Burden of Mental Illnesses in the US

Model implementation plan for anxiety, Alzheimer's, bipolar and schizophrenia

October, 2016

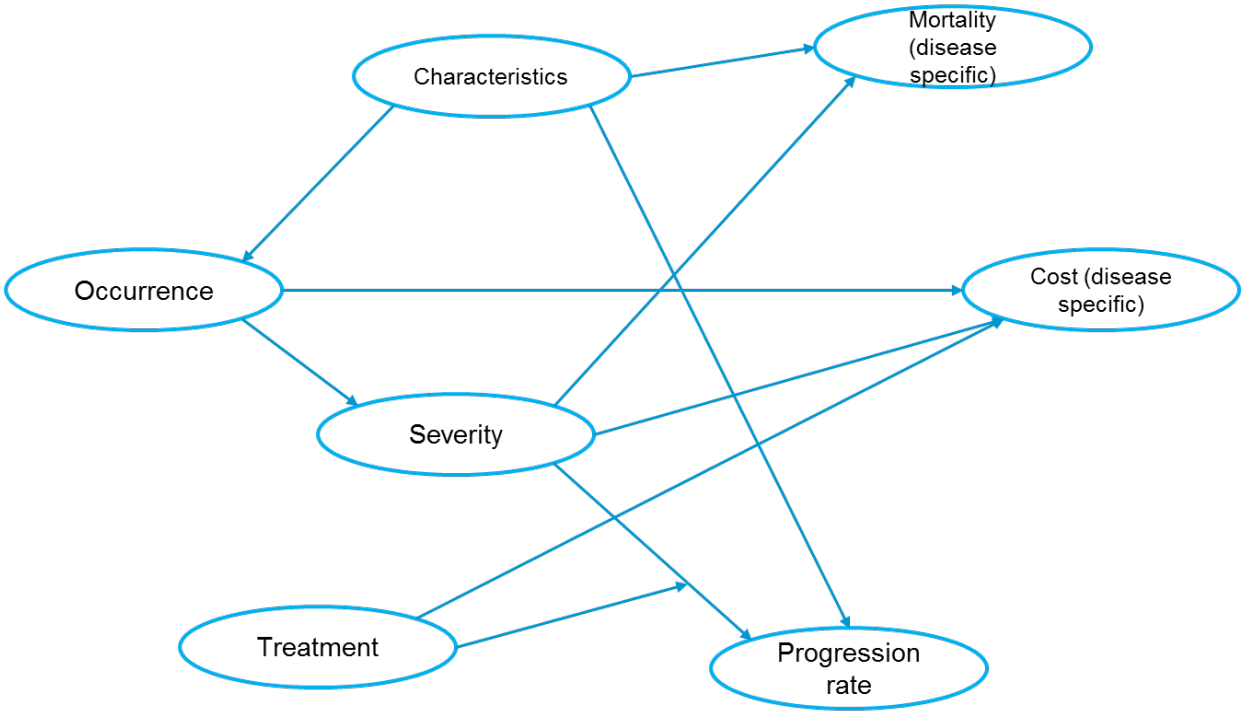
Contents

Overview

Model schematic

This document is to provide detailed specification for the mental conditions added to the Disease Prevention Microsimulation model (DPMM). The simulation of each condition will follow the guidance of an influence diagram, in which the relationships of key components are illustrated. A generic version is shown in Exhibit 1. The actual diagram for each condition will be unique to that condition's natural course of progression and treatment endpoints.

Exhibit 1 Generic influence diagram for disease modeling



Population

For this project we focused on each of three subpopulations to estimate their impact to the burden of state, including state employees, Medicaid beneficiaries and state prison inmates. The first two cohorts were identified through insurance and employment status variables of in-house base population data set. The state incarcerated cohort can be approximated based on published demographic mix information, with adjustment to the prevalence of mental conditions (Exhibit 2).

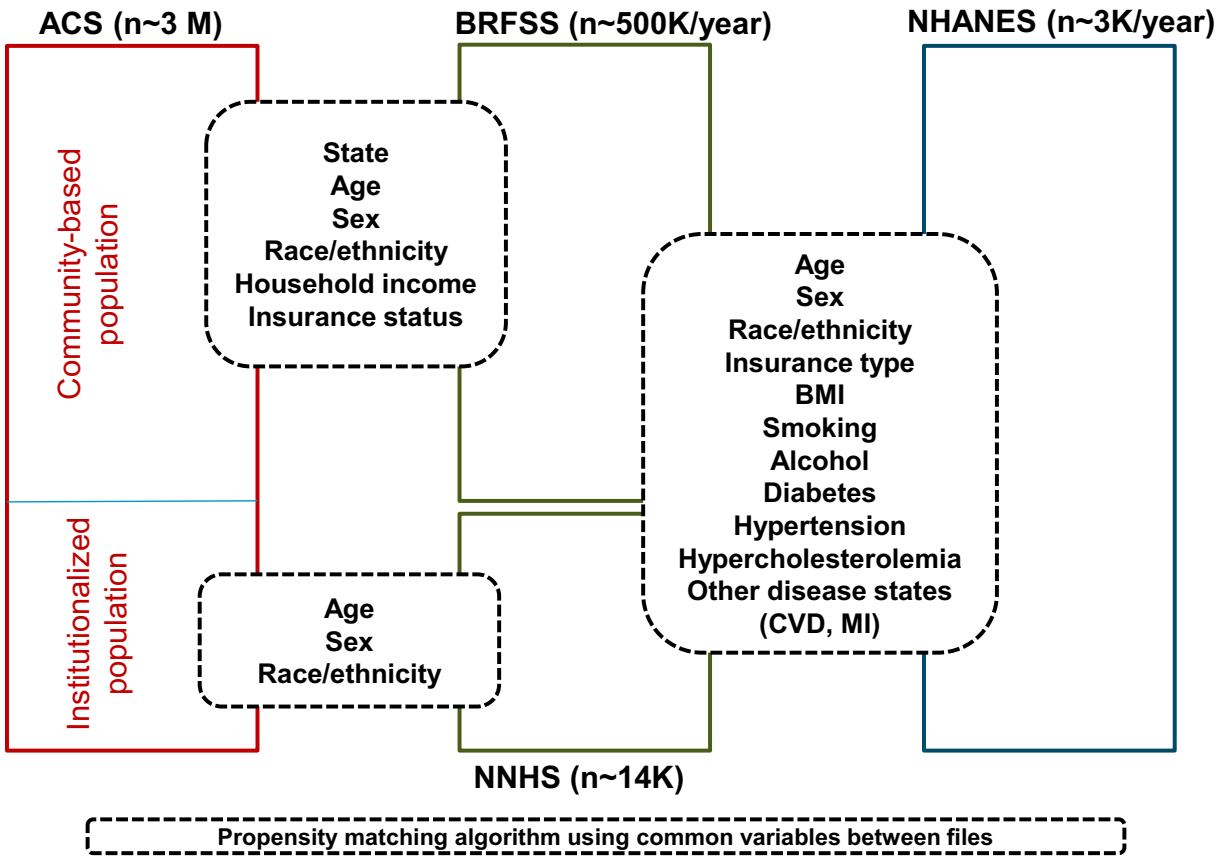
Exhibit 2 Prevalence of mental disorders in target subpopulations

Mental disorders (%)	State employees (Female)	Prison inmates (Female)	Medicaid beneficiaries (Female)
Severe anxiety	4.1 (5.2)	5.5 (6.1)	6.7 (7.0)
Major Depressive Disorder	6.7 (8.2)	16.5 (17.3)	14.6 (15.4)
Bipolar disorder	2.8 (2.8)	7.0 (6.4)	4.0 (3.7)
Schizophrenia	1.1 (1.1)	3.5 (4.7)	5.1 (3.9)
Dementia (age above 65)	11.1 (11.1)	27.8 (27.8)	21.3 (21.3)

The base population data sets were generated from multiple public data sources. To achieve the most accurate and complete clinical information for each individual, state level records from the American Community Survey (ACS, 2014) and Behavioral Risk Factor Surveillance System (BRFSS, 2013-2014) were merged to National Health and Nutrition Examination Survey (NHANES, 2005-2014) data through propensity match algorithm based on their age, gender, race, BMI, and insurance, diabetes, smoking, hypertension, and hyperlipidemia status. The combined data files provide metrics on SBP, total cholesterol, HDL-C, and HbA1c as well as other chronic illness conditions for each US state. In addition, to better estimate the future clinical and economic burden, we produce the state level population projections from 2015 to 2030 based on published and IHS internal state and national projections in which the projected sample weights were assigned yearly to each of the demographic subsets. Each demographic subset is defined as a unique combination of 10-year age group, gender, and race.

Repeated sampling from the above mentioned state population file, using ACS sample weights to determine selection probability, produced representative samples of 100,000 adults for each state. In each modelled year, the sample sizes from the microsimulation model were compared with population projections for every demographic subset. If the actual number of individuals is less than projected population size, then persons with matching demographics are randomly selected to replenish the batch. If the actual model sample size is higher than projected, then the subset size is adjusted by randomly removing a small number of individuals, equal to the difference of the model sample size and the projected sample size. Additionally, as the result of population aging in the model, individuals who are 20 at initial year need to be supplemented each year since no one younger than 20 are included in the modelled adult population. We fulfilled this step by bootstrapping this specific age group of samples each time to maximize the heterogeneity in characteristics.

Exhibit 3 Algorithm to generate the starting population



Costing

Direct medical expenditure and indirect costs are estimated for each of three subpopulations. Direct medical expenditure was estimated using regressing equation from DPMM based on individual's overall health profile. For state employees, indirect cost is presented as lost value due to reduced productivity from absenteeism and presenteeism. For Medicaid beneficiaries, we estimated the extra care cost due to prolonged nursing home stay (>=90 days) from those with

mental conditions.[1] For state prison inmates, the indirect cost is calculated based on statistics report that those who had mental health problems on average had 4 month longer sentences than prisoners without. [2]

[1] David C. Grabowski, et all., Mental Illness In Nursing Homes: Variations Across States. Health Aff (Millwood). 2009 May–Jun; 28(3): 689–700.

[2] Doris J. James et al., Bureau of Justice Statistics Special Report: Mental Health Problems of Prison and Jail Inmates. September 2006, NCJ 213600. Corrections Statistics by State, USDJ. http://nicic.gov/statestats/

Alzheimer's disease (AD)

The modeling of AD will follow a similar structure as the NICE HTA submission of donepezil by Eisai/Pfizer in 2010.[3] In the submission the disease is characterized by MMSE (Mini-Mental State Examination) scores.[4]

Exhibit 4 MMSE scores and severity of AD

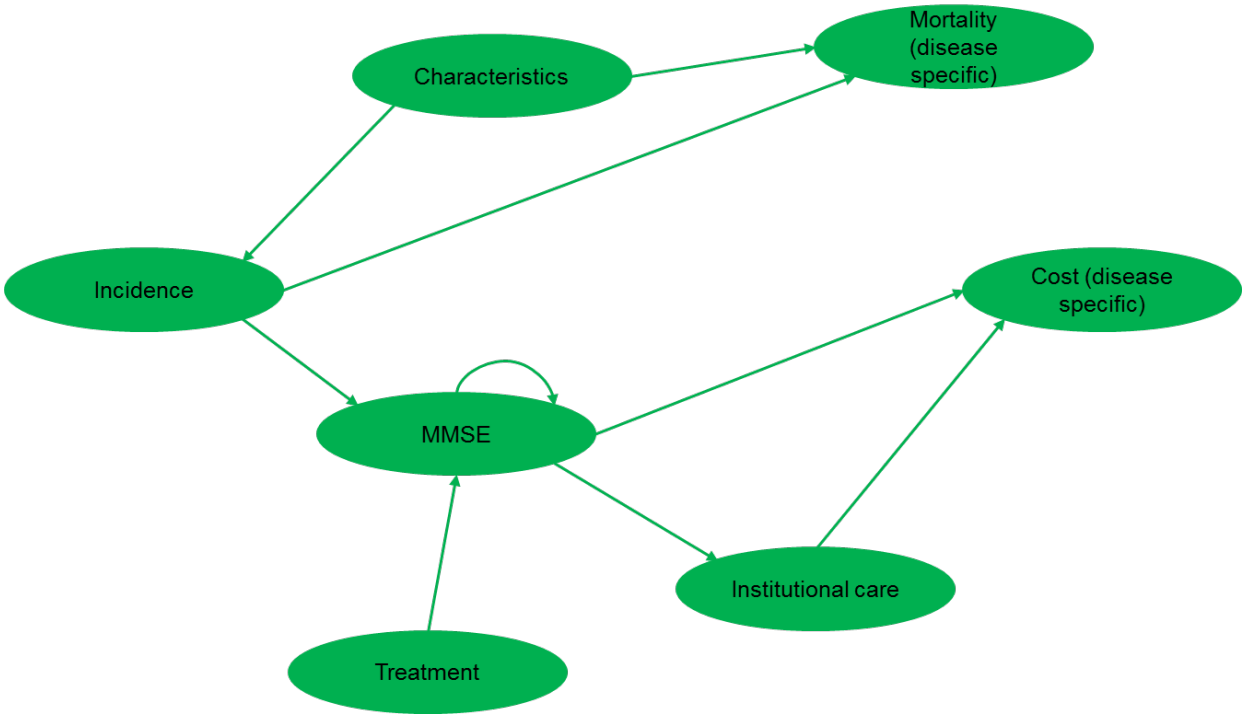
MMSE range	AD severity
21-26	Mild
10-20	Moderate
<10	Severe

The simulation of the disease is based on the progression of MMSE over time with or without treatment. (Exhibit 5)

[3] Eisai/Pfizer, Donepezil: Submission to the National Institute for Health and Clinical Excellence Multiple Technology Appraisal, http://www.nice.org.uk/guidance/TA217/documents/alzheimers-disease-donepezil-galantamine-rivastigmine-and-memantine-review-eisai-ltdpfizer-ltd-joint-submission2, March 5 2010, accessed October 23, 2015

[4] Bond, M, et al., The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model, Health Technology Assessment 2012, Vol 16, No. 21

Exhibit 5 Influence diagram of AD



Initial prevalence: Many epidemiology studies found AD to be more prevalence in women than in men. The prevailing explanation for this is that on average women have longer life spans than men and are thereby more likely to reach an age of high risk for AD. There is no evidence that one gender is more likely to develop dementia at any given age.[5]

96% of all AD patients are age 65 and older.[5] In 2006 there were only 200,000 AD patients who are younger than age 65 (prevalence rate 7/100,000). Due to this extremely low prevalence we assume only those aged 65 and older can get AD.

[5] Fargo, K., Bleiler, L., Alzheimer's Association Report:2014 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, 10 (2014)

The prevalence of dementia by age group and race is depicted in Exhibit 6. The source didn't report any data on the ethnic group "Non-Hispanic Other". To be conservative we assume it has the same prevalence as "White" population, which has the lowest known prevalence of all races. Because AD accounts for an average of 70% of all dementia cases,[6] the prevalence of AD can be calculated in Exhibit 7.

