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Anti-Anhedonic Effects of Auvelity® (Dextromethorphan-Bupropion) Mediate Improvements in Functioning and Quality of Life in Major Depressive Disorder

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Key Objective

To assess how much of the treatment benefit of dextromethorphan-bupropion on functioning and quality of life (QoL) in major depressive disorder (MDD) is attributable to reduction in anhedonia

Introduction

- Anhedonia, the diminished capacity to experience enjoyment or pleasure, is highly prevalent in MDD, with estimates ranging as high as 75%[1,2]
- Anhedonia in patients with MDD is associated with poorer disease prognosis, suboptimal treatment response, diminished QoL and poorer daily function[3,4]
- Conventional antidepressants (i.e., SSRIs, SNRIs) exhibit variable efficacy in improving anhedonia, and are associated with emotional blunting[5,6]
- Dextromethorphan-bupropion is a novel, oral NMDA receptor antagonist and sigma-1 receptor agonist approved for the treatment of MDD in adults[7]
- In addition to improvement in depressive symptoms, the Phase 3 GEMINI trial of dextromethorphan-bupropion showed statistically significant improvement in functional disability (SDS) and QoL (Q-LES-Q-SF) at Week 2 and at every time point thereafter[8]
- Previous post hoc analyses showed dextromethorphan-bupropion led to significantly greater improvements in anhedonia and interest-activity symptoms relative to placebo as early as Week 1[9]
- In this post hoc analysis, we evaluate whether the improvement in anhedonia resulting from dextromethorphan-bupropion treatment mediates improvements in the domains of QoL and daily function

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Methods

GEMINI Phase 3 Study Design

Screening Period: Patients with a confirmed diagnosis of moderate or severe MDD

N = 327 → 1:1 randomization

Double-blind Dosing Period (6 weeks): Daily x 3 days, then BID
- Dextromethorphan-bupropion (n = 163)
- Placebo (n = 164)

Primary endpoint: Change from baseline in MADRS total score compared to placebo at Week 6

Secondary endpoints included: Change from baseline in SDS total score compared to placebo by week; Change from baseline in Q-LES-Q-SF score compared to placebo at by week

Inclusion criteria included:
- ✓ Adults 18-65
- ✓ DSM-5 criteria for current MDD w/o psychotic features
- ✓ MADRS total score of ≥25

Exclusion criteria included:
- ✗ TRD, panic disorder, or a primary anxiety disorder
- ✗ History of seizure disorder
- ✗ Risk of suicide
- ✗ Concomitant psychotropic medications

BID, twice daily; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SDS, Sheehan Disability Scale; TRD, treatment resistant depression.

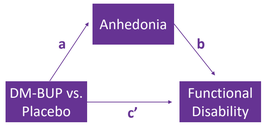
Statistical Methods

- Anhedonia was assessed using the MADRS-Anhedonia factor subscale, consisting of MADRS items 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel)[10]
- This post hoc analysis used a longitudinal mediation model to evaluate if, and to what extent, improvements in anhedonia mediated the total effect of dextromethorphan-bupropion on functioning (SDS) and QoL (Q-LES-Q-SF), distinguishing indirect effects (mediated through anhedonia) from direct effects (attributable to other mechanisms)
- Additionally, the extent to which improvements in anhedonia mediated the total effect of dextromethorphan-bupropion on SDS Social Life, SDS Work/School, and SDS Family/Home subscales was also evaluated

Primary Analysis

Total Effect = c

Mediation Analysis



Indirect Effect = a × b

Direct Effect = c'

Total Effect = Indirect Effect + Direct Effect

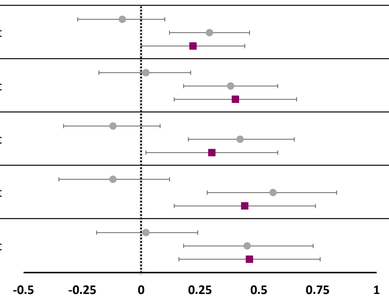
Relative Indirect Effect = Indirect Effect / Total Effect

DM-BUP, dextromethorphan-bupropion; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SDS, Sheehan Disability Scale.

