Assessment of Withdrawal Symptoms After Discontinuation of AXS-05 (Dextromethorphan-Bupropion) Treatment: Results From the GEMINI Trial

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Key Question

- Does discontinuing AXS-05 without tapering in patients with MDD cause increased withdrawal symptoms, based on the 20-item Physician Withdrawal Checklist (PWC-20), compared to placebo?

Conclusions

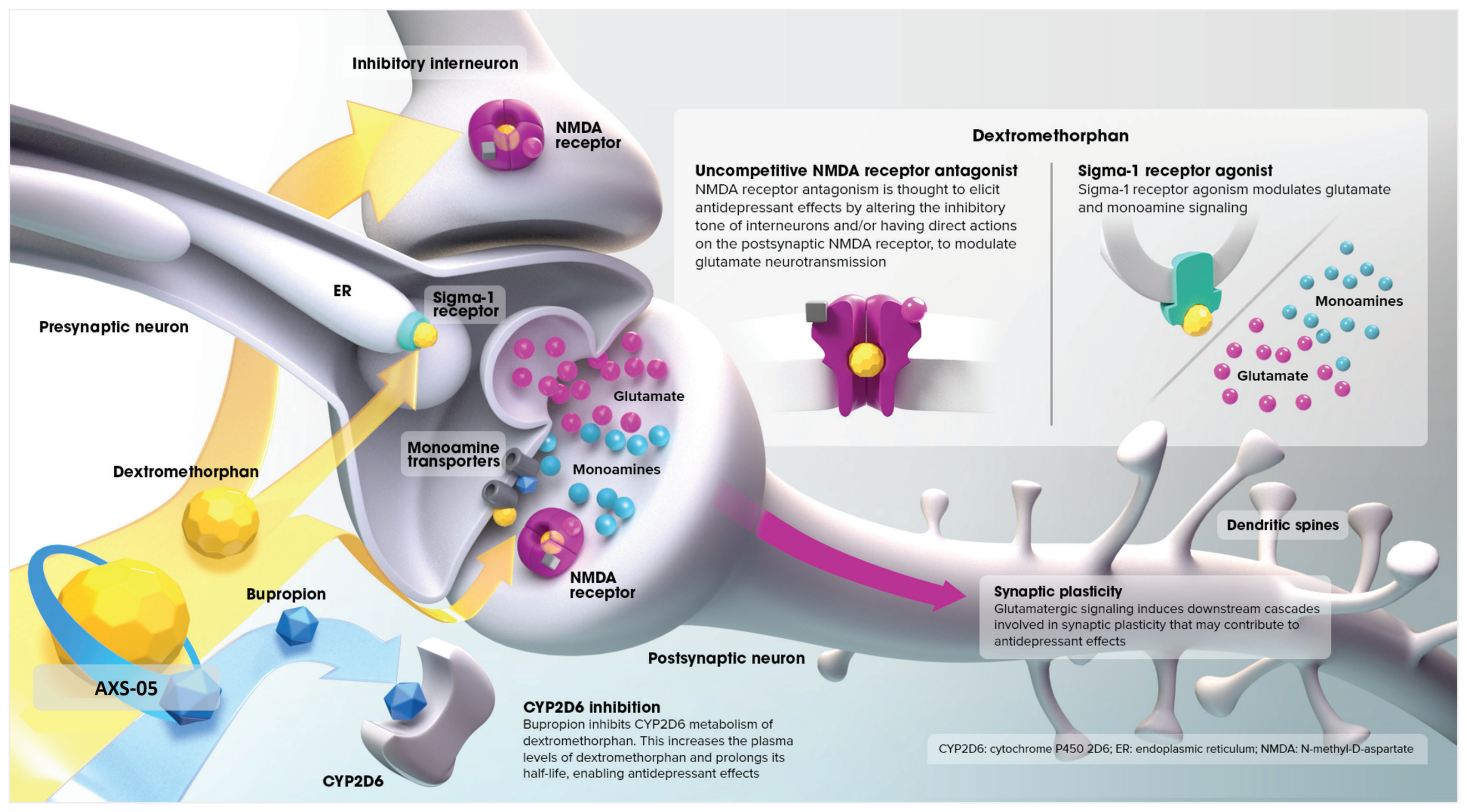
- Discontinuation of AXS-05 without taper was well tolerated with similar rates of symptoms compared to placebo
  - Only 2 of 20 symptoms (nausea/vomiting; dizziness/lightheadedness) occurred more frequently in patients treated with AXS-05 than with placebo, and most of those symptoms were reported as mild
- These results expand on the existing efficacy, tolerability, and safety findings of AXS-05 and suggest that AXS-05 can be discontinued without taper with limited withdrawal effects after 6 weeks of treatment
- Rates of withdrawal symptoms were notable in the placebo group and numerically higher than the AXS-05 group in several instances, highlighting the need for controlled data when studying withdrawal symptomss

