AXSOME THERAPEUTICS

Psychopharmacology of AXS-05: Potential Clinical Implications

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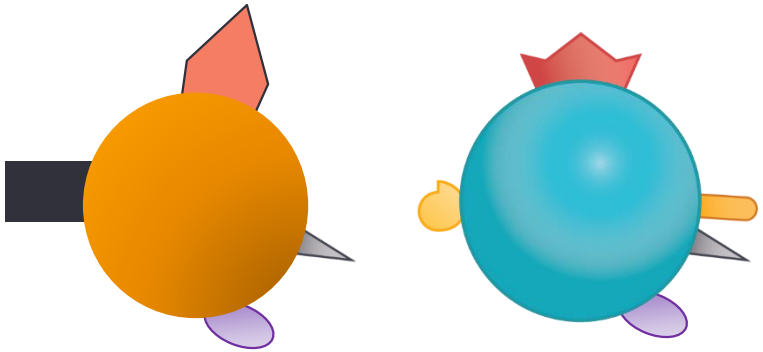
What Is AXS-05?



- 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

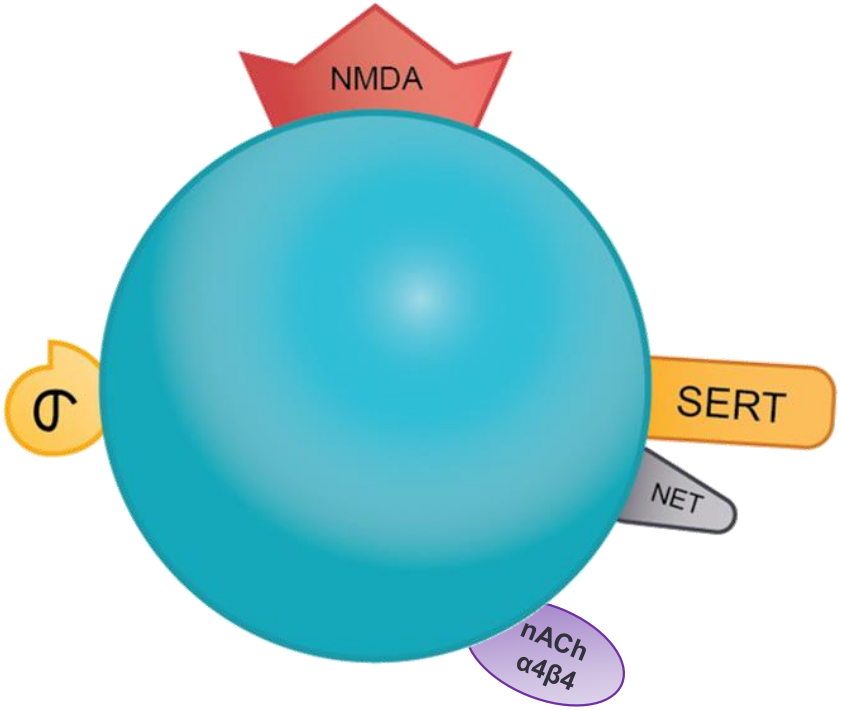
[1]Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* Cambridge University Press; 2013.

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

Dextromethorphan[1]

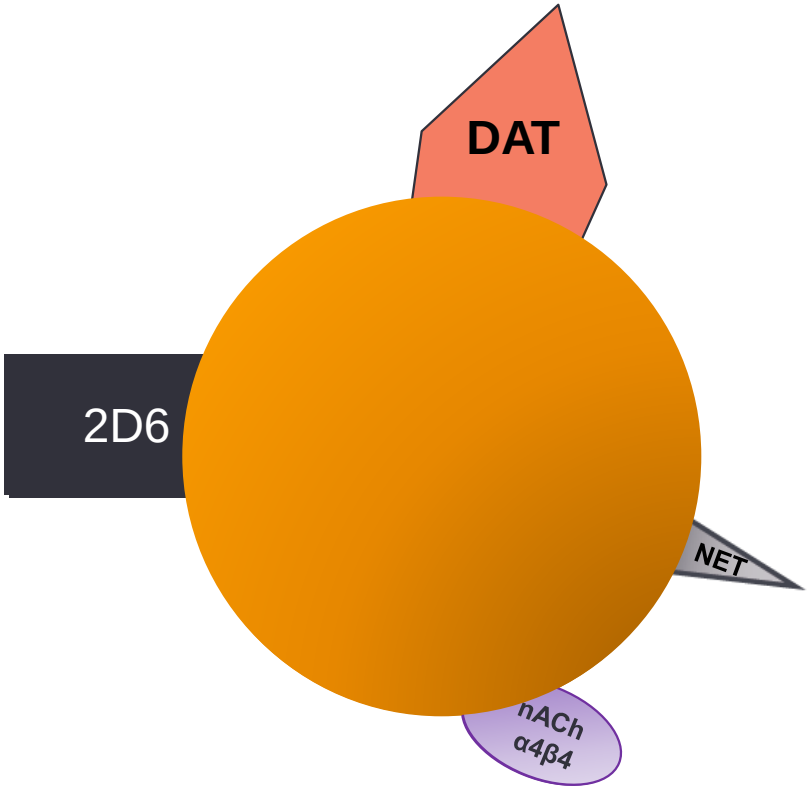


Abbreviations: SERT= Serotonin Reuptake Transporter; NET = Norepinephrine Reuptake Transporter; nACh = Nicotinic Acetylcholine Receptor; CYP 450 2D6 = Cytochrome P450 2D6; NMDA = N-methyl-D-aspartate

[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

Bupropion[1]

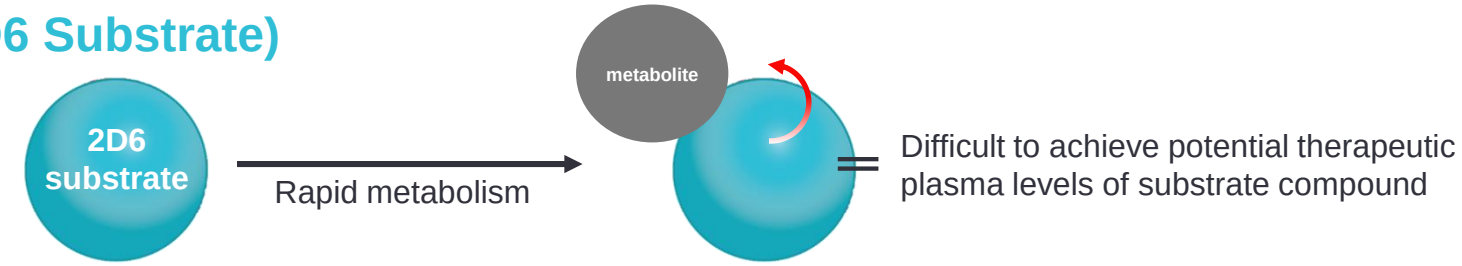


Abbreviations: DAT = Dopamine Reuptake Transporter;; NET = Norepinephrine Reuptake Transporter; nACh = Nicotinic Acetylcholine Receptor; CYP 450 2D6 = Cytochrome P450 2D6

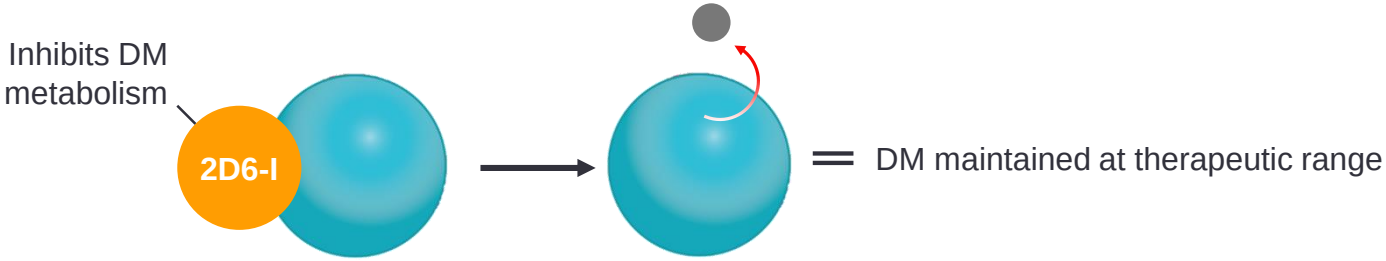
[1]Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* Cambridge University Press; 2013.

