Effects of AXS-05 (Dextromethorphan-Bupropion) in Improving Anhedonia and Interest-Activity Symptoms of MDD and the Associated Improvements in Functional Impairment

Roger S McIntyre,[1-3] Sagar V Parikh,[4] Rakesh Jain,[5] Zachariah Thomas,[6] Graham Eglit,[6] Andrew J Cutler[7]

[1]University of Toronto, Toronto, ON, Canada; [2]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [3]Department of Pharmacology, University of Toronto, Toronto, ON, Canada; [4]University of Michigan, Ann Arbor, MI, USA; [5]Department of Psychiatry, Texas Tech University School of Medicine-Permian Basin, Midland, TX, USA; [6]Axsome Therapeutics Inc. New York, NY, USA; [7]Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY, USA

Objective

- To evaluate the efficacy of Auvelity® (AXS-05) on treating anhedonia symptoms and diminished interest-activity in individuals with MDD
- To assess the relationship between anhedonia symptoms and functional impairment in individuals with MDD

Conclusions

- This pooled post hoc analysis showed that AXS-05 compared with controls significantly improved anhedonia and impaired interest-activity symptoms starting as early as Week 1
- AXS-05 exhibited comparable reductions in total MADRS scores regardless of severity of baseline interest-activity symptoms
- Functional improvements with AXS-05 treatment as measured by the SDS were positively correlated with the improvement in anhedonia symptoms in the Phase 3 GEMINI study
- These results suggest AXS-05 may have benefits in reducing anhedonia and improving interest-activity, symptoms of MDD that can be very difficult to resolve with monoaminergic-targeted therapies

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BACKGROUND

- Major depressive disorder (MDD) is a disabling and prevalent disorder that is a leading cause of suicide in the US[1,2]
- Anhedonia, or impairments in the motivation/reward system, including inability to anticipate and/or experience pleasure, is present in up to 75% of individuals diagnosed with MDD[3]; it is also associated with functional impairment, reduced quality of life, suicidality, and a more chronic course of disease[4,5]
  - Anhedonia can be conceptualized partly as a loss of interest or pleasure in activities (referred to as "interest-activity")[6]
- Current serotonergic and noradrenergic antidepressants have shown limited efficacy in treating anhedonia and residual anhedonia symptoms are associated with poorer patient outcomes[7]
- N-methyl-D-aspartate (NMDA) receptor antagonism has been shown to have antidepressant effects in animal models and clinical trials, establishing the role of glutamatergic dysfunction in the pathogenesis of depression[8,9]
  - Clinical evidence suggests that glutamatergic modulation can be effective at improving measures of anhedonia in patients with MDD[10]
- There is an urgent clinical need for new treatment modalities that can effectively resolve the broad range of depression symptoms, particularly anhedonia, and improve functional impairment associated with MDD

AXS-05

- Auvelity® (AXS-05) (45-mg dextromethorphan/105-mg bupropion) is a novel, oral NMDA receptor antagonist, sigma-1 receptor agonist, and aminoketone CYP2D6 inhibitor (**Figure 1**)[13]
  - The dextromethorphan component of AXS-05 is an antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist that modulates monoamine and glutamate neurotransmission; sigma-1 agonism is also associated with anti-inflammatory and neuroprotective activity
  - The bupropion component of AXS-05 is an aminoketone and a CYP2D6 inhibitor that serves to increase the bioavailability of dextromethorphan by inhibiting its metabolism, and it is a weak norepinephrine and dopamine reuptake inhibitor[13,16]