Exhibit 6 Proportion of people aged 65 or older with dementia[5,7]

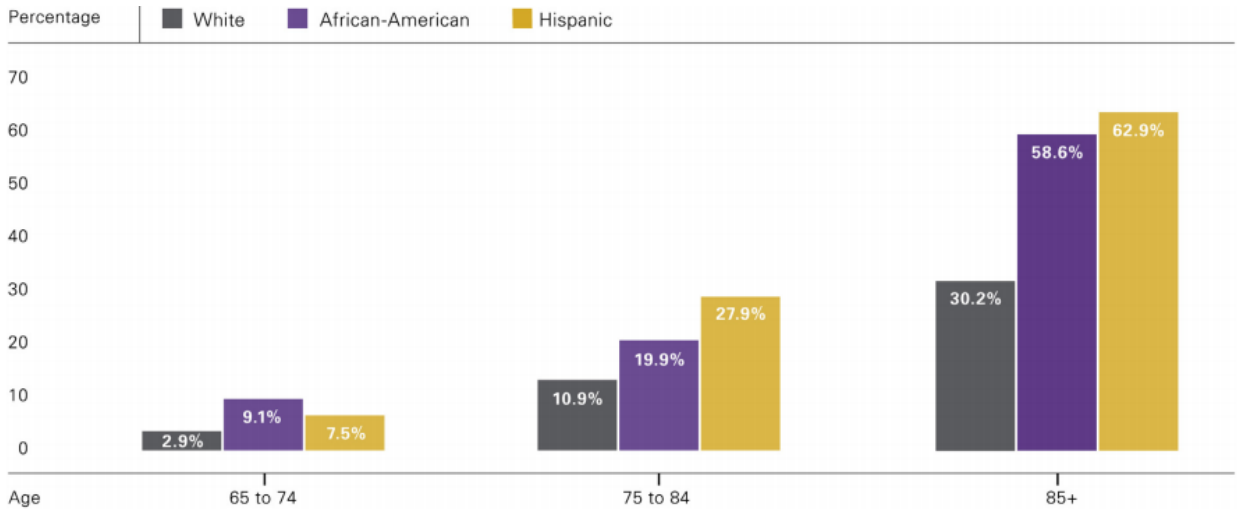


Exhibit 7 Prevalence of AD by age and race

Age group	Race/ethnicity	Prevalence
65-74	Hispanic	5.3%
	Non-Hispanic white	2.0%
	Non-Hispanic black	6.4%

[6] Alzheimer's Association, "What is Alzheimer's", http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp, 2015, accessed Nov 18, 2015

[7] Gurland BJ, Wilder DE, Lantigua R, Stern Y, Chen J, Killeffer EH, et al. Rates of dementia in three ethnoracial groups. Int J Geriatr Psychiatry 1999;14:481–93.

	Non-Hispanic other	2.0%
75-84	Hispanic	19.5%
	Non-Hispanic white	7.6%
	Non-Hispanic black	13.9%
	Non-Hispanic other	7.6%
85+	Hispanic	44.0%
	Non-Hispanic white	21.1%
	Non-Hispanic black	41.0%
	Non-Hispanic other	21.1%

Because the progression of AD is highly correlated with age, it is assumed that younger prevalent population also has milder disease. A MMSE score will be randomly generated for each age group. Age group 65-74 will be assigned a randomly generated MMSE score between 21 and 26 (inclusive, equal probability for each score). By the same token, age group 75-84 will be randomly assigned a score between 10-20, and age group 85+ will be between 1-10.

Incidence: It was projected that in 2014, there will be approximately 59,000 new cases among people aged 65 to 74 years (incidence rate 224/100,000), 172,000 new cases among people aged 75 to 84 years (incidence rate 1,260/100,000), and 238,000 new cases among people aged 85 years and older (Incidence rate 3,887/100,000).[8] New AD cases are assumed to have the mildest disease (MMSE 26).

Disease progression and treatment effect: Because AD is irreversible, MMSE will decline continuously after disease occurrence. The annual rate of MMSE decline with and without treatment (donepezil) is as follows:[3]

[8] Hebert LE, Beckett LA, Scherr PA, Evans DA. Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050. Alzheimer Dis Assoc Disord 2001;15:169–73.

Annual decline in MMSE = Tx_effect + norm(0,0.5) - 0.429PM1 – 0.004PM2 + 0.1415PM3 – 0.079PrevMMSEChange + 0.0747Ageorig

Among the variables, norm(0,0.5) is a standard normal distribution with a standard deviation of 0.5. This represents the random variation in treatment effects among individuals. Tx_Effect is a constant with the value being 2.4671 for treated and 0 for untreated. PM1, PM2 and PM3 are the individual's previous MMSE score partitioned over the scale of MMSE. PM1= min(PrevMMSE,9), PM2=max(0,min(PrevMMSE-9,9)), PM3=max(0,min(PrevMMSE-18,12)). PrevMMSEChange is the individual's last known MMSE decline. Ageorig is the age at baseline (age of disease incidence for those developed the disease during the course of simulation, or age at time 0 for those came into the model with AD).

The % population under treatment is unclear and thus needs to be calibrated. Calibration target is the total annual direct medical cost attributable to AD in the US, which is estimated to be $218.6billion (2015 USD).[10]

Mortality: Bowne et al. followed up 327 newly diagnosed AD patients for a median of 3.3 years and compared their mortality rate with a comparable community population.[9] The reported RR of death for every 5-point increase in MMSE is 1.4 (95% CI: 1.2-1.7). To give more granularity we derived the RR of death for every point of increase in MMSE to be 1.4^(1/5)=1.07 with the assumption that an AD patient with an MMSE score of 26 (mildest case) has the same mortality as the general population.

Because mortality *among* AD patients is different from mortality *due to* AD, AD-specific death can be calculated by subtracting all-cause death from death *among* AD patients.

Death due to AD = All cause death for AD patients – All cause death a community population

For example, for someone with an MMSE score of 20, the RR of death *due to* AD is 1.07^(26-20)-1=0.50. The probability of dying *due to* AD is 0.50 * all-cause mortality from the life table. (See appendix. "Non-Hispanic Other" population will use the national life table for males and females)

[9] Bowen JD et al, Predictors of mortality in patients diagnosed with probably Alzheimer's disease, Nuerology, 1996

Cost: Cost drivers of AD include community based care and institutionalized care. The percentage of people in community based or institutional care were reported to be as follows:[4]

Exhibit 8 Community based care and institutional care by MMSE score

MMSE score	Severity scale	Home (%)	Institutional care (%)
25–30	Mild	87.1	12.9
20–24	Mild to moderate	74.4	25.6
15–19	Moderate	61.7	38.3
10–14	Moderate to severe	49.0	51.0
0–9	Severe	30.0	70.0

The annual direct medical cost of community based care and institutional care is calculated by Alzheimer's Association as follows: [10]

Exhibit 9 Annual direct medical cost of AD by setting

table 8 Average Annual Per-Person Payments for Health Care and Long-Term Care Services, Medicare Beneficiaries Age 65 and Older, with and without Alzheimer's Disease and Other Dementias and by Place of Residence, in 2013 Dollars

	Beneficiaries with Alzheimer's Disease and Other Dementias by Place of Residence			Beneficiaries without Alzheimer's Disease and Other Dementias
Payment Source	Overall	Community-Dwelling	Residential Facility	
Medicare	$21,095	$18,787	$24,319	$8,005
Medicaid	10,771	237	25,494	561
Uncompensated	290	417	114	328
HMO	1,058	1,642	241	1,543
Private insurance	2,407	2,645	2,074	1,619
Other payer	964	174	2,067	153
Out of pocket	9,970	3,370	19,196	2,431
Total*	**46,669**	**27,465**	**73,511**	**14,772**

*Payments from sources do not equal total payments exactly due to the effect of population weighting. Payments for all beneficiaries with Alzheimer's disease and other dementias include payments for community-dwelling and facility-dwelling beneficiaries.

Created from unpublished data from the Medicare Current Beneficiary Survey for 2008.[155]

[10] Alzheimer's Association, 2014 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, Volume 10, Issue

The increased cost compared to those without AD is directly related to the disease. Consequently, AD-specific cost can be calculated as follows:

- Annual direct medical cost for community dwelling patients: ($27,465-$14,772)*(444.65/425.13)=$13,276. The allocation of this cost to different settings (I/P, O/P, Rx, etc.) will the derived from a generic analysis on MEPS data.
- Annual direct medical cost for institutionalized patients: ($73,511-$14,772)*(444.65/425.13)=$**61,436**

Because all AD patients are over 65 years old, it is assumed they incur no absenteeism cost. The indirect burden of AD is mainly caused by the absenteeism of family members who provide care to the *community-dwelling* patient.

The number of AD patients was estimated to be approximately 5 million in 2014, who collectively received 17.7 billion hours of unpaid care from family and other unpaid caregivers.[10] This translates into 3,540 hours of unpaid care per patient per year. Each hour of unpaid care is valued at $13.02 per hour (inflated from 2013 cost) [10], resulting in a total unpaid care giver cost of 3,540*$13.02= $46,090 per year (2015 cost).

Key assumptions:

- Because the prevalence of AD is 0.007% in the population younger than 65, we assume only those aged 65 and older can get AD
- By the same token, we assume AD patients incur no absenteeism cost.
- Only those living in community incurs caregiver absenteeism cost
- Because the progression of AD is highly correlated with age, older prevalent populations are assumed to have more severe disease than younger prevalent population
- An AD patient with an MMSE score of 26 has the same mortality rate as the general population

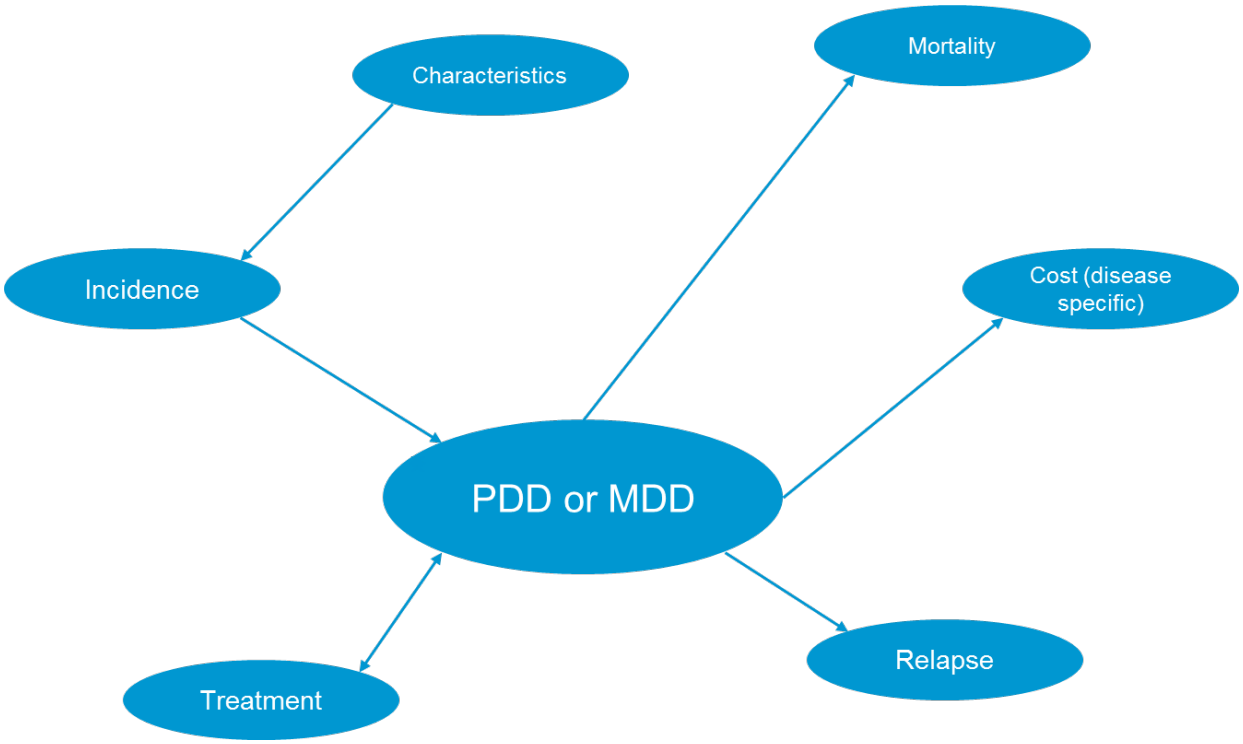
Depressive disorder

In 2010, the United States spent $135 billion on mental health treatment, or about 5.6% of the national health care spending. Unlike overall health spending, the vast majority of behavioral

health services are publicly funded. Medicaid, currently the largest source of financing for behavioral health services in the nation, covers a quarter of all expenditures.[11]

The modeling of depression includes major depressive disorder (MDD) which has symptoms lasting ≥2 weeks, and persistent depression disorder (PDD), which is characterized by depressive symptoms often lasting for ≥2 years without remission. The definition of PDD covers that of chronic major depressive disorder, dysthymia, and long-term depression.[12] MDD episode will be modeled as an event because the majority of MDD ends within a year. PDD is a life-long condition with much longer episodes and relapses.

Exhibit 10 Influence diagram of depression



[11] SAMSHA Spending estimates project, 2010.
[12] Coryell, W, Depressive disorders, http://www.merckmanuals.com/professional/psychiatric-disorders/mood-disorders/depressive-disorders, 2013, accessed Nov 23, 2015

Initial prevalence: The prevalence of depressive disorder can be determined via the patient health questionnaire (PHQ-8) dataset of BRFSS.[13] A PHQ-8 score of 0 to 9 is defined as no depression while a score of 10 to 24 points is defined as depression.[14] NIH reported the prevalence of PDD and MDD to be 1.5%[15] and 6.7%[16] among US adults, respectively. Consequently the proportion of the prevalent population that has PDD and MDD can be calculated to be 18.3% and 81.7%, respectively.

Incidence: The incidence of MDD among those without PDD or MDD was already part of the DPMM. The logic is detailed below.

- Derive baseline annual risk of depression for male, not type-II/III obese, non-smoker and non-diabetic, from NHANES
- Extract the following odd ratios from published literature

Condition	OR	CI	Source
Female	2.62	1.76-2.32	Onyike et al. Is obesity associated with major depression? American J Epid 2003
Type-II obese	1.9	0.79-4.6	Same as above
Type-III obese	4.63	2.06-10.42	Same as above
Smoking	2.24	1.32-3.81	Same as above

[13] Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009; 114:163--73.
[14] http://www.cdc.gov/mentalhealthsurveillance/documents/11_gsps_user_guide_appendix_e.pdf, accessed November 30, 2015
[15] http://www.nimh.nih.gov/health/statistics/prevalence/dysthymic-disorder-among-adults.shtml, accessed November 30, 2015
[16] http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml, accessed November 30, 2015

Diabetes	1.24	1.09-1.40	Nouwen et al., Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis, the European Depression in Diabetes (EDID) Research Consortium, 2010
Alcohol abuse	Not significant at 0.01	-	Onyike et al. Is obesity associated with major depression? American J Epid 2003

- Methodology of converting odds ratio to relative risk, using smoking population as an example
    1. Convert the baseline risk of depression to odds: baseline odds of depression = risk / (1- risk)
    2. Calculate the odds of depression among smokers: odds of depression (smoker) = baseline odds of depression * odds ratio of smoking (2.24)
    3. Convert the odds of depression among smokers to risk: risk of depression (smoker) = odds of depression (smoker)/(1+odds of depression(smoker))
- Calculate the risk of depression by multiplying baseline risk with risk ratios.

