Choosing a Second-Generation Antidepressant using Demographic Characteristics and Clinical Symptoms of Depression

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Choosing a Second-Generation Antidepressant using Demographic Characteristics and Clinical Symptoms of Depression

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Abstract

Depression is the sixth most costly health condition in the United States, and depression that does not respond to its first trial of antidepressant treatment adds an annual cost of $9,529 per person per year. Thus, choosing an effective starting antidepressant can decrease the overall cost of depression to society. A secondary analysis of data from the Collaborative Psychiatric Epidemiology Survey (CPES) was performed to create models that can predict the efficacy of second-generation antidepressants in treating sadness. Two sets of Principal Component Analyses (PCAs) and logistic regressions were performed on variables associated with patient demographics, clinical symptoms, past medical history, and current mental health treatments: the first set explored associations between symptom clusters and drug efficacy, and the second set created models to predict the efficacy of each of the seven antidepressants. This study found that when treating sadness, paroxetine and venlafaxine should be avoided in depression with low moods, fluoxetine should be avoided in depression with high anxiety, and sertraline should be avoided in depression with high levels of fatigue. In addition, the models created to predict drug efficacy had a mean accuracy of 84% and internal validity of 62%. Since fewer than 50% of patients currently respond to their first antidepressant, the use of this model could provide a modest improvement to choosing efficacious starting antidepressants, subsequently decreasing the total disease burden depression poses onto society.

Keywords: Mental health, medication, treatment, resistant depression, affective disorders
Choosing a Second-Generation Antidepressant using Demographic Characteristics and Clinical Symptoms of Depression

Major Depressive Disorder (MDD) is a mood disorder characterized by persistent feelings of sadness or loss of interest that can be accompanied by sleep disturbances, appetite changes, decreased energy, difficulty with concentration, psychomotor changes, and suicidal ideation (American Psychiatric Association [APA], 2013). In 2015, 4.4% of the global population suffered from depression (World Health Organization [WHO], 2017). Together, depressive disorders lead to 50 million Years Lived with Disability (YLD) per year, making them the single largest contributor of non-fatal health loss in the world (WHO, 2017).

Healthy People 2020 contains 42 different topics, 12 of which have been identified as ‘Leading Health Indicators (LHI)’, a designation that signifies the topic is of particular importance to the health of the nation (U.S. Department of Health and Human Services, 2014). Mental health is designated an LHI, and within the topic of mental health, the US Department of Health and Human Services specifically targets two measures: 1) suicide rates and 2) the prevalence of Major Depressive Episodes (MDE) in adolescents. In 2007, there were 11.3 suicides per 100,000 people. The Healthy People 2020 goal is to lower that rate to 10.2 suicides per 100,000 people, a 10% improvement from baseline. Similarly, in 2008, 9.3% of adolescents had an MDE within the past year, and the Healthy People 2020 goal is to lower that rate to 7.5%, a 10% improvement from baseline.

In the United States, depressive disorders are the 6th most costly health condition. While there are many different treatments for depression such as psychotherapy and lifestyle modifications, many people choose a pharmacological approach: 50% of adults with a major depressive episode are treated with medication (Center for Behavioral Health Statistics and
Quality, 2017), and up to one-fourth of people on an antidepressant stay on the medication for at least 10 years (Pratt, Brody, & Gu, 201). In fact, antidepressants were the most commonly prescribed medication family in 2005, surpassing medications used to treat hypertension and hyperlipidemia (Cherry, Woodwell, & Rechtsteiner, 2007). Together, antidepressant medications comprise nearly one-third of the total spending on depressive disorders (Dieleman et al., 2016).

Treatment-resistant depression, defined here as depression that does not respond to its first trial of antidepressants, is associated with poorer quality of life, functional status, and well-being compared to treatment-responsive depression (Mauskopf et al., 2009). In addition to this increased morbidity, the risk of mortality is higher in treatment-resistant depression: approximately 30% of this population attempt suicide at least once in their life (Hantouche, Angst, & Azorin, 2010). This is twice the rate when compared to treatment-responsive depression, and 15 times the rate when compared to the general population (Bernal et al., 2007). There is also an increase in societal costs due to higher rates of healthcare utilization: this population has twice as many general medical visits per year than treatment-responsive depression (Mrazek, Hornberger, Altar, & Degtiar, 2014).

As a result, treatment-resistant depression adds a direct and indirect annual cost of $9,529 per person per year relative to treatment-responsive depression (Mrazek et al., 2014). In 2012, there were 1.9 million adults with treatment-resistant depression in the United States. Using this prevalence rate, treatment-resistant depression adds an additional overall societal cost of $18.1 billion per year. This brings the total societal cost of depressive disorders to $188 billion. For comparison, the societal cost of cancer is $131 billion and the societal cost for diabetes is $173 billion (Mrazek et al., 2014). Choosing an effective starting antidepressant has the potential to
decrease the overall societal cost of depressive disorders by almost 10%. However, there are no strict protocols to guide physicians in this process.

The American Psychiatric Association (APA, 2010) guidelines state that most patients will have optimal responses to selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), mirtazapine, or bupropion. Since meta-analyses designed to detect differences between the efficacies of these first-line antidepressants have produced mixed results (Hansen, Gartlehner, Lohr, Gaynes, & Carey, 2005; Gartlehner et al., 2011; Brunoni, Fraguas, & Fregni, 2009; Cipriani et al., 2009), physicians are advised to pick antidepressants based on side effect profile, safety, tolerability, and patient preferences. Fewer than 50% of patients respond to their first antidepressant (Singh et al., 2017). In these patients, physicians can either increase the dosage, add on a second medication, or switch to a different antidepressant medication. This process continues until an effective medication regimen is achieved.

The fact that most patients need to try multiple antidepressants before finding an effective regimen suggests disparate efficacies between antidepressants at the individual level despite comparable efficacies between antidepressants at the population level. A better understanding of the factors that influence an individual’s response to different antidepressants can help physicians better choose effective starting antidepressants for individual patients, thus increasing quality of life and functional status while decreasing the overall cost of depression to society.

Purpose of Study

The purpose of this study is to explore the impact symptom clusters have on second-generation antidepressants’ efficacy in treating sadness and to create models that use demographic and clinical characteristics to predict this efficacy. Understanding how symptom
clusters impact drug efficacy can provide broad generalizations that guide physicians when choosing an antidepressant, and creating models can provide a tool that specifically tailors a physician’s choice of antidepressant to each patient. Together, these methods have the potential to decrease the overall morbidity and societal cost of depressive disorders.

**Review of Literature**

**First and Second-Generation Antidepressants**

Antidepressants are broadly grouped into two categories: first-generation antidepressants and second-generation antidepressants. First-generation antidepressants include tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which began appearing on the market in the 1950’s and 1960’s (Hillhouse & Porter, 2016). Second-generation antidepressants include SSRIs, SNRIs, and atypical antidepressants (e.g., bupropion, mirtazapine, and trazodone), which began appearing on the market in the 1980’s (Hillhouse & Porter, 2016). With over 25 different antidepressants across five different drug classes, it can be difficult for a physician to choose the optimal medication for their patients. In order to aid physicians in this process, many studies have been conducted to compare the different antidepressants. These studies have found first and second-generation antidepressants to be comparable in efficacy (Williams et al., 2000). However, first-generation antidepressants are associated with more severe adverse effects, leading to a greater discontinuation rate (Song et al., 1993; Montgomery et al., 1994; Williams et al., 2000).

**Efficacy.** Many studies have found that first and second-generation antidepressants have comparable efficacies. A 1993 meta-analysis of 63 randomized-controlled trials (RCT) look at the efficacy and acceptability of SSRIs compared to TCAs (Song et al., 1993). This meta-analysis found no differences in changes of the mean Hamilton-Depression Rating Scale (HAM-
D) when subjects were treated with SSRIs versus TCAs. Similarly, a 2000 systematic review of 315 RCTs found no difference in the efficacy between first and second-generation antidepressants. (Williams et al., 2000).