Figure 1. AXS-05 Mechanism of Action

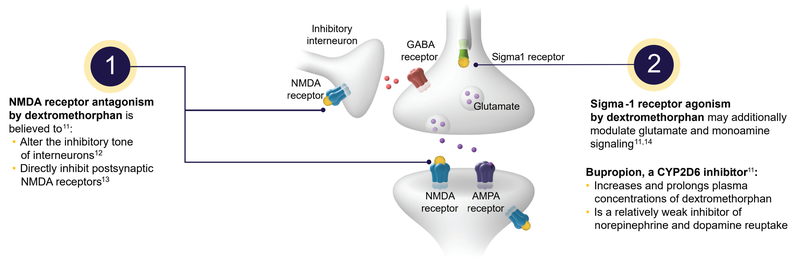
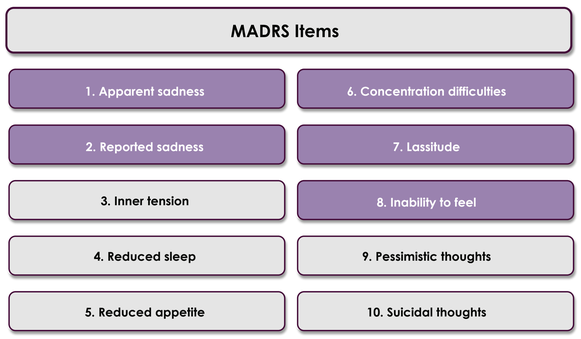


Figure adapted from reference 15: Kadriu B, et al. *Int J Neuropsychopharmacol*. 2019;22(2):119-35.
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA; gamma-aminobutyric acid; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate.

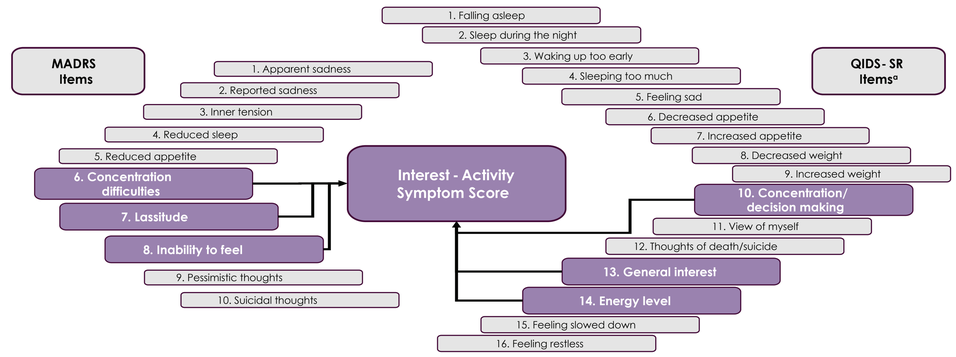
METHODS

Figure 2. MADRS Anhedonia Sub Score (A) and Interest-Activity Symptom Score from MADRS and QIDS-SR (B)

A. MADRS Anhedonia Sub Score



B. Interest-Activity Symptom Score from MADRS and QIDS-SR



[a]The QIDS-SR items (with scores from 0 to 3) were doubled for equal weight with the MADRS items (with scores from 0 to 6).
MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Report.

Study design

- This was a pooled post hoc analysis of data from two double-blind, randomized, controlled, 6-week trials of AXS-05 in adult participants (age 18-65 years) with moderate to severe MDD (defined as a score of ≥25 on the Montgomery-Åsberg Depression Rating Scale [MADRS] and a score of ≥4 on the Clinical Global Impressions severity scale [CGI-S])
  - GEMINI (NCT04019704) was a phase 3, placebo-controlled study (modified intent-to-treat population: AXS-05, n=156; placebo, n=162)[17]
  - ASCEND (NCT03595579) was a phase 2 study that used bupropion as an active control (efficacy population: AXS-05, n=43; bupropion, n=37)[18]
  - In this analysis, data from the AXS-05 arms were pooled, and the active control and placebo arm were pooled (control)

Post hoc analyses

- Anhedonia symptoms were evaluated using the MADRS Anhedonia subscale (Items 1, 2, 6, 7, 8) and the Interest-Activity scale (MADRS Items 6, 7, 8 and Quick Inventory of Depressive Symptomatology Self Report [QIDS-SR] Items 10, 13, 14) (**Figure 2**)

Key analyses

- Least square mean difference (LSMD) from baseline in the MADRS anhedonia sub score and interest-activity score
- Percentage of responders (participants achieving ≥50% reduction) in MADRS anhedonia sub score and Interest-Activity symptom score
- LSMD from control on the MADRS total score at low (1 SD below the mean; less severe impairment) average, and high (1 SD above the mean; more severe impairment) baseline interest activity scores
- Correlation between improvements in the MADRS anhedonia subscale and SDS (Sheehan Disability Scale; GEMINI only)

