Psychopharmacology of AXS-05: Potential Clinical Implications

Dr. Stephen M. Stahl
Adjunct Professor of Psychiatry, University of California San Diego
Honorary Visiting Senior Fellow, University of Cambridge, U.K
Chairman, Neuroscience Education Institute
Editor-in-Chief, CNS Spectrums
Director of Psychopharmacology Services and Senior Academic Advisor, California Department of State Hospitals

© Axsome Therapeutics, Inc.
Forward-Looking Statements & Safe Harbor

Certain information contained in this presentation may include “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as “predicts,” “believes,” “potential,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company’s statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation and completion of the trials, interim analyses and receipt of interim results; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration or other regulatory authority approval of, or other action with respect to, our product candidates; the Company’s ability to obtain additional capital necessary to fund its operations; the Company’s ability to generate revenues in the future; the Company’s ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company’s research and development programs; the enforceability of the Company’s license agreements; the acceptance by the market of the Company’s product candidates, if approved; and other factors, including general economic conditions and regulatory developments, not within the Company’s control. These factors could cause actual results and developments to be materially different from those expressed in or implied by such statements. Forward-looking statements are not guarantees of future performance, and actual results may differ materially from those projected. The forward-looking statements are made only as of the date of this presentation and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such data after the date of this presentation. In addition, these projections, assumptions and estimates are necessarily subject to a high degree of uncertainty and risk.
What Is AXS-05?

• Two Drugs
  – Bupropion
  – Dextromethorphan

• Seven Mechanisms
  – Dopamine reuptake blockade (bupropion)
  – Serotonin reuptake blockade (dextromethorphan)
  – Norepinephrine reuptake blockade (both)
  – Alpha 4 beta 2 nicotinic antagonist (both)
  – CYP450 2D6 inhibitor (bupropion)
  – NMDA receptor antagonist (dextromethorphan)
  – Sigma 1 agonist (dextromethorphan)

Abbreviations: CYP 450 2D6 = Cytochrome P450 2D6; NMDA = N-methyl-D-aspartate
1Figure adapted from: Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge University Press; 2013.
What Is AXS-05?

• Five approved therapeutic targets
  – Major depressive disorder
  – Obesity (with naltrexone)
  – Pseudobulbar affect (with quinidine)
  – Cough suppressant
  – Smoking cessation

• Three potential therapeutic targets where there is unmet need
  – Treatment-resistant depression
  – Agitation in Alzheimer’s disease
  – Smoking cessation
Dextromethorphan: 5 Key Mechanisms of Action Plus a CYP450 2D6 Substrate

Abbreviations: SERT = Serotonin Reuptake Transporter; NET = Norepinephrine Reuptake Transporter; nACh = Nicotinic Acetylcholine Receptor; CYP 450 2D6 = Cytochrome P450 2D6; NMDA = N-methyl-D-aspartate

1 Figure adapted from: Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge University Press; 2013.
Bupropion: 4 Mechanisms of Action As NE and DA Reuptake Inhibitor, and CYP450 2D6 Inhibitor With α4β2 nACh Antagonism

Abbreviations: DAT = Dopamine Reuptake Transporter;; NET = Norepinephrine Reuptake Transporter; nACh = Nicotinic Acetylcholine Receptor; CYP 450 2D6 = Cytochrome P450 2D6

1Figure adapted from: Stahl SM. Stahl’s Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge University Press; 2013.
AXS-05: A Novel Combination Therapy for CNS Disorders

DM (2D6 Substrate)

Rapid metabolism

Difficult to achieve potential therapeutic plasma levels of substrate compound

Inhibits DM metabolism

DM maintained at therapeutic range

BUP (2D6-I)

Abbreviations: DM = Dextromethorphan; BUP = Bupropion; 2D6-I = Cytochrome P450 2D6 Inhibitor.
Phase 1 Results

**Dextromethorphan AUC**

<table>
<thead>
<tr>
<th>Dose†</th>
<th><strong>AUC\textsubscript{0-12} ng*hr/mL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>DM 20 mg + Q 10 mg</td>
<td>525</td>
</tr>
<tr>
<td>DM 30 mg + Q 10 mg</td>
<td>883</td>
</tr>
</tbody>
</table>

**Dextromethorphan C\textsubscript{max}**

<table>
<thead>
<tr>
<th>Dose†</th>
<th><strong>C\textsubscript{max} ng/mL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>DM 20 mg + Q 10 mg</td>
<td>53</td>
</tr>
<tr>
<td>DM 30 mg + Q 10 mg</td>
<td>85</td>
</tr>
</tbody>
</table>