AXS-05: A Novel Combination Therapy for CNS Disorders

DM (2D6 Substrate)

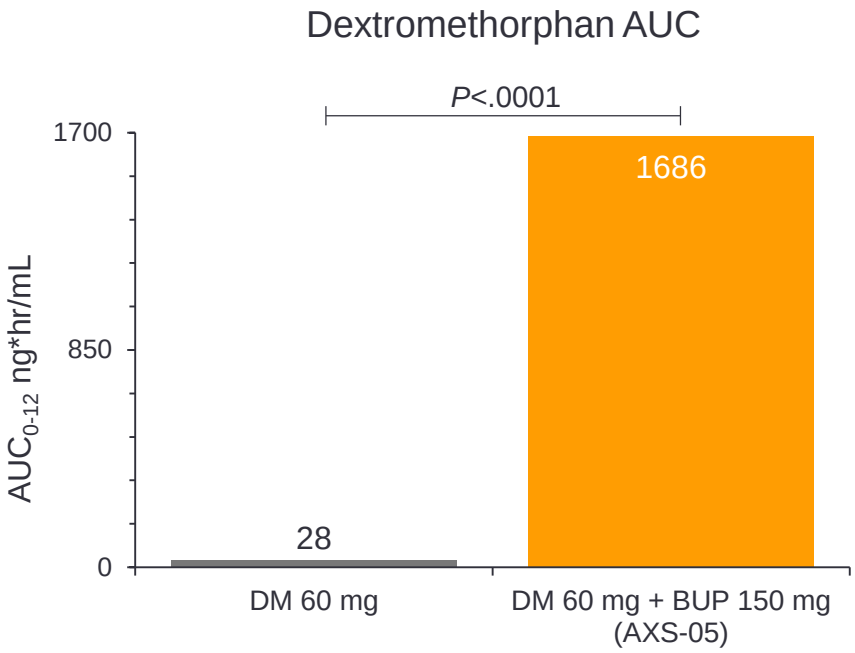


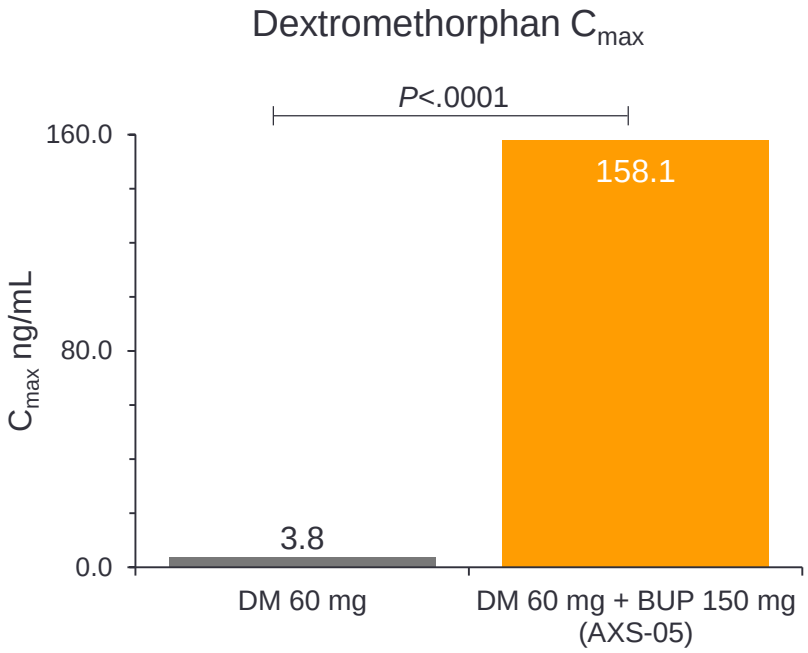
BUP (2D6-I)



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

Phase 1 Results





Dose†	AUC_{0-12} ng*hr/mL
DM 20 mg + Q 10 mg	525
DM 30 mg + Q 10 mg	883

Dose†	C_{max} ng/mL
DM 20 mg + Q 10 mg	53
DM 30 mg + Q 10 mg	85

Axsome data on file.
†Nuedexta® NDA 021879, FDA Clinical Pharmacology Review.
Abbreviations: DM = Dextromethorphan; Q = Quinidine; BUP = Bupropion

AXSOME THERAPEUTICS

WHAT IS THE COMPELLING REASON TO BELIEVE THESE COMBINATIONS OF MECHANISMS WOULD BE EFFECTIVE FOR TREATMENT-RESISTANT DEPRESSION?

Treatment-Resistant Depression (TRD) Overview

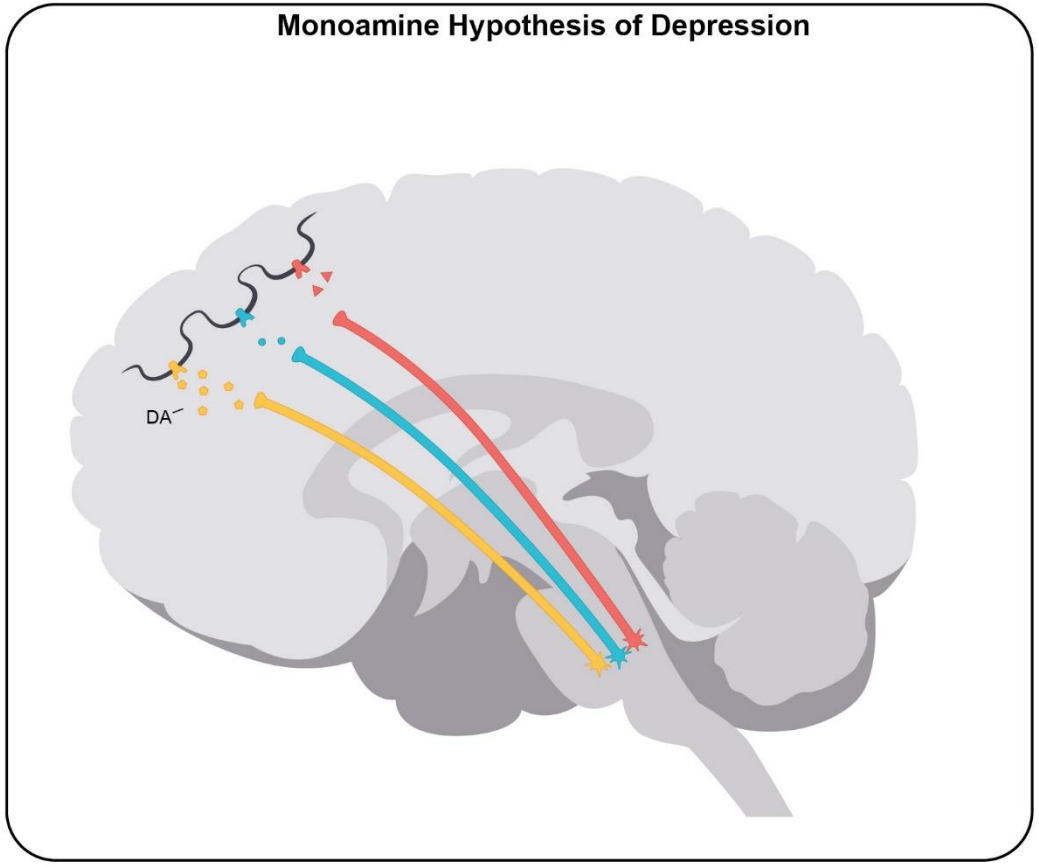
- Major Depressive Disorder (MDD) is a leading cause of disease burden in the United States[5]
- 63% and 44% of MDD patients have inadequate response to initial therapy and second-line therapy, respectively [2,3]
- Only 1 approved drug for TRD creates an unmet medical need
- AXS-05 combines the MOA of 4 distinct anti-depressant drug classes into 1 novel oral therapeutic

3M patients in the US[1,2,4]

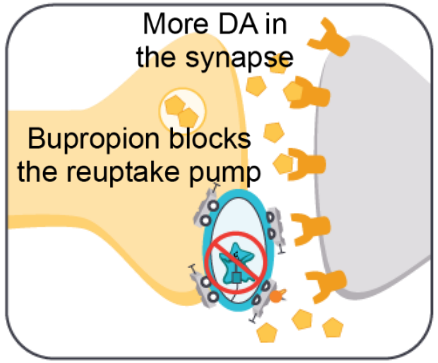
[1]Marcus SC, et al. *Arch Gen Psychiatry.* 2010;67:1265-1273.
[2]Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905-1917.
[3]Bschor T, et al. *J Clin Psychiatry*. 2018;79(1).
[4]U.S. Census Bureau. Population April 1, 2010 to July 1, 2013. Accessed April 12, 2018.
[5]Mathers CD, et al. *PLoS Me*d. 2006; 3(11): e442.
Abbreviations: MOA = Mechanism of Action; MDD = Major Depressive Disorder; TRD = Treatment-Resistant Depression.

