# An Actuarial Analysis of Treatment Resistance in Patients with Major Depressive Disorder in a Commercially Insured Population

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# EXECUTIVE SUMMARY

Major depressive disorder (MDD) is a common psychiatric illness among adults with annual prevalence rates reported at 6.6% and lifetime prevalence rates of 16.2%.[1] The medical cost incurred for commercially insured patients with MDD is substantially higher than that of the average commercially insured member and higher non-medical costs (lost work time, productivity) are consistently reported in studies. Treatment Resistance, defined as failure to respond to adequate dose and adequate duration of conventional antidepressant therapy, is common with reports of occurrence in up to 30% of MDD patients.[2] Treatment Resistance among MDD patients is associated with a high risk for suicide, high relapse rates and high healthcare utilization rates compared to patients who benefit from first line treatment attempts.[3] The medical cost incurred for adults with treatment resistant forms of MDD is consistently higher than MDD patients who benefit from initial treatment, and is driven by a higher use of inpatient services (both general and depression related), outpatient services and a higher use of antidepressant therapies and non-antidepressant psychotropic drugs.[4, 5, 6, 7, 8]

For those with initial Treatment Resistance, the likelihood of an adequate response to subsequent treatment attempts is reported to decrease with each additional stage of treatment.[3] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that for MDD patients who did not achieve remission in first-stage treatment, a third of the study population did not achieve remission after completing up to 4 stages of clinically adequate treatment.[3] In an extension of that study, investigators found that patients who underwent multiple-stage treatment and did achieve remission were more likely to experience a relapse within the following year compared to those patients who benefited from initial treatment at earlier levels of Treatment Resistance.[9]

We used Thomson Reuters MarketScan® 2006 through 2010 commercial claims data to identify the prevalence, medical costs and patterns of care associated with individuals coded with MDD and in particular, the subset of MDD patients who failed to benefit from treatment with first line antidepressant therapy (Treatment Resistance cohort). We developed a claims based methodology to identify MDD patients with Treatment Resistance, based on the Antidepressant Treatment History Form (ATHF) criteria.[10] Using the ATHF criteria, Treatment Resistance was identified after evidence of an inadequate response to first line antidepressant therapy (8+ weeks of adequate dosing) which follows the American Psychiatric Association (APA) treatment guidelines for MDD patients (See Methodology section and MDD primer in Appendices A and B).[11]

We performed a snapshot and longitudinal analysis of the MDD commercially insured population. The snapshot analysis provides the costs incurred and distribution of treatment patterns occurring among the MDD population in a 12 month period (2010) with 24 month look back to establish new (newly diagnosed or new episode) versus existing MDD patients. The longitudinal analysis provides the costs incurred and treatment patterns observed for a 24 month period from a new MDD index date (2008 index year with 24 month look back and 24 month look forward time frame).

For each analysis, we segmented the MDD population into six mutually exclusive cohorts (listed below) based on their antidepressant therapy utilization. We consider that cohorts 3 and 4 represent MDD patients who exhibit adequate response to single antidepressant treatment and cohort 5 represents MDD patients exhibiting an episode of initial Treatment Resistance. Cohort 6 also represents a Treatment Resistance population although the sample size of this cohort is quite small.

1. *No Antidepressant* (no pharmacy claim for antidepressant during study period, yet meets MDD ICD-9 coding logic)
2. *Inadequate Antidepressant* (less than 8 weeks of adequate antidepressant dosing)
3. *Short Term Adequate Antidepressant without Treatment Resistance* (8+ weeks adequate single antidepressant dosing and up to an additional 5 months of adequate dosing of the same antidepressant)
4. *Long Term Adequate Antidepressant without Treatment Resistance* (8+ weeks of adequate single antidepressant dosing and an additional 6 months or more of adequate dosing of the same antidepressant)
5. *Treatment Resistance* (8+ weeks of adequate single antidepressant dosing followed by claims for either switching or adding a distinctly different antidepressant, adding specific atypical antipsychotics (AAPs), adding thyroid supplement or lithium carbonate)
6. *Electroconvulsive Therapy (ECT)*

Several findings emerge from this analysis that highlights the need for payers/employers to investigate the care patterns among their MDD population, including:

- MDD is a common illness among the 18-64 year old commercially insured population:
  - There was an overall prevalence of 2.6% MDD patients in MarketScan 2010 (among 18-64 year olds)
    - 0.5% prevalence were new MDD patients
    - 2.1% prevalence were existing MDD patients

- Patients with MDD are expensive
  - The per patient per month (PPPM) cost of MDD patients and the per member per month (PMPM) contribution to total population spend is similar to that of patients with diabetes
  - The PMPM cost contribution of MDD patients is approximately 6% of the total population spend as shown in the table below.

| Commercial Population 0-64 year olds | MDD | Diabetes | Hypertension | Total Population |
|---|---|---|---|---|
| Claim based prevalence | 2.0% | 3.6% | 9.2% | |
| $PPPM | $1,127 | $1,204 | $946 | |
| $PMPM | $19.86 | $44.77 | $89.15 | $350.34 |

Source: Milliman analysis of MarketScan® 2010 data (see methodology for coding logic)

- The majority of existing MDD patients in a snapshot year do not receive adequate or effective antidepressant therapy:
  - 51.6% of existing MDD patients in our 2010 snapshot (12 months exposure for MDD) do not receive adequate or effective antidepressant therapy. The 51.6% is comprised of:
    - 4.2% received No Antidepressant medications
    - 24.5% received Inadequate Antidepressant treatment
    - 22.8% demonstrated Treatment Resistance
    - 0.1% received ECT

- The majority of new MDD patients do not receive adequate or effective antidepressant therapy during the 24 months after index diagnosis:
  - 57.9% of new MDD patients in our 2008 index year - 24 month longitudinal analysis do not receive adequate or effective antidepressant therapy. The 57.9% is comprised of:
    - 13.8% received No Antidepressant medications
    - 29.1% received Inadequate Antidepressant treatment
    - 14.9% demonstrated Treatment Resistance
    - 0.1% received ECT

- Among the patients who receive antidepressant medication treatment, a significant portion meet criteria for initial Treatment Resistance, and the prevalence of Treatment Resistance increases with more exposure time for the new MDD patients:
  - 22.8% of existing MDD patients in the 2010 snapshot analysis meet Treatment Resistance criteria (23.8% of MDD patients who have 1+ claim for an antidepressant)
  - 4.4% of new MDD patients in the 2010 snapshot analysis meet Treatment Resistance criteria (5.4% of the MDD patients who have 1+ claim for an antidepressant)
  - 14.9% of new MDD patients in the 24 months after index diagnosis meet Treatment Resistance criteria (17.3% of the MDD patients who have 1+ claim for an antidepressant)

- Slightly over half of the existing MDD patients with Treatment Resistance take 3 distinct antidepressant drugs during the snapshot year and almost 20% take 4 distinct types of antidepressants during the snapshot year. In addition, the use of other psychotropic drugs is significantly higher when compared to the Long Term Adequate Antidepressant without Treatment Resistance cohort including antianxiety drugs, anticonvulsants, attention deficit hyperactivity disorder (ADHD) drugs and antipsychotics.

- MDD patients meeting criteria for initial Treatment Resistance have statistically significantly higher costs than those receiving Long Term Adequate Antidepressant Therapy without Treatment Resistance:
  - Snapshot analysis (2010 dollars)
    - $406 PPPM higher cost comparing new MDD patients with Treatment Resistance cohort to new Long Term Adequate Antidepressant without Treatment Resistance cohort (p value < 0.001)
    - $584 PPPM higher cost comparing existing MDD patients with Treatment Resistance to existing Long Term Adequate Antidepressant without Treatment Resistance cohort (p value < 0.001)
    - The difference in cost between these two cohorts is $2.02 on a PMPM basis or 10% of the total MDD PMPM ($19.86 PMPM)
  - Longitudinal analysis
    - No statistically significant cost difference between the Treatment Resistance cohort and the Long Term Adequate Antidepressant w/o Treatment Resistance cohort in the 24 months prior to MDD diagnosis
    - $1,080 higher PPPM cost in the index MDD diagnosis month for Treatment Resistance cohort versus Long Term Adequate Antidepressant without Treatment Resistance cohort (p value< 0.001)
    - $155 higher PPPM cost in the 2-12 months after index date for Treatment Resistance cohort versus Long Term Adequate Antidepressant without Treatment Resistance cohort (p value < 0.001)
    - $186 higher PPPM cost in the 13-24 months after index date for Treatment Resistance cohort versus Long Term Adequate Antidepressant without Treatment Resistance cohort (p value < 0.001)

Our findings support published findings regarding the burden of MDD and in particular, cost and quality of care issues for the subset of MDD patients exhibiting Treatment Resistance. We identified a substantial portion of MDD patients with inadequate response to first line antidepressant therapy (initial Treatment Resistance) and observed their subsequent utilization of multiple antidepressants and other psychotropic drugs in the year of the initial Treatment Resistance. When compared to the MDD cohort with Long Term Adequate Antidepressant without Treatment Resistance cohort, the Treatment Resistance cohort had almost twice the rate of MDD related inpatient admissions, ER visits and professional claims. This utilization of MDD related services contributes to the $2.02 PMPM higher cost of MDD patients with Treatment Resistance and a portion of that cost might be avoided with an earlier adequate response to initial Treatment Resistance. Benefit coverage for efficacious therapies to treat MDD patients who fail to benefit from initial antidepressant medication treatment should be evaluated by payers/employers. We hope the findings in our analysis provide insights for payers/employers as they attempt to bring better management to the MDD population.

This report was commissioned by Neuronetics, Inc. which manufactures the NeuroStar TMS Therapy™ system, a Transcranial Magnetic Stimulation device for the treatment of major depression. The findings reflect the research of the authors; Milliman does not intend to endorse any product or organization. If this report is reproduced, we ask that it be reproduced in its entirety, as pieces taken out of context can be misleading. As with any economic or actuarial analysis, it is not possible to capture all factors that may be significant. Because we present national average data, the findings should be interpreted carefully before they are applied to any particular situation.

## BACKGROUND

Major Depressive Disorder (MDD) is a psychiatric illness characterized by "an episode of depressed mood or loss of interest in almost all activities for a period of at least two weeks".[12] MDD induces a pervasive hopelessness and fatigue that impairs patients' ability to carry out their usual daily occupational and social activities (See Appendix C for a primer on MDD). MDD is one of the most common psychiatric conditions among adults age 18 years and older. The prevalence of MDD among adults age 18 and older is estimated to be 6.6% annually and 16.2% over one's lifetime and women have almost twice the prevalence as men.[1] The cause of Treatment Resistance among MDD patients is not known but contributing factors include inability to tolerate drug therapy side effects, non-compliance with drug therapy, inadequate dosing and duration of drug therapies, limitations in the long term efficacy of drug therapies and presence of comorbid psychiatric conditions.