Results

SDS Total Score Mediation by MADRS Anhedonia Score

Week	Effect Type	Difference from Placebo (95% CI)	Relative Indirect Effect
Week 1	Direct	-0.08 (-0.26, 0.11)	-0.35
	Indirect	**0.29 (0.12, 0.46)**	1.35
	Total	0.22 (0.00, 0.44)	
Week 2	Direct	0.02 (-0.17, 0.22)	0.05
	Indirect	**0.38 (0.18, 0.58)**	0.95
	Total	**0.40 (0.14, 0.66)**	
Week 3	Direct	-0.12 (-0.32, 0.09)	-0.38
	Indirect	**0.42 (0.19, 0.64)**	1.38
	Total	**0.30 (0.02, 0.58)**	
Week 4	Direct	-0.12 (-0.36, 0.11)	-0.29
	Indirect	**0.56 (0.29, 0.84)**	1.29
	Total	**0.44 (0.14, 0.74)**	
Week 6	Direct	0.02 (-0.20, 0.23)	0.03
	Indirect	**0.45 (0.17, 0.72)**	0.97
	Total	**0.46 (0.16, 0.76)**	

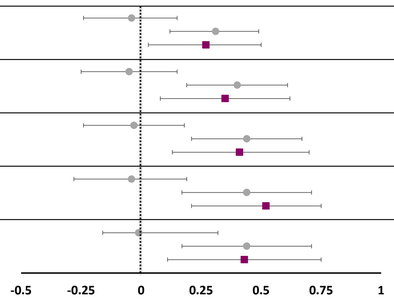


- At Week 6, the indirect effect of dextromethorphan-bupropion on SDS Total Score was significant (-0.45; 95% CI, -0.72 to -0.17) and closely approximated the total effect (-0.46; 95% CI, -0.76 to -0.16), whereas the direct effect was not significant, supporting anti-anhedonic response as a key mediator of functional improvement; similar patterns were observed across weeks

Bold differences from placebo indicate statistically significant effects. MADRS, Montgomery-Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale.

Q-LES-Q-SF Score Mediation by MADRS Anhedonia Score

Week	Effect Type	Difference from Placebo (95% CI)	Relative Indirect Effect
Week 1	Direct	-0.04, (-0.25, 0.15)	-0.17
	Indirect	**0.31 (0.13, 0.49)**	1.17
	Total	**0.27 (0.02, 0.50)**	
Week 2	Direct	-0.05 (-0.25, 0.15)	-0.14
	Indirect	**0.40 (0.19, 0.61)**	1.14
	Total	**0.35 (0.08, 0.62)**	
Week 3	Direct	-0.03 (-0.24, 0.18)	-0.07
	Indirect	**0.44 (0.21, 0.67)**	1.07
	Total	**0.41 (0.12, 0.70)**	
Week 4	Direct	-0.04 (-0.28, 0.19)	-0.08
	Indirect	**0.44 (0.17, 0.71)**	1.08
	Total	**0.52 (0.21, 0.75)**	
Week 6	Direct	-0.01 (-0.24, 0.23)	-0.02
	Indirect	**0.44 (0.17, 0.71)**	1.02
	Total	**0.43 (0.11, 0.75)**	

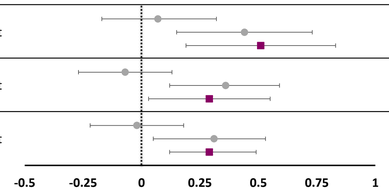


- Likewise, the indirect effect on Q-LES-Q-SF was significant (0.44; 95% CI, 0.17 to 0.71) and was nearly equal to the significant total effect (0.43; 95% CI, 0.11 to 0.75), while the direct effect was not significant; similar patterns were observed across weeks

Bold differences from placebo indicate statistically significant effects. MADRS, Montgomery-Åsberg Depression Rating Scale; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form.