**Adverse effects.** While there are no significant differences between the efficacies of first and second-generation antidepressants, studies have shown that second-generation antidepressants have a more favorable side effect profile than first-generation antidepressants (Song et al., 1993; Montgomery et al., 1994; Williams et al., 2000). Adverse effects of TCAs include anticholinergic symptoms and potentially fatal cardiac arrhythmias. Side effects of MAOIs include dangerous and potentially lethal interactions with foods rich in tyramine (e.g., aged cheeses, smoked meats, and alcoholic beverages). In contrast, second-generation antidepressants are associated with non-life-threatening side effects, such as constipation, diarrhea, nausea, and sexual dysfunction (Santarsieri & Schwartz, 2015).

One systematic review conducted in 2000 found no significant differences in discontinuation rates between first and second-generation antidepressants despite significantly different side effect profiles (Williams et al., 2000). However, many other studies have found a significant—albeit modest—increase in discontinuation rates of first-generation antidepressants compared to second-generation antidepressants due to side effects (Song et al., 1993; Montgomery et al., 1994; Mulrow et al., 2000; Warden et al., 2009). Due to an overall better side effect profile despite comparable efficacies, second-generation antidepressants are preferred over first-generation antidepressants.

**Second-Generation Antidepressants**

Due to a better side effect profile, second-generation antidepressants have become the established first-line pharmacological treatment for depression (APA, 2010). More recent studies...
have focused on differentiating efficacies, side effects, and tolerability of different second-generation antidepressant medications.

**Efficacy.** Results comparing the efficacy of different second-generation antidepressants have been mixed. A meta-analysis of 234 RCTs published in 2011 found no clinically relevant differences in the efficacies of second-generation antidepressants (Gartlehner et al., 2011). Similarly, a systematic review published in 2012 found that all SSRIs studied had comparable efficacies (Thaler et al., 2012).

In contrast, a systematic review of 117 RCTs conducted from 1991 to 2007 found clinically relevant differences between second-generation antidepressants. Escitalopram, mirtazapine, sertraline, and venlafaxine were significantly more effective than fluoxetine, duloxetine, and paroxetine (Cipriani et al., 2009).

A systematic review of 46 head-to-head RCTs comparing second-generation antidepressants had mixed results: 20 of the trials reported no statistically significant differences in any efficacy measure, while one study found escitalopram to be more effective than citalopram, and another study found paroxetine to be more effective than fluoxetine (Hansen et al., 2005). The authors of this systematic review found that most of the studies were sponsored by pharmaceutical companies, and sponsored studies were statistically more likely to favor the sponsor’s antidepressant. In addition, many of these studies had small sample sizes, which could account for differences in study results (Hansen et al., 2005).

**Adverse effects.** Different drug classes of second-generation antidepressants have different side effects. Second-generation antidepressants fall into two main categories: activating drugs and sedating drugs. SSRIs, SNRIs, and bupropion are considered activating drugs while mirtazapine and trazodone are sedating drugs.
**Activating drugs.** As activating drugs, SSRIs, SNRIs, and bupropion can lead to symptoms such as increased energy, anxiety, and insomnia.

In addition, SSRIs are commonly associated with gastrointestinal side effects, including nausea, vomiting, and diarrhea. These side effects are dose-dependent and usually attenuate after a few weeks of treatment. While sexual side effects such as a loss of libido can occur with any antidepressant, this effect is especially prominent with SSRIs (APA, 2013).

SNRIs are also associated with nausea and vomiting. In addition, SNRIs can cause hypertension and dry mouth (APA, 2013).

Bupropion is also associated with nausea and vomiting. Like SNRIs, hypertension and dry mouth are common in bupropion. However, because bupropion does not have serotonergic activity, it is not associated with sexual dysfunction. In addition, bupropion has been associated with increased seizures in those with a history of bulimia nervosa and should be avoided in this population (APA, 2013).

**Sedating drugs.** Mirtazapine and trazodone are sedating drugs, so they are often used in people with insomnia or hyperactivity. In addition, mirtazapine is commonly associated with dry mouth and weight gain while trazodone can cause priapism, a medical emergency characterized by a sustained penile erection (APA, 2013).

**Serotonin syndrome.** All antidepressants with serotonergic activity can cause serotonin syndrome, which is a medical emergency characterized by abdominal pain, diarrhea, flushing, sweating, hyperthermia, lethargy, mental status changes, myoclonus, rhabdomyolysis, renal failure, and cardiovascular shock. Thus, physicians should use caution when prescribing more than one antidepressant with serotonergic activity (APA, 2013).
Choosing an Antidepressant based on Readily Accessible Information

According to the APA, second-generation antidepressants like SSRIs, SNRIs, mirtazapine, and bupropion are all first-line pharmacological treatments for major depressive disorder (APA, 2010). Selection of a specific medication is nuanced and should be based on readily accessible information such as side effect profile, patient demographics, co-occurring disorders, prior treatment experiences, and patient preference.

**Medication side-effect profile.** For depression characterized by low energy, one of the more activating agents like SSRIs, SNRIs, and bupropion may be preferred. If sexual side effects are a concern for the patient, then bupropion can be used. If the patient has a history of seizures or an eating disorder, then bupropion is contraindicated since it can lower the seizure threshold. Trazodone is a good choice for depression characterized by insomnia (Thaler et al., 2012), and mirtazapine’s side effect of weight gain can be utilized for those with a loss of appetite (Uguz, Sahingoz, Gungor, Aksoy, & Askin, 2015).

**Patient demographics.** Many studies have looked at whether patient demographics, such as age, gender, race, and socioeconomic status affect antidepressant efficacy.

**Age.** Studies that explored the association between age and drug efficacy used a range of minimum ages to define older age, with age cutoffs ranging from 50 to 70 years old. These studies found that nonresponse to antidepressant medication in general is more likely in older patients (Sherbourne, Schoenbaum, Wells, & Croghan, 2004). However, there is no difference in efficacies between various second-generation antidepressants in this population (Gartlehner et al., 2011). Thus, physicians can expect a poorer response to medication in older patients, but older age cannot be used as the basis of recommending a specific medication. In pediatric patients,
however, fluoxetine can be recommended because it is the only antidepressant approved for
treating depression in children ages eight and older (March et al., 2004).

**Gender.** Potential reasons for sexual differences in antidepressant response include
differences between males and females with respect to hormone levels, drug metabolism, and
behavioral characteristics (Sramek, Murphy, & Cutler, 2016; Yonkers, Kando, Cole, &
Blumenthal, 1992). Estrogen and progesterone have been theorized to be implicated in the
pathogenesis of depression. This is supported by the observation that differences in the
prevalence of MDD between males and females do not emerge until puberty (Faravelli, Scarpato,
Castellini, & Lo Sauro, 2013) and disappear after menopause (Bebbington et al., 2003). Estrogen
and progesterone have also been shown to decrease gastric motility, which affects the clearance
of antidepressants (Young et al., 2009; Hutson, Roehrkassee, & Wald, 1989). In addition, females
have a higher percentage of body fat than men (Blaak, 2001), which can affect metabolism of
lipophilic antidepressant medications.

While there is a theoretical basis for differences in antidepressant response between
males and females, studies looking at this effect have had mixed results. In many studies,
females have been shown to respond better than males to serotonergic agents (Kornstein et al.,
2000; Naito et al., 2007; Young et al., 2009). In addition, a few studies have shown males
respond better than females to TCAs and MAOIs (Kornstein et al., 2000; Frank, Carpenter, &
Kupfer, 1988), and one study found females responded better to MAOIs than males (Quitkin et
al., 2002). However, there have also been many studies that found no significant difference
between males and females in the response to SSRIs, MAOIs, or TCAs (Entsuah, Huang, &
Thase, 2001; Quitkin et al., 2002; Parker, Parker, Austin, Mitchell, & Brotchie, 2003; Wohlfarth
et al., 2004; Pinto-Meza, Usall, Serrano-Blanco, Suarez, & Haro, 2006; Kornstein et al., 2014; Cuijpers et al., 2014).

