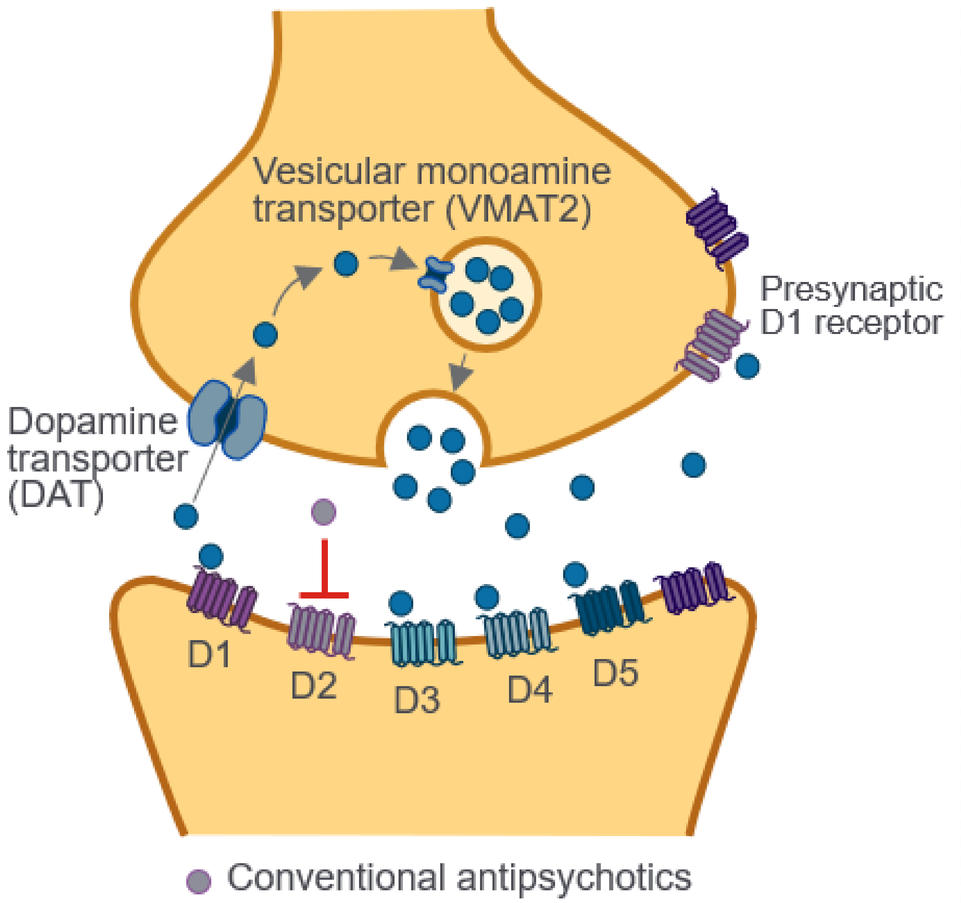
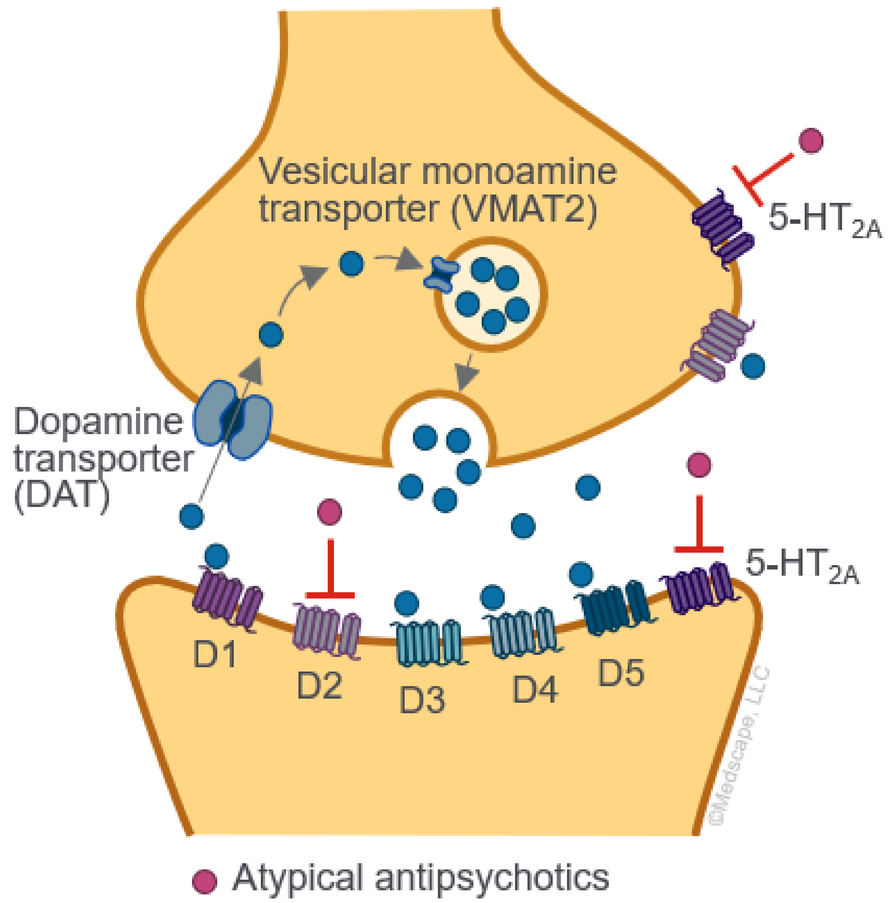
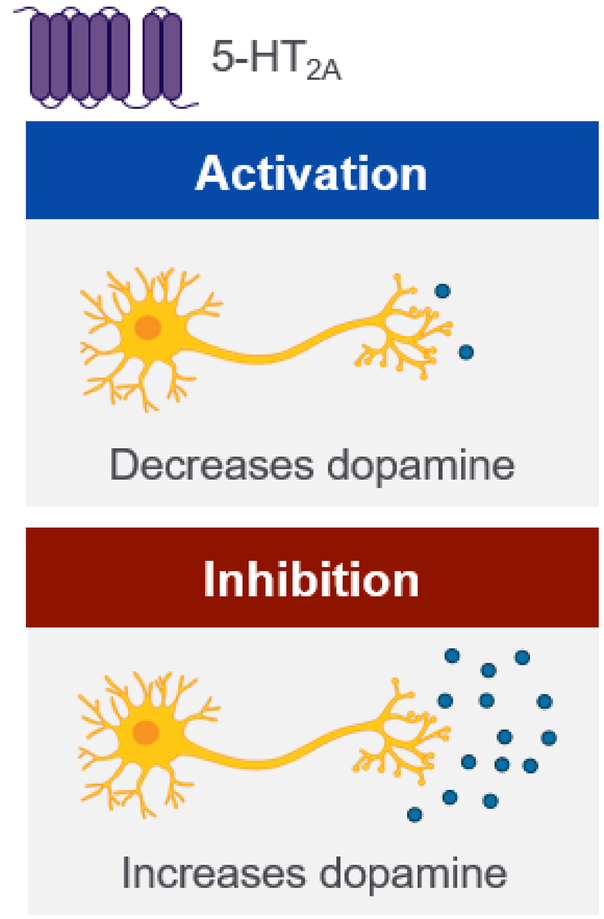
Reduce positive symptoms

Conventional Antipsychotics
(block dopamine D2 receptors)



Atypical Antipsychotics
(block dopamine D2 receptors and serotonin 5-HT2A receptors)