Axsome data on file.
†Nuedexta\textsuperscript{®} NDA 021879, FDA Clinical Pharmacology Review.
Abbreviations: DM = Dextromethorphan; Q = Quinidine; BUP = Bupropion
WHAT IS THE COMPELLING REASON TO BELIEVE THESE COMBINATIONS OF MECHANISMS WOULD BE EFFECTIVE FOR TREATMENT-RESISTANT DEPRESSION?
Major Depressive Disorder (MDD) is a leading cause of disease burden in the United States. 63% and 44% of MDD patients have inadequate response to initial therapy and second-line therapy, respectively. Only 1 approved drug for TRD creates an unmet medical need. AXS-05 combines the MOA of 4 distinct antidepressant drug classes into 1 novel oral therapeutic.


Abbreviations: MOA = Mechanism of Action; MDD = Major Depressive Disorder; TRD = Treatment-Resistant Depression.
Conventional Antidepressant Mechanisms of Bupropion

Bupropion increases availability of DA by blocking reuptake

Monoamine Hypothesis of Depression


Abbreviations: NE = Norepinephrine; DA = Dopamine; 5-HT = Serotonin.
Bupropion increases availability of DA by blocking reuptake\(^1\)

Bupropion increases NE as an NE reuptake inhibitor\(^1\)


Abbreviations: NE = Norepinephrine; DA = Dopamine; 5-HT = Serotonin.
# Additive Effects of AXS-05 to Address Monoamine Hypothesis of Depression

**AXS-05** = Bupropion + Dextromethorphan

<table>
<thead>
<tr>
<th>Depression</th>
<th>DA</th>
<th>NE</th>
<th>σ1</th>
<th>NE</th>
<th>5-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Darker shading = Evidence for high importance for disease  
Lighter shading = Evidence for target to have some relevance for disease  
No shading = No evidence for involvement

Abbreviations: NE = Norepinephrine; DA = Dopamine; 5-HT = Serotonin.
Conventional Antidepressant Mechanisms and Additive Effects of Dextromethorphan

DM further increases NE as an NE reuptake inhibitor$^{1,2}$

Abbreviations: DM = Dextromethorphan; NE = Norepinephrine


© Axsome Therapeutics, Inc.
Conventional Antidepressant Mechanisms and Additive Effects of Dextromethorphan

DM increases 5-HT as a 5-HT reuptake inhibitor and σ1 agonist that boosts 5-HT activity from the dorsal raphe\(^1,\)\(^2\)

DM further increases NE as an NE reuptake inhibitor\(^1,\)\(^2\)

---


Abbreviations: NE = Norepinephrine; DA = Dopamine; 5-HT = Serotonin
Combination Treatments for TRD

• Monoaminergic combinations
  – Combining antidepressants of differing mechanisms may be superior to monotherapy\(^1\)
  – Augmenting with an atypical antipsychotic (aripiprazole, olanzapine, quetiapine, brexpiprazole, cariprazine)

Abbreviations: TRD = Treatment-Resistant Depression.
Combination Treatment From Initiation of Therapy

• Problem: current treatments based on monoamine pathways may be ineffective

• Potential solution: evidence that combinations of mechanisms are effective when single mechanisms fail

• Also, seems not be about which therapy but when therapy, so why not give the best treatments first?

• Analogy with tuberculosis, HIV
A randomized trial was conducted to assess effects of antidepressant monotherapy or combination therapy on HAM-D for 6 weeks\(^1\)

Combination therapies reduced depression scores


Abbreviations: MDD = Major Depressive Disorder; HAM-D = Hamilton Depression Rating Scale
Combination Treatments for TRD

• Non-monoamine approaches
  – Opioid augmentation (ALKS 5461)
  – Ketamine infusions/intranasal

Abbreviations: TRD = Treatment-Resistant Depression.
Ketamine: 4 Key Mechanisms of Action, Including Glutamate NMDA Receptor Antagonism/σ1 Agonism

1Figure adapted from: Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge University Press; 2013. Abbreviations: SERT = Serotonin Reuptake Transporter; NET = Norepinephrine Reuptake Transporter; NMDA = N-methyl-D-aspartate
Glutamate Receptors

1Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013. Abbreviations: Glu = Glutamate; vGluT = Glutamate Vesicular Transporter; NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.
Overlap in Binding Properties of DM and Ketamine for Monoamines (NE and 5-HT)

**Ketamine**
- 5-HT reuptake inhibition
  - Rat brain synaptosomes
  - Human kidney cells
  - Ketamine $K_i$: 162 µM
  - DM $K_i$: 23 nM

**Dextromethorphan**
- NE reuptake inhibition
  - Rat brain synaptosomes
  - Human kidney cells
  - Ketamine $K_i$: 67 µM
  - DM $K_i$: 240 nM

**SERT: DM >> ketamine**

**NET: DM >> ketamine**

---

1 Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.