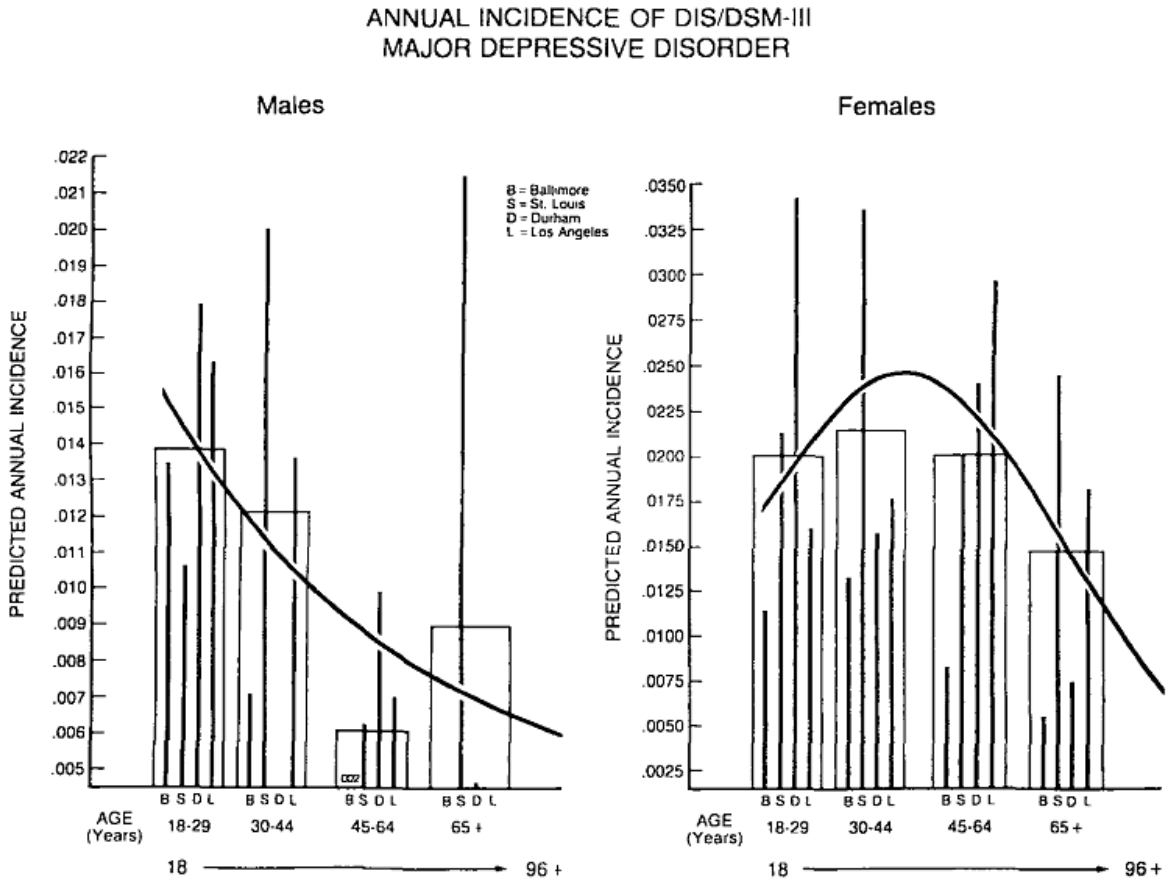
By definition, incidence calculated this way includes both MDD and PDD. Rubio et al. reported the 12-month prevalence of PDD within the population with depressive disorder was 26.5%.[17]

The incidence rate will be applied to individuals of all ages. According to Eaton, et al.,[18] major depressive disorder was observed in people from all age groups. (Exhibit 11)

[17] Rubio, et al., Epidemiology of chronic and non-chronic major depressive disorder: results from the national epidemiologic survey on alcohol and related conditions, Depression and anxiety, 2011

[18] Eaton, WW, et al., The incidence of specific DIS/DSM-III mental disorders: data from the NIMH epidemiologic catchment area program, Acta Psychiatr Scand, 1989:79:163-178

Exhibit 11 Incidence of major depressive disorder in the overall population[18]



Natural course of the disease: The majority of MDD episodes end within a year, and thus will be modeled as an event. Eaton et al. reported the median duration of MDD episodes to be 8-12 weeks. [19] Rubio et al. reported that the duration of longest MDD episode is 0.39 years.[17]

As mentioned above, PDD is a life-long condition with much longer episodes and relapses.

Klein et al. reported the Kaplan-Meier curve for time to recovery from a PDD episode and time to relapse after recovery, as follows: [20]

[19] Eaton, WW, Natural history of Diagnostic Interview Schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up, Arch Gen Psychiatry, 1997, 54(11), 993-9

Exhibit 12 Time to recovery (left) and time to relapse (right) for PDD[20]

FIGURE 1. Kaplan-Meier Survival Analysis of Time to Recovery From Dysthymic Disorder in 82 Patients Over a 10-Year Follow-Up Period

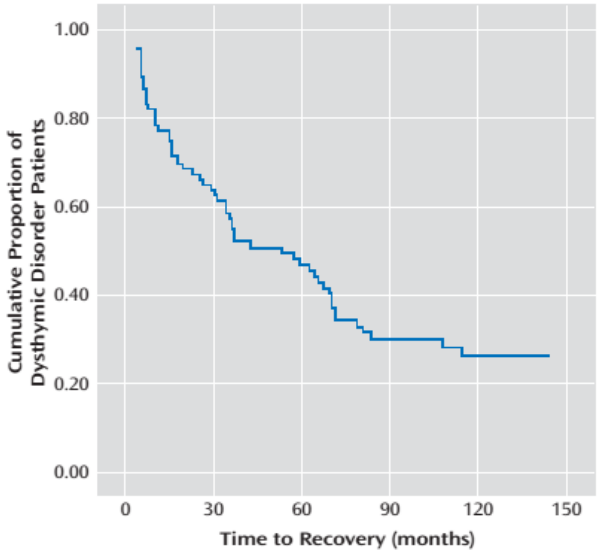
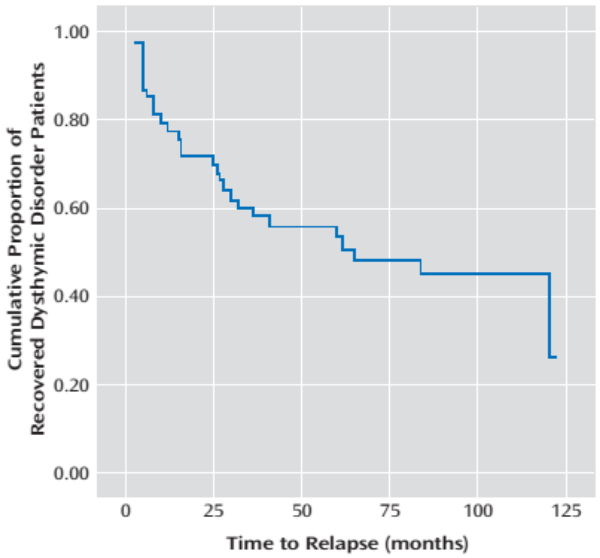


FIGURE 2. Kaplan-Meier Survival Analysis of Time to Relapse of Dysthymic Disorder in 53 Patients Who Recovered From Dysthymic Disorder Over a 10-Year Follow-Up Period



The annual probability of recovering from a PDD episode can thus be estimated to be 0.15 per year (average estimated probability using data from 30, 60, 90, and 120 months).

By the same token, the annual probability of relapsing after recovery is 0.12 (average estimated probability using data from 25, 50, 75, and 100 months). This is based on a naturalistic population that closely mimics the general population with depressive disorder, with some patients receiving medication while others don't.

The long-term diagnostic 'stability' of either PDD or MDD is strong. In other words, once diagnosed, patients are far more likely to stay in PDD or MDD than to cross into the other type. Klein et al. found the odds of exhibiting a chronic depressive course were 14 times greater for patients with dysthymic disorder than for patients with nonchronic major depressive disorder

($p<0.001$), and the odds of having a nonchronic depressive course were 12 times greater for patients with nonchronic major depressive disorder than for patients with dysthymic disorder ($p<0.001$). [20]

Mortality: Depression likely lead to an unhealthy lifestyle which in turn may cause increased probability of death due to CVD and other physical illnesses. The higher incidence of physical illnesses among patients with depression is also incorporated implicitly in the modeling of those physical illnesses. The only cause of death directly associated with depression is suicide.

The evidence on suicide rate is scarce as it is neither feasible nor ethical to carry out double-blind studies on suicide reduction. For an insured and treated population, Simon et al. reported the suicide rate to be 118/100,000 person years for men (95% CI: 66-170), and 36/100,000 person years for women (95% CI: 18-54),. [21] The study didn't find any correlation between age and suicide rate in patients with depression. Even though an upward trend in suicide rate is observed among older patients, this was likely due to an higher suicide rate among older population overall (healthy or unhealthy).

In long-term follow up on untreated depression, 550 suicides per 100,000 person years were recorded.[22] This number is extrapolated into untreated suicides for men and women using the following method:

- Women are more likely to have depression than men. In a long-term follow-up study, [21] female patients recorded 44,242 person-years while male patients recorded 16,938 person-years. This means women accounts for 72% of depression person-years while men accounts for the remaining 28%.
- Assuming the relative risk of men committing suicide is the same between treated and untreated population, the relative risk is 118/36=3.28
- Suppose the suicide rate for untreated women is X/100,000 person years, the following equation holds:

[20] Klein DN, et al., Ten-year Prospective follow-up study of the naturalistic course of dysthymic disorder and double depression, AM J psychiatry, 2006; 163:872-880

[21] Simon, GE, Vonkorff, M, Suicide mortality among patients treated for depression in an insured population, Am J Epi, 1998, Vol. 147, No.2

[22] Coppen A, Lithium in unipolar depression and the prevention of suicide, The journal of clinical psychiatry, 2000:61 Suppl 9:52-56

$$X*72\% + X*3.28*28\% = 550$$

Solve the equation for X = 336

In summary, the suicide rate for treated and untreated patients with active MDD or PDD episodes are the following:

Exhibit 13 Suicide rate for treated and untreated active depression episodes

	Male (per 100,000 person years)	Female (per 100,000 person years)
Treated	118	36
Untreated	1,100	336

When patients are not in active PDD or MDD episodes, they have the same suicide rate as the general population.

Treatment effect: Since the rate of recovery and relapse is summarized from a naturalistic population, it already reflects current landscape for treatment effect and % treated. Treatment effect on suicide rate is detailed in the "mortality" section. According to a government website, 50-75% (average 62.5%) of patients with mental illnesses are untreated in the US.[23] The treated rate is thus set to be 37.5%. This constitutes the base case of the model.

Treatment effect for better pharmaceuticals developed in the future will be expressed as a relative term that increases the probability of recovery and reduces the risk of relapse following a recovery.

[23] State Government of Oklahoma, https://www.ok.gov/odmhsas/documents/suicide%20infographic.pdf, accessed Dec 4, 2015

Cost: Greenberg et al. [24] researched the direct and indirect cost of MDD in the US, and reported cost burden in different settings.

The duration of MDD episode was reported to be 8-12 weeks (median duration) in a 1997 study,[19] 8 weeks (median duration, range 2- 520 weeks) in an adolescent population,[25] and 20 weeks (longest duration) in a 2011 study. [17] To be conservative we used the longest average duration of MDD episode (20 weeks) for calculations here.

Exhibit 14 Direct and indirect cost for MDD episodes

Cost driver	Cost in 2015 USD (inflated from 2012 USD)
Rx	$11,832
Inpatient	$5,227
Outpatient	$10,820
ED	$173
Other	$1,620
Missed work days	12.3 (=31.9*20/52)**Error! Bookmark not defined.**

There is scarce cost data for PDD in the US, and thus we need to use MDD data as a proxy to estimate PDD cost assuming monthly cost for MDD and PDD are the same. Per month cost can be calculated using the duration of MDD, which is listed in the following table.

[24] Greenberg, PE, et al., The economic burden of adults with major depressive disorder in the US (2005 and 2010), J Clin Psychiatry, 76:2 2015

[25] Lewinsohn, PM, et al., Major depression in community adolescents: age at onset, episode duration, and time to recurrence, J Am Acad Adolesc Psychiatry, 1994

Exhibit 15 Monthly cost for PDD episodes

Cost driver	Cost in 2015 USD (inflated from 2012 USD)
Rx	$2,528
Inpatient	$1,117
Outpatient	$2,312
ED	$37
Other	$346
Missed workdays 2.7 (=31.9/12)[Error! Bookmark not defined.]	

As noted in earlier in the document, presenteeism costs will be assessed as roughly 3 times the cost of absenteeism following previous MDD literature estimates.

- Long term care: Total number of nursing home residents in 2005 was 1.34 million. (Exhibit 29)[40] In another report, 154 thousand (15.5%) out of 996 thousand newly admitted nursing home residents had depression in 2005.[41] So the total number of depression patients admitted to nursing home was 1.34million*15.5%= 207.7 thousand.

  Total number of depression patients was about 24.2 million (295.5 million population * 1.5%+6.7% prevalence). This means 0.86% of all existing depression patients are admitted to nursing home each year. The cost of nursing home is the same as for Alzheimer's disease, which is $61,436/year.