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Dopaminergic pathways

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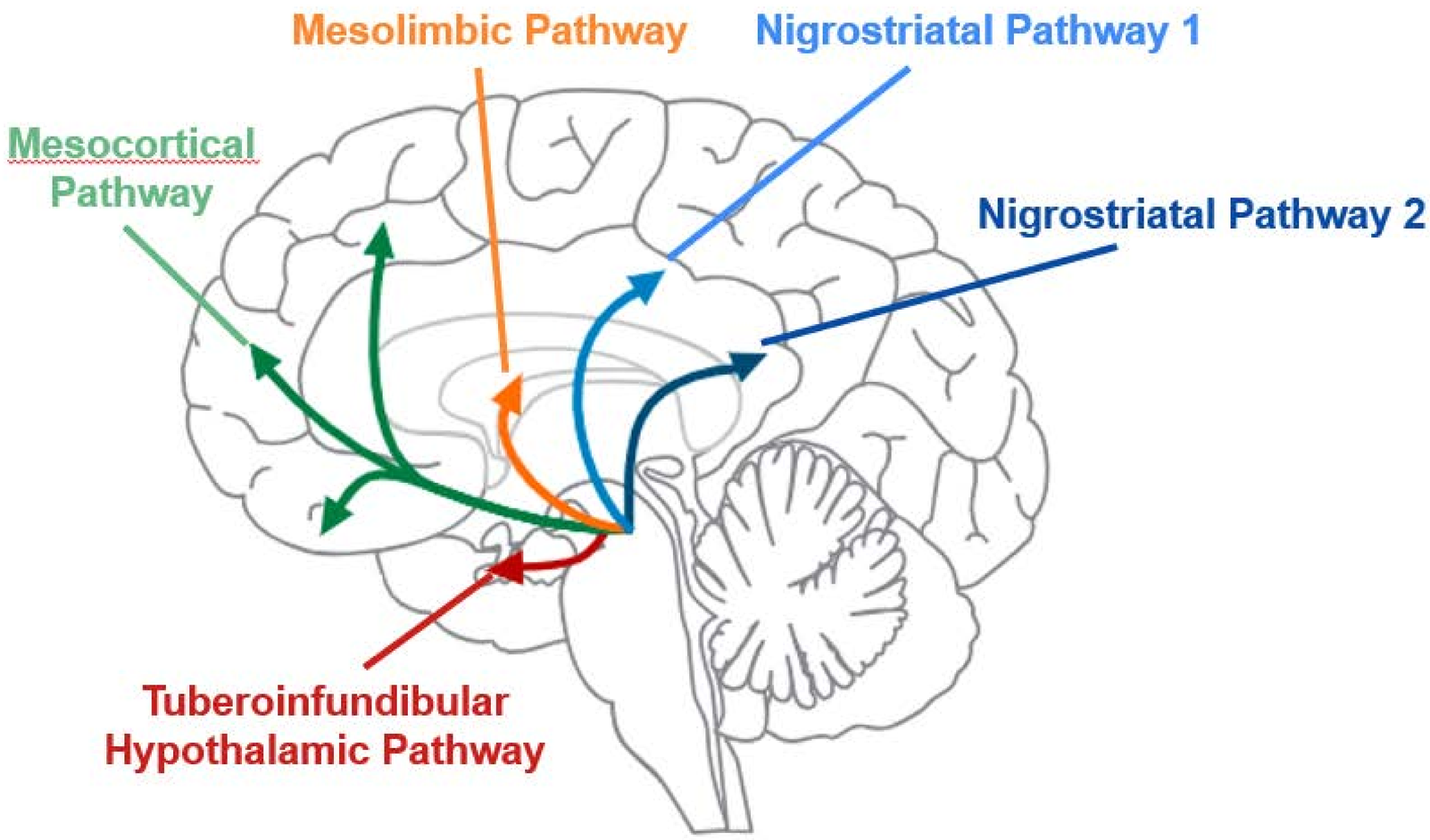

Mesocortical Pathway
Negative symptoms, cognitive impairment, depression

Mesolimbic Pathway
Negative symptoms

Nigrostriatal Pathway 1
Psychosis

Nigrostriatal Pathway 2
Dystonia, akinesia, rigidity, tremor, dyskinesia

Tuberoinfundibular Hypothalamic Pathway
Prolactin elevation, amenorrhea, galactorrhea, sexual dysfunction

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D2R blocking AP limitations

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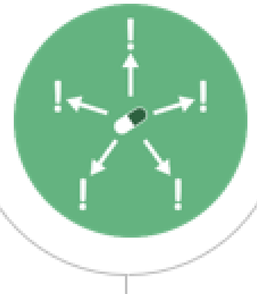
High rates of discontinuations

- Up to 67% of patients discontinue medication during first year of treatment
- Lack of efficacy a common reason

Treatment resistance

- Ranging from 23% in patients with first-episode psychosis to 56% in patients with chronic schizophrenia

Inefficacy against negative and cognitive symptoms



Intolerability

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D2R blocking AP side effects

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- Hyperprolactinemia
- Extrapyramidal symptoms
- Weight gain
- Somnolence
- Secondary negative and cognitive symptoms

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Newer antidopaminergic APs

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Agent	Antagonist(s)	Partial Agonist(s)	Other
Aripiprazole	5-HT2A	D2, 5-HT1A	
Asenapine	D2, 5-HT2A, 5-HT2C, 5-HT7		Affinity for α1 and α2 receptors; No affinity for muscarinic receptors
Lurasidone	D2, 5-HT2A, 5-HT2B, 5-HT7	5-HT1A	
Brexpiprazole	5-HT2A	D2, 5-HT1A	
Cariprazine	5-HT2A, 5-HT2B, 5-HT7	D2, D3, 5-HT1A	
Lumateperone	D2 (postsynaptic), 5-HT2A	D2 (presynaptic)	Phosphorylation at GluN2B receptors; D1-regulated NMDA and AMPA agonist
Olanzapine + Samidorphan	D2, 5-HT2A, μ-opioid receptors		κ- and δ-opioid receptors

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Drugs in the pipeline for the treatment of schizophrenia

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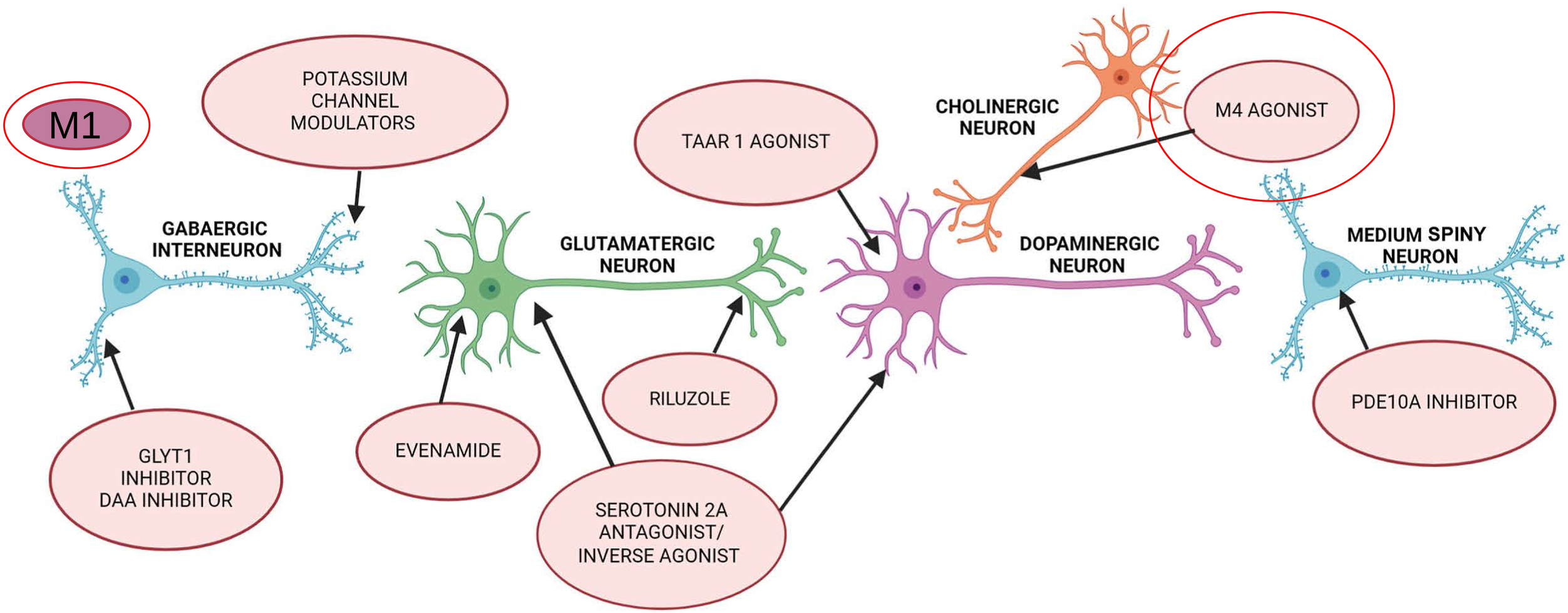

Howes et al. Biol Psychiatry 2024

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Cholinergic system and schizophrenia