In terms of adverse effects, a meta-analysis of 234 RCTs found one trial in which men were reported to have a higher risk of sexual dysfunction than women when taking paroxetine, and another trial in which women were reported to have greater sexual dysfunction when taking paroxetine compared to sertraline (Gartlehner et al., 2011).

**Pregnancy.** Paroxetine and nortriptyline should be avoided in pregnancy since they are in the Food and Drug Administration (FDA) Pregnancy Category D (i.e., there is positive evidence of human fetal risk based on adverse reaction data or studies in humans) (Lin & Stevens, 2014). Most other antidepressants are Category C (i.e., there are no adequate or well-controlled studies in humans) and should be used with caution (Lin & Stevens, 2014).

**Race.** A meta-analysis of 234 RCTs found there were no head-to-head trials or studies directly comparing differences in efficacy between groups identified by race or ethnicity (Gartlehner et al., 2011). Thus, physicians cannot choose an antidepressant based on race using the present data.

**Socioeconomic status.** Unemployment has been shown to be a predictor of nonresponse to antidepressants in patients with depression (Sherbourne et al., 2004). This suggests that physicians can expect a poorer response to antidepressants in general for patients of a lower socioeconomic status. However, socioeconomic status cannot be used as the basis for predicting which specific antidepressant will be most efficacious in these patients.

While socioeconomic status cannot help physicians choose an antidepressant based on efficacy, it can help physicians choose an antidepressant based on cost. For patients in which cost is a barrier to treatment, citalopram, fluoxetine, and sertraline are relatively low-cost SSRIs.
In contrast, escitalopram, fluvoxamine, and milnacipran, are more expensive SSRIs. Low-cost atypical antidepressant options include mirtazapine, and trazodone (Lin & Stevens, 2014).

**Clinical presentation.** Since depression is a heterogenous disease and can present in many ways, most psychiatrists pick antidepressant medications for their patients based on symptom clusters within the clinical presentation (Zimmerman et al., 2004). Common symptom clusters upon which psychiatrists base their antidepressant choices are anxiety, sleep, fatigue, and pain (Zimmerman et al., 2004; Lin & Stevens, 2014; Thaler et al., 2012). Based on this method, psychiatrists would choose a sedating drug for those with anxiety or insomnia, an activating drug for those with fatigue, and an SNRI for those with neuropathic pain. While the choices psychiatrists make are theoretically logical from a neurobiological point of view, empirical evidence has been sparse and inconclusive. Choosing antidepressants based on the predominant clinical presentation of depression has been shown to improve treatment outcomes in many trials (Fava et al., 1997; Kornstein & Schneider, 2001), but a few trials have found that there is no superior antidepressant for any specific symptom cluster (Thaler et al., 2012; Gaynes et al., 2011). These trials, however, were often underpowered.

**Anxiety.** Since anxiety is regulated by serotonergic neurons in the limbic system, SSRIs should theoretically be the optimal treatment in anxiety-predominant depression (Lin & Stevens, 2014). This is supported by the fact that most SSRIs are also FDA approved to treat generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder (Lin & Stevens, 2014). Since norepinephrine is associated with the sympathetic fight or flight response, drugs that increase norepinephrine, such as SNRIs and bupropion, should theoretically be avoided in this population due to their potential to provoke anxiety (Lin & Stevens, 2014). While this makes theoretical sense, a systematic review of RCTs found that treatment efficacy did not differ
between antidepressant medications in treating anxiety associated with depression (Thaler et al., 2012).

**Insomnia.** Sleep is regulated by 5HT2a receptors in the brainstem (Thase, 1999). Thus, antidepressants that block 5HT2A receptors, such as mirtazapine and trazodone, should be optimal treatments in insomnia-predominant depression. In fact, studies have shown that mirtazapine shortens sleep onset time and increases sleep duration (Thase, 1999). Trazodone and mirtazapine are common drugs chosen by psychiatrists in treating depression with insomnia (Lin & Stevens, 2014). Like anxiety-predominant depression, drugs with norepinephrine activity, such as SNRIs and bupropion, should be avoided in insomnia-predominant depression due to their activating effects.

While a 2012 systematic review found fluoxetine and mirtazapine to be equally effective at treating depression with insomnia, trazodone was found to be significantly better at improving sleep disturbance when compared to both fluoxetine and venlafaxine (Thaler et al., 2012).

**Fatigue.** Fatigue-predominant depression often comes clustered with decreases in energy, attention, and concentration. These symptoms are regulated by a decrease in dopamine and norepinephrine (Lin & Stevens, 2014). In fact, psychiatrists most commonly prescribe SNRIs, bupropion, and fluoxetine (an SSRI with some norepinephrine activity) to treat depression with fatigue (Lin & Stevens, 2014). Sedating drugs, such as trazodone and mirtazapine, should be avoided in these patients.

Analysis of the data from the ‘Sequenced Treatment Alternatives to Relieve Depression’ (STAR*D) trial found that augmentation with bupropion was more likely than buspirone to produce remission in patients with depression characterized by low energy. However, switching
to venlafaxine, an SNRI, or bupropion was less likely to produce remission than switching to sertraline, an SSRI (Gaynes et al., 2011).

**Pain.** Pain is thought to be mediated by decreases in serotonin and norepinephrine, which affects the endogenous opioid system (Ozdemir, Gursoy, & Bagcivan, 2012). Thus, SNRIs should theoretically be optimal in depression with pain. In fact, many SNRIs are FDA approved to treat both depression and neuropathic pain, such as pain from fibromyalgia or diabetic neuropathy (Lin & Stevens, 2014).

The costs, indications, and potential side effects of second-generation antidepressants are summarized in Table 1.

<table>
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<th>Table 1</th>
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<tr>
<td><strong>Second-Generation Antidepressants</strong></td>
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<tr>
<td>Cost¹</td>
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<td>Pregnancy Category²</td>
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<tr>
<td>Other Indications</td>
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<td>Contraindications</td>
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<td>Side Effects</td>
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<td>Diarrhea/Constipation</td>
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<td>Decreased Libido</td>
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<td>HTN</td>
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<tr>
<td>Dry Mouth</td>
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<td>Serotonin Syndrome</td>
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<td>Priapism</td>
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<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Fatigue</td>
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<td>Weight</td>
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¹$= less than $50 per month; $$= $50-$100/month
²C= there are no adequate or well-controlled studies in humans; D=There is positive evidence of human fetal risk based on adverse reaction data or human studies
Choosing an Antidepressant based on Genomic and Imaging Data

Despite using medication side effect profiles, patient demographics, and clinical presentation to guide the selection of antidepressants, less than 50% of patients respond to their first antidepressant, and many patients must try multiple drugs before finding one that works (Singh et al., 2017; Aldi, Baethge, Heinz, Langlitz, & Bauer, 2005). Thus, researchers have attempted to help guide physicians in their choice of antidepressants by utilizing genomic data and imaging data.

Genomic data. Although gene expression analysis is difficult to do in MDD because brain tissue is relatively inaccessible, single nucleotide polymorphisms (SNPs) of various genes can be obtained from any tissue in the body. Multiple SNPs have been studied for their association with antidepressant treatment response, and many companies are now advertising proprietary algorithms that use a patient’s DNA sample to guide the choice of antidepressants (Rosenblat, Lee, & McIntyre, 2018).

ABCBI. The ABCBI gene codes for p-glycoprotein, a protein involved in the transport of compounds out of the blood brain barrier. Thus, this gene can theoretically affect drug concentration levels at the brain, making it a promising target in studying antidepressant efficacy. In 2015, Schatzberg et al. looked at 10 different SNPs in 683 patients and found that functional polymorphisms in rs1024583 differentially affected response to antidepressants. Those homozygous for the T allele had increased activity of p-glycoprotein and a poorer response to escitalopram and sertraline. This could be because the overactive p-glycoprotein is transporting the drug out of the cerebrospinal fluid, decreasing the levels of the drug at the brain. However, those homozygous for the T allele also had a significantly better response to venlafaxine, a result the researchers could not explain. Efficacy to these three drugs was also inversely correlated with
side effect levels. These results are consistent with many other studies (Uhr et al., 2008; Lin et al., 2011; Singh, Bousman, Ng, Byron, & Berk, 2012) while others have had inconsistent results (Perlis, Fijal, Dharia, Heinloth, & Houston, 2010).

