

Pharmaco-economic Impact of Treatment Resistant Depression, Alzheimer's Disease Agitation, and Nicotine Dependence

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AXS-05 and Neuropsychiatric Disorders

- Axsome Therapeutics is developing AXS-05 for:
 - Treatment Resistant Depression
 - Agitation associated with Alzheimer's Disease
 - Nicotine Dependence
- Strong scientific rationale supports the clinical development of AXS-05 for these conditions.
- Furthermore, each of these conditions represents a significant unmet need:
 - No drug approved for AD agitation
 - Only one product approved for treatment resistant depression
 - Current treatments for nicotine dependence are few and suffer from limited efficacy and low adherence
- Each condition is associated with significant clinical, social and economic burden.

Economic Impact of Treatment Resistant Depression (TRD)

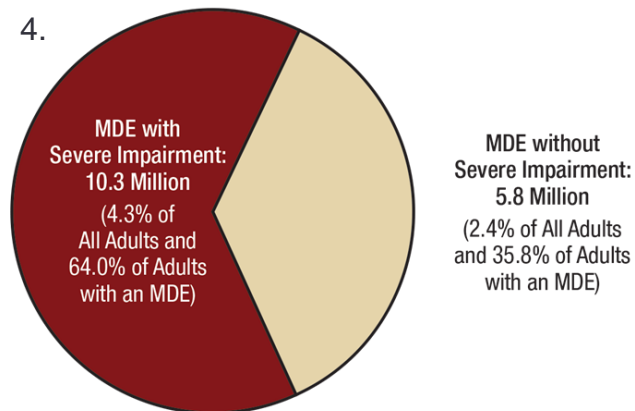
- Lifetime Prevalence of MDD is 20%.
- Over 16 million U.S. adults had a past year major depressive episode.
- Annual US Healthcare Costs = \$210.5 billion:¹
 - 50% are direct medical costs
 - 50% absenteeism, presenteeism and more generally suicide
- TRD accounts for \$29-48 billion of these total costs.²
- Patients with TRD have 2-3 times the healthcare costs of patients with MDD.³
- Health care costs increase with successive antidepressant treatment failures.³

¹Greenberg PE et al. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry*. 2015 Feb;76(2):155-62.

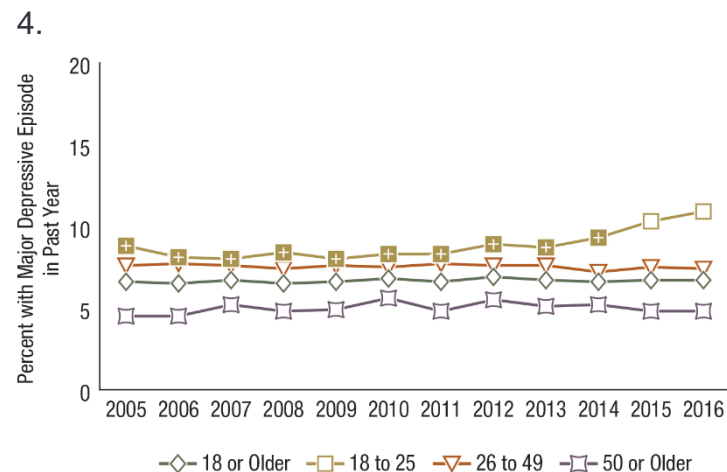
²Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv*. 2014 Aug 1;65(8):977-87.

³Amos TB et al. Direct and Indirect Cost Burden and Change of Employment Status in Treatment-Resistant Depression: A Matched-Cohort Study Using a US Commercial Claims Database. *J Clin Psychiatry*. 2018 Feb 20;79(2).

⁴Substance Abuse and Mental Health Services Administration. (2017). *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.