Introduction

- Traditional oral antidepressants act primarily via the monoamine pathway[1], and can be associated with withdrawal effects upon discontinuation in up to 56% of patients[2]
- As a class, antidepressants are associated with a higher risk of withdrawal symptoms compared with other medications[3]
- Antidepressant withdrawal symptoms can be wide ranging and include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal (eg, anxiety and agitation)[4]
  - Among those experiencing withdrawal symptoms, nearly half (46%) rate these symptoms as severe[2]
  - In an analysis of more than 20,000 cases of antidepressant withdrawal, the most frequently reported symptoms were dizziness (13.13%), nausea (9.48%), paresthesia (8.30%), headache (7.35%), and anxiety (5.72%)[3]

AXS-05: A Novel, Oral NMDA Receptor Antagonist

Figure 1. AXS-05 mechanism of action



- AXS-05 [dextromethorphan-bupropion (Auvelity® extended-release tablet)] is a novel, oral, *N*-methyl-*D*-aspartate (NMDA) receptor antagonist with multimodal activity approved by the United States Food and Drug Administration for the treatment of major depressive disorder (MDD) in adults[5]
  - The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist[5,6]
  - The bupropion component of AXS-05 is an aminoketone and CYP450 2D6 inhibitor, which serves primarily to increase the bioavailability of dextromethorphan and is a norepinephrine and dopamine reuptake inhibitor[5,6]
- The efficacy and safety of AXS-05 in patients with MDD have been previously established[5-7]; however, assessment of potential withdrawal symptoms upon discontinuation of AXS-05 in MDD has not been previously reported

Methods & Study Design

- GEMINI was a 6-week, randomized, double-blind, placebo-controlled trial (NCT04019704) conducted from June 20, 2019, to December 5, 2019, at 40 sites in the United States[6,8]

Table 1. Key inclusion / exclusion criteria

Inclusion	Exclusion
▪ Adults aged 18–65 years ▪ DSM-5[9] criteria for MDD without psychotic features ▪ MADRS[10] total score ≥25 ▪ CGI-S[11] score ≥4 at baseline	▪ History of depressive episode with psychotic or catatonic features, treatment-resistant depression[a], schizophrenia, bipolar disorder, panic disorder, OCD, bulimia or anorexia nervosa, persistent neurocognitive disorder, or primary anxiety disorder ▪ Alcohol/substance use disorder within 1 year ▪ Clinically significant risk of suicide or harm to self or others ▪ Seizure disorder

[a]Defined as 2 or more failed prior treatments of adequate dose and duration in the current depressive episode.
CGI-S, Clinical Global Impression-Severity; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; OCD, obsessive compulsive disorder.