**5HTTLPR and 5HT2a.** Polymorphisms in the serotonin transporter 5HTTLPR and the serotonin postsynaptic receptor 5HT2a have been studied with relation to SSRI efficacy. Again, study results have been mixed (Anguelova, Benkelfat, & Turecki, 2003). McMahon et al. (2006) found polymorphisms in these genes to be correlated with treatment response to citalopram, while Leuchter et al. (2009) found that these polymorphisms were not significant predictors of treatment response to escitalopram or bupropion.

**UBE3C.** A third gene that shows promise in predicting antidepressant response is UBE3C, which encodes for the ubiquitin protein ligase E3C (Leuchter et al., 2010). This gene has been shown to be significantly downregulated in a stress-induced manner in the ventromedial prefrontal cortex and has been associated with escitalopram and nortriptyline treatment response.

**Brain structure and function.** Measures of brain structure and function, such as quantitative electroencephalogram (QEEG) and magnetic resonance imaging (MRI) scans, have been studied in their ability to predict response to antidepressant treatment.

**QEEG.** Currently, the best-documented brain functional biomarker in predicting antidepressant response is QEEG (Leuchter et al., 2009; Leuchter et al., 2010; Koenig, Studer, Hubl, Melie, & Strik, 2005). In particular, the Antidepressant Treatment Response Index (ATR), a type of QEEG, has been shown to significantly predict remission of depressive symptoms with escitalopram (Leuchter et al., 2009).

**MRI.** There are two common ways that MRIs are utilized in predicting antidepressant response: intrinsic connectivity analysis and task-related analyses. In intrinsic connectivity
analyses, the patient lays in the scanner with their eyes closed, allowing researchers to obtain a picture of brain anatomy. In task-related analyses, a functional MRI (fMRI) is utilized. Typically, subjects lay in the machine with their eyes open, and researchers measure levels of activity in different areas of the brain while the subject views negative emotional facial expressions.

**Intrinsic connectivity analysis.** Intrinsic connectivity analyses have found that patients with depression have decreased corticolimbic connectivity (Anand et al., 2005) and reduced gray matter in the anterior cingulate cortex (Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009), subgenual cingulate cortex (Hajek, Kozeny, Kopecek, Alda, & Hoschl, 2008), and the hippocampus (McKinnon, Yucel, Nazarov, & MacQueen, 2009). Changes in the hippocampus may be useful in predicting antidepressant treatment response: larger hippocampi are associated with better responses to antidepressants while smaller hippocampi are associated with poorer responses to antidepressants. This result has been obtained in citalopram, venlafaxine, bupropion, mirtazapine, sertraline, fluoxetine, and fluvoxamine (MacQueen, Yucel, Taylor, Macdonald, & Joffe, 2008; Vakili et al., 2000; Frodl et al., 2008). In addition, levels of cerebral metabolism, white-matter lesions, and levels of brain atrophy pretreatment may be useful predictors of treatment outcome (Leuchter et al., 2009). However, other studies have shown that structural MRI imaging does not seem to be a useful predictor of antidepressant response (Schmaal et al., 2015).

**Task-related analysis.** Task-related analyses have found increased activity in the amygdala in depressed patients while looking at negative emotional facial expressions (Surguladze et al., 2005). Fu et al. (2008) used this information along with machine learning techniques to create an algorithm that could differentiate two different groups: 1) patients with depression from patients without depression, and 2) whether a patient with depression will
respond to treatment. This algorithm was able to correctly distinguish between patients with depression and patients without depression with an 84% sensitivity and 89% specificity. While the sample size was too small to significantly differentiate patients who will respond to treatment from those who will not, the data showed a trend toward significance.

Another study found decreased connections between the amygdala and anterior cingulate, and eight weeks of fluoxetine administration increased these connections between the amygdala and anterior cingulate (Chen et al., 2008).

Choosing an Antidepressant by Combining Multiple Variables

Rather than looking at the impact of individual factors (e.g., demographic, genomic information, brain imaging, etc.) that each have a minimal ability to predict treatment response, it may be beneficial to simultaneously use multiple variables to predict an individual’s response to treatment. These variables may have additive effects, increasing our ability to accurately predict treatment response. Machine learning is one such way of simultaneously utilizing many variables to empirically predict antidepressant response. A literature review found only one study that has used machine learning to predict antidepressant treatment response (Chekroud et al., 2016). This study used the STAR*D trial data to develop an algorithm to assess whether patients will achieve remission of depression following a 12-week course of citalopram. This algorithm used 25 predictive variables and was able to predict outcomes within the STAR*D cohort with 64.6% accuracy ($p < .0001$). This model was then externally validated with the escitalopram treatment group of the ‘Combining Medications to Enhance Depression Outcomes’ (COMED) trial with an accuracy of 59.6% ($p < .0001$). Although demographic information, clinical presentation, symptom clustering, imaging, and genomic data each provide minimal information on which patients might respond best to which drug, combining all these factors together into a single
algorithm seems to have an additive effect. Chekroud et al. (2016) found significant results by doing this with citalopram, and if this same process were repeated for all commonly used first-line antidepressants, clinicians would be equipped with empirical evidence to confidently prescribe a specific drug to a specific patient.

**Methods**

This study utilized a secondary analysis of data from the Collaborative Psychiatric Epidemiology Surveys (CPES), a pre-existing, de-identified data set. Demographic characteristics, clinical symptoms, past medical history, current medications and treatments, and compliance were extracted from participants who had reported using one of the seven drugs of interest (i.e., citalopram, fluoxetine, paroxetine, sertraline, venlafaxine, bupropion, and trazadone) within the past year. Chi-square analyses were then conducted to screen for variables significantly associated with the efficacy of each drug. Variables that were significantly associated with drug efficacy ($p < .05$) were included in all subsequent analyses.

In the first set of analyses, clinical symptoms were grouped into five symptom clusters (i.e., mood, anxiety, fatigue, insomnia, and appetite) and included in a multivariable logistic regression to look for associations between symptom clusters and a drug’s efficacy in treating sadness. Demographics, past medical history, current medications and treatments, and compliance were controlled for by using a principal component analysis (PCA) with the resulting PCs included as independent variables in the logistic regression.

In the second set of analyses, fifty percent of the subjects were removed from the analyses to form a testing cohort. The remaining 50% constituted the training cohort. A PCA that included all clinical symptoms, demographics, past medical history, current medications and treatments, and compliance was run on the training cohort, and the resulting PCs were included
in a regression analysis to create models that predict each drug’s efficacy in treating sadness. Accuracy and internal validity of the models were tested using the training cohort and the testing cohort, respectively.

This study is exempt from Institutional Review Board (IRB) evaluation, per 45 Code of Federal Regulations (CFR) part 46 of the Human Subjects Regulations Decision Chart 1 (see Appendix A).

**Study Sample**

Data from the CPES \((N = 20,013)\) was obtained through the Inter-university Consortium for Political and Social Research (ICPSR). The CPES includes data collected from 2001 to 2003 and is a combination of three separate surveys all administered by trained lay interviewers: the National Comorbidity Survey Replication (NCS-R) \((n = 9,282)\), the National Survey of American Life (NSAL) \((n = 6,082)\), and the National Latino and Asian American Study (NLAAS) \((n = 4,649)\). All subjects were adults living in households within the United States. Institutionalized adults and people living on a military base were excluded from this sample. In addition, the NCS-R and NSAL excluded non-English speakers. The CPES used a multi-stage probability sampling design to create a representative sample of the total United States population, as well as special populations including Asian and Latino adults. The average response rate for the CPES was 72.1%. Further details of the methodology of the CPES are provided elsewhere (Pennel et al., 2004).