AXSOME THERAPEUTICS

Conventional Antidepressant Mechanisms of Bupropion

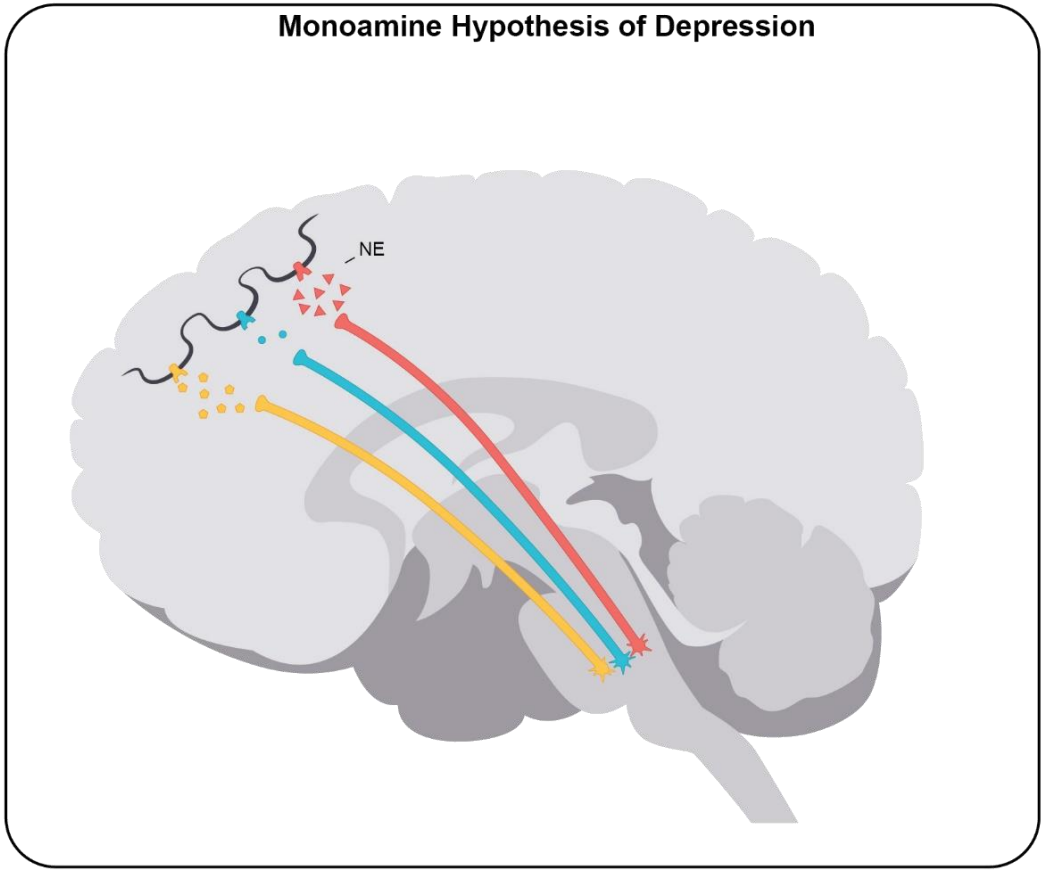


Bupropion increases availability of DA by blocking reuptake[1]



[1]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
Abbreviations: NE = Norepinephrine; DA = Dopamine; 5-HT = Serotonin.

Conventional Antidepressant Mechanisms of Bupropion



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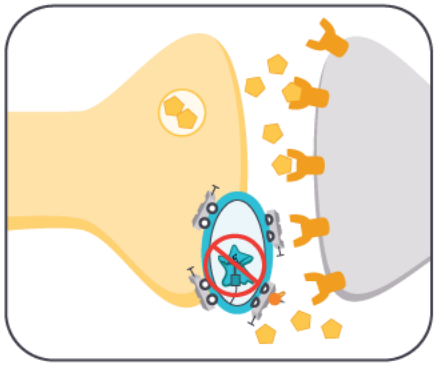
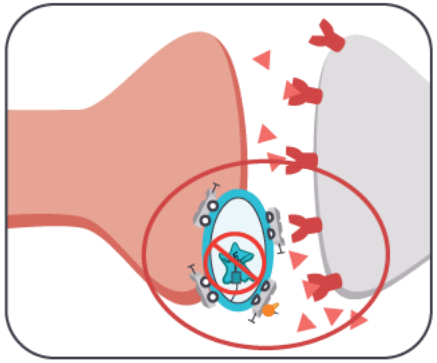


Bupropion increases NE as an NE reuptake inhibitor[1]



[1]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
Abbreviations: NE = Norepinephrine; DA = Dopamine; 5-HT = Serotonin.

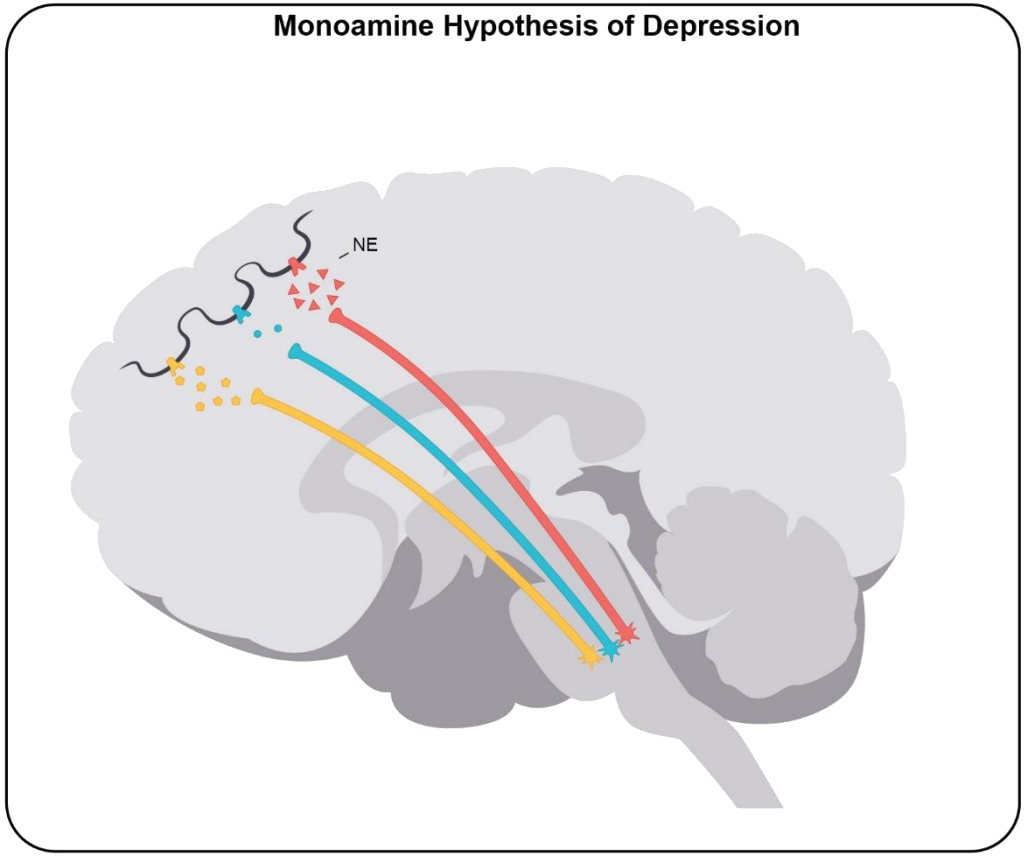
Additive Effects of AXS-05 to Address Monoamine Hypothesis of Depression

AXS-05 =	Bupropion		+	Dextromethorphan		
	DA	NE		σ1	NE	5-HT
Depression			+			

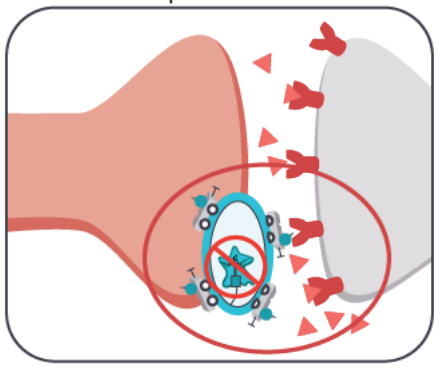
Darker shading = Evidence for high importance for disease
Lighter shading = Evidence for target to have some relevance for disease
No shading = No evidence for involvement

Abbreviations: NE = Norepinephrine; DA = Dopamine; 5-HT = Serotonin.