Key assumptions:

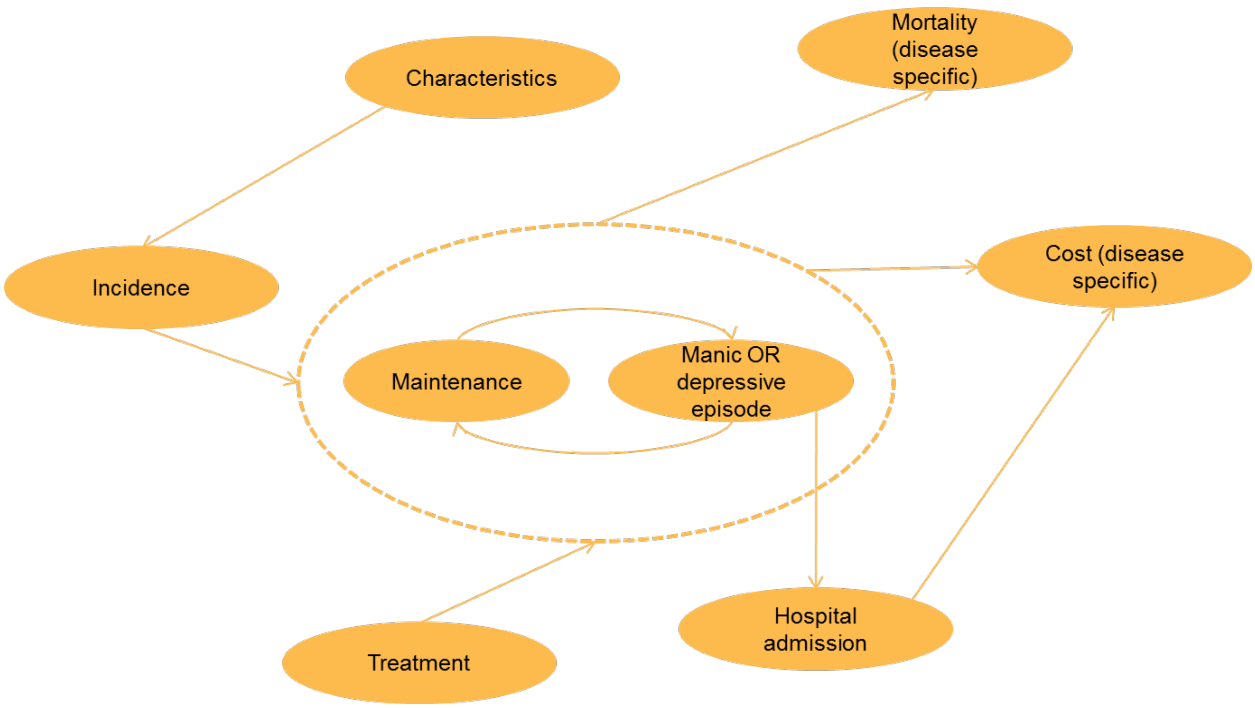
- Patients with PDD will remain on its course and not cross into the natural course of MDD, and vice versa
- Suicide rate is the same in episodes of PDD and MDD. When patients are not in active PDD or MDD episodes, they have the same suicide rate as the general population.
- The relative risk of men committing suicide is the same between treated and untreated population
- Monthly cost of MDD or PDD episodes is the same

Bipolar Disorder (BD)

Bipolar disorder does not currently have a cure, and will be modeled as a life-long disease in the DPMM. At present, treatment for the condition focuses on managing mood swings and associated symptoms in order to decrease the frequency and severity of episodes of depression and mania.[26] The simulation of BD will focus on maintaining condition stability as shown in Exhibit 16 .

There are 2 main subtypes of BD – type I and type II. Type I BD is characterized by manic episodes while type II is defined by a pattern of depressive episodes. It is thusly assumed that type I BD patients start with a manic episode while type II patients start with a depressive episode.

Exhibit 16 Influence diagram for bipolar disorder



[26] Bipolar Disorder- Treatment http://www.nhs.uk/conditions/bipolar-disorder/pages/treatment.aspx

Prevalence: The initial prevalence of BD in 2007 can be obtained from the National Health Interview Survey (2007) [27] that asked "Have you EVER been told by a doctor or other health professional that you had bipolar disorder?" (Variable name: BIPDIS) [28]

Merikangas KR et al also provided lifetime and 12-month prevalence of the condition in their 2007 paper (Exhibit 17).[29] According to this study, 0.6/(0.6+0.8)=42.9% of the prevalence population have BP-I and the other 57.1% have BP-II.

Exhibit 17 Lifetime and 12 month prevalence and age of onset of bipolar disorder %

Table 1. Lifetime and 12-Month Prevalence and Age at Onset of *DSM-IV*/CIDI Bipolar Disorder in the 9282 Respondents

	Any BPD	BP-I	BP-II	Subthreshold BPD
Prevalence, mean (SD)				
Lifetime	4.4 (24.3)	1.0 (13.2)	1.1 (10.6)	2.4 (23.3)
12 mo	2.8 (18.9)	0.6 (9.2)	0.8 (9.9)	1.4 (15.1)
Age at onset, y*				
Mean (SE)	20.8 (11.8)	18.2 (11.6)	20.3 (9.7)	22.2 (12.6)
IQR†	12.6-24.9	12.3-21.2	12.1-24.0	13.0-28.3

Abbreviations: BPD, bipolar disorder; BP-I, *DSM-IV* bipolar I disorder; BP-II, *DSM-IV* bipolar II disorder; CIDI, Composite International Diagnostic Interview; IQR, interquartile range.

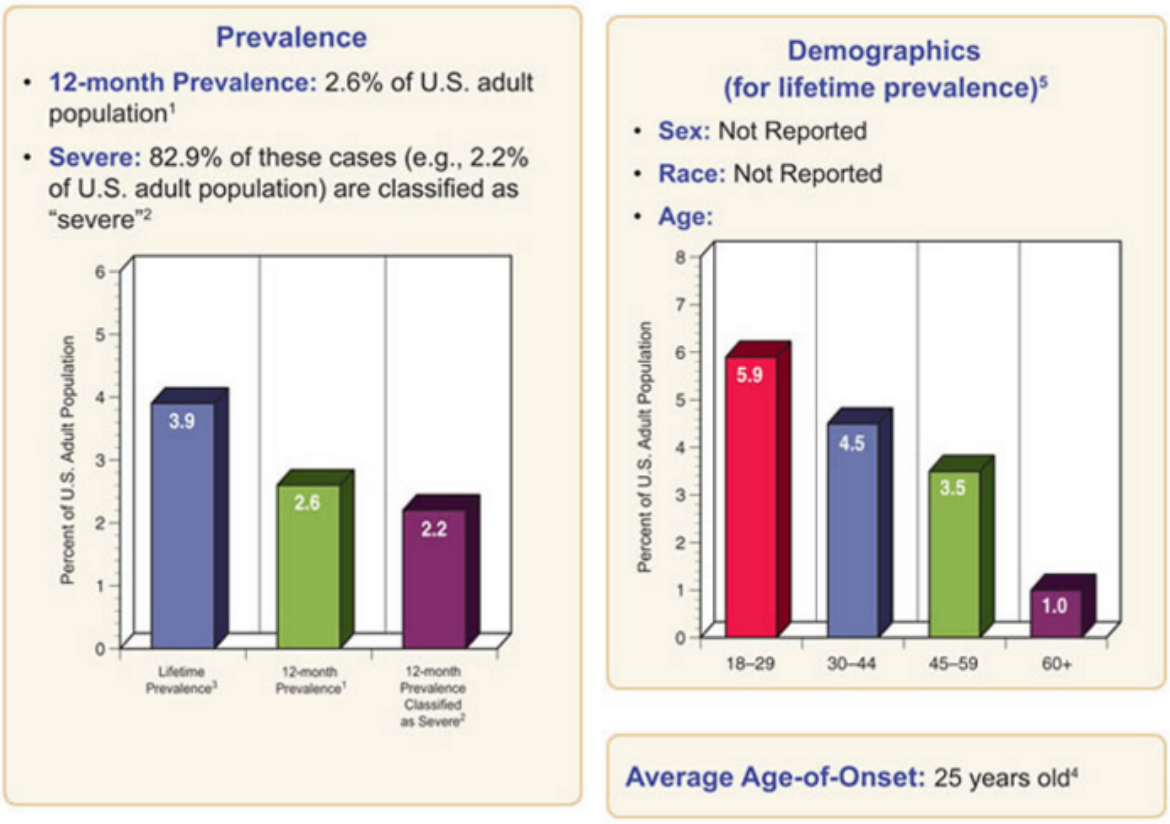
*Retrospectively reported age at onset of the first manic/hypomanic or major depressive episode. The means differ significantly across the 3 BPD subgroups at the $P=.05$ level using a 2-sided test ($\chi^2_2=7.8$; $P=.02$).

†The range between the 25th and 75th percentiles on the age-at-onset distribution.

For data verification purpose, publically available prevalence data on a population level is scarce, with the below exhibit from the National Institute of Health among the most recently reported statistics for the USA, from 2005. Due to the ambiguity of "lifetime", "lifetime prevalence" is not suitable for modeling use. But it provides a data point that the modelers can use to verify prevalence numbers produced by the model.

Exhibit 18 NIMH Statistics 2005

[27] http://www.cdc.gov/nchs/nhis/quest_data_related_1997_forward.htm
[28] ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Survey_Questionnaires/NHIS/2007/English/qadult.pdf
[29] Merikangas KR et al. Lifetime and 12-month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication_Arch Gen Psych_2007



Incidence: In a study by Kroon et al. a longitudinal electronic record of 800,000 patients in the Netherlands was analyzed for the primary outcome of interest, Bipolar I or II disorder defined according to DSM-IV criteria. Age and gender specific incidence rates (IRs) were calculated by dividing the total number of incident cases by the total number of person years at risk, per calendar year. [30] The analysis was done on a population older than 15 years, over time frame 1996 – 2007. Overall incidence of bipolar disorder was found to be 6.2 per 100,000 person years (95% CI: 5.7-8.3). For modeling purposes we will be using the overall incidence of the condition (Exhibit 19).

Exhibit 19 Overall annual incidence rates for bipolar disorder

Bipolar Disorder	Incidence Rate

[30] Kroon JS et al. Incidence rates and risk factors of bipolar disorder in the general population: a population-based cohort study. Bipolar Disorders_2013

BP-I	4.3/100,000 PY (95% CI: 3.4–5.5), **69**% of incidence with BP-I
BP-II	1.9/100,000 PY (95% CI: 1.3–2.7), **31%** of incidence with BP-II

Exhibit 20 Incidence rates by age group and gender (final model inputs)

Age groups	Female IR/ 100,000 person years			Male IR/ 100,000 person years		
	Overall	BP-I*	BP-II*	Overall	BP-I*	BP-II*
15- 24	8.4	5.8	2.6	7.1	4.9	2.2
25 – 34	4.2	2.9	1.3	5.9	4.1	1.8
35 – 44	8.2	5.6	2.5	7.3	5.0	2.3
45 -54	13.0	9.0	4.0	10.6	7.3	3.3
55 – 64	5.7	3.9	1.8	9.6	6.6	3.0
65 – 74	5.1	3.5	1.6	1.4	1.0	0.4
75+	0.0	0.0	0.0	2.2	1.5	0.7

*Estimated from the % BP-I and % BP-II in Exhibit 19

Course of Disease: Soares et al. performed a systematic review that analyzed the clinical and cost effectiveness of pharmacological and/or psychosocial interventions, and in doing so reported the relapse rates for patients who had a previous manic or depressive episode, by treatment intervention.[31] The relapse rates for patients on placebo will be used to model the natural course of the disease. (Exhibit 21) As the data assumes the probability of a relapse based on whether the previous episode was depressive or manic, we will use BP-I and BP-II incidence rates to indicate what the previous episode is, as BP-I is characterized by more manic episodes, and BP-II is characterized by more depressive episodes.

[31] Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health Technol Assess 2007;11(39).

Exhibit 21 Probability of relapse after depressive and manic episodes (untreated population)

Probability of relapse	Previous acute depressive episode	Previous acute manic episode
All	0.80 (0.62-1.0)	0.57 (0.46-0.69)
Depressive episode	0.62 (0.46-0.77)	0.18 (0.11-0.27)
Manic episode	0.18 (0.08-0.32)	0.38 (0.29-0.48)

Treatment effect: In their systematic review, Soares et al examined the effects of multiple therapies for preventing relapses in bipolar disorder.[32] Lithium has been the standard of care for bipolar disorder and thus will be used to represent treatment effect in the model.

[32] Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health Technol Assess 2007;11(39).

Exhibit 22 Efficacy of common bipolar disorder medications

TABLE 80 *Results of the evidence synthesis: probability of relapse for patients with pretrial acute depressive episode (Analysis 1) and pretrial acute manic episode (Analysis 2)*[a]

	Analysis 1			Analysis 2		
	Posterior mean	**2.5% CrI**	**97.5% CrI**	**Posterior mean**	**2.5% CrI**	**97.5% CrI**
Type of relapse: all						
Lithium	0.46	0.37	0.56	0.27	0.22	0.32
Placebo	0.80	0.62	1.0	0.57	0.46	0.69
Divalproex/valproate	0.42	0.26	0.61	0.29	0.22	0.38
Imipramine	0.64	0.37	0.95	0.64	0.44	0.83
Lamotrigine	0.50	0.27	0.78	0.42	0.26	0.61
Olanzapine	0.58	0.40	0.75	0.23	0.16	0.31
Carbamazepine	0.84	0.51	1.0	0.66	0.30	1.0
Lithium + imipramine	0.43	0.24	0.68	0.37	0.21	0.57
Type of relapse: depression						
Lithium	0.38	0.29	0.47	0.07	0.05	0.10
Placebo	0.62	0.46	0.77	0.18	0.11	0.27
Divalproex/valproate	0.31	0.17	0.49	0.05	0.03	0.09
Imipramine	0.29	0.13	0.50	0.05	0.02	0.12
Lamotrigine	0.33	0.15	0.55	0.06	0.02	0.13
Olanzapine	0.55	0.37	0.72	0.14	0.08	0.21
Carbamazepine	0.64	0.38	0.92	0.23	0.07	0.62
Lithium + imipramine	0.28	0.12	0.49	0.05	0.02	0.11
Type of relapse: mania						
Lithium	0.08	0.04	0.13	0.20	0.15	0.24
Placebo	0.18	0.08	0.32	0.38	0.29	0.48
Divalproex/valproate	0.10	0.04	0.19	0.23	0.16	0.32
Imipramine	0.34	0.15	0.59	0.59	0.39	0.77
Lamotrigine	0.17	0.06	0.32	0.36	0.21	0.52
Olanzapine	0.03	0.01	0.06	0.08	0.05	0.12
Carbamazepine	0.24	0.05	0.57	0.43	0.17	0.76
Lithium + imipramine	0.14	0.05	0.30	0.31	0.16	0.51

[a] Marginal posterior distributions estimated on the log-odds scale, under the assumption that the relative treatment effect is additive to the (lithium) baseline.

Exhibit 23 Probability of relapse after depressive and manic episodes (treated population)

Probability of relapses	Previous acute depressive episode	Previous acute manic episode
All	0.46 (0.37-0.56)	0.27 (0.22-0.32)
Depressive episode	0.38 (0.29-0.47)	0.07 (0.05-0.10)
Manic episode	0.07 (0.04-0.13)	0.20 (0.15-0.24)

Mortality: Roshanaei-Moghaddam et al. report that patients diagnosed with bipolar spectrum experience increased premature mortality, with possible underlying causes including unhealthy lifestyle, biological factors, adverse pharmacologic effects and disparities in health care.[33] Only suicide risk is consdered in the model as death due to other clinical causes have already been captured by the modelign of other conditions.