A subsample of participants who had taken one of the seven drugs of interest was included in this study. Participants were asked whether they had taken a prescription medication for ‘emotions, nerves, mental health, substance use, energy, concentration, sleep, or ability to cope with stress’ within the past year. Those who endorsed this statement were asked to select
the name of the medication they had taken, and each participant could choose up to 20 medications. Because subsequent questions about compliance, reason for taking the medication, and effectiveness were only asked about the first three medications the participants selected, our analysis was limited to the first three medications participants cited. Any participant who listed fluoxetine \((n = 217)\), sertraline \((n = 330)\), citalopram \((n = 139)\), paroxetine \((n = 283)\), venlafaxine \((n = 99)\), bupropion \((n = 154)\), or trazadone \((n = 105)\) as one of their first three medications were included in this study \((n = 1,162)\). Eighty-nine percent of the mentions of any of these seven medications were captured within the first three mentions.

**Outcome Measures**

In the CPES survey, participants were asked to list the reasons for which they were taking the medication (e.g., sadness, sleep, concentration, etc.) for each of their first three medication mentions. This study included all participants who were taking their medication to treat sadness. Then, participants were asked, “Overall, how effective was [medication name] in doing the things you expected it to do – very, somewhat, not very, or not at all effective?” In this study, answers of “very effective” were coded as effective, while “somewhat effective,” “not very effective,” and “not at all effective” were coded as ineffective.

**Covariates**

**Demographic characteristics.** Age, sex, body-mass index (BMI), race-ethnicity, marital status, educational attainment, insurance status, employment status, and income to needs ratio were included in the analyses.

**Substance use.** Smoking status, alcohol consumption, illegal uses of prescription drugs, marijuana use, and cocaine use were included in the analyses. For each substance, participants were asked the question, “Did you use [substance] at any time within the past 12 months?”
Options included “yes,” “no,” “don’t know,” and “refused to answer.” Alcohol consumption included both the frequency at which the participant typically drinks alcohol as well as the quantity of alcohol consumed during each occurrence over the past year.

**Overall health status.** Participants were asked to rate their overall mental health and overall physical health. Options included “excellent,” “very good,” “good,” “fair,” and “poor.” To assess overall functional status, participants were asked whether they had been “limited in any way for the past three months because of any impairment or health problems.” Participants who responded with a “yes,” were subsequently asked how long this impairment lasted.

**Diagnoses.** Psychiatric diagnoses were based on the WHO World Mental Health Composite International Diagnostic Interview (WMH-CIDI) using Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) diagnostic codes. Diagnoses made in this manner are comparable to those made by clinicians (Kessler & Ustun, 2004; Kessler et al., 2005).

For physical diagnoses, participants were given a list of 20 different possible chronic, physical diagnoses and were told to choose all that apply. This list is a modified checklist from the National Health Interview Survey.

**Symptoms.** Symptom type and severity were derived from the Kessler Psychological Distress Scale (K10), a ten-question screening tool that measures symptoms associated with anxiety and depression (Kessler et al., 2002). For this scale, participants were asked to think about “the one month in the past 12 months when you were at your worst emotionally in terms of being anxious, depressed, or emotionally stressed. If there was no month like this, think of a typical month in the past 12 months.”

While the K10 asked about symptoms present within the past year, three additional questions in the screening section of the CPES questionnaire asked about present symptoms.
These three questions from the screening questionnaire were included to provide additional information about current sleep, appetite, and anxiety. For sleep, participants were asked, “How often do you have trouble getting to sleep or staying asleep?” For appetite, they were asked, “How often do you have loss of appetite?” For anxiety, they were asked, “How often have you been bothered by nervousness, feeling fidgety, or tense?” For each of these questions, participants have the option of choosing “nearly all the time,” “pretty often,” “not very much,” or “never.”

Medications.

Categorization. If a medication mentioned was not one of the seven medications of interest, it was classified into a group based on drug class. Twelve drug groups were used: stimulants, anti-psychotics, benzodiazepines, non-benzodiazepine hypnotics (NBH), antihistamines, barbiturates, mood stabilizers, anticholinergic, anti-convulsant, alpha agonist, other anxiolytic, and other non-anxiolytic. Medications that are a mix of two different medications were coded as being in both medications’ drug classes (e.g., Etrafon, which is a combination of amitriptyline and perphenazine, was coded as both a TCA and an antipsychotic medication).

Noncompliance. To assess medication compliance, participants were asked, “How many days out of 30 did you typically either forget to take it or take less of it than you were supposed to?” Although there is no consensus on the threshold that should be used to define non-compliance, previous studies have used compliance rates between 80% and 95% (Faravelli et al., 2013). This study defined strict compliance as taking the medication at least 90% of the time, and liberal compliance was defined as taking the medication at least 80% of the time (Jeon-Slaughter, 2012). Thus, those who missed their medication more than three days per month were
considered noncompliant using the strict definition and those who missed their medication more than six times per month were considered noncompliant using the liberal definition.

**Other treatments.** To understand the kinds of treatment each participant had tried in conjunction with their medications, we included three variables: 1) whether the participant had ever had a therapy session for >30 minutes, 2) whether the participant had ever been hospitalized for problems with their nerves, mental health, or use of alcohol or drugs, and 3) whether the participant had used any alternative therapies in the past year. Examples of alternative therapies provided to the participant were acupuncture, biofeedback, chiropractic, energy healing, exercise or movement therapy, herbal therapy, high dose megavitamins, homeopathy, hypnosis, imagery techniques, massage therapy, prayer or other spiritual practices, relaxation or meditation techniques, special diets, spiritual healing by others, and any other non-traditional remedies or therapies.

**Statistical Analysis**

SPSS version 25 was used to conduct statistical analyses. Descriptive analyses were performed on all 97 covariates for each of the seven drug groups. This included nine demographic characteristics, four variables on health status, 27 lifetime mental health diagnoses, 13 depression symptoms, six variables on treatments and substances, 24 possible current medications, and 14 variables on compliance (see Table 2).
### Table 2

**Variables Included in Study**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Overall Health Status</th>
<th>Lifetime MH Dx</th>
<th>Limited Symptoms</th>
<th>Tnt and Substances</th>
<th>Medications in Last Year</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEX</td>
<td>Limited in Any Way</td>
<td>MDD</td>
<td>KU Survey</td>
<td>ever hospitalized</td>
<td>Fluoxetine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Age</td>
<td>Overall PH</td>
<td>Dysthymia</td>
<td>Hopeless</td>
<td>Ever gone to therapy</td>
<td>Sertraline</td>
<td>Sertraline</td>
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<tr>
<td>Race-Ancestry</td>
<td>Physical Da (Y/N)</td>
<td>Bipolar 1</td>
<td>Fidgety</td>
<td>Illicit Drug Use</td>
<td>Citalopram</td>
<td>Citalopram</td>
</tr>
<tr>
<td>BMI</td>
<td>Total # Phys Da</td>
<td>Mania</td>
<td>Worthless</td>
<td>Alternative therapies</td>
<td>Paroxetine</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Marital Status</td>
<td>Overall MH</td>
<td>Bipolar 2</td>
<td>Tired</td>
<td>Alcohol Frequency</td>
<td>Venlafaxine</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Employment Status</td>
<td>Bipolar Subthreshold</td>
<td>Hypomania</td>
<td>Nothing calmed you</td>
<td>Alcohol Quantity</td>
<td>Bupropion</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Insurance</td>
<td>GAD</td>
<td>Could not sit still</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income to Needs Ratio</td>
<td></td>
<td>PD</td>
<td>Depressed</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>High School Diploma</td>
<td></td>
<td>PA</td>
<td>Nothing cheered you up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening Survey</td>
<td></td>
<td>PTSD</td>
<td>Everything was an effort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific Phobia</td>
<td></td>
<td>Social Phobia</td>
<td>Screening Survey</td>
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<tr>
<td>Adult Separation Anxiety</td>
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<td>Anxiety</td>
<td>Insomnia</td>
<td></td>
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<tr>
<td>Separation Anxiety</td>
<td></td>
<td>Agoraphobia</td>
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<td></td>
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<tr>
<td>with Panic</td>
<td></td>
<td></td>
<td>Apprehensive</td>
<td></td>
<td></td>
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<tr>
<td>without panic</td>
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<tr>
<td>Binge Eating</td>
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<tr>
<td>Bulimia</td>
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<tr>
<td>Anorexia</td>
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<tr>
<td>Alcohol Dependence</td>
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<td></td>
<td></td>
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<tr>
<td>Alcohol Abuse</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Drug Dependence</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Drug Abuse</td>
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<td></td>
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<tr>
<td>ODD</td>
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</tr>
</tbody>
</table>