Medical claim costs and indirect costs associated with depression (including lost earnings due to reduced productivity, time off from work, and depression-related suicide attempts and suicide) are substantial for the MDD population. Greenberg et al estimated medical costs of $12 billion for US adults with MDD and $24 billion in indirect workplace costs, and over $7 billion in depression-related suicide costs (US 1990 values).[13] Stewart et al estimated workers with MDD had 5.6 hours a week of lost productive work time versus 1.5 for workers without MDD.[14] Birnbaum et al (2010) analyzed workplace performance among depressed workers, and found that depressed workers reported significantly less productive hours than their non-depressed peers (the monthly work performance was reduced by 14.8 hours for the severely depressed and by 12.0 hours for the moderately depressed compared to non-depressed workers).[15]

A significant percentage of MDD patients do not experience complete remission (i.e. a symptom-free stage) following their first-stage treatment with antidepressant medication. Treatment Resistance refers to "the occurrence of an inadequate response following adequate antidepressant therapy among patients suffering from unipolar depressive disorders"[16]. Treatment Resistance extends on a continuum of progressively more severe stages. It has been shown that with each successive course of unsuccessful (but adequately dosed) treatment, it becomes progressively less likely for a patient to reach an asymptomatic stage, or remission of symptoms. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that at least 67.1% of patients did not achieve remission in first-stage treatment, even when administered under conditions of adequate dosing and adequate duration of exposure.[17] After completing up to 4 stages of clinically adequate treatment, a third of the study population did not achieve remission.[3] In addition, with each additional stage of treatment, a patient's likelihood of remission was shown to diminish. Patients who underwent multiple-stage treatment and did achieve remission were also more likely to experience a relapse within the following year compared to those patients who benefited from initial treatment at earlier levels of Treatment Resistance.[9]

Treatment Resistance in MDD has received wide clinical attention.[4, 16, 7, 6, 10] As noted above, Treatment Resistance extends on a continuum, and there are several conventional approaches to staging this aspect of illness severity. In general, researchers consider four key elements that determine the adequacy of treatment and inadequacy of response: i.e. dosage adequacy; duration of exposure to an adequate dose of treatment; treatment adherence; and clinical outcome.[10, 18] In addition, the literature discourages viewing Treatment Resistance as a dichotomous concept, emphasizing instead the need to evaluate Treatment Resistance on a continuum, from mild to complex.[4] Several clinical staging algorithms have been developed in an effort to assess the various levels of resistance, such as the Thase & Rush staging, and the Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (ATRQ) staging (see Appendix C).[19, 16] The Antidepressant Treatment History Form (ATHF) is a semi-structured interview method that has been used to establish gradations of antidepressant Treatment Resistance. The ATHF is the only method that has been demonstrated in replicated studies to show prospective validity in characterizing the severity of Treatment Resistance.[10, 20, 21] In this report, we adapted the definitions and methodology for defining Treatment Resistance contained within the ATHF to allow us to categorize initial Treatment Resistance in a claims database in a manner that approximated the first stage category defined by the ATHF methodology (ATHF=1). We focused on identifying the earliest stage of Treatment Resistance in order to capture the entire Treatment Resistance MDD population and their course of therapy. We assumed that the cost burden of treatment resistance would be evident even at this earliest stage of treatment resistance, highlighting the need for efficacious treatment alternatives for the Treatment Resistance population.

Establishing and defining treatment resistance in patients with MDD using the criteria of failing to benefit from adequate dosing and duration of antidepressant therapy can be difficult because patients with major depression are frequently administered doses of medication that fall below accepted thresholds for adequacy. Studies have suggested that only about half of the total number of patients diagnosed with major depression receive a single adequate medication trial during their index episode.[16] The most common clinical reason this may occur is due to the emergence of adverse side effects early in treatment that are unacceptable to the patient, leading them to discontinue therapy. Furthermore, because the onset of clinical benefit from antidepressant medication can often lag the first dose by as long as 8 to 12 weeks, patients may discontinue treatment prematurely because of the perceived lack of efficacy. The "treatment resistance" exhibited by such patients should ideally be referred to as "pseudoresistance" because adequate treatment has not (yet) been administered, and therefore true treatment resistance has not been documented.[16] Using strict criteria for treatment resistance, studies have suggested that only about half of the total number of patients diagnosed with major depression receive a single adequate medication trial during their index episode.[10]

A common definition in use in research and clinical practice is "treatment-resistant depression" usually described in shorthand by the acronym "TRD", and used to refer to patients who have failed to benefit from two different antidepressant medications of two different chemical classes. This definition allows the continuum of Treatment Resistance to be reduced to a categorical distinction. The TRD designation has been used to segment MDD patients for several MDD medical cost analyses.

Treatment Resistance among depressed patients is usually associated with substantially higher medical costs compared to non-TRD patients.[4, 7] Greenberg et al (2004) analyzed claims data for employees of a large Fortune 100 company using the categorical "TRD" designation, to show that the per person per year medical cost for TRD patients was more than double than that for the non-TRD patients ($14,490 vs. $6,665).[5] In a more recent study, Gibson et al (2010) estimated that medical costs for patients diagnosed with the categorical "TRD" grouping are 40 percent greater than for MDD patients not diagnosed as TRD.[4] The study identified annual costs for patients with mild TRD (using the MGH ATRQ rating) exceed that for non-TRD patients by $1,530 and the cost difference is tripled when non-TRD patients are compared with complex TRD. In addition, depression-related and total medical costs increased significantly as treatment-resistant depression increased in severity. [8]

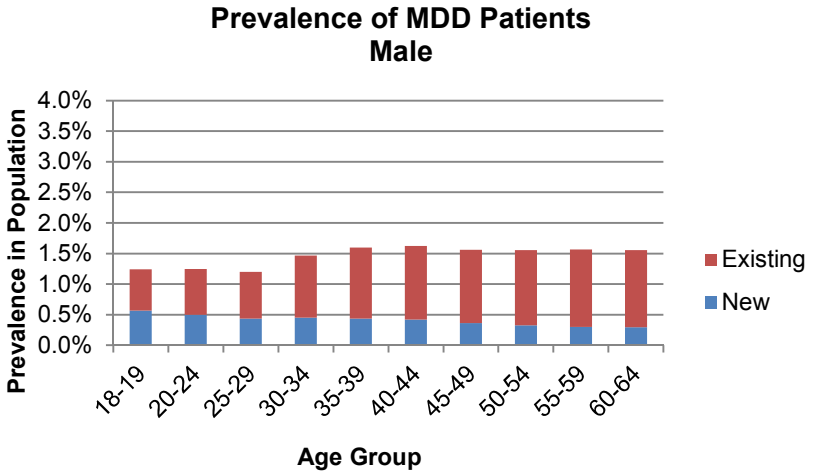
In this report we analyzed commercial claims data to identify the prevalence, medical costs and patterns of care associated with MDD and in particular MDD patients with early stage Treatment Resistance, consistent with the definitions used in the ATHF methodology. We developed a claims based identification methodology for Treatment Resistance, translating clinical guideline definitions into claims based logic. The results highlight the challenges of MDD treatment and quality of care concerns for MDD patients with initial Treatment Resistance.

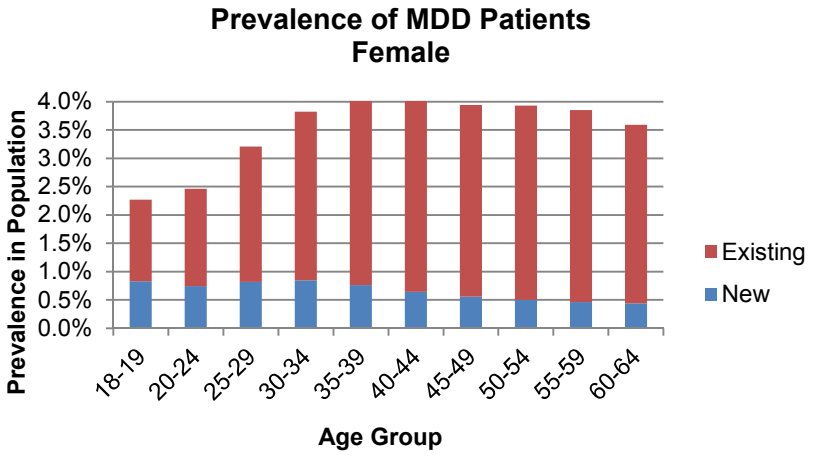
# FINDINGS FROM CLAIM DATA ANALYSIS

## Snapshot Analysis

This snapshot analysis provides the experience a payer/employer could observe on an annual basis considering that patients can be diagnosed with MDD at any point during the year. In a large subset of MarketScan claims data, we identified a 2010 MDD prevalence rate of 2.6% (n= 133,394) among 18-64 year olds. This was comprised of a new onset (new) MDD prevalence rate of 0.5% (n=32,024) (no claims coded with MDD in the 24 months prior to the 2010 index date) and 2.1% (n=133,394) for previously diagnosed (existing) MDD patients. Females had 2.5 times the prevalence of men and prevalence peaked in 35-44 year olds for both men and women. Claims coding practices, care seeking behavior and our required claims coding MDD identification logic results in claim based prevalence rates for MDD falling below survey based rates. This lower prevalence is often found for other chronic conditions when analyzing claims data.

**Figure 1: Prevalence of MDD Patients by Demographic Distribution**




Source: Milliman analysis of MarketScan® 2008-2010

The prevalence of MDD on a total population basis (0-64 year olds) is 2.0% and the contribution to total population per member per month cost is $20 or approximately 6% of total PMPM spend ($350 PMPM). The PMPM cost of the MDD population is similar to that of the diabetes population shown in Table 1.

**Table 1: Prevalence and Cost of MDD, Diabetes and Hypertension in a Commercially Insured Population (ages 0-64)**

| Commercial Population 0-64 year olds | MDD | Diabetes | Hypertension | Total Population |
|---|---|---|---|---|
| Claim based prevalence | 2.0% | 3.6% | 9.2% | |
| $PPPM | $1,127 | $1,204 | $946 | |
| $PMPM | $19.86 | $44.77 | $89.15 | $350.34 |

Source: Milliman analysis of MarketScan® 2010 (see methodology section for coding logic)

In order to identify treatment patterns and adequacy of treatment for MDD patients, we classified new and existing MDD patients into 6 MDD cohorts based on antidepressant prescription claims (see Methodology). We characterize four of our cohorts as having inadequate treatment or Treatment Resistance -- No Antidepressant, Inadequate Antidepressant, Treatment Resistance and ECT while two of our cohorts are considered adequately treated-- Short and Long Term Adequate Antidepressant without Treatment Resistance.