Figure 2. Study design

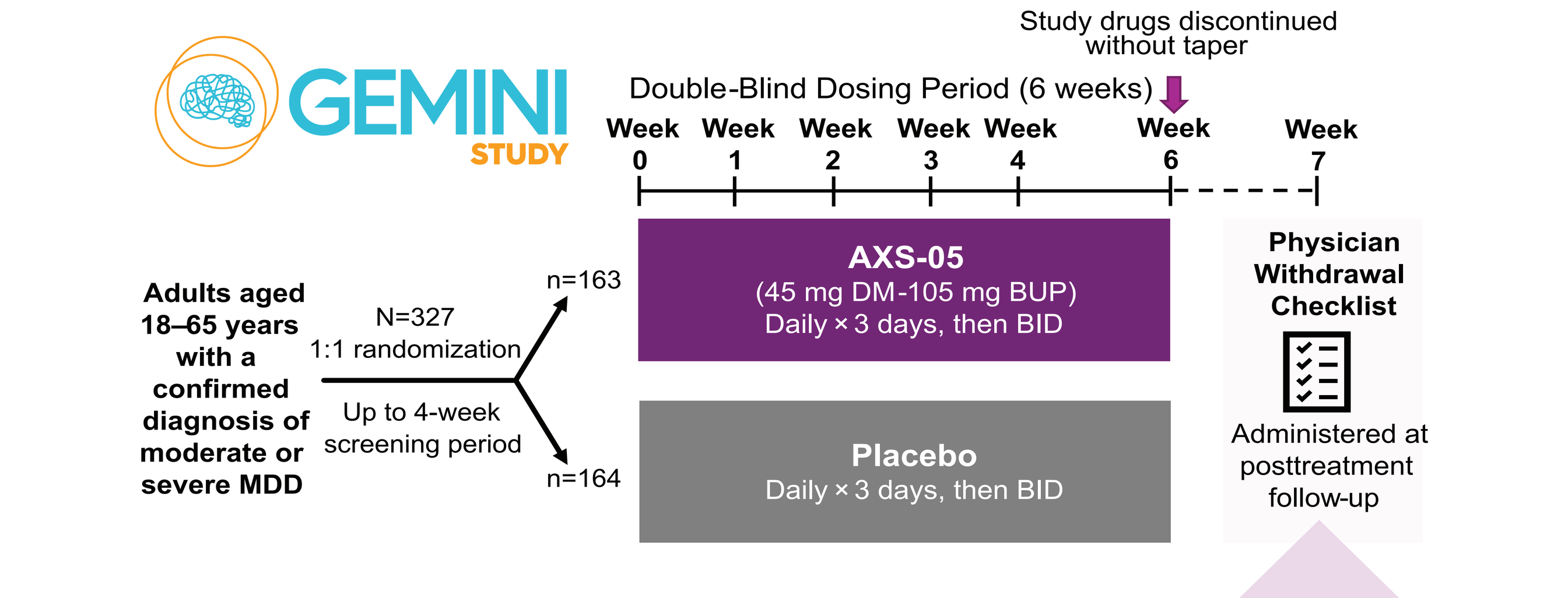


Table 2. Physician withdrawal checklist (PWC-20)

Category	Symptoms
Cognitive	Poor coordination; dizziness/lightheadedness; increased acuity for sound, smell, touch, pain; depersonalization/derealization
Fatigue	Fatigue/lethargy/lack of energy; weakness; paresthesias
Gastrointestinal	Loss of appetite; nausea/vomiting; diarrhea
Mood	Anxiety/nervousness; irritability; dysphoric mood/depression; restlessness/agitation; difficulty concentrating, remembering
Somatic	Insomnia; diaphoresis; tremor/tremulousness; headaches; muscle aches or stiffness

BID, twice daily; BUP, bupropion; DM, dextromethorphan; MDD, major depressive disorder; PWC-20, Physician Withdrawal Checklist.

- Current analysis: Systematic evaluation of withdrawal symptoms between AXS-05 and placebo groups
- The PWC-20 evaluates the presence and severity of 20 withdrawal symptoms that comprise the following categories: somatic symptoms, mood symptoms, cognitive symptoms, fatigue symptoms, and gastrointestinal symptoms[12]
- Study drug was discontinued without taper at the end of Week 6 and the PWC-20 was administered at Week 7, at which time all subjects had been off drug for 1 week
- Data were analyzed for the modified intent-to-treat population, defined as all patients who were randomized, received ≥1 dose of the study drug, and had ≥1 postbaseline assessment. The proportion of patients experiencing withdrawal symptoms in each group was evaluated using the chi square test