Tnt=treatment; PH=Physical health; Da=Dx; MH=Mental health; MDD=Major depressive disorder; GAD=Generalized anxiety disorder; PD=Panic disorder; PA=Panic Attack; PTSD=PSTd-trumatic stress disorder; ADD=Attention deficit disorder; ODD=Oppositional defiant disorder; TCA=Tricyclic antidepressant; MAO=Monoamine oxidase inhibitor; NBH=Non-benzodiazepine hypnotic

*Includes carbamazepine, lamotrigine, valproate, and lithium

*Includes amantadine, nefazodone, dicyclomamine, reserpine, and disulfiram
To screen for variables, individual chi-square analyses were performed for every combination between the 97 variables studied and the efficacy of the seven drugs. All variables significantly associated with drug efficacy ($p < .05$) were included in two separate, subsequent analyses: one to find associations between symptom clusters and drug efficacy, and another to create a model that predicts drug efficacy.

**Symptom cluster associations.** Following the chi-square analyses, variables associated with symptom types (i.e., questions from the K10 and screening surveys) were standardized on a scale ranging from zero to one. People with a value of zero experienced the symptom none of the time while those with a value of one experienced the symptom all the time. Symptoms associated with decreased mood were summed to create a total mood score, and this process was repeated to create an anxiety score, fatigue score, insomnia score, and appetite score. The symptoms that make up each score are shown in Table 3.

Table 3

<table>
<thead>
<tr>
<th>Survey Questions Included in Each Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood Score</strong></td>
</tr>
<tr>
<td><strong>K10 Survey</strong></td>
</tr>
<tr>
<td>Hopelessness</td>
</tr>
<tr>
<td>Worthlessness</td>
</tr>
<tr>
<td>Depressed</td>
</tr>
<tr>
<td>Nothing cheered you up</td>
</tr>
<tr>
<td>Screening Survey</td>
</tr>
</tbody>
</table>

A PCA was conducted using the variables that screened positive on the chi-square analyses. This PCA did not include clinical symptoms. A regression method was used to calculate factor scores, and components with an Eigenvalue $\geq 1$ were included in subsequent analyses.
The resulting principal components were included in a multivariable logistic regression analysis. The dependent variables were the principal components and relevant symptom scores. The independent variable was the drug’s efficacy in treating sadness.

**Model creation.** In a separate analysis, 50% of the participants were removed from the data to form the testing cohort. The remaining 50% of participants constituted the training cohort. For each of the seven drugs, a separate PCA was performed using the variables that screened positive on the chi-square tests. This time, the clinical symptoms were included. A regression method was used to calculate factor scores, and components with an Eigenvalue $\geq 1$ were included in subsequent analyses.

A multivariable logistic regression was performed on the training cohort using principal components as the independent variables and effectiveness of the drug in treating sadness as the dependent variable. These models were then applied to the testing cohort to assess their validity.

Methods for the statistical analysis are summarized in Figure 1.
Results

Descriptive Analysis

In total, 1,162 participants took one of the seven drugs of interest within the past 12 months. Within the past 12 months, 85.97% of people took only one of the seven medications, 13.16% took two of the seven medications, and 0.86% took three of the seven medications. The subsample of participants who took fluoxetine, sertraline, citalopram, paroxetine, venlafaxine, bupropion, and trazodone represent 2,374,066.524 (SE= 304,321.115), 2,872,686.689 (SE=
213,522.755, 1,333,959.677 (SE=251,037.292), 2,179,510.792 (SE=253,542.893),
1,004,892.689 (SE=120,447.118), 1,345,820.685 (SE=163,977.012), and 402,731.505
(SE=56,266.937) of the total United States population, respectively. The percentage of people
who found fluoxetine, sertraline, citalopram, paroxetine, venlafaxine, bupropion, and trazodone
to be effective were 52.8%, 59.3%, 40.8%, 51.9%, 58.9%, 46.3%, and 72.0%, respectively (see
Figure 2).

![Figure 2. Effectiveness of each drug](image_url)

In each of the seven groups, there were more than twice as many women as men, more
than three quarters of participants were privately insured, and more than 80% identified as non-
Latino white. Mean age of these seven groups ranged from 42.3 to 49.7, and mean income to
needs ratio ranged from 3.90 to 4.87 (see Table 4).
Table 4

Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine (%)</th>
<th>Sertraline (%)</th>
<th>Citalopram (%)</th>
<th>Paroxetine (%)</th>
<th>Venlafaxine (%)</th>
<th>Bupropion (%)</th>
<th>Trazodone (%)</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>24.9</td>
<td>24.9</td>
<td>30.1</td>
<td>29.3</td>
<td>29.7</td>
<td>30.7</td>
<td>21.4</td>
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<tr>
<td>Female</td>
<td>75.1</td>
<td>75.1</td>
<td>69.9</td>
<td>70.7</td>
<td>70.3</td>
<td>69.3</td>
<td>78.6</td>
</tr>
<tr>
<td><strong>Mean Age (sd)</strong></td>
<td>45.9 (14.8)</td>
<td>45.3 (15.2)</td>
<td>44.8 (15.1)</td>
<td>45.1 (15.6)</td>
<td>43.5 (12.9)</td>
<td>42.3 (12.4)</td>
<td>49.7 (13.2)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>36.2</td>
<td>39.8</td>
<td>41.6</td>
<td>43.5</td>
<td>26.8</td>
<td>48.0</td>
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<tr>
<td>≥25</td>
<td>63.8</td>
<td>60.2</td>
<td>58.4</td>
<td>56.5</td>
<td>73.2</td>
<td>52.0</td>
<td>66.4</td>
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<td>Non-Latino</td>
<td>88.6</td>
<td>81.1</td>
<td>85.6</td>
<td>82.2</td>
<td>87.9</td>
<td>90.0</td>
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<td>White</td>
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<td>6.9</td>
<td>3.8</td>
<td>5.2</td>
<td>3.2</td>
<td>2.6</td>
<td>4.4</td>
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<td>African</td>
<td>5.3</td>
<td>9.4</td>
<td>6.8</td>
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<td>Hispanic</td>
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<td>1.1</td>
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<td>1.2</td>
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<td>Asian</td>
<td>2.9</td>
<td>1.5</td>
<td>3.3</td>
<td>3.9</td>
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<td>Other</td>
<td>87.9</td>
<td>87.7</td>
<td>81.7</td>
<td>87.7</td>
<td>91.5</td>
<td>88.9</td>
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<td><strong>Marital Status</strong></td>
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<tr>
<td>Married or cohabiting</td>
<td>49.2</td>
<td>54.7</td>
<td>58.6</td>
<td>52.7</td>
<td>44.5</td>
<td>57.1</td>
<td>65.6</td>
</tr>
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<td>Divorced, separated,</td>
<td>30.8</td>
<td>27.9</td>
<td>21.2</td>
<td>23.5</td>
<td>31.2</td>
<td>21.3</td>
<td>24.8</td>
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<tr>
<td>or widowed</td>
<td>20.0</td>
<td>17.4</td>
<td>20.2</td>
<td>23.7</td>
<td>24.4</td>
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<td>No</td>
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<td>Employed</td>
<td>41.9</td>
<td>42.5</td>
<td>39.9</td>
<td>50.9</td>
<td>33.9</td>
<td>40.9</td>
<td>53.2</td>
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<td>Unemployed</td>
<td>58.1</td>
<td>57.5</td>
<td>60.1</td>
<td>49.1</td>
<td>66.1</td>
<td>59.1</td>
<td>46.8</td>
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<tr>
<td><strong>Mean Income to Needs Ratio (sd)</strong></td>
<td>4.03 (3.84)</td>
<td>4.02 (3.98)</td>
<td>4.20 (3.44)</td>
<td>3.90 (3.56)</td>
<td>4.48 (4.04)</td>
<td>4.87 (4.23)</td>
<td>3.91 (3.77)</td>
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</tbody>
</table>

sd = standard deviation

Chi-square Analysis

Chi-square tests found 15, 21, 13, 16, 9, and 16 of the 97 variables to be correlated with the effectiveness of fluoxetine, sertraline, citalopram, paroxetine, venlafaxine, bupropion, and trazodone, respectively (p < .05) (see Table 5).
Table 5