Conventional Antidepressant Mechanisms and Additive Effects of Dextromethorphan

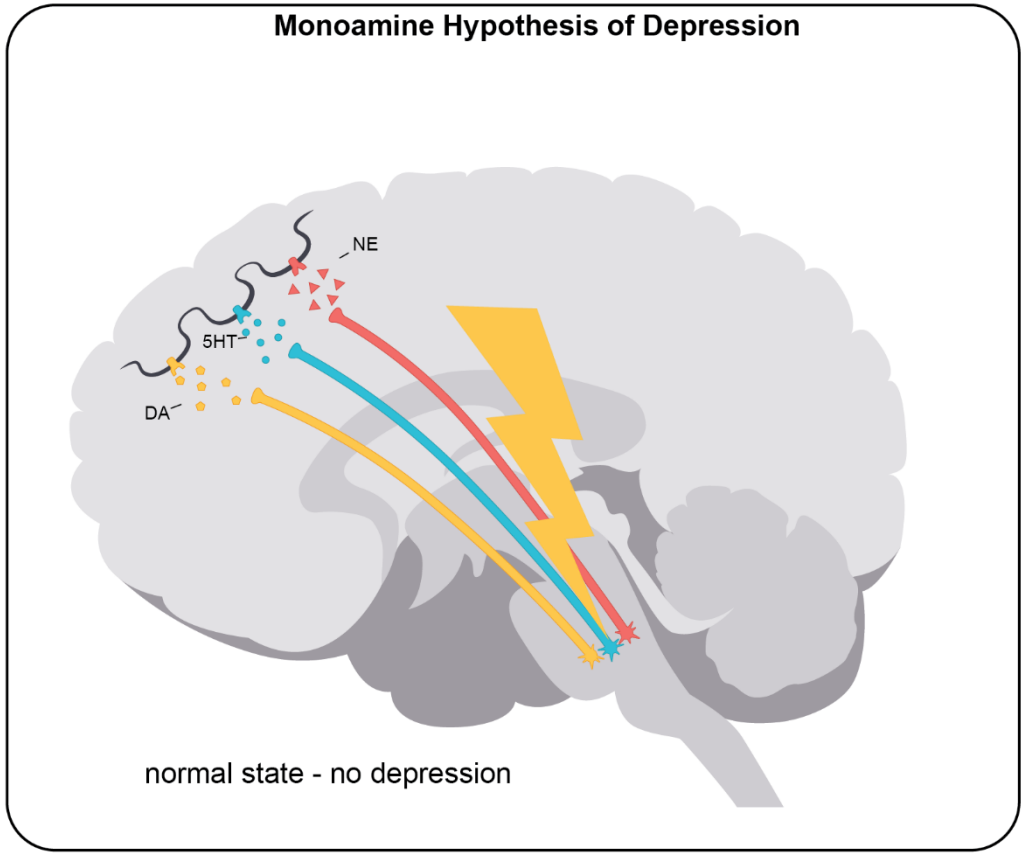


DM further increases NE as an NE reuptake inhibitor[1,2]



[1]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[2]Lauterbach EC. *Med Hypotheses*. 2012;78(6):693-702.
Abbreviations: DM = Dextromethorphan; NE = Norepinephrine

Conventional Antidepressant Mechanisms and Additive Effects of Dextromethorphan



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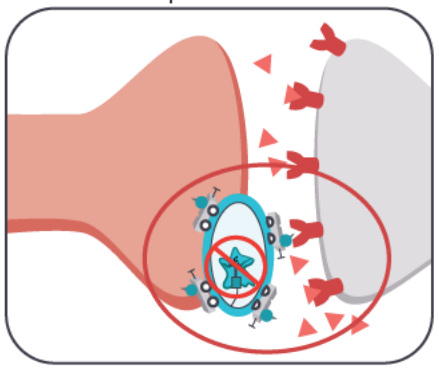
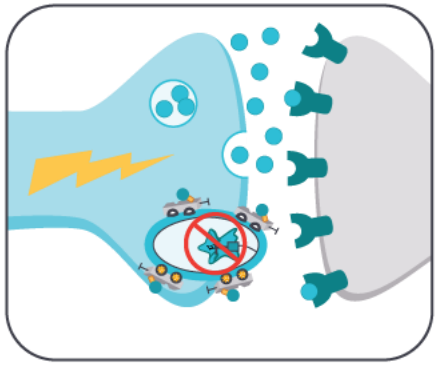


DM increases 5-HT as a 5-HT reuptake inhibitor and σ1 agonist that boosts 5-HT activity from the dorsal raphe[1,2]



[1]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[2]Lauterbach EC. *Med Hypotheses*. 2012;78(6):693-702.
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)

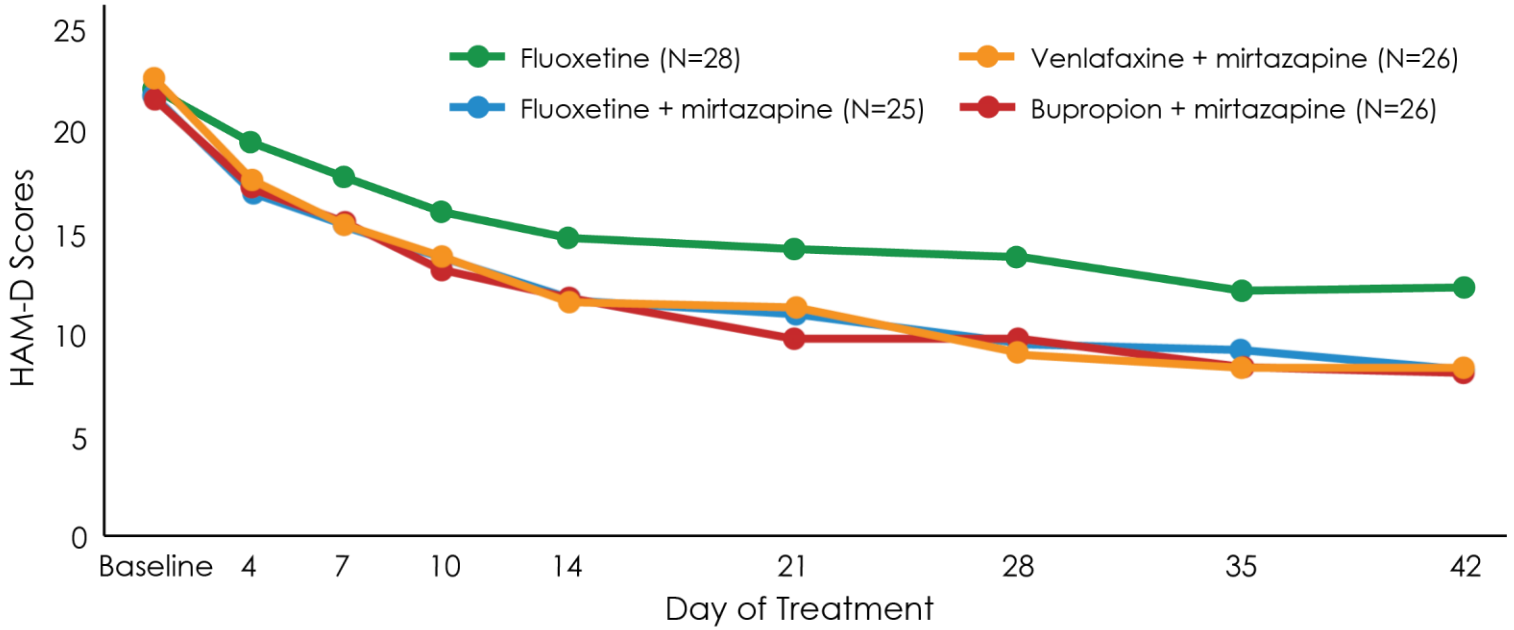
[1]Henssler J, et al. *Can J Psychiatry*. 2016;61(1):29-43.
Abbreviations: TRD = Treatment-Resistant Depression.

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

Combination of Antidepressant Medications From Treatment Initiation for MDD

- 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



*Statistically significant difference between fluoxetine monotherapy and all combination treatment groups (F=3.87; df=3,101; *P*=.011)

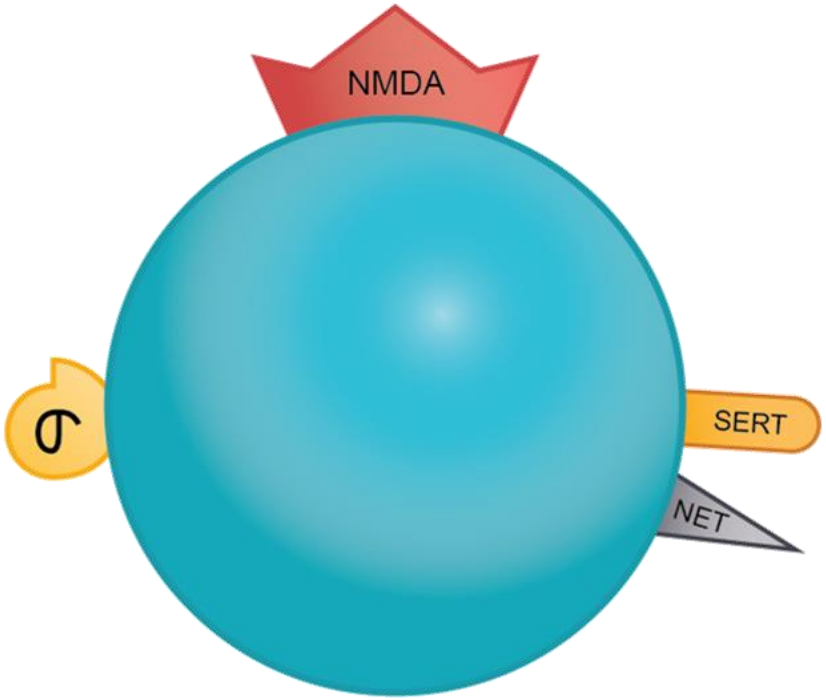
[1]Blier P, et al. *Am J Psychiatry*. 2010;167:281-288.
Abbreviations: MDD = Major Depressive Disorder; HAM-D = Hamilton Depression Rating Scale