16.2 Million Adults with a Past Year MDE (6.7% of All Adults)



Higher Healthcare Costs Associated with Treatment Resistant Depression

| Category | M | SD ^b | Median | Lowest | Highest | N of studies |
|---------------------------------|--------|-----------------|--------|--------|---------|--------------|
| Treatment-resistant depression | | | | | | |
| Health care (direct costs) | | | | | | |
| Depression drugs | 2,667 | 1,026 | 3,736 | 1,346 | 7,568 | 4 |
| Nondepression drugs | 2,556 | 141 | 2,580 | 2,216 | 2,963 | 3 |
| Hospitalizations | | | | | | |
| Emergency care | 392 | — | — | — | — | 1 |
| Nonpsychiatric medical care | 2,508 | 786 | 2,986 | 2,253 | 3,719 | 2 |
| Psychiatric visits | 593 | 324 | 790 | 488 | 1,092 | 2 |
| Physician visits | 4,829 | 2,431 | 3,351 | 1,085 | 5,618 | 2 |
| Psychotherapy | 978 | 344 | 770 | 449 | 1,090 | 2 |
| Total ^c | 13,196 | 219 | 13,402 | 13,152 | 14,417 | 3 |
| Productivity (indirect costs) | | | | | | |
| Absenteeism | 2,625 | 987 | 2,025 | 1,105 | 2,945 | 2 |
| Disability | 4,299 | 815 | 3,804 | 3,044 | 4,564 | 2 |
| Total | 6,924 | 1,801 | 5,829 | 4,149 | 7,509 | 2 |
| Total direct and indirect costs | 20,120 | | | | | |
| Treatment-responsive depression | | | | | | |
| Health care (direct costs) | | | | | | |
| Depression drugs | 898 | 162 | 561 | 385 | 939 | 3 |
| Nondepression drugs | 1,407 | 75 | 1,369 | 1,094 | 1,422 | 3 |
| Hospitalizations | | | | | | |
| Emergency care | 224 | — | — | — | — | 1 |
| Nonpsychiatric medical care | 1,438 | 119 | 1,418 | 1,332 | 1,505 | 2 |
| Psychiatric visits | 99 | 23 | 95 | 79 | 112 | 2 |
| Physician visits | 1,708 | 1,864 | 2,021 | 666 | 3,376 | 2 |
| Psychotherapy | 255 | 176 | 284 | 156 | 412 | 2 |
| Total ^c | 7,715 | 456 | 6,902 | 6,375 | 7,832 | 3 |
| Productivity (indirect costs) | | | | | | |
| Absenteeism | 1,125 | 849 | 1,268 | 651 | 1,885 | 2 |
| Productivity | 1,751 | 464 | 1,829 | 1,492 | 2,166 | 2 |
| Total | 2,876 | 1,312 | 3,096 | 2,142 | 4,050 | 2 |
| Total direct and indirect costs | 10,592 | | | | | |

^a Costs are for private payers and are reported in 2012 dollars.

^b An SD and other data were not reported when only one study provided results.

^c May include other costs that are not listed

Cost of Agitation in Alzheimer's Disease

- Alzheimer's Disease affects approximately 5 million people in the U.S. & 50 million worldwide.
- Approximately 50% of patients have agitation.
- Annual societal costs of AD worldwide = \$818 billion:¹
 - 70% of the costs come from the US and Western Europe.
- There is little information on the cost contribution of agitation in AD.
- Agitation in people with AD represents a substantial monetary burden over and above the costs associated with cognitive impairment.
- Prospective cohort UK study¹ of AD sufferers (n=224) were followed for 56 months:
 - Total monetary cost of dementia in 2014 was £26 billion
 - Adjusted annual cost/person with AD with significant agitation = £33,075 vs £28,983
 - Mean excess cost associated with agitation =£4091/person/year
 - The excess cost associated with agitation was £2 billion a year across all people with AD in the UK
 - Agitation accounts for 12% of health and social care costs of AD each year
 - Potential to save money with effective intervention

¹Morris S et al. Monetary costs of agitation in older adults with Alzheimer's disease in the UK: prospective cohort study. *BMJ Open*. 2015 Mar 13;5(3) .

The Social and Economic Consequences of Smoking

- More than 49 million Americans smoke (approximately 1 in 5 adults):
 - Almost 60% are daily smokers
- Tobacco has killed more than 20 million people since 1964.
- Mortality rate of smokers 2-3 times that of those who never smoked.¹
- Smoking is the largest preventable cause of death.
- Significant annual burden of smoking-attributable mortality in the US with millions more living with smoking-related diseases.²
- Total economic cost of smoking in the US is estimated at more than \$300 billion a year³ which represents between 5-14% of total healthcare expenditure.
- Annual smoking-attributable economic costs in the US:^{2,4}
 - \$289–332.5 billion (2009-2012), including \$132.5–175.9 billion for direct medical care of adults, \$151 billion for lost productivity due to premature death estimated from 2005–2009, and \$5.6 billion (in 2006) for lost productivity due to exposure to secondhand smoke.

¹Carter BD et al. Smoking and mortality—beyond established causes. *N Engl J Med*. 2015 Feb 12;372(7):631-40.