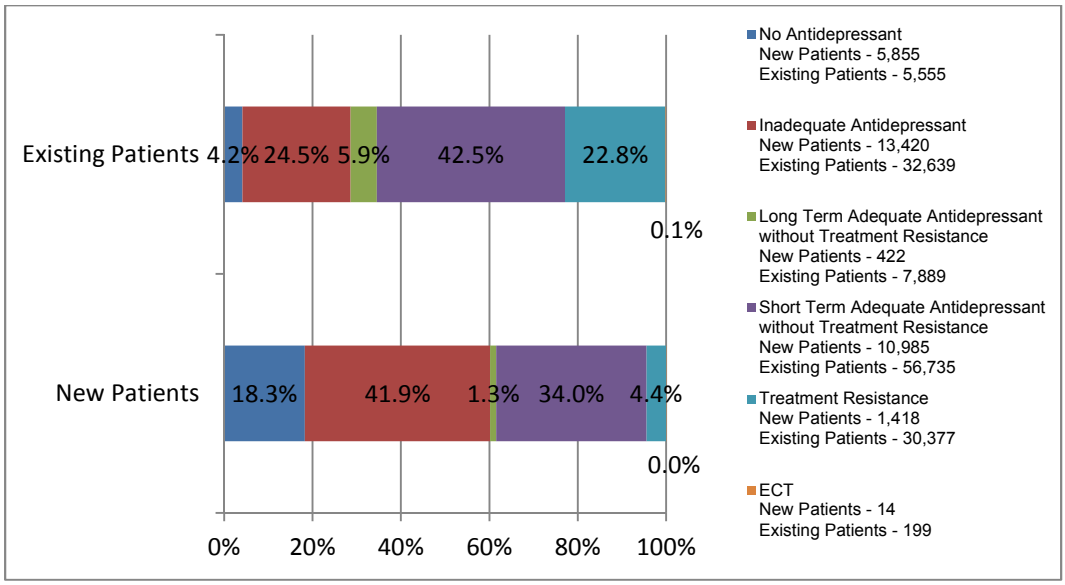
In the snapshot analysis, patients have on average, 6 months duration of MDD following the index MDD claim because patients can be diagnosed at any point during the year. Therefore, claims experience likely understates the duration of drug therapy for some patients. This means some patients may have been incorrectly assigned to the Inadequate Antidepressant therapy cohort and could be assigned to the adequate antidepressant therapy cohorts given longer claim duration. In the next section we describe the longitudinal analysis which follows new MDD patients for 24 months and assigns a smaller portion of the MDD patients to the inadequate therapy cohorts and a higher portion to Treatment Resistance.

In Figure 2, we provide the distribution and sample size of MDD patients by the 6 MDD cohorts split by new and existing MDD patients.

- The majority of MDD patients do not receive adequate or effective antidepressant therapy:
  - 51.6% of existing MDD patients in our 2010 snapshot (12 months exposure for MDD) do not receive adequate or effective antidepressant therapy.
    The 51.6% is comprised of:
    - 4.2% received No Antidepressant medications
    - 24.5% received Inadequate Antidepressant treatment
    - 22.8% demonstrated Treatment Resistance
    - 0.1% received ECT
  - 64.6% of new MDD in our 2010 snapshot (on average 6 months exposure for MDD) do not receive adequate or effective antidepressant therapy.
    The 64.6% is comprised of:
    - 18.3% received No Antidepressant medications
    - 41.9% received Inadequate Antidepressant treatment
    - 4.4% demonstrated Treatment Resistance

- Among all MDD patients and specifically among those who receive antidepressant medication treatment, a significant portion meet criteria for initial Treatment Resistance:
  - 22.8% of existing MDD patients in the 2010 snapshot analysis and 23.8% of existing MDD patients with 1+ claim for an antidepressant meet Treatment Resistance criteria
  - 4.4% of new MDD patients in the 2010 snapshot analysis and 5.4% of new MDD patients with 1+ claim for an antidepressant meet Treatment Resistance criteria

### Figure 2: Percentage of MDD patients by Treatment Type in Snapshot Analysis




Source: Milliman analysis of MarketScan® 2008-2010
New MDD patients have on average 6 months of claims experience after index date

The comparison between the Treatment Resistance and Long Term Adequate Antidepressant without Treatment Resistance cohort provides a proxy comparison for MDD patients who respond to single antidepressant therapy and those who have initial Treatment Resistance. In Tables 2 and 3 we compare these cohorts' costs split by inpatient, ER, facility, physician and pharmacy costs and further split these (except facility) by MDD related, psychiatric related and other. New and existing MDD patients meeting criteria for initial Treatment Resistance have statistically significantly higher costs than the Long Term Adequate Antidepressant without Treatment Resistance cohort:

- $406 PPPM higher cost comparing new Treatment Resistance cohort to the new Long Term Adequate Antidepressant without Treatment Resistance cohort (p value <0.001)
- $584 PPPM higher comparing existing Treatment Resistance cohort to the existing Long Term Adequate Antidepressant without Treatment Resistance cohort (p value <0.001)
- The difference in cost between these two cohorts is $2.02 on a PMPM basis or 10% of the total MDD PMPM ($19.86 PMPM)
- The MDD related and psychiatric related services are noticeably higher costs in the new Treatment Resistance cohort compared to the Long Term Adequate Antidepressant without Treatment Resistance cohort

### Table 2: Average PPPM in 2010 for New MDD Patients in Snapshot Analysis

| Claim Categories | No Antidepresants | Inadequate Antidepresants | Short Term Adequate Antidepresants without Treatment Resistance | **Long term Adequate Antidepresants without Treatment Resistance** | **Treatment Resistance** | ECT | Total |
|---|---|---|---|---|---|---|---|
| IP_MDD | $496 | $107 | $96 | **$45** | **$188** | $3,474 | $178 |
| IP_PSY | $6 | $2 | $2 | **$0** | **$13** | $53 | $3 |
| IP_NonPSY | $205 | $86 | $59 | **$27** | **$122** | $0 | $99 |
| ER_MDD | $33 | $5 | $6 | **$4** | **$9** | $24 | $11 |
| ER_PSY | $5 | $4 | $4 | **$2** | **$10** | $0 | $4 |
| ER_NonPSY | $29 | $20 | $18 | **$12** | **$32** | $11 | $22 |
| Prof_MDD | $35 | $27 | $34 | **$44** | **$72** | $298 | $33 |
| Prof_PSY | $12 | $9 | $12 | **$10** | **$28** | $74 | $11 |
| Prof_NonPSY | $131 | $83 | $89 | **$138** | **$143** | $53 | $97 |
| Facility | $169 | $95 | $94 | **$140** | **$177** | $819 | $113 |
| Rx_Antidep | $0 | $7 | $17 | **$27** | **$36** | $26 | $11 |
| Rx_PSY | $9 | $7 | $10 | **$15** | **$37** | $182 | $10 |
| Rx_NonPSY | $41 | $30 | $37 | **$71** | **$75** | $30 | $37 |
| Total | $1,172 | $482 | $479 | **$535** | **$941** | $5,043 | $629 |

Source: Milliman analysis of MarketScan® 2008-2010. See methodology for claim category definitions

### Table 3: Average PPPM in 2010 for Existing MDD Patients in Snapshot Analysis

| Claim Categories | No Antidepresants | Inadequate Antidepresants | Short Term Adequate Antidepresants without Treatment Resistance | **Long term Adequate Antidepresants without Treatment Resistance** | **Treatment Resistance** | ECT | Total |
|---|---|---|---|---|---|---|---|
| IP_MDD | $401 | $177 | $168 | **$153** | **$239** | $1,955 | $198 |
| IP_PSY | $7 | $4 | $3 | **$0** | **$6** | $132 | $4 |
| IP_NonPSY | $361 | $225 | $197 | **$131** | **$230** | $166 | $214 |
| ER_MDD | $24 | $9 | $10 | **$7** | **$11** | $34 | $10 |
| ER_PSY | $10 | $9 | $8 | **$4** | **$10** | $12 | $9 |
| ER_NonPSY | $67 | $50 | $44 | **$25** | **$54** | $62 | $48 |
| Prof_MDD | $101 | $38 | $43 | **$40** | **$73** | $577 | $52 |
| Prof_PSY | $21 | $18 | $19 | **$13** | **$28** | $84 | $20 |
| Prof_NonPSY | $286 | $236 | $224 | **$215** | **$302** | $215 | $247 |
| Facility | $317 | $232 | $221 | **$202** | **$293** | $980 | $244 |
| Rx_Antidep | $0 | $28 | $37 | **$61** | **$83** | $114 | $46 |
| Rx_PSY | $31 | $26 | $31 | **$31** | **$91** | $226 | $44 |
| Rx_NonPSY | $108 | $95 | $100 | **$129** | **$172** | $110 | $118 |
| Total | $1,734 | $1,147 | $1,105 | **$1,010** | **$1,594** | $4,667 | $1,253 |

Source: Milliman analysis of MarketScan® 2008-2010. See methodology for claim category definitions

Table 4 and 5 provides the utilization per 1000 rates for MDD patients for inpatient admissions, ER visits and professional claims coded with either MDD ICD9 codes or psychiatric ICD9 codes or other. Prescription drug utilization is presented as the number of prescriptions per 1000 MDD patients (where days' supply was converted into prescriptions assuming a 30 day supply). The higher cost for the Treatment Resistance cohort shown in

Table 2 and 3 is driven by higher utilization of services, in particular a higher utilization of MDD related and psychiatric related inpatient admissions, ER visits, professional claims and psychotropic drugs. Inpatient admissions and ER visits are significantly higher than the average inpatient admission utilization of 64 admissions/1000 and 172 ER visits/1000 for a typical commercially insured population.[22] We do not provide facility utilization as it would not be meaningful in this context.