Predictors of Drug Effectiveness ($p < .05$)

<table>
<thead>
<tr>
<th>Sertraline</th>
<th>Citalopram</th>
<th>Paroxetine</th>
<th>Venlafaxine</th>
<th>Bupropion</th>
<th>Trazodone</th>
<th>Fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td><strong>Demographic</strong></td>
<td><strong>Demographic</strong></td>
<td><strong>Demographic</strong></td>
<td><strong>Demographic</strong></td>
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<tr>
<td>Age</td>
<td>Employment Status</td>
<td>Age</td>
<td>Lifetime MH Dx</td>
<td>Lifetime MH Dx</td>
<td>Income to Needs</td>
<td>Sex</td>
</tr>
<tr>
<td>Income to Needs</td>
<td>Age</td>
<td>Lifetime MH Dx</td>
<td>MDD</td>
<td>PTSD</td>
<td>Lifetime MH Dx</td>
<td>Bipolar 2</td>
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<tr>
<td>Marital Status</td>
<td>Income to Needs</td>
<td>Bipolar Subthreshold</td>
<td>Drug Dependence</td>
<td>Conduct Disorder</td>
<td>PTSD</td>
<td>Bipolar Subthreshold</td>
</tr>
<tr>
<td><strong>Lifetime MH Dx</strong></td>
<td><strong>Overall Health Status</strong></td>
<td><strong>Bipolar Subthreshold</strong></td>
<td><strong>Phys Dx (Y/N)</strong></td>
<td><strong>K10</strong></td>
<td><strong>PTSD</strong></td>
<td><strong>Bipolar Subthreshold</strong></td>
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<tr>
<td>Hypomania</td>
<td>Total # Phys Dx</td>
<td>K10</td>
<td>Hopeless</td>
<td>Hopeless</td>
<td>Specific Phobia</td>
<td>Specific Phobia</td>
</tr>
<tr>
<td>GAD</td>
<td>Lifetime MH Dx</td>
<td>K10</td>
<td>Hopeless</td>
<td>Hopeless</td>
<td>Agoraphobia with PD</td>
<td>Agoraphobia without PD</td>
</tr>
<tr>
<td>ODD</td>
<td>Dysthymia</td>
<td>K10</td>
<td>Hopeless</td>
<td>Hopeless</td>
<td>Alcohol dependence</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>K10</td>
<td>Bipolar Subthreshold</td>
<td>K10</td>
<td>Tired</td>
<td>Tired</td>
<td>Alcohol dependence</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Hopeless</td>
<td>Depressed</td>
<td>Depressed</td>
<td>Depressed</td>
<td>Depressed</td>
<td>Drug dependence</td>
<td>Drug dependence</td>
</tr>
<tr>
<td>Worthless</td>
<td>PTSD</td>
<td>PTSD</td>
<td>PTSD</td>
<td>PTSD</td>
<td>Drug abuse</td>
<td>Drug abuse</td>
</tr>
<tr>
<td>Depressed</td>
<td>Binge Eating</td>
<td>Screening</td>
<td>Insomnia</td>
<td>Appetite</td>
<td>Other medication</td>
<td>Other medication</td>
</tr>
<tr>
<td>Everything was effort</td>
<td>K10</td>
<td>Everything was effort</td>
<td>Everything was effort</td>
<td>Everything was effort</td>
<td>K10</td>
<td>K10</td>
</tr>
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<td><strong>Screening</strong></td>
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<td><strong>Screening</strong></td>
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<td><strong>Screening</strong></td>
<td><strong>Screening</strong></td>
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<td>Worthless</td>
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<td>Anxiety</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Meds and Comp</td>
<td>Meds and Comp</td>
<td>Meds and Comp</td>
<td>Meds and Comp</td>
<td>Meds and Comp</td>
<td>Meds and Comp</td>
</tr>
<tr>
<td>Appetite</td>
<td>Nothings cheered you up</td>
<td>Total # Meds</td>
<td>Total # Meds</td>
<td>Total # Meds</td>
<td>Total # Meds</td>
<td>Total # Meds</td>
</tr>
<tr>
<td>Meds and Comp</td>
<td>Everything was an effort</td>
<td>Anti-psychotic</td>
<td>Anti-psychotic</td>
<td>Anti-psychotic</td>
<td>Anti-psychotic</td>
<td>Anti-psychotic</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Screening</td>
<td>Illicit Drug Use</td>
<td>Bupropion</td>
<td>Trazodone</td>
<td>Antipsychotic</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Sertraline Strict Comp</td>
<td>Appetite</td>
<td>Meds and Comp</td>
<td>Total # Meds</td>
<td>TCA</td>
<td>Benzodiazepine</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td><strong>Meds and Comp</strong></td>
<td><strong>Illicit Drug Use</strong></td>
<td><strong>Meds and Comp</strong></td>
<td><strong>Total # Meds</strong></td>
<td><strong>TCA</strong></td>
<td><strong>Benzodiazepine</strong></td>
<td><strong>Benzodiazepine</strong></td>
</tr>
<tr>
<td><strong>Appetite</strong></td>
<td><strong>TCA</strong></td>
<td><strong>Anti-Convulsant</strong></td>
<td><strong>Citalopram Strict Comp</strong></td>
<td><strong>Citalopram</strong></td>
<td><strong>Fluoxetine</strong></td>
<td><strong>Fluoxetine</strong></td>
</tr>
</tbody>
</table>

Comp=Compliance
Symptom Cluster Associations

The logistic regression analysis found that when controlling for demographics, past medical history, current mental health treatments and medications, and medication compliance, an increase in the anxiety score led to significantly increased odds that fluoxetine would be ineffective at treating sadness, an increase in the fatigue score led to significantly increased odds that sertraline would be ineffective at treating sadness, an increase in the mood score led to significantly increased odds that paroxetine and venlafaxine would be ineffective at treating sadness (see Table 6). The efficacy of bupropion in treating sadness was not associated with the presence or severity of any clinical symptoms. Regression results for trazodone were excluded due to a small sample size.

Table 6

Multivariable Logistic Regression Results

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Score</td>
<td>2.117</td>
<td>0.994</td>
<td>4.507</td>
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<tr>
<td>Anxiety Score</td>
<td>4.014</td>
<td>1.527</td>
<td>10.554</td>
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<tr>
<td>Fatigue Score</td>
<td>1.893</td>
<td>0.232</td>
<td>15.442</td>
</tr>
<tr>
<td>Appetite Score</td>
<td>1.138</td>
<td>0.171</td>
<td>7.557</td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mood Score</td>
<td>0.514</td>
<td>0.164</td>
<td>1.606</td>
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<tr>
<td>Fatigue Score</td>
<td>30.957</td>
<td>1.914</td>
<td>500.723</td>
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<td>Insomnia Score</td>
<td>0.944</td>
<td>0.166</td>
<td>5.382</td>
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<td>Appetite Score</td>
<td>7.102</td>
<td>0.904</td>
<td>55.766</td>
</tr>
<tr>
<td>Citalopram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Score</td>
<td>1.733</td>
<td>0.849</td>
<td>3.540</td>
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<tr>
<td>Appetite Score</td>
<td>0.256</td>
<td>0.037</td>
<td>1.781</td>
</tr>
<tr>
<td>Paroxetine</td>
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<td></td>
</tr>
<tr>
<td>Mood Score</td>
<td>2.831</td>
<td>1.017</td>
<td>7.879</td>
</tr>
<tr>
<td>Anxiety Score</td>
<td>2.021</td>
<td>0.286</td>
<td>14.296</td>
</tr>
<tr>
<td>Fatigue Score</td>
<td>0.891</td>
<td>0.336</td>
<td>2.362</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Score</td>
<td>1.876</td>
<td>1.041</td>
<td>3.379</td>
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<tr>
<td>Insomnia Score</td>
<td>2.463</td>
<td>0.522</td>
<td>11.621</td>
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<tr>
<td>Appetite Score</td>
<td>2.435</td>
<td>0.400</td>
<td>14.841</td>
</tr>
</tbody>
</table>