SDS Sub-domain Score Mediation by MADRS Anhedonia Score

Week	Effect Type	Difference from Placebo (95% CI)	Relative Indirect Effect
Social Life	Direct	0.07 (-0.17, 0.32)	0.14
	Indirect	**0.44 (0.15, 0.73)**	0.86
	Total	**0.51 (0.19, 0.83)**	
Family/ Friends	Direct	-0.07 (-0.27, 0.13)	-0.23
	Indirect	**0.36 (0.12, 0.59)**	1.23
	Total	**0.29 (0.03, 0.55)**	
Work/ School	Direct	-0.02 (-0.22, 0.18)	-0.07
	Indirect	**0.31 (0.05, 0.53)**	1.07
	Total	**0.29 (0.12, 0.49)**	



- Consistent findings were observed for SDS subscales at Week 6, in which indirect effects (via anhedonic improvement) were significant, while direct effects (not mediated by anhedonic response) were not

Bold differences from placebo indicate statistically significant effects. MADRS, Montgomery-Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale.

Safety and Tolerability

		Dextromethorphan-bupropion (n=162)	Placebo (n=164)
Any TEAE		**100 (61.7%)**	**74 (45.1%)**
TEAEs in ≥5% of participants	Dizziness	26 (16.0%)	10 (6.1%)
	Nausea	21 (13.0%)	14 (8.5%)
	Headache	13 (8.0%)	6 (3.7%)
	Diarrhea	11 (6.8%)	5 (3.0%)
	Somnolence	11 (6.8%)	5 (3.0%)
	Dry mouth	9 (5.6%)	4 (2.4%)

- The most commonly reported AEs were dizziness, nausea, and headache

AE, adverse event; TEAEs, treatment emergent adverse events.

Conclusions

- In this post hoc analysis of Phase 3 data in patients with MDD, improvements in anhedonia observed in patients taking dextromethorphan-bupropion significantly mediated improvements observed in functioning and QoL
- For functional and QoL outcomes, indirect effects mediated through anhedonia were significant as early as week 1, with significance maintained at week 6, and approached total treatment effects
- This post-hoc analysis has two main limitations:
  - The anhedonia mediator was a subscale from the MADRS and is thus correlated with overall depression; as such, the mediating effect may involve broader depression improvement rather than just anhedonia-specific improvement
  - The pathway relating anhedonia improvement to functional ability/QoL may be confounded by unmeasured variables and should not be interpreted causally
- These findings suggest that improvement in anhedonia may be a key mediator of the beneficial effects of dextromethorphan-bupropion in improving daily function and QoL

Disclosures

A Cutler has served as a consultant/on an advisory board for AbbVie, Acadia, Actinogen, Alfasigma, Alkermes, Anavex Life Sciences, Arrivo BioVentures, Autobahn Therapeutics, Axsome, Biogen, Biohaven, Boehringer Ingelheim, Brii Biosciences, Bristol Myers Squibb, Cerevel, Cognitive Research Corporation, Collegium Pharmaceutical, Corium, Delpor, Evolution Research Group, 4M Therapeutics, Intra-Cellular Therapies, J&J Innovative Medicine, Jazz Pharma, Karuna, Knight Therapeutics, LivoNova, Lundbeck, Luye Pharma, MapLight Therapeutics, MedAvante-ProPhase, Mentavi, Neumora, Neurocrine, Neuroscience Education Institute, NeuroSigma, Noven, Otsuka, PaxMedica, Relmada, Sage Therapeutics, Sirtsei Pharmaceuticals, Supernus, Teva, Thynk, Tris Pharma, Vanda Pharmaceuticals, and VistaGen; served on speakers bureaus for AbbVie, Alfasigma, Alkermes, Axsome, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Intra-Cellular Therapies, Ironshore Pharmaceuticals, J&J, Lundbeck, Neurocrine, Noven, Otsuka, Supernus, Teva, Tris Pharma, and Vanda Pharmaceuticals; owns stock options/equity for 4M Therapeutics; and served on data safety monitoring boards for Alar Pharma, COMPASS Pathways, Freedom Biosciences, and Pain Therapeutics.

G Eglit and **S Alter** are employees of Axsome Therapeutics and may hold stock.

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