### Table 4: Annualized Utilization Rate (per 1000 patients) in 2010 for New MDD Patients in Snapshot Analysis

| Claim Categories | No Antidepresants | Inadequate Antidepresants | Short Term Adequate Antidepresants without Treatment Resistance | **Long term Adequate Antidepresants without Treatment Resistance** | **Treatment Resistance** | ECT | Total |
|---|---|---|---|---|---|---|---|
| IP_MDD | 366 | 99 | 94 | **60** | **227** | 1,502 | 152 |
| IP_PSY | 10 | 4 | 4 | **0** | **24** | 142 | 6 |
| IP_NonPSY | 95 | 52 | 37 | **29** | **80** | 0 | 56 |
| ER_MDD | 215 | 39 | 43 | **27** | **61** | 115 | 73 |
| ER_PSY | 37 | 27 | 24 | **22** | **63** | 0 | 29 |
| ER_NonPSY | 197 | 132 | 134 | **95** | **209** | 119 | 148 |
| Prof_MDD | 2,977 | 2,396 | 3,342 | **3,821** | **6,725** | 15,236 | 3,040 |
| Prof_PSY | 835 | 762 | 1,102 | **1,022** | **2,360** | 6,874 | 968 |
| Prof_NonPSY | 5,625 | 4,197 | 4,744 | **7,636** | **7,154** | 3,822 | 4,820 |
| Rx_Antidep | 0 | 2,298 | 4,368 | **7,473** | **8,717** | 5,095 | 2,936 |
| Rx_PSY | 1,305 | 1,496 | 1,972 | **2,283** | **6,054** | 13,264 | 1,840 |
| Rx_NonPSY | 5,895 | 5,708 | 7,127 | **12,688** | **11,536** | 5,949 | 6,575 |

Source: Milliman analysis of MarketScan® 2008-10. See methodology for claim category definitions

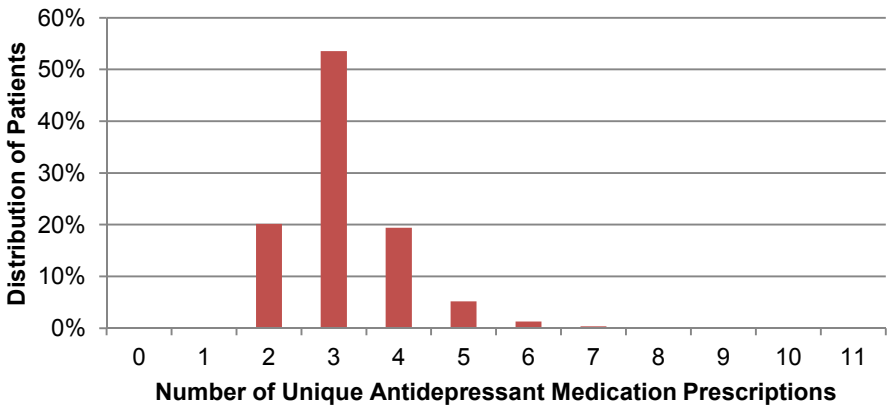
### Table 5: Annualized Utilization Rate (per 1000 patients) in 2010 for Existing MDD Patients in Snapshot Analysis

| Claim Categories | No Antidepresants | Inadequate Antidepresants | Short Term Adequate Antidepresants without Treatment Resistance | **Long term Adequate Antidepresants without Treatment Resistance** | **Treatment Resistance** | ECT | Total |
|---|---|---|---|---|---|---|---|
| IP_MDD | 286 | 131 | 132 | **101** | **198** | 1,494 | 154 |
| IP_PSY | 7 | 5 | 4 | **1** | **10** | 104 | 6 |
| IP_NonPSY | 196 | 130 | 112 | **72** | **133** | 158 | 122 |
| ER_MDD | 152 | 56 | 59 | **40** | **71** | 197 | 64 |
| ER_PSY | 67 | 56 | 52 | **22** | **65** | 76 | 55 |
| ER_NonPSY | 449 | 327 | 291 | **172** | **349** | 360 | 313 |
| Prof_MDD | 8,612 | 3,392 | 3,818 | **3,662** | **6,602** | 26,359 | 4,572 |
| Prof_PSY | 1,558 | 1,411 | 1,527 | **1,100** | **2,293** | 6,646 | 1,657 |
| Prof_NonPSY | 13,725 | 11,592 | 11,082 | **11,535** | **14,860** | 10,868 | 12,204 |
| Rx_Antidep | 30 | 5,081 | 6,366 | **8,215** | **11,911** | 12,684 | 7,169 |
| Rx_PSY | 4,024 | 4,293 | 4,590 | **4,137** | **10,514** | 19,853 | 5,839 |
| Rx_NonPSY | 14,741 | 16,420 | 16,524 | **19,352** | **25,549** | 19,879 | 18,652 |

Source: Milliman analysis of MarketScan® 2008-10. See methodology for claim category definitions

For existing MDD patients with Treatment Resistance, slightly over 50% take 3 distinct antidepressant drugs during the snapshot year and almost 20% take 4 distinct types of antidepressants during the snapshot year (Figure 3). This provides insight into the number of attempts at antidepressant switches and augmentation that the Treatment Resistance cohort experiences.

**Figure 3: Distribution of Treatment Resistance Patients by Number of Unique Antidepressant Medication Prescriptions Filled in 2010 (Snapshot Analysis)**




Source: Milliman analysis of MarketScan® 2008-10

The use of multiple psychotropic drug therapies is very apparent when we examine the use of drugs by class for each MDD cohort. Table 6 provides the annual experience for the existing MDD patients in the snapshot analysis. More individuals in the Treatment Resistance cohort use additional classes of drugs than those in other cohorts. Although the criteria to define a Treatment Resistance patient includes augmentation with thyroid hormone replacement drugs or second generation antipsychotic drugs, the use of other (non-psychotropic) drug classes is also significantly higher among the Treatment Resistance cohort compared to the other cohorts.

**Table 6: Percentage of Existing MDD Patients Filled At Least One Psychotropic Drug in Any Group in 2010 in Snapshot Analysis**

| Drug Class | No Antidepresants | Inadequate Antidepresants | Short Term Adequate Antidepresants without Treatment Resistance | **Long term Adequate Antidepresants without Treatment Resistance** | **Treatment Resistance** | ECT |
|---|---|---|---|---|---|---|
| antidepressants | 0% | 100% | 100% | **100%** | **100%** | 96% |
| antianxiety | 24% | 25% | 28% | **24%** | **38%** | 65% |
| thyroid supplements | 7% | 9% | 5% | **0%** | **25%** | 15% |
| hypnotics | 11% | 14% | 16% | **14%** | **24%** | 44% |
| AHDH antinarcolepsy | 6% | 6% | 8% | **7%** | **12%** | 30% |
| psychotherapeutic | 3% | 2% | 3% | **2%** | **4%** | 5% |
| anticonvulsant | 16% | 16% | 19% | **16%** | **33%** | 65% |
| antipsychotic antimanic | 6% | 6% | 6% | **1%** | **23%** | 80% |

Source: Milliman analysis of MarketScan® 2008-10. The Long and Short Term Adequate Antidepressant without Treatment Resistance cohort may have some use of thyroid hormone replacement prior to adequate antidepressant dosing and use of antipsychotic/antimanic drugs not included in the definition of Treatment Resistance

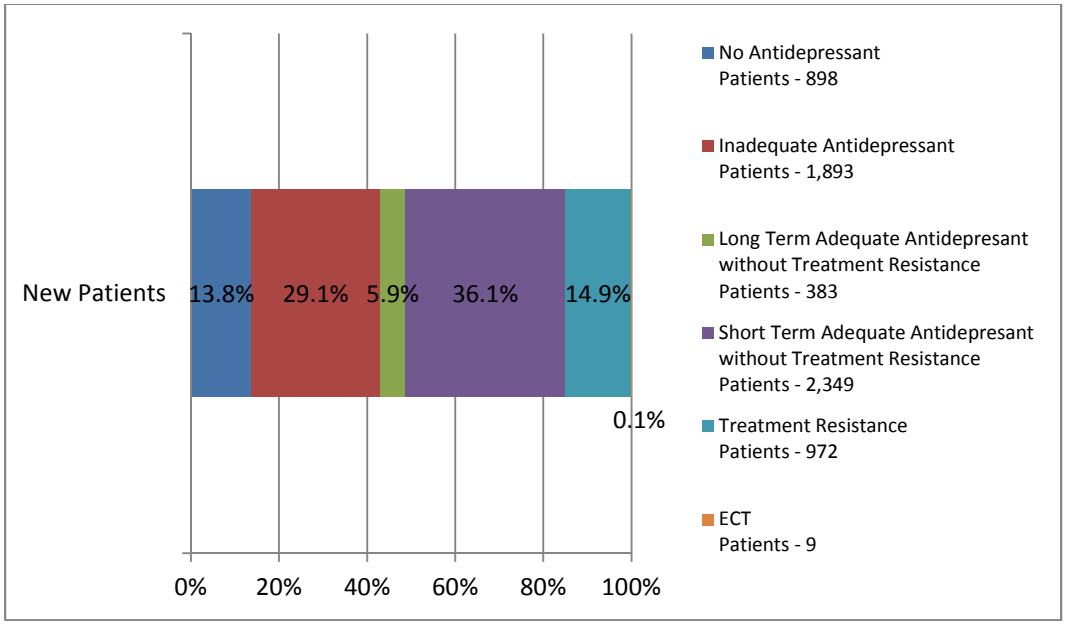
## Longitudinal Analysis

We performed a 2 year longitudinal analysis of new MDD patients using 2008 as the index year among patients with 5 years of continuous exposure (2006-2010). We identified new MDD patients as those without claims coded with MDD in the 24 months prior to the first claim coded with MDD in 2008. The sample size of new MDD patients was 6,504. We followed each patient for 24 months from index date and classified each patient into one of the 6 MDD sub-cohorts based on their experience during the 24 months. Figure 4 shows the distribution and sample size of new MDD patients by MDD cohort (refer to Figure 2 for comparison of snapshot analysis distribution).