Combination Treatments for TRD

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

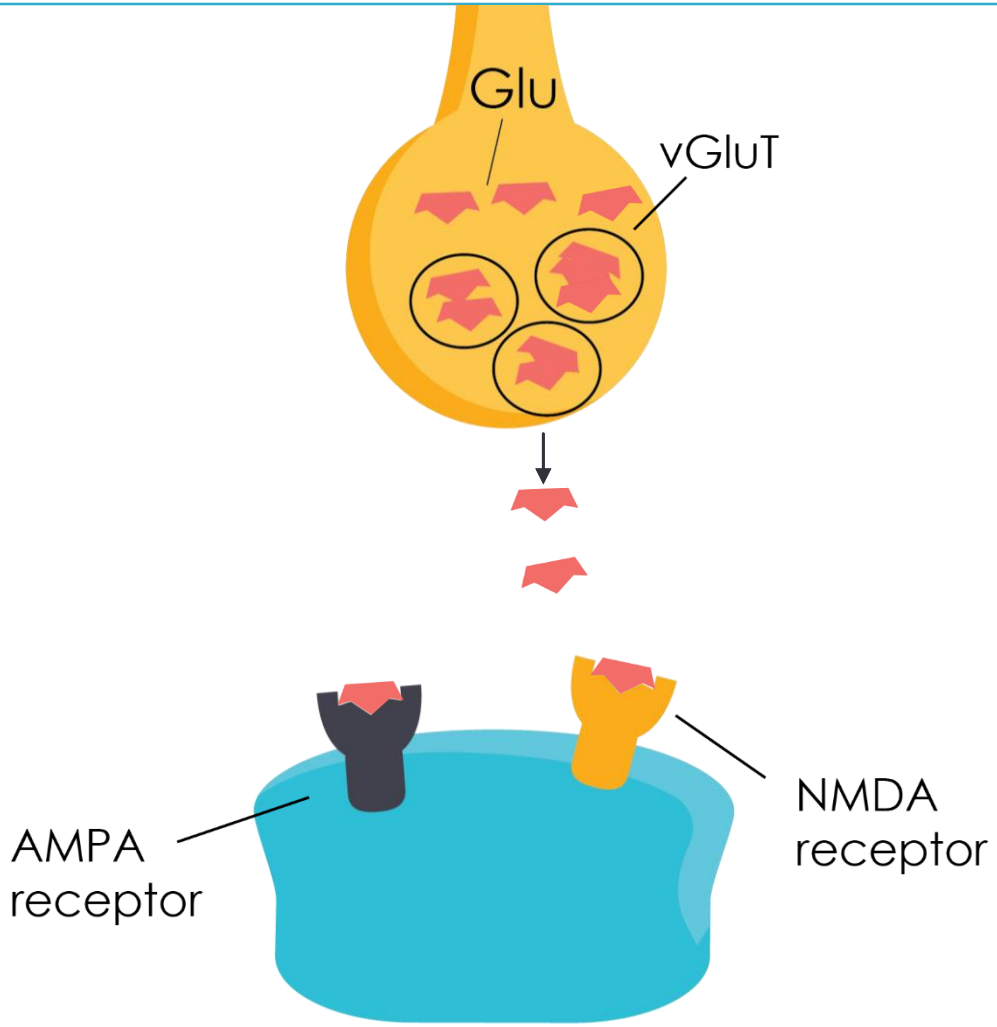
Abbreviations: TRD = Treatment-Resistant Depression.

Ketamine: 4 Key Mechanisms of Action, Including Glutamate NMDA Receptor Antagonism/σ1 Agonism



[1]Figure 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

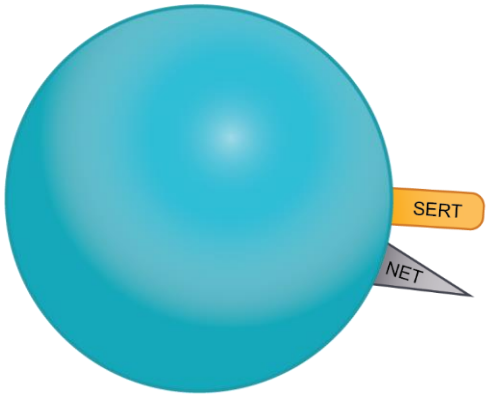
Glutamate Receptors



[1]Figure 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[1]



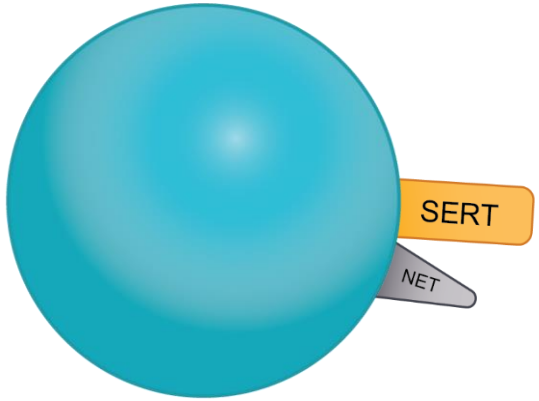
5-HT reuptake inhibition
Rat brain synaptosomes[2]
Human kidney cells[3]

Ketamine K_i: 162 µM
DM K_i: 23 nM

NE reuptake inhibition
Rat brain synaptosomes[2]
Human kidney cells[3]

Ketamine K_i: 67 µM
DM K_i: 240 nM

Dextromethorphan[1]



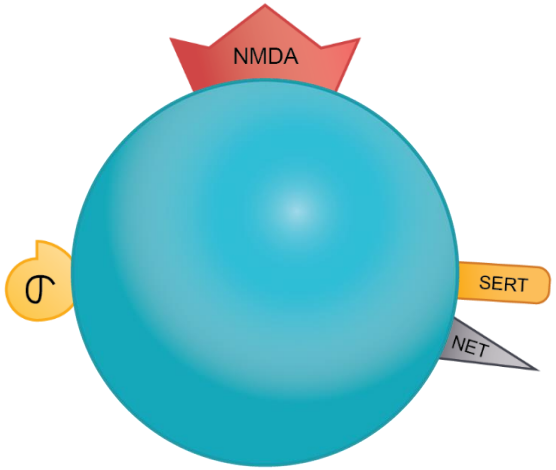
SERT: DM >> ketamine[4]

NET: DM >> ketamine[4]

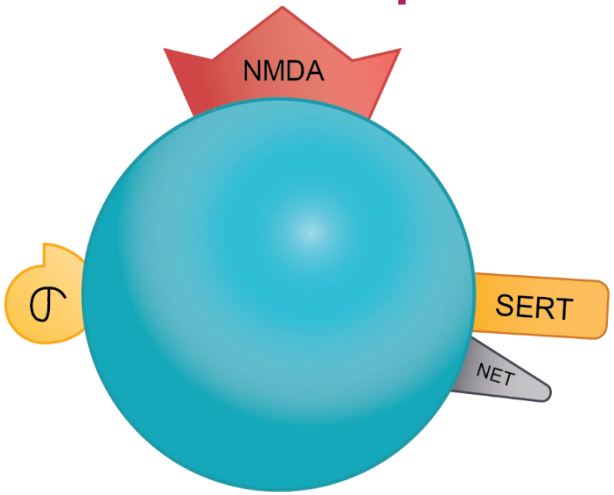
[1]Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[2]Taylor CP, et al. *Parmacol Ther*. 2016;164:170-182.
[3]Nishimura M, et al. *Anesthesiology: The Journal of the American Society of Anesthesiology*.1998;88(3):768-774.
[4]Lauterbach EC. *Med Hypotheses*. 2012;78(6):693-702.
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[1]



Dextromethorphan[1]



NMDA receptor *Rat cerebellar granule neurons*[2]	σ1 agonist activity *Rat cerebellum*[3] *or PC12 cells*[4]
Ketamine IC_{50}: 1047 nM DM IC_{50}: 402 nM	Ketamine K_i: 140 µM DM K_i : 150 nM