Tondo et al.[34] reported suicide rates specifically related to bipolar disorder.

- Suicide rates in bipolar disorder patients average 0.4% per year, nearly 28 times higher than the international base rate of 0.0143% per year

From the Soares et al. paper, it was reported that lithium reduces suicides rates by 80%.[32] National statistics from 2005 indicate that 48.8% of those with bipolar disorder get treated, so the assumption is that this population will have their suicide risk (0.4% per year, according to Tondo et al.) reduced by 80%. For the remaining 51.2% who are untreated, the suicide rate (x%) has been calculated using the following equation:

$$x\%*51.2\% + x\%*(1-80\%)*48.8\% = 0.4\%$$

$$X= 0.66\%$$

In conclusion, annual mortality due to suicide for treated and untreated bipolar cases are 0.66% and 0.13%, respectively.

Cost:

Bipolar disorder is noted as the most expensive of the behavioral health illnesses.[35] However, according to 2005 statistics, less than half are receiving treatment. Cost for treated patients and overall patients can be extracted from literature. The cost of untreated cases can then be "backed out" following

[33] Roshanaei-Moghaddam et al. Premature Mortality From General Medical Illnesses Among Persons
With Bipolar Disorder: A Review

[34] Tondo, L., Suicidal behavior in dipolar disorder: risk and prevention, CNS Drugs, 2003; 17(7): 491-511

[35] Peele et al, Insurance expenditures on bipolar disorder clinical and parity implications, Am j Psychia, 2003

Exhibit 25 through the following equation:

Cost of treated case * treated % + cost of untreated case * untreated % = Cost of an average BP case

Exhibit 24 Percent of bipolar patients receiving treatment

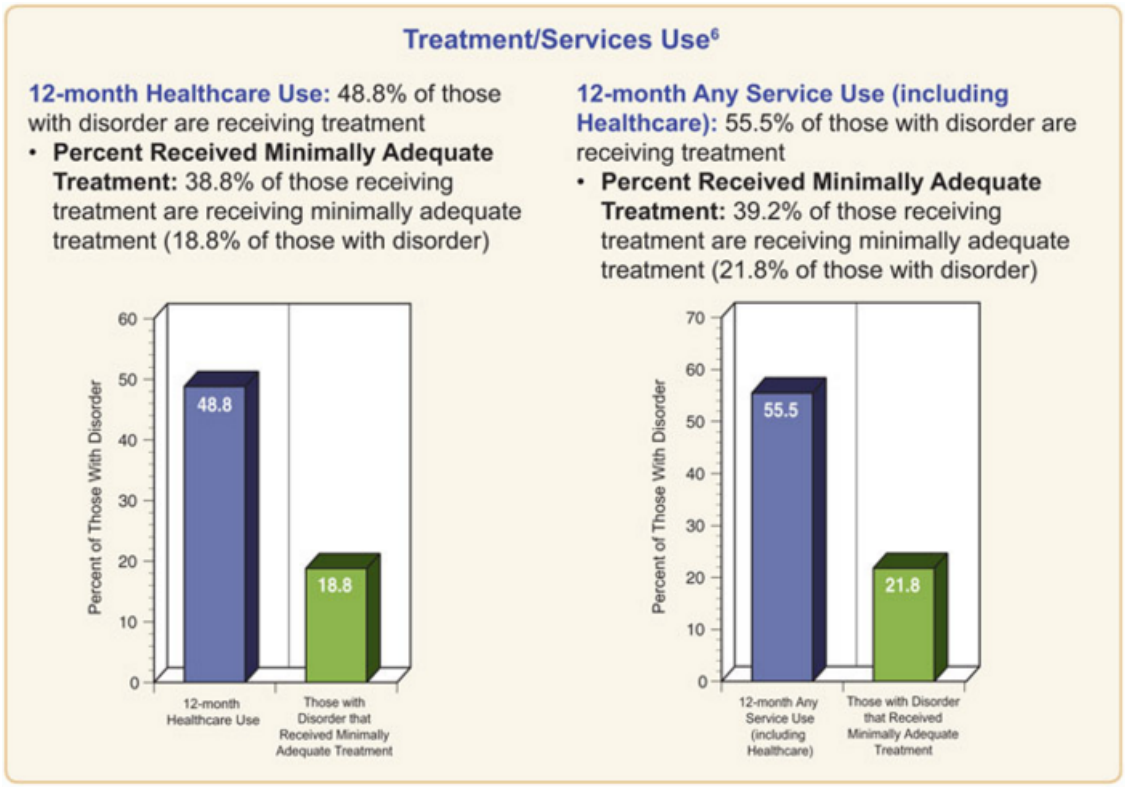
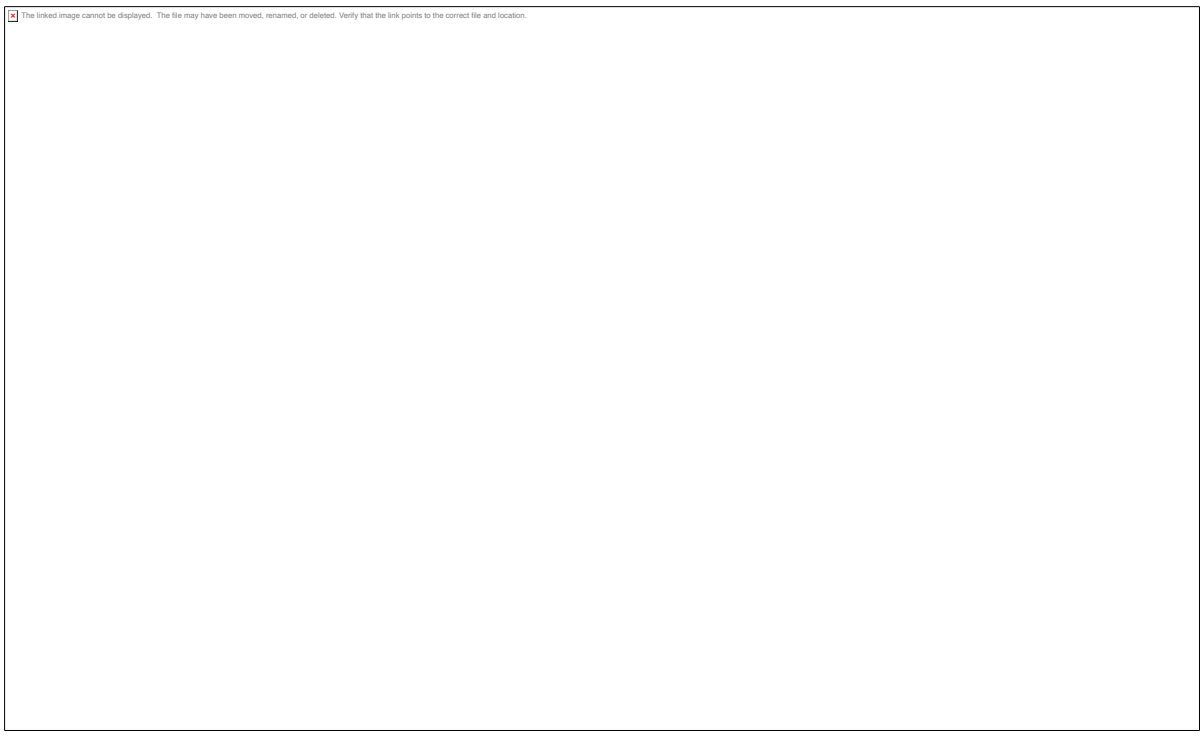


Exhibit 25 General calculation flow of cost and mortality rates



- Cost for treated patients:

In the model, the cost per person receiving treatment for bipolar disorder is sourced from Guo et al.'s work, which analyzed the costs related to Medicaid patients with bipolar disorder.[36] A major caveat is that the data is dated, as it presents costs in 2002 dollars. However, the report breaks down the costs associated with the disorder according to different settings, and goes a step further and estimates that in patients with bipolar disorder and comorbid conditions, only 30% of the monthly mean costs incurred ($22,110) are directly associated with the disorder, which brings the mean cost per patient per year to $6,633 in 2002 dollars. (Treated patient cost)

[36] Guo J et al_Treatment costs related to bipolar disorder and comorbid conditions among medicaid patients with bipolar disorder_Pysch Serv_2007

Exhibit 26 Costs of bipolar disorder in a Medicaid population[36]

Table 2

Utilization and costs of treatment related to bipolar disorder and to comorbid conditions among 13,471 Medicaid patients with bipolar disorder[a]

Variable	Charges for treatment ($)	Reimbursed treatment ($)	Number[b]	Cost per unit	% of total cost	% related to bipolar disorder	% related to comorbid conditions
Inpatient care	128,294,262	66,645,686	140,998	473	34.9	11.7	23.2
Emergency room	26,712,789	11,944,764	180,297	66	6.3	.6	5.7
Outpatient	62,835,250	29,825,263	122,430	244	15.6	2.8	12.8
Mental health services	6,678,019	15,867,739	46,298	343	8.3	3.6	4.7
Physician visits	39,250,019	20,755,645	396,309	52	10.9	1.9	8.9
Laboratory tests	1,241,812	575,367	14	.3	.1	.2	
Other medical services	42,876,172	20,755,278	315,472	66	10.9	1.2	9.7
Prescriptions	34,490,891	24,416,370	568,093	43	12.8	8.1	4.7
Total	362,379,214	190,786,112			100.0	30.0	70.0
Mean cost per patient-year[c]	22,110	11,641					

[a] Costs in 2002 dollars. Percentages are based on reimbursed costs.
[b] Refers to number of hospital days, emergency room visits, discrete mental health services, physician visits, laboratory tests, discrete prescriptions, and other medical services.
[c] Mean reimbursed cost per patient year was calculated as [(total cost/total number of patients)/mean enrollment months] × 12.

Alternatively, Brook et al.[37] report that the cost per year for an indivdual in an employee sponsored health plan is $9,983 (2001 cost). Again, this cost is for an individual who is receiving treatment.

The model cost input for treated patients will be the average from the 2 sources (inflated to 2015 dollars), which is $13,300.

- Cost of an average patient: Surprisingly few studies have been done for the overall economic burden of bipolar disorder in more recent years. One study that is often referenced is Wyatt et al.'s work on the economic burden of manic-depressive disorder, which reports the table below.[38] The same paper estimated that there were approximately 2.5 million individuals with bipolar disorder in the 1991, making the overall per person cost $18,084. Using data from official sources[39], the Medical CPI was used to calculate what the 1991 total value reported above would be in 2015 dollars, for an amount of $47,570.

[37] Brook RA et al. Incurring Greater Health Care Costs: Risk Stratification of Employees With Bipolar Disorder. Prim Care Companion J Clin Psychiatry. 2006; 8(1): 17–24.
[38] Wyatt RJ et al. An economic evaluation of manic-depressive disorder. Soc Psychiatry Psychiatr Epidemiol. 1995 Aug; 30(5): 213–219.
[39] US Bureau of Labor Statistics http://www.bls.gov/cpi/

Exhibit 27 Overall cost of bipolar disorder

Costs of manic-depressive illness-rounded totals in millions[a]

Direct costs			
Treatment-related	Total inpatient costs	$2,350 million	
	Total outpatient costs	$300 million	
	Total nursing home, intermediate, domiciliary care costs	$2,980 million	
	Medication	$130 million	
	Substance abuse	$720 million	
	Shelters	$80 million	
Non-treatment-related	Total crime (includes jails/prisons)	$2,260 million	
	Suicide	$190 million	
	Research/Training	$50 million	
Subtracted from direct costs	Transfer costs	$1,300 million	
Total Direct Costs			$7,570 million
Indirect costs			
	Lost productivity homemakers	$3,150 million	
	Lost productivity institutions	$2,860 million	
	Lost productivity suicide	$7,840 million	
	Lost family productivity	$6,220 million	
	Lost compensation	$17,570 million	
Total indirect costs			$37,630 million
1991 Total (direct and indirect)			$45,210 million

[a]All figures, including totals, are rounded from the original figures

Cost of untreated patients: When calculating the cost for untreated bipolar disorder patients, the cost of untreated was "backed out" following the flow depicted in

Exhibit 25.

$13,300*48.8% + cost for untreated * 51.2% = $47,570

Cost for untreated = $80,234

- Summary of disease cost: The cost for treated and untreated cases of BPD has been calculated in the steps above. Exhibit 27 provides the percentage breakdown of direct costs into inpatient, outpatient, and Rx costs, assuming untreated patients will NOT accumulate Rx cost.

Exhibit 28 Disease cost of bipolar disorder (2015 USD)

Type of patients	Inpatient cost	Outpatient	Rx	Total
Treated	$11,243	$1,435	$622	$13,300
Untreated	$71,151	$9.083	0	$80,234

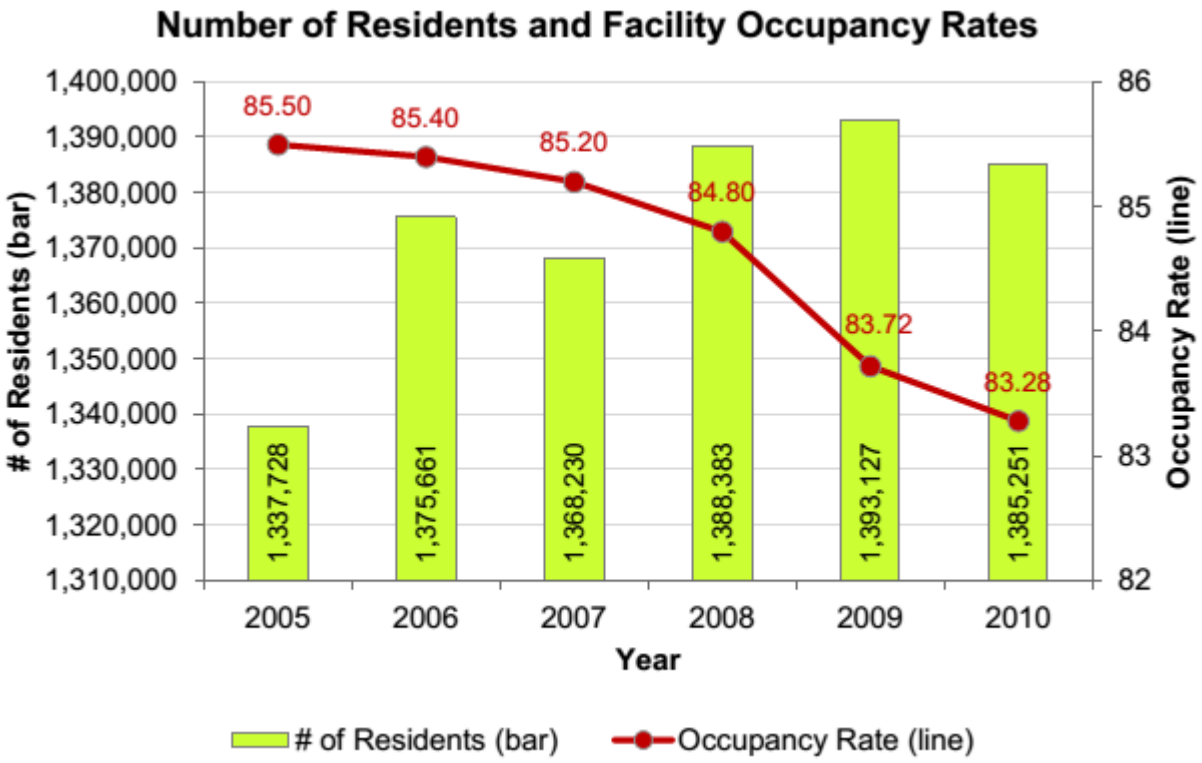
- Long term care: Total number of nursing home residents in 2005 was 1.34 million. (Exhibit 29)[40] In another report, 5,299 (0.53%) out of 996 thousand newly admitted nursing home residents had bipolar disorder in 2005. [41] So the total number of bipolar disorder patients admitted to nursing home was 1.34million*0.53%= 7,100.