RESULTS

Study population

Table 1. Baseline Demographics and Clinical Characteristics (ASCEND/GEMINI)

Parameter	AXS-05 (n=199)	Control[a] (n=199)
Age, median (range), y	**41 (18-64)**	**39 (18-65)**
Women, n (%)	**120 (60)**	**143 (72)**
Race, n (%)		
White	114 (57)	112 (56)
Black or African American	70 (35)	68 (34)
Asian	10 (5)	8 (4)
Other	5 (3)	11 (6)
BMI, median (range), kg/m²	**29.1 (18.2-39.8)**	**29.6 (18.1-39.7)[b]**
Prior ADT during index MDE, n (%)		
No prior ADT	155 (78)	135 (68)
Prior ADT	44 (22)	64 (32)
Baseline MADRS Total score, mean (SD)	**33.2 (4.4)**	**32.9 (4.4)**
Baseline MADRS Anhedonia score, mean (SD)[c]	**19.5 (2.6)**	**19.5 (2.4)**
Baseline Interest-Activity score, mean (SD)[d]	**22.6 (4.5)**	**22.4 (4.8)**
CGI-S score, mean (SD)	**4.6 (0.6)**	**4.6 (0.6)**
SDS score, mean (SD)[e]	**20.3 (6.0)**	**19.3 (5.8)**

[a]ASCEND, bupropion; GEMINI, placebo. [b]n=198. [c]Maximum MADRS anhedonia score is 30. [d]Maximum Interest-Activity score is 36. [e]GEMINI only.
ADT, antidepressant treatment; BMI, body mass index; CGI-S, Clinical Global Impressions severity scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; SDS, Sheehan Disability Scale.

- The pooled baseline demographics and clinical characteristics from GEMINI and ASCEND were similar between AXS-05 and control arms (**Table 1**)

MADRS anhedonia subscale and SDS correlation (GEMINI only)

Table 2. Within-Subject Correlation Between SDS and MADRS Anhedonia Score over the 6-week GEMINI trial

MADRS Anhedonia Score Correlations	AXS-05	
	Within-subject Correlation Coefficient (95% CI)	*P* value
SDS Total Score	**0.75 (0.72, 0.78)**	**<.001**
Work/School	0.64 (0.59, 0.68)	<.001
Social Life	0.72 (0.68, 0.75)	<.001
Family Life/Home Responsibilities	0.68 (0.65, 0.72)	<.001

MADRS, Montgomery-Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale.

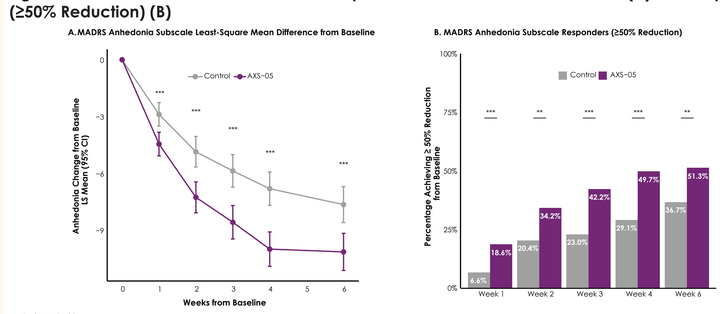
- There were positive correlations (0.75 correlation coefficient; P<.001) between MADRS Anhedonia subscale and SDS scores over the 6-week treatment period with AXS-05 (**Table 2**)

Safety

- The most commonly reported adverse reactions (≥5% and twice the rate of placebo) with AXS-05 were dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis

Anhedonia subscale

Figure 3. MADRS Anhedonia Subscale Least-Square Mean Difference from Baseline (A) and Responders (≥50% Reduction) (B)