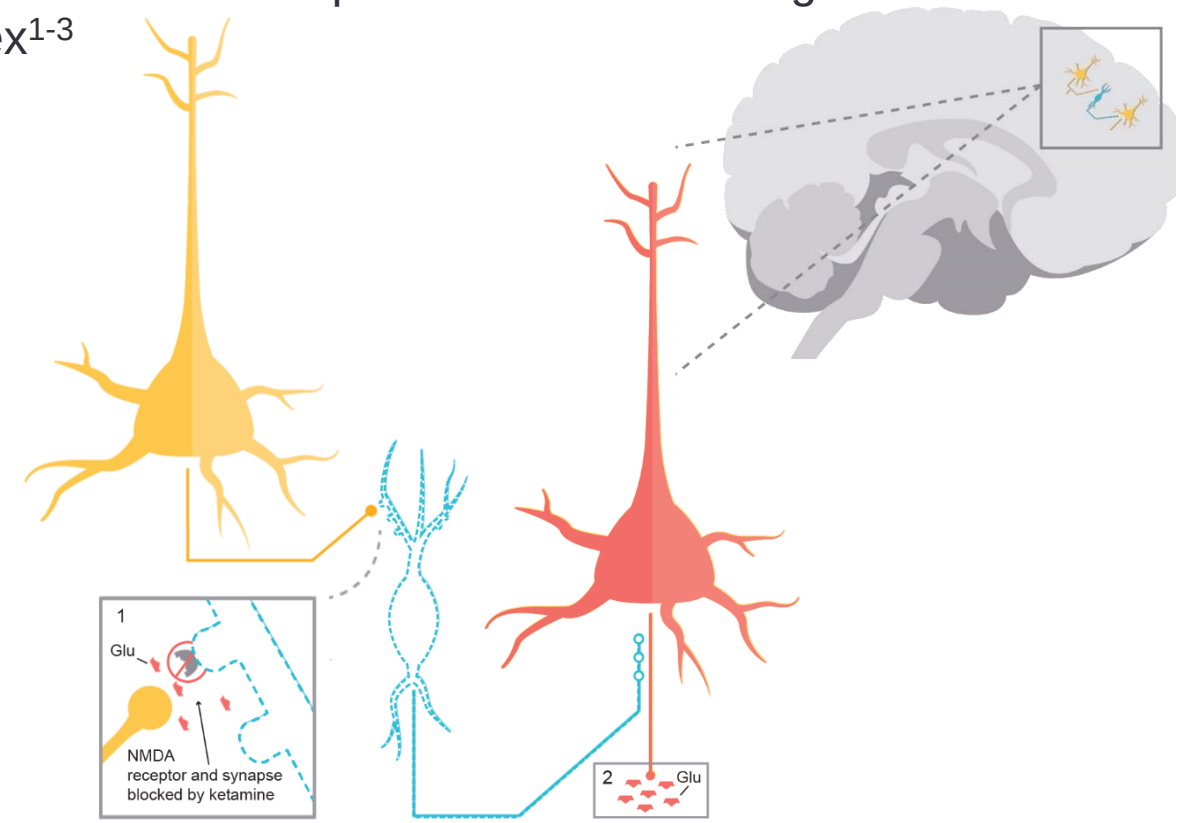
NMDA antagonism: DM > ketamine[5]

σ1 agonism: DM > ketamine[5]

[1]Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[2]Berman FW, et al. J Biochem Toxicol. 1996;11(5):217-226.
[3]Werling LL, et al. *Exp Neurol*. 2007;207(2):248-257.
[4]Robson MJ, et al. *Eur Neuropsychopharmacol*. 2012; 22(4):308-317.
[5]Lauterbach EC. *Med Hypotheses*. 2012;78(6):693-702.
Abbreviations: DM = Dextromethorphan; SERT= Serotonin Reuptake Transporter; NET = Norepinephrine Reuptake Transporter; NMDA = N-methyl-D-aspartate.

Unconventional Antidepressant Mechanisms: Ketamine and DM Actions on NMDA Receptors

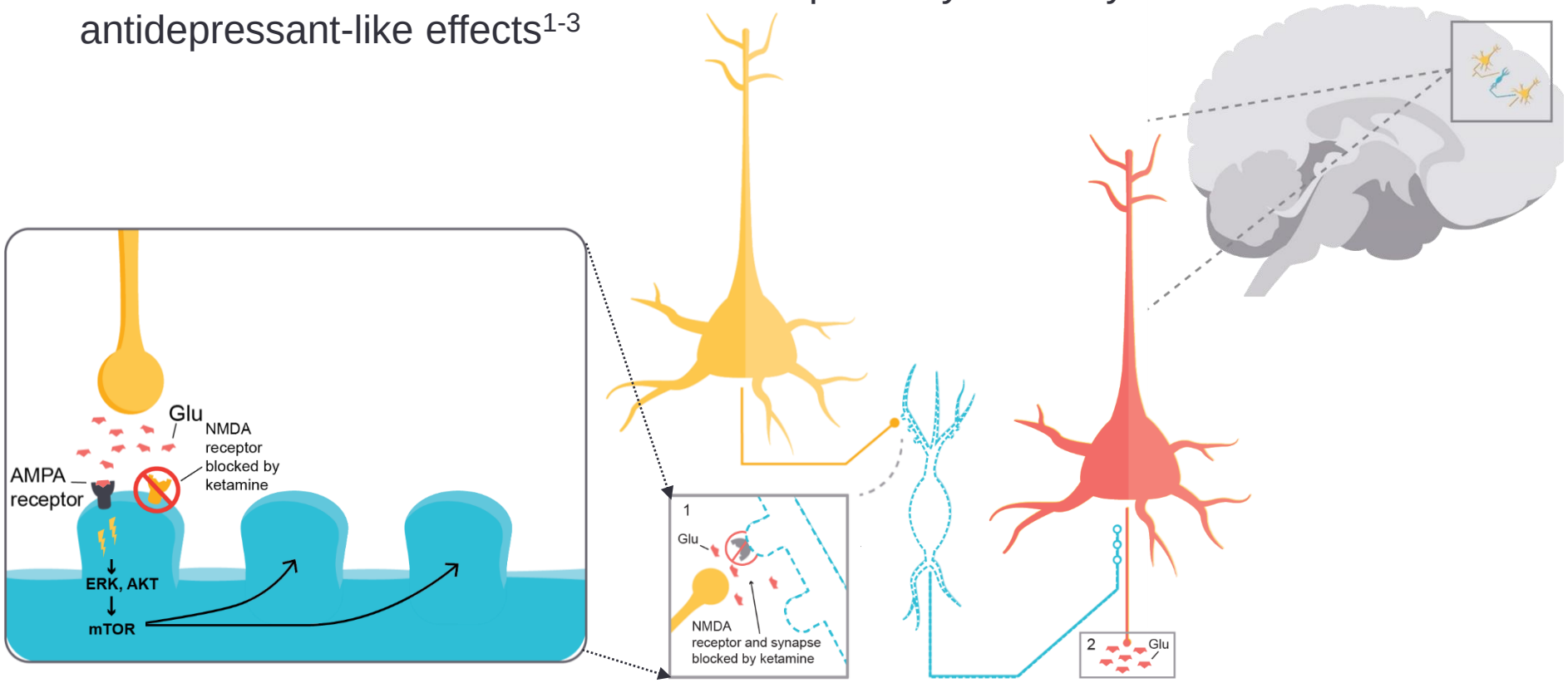
- Ketamine and DM are potent NMDAR antagonists, which may have rapid antidepressant activity hypothesized to take place from increased glutamate activity in the prefrontal cortex[1-3]



[1]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[2]Zarate C, et al. *Harv Rev Psychiatry*. 2010;18(5):293-303.
[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]



[1]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[2]Zarate Niciu MJ, et al. J Neural Transm (Vienna). 2014;121(8):907-924.
[3]Freudenberg F, et al. Neurosci Biobehav Rev. 2015;52:193-206.
Abbreviations: DM = Dextromethorphan; Glu = glutamate; NMDAR = N-methyl-D-aspartate Receptor; ; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.

Double Synergy Combining DM With Bupropion for Treatment of TRD From Unconventional Mechanisms

AXS-05 =	Bupropion		+	Dextromethorphan			
	DA	NE		σ1	NE	5-HT	NMDA
Depression			+				

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.