The majority of new MDD patients (57.9%) do not receive adequate or effective antidepressant therapy during the 24 months after index diagnosis:

- 57.9% of new MDD patients in our 2008 - 24 month longitudinal analysis do not receive adequate or effective antidepressant therapy. This includes the No Antidepressant cohort which may include MDD patients adequately treated with psychotherapy alone. The 57.9% is comprised of:
  - 13.8% received No Antidepressant medications
  - 29.1% received Inadequate Antidepressant treatment
  - 14.9% demonstrated Treatment Resistance
  - 0.1% received ECT

### Figure 4: Percentage of New MDD Patients by Type in Longitudinal Analysis




Source: Milliman analysis of MarketScan® 2006-2010

Again, we compare the Long Term Adequate Antidepressant without Treatment Resistance cohort to the Treatment Resistance cohort to identify treatment patterns and cost drivers for each group. We analyzed the costs for the new MDD cohort for the 24 months leading up to the index date and the 24 months after the index date. The costs are dramatically higher for the Treatment Resistance cohort in the index month and in the 2 to 24 months after index date yet the costs are similar in the 24 months prior to MDD diagnosis. In particular as shown in Table 7:

- No statistically significant cost difference between the Treatment Resistance cohort and the Long Term Adequate Antidepressant w/o Treatment Resistance cohort in the 24 months prior to MDD diagnosis
- $1,081 higher cost in the index diagnosis month for Treatment Resistance cohort versus Long Term Adequate Antidepressant without Treatment Resistance cohort (p value <0.001)
- $155 higher PPPM cost in the 2-12 months after index date for Treatment Resistance cohort versus Long Term Adequate Antidepressant without Treatment Resistance cohort (p value <0.001)
- $186 higher PPPM cost in the 13-24 months after index date for Treatment Resistance cohort versus Long Term Adequate Antidepressant without Treatment Resistance cohort (p value <0.001)

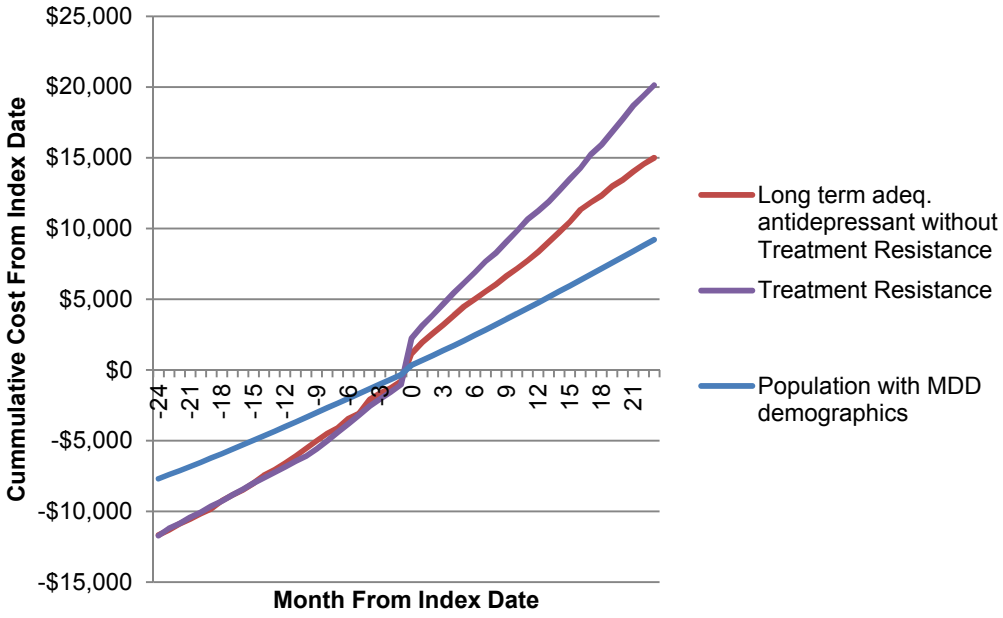
**Table 7: PPPM of New MDD Patients in Longitudinal Analysis**

| Time from Index Date | No Antidepresants | Inadequate Antidepresants | Short Term Adequate Antidepresants without Treatment Resistance | **Long term Adequate Antidepresants without Treatment Resistance** | **Treatment Resistance** | ECT |
|---|---|---|---|---|---|---|
| 13 to 24 Months Before Index Date | $404 | $378 | $327 | **$422** | **$406** | $372 |
| 1 to 12 Months Before Index Date | $619 | $578 | $484 | **$551** | **$571** | $613 |
| Index Month | $5,474 | $1,939 | $1,480 | **$1,156** | **$2,235** | $27,449 |
| 2 to 12 Months After Index Date | $636 | $619 | $584 | **$599** | **$764** | $3,519 |
| 13 to 24 Months After Index Date | $624 | $542 | $556 | **$604** | **$790** | $3,301 |
| 2 to 24 Months After Index Date | $630 | $580 | $570 | **$601** | **$777** | $3,410 |

Source: Milliman analysis of MarketScan® 2006-2010
Index Month was in 2008

In Figure 5, we provide a comparison of the cumulative costs between the Treatment Resistance and the Long Term Adequate Antidepressant without Treatment Resistance cohorts. The costs in the months prior to the index date (months 0 to -24) are very similar for the two cohorts and after index date the costs for the Treatment Resistance cohort increase at a faster rate than the Long Term Adequate Antidepressant without Treatment Resistance cohort. We also include cumulative costs for a cohort of non MDD commercially insured individuals with the same demographics of the MDD population which shows a cumulative cost over the 5 years that is less steep than that of the MDD populations.

**Figure 5: Cumulative Cost by Months from Index Date for New MDD Patients (Treatment Resistance and Long Term Adequate Antidepressant without Treatment Resistance)**




Source: Milliman analysis of MarketScan® 2006-2010
Index Month was in 2008

The cost difference between the two cohorts on a PPPM basis shows the Treatment Resistance cohort has $215 PPPM higher costs than the Long Term Adequate without Treatment Resistance cohort (p value <0.001). MDD related inpatient admissions make the largest contribution to this difference and all services are higher except RX non-psych (non-psychotropic prescriptions). See Table 8.

### Table 8: Average $PPPM in 24 Months after Index Date

| Claim Category | No Antidepresants | Inadequate Antidepresants | Short Term Adequate Antidepresants without Treatment Resistance | **Long term Adequate Antidepresants without Treatment Resistance** | **Treatment Resistance** | ECT | Total | Difference between TRD and Non TRD Long Term Adequate Antidepressant |
|---|---|---|---|---|---|---|---|---|
| IP_MDD | $185 | $44 | $42 | **$31** | **$108** | $2,220 | $75 | $76 |
| IP_PSY | $5 | $1 | $0 | **$0** | **$6** | $769 | $3 | $6 |
| IP_NonPSY | $150 | $119 | $100 | **$66** | **$89** | $278 | $109 | $24 |
| ER_MDD | $12 | $3 | $4 | **$1** | **$5** | $9 | $5 | $4 |
| ER_PSY | $5 | $4 | $4 | **$2** | **$6** | $25 | $4 | $4 |
| ER_NonPSY | $27 | $28 | $26 | **$22** | **$25** | $6 | $26 | $3 |
| Prof_MDD | $30 | $19 | $23 | **$27** | **$45** | $208 | $27 | $19 |
| Prof_PSY | $11 | $12 | $11 | **$12** | **$22** | $95 | $13 | $10 |
| Prof_NonPSY | $177 | $156 | $156 | **$156** | **$183** | $139 | $163 | $27 |
| Facility | $148 | $144 | $132 | **$117** | **$146** | $457 | $139 | $28 |
| Rx_Antidep | $0 | $13 | $23 | **$51** | **$53** | $70 | $23 | $2 |
| Rx_PSY | $18 | $25 | $18 | **$21** | **$43** | $120 | $24 | $22 |
| Rx_NonPSY | $72 | $76 | $76 | **$127** | **$116** | $171 | $84 | -$11 |
| Total | $840 | $644 | $618 | **$632** | **$847** | $4,567 | $697 | $216 |

Source: Milliman analysis of MarketScan® 2006-2010. See methodology for claim category description
Index Month was in 2008

Table 9 shows the annual utilization rates of all services (except facility claims as these would not be meaningful) and is consistent with the findings above. The Treatment Resistance cohort has:

- More than four times the utilization of MDD related and psychiatric related inpatient admissions,
- About twice as many MDD related and psychiatric related ER visits, and
- Twice the amount of non-antidepressant psychiatric drug claims.

This pattern of utilization illustrates the high use of health care services for the Treatment Resistance cohort when compared to those patients who appear to receive adequate short and long term antidepressant treatment that is consistent with recommended practice guidelines, i.e., the Long Term Adequate Antidepressant without Treatment Resistance cohort.

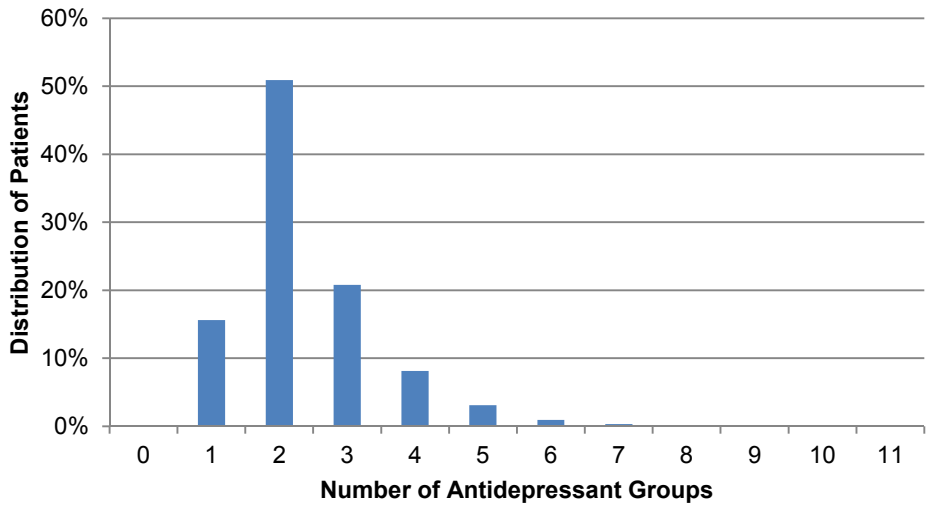
### Table 9: Annualized Utilization Rate (per 1000 patients) in 24 Months after Index Date

| Claim Category | No Antidepresants | Inadequate Antidepresants | Short Term Adequate Antidepresants without Treatment Resistance | **Long term Adequate Antidepresants without Treatment Resistance** | **Treatment Resistance** | ECT | Total |
|---|---|---|---|---|---|---|---|
| IP_MDD | 159 | 53 | 46 | **22** | **111** | 1,667 | 74 |
| IP_PSY | 11 | 3 | 1 | **0** | **9** | 278 | 5 |
| IP_NonPSY | 104 | 78 | 70 | **46** | **72** | 167 | 76 |
| ER_MDD | 123 | 27 | 29 | **14** | **38** | 222 | 42 |
| ER_PSY | 40 | 25 | 23 | **10** | **41** | 222 | 28 |
| ER_NonPSY | 252 | 222 | 194 | **134** | **195** | 56 | 207 |
| Prof_MDD | 3,066 | 1,986 | 2,538 | **2,846** | **4,776** | 14,889 | 2,820 |
| Prof_PSY | 1,132 | 1,139 | 1,196 | **1,516** | **2,183** | 7,500 | 1,345 |
| Prof_NonPSY | 9,860 | 9,740 | 8,803 | **9,867** | **11,104** | 9,833 | 9,629 |
| Rx_Antidep | 0 | 2,504 | 4,406 | **7,589** | **8,589** | 4,944 | 4,057 |
| Rx_PSY | 2,030 | 2,611 | 2,449 | **2,051** | **5,812** | 8,111 | 2,925 |
| Rx_NonPSY | 10,761 | 11,752 | 11,748 | **15,672** | **16,103** | 19,111 | 12,505 |

Source: Milliman analysis of MarketScan® 2006-2010. See methodology for claim category definitions
Index Month was in 2008

A significant number of antidepressant treatment switches and additions for the treatment resistant cohort are apparent when we examine the portion of the cohort taking more than 1 distinct antidepressant during the 24 months after index date. Approximately 50% take 2 distinct antidepressant drugs, 20% take 3 distinct antidepressants and 15% take 4 or more distinct antidepressants during the 24 months after index date. This highlights the issue of switching and augmentation attempts that accompanies the pattern of higher resource utilization (Figure 6).