Abbreviations: DM = Dextromethorphan; SERT = Serotonin Reuptake Transporter; NET = Norepinephrine Reuptake Transporter; 5-HT = Serotonin.
Overlap in Binding Properties of DM and Ketamine for Unconventional Mechanisms

Ketamine

NMDA receptor
*Rat cerebellar granule neurons*¹

Ketamine IC₅₀: 1047 nM
DM IC₅₀: 402 nM

*σ¹ agonist activity
*Rat cerebellum*² or *PC12 cells*⁴

Ketamine Kᵢ: 140 µM
DM Kᵢ: 150 nM

Dextromethorphan

NMDA antagonism: DM > ketamine⁵

*σ¹ agonism: DM > ketamine⁵

Abbreviations: DM = Dextromethorphan; SERT = Serotonin Reuptake Transporter; NET = Norepinephrine Reuptake Transporter; NMDA = N-methyl-D-aspartate.

¹Figure adapted from: Stahl SM. *Stahl’s Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
• Ketamine and DM are potent NMDAR antagonists, which may have rapid antidepressant activity hypothesized to take place from increased glutamate activity in the prefrontal cortex\(^1\)\(^\text{-}\)\(^3\)

\(^3\)Nguyen L, Matsumoto RR. *Behav Brain Res*. 2015;295:26-34.

Abbreviations: DM = Dextromethorphan; Glu = glutamate; NMDAR = N-methyl-D-aspartate Receptor.
Unconventional Antidepressant Mechanisms: Ketamine and DM Actions on NMDA Receptors

• Activation of AMPA receptors induced by NMDA receptor blockade induces downstream cascades involved in neural plasticity that may underlie antidepressant-like effects\(^1-^3\)


Abbreviations: DM = Dextromethorphan; Glu = glutamate; NMDAR = N-methyl-D-aspartate Receptor; \(\); AMPA = \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.
# Double Synergy Combining DM With Bupropion for Treatment of TRD From Unconventional Mechanisms

<table>
<thead>
<tr>
<th>AXS-05 = Bupropion + Dextromethorphan</th>
<th>DA</th>
<th>NE</th>
<th>σ1</th>
<th>NE</th>
<th>5-HT</th>
<th>NMDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Darker shading = Evidence for high importance for disease  
Lighter shading = Evidence for target to have some relevance for disease  
No shading = No evidence for involvement

Abbreviations: DM = Dextromethorphan; NE = Norepinephrine; DA = Dopamine; 5-HT = Serotonin; NMDA = N-methyl-D-aspartate; TRD = Treatment-Resistant Depression.
Summary of Advantages of Combining DM With Bupropion for TRD

• Similar to quinidine, bupropion enhances and controls delivery of DM to reduce side effects and maintain duration of action

• Unlike quinidine combination with DM or deuteration of DM, bupropion also enhances the monoamines dopamine and norepinephrine with a proven antidepressant

Abbreviations: DM = Dextromethorphan; TRD = Treatment-Resistant Depression.
Clinical Rationale: DM and Quinidine Reduce Depressive Symptoms in TRD

- Patients with TRD had failed to respond to >2 antidepressant medication trials
- Patients started on DM/Q 20/10 mg daily and titrated to DM/Q 20/10 mg every 12 h during Week 2
- Patients titrated to DM/Q 45/10 mg every 12 h and maintained through Week 10

- 45% of patients had ≥50% reduction in MADRS
  **P<.01 versus baseline

Abbreviations: DM = Dextromethorphan; TRD = Treatment-Resistant Depression; Q = Quinidine.
WHAT IS A COMPELLING REASON TO BELIEVE THESE COMBINATIONS OF MECHANISMS WOULD BE EFFECTIVE FOR ALZHEIMER’S AGITATION?
**Double Synergy From Combining DM With Bupropion Across Disease States**