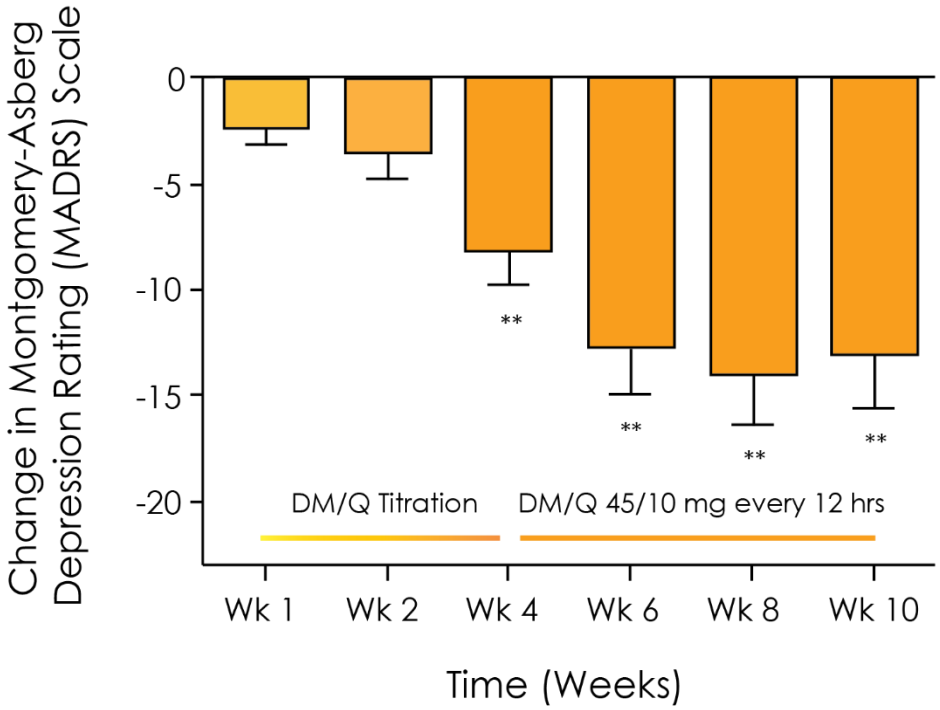
Summary of Advantages of Combining DM With Bupropion for TRD

- 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[1]
- 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

[1]Murrough J, et al. *J Affect Disord*. 2017;218:277-283.
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

AXS-05 =	Bupropion		+	Dextromethorphan			
	DA	NE		σ1	NE	5-HT	NMDA
Depression			+				
AD Agitation	2D6 Inhibition		+				

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

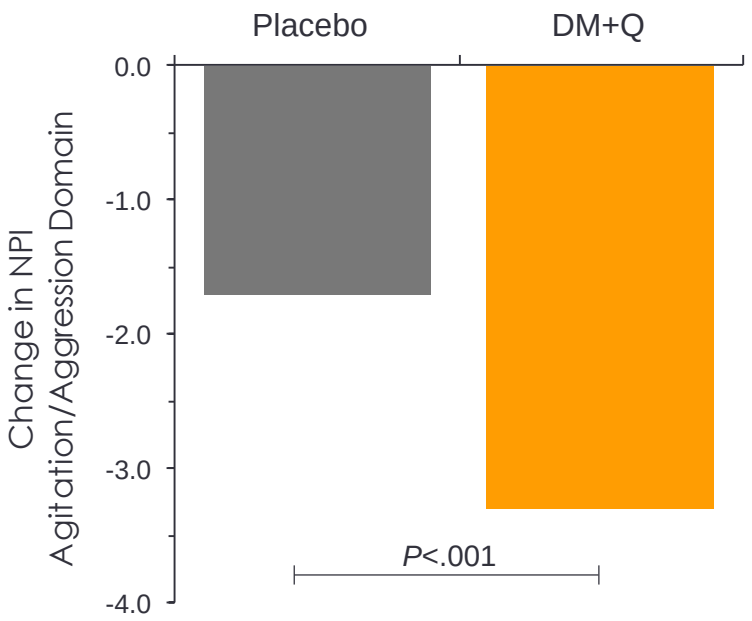
2M patients in the U.S.[1,2]

[1]Ryu SH, et al. *Am J Geriatr Psychiatry*. 2005;13:976-983.
[2]Hebert LE, et al. *Neurology*. 2013;80:1778-1783.
[3]Steinberg M, et al. *Int J Geriatr Psychiatry*. 2008;2:170-177.
[4]Antonsdottir IM, et al. *Expert Opin Pharmacother*. 2015;11:1649-1656.
[5]Rabins PV, et al. *Alzheimers Dement*. 2013; 9:204-207.
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

Change in Agitation/Aggression Scores in AD with DM and Metabolic Inhibitor Quinidine (Q)

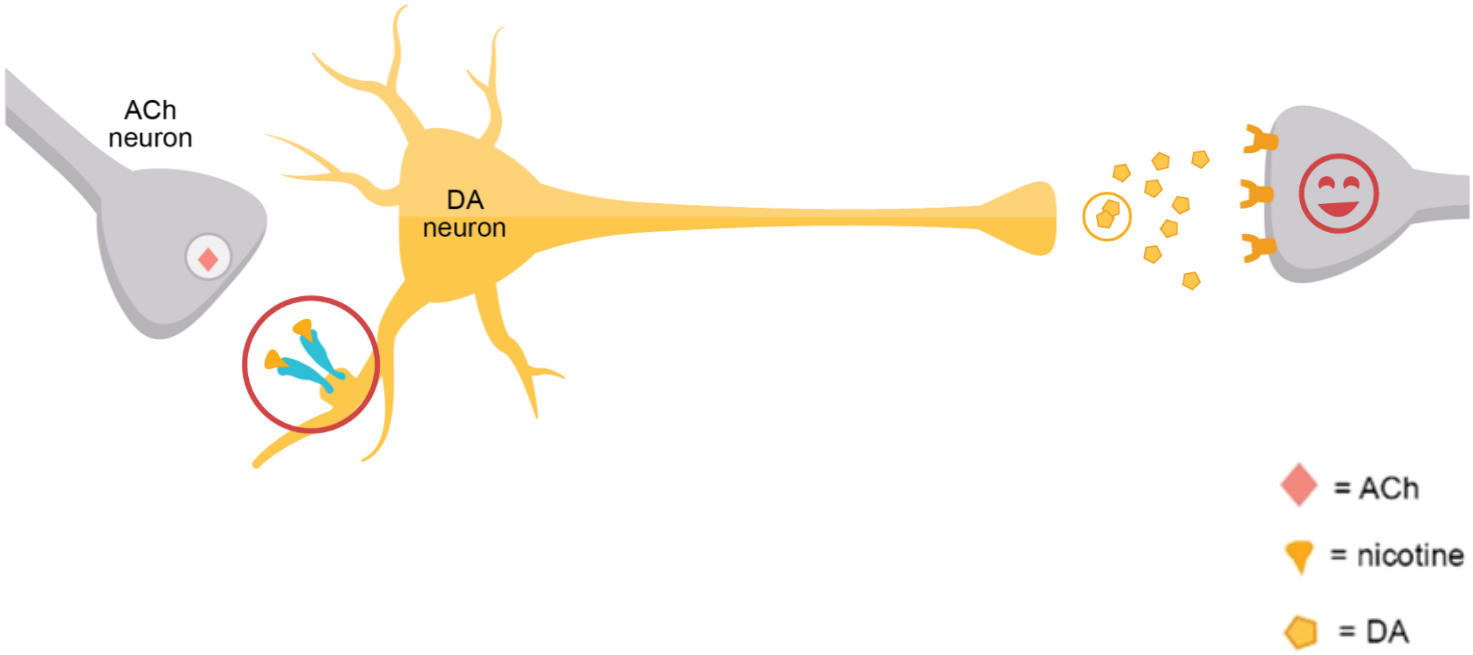


[1]Cummings J, et al. *JAMA*. 2015;314:1242-1254..
Abbreviations: DM = Dextromethorphan; Q = Quinidine; AD = Alzheimer's Disease; NPI = Neuropsychiatric Inventory.