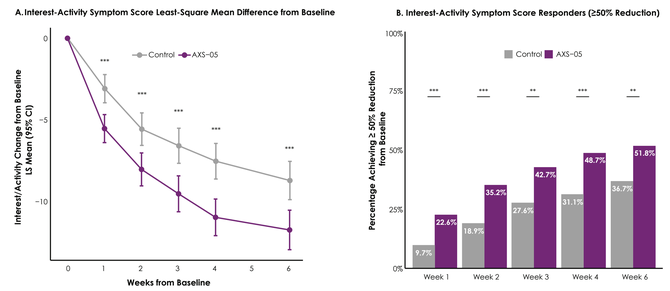


**P<.01; ***P<.001.

- By Week 6, improvement from baseline on the anhedonia subscale was -10.1 for AXS-05 compared with -7.6 for control (LSMD, -2.5 [95% CI, -3.9 to -1.1]; *P*<.001), with significant differences observed as early as Week 1 and sustained through Week 6 (**Figure 3**)
- Rates of response in anhedonia symptoms were significantly greater for AXS-05 (18.6%) vs control (6.6%) at Week 1 (*P*<.001) and at every timepoint thereafter

Interest-activity symptom score

Figure 4. Interest-Activity Symptom Score Least-Square Mean Difference from Baseline (A) and Responders (≥50% Reduction) (B)

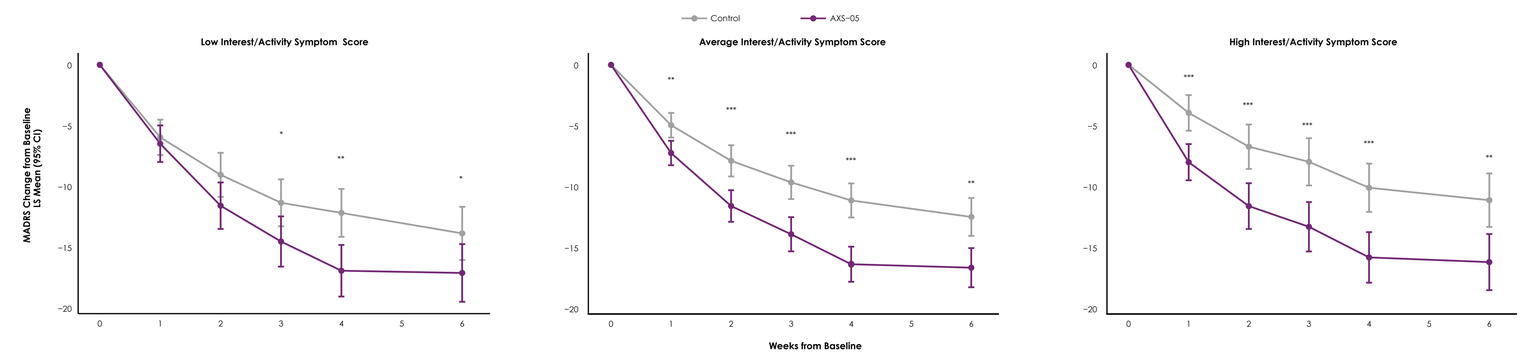


**P<.01; ***P<.001.

- By Week 6, the LSMD from baseline for AXS-05 vs control was -3.0 (95% CI, -4.7 to -1.3; *P*<.001); significant differences were observed as early as Week 1 and sustained through Week 6 (**Figure 4**)
- Rates of response based on Interest-Activity symptom score were significantly greater for AXS-05 (22.6%) compared with control (9.7%) at Week 1 (*P*<.001) and remained significantly greater at every timepoint thereafter

Difference from control on MADRS total score at low, average, and high baseline activity symptom score

Figure 5. Least-Square Mean Difference in MADRS Total Score by Baseline Interest-Activity Symptom Score



*P<.05;**P<.01; ***P<.001.

- At week 1, AXS-05 significantly improved MADRS total score from baseline in patients with average interest-activity score (*P*=.002), and high interest-activity score (ie, more severe; *P*<.001) and maintained through Week 6 (**Figure 5**)
- Significant improvements for participants with low Interest-Activity score treated with AXS-05 were observed starting at Week 3 (*P*=.025) and were maintained through Week 6