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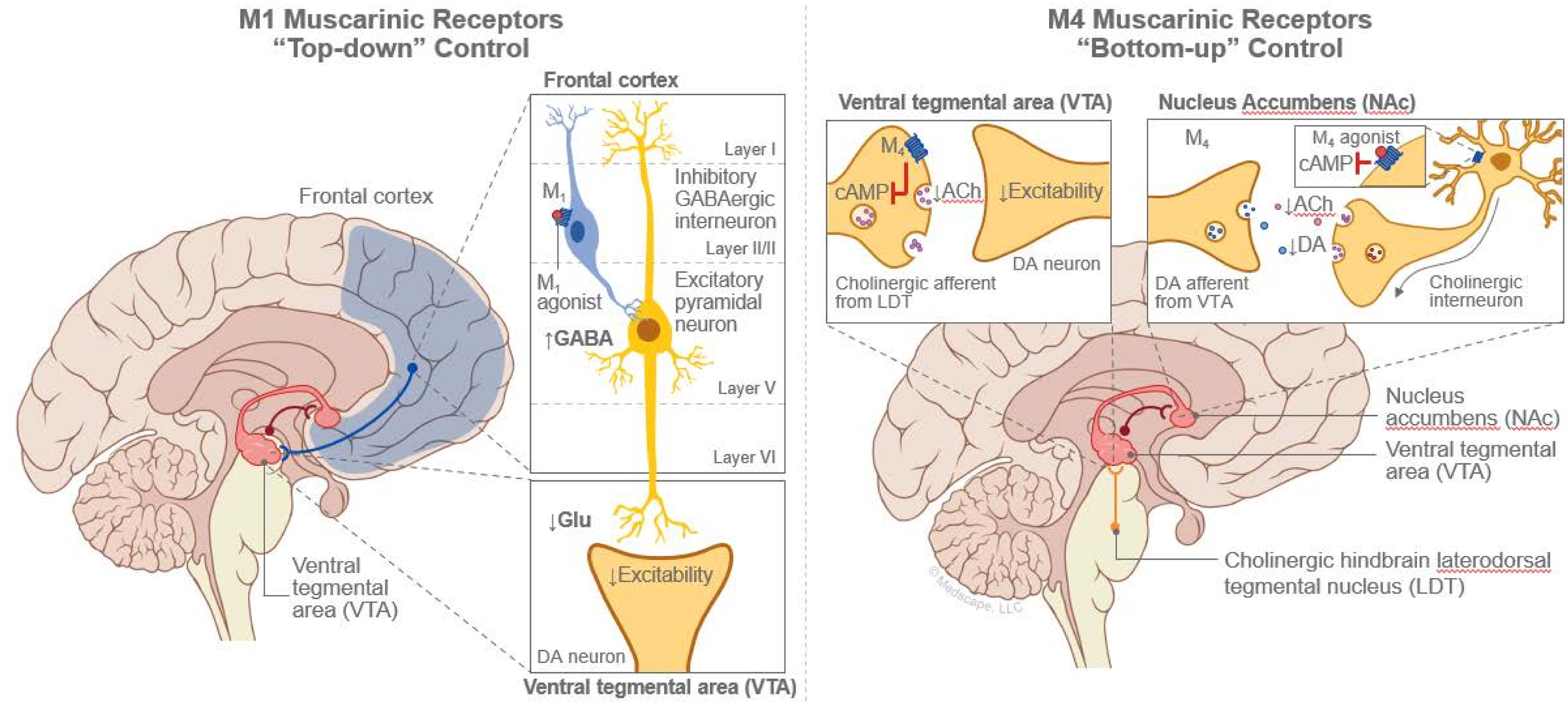

Paul SM, et al. Am J Psychiatry. 2022;179:611-627.

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Study design of EMERGENT trials

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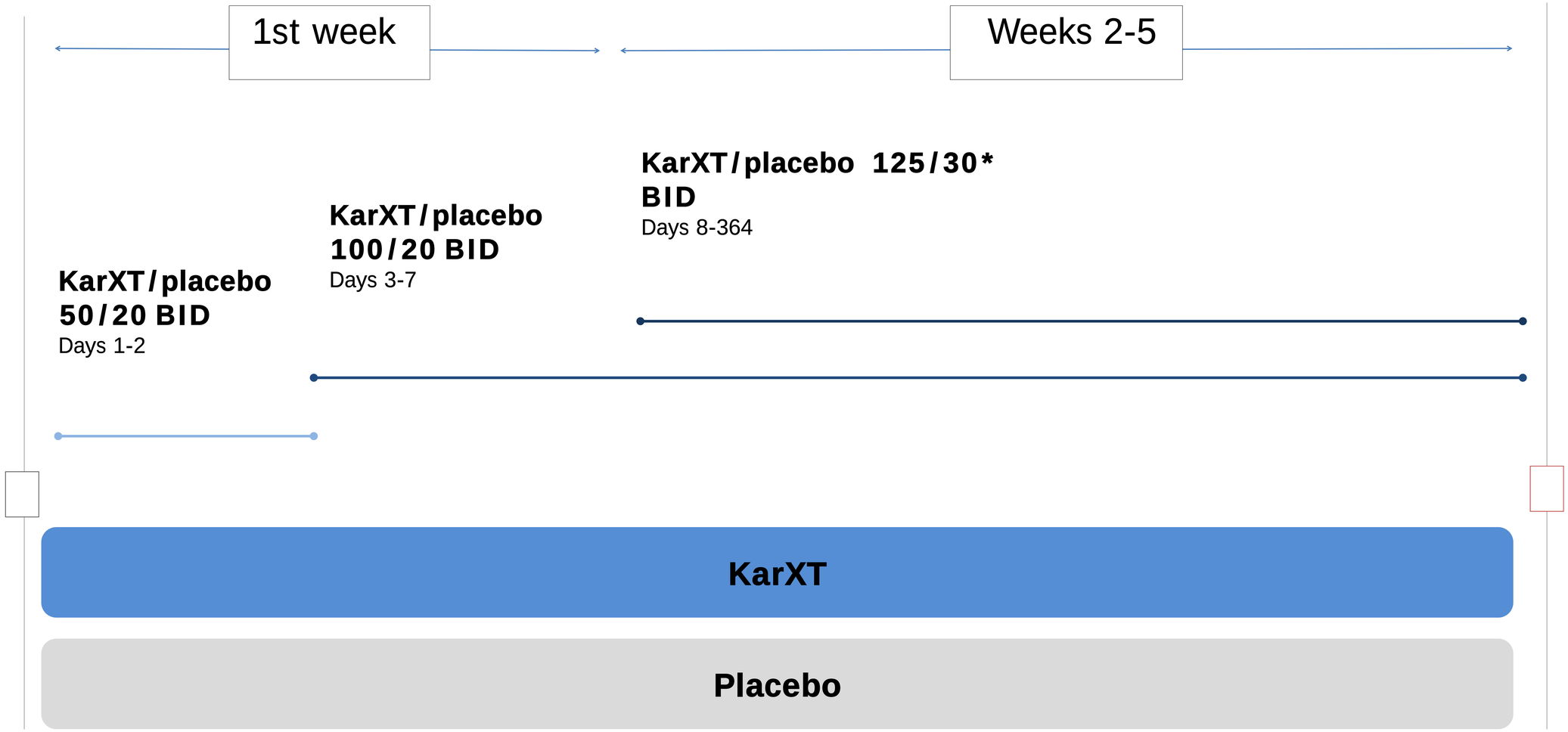
Double-blind Inpatient Treatment Period



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Main result of EMERGENT phase 3 trials