Key Findings

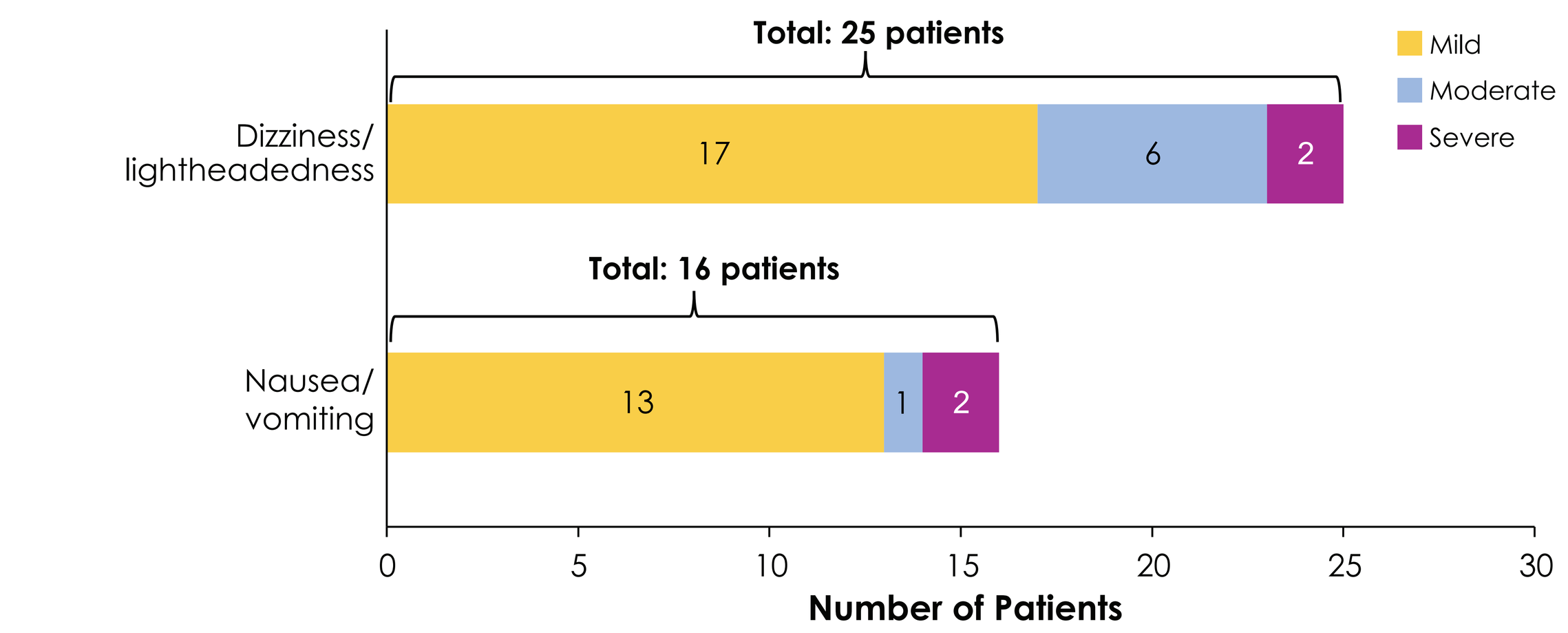
Table 3. Baseline demographic and clinical characteristics[a]

Characteristic	AXS-05 (n=156)	Placebo (n=162)
Demographic characteristics		
Age, years, mean (SD)	42.1 (12.8)	41.2 (13.8)
Sex (female), n (%)	95 (60.9)	117 (72.2)
Race, n (%)		
White	84 (53.8)	92 (56.8)
Black or African American	58 (37.2)	54 (33.3)
Asian	9 (5.8)	8 (4.9)
Multiple	3 (1.9)	2 (1.2)
Other	2 (1.3)	6 (3.7)
BMI, kg/m^2, mean (SD)	29.3 (5.61)	29.3 (5.69)
Clinical characteristics		
MADRS total score[b], mean (SD)	33.6 (4.43)	33.2 (4.36)
CGI-S score[c], mean (SD)	4.6 (0.59)	4.6 (0.57)

[a]Modified intent-to-treat population. [b]MADRS scores range from 0–60, with higher scores indicating more severe depression. [c]CGI-S scores range from 1–7, with higher scores representing more severe disease.
BMI, body mass index; CGI-S, Clinical Global Impression-Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation.