### Figure 6: Distribution of Treatment Resistant Patients by Number of Antidepressant Group Utilization in 24 Months from Index Date in Longitudinal Analysis




Source: Milliman analysis of MarketScan® 2006-10. Index month was in 2008

The Treatment Resistance cohort also utilizes significantly higher numbers of concomitantly prescribed psychotropic drugs including antianxiety medications, hypnotics, anticonvulsants and antipsychotic or antimanic medications (Table 10).

**Table 10: Percentage of New MDD Patients Having At least one Psychotropic Drug in each Group During 24 Months after Index Date in Longitudinal Analysis**

| Class of Psychotropic Drugs | No Antidepresants | Inadequate Antidepresants | Short Term Adequate Antidepresants without Treatment Resistance | **Long term Adequate Antidepresants without Treatment Resistance** | **Treatment Resistance** | ECT |
|---|---|---|---|---|---|---|
| antidepressants | 0% | 100% | 100% | **100%** | **100%** | 56% |
| antianxiety | 20% | 32% | 33% | **24%** | **43%** | 56% |
| thyroid supplements | 7% | 9% | 4% | **0%** | **23%** | 11% |
| hypnotics | 10% | 19% | 19% | **17%** | **27%** | 22% |
| AHDH antinarcolepsy | 4% | 6% | 8% | **5%** | **9%** | 11% |
| psychotherapeutic | 2% | 5% | 4% | **2%** | **5%** | 0% |
| anticonvulsant | 10% | 13% | 14% | **14%** | **27%** | 44% |
| antipsychotic antimanic | 6% | 5% | 5% | **1%** | **18%** | 67% |

Source: Milliman analysis of MarketScan® 2006-10
Index Month was in 2008
Long and Short Term Adequate Antidepressant without Treatment Resistance cohorts may have some use of thyroid prior to adequate antidepressant dosing and use of antipsychotic/antimanic drugs not included in the definition of Treatment Resistance

## IMPLICATIONS FOR PAYERS AND EMPLOYERS

Studies report that approximately 76% of MDD patients fail to achieve remission after a first course of antidepressant drug therapy and 30% fail to achieve remission long term. Our commercial claims based analysis identified 15% of new MDD patients exhibiting Treatment Resistance in the first 24 months after index date and 23% of existing MDD patients exhibiting Treatment Resistance in a 12 month snapshot analysis.

The medical claim costs associated with Treatment Resistance have been estimated to be up to twice that for MDD patients who do not demonstrate Treatment Resistance. Our comparison between the Treatment Resistant and Long Term Adequate Antidepressant without Treatment Resistance cohort provides a proxy comparison: MDD patients who respond to single antidepressant therapy and receive appropriate treatment by current guideline recommendations over the short and longer term, and those patients who demonstrate initial Treatment Resistance, and generally have a more complex clinical course to their illness. Both new and existing MDD patients meeting criteria for initial Treatment Resistance have statistically significantly higher costs than those receiving short and long term adequate antidepressant therapy who do not exhibit Treatment Resistance. We identified:

- $406 PPPM higher cost comparing the Treatment Resistance cohort to Long Term Adequate Antidepressant without Treatment Resistance cohort among the new MDD patients (p value < 0.001)
- $584 PPPM higher cost comparing the Treatment Resistance cohort to Long Term Adequate Antidepressant without Treatment Resistance cohort among existing MDD patients (p value < 0.001).

The difference in cost between these two cohorts is $2.02 on a PMPM basis or 10% of the total MDD PMPM ($19.86 PMPM) and a portion of that cost might be avoided with interventions that provide an adequate response at the point at which initial Treatment Resistance is observed. In addition, the burden for employers is very likely to be greater than reflected in the costs presented here as our medical cost analysis does not consider the lost productivity and disability costs that have been reported in the MDD population.

Our analysis identifies a high degree of variation in choice of antidepressant drugs among MDD patients who demonstrate Treatment Resistance and high utilization of all classes of psychotropic drugs, highlighting the challenge of treating MDD patients who do not respond to the first course of antidepressant drug therapy. We identified significantly higher utilization of services coded with MDD ICD9 codes and psychiatric ICD9 codes among the Treatment Resistance cohort which contributed to the higher costs.

Although we focus attention on the Treatment Resistance cohort that actually receives adequate dose and duration of therapy but fails to achieve remission, payers and employers should be equally concerned about the 29% of new MDD patients who never receive adequate dosing of antidepressants during the 24 months after index date and the 14% who are never prescribed an antidepressant. We found that new MDD patients who never receive adequate antidepressant dosing over the 24 months from index date have higher costs and utilization of MDD related services and most other services than MDD patients receiving short and long term adequate antidepressant treatment without demonstrating Treatment Resistance. And the MDD patients who do not have any antidepressant therapy have higher costs than all cohorts except the Treatment Resistance cohort and ECT cohort.

Our analysis highlights significant quality of care issues for commercially insured MDD patients, and both payers and employers should consider investigating the claim experience of their own MDD members. We have provided claims based logic for identifying cohorts of MDD patients whose treatment course and response to therapy is suboptimal. Payers/employers can replicate this claim based analysis with their own insured population's employees to identify opportunities for improved management of their MDD population. Health plans/employers with a behavioral health carve out vendor should expect this type of reporting on the MDD population.

Although HEDIS has a metric for antidepressant medication management, it does not address adequate dosing of antidepressants. The measure follows the use of antidepressants for 12 weeks and 6 months after a new episode of MDD. The measure identifies the no antidepressant prescribing and short duration of treatment quality issues but does not address the adequacy of the treatment dosage. In our longitudinal analysis, we found that for MDD patients who take antidepressants (87% of total MDD patients), 34% did not take an adequate dosage. Adequate dosing should be considered as a HEDIS metric.

Lastly, payers and employers should evaluate coverage policies for evidence based therapies for MDD and treatment resistant MDD to insure access to evidence based, FDA approved therapies. Identifying and targeting MDD patients during the initial phase of Treatment Resistance with efficacious therapies is critical as studies show remission becomes less likely with each successive course of therapy.

# APPENDIX A: METHODOLOGY

## Data Source

Thomson Reuters MarketScan claims data contains all paid claims generated by approximately 30 million commercially insured lives annually from approximately 100 private sector payers. The MarketScan database represents the inpatient and outpatient healthcare service use of individuals nationwide who are covered by the benefit plans of large employers, health plans, government and public organizations. The MarketScan database links paid claims and encounter data to detailed patient information across sites and types of providers, and over time. Member identification codes are consistent from year to year and allow for multiyear longitudinal studies. The database contains ICD-9-CM diagnosis codes; procedure codes and diagnosis-related group (DRG) codes; national drug codes (NDCs); and site of service information and the amounts allowed and paid by commercial insurers. For this study, we used MarketScan 2006 through 2010.

To insure the data was representative of all paid claims for a commercially insured population, we limited the data to that generated by full time employees and their families under age 65, having pharmacy benefits and we removed contributors with capitated services as claims may be incomplete.

## Definition of Snapshot and Longitudinal Analyses

We created an annual snapshot MDD cohort and a longitudinal MDD cohort in order to quantify the prevalence, treatment characteristics and cost of MDD patients in a given benefit period year (snapshot cohort) and to quantify the prevalence, characteristics and costs of new MDD patients who develop TRD (longitudinal analysis).

For the snapshot analysis, the examined population was limited to 18-64 year olds (age in 2010) We further required continuous enrollment for the two year look back period (2008-2009) to establish new versus existing MDD and at least one day of eligibility in 2010.The resulting sample of 6.3 million members comprised our study population. For the snapshot analysis, we used 2010 to identify the MDD population and 2008- 2009 to perform a look back to classify MDD patients as “new” or “existing” in 2010. New MDD patients were those without any claim coded with an MDD diagnosis code or any claim for an antidepressant in the 24 months before the index MDD claim.

For the longitudinal analysis, we identified MDD patients in 2008 and looked back to 2006 and 2007 to define new and existing MDD patients in 2008. For the longitudinal analysis, the population was limited to 18-64 year olds (age in 2008) with a requirement to have eligibility in all of 2006 to 2010 which resulted in a sample of 1.7 million members for our study.

We used the following observation and look back periods to analyze new and existing MDD patients

| Type of analysis | Patient | Observation Period | Look back to Define New or Existing |
|---|---|---|---|
| **Snapshot** | New | Index date to end of 2010 | 2008 and 2009 |
| | Existing | Index date to end of 2010 | 2008 and 2009 |
| **Longitudinal** | New | Index date in 2008 for 24 months | 2006 and 2007 |

### MDD Patient Definitions: Inclusion Criteria

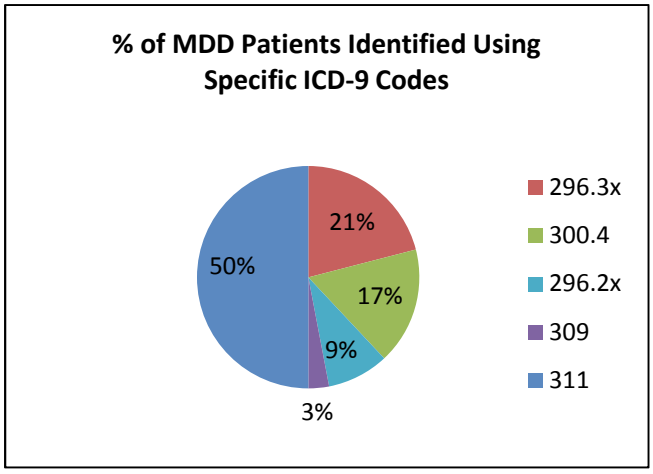
We used the following logic to identify MDD patients:

- One inpatient claim, or
- One ER claim, or
- One observation claim, or
- Two physician evaluation and management (E&M) claims on separate dates of service, or
- One physician E&M claim coded with an MDD ICD9 code in any position of the claim and 1+ antidepressant pharmacy claim (NDC codes available upon request),

coded with any of the following MDD ICD9 codes in any position of the claim:

| MDD ICD-9 Diagnosis Codes | Description |
|---|---|
| 296.2x | major depressive disorder single episode |
| 296.3x | major depressive disorder recurrent episode |
| 300.4 | dysthymic disorder |
| 309.0 | adjustment disorder with depressed mood |
| 311 | depressive disorder not elsewhere classified |

The portion of MDD patients identified by ICD-9 code is presented in the pie graph below. If patients had claims with more than one ICD-9, we used the following hierarchy to assign them to one ICD-9 cohort: (1-Highest) 296.3x, (2) 300.4, (3) 296.2x, (4) 309, (5-Lowest) 311.