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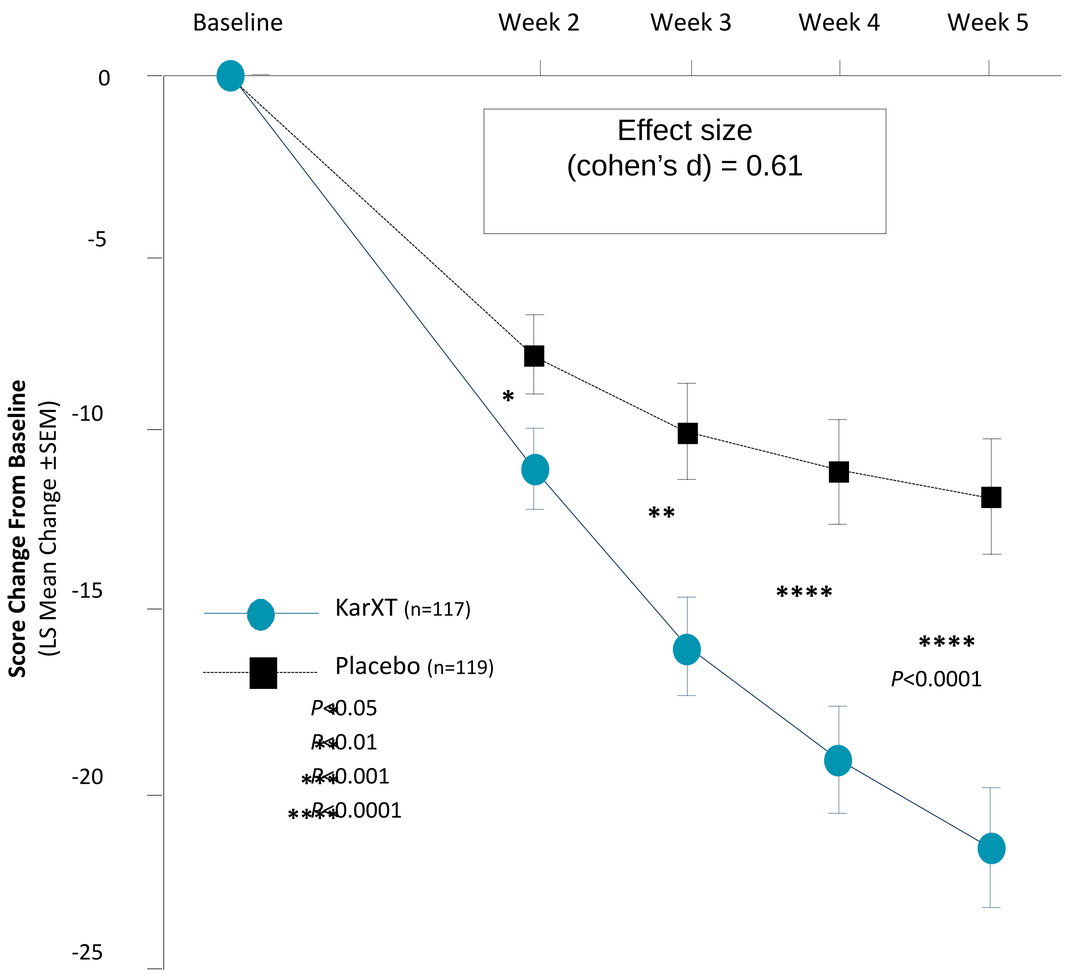
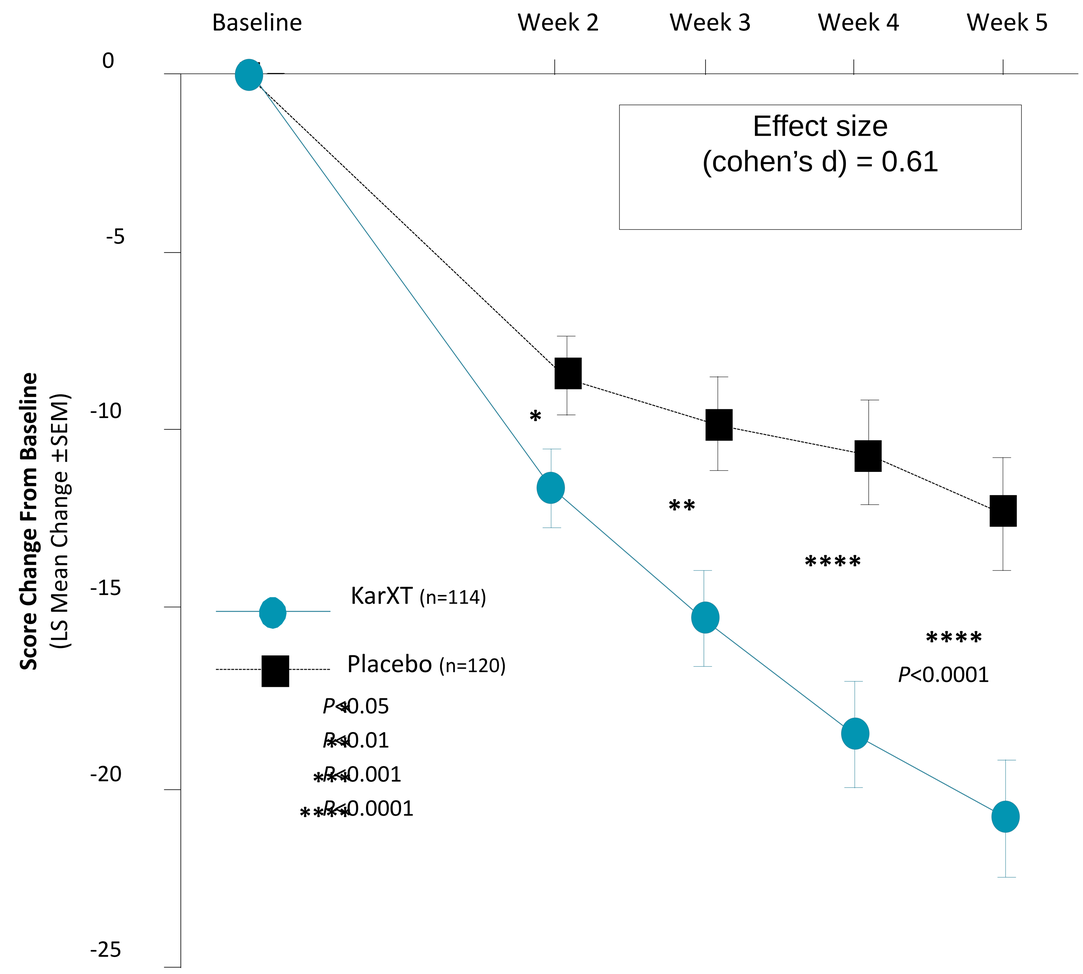
EMERGENT-2[1]



9.6-point placebo-adjusted reduction at Week 5
(-21.2 KarXT vs -11.6 placebo)

EMERGENT-3[2]



8.4-point placebo-adjusted reduction at Week 5
(-20.6 KarXT vs -12.2 placebo)

Kaul I et al. Lancet 2024, Brannan et al. N Engl J Med 2021

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Main result of EMERGENT phase 3 trials: Cognition

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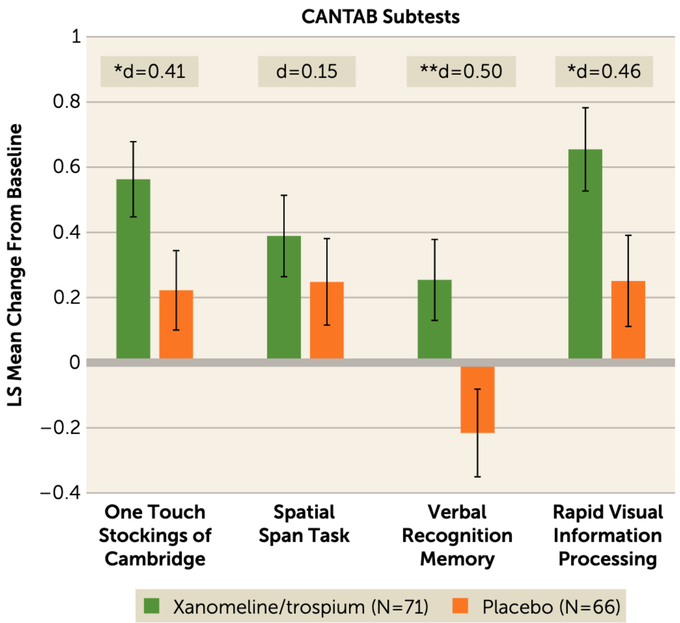

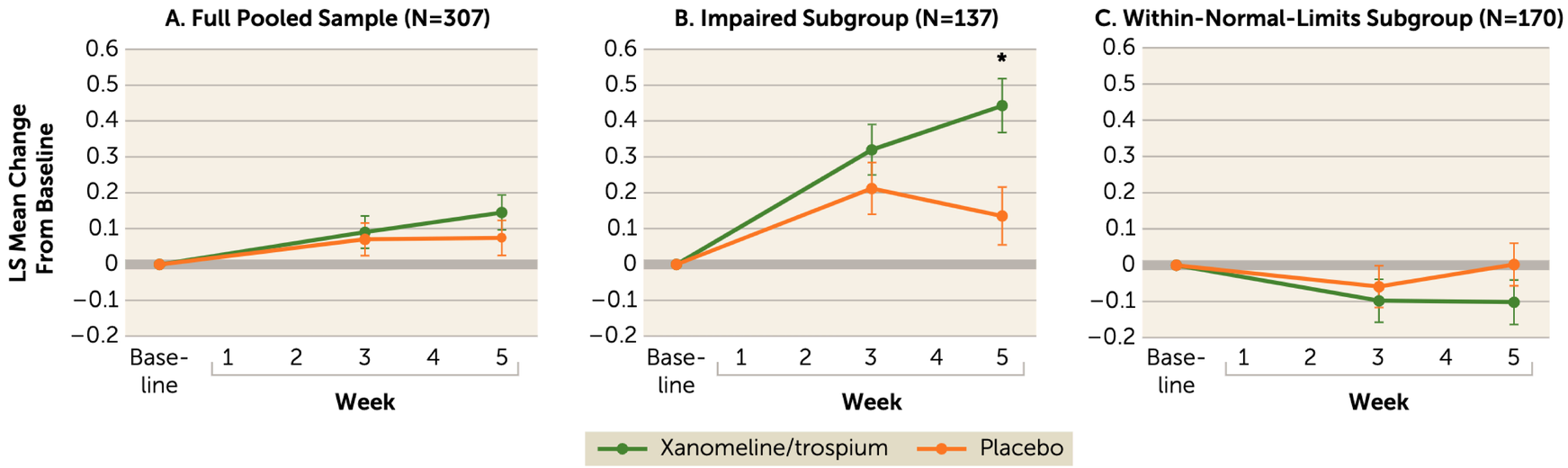

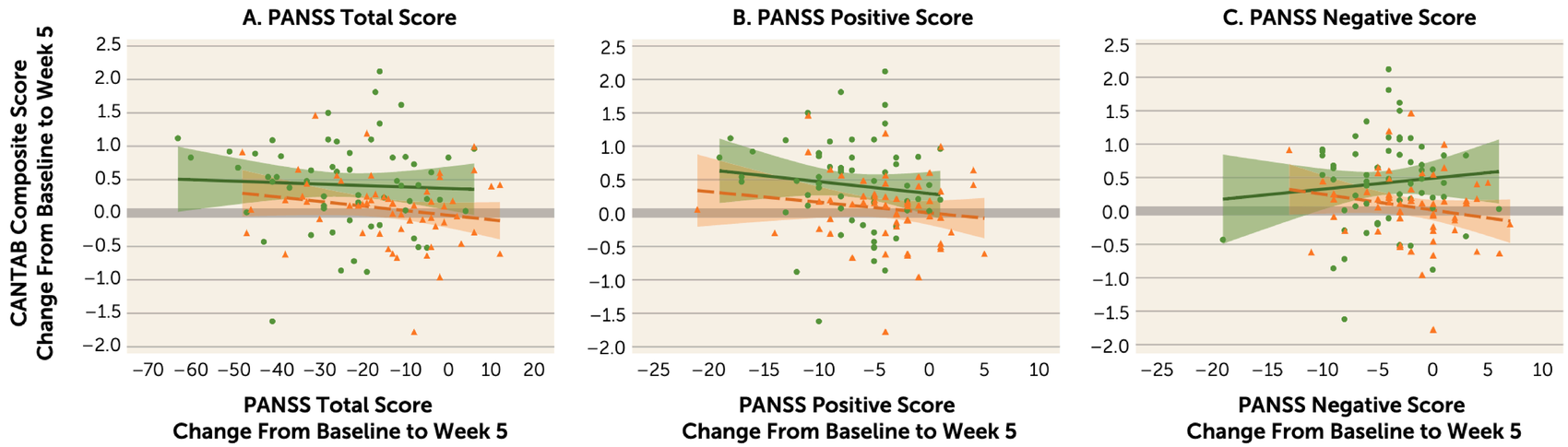

Harvey et al. Am J Psychiatry 2025

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Main result of EMERGENT phase 3 trials: Negative symptoms