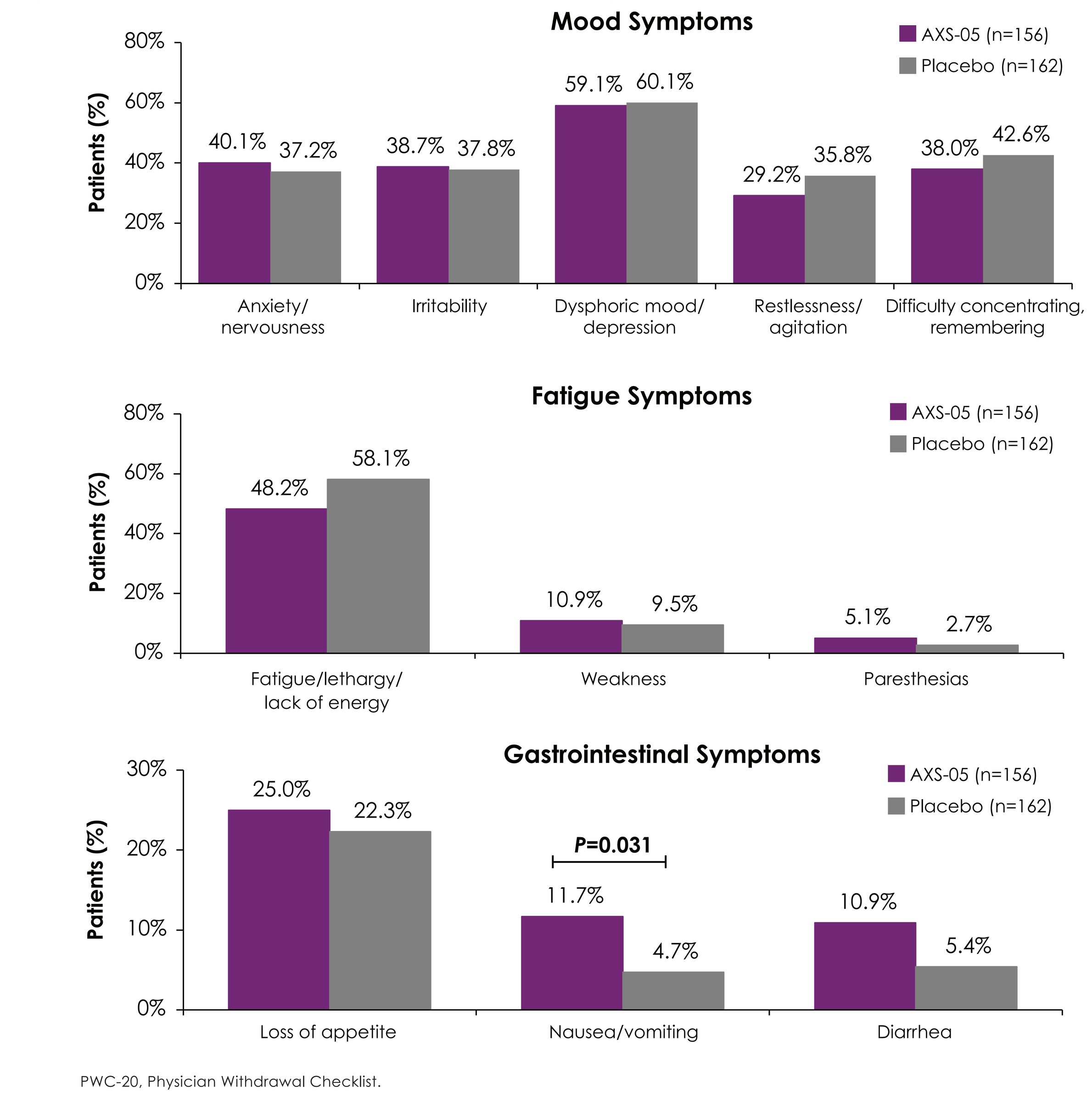
- Baseline disease severity demonstrated the patient population had moderate to severe depression; demographics were generally similar across treatment groups