<table>
<thead>
<tr>
<th>AXS-05 =</th>
<th>Bupropion</th>
<th>+</th>
<th>Dextromethorphan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DA</td>
<td>NE</td>
<td>σ1</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>AD Agitation</strong></td>
<td>2D6 Inhibition</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Darker shading = Evidence for high importance for disease  
Lighter shading = Evidence for target to have some relevance for disease  
No shading = No evidence for involvement

Abbreviations: DM = Dextromethorphan; NE = Norepinephrine; DA = Dopamine; 5-HT = Serotonin; NMDA = N-methyl-D-aspartate.
Agitation in AD Overview

• Agitation and aggression seen in approximately 45% of AD patients during 5-year period\(^3\)

• Characterized by emotional distress, aggressive behaviors, disruptive irritability, disinhibition, and caregiver burden\(^4\)

• Associated with\(^4,5\):
  – Accelerated cognitive decline
  – Earlier nursing home placement
  – Increased mortality

• No approved medication = unmet medical need

• Proof of concept: DM plus metabolic inhibitor reduced agitation in AD patients


Abbreviations: DM = Dextromethorphan; AD = Alzheimer’s Disease.
Agitation in AD Clinical Rationale

• Randomized, double-blind, placebo-controlled, 2-stage trial
  – Placebo (n=125), 30 mg DM + 10 mg quinidine (Q) (n=93), for stage 1
• DM+Q treatment reduced agitation/aggression in AD by 46% vs 24% for placebo (P<.001)—primary endpoint
• Statistically significant improvement in multiple secondary endpoints
• DM plasma levels achieved with AXS-05 in target therapeutic range
• Potential for additional contribution from bupropion component of AXS-05

Abbreviations: DM = Dextromethorphan; Q = Quinidine; AD = Alzheimer’s Disease; NPI = Neuropsychiatric Inventory.
WHAT IS A COMPELLING REASON TO BELIEVE THESE COMBINATIONS OF MECHANISMS WOULD BE EFFECTIVE FOR SMOKING CESSATION?
Conventional Smoking Cessation Mechanisms of AXS-05 From Bupropion

• Nicotine acts on α4β2 nicotinic cholinergic receptors in the mesolimbic DA pathway\(^1\)

• Nicotine's actions at α4β2 postsynaptic receptors on dopaminergic neurons cause DA release\(^1\)


Abbreviations: DA = Dopamine; ACh = Acetylcholine; VTA = Ventral Tegmental Area.
Conventional Smoking Cessation
Mechanisms of AXS-05 From Bupropion

- With the discontinuation of smoking, there is a lack of nicotine\(^1\)
- During withdrawal, dopamine is no longer released at the same levels\(^1\)

Abbreviations: DA = Dopamine; ACh = Acetylcholine; VTA = Ventral Tegmental Area.
Bupropion is a DA reuptake inhibitor\(^1\)

It increases the availability of DA to replace the deficit of dopamine and to alleviate cravings during smoking cessation\(^1\)

---


Abbreviations: DA = Dopamine; ACh = Acetylcholine; VTA = Ventral Tegmental Area.
Dextromethorphan and Bupropion Combination May Block Rewarding Effects of Smoking

• Nicotine's actions at α4β2 postsynaptic receptors on dopaminergic neurons cause DA release\(^1\)

• DM, bupropion, and bupropion’s active metabolite (2S,3S)-hydroxybupropion block nicotinic α4β2 receptors\(^2,3\)

• Both DM and Bupropion are relatively weak α4β2 antagonists, but together they may have synergistic effects


Abbreviations: DA = Dopamine; ACh = Acetylcholine; VTA = Ventral Tegmental Area.
Summary: Double Synergy Combining DM With Bupropion

• An additive approach across all 3 disease states:
  – For TRD, adding BUP to DM has the effect of boosting monoamines for conventional depression treatment while targeting unconventional mechanisms (Sigma-1 and NMDA)
  – For Alzheimer’s disease agitation, adding BUP to DM increases DM plasma concentrations to target mechanisms hypothesized to have importance for both Alzheimer’s disease and emotional regulation (Sigma-1 and NMDA)
  – For smoking cessation, adding BUP to DM has the effect of boosting dopamine for conventional smoking cessation treatment while also targeting receptors related to the rewarding effects of nicotine (α4β2)

Abbreviations: DM = Dextromethorphan; BUP = Bupropion; TRD = Treatment-Resistant Depression; NMDA = N-methyl-D-aspartate.
AXSOME THERAPEUTICS

Thank you.

For more information, please contact
Mark Jacobson
SVP, Operations
212-332-3243
mjacobson@Axsome.com
axsome.com