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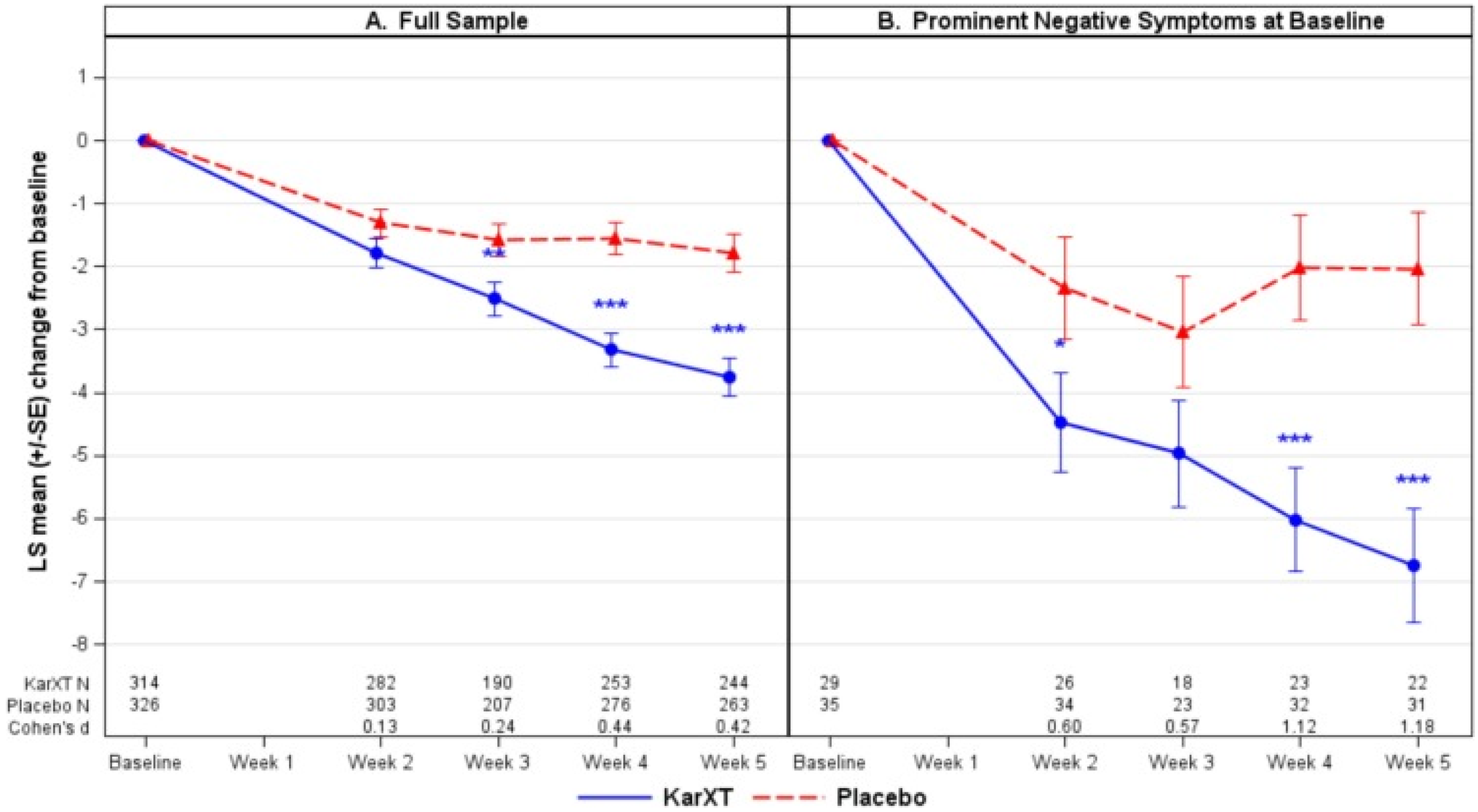

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Side effect profile

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Adverse Events, n (%)	KarXT (n=89)	Placebo (n=90)
Any TEAE	48 (53.9%)	39 (43.3%)
Serious TEAE	1 (1.1%)[a]	0 (0%)
Severe TEAE	1 (1.1%)[a]	1 (1.1%)[b]
TEAE leading to study discontinuation	2 (2.2%)[c]	2 (2.2%)[d]
Most common AEs (≥5% KarXT arm)		
Constipation	15 (16.9%)	3 (3.3%)
Nausea	15 (16.9%)	4 (4.4%)
Dry mouth	8 (9.0%)	1 (1.1%)
Dyspepsia	8 (9.0%)	4 (4.4%)
Vomiting	8 (9.0%)	4 (4.4%)
Headache	6 (6.7%)	5 (5.6%)
Somnolence	5 (5.6%)	4 (4.4%)

- No side effects associated with dopamine receptor antagonism
- Most AEs are pro-cholinergic (from xanomeline) like nausea or peripheral anticholinergic (from trospium) like constipation
- None of these were “deal breakers” for subjects in the study; no AE related discontinuation
- Because general effects of muscarinic agonists on heart rate and BP, a separate study will be done.

Brannan et al. N Engl J Med 2021

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Side effect profile

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Continuous outcomes	K	SMD (95% CI)†	I^2 (%)
Simpson–Angus Scale score	3	0.06 (–0.09, 0.21)	0
Barnes Akathisia Rating Scale score	3	0.01 (–0.14, 0.16)	0
Body weight	3	–0.10 (–0.30, 0.09)	41
Body mass index	2	–0.05 (–0.31, 0.20)	45
Systolic blood pressure	2	–0.14 (–0.50, 0.22)	72
Diastolic blood pressure	2	–0.09 (–0.34, 0.15)	38
QTc interval	2	–0.16 (–0.35, 0.03)	0
Serum total cholesterol	2	0.09 (–0.11, 0.29)	11
Serum triglyceride	2	0.22 (0.03, 0.41)	0
Blood glucose	2	0.02 (–0.17, 0.21)	0

Dichotomous outcomes	K	RR (95% CI)‡	I^2 (%)
All-cause discontinuation	3	1.20 (0.94, 1.55)	0
Discontinuation due to adverse events	3	1.42 (0.75, 2.72)	0
Discontinuation due to withdrawal of consent	3	1.37 (0.97, 1.93)	0
At least one adverse event	3	1.32 (1.17, 1.50)	0
Headache	3	1.06 (0.69, 1.65)	0
Somnolence	3	1.36 (0.60, 3.11)	0
Insomnia	3	0.68 (0.33, 1.39)	0
Dizziness	2	1.95 (0.78, 4.90)	2
Akathisia	3	1.29 (0.28, 6.01)	0
Agitation	2	0.58 (0.08, 4.33)	53
Dry mouth	2	4.31 (1.23, 15.11)	0
Tachycardia	2	0.62 (0.06, 6.26)	48
Hypertension	2	6.04 (1.78, 20.46)	0
Nausea	3	4.56 (2.29, 9.08)	23
Vomiting	3	7.81 (1.30, 46.94)	70
Dyspepsia	3	3.18 (1.36, 7.47)	49
Gastroesophageal reflux disease	2	7.94 (0.95, 66.30)	0
Diarrhea	3	1.66 (0.45, 6.12)	49
Constipation	3	2.65 (1.65, 4.27)	0
Increased weight	3	1.03 (0.39, 2.72)	0
Decreased appetite	2	3.99 (0.45, 35.85)	0

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Who may be good candidates for muscarinic antipsychotic treatment?