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

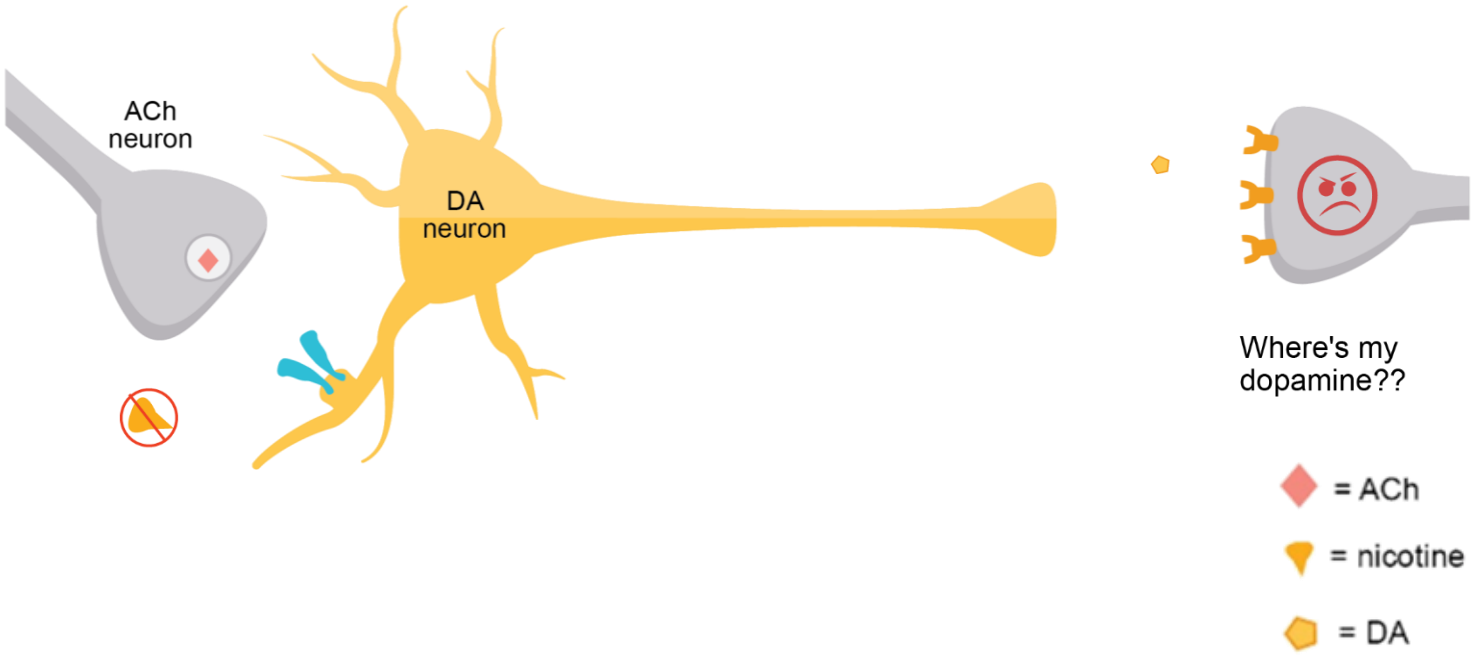
- Nicotine acts on α4β2 nicotinic cholinergic receptors in the mesolimbic DA pathway[1]
- Nicotine's actions at α4β2 postsynaptic receptors on dopaminergic neurons cause DA release[1]



[1]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
Abbreviations: DA = Dopamine; ACh = Acetylcholine; VTA = Ventral Tegmental Area.

Conventional Smoking Cessation Mechanisms of AXS-05 From Bupropion

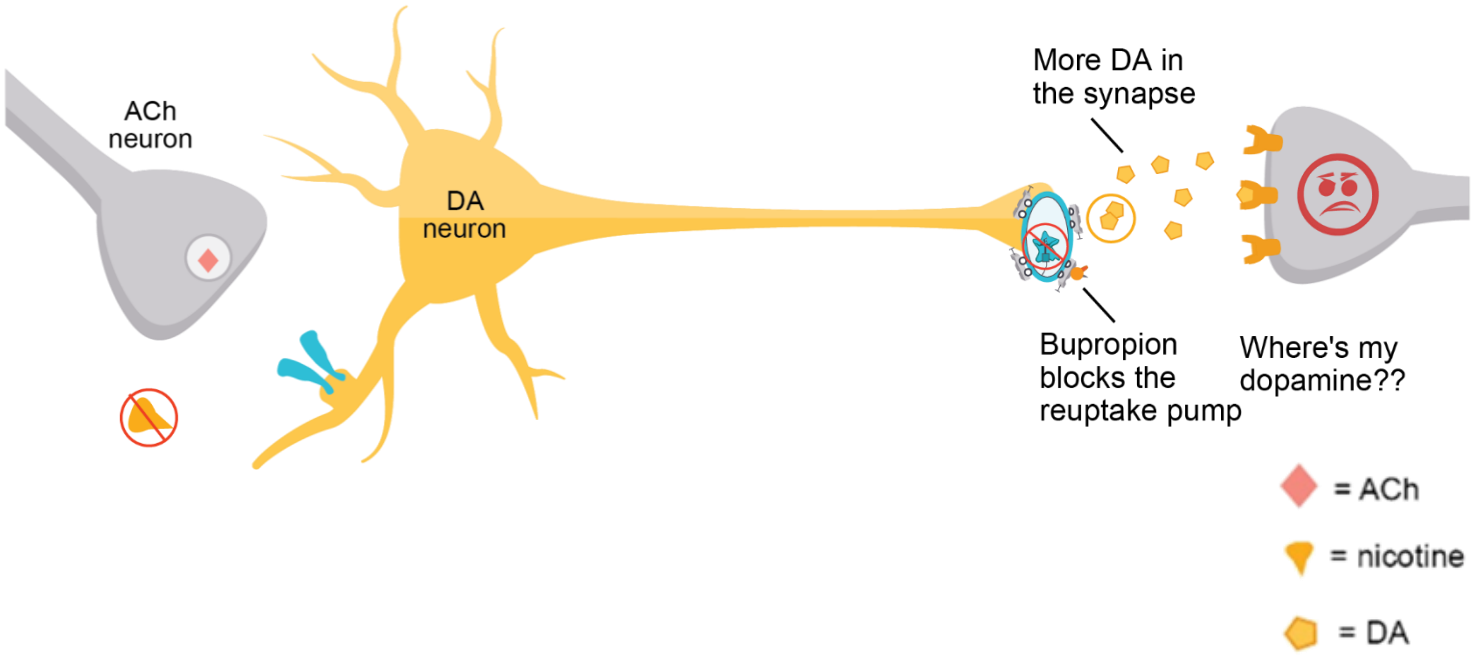
- With the discontinuation of smoking, there is a lack of nicotine[1]
- During withdrawal, dopamine is no longer released at the same levels[1]



[1]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
Abbreviations: DA = Dopamine; ACh = Acetylcholine; VTA = Ventral Tegmental Area.

Conventional Smoking Cessation Mechanisms of AXS-05 From Bupropion

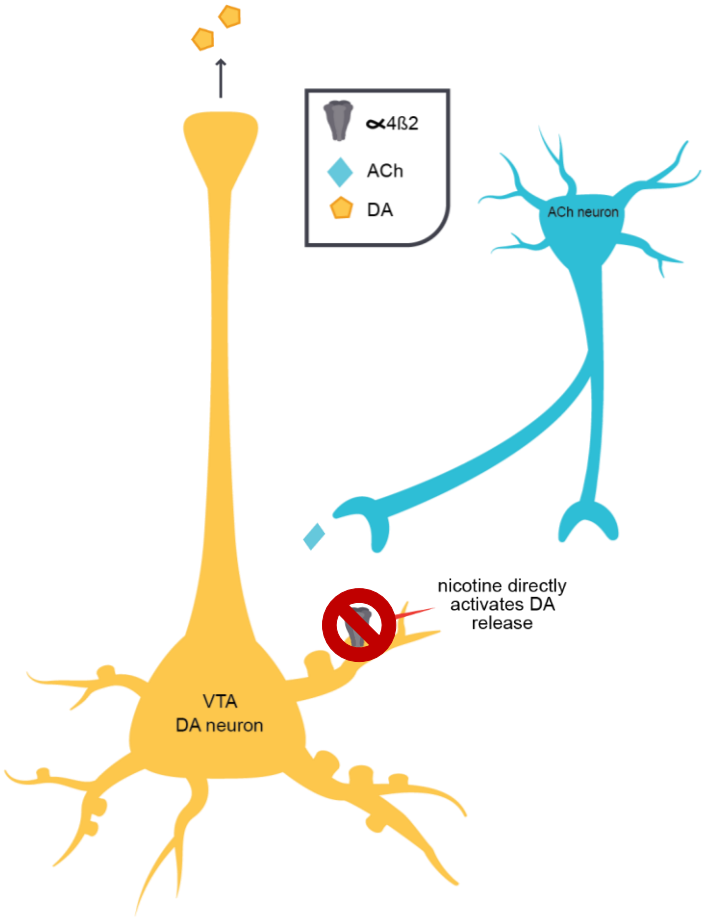
- Bupropion is a DA reuptake inhibitor[1]
- It increases the availability of DA to replace the deficit of dopamine and to alleviate cravings during smoking cessation[1]



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



[1]Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press; 2013.
[2]Carroll FI, et al. *Adv Pharmacol*. 2014;69:177-216.
[3]Damaj MI, et al. *J Pharmacol Exp Ther*. 2005;312(2):780-785.
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.

Q&A

AXSOME
THERAPEUTICS

Thank you.

For more information, please contact

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