We then excluded individuals with one or more claims coded with any of the conditions below (ICD9 in any position of the claim) during the study period to distinguish primary MDD. These criteria excluded 5.4% of the starting MDD population.

Conditions excluded from the MDD cohort:

| ICD-9 Diagnosis Codes | Description |
|---|---|
| 290.xx | dementia |
| 295.xx | schizophrenia |
| 297.xx | delusional disorder |
| 298.xx | nonorganic psychoses |
| 299.xx | pervasive developmental disorders |
| 317.xx-319.xx | mental retardation |
| 331.xx | cerebral degenerations |
| 332.xx | Parkinson's disease |
| 797.xx | senility w/o psychosis |
| 296.0, 296.1, 296.5, 296.7, 296.80, 296.82, 296.89 | manic depression or bipolar |

### Categorization of MDD patients

We categorized all MDD patients into 6 mutually exclusive cohorts described in the table below. Antidepressant therapy use and response distinguishes this categorization.

| MDD Sub-cohort | Description |
|---|---|
| No Antidepressant | Patients meeting MDD inclusion criteria, who did not receive an antidepressant prescription during the observation period |
| Inadequate Antidepressant | Patients meeting MDD inclusion criteria who received an antidepressant prescription below the dose and/or duration threshold of clinical treatment adequacy consistent with the claims logic based adaptation of the ATHF treatment resistance criteria |
| Short Term Adequate Antidepressant without Treatment Resistance | Patients meeting MDD inclusion criteria who received an antidepressant prescription at or above the dose and duration (8+ weeks) threshold of clinical treatment adequacy AND who subsequently received an eligible prescription for a new antidepressant (switch) or an additional prescription (augmentation or combination), i.e., consistent with the claims logic based adaptation of the ATHF treatment resistance criteria |
| Long Term Adequate Antidepressant without Treatment Resistance | Patients meeting MDD inclusion criteria who received an antidepressant prescription at or above the dose and duration threshold of clinical treatment adequacy AND who subsequently remained on the same antidepressant medication at or above criteria for clinical adequacy for at least six additional months without interruption |
| Treatment Resistance | Patients meeting MDD inclusion criteria who received an antidepressant prescription at or above the dose and duration threshold of clinical treatment adequacy AND DID NOT subsequently remain on the same antidepressant medication at or above criteria for clinical adequacy for at least six additional months without interruption |
| Electroconvulsive Therapy (ECT) | Patients meeting MDD inclusion criteria who had a claim for electroconvulsive therapy (ECT) at any time during the observation period |

For the definition of initial Treatment Resistance we used the ATHF=1 criteria [10] and created claims logic to mimic this questionnaire based definition. The duration of treatment requirements used in these category designations also follow the current 3rd Edition Practice Guidelines for the Treatment of Patients with Major Depressive Disorder, promulgated by the American Psychiatric Association (APA) (see MDD primer in Appendix B).[11] We used a requirement of 8+ weeks of adequate dose and duration of the same single antidepressant to occur prior to determining Treatment Resistance, although the ATHF considers a minimum duration of adequate dosing to be at a 4+ week threshold. The approach used in our analysis establishes a more conservative designation of initial Treatment Resistance.

An MDD patient was designated as having initial Treatment Resistance if any of the following occurred after 8+ weeks of a single antidepressant of adequate dose:

- Switch to a distinctly different antidepressant
- Addition of a distinctly different antidepressant
- Addition of lithium carbonate drug therapy or claim coded with ICD-9 procedure code 94.22 (lithium therapy)
- Addition of specific antipsychotics: risperidone, clozapine, quetiapine fumarate, olanzapine, aripiprazole, ziprasidone
- Addition of a thyroid supplement

For purposes of the ATHF methodology, only the following allowed antidepressant medications are considered in determining Treatment Resistance. The minimum effective total daily dose described in the ATHF methodology for each eligible antidepressant medication appears in the table below. [10]

| Antidepressant | Minimum Effective Total Daily Dose |
|---|---|
| **Tricyclic (TCA)** | |
| Amitriptyline | 200 mg |
| Imipramine | 200 mg |
| Desipramine | 200 mg |
| Trimipramine | 200 mg |
| Clomipramine | 200 mg |
| Maprotilene | 200 mg |
| Doxepin | 200 mg |
| Nomifensine | 200 mg |
| Nortriptyline | 75 mg |
| Protriptyline | 40 mg |
| **Selective serotonin reuptake inhibitors (SSRI)** | |
| Fluoxetine | 20 mg |
| Citalopram | 20 mg |
| Fluvoxamine | 200 mg |
| Paroxetine | 20 mg |
| Paroxetine CR | 25 mg |
| Sertraline | 100 mg |
| Escitalopram | 10 mg |
| **Serotonin and norepinephrine reuptake inhibitors (SNRI)** | |
| Venlafaxine (incl. IR & XR) | 225 mg |
| Duloxetine | 40 mg |
| Desvenlafaxine | 50mg |

| **Other Antidepressants** | |
|---|---|
| Bupropion (incl. IR, SR, & XL) | 300 mg |
| Mirtazapine | 30 mg |
| Nefazodone | 300 mg |
| Trazodone | 400 mg |
| Amoxapine | 400 mg |
| **Monoamine oxidase inhibitors (MAOI)** | |
| Phenelzine | 60 mg |
| Selegiline | 40 mg |
| Selegiline transdermal patch | 60 mg |
| Tranylcypromine | 40 mg |
| Isocarboxazid | 40 mg |

The following codes were used to identify MDD patients receiving ECT:

| **ICD9 procedure codes for ECT** | **Description** |
|---|---|
| 94.23 | neuroleptic therapy |
| 94.24 | chemical shock therapy |
| 94.26 | subconvulsive shock therapy |
| 94.27 | other electroshock therapy |
| **CPT codes for ECT** | **Description** |
| 90870 | ECT therapy |

### Sample Size of MDD patients

The table below shows the sample size of the MDD population meeting the identification criteria and the portion of new versus existing MDD patients:

| | **Number of Invididuals** | |
|---|---|---|
| | **Snapshot Analysis** | **Longitudinal Analysis** |
| Total Population in MarketScan meeting eligibility criteria | 6,259,735 | 1,671,512 |
| MDD Patients | 165,418 | 35,696 |
| New Patients | 32,024 | 6,504 |
| Existing Patients | 133,394 | 29,192 |

Source: Milliman analysis of MarketScan® 2006 to 2010

### Claim Service Categories and Costs

We grouped each claim for each MDD individual into 13 service categories in order to analyze the cost contribution of particular healthcare services for MDD patients. We further split non-MDD psychiatric and MDD related services among inpatient admissions, emergency room, professional claims, and prescription drugs. The table below provides logic that we used to categorize claims.

| Claim Category Name | Definition |
|---|---|
| IP_MDD | Inpatient Claims with Psychiatric DRG and MDD ICD9 Dx in any position of the claim |
| IP_PSY | Inpatient Claims with Psychiatric DRG other than IP_MDD |
| IP_NonPSY | Inpatient Claims other than IP_MDD or IP_PSY |
| ER_MDD | Outpatient Claims with Place of Service=23 (ER) and MDD ICD9 Dx in any position of the claim |
| ER_PSY | Outpatient Claims with Place of Service=23 (ER) and Psychiatric ICD9 Dx in any position of the claim, and not ER_MDD |
| ER_NonPSY | Outpatient Claims with Place of Service=23 (ER) and not ER_MDD or ER_PSY |
| Prof_MDD | Outpatient Professional Claims with MDD ICD9 Dx in any position of the claim |
| Prof_PSY | Outpatient Professional Claims with Psychiatric ICD9 Dx in any position of the claim and not Prof_MDD |
| Prof_NonPSY | Outpatient Professional Claims with not Prof_MDD nor Prof_PSY |
| Facility | Outpatient Facility Claims other than ER |
| Rx_Antidep | Rx claims with Antidepressant NDC |
| Rx_PSY | Rx claims with Psychiatric NDC and not Rx_Antidep |

The following table lists the DRG codes used to identify inpatient psychiatric admissions:

| Psych DRGs | Description |
|---|---|
| 880 | Acute adjustment reaction & psychosocial dysfunction |
| 881 | Depressive neuroses |
| 882 | Neuroses except depressive |
| 883 | Disorders of personality & impulse control |
| 884 | Organic disturbances & mental retardation |
| 885 | Psychoses |
| 886 | Behavioral & developmental disorders |
| 887 | Other mental disorder diagnoses |

The psychiatric ICD-9 codes include:

| Psychiatric ICD9 Codes |
|---|
| 290-319.xx |

# APPENDIX B: ANTIDEPRESSANT USAGE

The type of antidepressants utilized by Treatment Resistant existing MDD patients is dominated by several specific antidepressant medications shown in the table below.

### Utilization of Antidepressants for Treatment Resistant Patients (per 1000 patients) among Existing MDD Patients in 2010 Snapshot Analysis

| Antidepressant Group | Utilization (Num Rx Per 1000 Patients) |
|---|---|
| Bupropion | 2,370 |
| Escitalopram | 1,333 |
| Duloxetine | 1,269 |
| Citalopram | 1,182 |
| Fluoxetine | 1,130 |
| Sertraline | 1,115 |
| Trazodone | 970 |
| Venlafaxine | 651 |
| Desvenlafaxine | 535 |
| Paroxetine | 429 |
| Amitriptyline | 317 |
| Mirtazapine | 241 |
| Nortriptyline | 122 |
| Paroxetine CR | 78 |
| Doxepin | 52 |
| Imipramine | 29 |
| Fluvoxamine | 27 |
| Nefazodone | 19 |
| Desipramine | 16 |
| Clomipramine | 12 |
| Selegiline TD Patch | 6 |
| Protriptyline | 4 |
| Tranylcypromine | 2 |
| Maprotiline | 1 |
| Phenelzine | 1 |
| Isocarboxazid | 0 |
| Amoxapine | 0 |
| Trimipramine | 0 |
| Total Antidepressant | 11,911 |

Source: Milliman analysis of MarketScan® 2008-10

A variety of antidepressants are used among new MDD patients over the first 24 months from MDD diagnosis, although 3 are used more commonly than others (escitalopram, citalopram and bupropion).