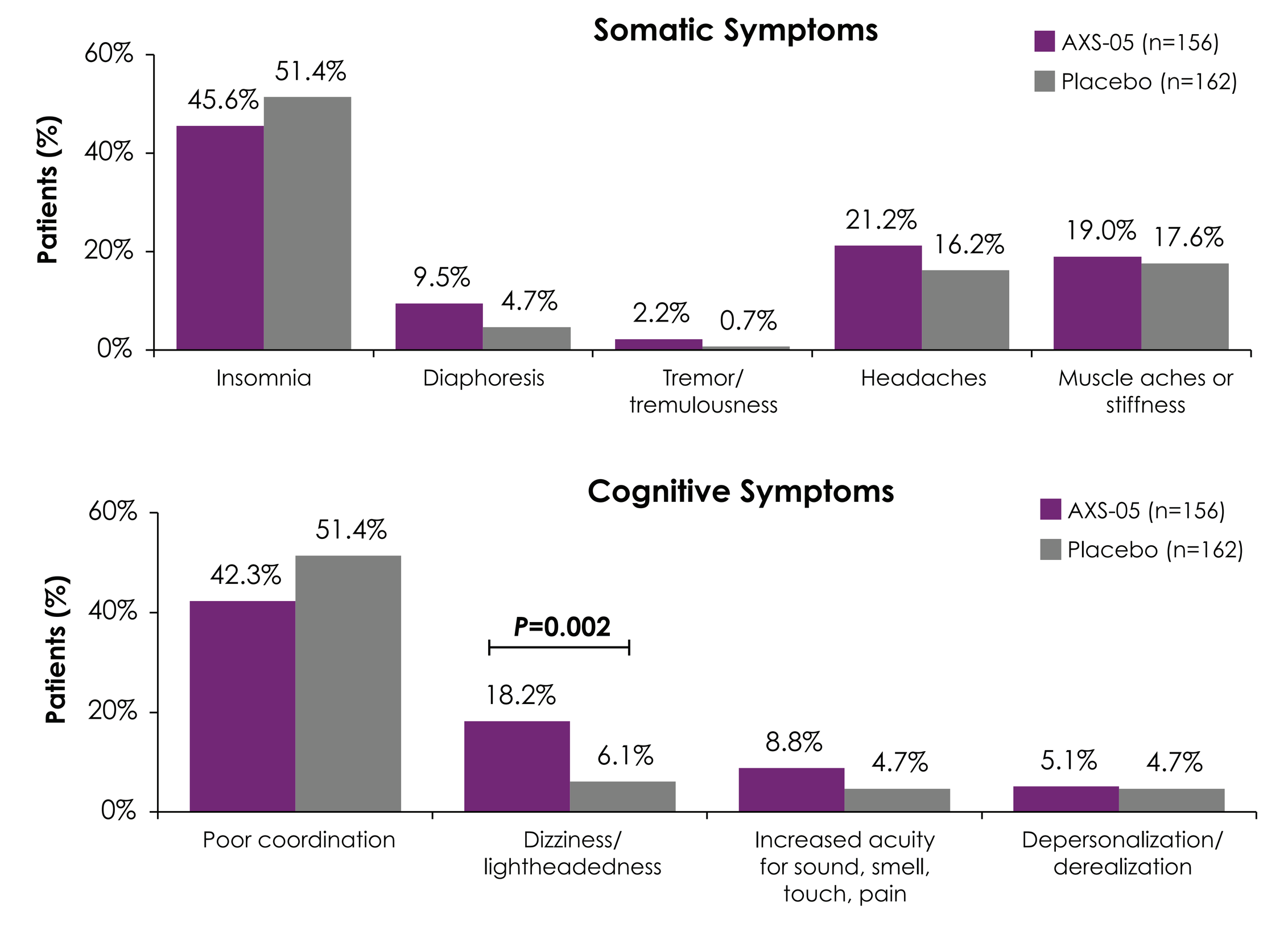
Figure 4. Severity assessment of dizziness/lightheadedness and nausea/vomiting



- The severity of dizziness/lightheadedness and nausea/vomiting following discontinuation of AXS-05 was mild or moderate in 92% (n=23/25) and 88% (n=14/16), respectively, of patients reporting these symptoms

Figure 3. PWC-20 symptoms by category in patients treated with AXS-05 or placebo





- No significant differences were found between the AXS-05 and placebo groups for 18 of 20 withdrawal symptoms evaluated by the PWC-20; dizziness/lightheadedness and nausea/vomiting were reported for a significantly greater percentage of patients in the AXS-05 group compared with the placebo group
- Notably, several withdrawal symptoms occurred at numerically higher rates in the placebo group compared with the AXS-05 group, which highlights the importance of controlled trial data when evaluating withdrawal symptoms

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Disclosures

R. Jain is a consultant to Axsome. **C. Streicher, Z. Thomas,** and **H. Tabuteau** are current employees of Axsome Therapeutics. **A. Jones** is no longer affiliated with Axsome.

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