  Total number of bipolar disorder patients was about 8.3 million (295.5 million population * 2.8% prevalence). This means 0.086% (7,100/8.3 million) of all existing bipolar patients are admitted to nursing home each year. The cost of nursing home is the same as for Alzheimer's disease, which is $61,436/year.

[40] Harrington, C., Nursing facilities, staffing, residents, and facility deficiencies, 2005 through 2010, Department of social & behavior sciences, University of California San Francisco, October 2011

[41] Fullerton, CA, Trends in mental health admissions to nursing homes, 1999-2005, Psychiatry services, Vol.60, No.7, July 2009

Exhibit 29 Number of nursing home residents 2005-2010[40]



- Missed work days: Hirschfeld reported an annual number of missed work days to be 49.5 per worker. [42] Assuming the number of missed work days is linearly correlated with the number of relapses, then the relative reduction of relapse rate is the same as reduction in missed work days. The number of missed work day for treated and untreated cases can then be "backed out" following the same approach as above (Exhibit 25)

  Relative reduction due to treatment (lithium) is 0.52. (Exhibit 22) Suppose x is the number of missed workdays for untreated patients, the following equation holds:

  $$x*51.2\% + x*0.52*48.8\% = 49.5$$

  $$x=64.6$$

[42] Hirschfeld R et al, Bipolar Disorder—Costs and Comorbidity, Am J Man Care_2005

Exhibit 30 Number of missed work days per year for treated and untreated bipolar disorder patients

Type of patients	Proportion	Missed work days
Treated	48.8%	33.6
Untreated	51.2%	64.6
Overall	100%	49.5

Benchmarking: "The costs per person associated with bipolar disorder have been estimated to be more than twice that of unipolar depression, making it one of the most expensive behavioral healthcare challenges[43]"

Key assumptions

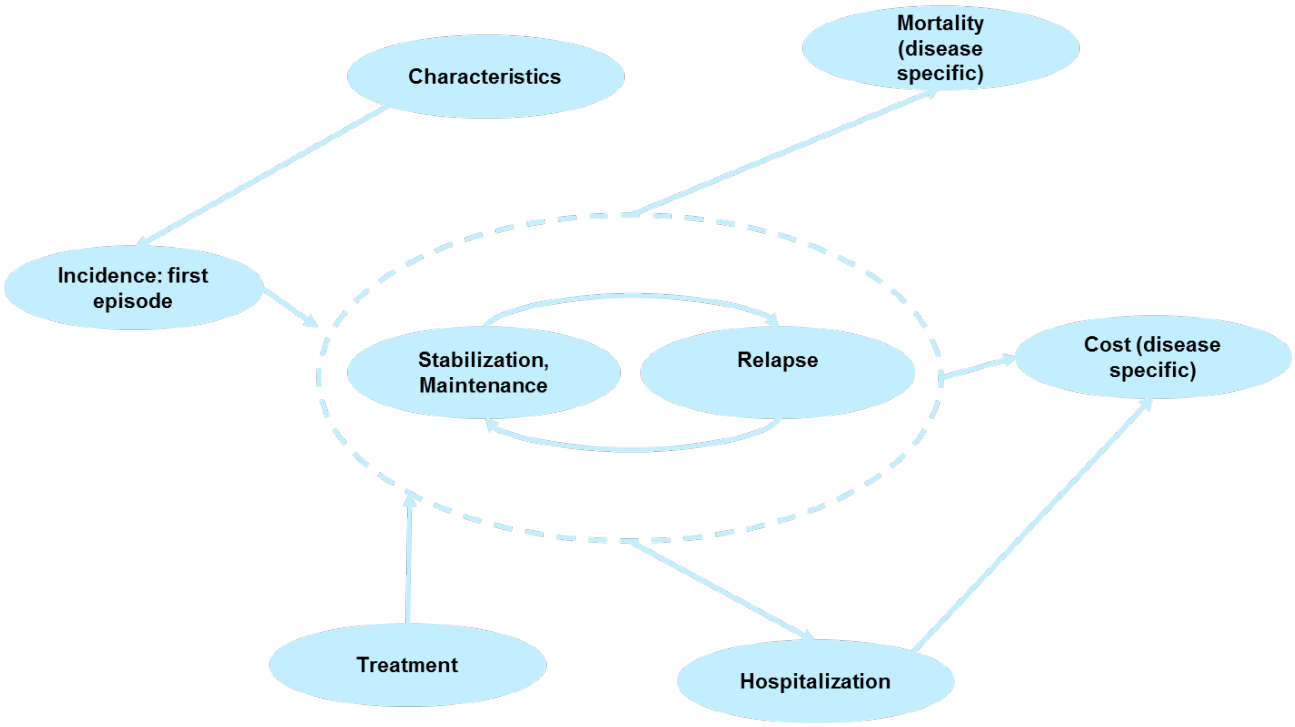
- We know the prevalence of BP-I and BP-II. If BP-I, we assume the patient will start with a manic episode. If BP-II, we assume patient will start with depressive episode
- Natural course of relapse will depend on the previous episode (manic or depressive, dictated by whether individual has BP-I or BP-II)
- Our model will use Lithium as the default treatment, as it appears to be the standard of care, first line treatment for the condition
- Separating the condition out into BD I and BD II will be a future refinement
- Missed work days is linearly correlated with the number of relapses (manic or depressive)

[43] http://www.sunovion.com/news/LAT307-13_Bipolar_Depression_Fact_Sheet.pdf

Schizophrenia

Schizophrenia is a life-long chronic illness and will be modeled as such in the DPMM. Treatment goals for the condition center on the following: 1) reduce or eliminate symptoms, 2) maximize quality of life and adaptive functioning, and 3) enable recovery by assisting patients in attaining persona life goals.44 The simulation of schizophrenia in the model will be done as shown in Exhibit 31.

Exhibit 31 Influence diagram for schizophrenia



[44] Lehman AF et al. Practice Guideline for the Treatment of Patients With Schizophrenia Second Edition. Work Group on Schizophrenia 2005

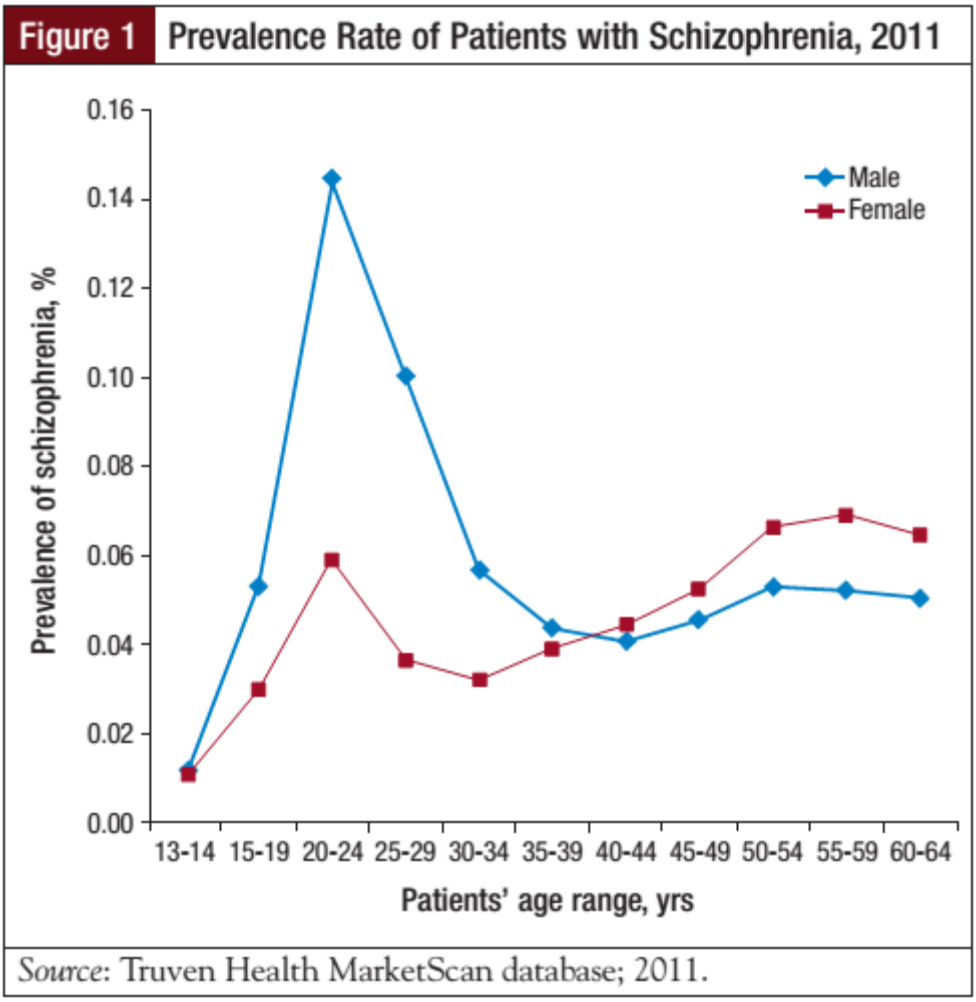
Prevalence: In 1993, the National Institute of Mental Health (NIMH) reported that the prevalence of schizophrenia in the USA was 1.1% of the adult population.[45] In their 2006 paper Wu et al. report that the estimated *lifetime* prevalence of schizophrenia and schizophreniform disorder in community epidemiological surveys using fully structured lay-administered diagnostic interviews have been in the range 0.3–1.6%.[46] Fitch et al. analyzed MarketScan claims database and reported prevalence rate as depicted in Exhibit 32.[47]

[45] http://www.nimh.nih.gov/health/statistics/prevalence/schizophrenia.shtml

[46] Wu EQ et al. Annual prevalence of diagnosed schizophrenia in the USA: a claims data analysis approach. Psychological Medicine, 2006, 36, 1535–1540

[47] Fitch, K, Iwasaki, K, Villa, K, Resource utilization and cost in a commercially insured population with schizophrenia, Am Health Drug Benefits, 2014, 7(1):18-26

Exhibit 32 Prevalence rate of schizophrenia



The final prevalence rates used in the model are converted from Exhibit 32 above (keeping 2 decimal places).

Exhibit 33 Prevalence rates for schizophrenia for model inputs (%)

Age group	Prevalence rate (Male)	Prevalence rate (Female)
20-24	0.15%	0.06%
25-29	0.10%	0.04%
30-34	0.06%	0.04%
35-39	0.04%	0.04%

40-44	0.04%	0.04%
45-49	0.04%	0.05%
50-54	0.05%	0.06%
55-59	0.05%	0.06%
60-64	0.05%	0.06%
65+	0.05%	0.06%

Incidence: A 2014 systematic review, by Van Der Werf et al. sought to recalculate the incident rates from published studies by age and sex, hoping to update previous estimates by the inclusion of new studies that were more recently published.[48] However, of the papers included in the meta-analysis, the only paper set in the USA was a 1967 paper by Malzberg et al. Cowan et al. examined the incidence of adult onset schizophrenic disorders in the US military.[49] While the obvious caveat is that the demographics of the military population are not an equivalent match to that of the US civilian population, the military is drawn from all socioeconomic and educational sectors of the US, as well as all states and territories. The study population includes both sexes, and members of all racial subgroups, and the age range 17 to over 60 years.

The most detailed data come from Fitch et al., which provided incidence rates by gender and age. (Exhibit 34) Final model inputs can then be calculated in Exhibit 35 (rounded to the nearest 0.005%)

[48] Van der Werf et al. Systematic review and collaborative recalculation of 133693 incident cases of schizophrenia. Pysch Med 2014

[49] Cowan DV et al. Incidence of adult onset schizophrenic disorders in the US Military: Patterns by sex, race and age. Schizophrenia Research. 2011

Exhibit 34 Incidence rates of schizophrenia

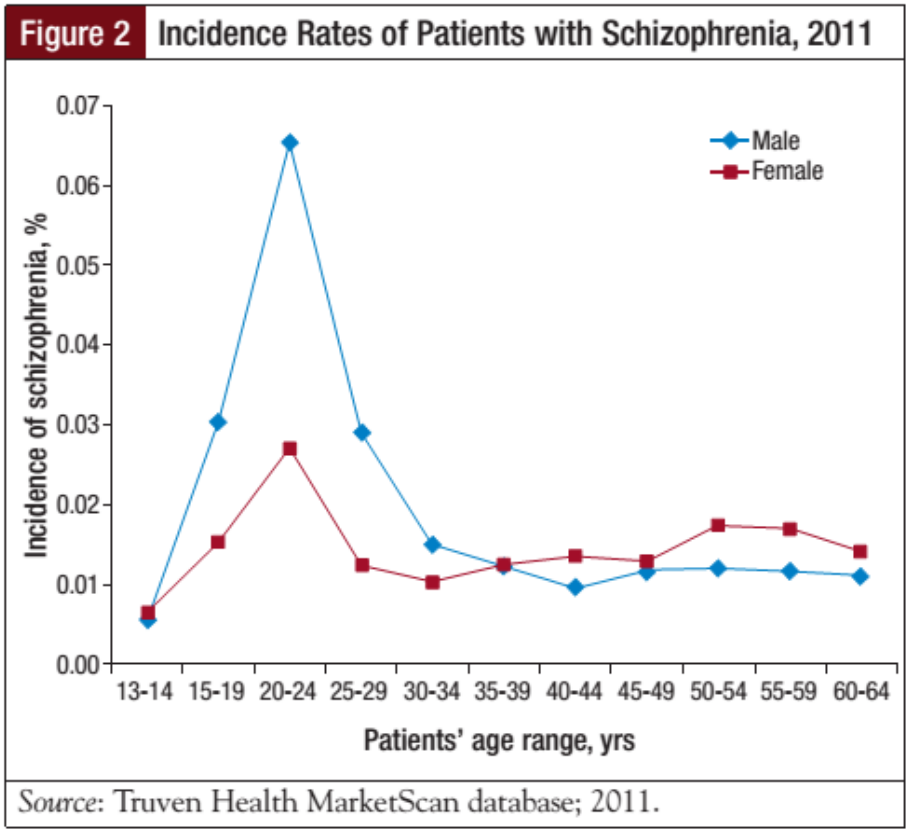


Exhibit 35 Incidence rate of first schizophrenic hospitalization by sex and age (%)