### Utilization of Antidepressants for new MDD Treatment Resistance Patients (per 1000 patients) in 24 months After Index Date in Longitudinal Analysis

| Antidepressant Group | Utilization (Num Rx Per 1000 Patients) |
|---|---|
| Escitalopram | 1,594 |
| Citalopram | 1,479 |
| Bupropion | 1,385 |
| Fluoxetine | 860 |
| Sertraline | 748 |
| Duloxetine | 721 |
| Trazodone | 526 |
| Paroxetine | 334 |
| Venlafaxine | 323 |
| Desvenlafaxine | 263 |
| Mirtazapine | 127 |
| Amitriptyline | 110 |
| Paroxetine CR | 62 |
| Nortriptyline | 31 |
| Doxepin | 12 |
| Clomipramine | 4 |
| Imipramine | 3 |
| Desipramine | 3 |
| Selegiline TD Patch | 3 |
| Fluvoxamine | 1 |
| Nefazodone | 1 |
| Protriptyline | 1 |
| Amoxapine | 0 |
| Isocarboxazid | 0 |
| Maprotiline | 0 |
| Phenelzine | 0 |
| Tranylcypromine | 0 |
| Trimipramine | 0 |
| Total Antidepressant | 8,589 |

Source: Milliman analysis of MarketScan® 2006-10
Index Month was in 2008

## APPENDIX C: PRIMER ON MDD AND TRD

*Criteria for Major Depressive Episode (DSM-IV, p. 327)*[12]

"A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g. appears tearful). Note: In children and adolescents, can be irritable mood.

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.

4. Insomnia or hypersomnia nearly every day

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6. Fatigue or loss of energy nearly every day

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation."

*Staging of MDD*

More than half of the patients diagnosed with MDD fail to achieve remission, or even satisfactory benefit from a first course of antidepressant medication. These patients exhibit Treatment Resistance at various levels of severity. Mild resistance may include an inadequate response to a single antidepressant trial, whereas greater resistance often refers to failure of two monotherapy trials, or one or more augmentation trials.

In view of the fact that Treatment Resistance falls on a continuum, a number of clinical algorithms to "stage" the various degrees of Treatment Resistance have been developed. These algorithms are intended to classify Treatment Resistance into several stages depending on "the number of trials adequately delivered in terms of adherence, duration, and dose" to the diagnosed patients (Rush et al, 2003).[23] A staging model proposed by Thase and Rush (1997)[19] is summarized in the following table:

| Stage | Definition |
|---|---|
| | |
| **Stage I** | Failure of at least one adequate trial of one major class of antidepressant |
| **Stage II** | Stage I Resistance + Failure of adequate trial of antidepressant in a different class |
| **Stage III** | Stage II Resistance + Failure of an adequate trial of a TCA |
| **Stage IV** | Stage III Resistance + Failure of an adequate trial of a MAOI |
| **Stage V** | Stage IV Resistance + Failure of a course of bilateral ECT |

Another staging model outlined in Fava (2003),[16] often referred to as the Massachusetts General Hospital (MGH) Staging Method, is a point system with higher scores reflecting greater Treatment Resistance. This algorithm is briefly summarized in the following table:

| MGH Staging Method |
|---|
| |
| (1) Nonresponse to each adequate trial of a marketed antidepressant generates an overall score of resistance (1 point per trial) |
| (2) Optimization of dose, optimization of duration, and augmentation/combination of each trial increase the overall score (0.5 point per trial per optimization/strategy) |
| (3) Electroconvulsive therapy (ECT) increases the overall score by 3 points |

There is no clear consensus around a precise definition of treatment resistant depression (TRD). It may be broadly defined as "the administration of an adequate dose of an antidepressant medication (or at minimal plasma levels) for sufficient duration, with good treatment adherence, and yet resulting in nonresponse or lack of remission" (Sackeim, 2001).[10] Souery et al (2006) discuss a somewhat more stringent operational definition characterizing TRD as the failure to respond to two adequate trials of different classes of antidepressants.[24] Across definitions, the four key elements that are used to characterize TRD are: (i) maximal dosage; (ii) duration at maximal and submaximal dosage; (iii) compliance with treatment; and (iv) clinical outcome.

The Antidepressant Treatment History Form (ATHF) is a commonly used instrument to formally evaluate the adequacy of prior antidepressant treatment. In general, the ATHF levels for considering a trial adequate correspond to the minimal dosage at which clinical trials have shown the agent to be effective in major depression. ATHF imposes a conservative threshold for duration of treatment (i.e. 4 weeks) to classify patients as not responding or remitting to the trial.

The ATHF is also used to evaluate treatment outcomes. One of four possible treatment outcomes must emerge: i.e. (i) nonresponse (no substantial clinical improvement); (ii) significant residual symptoms; (iii) few or no residual symptoms; and (iv) response or remission, but relapse on current regimen. According to ATHF criteria, outcomes (i) and (iv) would imply that the trials were treatment failures. The ATHF is the only methodology that has been shown to have prospective validity as a definition of treatment resistance in that more severe stages of treatment resistance defined by the ATHF method prior to treatment have been shown to correlate with progressively poorer clinical outcomes (Prudic, 1996 and Sackeim, 2001).

*APA practice guidelines for MDD*

The definition of Treatment Resistance defined in the ATHF and used here is also generally consistent with the treatment discussion contained in the 3rd Edition of the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder. An excerpt from the drug therapy treatment recommendations of that document, for the treatment of MDD is provided below. [11]

*"An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder [I] and definitely should be provided for those with severe major depressive disorder unless ECT is planned [I]. Because the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference [I]. For most patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion is optimal [I]. In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments [I], given the necessity for dietary restrictions with these medications and the potential for deleterious drug-drug interactions. In patients who prefer complementary and alternative therapies, S-adenosyl methionine (SAMe) [III] or St. John's wort [III] might be considered, although evidence for their efficacy is modest at best, and careful attention to drug-drug interactions is needed with St. John's wort [I].*

*Once an antidepressant medication has been initiated, the rate at which it is titrated to a full therapeutic dose should depend upon the patient's age, the treatment setting, and the presence of co-occurring illnesses, concomitant pharmacotherapy, or medication side effects [I]. During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy, identify the emergence of side effects (e.g., gastrointestinal symptoms, sedation, insomnia, activation, changes in weight, and cardiovascular, neurological, anticholinergic, or sexual side effects), and assess patient safety [I]. The frequency of patient monitoring should be determined based upon the patient's symptom severity (including suicidal ideas), co-occurring disorders (including general medical conditions), cooperation with treatment, availability of social supports, and the frequency and severity of side effects with the chosen treatment [II]. If antidepressant side effects do occur, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect [I].*

*In assessing the adequacy of a therapeutic intervention, it is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose [I]. Generally, 4–8 weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention [II].*

***Strategies to Address Nonresponse***

*For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely [I], as an incomplete response to treatment is often associated with poor functional outcomes. If at least a moderate improvement in symptoms is not observed within 4–8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted [I]. It is also important to assess the quality of the therapeutic alliance and treatment adherence [I]. If medications are prescribed, the psychiatrist should determine whether pharmacokinetic [I] or pharmacodynamic [III] factors suggest a need to adjust medication doses. With some TCAs, a drug blood level can help determine if additional dose adjustments are required [I].*

*After an additional 4–8 weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan [I]. Consultation should also be considered [II].*

*A number of strategies are available when a change in the treatment plan seems necessary. For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached [II]. Particularly for those who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy [I] or with other agents [II] or changing to another non-MAOI antidepressant [I]. Patients may be changed to an antidepressant from the same pharmacological class (e.g., from one SSRI to another SSRI) or to one from a different class (e.g., from an SSRI to a tricyclic antidepressant [TCA]) [II]. For patients who have not responded to trials of SSRIs, a trial of an SNRI may be helpful [II]. Augmentation of antidepressant medications can utilize another non-MAOI antidepressant [II], generally from a different pharmacological class, or a non-antidepressant medication such as lithium [II], thyroid hormone [II], or a second-generation antipsychotic [II]. Additional strategies with less evidence for efficacy include augmentation using an anticonvulsant [III], omega-3 fatty acids [III], folate [III], or a psychostimulant medication [III], including modafinil [III]. If anxiety or insomnia are prominent features, consideration can be given to anxiolytic and sedative-hypnotic medications [III], including buspirone, benzodiazepines, and selective gamma-aminobutyric acid (GABA) agonist hypnotics (e.g., zolpidem, eszopiclone). For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy and should be considered [I]. In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a nonselective MAOI [II] after allowing sufficient time between medications to avoid deleterious interactions [I]. Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [II]. Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [III].*

***Continuation Phase***

*During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse [I]. Systematic assessment of symptoms, side effects, adherence, and functional status is essential [I] and may be facilitated through the use of clinician- and/or patient-administered rating scales [II]. To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for 4–9 months [I]. In general, the dose used in the acute phase should be used in the continuation phase [II]. To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended [I], with the best evidence available for cognitive-behavioral therapy.*

*Patients who respond to an acute course of ECT should receive continuation pharmacotherapy [I], with the best evidence available for the combination of lithium and nortriptyline. Alternatively, patients who have responded to an acute course of ECT may be given continuation ECT, particularly if medication or psychotherapy has been ineffective in maintaining remission [II].*

***Maintenance Phase***

*In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior major depressive episodes or who have chronic major depressive disorder should proceed to the maintenance phase of treatment after completing the continuation phase [I]. Maintenance therapy should also be considered for patients with additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorders [II]. Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes (including factors such as psychosis or suicide risk), the persistence of depressive symptoms after recovery, and the presence of co-occurring disorders [II]. Such factors also contribute to decisions about the duration of the maintenance phase [II]. For many patients, particularly for those with chronic and recurrent major depressive disorder or co-occurring medical and/or psychiatric disorders, some form of maintenance treatment will be required indefinitely [I].*

*During the maintenance phase, an antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose [II]. If a depression-focused psychotherapy has been used during the acute and continuation phases of treatment, maintenance treatment should be considered, with a reduced frequency of sessions [II]. For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression-focused psychotherapy but who have shown a response to ECT, maintenance ECT may be considered [III]. Maintenance treatment with vagus nerve stimulation is also appropriate for individuals whose symptoms have responded to this treatment modality [III].*

*Due to the risk of recurrence, patients should be monitored systematically and at regular intervals during the maintenance phase [I]. Use of standardized measurement aids in the early detection of recurrent symptoms [II].*

***Discontinuation of Treatment***

*When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks [I]. To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home [I]. A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome [II] when discontinuing antidepressants or reducing antidepressant doses. Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms [I]. After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur [I]."*

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