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- **Unsatisfaction with current treatment based on efficacy**
  - **Residual positive symptoms (ARISE)**

PANSS, PSP and CGI-S Change from Baseline by Treatment Group				
Endpoint	***XT* + APD**	**Placebo + APD**	**LSMD (95% CI)**	**p-value**
mITT Population, N	190	196		
Change in PANSS Total	-14.3 (1.01)	-12.2 (0.98)	-2.0 (-4.5, 0.5)	0.11
Change in PSP score	5.3 (0.75)	5.9 (0.73)	-0.6 (-2.4, 1.2)	0.52*
Change in CGI-S	-0.6 (0.06)	-0.5 (0.06)	-0.1 (-0.3, 0.04)	0.14*

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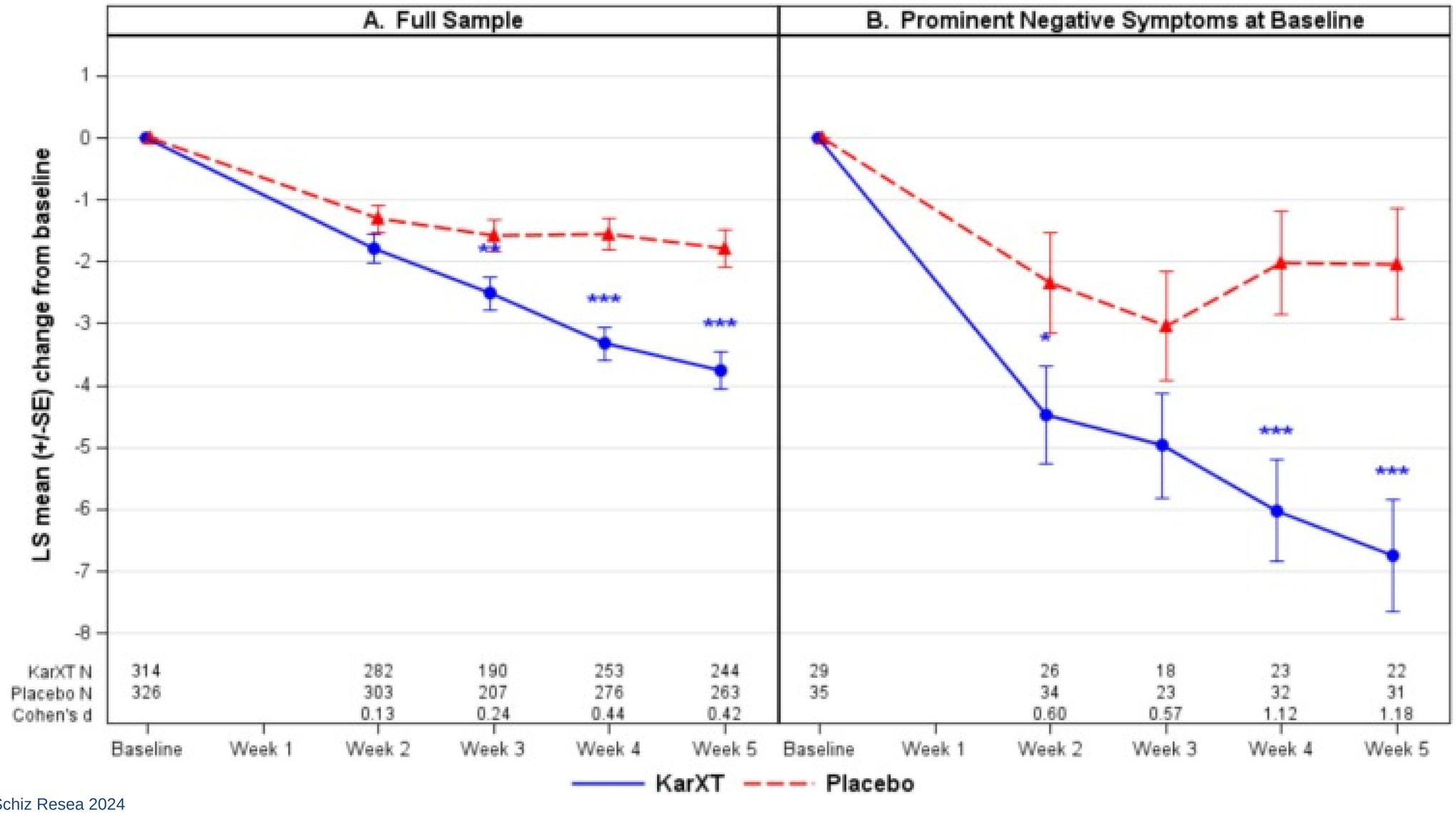
- **Unsatisfaction with current treatment based on efficacy**
  - **Positive symptoms**
  - **Negative symptoms**



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Who may be good candidates for muscarinic antipsychotic treatment?

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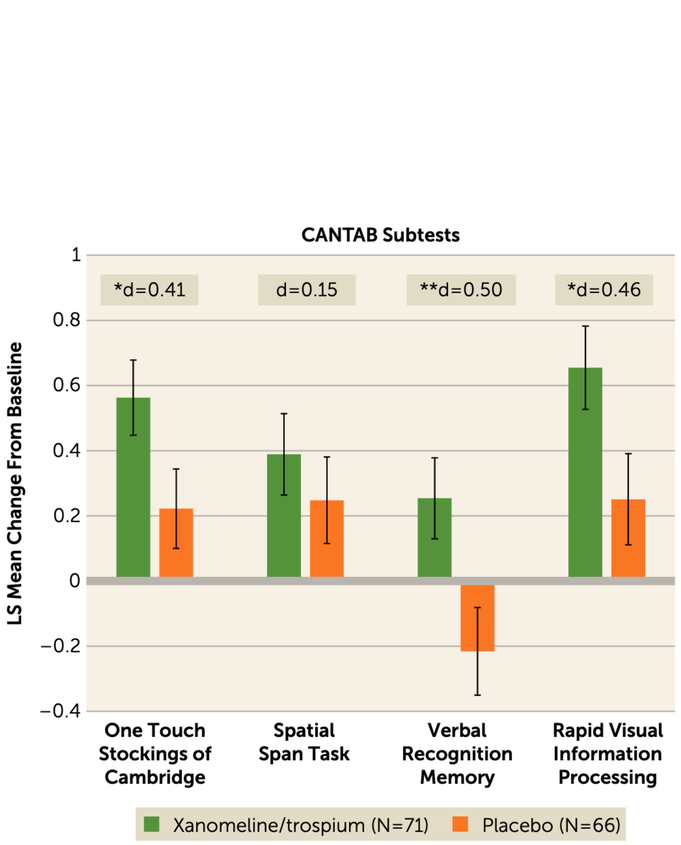
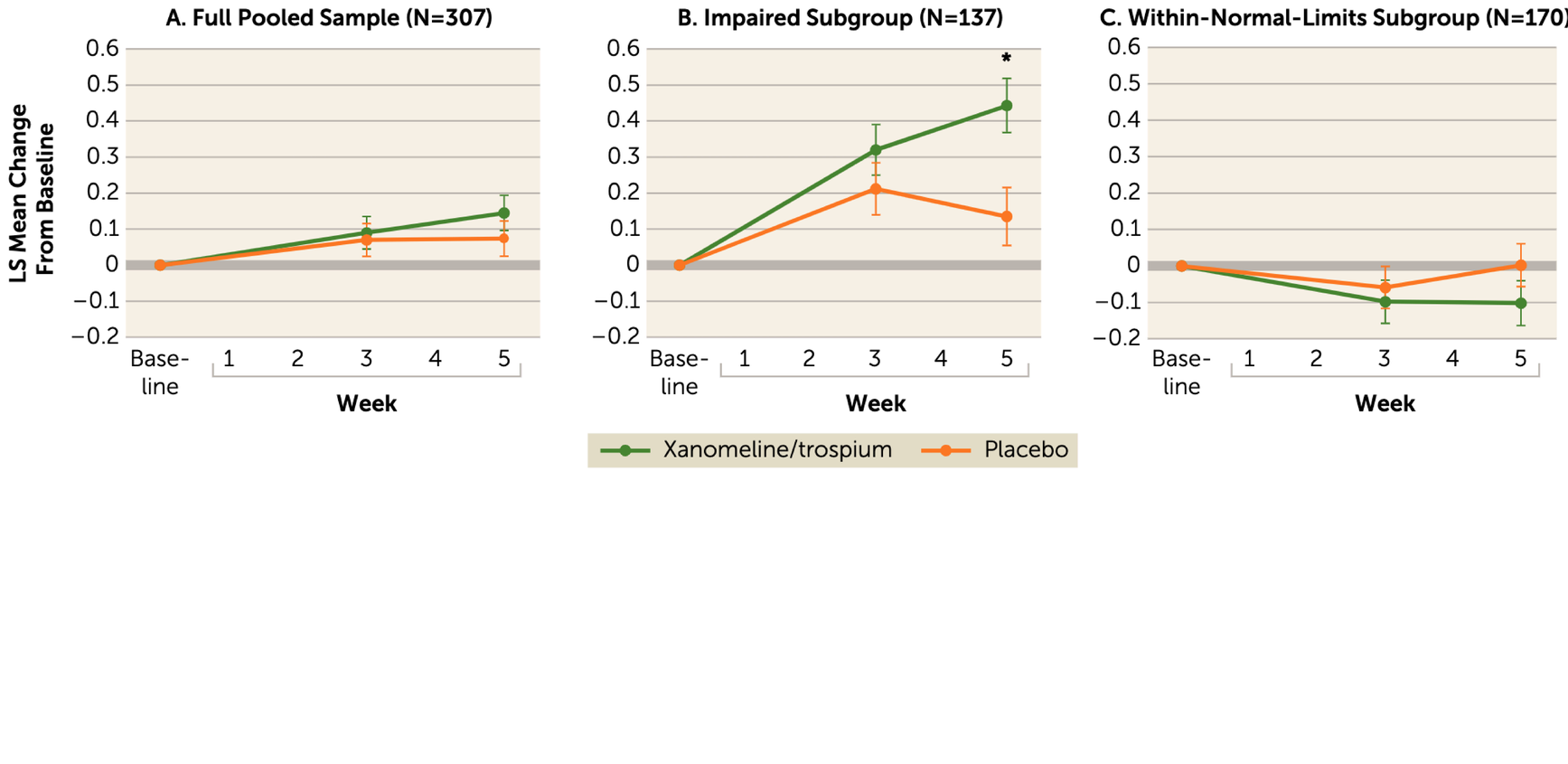
- **Unsatisfaction with current treatment based on efficacy**
  - Positive symptoms
  - Negative symptoms
  - **Cognitive symptoms**





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- **Unsatisfaction with current treatment based on side effects**
- Secondary negative/cognitive sx
- Hyperprolactinemia

Continuous outcomes	K	SMD (95% CI)†	I^2 (%)
Simpson–Angus Scale score	3	0.06 (–0.09, 0.21)	0
Barnes Akathisia Rating Scale score	3	0.01 (–0.14, 0.16)	0
Body weight	3	–0.10 (–0.30, 0.09)	41
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Who may be good candidates for muscarinic antipsychotic treatment?