Age group	Prevalence rate (Male)	Prevalence rate (Female)
20-24	0.065%	0.030%
25-29	0.030%	0.010%
30-34	0.015%	0.010%
35-39	0.010%	0.010%
40-44	0.010%	0.010%
45-49	0.010%	0.010%
50-54	0.010%	0.015%
55-59	0.010%	0.015%

60-64	0.010%	0.015%
65+	0.010%	0.015%

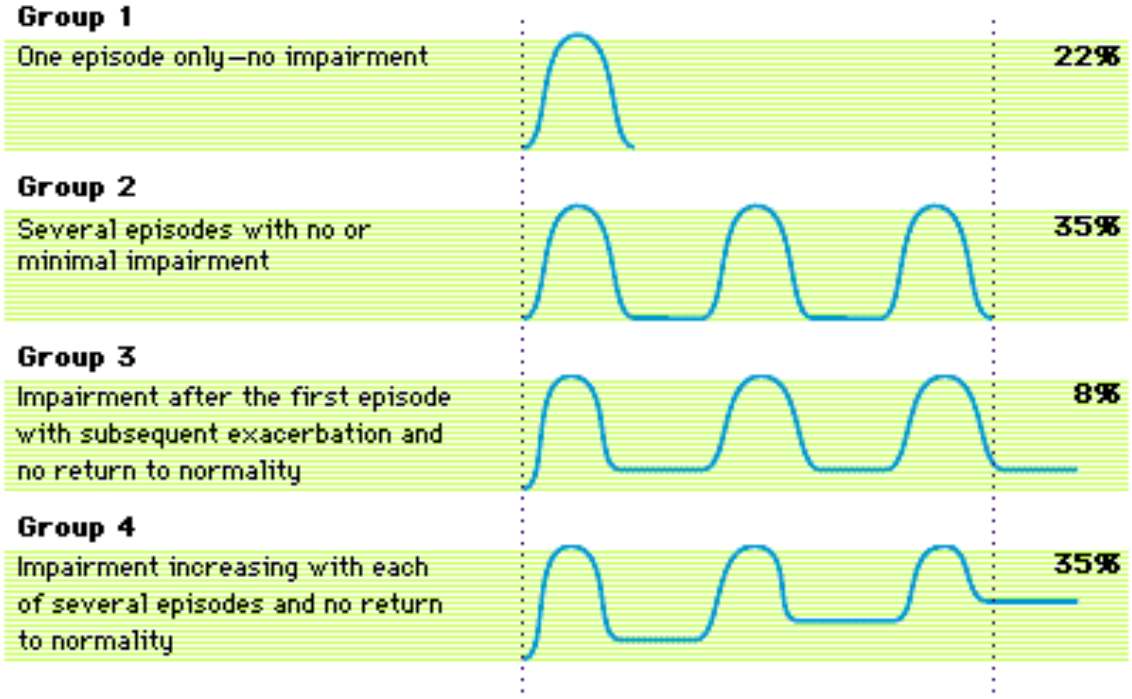
Data in Exhibit 35 can be verified independently by Cowan et al.[49] For instance, males usually experience disease onset earlier than females, echoed in the findings of Cowan et al. It has also been noted that women appear to have two peaks in the age of onset of disease, the fist after menarche and the second, after age 40, which the Cowan data reflects to an extent, with the incidence rate in females being higher than the males in the age 35+ category.[50]

Course of Disease: Schizophrenia is characterized by multiple relapses in most patients who have been diagnosed with the condition. It is noted that there is variation in patient experience, with some suffering only one episode and no permanent impairment, while at the other end of the spectrum, others may suffer multiple episodes and increasing impairment after each. While approximately 20% of patients who have a psychotic break will not have another, the majority of patients experience multiple relapses as seen in Exhibit 36.[51]

[50] Ochoa S et al. Gender Differences in Schizophrenia and First-Episode Psychosis: A Comprehensive Literature Review. Schizophrenia Research and Treatment Volume 2012, Article ID 916198

[51] http://www.schizophrenia.com/szfacts.htm

Exhibit 36 Schizophrenia disease course variance



Csernansky et al. reported that the risk of monthly relapse in schizophrenia is 3.5% in patients treated with depot antipsychotic drugs, resulting in an annual relapse rate of 42%. Non-compliance amongst patients was estimated to be 7.6% per month, and in these patients, relapse rates increased to 11% per month, making an annual relapse almost a certainty. [52]

The diagnosis of schizophrenia is often through the first hospitalization. To model the natural course of disease, we will use the relapse and re-admittance rates of patients on placebo as reported by Leucht et al in Exhibit 37.[53] Leucht et al note a lack of evidence pointing to differences in the efficacy of available antipsychotic drugs, and therefore assume any treatment has a similar effect in terms of the outcome of preventing relapses.

Exhibit 37 Probability of annual relapse and re-admittance for those treated with drugs vs. placebo

[52] Csernansky et al. Relapse and Rehospitalisation Rates in Patients with Schizophrenia Effects of Second Generation Antipsychotics. CNS Drugs. 2002

[53] Leucht et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet. 2012

Outcomes	Drug group	Placebo group	Risk ratio
% of patients who relapsed	27%	64%	0.40
% of patients readmitted (% of the total patient population)	10%	26%	0.38

Mortality: Kor et al. report that patients with schizophrenia are known to die earlier than expected, with up to 40% of excess premature mortality attributable to suicide and unnatural death. It is also reported that the lifetime suicide risk for those with schizophrenia is 4.9%.[54] Compared with the general population, schizophrenia patients have a 8.5 fold greater risk of suicide.[55] For the purpose of modeling, we'll use the 40% excess premature mortality as the basis of calculation.

Kasckow et al. report that clozapine, a second generation agent, reduced suicides rates by 88% two years after the start of treatment. In another study conducted over 1 year, current clozapine users had an 83% reduction in death by suicide compared to those who were using the drug but then stopped. National statistics report that 60% of schizophrenic patients get treated, so this population will have their lifetime suicide risk reduced by an average of 86%. For the 40% who are untreated, the suicide rate (x) has been calculated using the following equation:

$$x*40\% + x*(1-86\%)*60\% = 40\%$$

$$x = 82.6\%$$

This means untreated Schizophrenia patients have *82.6%* higher chance of dying due to unnatural causes. Treated cases have 82.6%*(1-86%)= *11.6%* higher chance of dying.

Treatment effect: As our model simulates relapse and hospitalizations as the primary outcomes of schizophrenia, we will use the reduction in % relapse and % re-admittance as measures of treatment effect. (Exhibit 37) Treatment effect will also be modeled via reduced mortality.

Cost: It is estimated that 40% of individuals with schizophrenia are untreated in any given year.[56] The condition is considered the most debilitating of all mental illnesses, and is estimated

[54] Hor K et al. Suicide and schizophrenia: a systematic review of rates and risk factors. J Psychopharmacol 2010.
[55] Kasckow J et al. Managing Suicide Risk in patients with Schizophrenia. CNS Drugs. 2011
[56] http://www.treatmentadvocacycenter.org/problem/consequences-of-non-treatment/schizophrenia

to cost approximately USD$63 billion a year (direct, societal and family costs) with 30% attributed to direct treatment. [57]

In Fitch's analysis of a commercially insured (treated) population, the cost of newly diagnosed schizophrenia cases in the first 2 years is reported below.[47]

Exhibit 38 First-month cost of newly diagnosed schizophrenia cases (2011 USD)

Table Snapshot Analysis: Mean PPPM and PMPM Costs and Resource Utilization for Patients with Schizophrenia Compared with Demographically Adjusted Total Commercially Insured Population

Variable	Patients with schizophrenia	Matched population with similar demographics, without schizophrenia
Total PPPM/PMPM cost, $	1806	419
Inpatient PPPM/PMPM cost, $	762	97
Outpatient PPPM/PMPM cost, $	592	239
Prescription drug PPPM/PMPM cost, $	452	83
Annual inpatient admissions per 1000 patients, N	636	48
Schizophrenia-related inpatient cases, N	322	—
Psychiatric/nonschizophrenia-related inpatient cases, N	155	—
Nonschizophrenia/nonpsychiatric-related inpatient cases, N	158	—
Annual emergency department visits per 1000 patients, N	2270	158
Schizophrenia-related emergency department visits, N	242	—
Psychiatric/nonschizophrenia-related emergency department visits, N	513	—
Nonschizophrenia/nonpsychiatric-related emergency department visits, N	1516	—

PMPM indicates per member per month; PPPM, per patient per month.
Source: Truven Health MarketScan database; 2011.

The cost attributable to schizophrenia can be calculated as the difference in cost between patients with and without the condition. (Exhibit 39) Cost attributable to schizophrenia accounts for 77% ($1387/$1806) of the total direct medical cost of patients with schizophrenia.

Exhibit 39 First-month cost of treated schizophrenia cases (2011 USD)

Setting	Cost attributable to Schizophrenia	% of total cost
Inpatient	$665	48%
Outpatient	$353	25%

[57] http://www.schizophrenia.com/szfacts.htm

Rx	$369	27%
Total	**$1,387**	**100%**

The same study reported the average total cost in the first and second year to be $23,512 and $15,252, respectively. Assuming 77% of these costs are directly related to schizophrenia, and that the distribution of inpatient, outpatient, and Rx cost remains the same as in the first month, we get the following table (inflated to 2015 USD).

Exhibit 40 Cost attributable to schizophrenia (2015 USD) for treated patients

Setting	First year	Subsequent years	% of total cost
Inpatient	$9,629	$6,246	48%
Outpatient	$5,015	$3,253	25%
Rx	$5,416	$3,514	27%
Total	**$20,060**	**$13,013**	**100%**

According to Exhibit 37, untreated patients have 2.37 (64%/27%) times more relapses and 2.6 (26%/10%) times more hospitalizations. Assuming outpatient visits for untreated patients has linear correlation with relapses, the cost for untreated patients can be calculated based on Exhibit 40.

Exhibit 41 Cost attributable to schizophrenia (2015 USD) for untreated patients

Setting	First year	Subsequent years
Inpatient	$25,035	$16,240
Outpatient	$11,886	$7,710
Rx	0	0
Total	**$36,921**	**$23,950**

Kazuhiro et al. reported the indirect cost of schizophrenia in the US is about the same as direct cost.[58] **Please note the indirect cost here includes absenteeism, presenteeism, and caregiver cost, and thus does not need to be converted to presenteeism like for other conditions.**

Exhibit 42 Total indirect cost of schizophrenia (2015 USD, no need to convert to presenteeism)

	First year	Subsequent years
Treated	$20,060	$13,013
Untreated	$36,921	$23,950

Key assumptions:

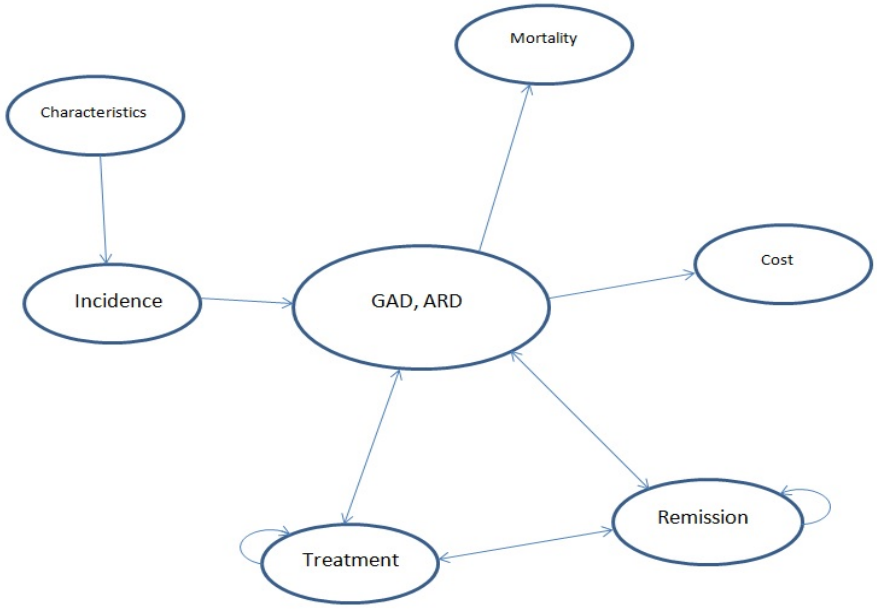
- Assuming the distribution of inpatient, outpatient, and Rx cost remains the same as in the first month

[58] Kazuhiro, TP, et al., Understanding the direct and indirect costs of patients with schizophrenia, F1000Res, Jul 6, 2015

Anxiety disorders

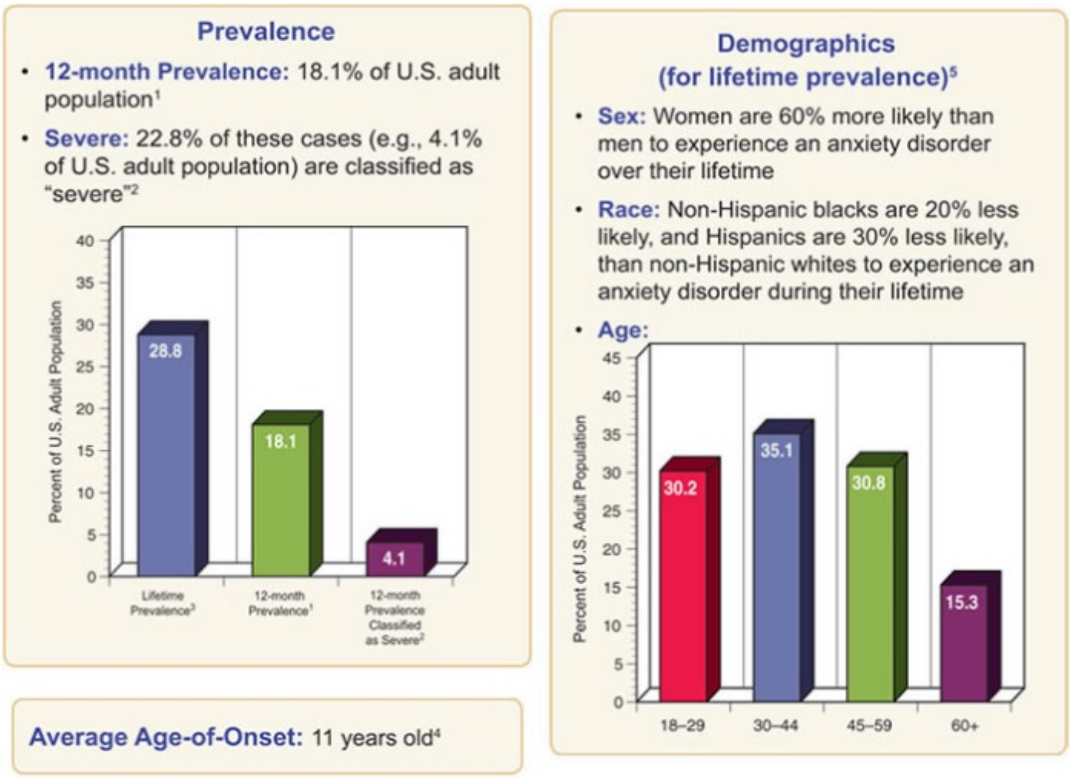
In Generalized Anxiety Disorder (GAD), the anxiety symptoms persist for at least 6 months.[1] Anxiety-Related Disorders (ARD) refer to other anxiety disorders with different clinical patterns from those attributed to GAD.[1] This includes social phobia, panic disorder, specific phobias and stress disorders.[1] Anxiety symptoms can interfere with social and personal activities, resulting in functional disability in untreated condition.[2] Both GAD and ARD are chronic conditions with periods of improvement and relapses.[1] By definition, severe anxiety disorders are those conditions with any of the following: a 12-month suicide attempt with serious lethality intent; work disability or substantial limitation of performance; substance dependence with serious role impairment; or 30+ days out of role in the year due to anxiety. [3]