²The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

³Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending attributable to cigarette smoking: an update. *Am J Prev Med*. 2015; 48(3):326–33.

⁴Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. U.S. Department of Health and Human Services.

Aggregate Health-Care Costs Attributable to Smoking^{1,2}

- The estimated smoking-attributable healthcare expenditure in 2013 was \$175.9 billion accounting for approximately 9% of total healthcare expenditure in US:
 - \$94.2B (for current smokers) and \$81.7B (for former smokers)

Annual Healthcare Costs (\$ billions)

| Age group | Former smokers | | | Current smokers | | | Total |
|-------------|----------------|---------|----------|-----------------|---------|----------|-------|
| | Males | Females | Subtotal | Males | Females | Subtotal | |
| 35–44 years | 0.5 | 0.3 | 0.8 | 3.0 | 2.4 | 5.4 | 6.2 |
| 45–54 years | 2.9 | 1.1 | 4.0 | 10.7 | 8.8 | 19.4 | 23.4 |
| 55–64 years | 8.6 | 5.5 | 14.1 | 17.4 | 12.8 | 30.2 | 44.3 |
| 65–74 years | 15.4 | 11.2 | 26.7 | 15.0 | 10.0 | 25.0 | 51.7 |
| ≥75 years | 18.6 | 17.6 | 36.2 | 5.9 | 8.3 | 14.2 | 50.4 |
| All ages | 46.0 | 35.7 | 81.7 | 52.0 | 42.2 | 94.2 | 175.9 |

¹Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. U.S. Department of Health and Human Services.

²The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014

High Socioeconomic Impact of Smoking Deaths

Average Annual Cost of Lost Productivity due to smoking-related deaths (2005-2009)

Value of lost productivity (\$ in thousands)^a

| Disease | Males | Females | Total |
|---|--------------------|-------------------|--------------------|
| Lung cancer | 20,326,794 | 14,084,073 | 34,410,868 |
| Other cancers ^b | 7,434,058 | 2,614,451 | 10,048,509 |
| Total—Cancers | 27,760,852 | 16,698,524 | 44,459,376 |
| Coronary heart disease | 20,646,966 | 7,420,262 | 28,067,228 |
| Other cardiovascular disease ^c | 11,209,038 | 5,454,808 | 16,663,845 |
| Total—Cardiovascular and metabolic diseases | 31,856,004 | 12,875,069 | 44,731,073 |
| Total—Pulmonary diseases^d | 9,963,054 | 8,402,054 | 18,365,108 |
| Total—Cancers, cardiovascular and metabolic diseases, pulmonary diseases | 69,579,910 | 37,975,647 | 107,555,557 |
| Total—All causes | 105,641,174 | 45,085,339 | 150,726,514 |

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

^aValue of lost productivity calculated based on potential value of future earnings in the United States in 2007, published by Grosse et al. 2009.

^bOther cancers comprised of cancers of the lip, pharynx and oral cavity, esophagus, stomach, pancreas, larynx, cervix uteri, kidney and renal pelvis, bladder, colon and rectum, liver, and acute myeloid leukemia.

^cOther cardiovascular disease comprised of other heart disease, cardiovascular disease, atherosclerosis, aortic aneurysm, other arterial diseases, and diabetes mellitus.

^dPulmonary diseases consist of pneumonia, influenza, tuberculosis, emphysema, bronchitis, and chronic airways obstruction.

Summary of Pharmaco-economic Findings

- Treatment Resistant Depression:
 - Major Depressive Episodes afflicted 16 million US adults last year
 - Annual healthcare costs for MDD amount to \$210.5 billion of which TRD accounts for approximately \$30-50 billion
 - Patients with TRD have 2-3 times the healthcare costs of patients with MDD
- Agitation associated with Alzheimer's Disease:
 - Worldwide annual healthcare costs of AD equal \$818 billion
 - Recent prospective evaluation estimated agitation to account for 12% of health and social costs of AD
- Nicotine Dependence:
 - Total annual economic cost of smoking in the US is estimated at more than \$300 billion

Conclusions

- Indications targeted by AXS-05 exact a substantial toll on patients' lives and result in significant socio-economic burden.
- These findings underscore the need for new treatments for these conditions.
- AXS-05 has shown promise as a potential treatment for these and other CNS disorders.
- AXS-05 may therefore have a potential significant clinical, economic and social impact.



Q&A

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Thank you.

For more information, please contact

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