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- **Other considerations**
  - **History of non-adherence with antipsychotic drugs**
  - **Ability to adhere to BID dosing on empty stomach**
  - **Chronic use of DA agents and risk of tardive dyskinesia**

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Dosing

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- For KarXT therapeutic doses are 100/20mg and 125/30mg. 50/20 is not considered a therapeutic dose

- BID dosing should be taken >1h before and >2h after eating. Failure to adhere to this may result in inadequate absortion of trospium, tipping the balance towards procholinergic side effects

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Titration schedule in EMERGENT trials

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KarXT 50/20 BID
Days 1-2

KarXT 100/20 BID
Days 3-7

KarXT/ 125/30 BID
Thereafter

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Monitoring of procholinergic side effects during titration

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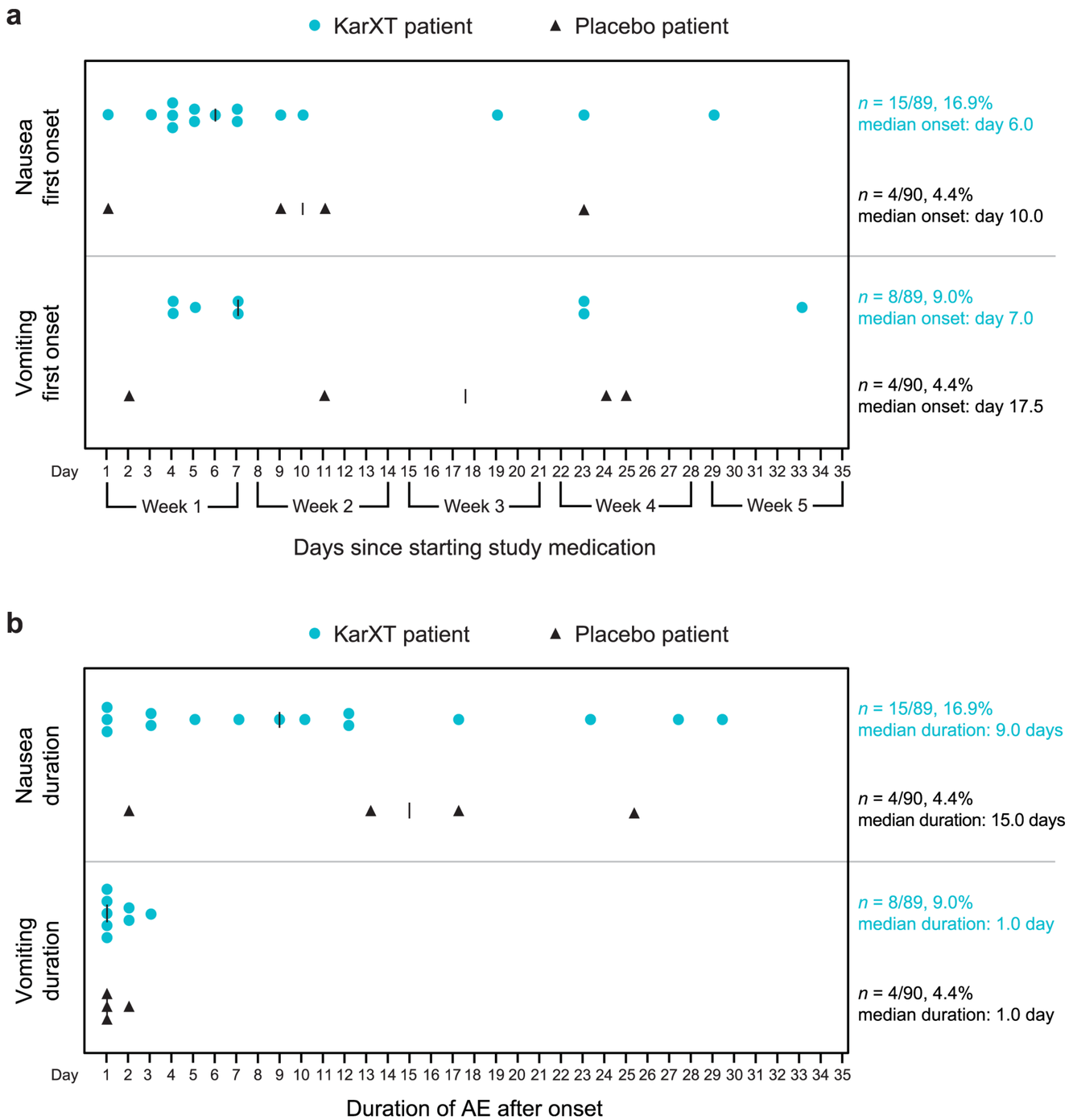

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Monitoring of anticholinergic side effects during titration

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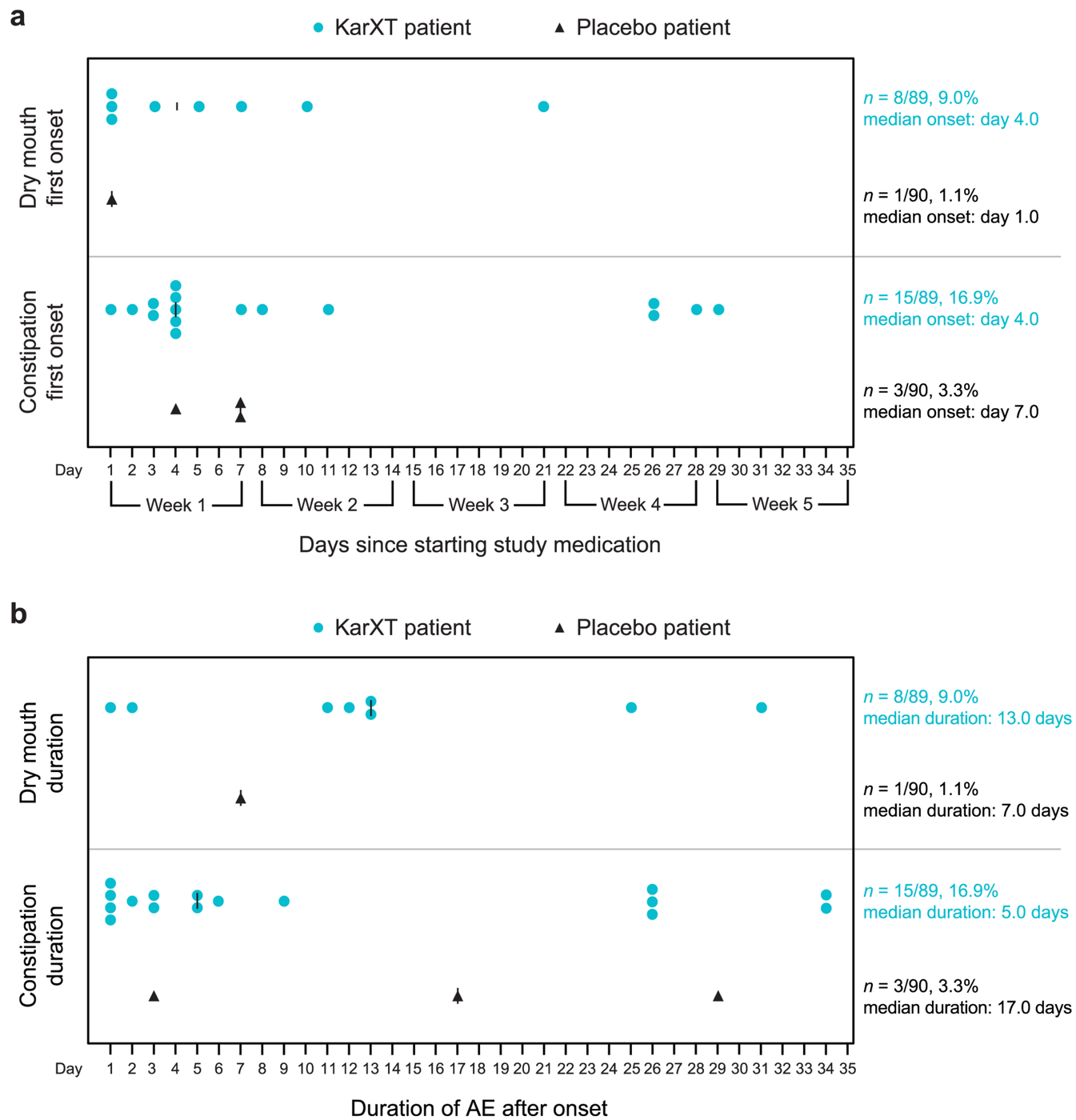