Exhibit 43 Influence diagram of anxiety disorders



GAD = Generalized Anxiety Disorder
ARD = Anxiety-Related Disorders

Prevalence: The prevalence of anxiety disorders was obtained from WHO World Mental Health (WMH) Survey conducted in 2001-2003, and reported by the National Institute of Mental Health (NIMH).[3,4] Anxiety disorders are the most common class of mental disorders with the rate of 18.1% for 12-month prevalence of total anxiety disorders. The NIMH reported 12-month prevalence of GAD, social phobia, panic disorder and post-traumatic stress disorder to be 3.1%, 6.8%, 2.7%, and 3.5% respectively. The prevalence of severe anxiety is 4.1% among US population. [3,4]



Data from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) were used to estimate the distribution of anxiety disorders by age, sex and race.[5, 12] The 12-month male: female prevalence ratio of anxiety disorders was 1:1.79 in the Collaborative Psychiatric Epidemiology Studies (CPES).[6] The 12-month prevalence rates of anxiety disorders by age, sex and race are presented in the following exhibit 2. This prevalence applies directly to state employee cohort. Medicaid beneficiaries and incarcerated population have higher prevalence compare to general population, with rate of 24.1% and 29.4% respectively.[26,27]

Exhibit 44. The prevalence of anxieity disorders by age, race and gender

%	White		Black		Non-Hispanic Other		Hispanics	
Age group	Male	Female	Male	Female	Male	Female	Male	Female
18-29	22.8	33.6	14.4	21.3	17.2	25.3	9.6	14.1
30-44	17.7	32.8	13.6	25.1	14.6	27.1	11.0	20.3
45-64	10.0	19.8	9.8	19.5	10.0	19.9	11.4	22.7
65+	3.6	8.7	5.0	12.1	5.5	13.2	6.8	16.3

Incidence: The NESARC is a nationally representative survey of the US population, conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).[7] The study sample include individuals age 18

years and older in the civilian non-institutional population residing in households and group living quarters. The NESARC used the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule – DSM-IV Version for the diagnostic interview.[7] According to the NESARC, the 1-year incidence for any anxiety disorder is 1.57 per 100 populations. The age-specific incidence rates of anxiety disorders and the male: female incidence ratio were obtained from the NESARC and presented the following exhibits. [7]

Wave 1 past-year drinking status and first incidence rates of psychiatric disorders	Both sexes		Sex				Age group at Wave 1							
	Estimate	S.E.	Male		Female		18–24 years		25–44 years		45–64 years		65 years and older	
			Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.
Any anxiety disorder	1.57	0.09	1.10	0.11	2.07	0.14	1.91	0.28	2.10	0.17	1.33	0.17	0.58	0.12
Any panic disorder	0.62	0.05	0.40	0.06	0.84	0.08	0.92	0.16	0.80	0.10	0.50	0.08	0.19	0.06
Panic without agoraphobia	0.52	0.05	0.34	0.06	0.68	0.07	0.75	0.15	0.65	0.09	0.42	0.08	0.18	0.06
Panic with agoraphobia	0.09	0.02	*0.05	0.02	0.13	0.03	*0.15	0.06	0.13	0.04	*0.07	0.02	*0.01	>0
Social phobia	0.32	0.04	0.27	0.05	0.36	0.05	0.45	0.12	0.40	0.07	0.31	0.06	*0.05	0.02
Specific phobia	0.44	0.05	0.33	0.06	0.55	0.07	0.49	0.15	0.59	0.09	0.43	0.08	*0.09	0.04
Generalized anxiety	1.12	0.07	0.72	0.08	1.50	0.12	1.00	0.18	1.60	0.14	0.92	0.13	0.47	0.10

The modal Age-Of-Onset (AOO) for Social phobia and OCD are in adolescence or early adulthood. Panic disorder, agoraphobia, and GAD have a median AOO in the early-mid-twenties and an interquartile range of up to two decades. PTSD has the latest and most variable distribution of AOO.[1] The incidence of total anxiety disorder varies across the age and sex groups, as shown in the following exhibit 3. This incident rate applies directly to state employee cohort. For Medicaid and incarcerated populations, we calculated incidence scalars based on ratio of prevalence between them and general population. Then the incidence scalar will be applied to calculate the incidence of the anxiety disorder in either population.

Exhibit 45 Incidence rate of anxiety by gender and age

Incidence rate (%)	Age group							
	18-24		25-44		45-64		65 and older	
	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.
Male	1.34	0.34	1.47	0.21	0.93	0.21	0.41	0.15
Female	2.52	0.44	2.77	0.26	1.75	0.26	0.76	0.19

Natural course of the disease: Anxiety disorders are chronic conditions with a waxing and waning course.[1, 10] The 12-month to lifetime prevalence ratio of anxiety disorders is high. This ratio modestly decline with increasing age, indicating that anxiety disorders are often persistent throughout the life course.[1]

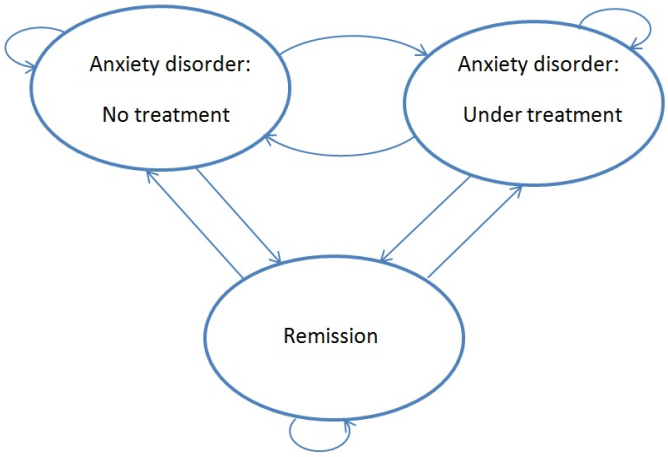
Approximately, 25% of patients with anxiety disorders experience remission before their symptoms are qualified for clinical diagnosis and they do not need treatment due to lack of symptoms.[10, 13] Remission is significantly related to four factors: time to onset of illness, time to pick of illness, the occurrence of threatening life events and the subsequent elimination of life stressors.[14] For those patients with remitted

anxiety disorders, overall recurrence rate was 23.5% in a 2-year follow-up assessment.[15] Two factors are significantly associated with the recurrence of anxiety disorders - disability (OR= 1.45, 95% CI: 1.06–1.97) and Anxiety Sensitivity Index (OR= 1.32, 95% CI: 1.02–1.71).[15]

Treatment effect: The efficacy of psychological and biological treatment for anxiety disorders is estimated to be between 60 and 85%.[18] The selective serotonin reuptake inhibitors (SSRIs) are the first-line medications according to the most clinical guidelines.[18] Cognitive-behavioral treatment (CBT) has also been accepted as a first-line therapy for anxiety disorders. Anxiety disorders are potentially treatable with pharmacotherapy and CBT; however, only 36.9% of patients with anxiety disorders receive treatment annually.[20] Previous studies have shown that the perceived need for help is low among individuals with anxiety disorders and it could result in under treatment and non-adherence to medications. [23] A systematic review included four studies investigating adherence to treatment for anxiety disorders in general. The attrition/ dropout rate averaged 38.7% which is a proxy for non-adherence rate in patients with anxiety disorders. [16]

The relationship between treatment effect and the natural course of anxiety disorders has been summarized in the following exhibit. The three states of "no treatment", "under treatment", and "remission" are mutually exclusive, since the first two states indicate active anxiety disorder. The transition from "under treatment" to "no treatment" is equal to non-adherence. To calculate the remission rate for patients under treatment, the average efficacy of anxiety treatment was assumed to be (60% + 85%)/ 2 = 72.5% for those who remained adherent. The adherence rate was 100% - 38.7% = 61.3%. Thus, the remission rate for patients under treatment is 61.3% * 72.5% = 44.4%. Transition from remission to the other states is equal to the recurrence of anxiety disorders. Since, the recurrence rate in 2-years follow up was 23.5%; we assumed that one-year recurrence rate would be 23.5% /2 = 11.8%.

Exhibit 46 Treatment effect diagram and table



Pe

Period 2

Anxiety Disorders	No treatment	Under treatment	Remission
No treatment	18.2%	56.8%	25%
Under treatment	38.7%	16.9%	44.4%
Remission	7.9%	3.9%	88.2%

Mortality: The relationship between anxiety disorders and mortality is complicated because most people with anxiety disorders do not die of their mental illness; rather, they die of heart disease, other chronic diseases, infections, suicide, and other causes.[17] Nepon et al., 2010 found that anxiety disorders are significantly associated with suicide attempts (OR=1.70, 95% CI: 1.40–2.08), after adjusting for sociodemographic factors and other mental disorders.[11] Panic disorder and PTSD were found to be independent risk factors for suicide attempts. There is no gender interaction in the relationship between anxiety disorders and lifetime suicide attempt.[11] One meta-analysis demonstrated that patients with anxiety disorders are at risk of cardiac death (HR= 1.48, 95% CI: 1.14-1.92), independent of demographic variables, biological risk factors, and health behaviors.[9]

According to a recent meta-analysis, anxiety disorders increase the risk of all-cause-mortality in general population by 43% (Pooled RR=1.43, 95% CI: 1.24-1.64).[17] It is reported that anxiolytic medication does not have a significant impact on the anxiety related mortality. There is controversy about the impact of gender on the mortality rates among patients with anxiety disorders. [24]

Costs: The overall cost of anxiety disorders in the US was estimated to be $42 billion a year in 1996, and it was almost one-third of total costs for mental illness in America.[19] The llifetime medical costs for a patient diagnosed with anxiety disorders average $6,475.[21]

Direct costs: Patients with anxiety disorders incur greater costs for medical care because they commonly misinterpret their anxiety symptoms as life-threatening illnesses and because their anxiety disorders frequently result in comorbid conditions such Coronary Heart Disease (CHD).[19] The risk of CHD and related costs is 26% higher for patients with anxiety disorders (HR= 1.26, 95% CI: 1.15-1.38).[9] The likelihood of ER visits and hospitalization is 3.70 and 1.62 folds higher respectively for patients with anxiety disorders in comparison to those without anxiety.[22] More than $22.84 billion of direct costs of anxiety disorders are associated with the repeated use of healthcare services.[20] According to the Medical Expenditure Panel Survey (MEPS) 2009-2010, the annual medical costs associated with anxiety disorders was $1657.52 (95% CI: $1189.41–$2125.63) per person.[25] A case-control study on MarketScan data estimated the annual medical costs of anxiety disorders at $1554.67 (95% CI: $1066.34–$2043.00) per person in 2000 (Exhibition 5).[22] This is attributable to a variety of anxiety disorders ranging from mild conditions to severe cases. [22] The summary of medical costs associated with anxiety disorders (2015 USD) is presented in exhibit 6.

Exhibit 47. Adjusted cost difference of anxiety and control group (2000 USD)

Costs	Anxiety (mean)	Control (mean)	Difference	95% CI*
Medical costs				
Outpatient	$2,552.41	$1,644.42	$907.99	$641.40–$1174.58
Inpatient	$718.25	$509.76	$208.49	–$76.72–$493.72
Outpatient drug costs	$1,118.38	$680.20	$438.18	$329.26–$547.10
Total medical costs	$4,389.04	$2,834.37	$1,554.67	$1,066.34–$2,043.00
Productivity costs				
Unofficial absences	$1,416.82	$989.32	$427.50	$229.54–$625.46
Official absences	$2,629.03	$2,371.89	$257.14	$111.02–$403.25
Total absences	$4,045.85	$3361.21	$684.64	$433.53–$935.75
Short-term disability	$462.48	$262.11	$210.37	$77.63–$323.13
Worker's comp	$2,884.89	$2,404.26	$480.63	–$66.16–$1,027.43
Total productivity costs	$7,393.23	$6,027.58	$1,365.65	$707.98–$2,023.32
Total costs	$11,782.27	$8,861.95	$2,920.31	$2,035.38–$3,805.26
Sample size	1917	1917		

Exhibit 48. Annual direct cost of anxiety disorders (2015 USD)

Setting	Costs per person	95% CI
Outpatient	$1,562.70	$1,103.88- $2,021.51
Inpatient	$358.82	$132.04- $849.72
Outpatient drug costs	$754.13	$566.67- $941.59
Total	$2,675.67	$1,835.23-$3,516.11

Indirect costs: consist of the costs of morbidity and mortality related to anxiety disorders. [19] DuPont et al. reported that approximately 75% of the costs of anxiety disorders were attributed to lost or reduced productivity. [19, 22] The total productivity cost for patients with anxiety disorders was estimated at $1365.65 (95% CI: $707-98–$2023.32) per person in 2000,[22] which inflated to $2350.35 in 2015 dollar. The costs of absenteeism associated with anxiety disorders to be $684.64 (95% CI: $433.53–$935.75) per person in 2000, [22] which is $1178.30 in 2015 dollar. In a period of one year, persons with anxiety disorders missed 13.23 workdays more than those without anxiety disorders. [22]

Key assumptions:

- Anxiety is modeled as a life time condition
- We obtained the lifetime prevalence rates from the NIMH and used the 12-month: lifetime prevalence ratios from other sources to estimate the 12-month prevalence of anxiety disorders. It is assumed that the 12-month: lifetime prevalence ratios are similar for GAD and total anxiety disorders.
- It is assumed that male: female ratio is constant across the race and ethnicity groups.
- It is assumed that the age distribution of anxiety is similar across the race and ethnicity groups.

- It is assumed the probability of receiving treatment after recurrence is same as the probability of getting treatment for patients with anxiety disorders in general.

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