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Monitoring of cardiovascular side effects during titration

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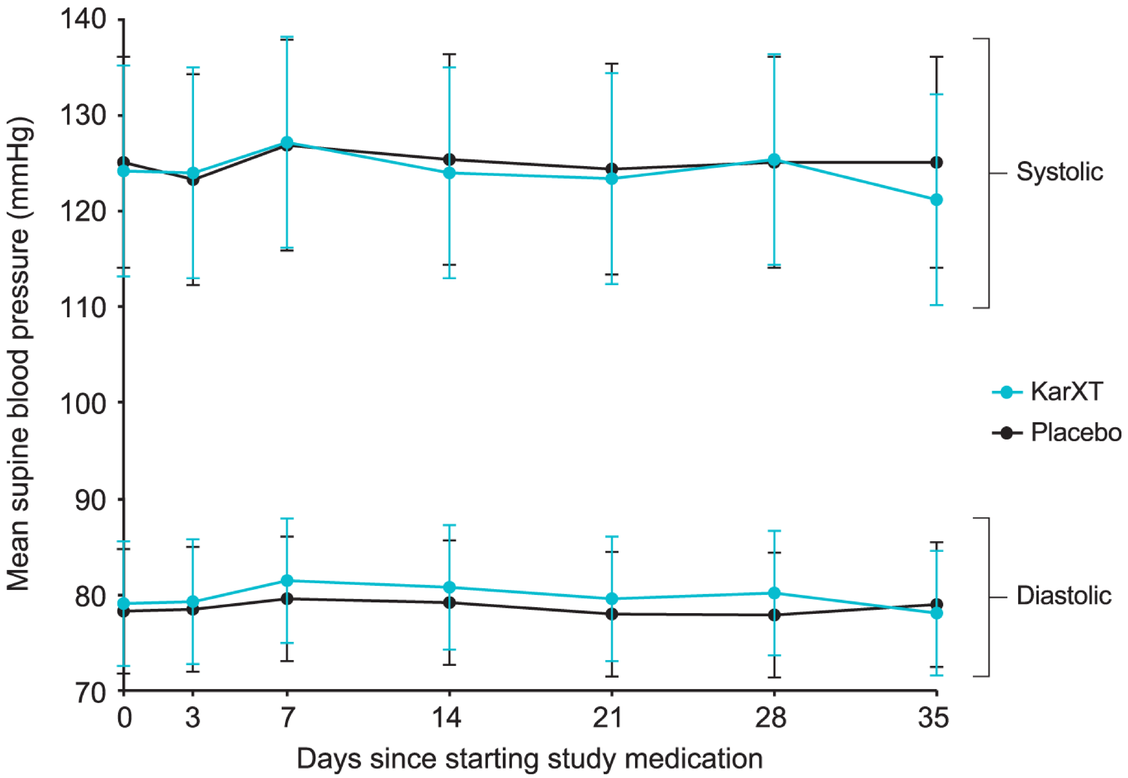

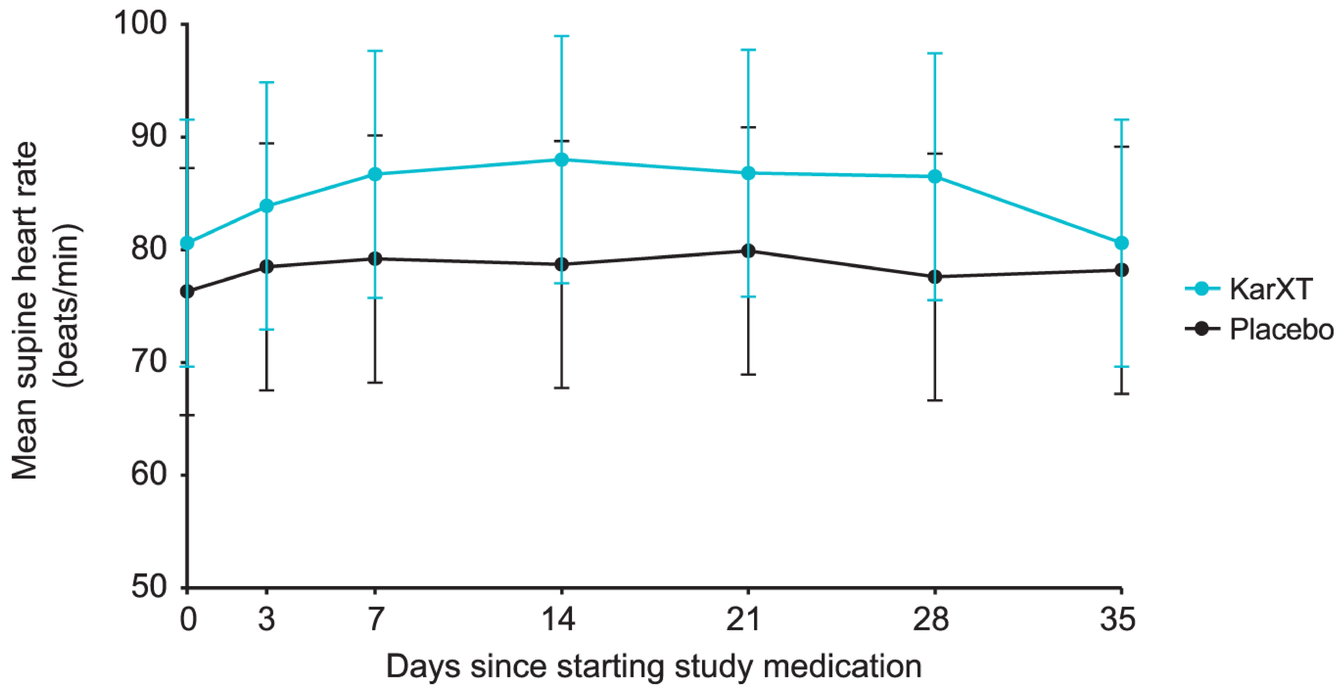

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Mitigation strategies for procholinergic side effects during titration

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- Slower titration may not reduce the incidence of procholinergic side effects, getting to 125/30 mg of KarXT relatively quickly may reduce the duration of these side effects
- Alternatively, slower titration over longer periods of time (e.g., 2-4 weeks) may be adequate if supplementary trospium is used proactively to counter procholinergic side effects
- Supplementary trospium should be used in consideration of concomitant drugs with anticholinergic burden and overall risk of anticholinergic side effects (e.g., caution in elderly men who may be more prone to urinary retention).
- Ondansetron PRN may also be a helpful tool during titration to mitigate nausea/vomiting
- Alternatively, anticholinergic side effects (e.g., constipation) may be mitigated by taking KarXT in a full stomach, which would prevent the absorption of trospium

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Estimating cholinergic burden during cross-titration

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Agent	Cholinergic Burden
Aripiprazole	Low
Olanzapine	Moderate-High
Quetiapine	Moderate
Risperidone	Low
Clozapine	High
Haloperidol	Low
Ziprasidone	Low
Lurasidone	Low
Paliperidone	Low
Chlorpromazine	High
Asenapine	Low
Benztropine	High
Trihexyphenidyl	High
Biperiden	High
Amantadine	Low
Procyclidine	High

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Cross-titration

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- The indication of KarXT is monotherapy and it is preferable to use it in that way. The limited amount of data for its use in augmentation is for positive symptoms and its superior efficacy was not statistically significant (i.e., ARISE).
- For switches, it is recommendable to start reducing the dose of the first antipsychotic after achieving a therapeutic dose of KarXT that can be tolerated. Special attention should be paid to the anticholinergic load that patients are coming in with at the moment of switch.
- Strategies for tipping the balance towards procholinergic (e.g., taking the medication on a full stomach), or anticholinergic (e.g., supplementing with trospium) should be done on an individual basis, and in consideration of the overall cholinergic load

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Special populations

- KarXT should not be used in individuals with:
    - Urinary retention
    - Moderate or severe hepatic impairment
    - Moderate or severe renal impairment
    - Gastric retention
    - Untreated narrow-angle glaucoma
- In geriatric patients:
    - Consider slower titration
    - Maximum recommended dose is 100/20 mg
    - Monitor for urinary retention, particularly in the presence of BPH
- In pregnant patients:
    - Safety not established
- In pediatric populations:
    - Safety not established
- In the presence of mild renal or hepatic impairment
    - Same dosage as in general population although increased oversight of side effects is recommended

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Summary

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Section 1: Muscarinic agents target downstream the dopaminergic system more selectively than dopaminergic antipsychotics, and as a consequence may have a more favorable side effect profile and may have some advantages in cognition and negative symptoms

Section 2: The use of muscarinic antipsychotics may be particularly helpful in those who struggle with negative or cognitive symptoms and/or who experience the usual side effects of dopaminergic antipsychotics

Section 3: The titration is a critical period for successful implementation of treatment. Especial attention must be paid to the factors that may tip the balance towards pro vs anti cholinergic state.

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Thanks for listening. Questions?

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