OR=Odds Ratio
Statistically significant values are bolded.
Model Creation

**Principal component analysis.** Fluoxetine, sertraline, citalopram, paroxetine, venlafaxine, bupropion, and trazodone had eight, six, seven, four, six, five, and five principal components (PCs), respectively (see Tables 7a-7g).
Table 7a

Principal Component Loadings for Fluoxetine

<table>
<thead>
<tr>
<th>Demographics</th>
<th>PC1</th>
<th>PC2</th>
<th>PC3</th>
<th>PC4</th>
<th>PC5</th>
<th>PC6</th>
<th>PC7</th>
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</thead>
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<tr>
<td>Sex</td>
<td>0.020</td>
<td>0.457</td>
<td>0.148</td>
<td>0.158</td>
<td>0.181</td>
<td>0.149</td>
<td>-0.373</td>
<td>-0.571</td>
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<tr>
<td>Lifetime MH Dx</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bipolar 2</td>
<td>-0.398</td>
<td>0.403</td>
<td>-0.438</td>
<td>0.095</td>
<td>-0.366</td>
<td>-0.167</td>
<td>-0.258</td>
<td>0.237</td>
</tr>
<tr>
<td>Bipolar Subthreshold</td>
<td>0.153</td>
<td>-0.092</td>
<td>-0.312</td>
<td>0.242</td>
<td>-0.225</td>
<td>0.482</td>
<td>0.599</td>
<td>-0.012</td>
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<tr>
<td>PA</td>
<td>-0.401</td>
<td>0.292</td>
<td>-0.221</td>
<td>0.002</td>
<td>0.187</td>
<td>0.304</td>
<td>0.095</td>
<td>0.078</td>
</tr>
<tr>
<td>Adult Separation Anxiety</td>
<td>-0.046</td>
<td>0.356</td>
<td>0.282</td>
<td>-0.363</td>
<td>-0.023</td>
<td>0.627</td>
<td>-0.136</td>
<td>0.092</td>
</tr>
<tr>
<td>Agoraphobia without PA</td>
<td>-0.499</td>
<td>0.489</td>
<td>-0.219</td>
<td>0.332</td>
<td>0.094</td>
<td>0.073</td>
<td>-0.187</td>
<td>0.388</td>
</tr>
<tr>
<td>Binge Eating</td>
<td>-0.023</td>
<td>0.276</td>
<td>0.627</td>
<td>0.332</td>
<td>-0.369</td>
<td>0.144</td>
<td>-0.061</td>
<td>0.162</td>
</tr>
<tr>
<td>Bulimia</td>
<td>-0.063</td>
<td>0.091</td>
<td>0.656</td>
<td>0.340</td>
<td>-0.354</td>
<td>-0.163</td>
<td>0.229</td>
<td>0.013</td>
</tr>
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<td>Txt and Substances</td>
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</tr>
<tr>
<td>Ever Hospitalized</td>
<td>-0.084</td>
<td>0.158</td>
<td>0.095</td>
<td>-0.719</td>
<td>0.046</td>
<td>0.105</td>
<td>0.223</td>
<td>0.096</td>
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<tr>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hopeless</td>
<td>0.793</td>
<td>0.123</td>
<td>-0.113</td>
<td>-0.081</td>
<td>0.010</td>
<td>0.133</td>
<td>-0.070</td>
<td>-0.008</td>
</tr>
<tr>
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<td>-0.086</td>
<td>0.016</td>
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<td>0.046</td>
<td>-0.179</td>
<td>0.321</td>
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<td>-0.214</td>
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<td>-0.108</td>
<td>-0.049</td>
<td>-0.191</td>
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<td>Nothing calmed you</td>
<td>0.631</td>
<td>0.053</td>
<td>0.106</td>
<td>0.379</td>
<td>0.312</td>
<td>0.277</td>
<td>-0.073</td>
<td>-0.163</td>
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<tr>
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<td>0.503</td>
<td>-0.186</td>
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<td>-0.271</td>
<td>0.108</td>
<td>0.179</td>
<td>0.080</td>
</tr>
<tr>
<td>Nothing cheered you up</td>
<td>0.584</td>
<td>0.493</td>
<td>-0.168</td>
<td>0.132</td>
<td>-0.075</td>
<td>-0.310</td>
<td>0.120</td>
<td>0.022</td>
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<tr>
<td>Everything was an effort</td>
<td>0.652</td>
<td>0.256</td>
<td>0.164</td>
<td>-0.087</td>
<td>0.273</td>
<td>-0.277</td>
<td>0.054</td>
<td>0.201</td>
</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.520</td>
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<td>0.272</td>
<td>-0.050</td>
<td>0.160</td>
<td>0.064</td>
<td>-0.122</td>
<td>0.449</td>
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<td>Appetite</td>
<td>0.365</td>
<td>-0.398</td>
<td>-0.194</td>
<td>0.433</td>
<td>0.049</td>
<td>0.066</td>
<td>0.093</td>
<td>-0.004</td>
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<td>0.439</td>
<td>-0.102</td>
</tr>
<tr>
<td>Citalopram</td>
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<td>0.213</td>
<td>-0.007</td>
<td>0.338</td>
<td>0.697</td>
<td>-0.008</td>
<td>0.183</td>
<td>0.144</td>
</tr>
</tbody>
</table>

The variables with the largest loadings into each of the principal components are shown in bold.
Table 7b

*Principal Component Loadings for Sertraline*

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<tr>
<th></th>
<th>PC1</th>
<th>PC2</th>
<th>PC3</th>
<th>PC4</th>
<th>PC5</th>
<th>PC6</th>
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<tbody>
<tr>
<td>Demographics</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.267</td>
<td>-0.579</td>
<td>0.145</td>
<td>0.265</td>
<td>-0.098</td>
<td>-0.081</td>
</tr>
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<td>Income to Needs</td>
<td>0.445</td>
<td>-0.088</td>
<td>0.255</td>
<td>-0.104</td>
<td>0.000</td>
<td>0.220</td>
</tr>
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<td>Marital status</td>
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<td>-0.441</td>
<td>0.221</td>
<td>-0.058</td>
<td>-0.146</td>
</tr>
<tr>
<td>Lifetime MH Dx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Subthreshold</td>
<td>-0.160</td>
<td>0.178</td>
<td>0.775</td>
<td>-0.036</td>
<td>0.200</td>
<td>0.169</td>
</tr>
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<td>Hypomania</td>
<td>0.030</td>
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<td>0.659</td>
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<td>GAD</td>
<td>-0.088</td>
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<td>Hopeless</td>
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<td>0.004</td>
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<td>0.428</td>
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<td>0.119</td>
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<td>0.752</td>
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<td>-0.030</td>
<td>-0.130</td>
<td>-0.068</td>
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<td>Screening Survey</td>
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<tr>
<td>Insomnia</td>
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<td>0.045</td>
<td>-0.183</td>
<td>-0.323</td>
<td>0.267</td>
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<tr>
<td>Appetite</td>
<td>0.309</td>
<td>0.420</td>
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<td>0.195</td>
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</table>

The variables with the largest loadings into each of the principal components are shown in bold.
Table 7c

Principal Component Loadings for Citalopram

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<td>Income to Needs</td>
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<td>0.067</td>
<td>0.093</td>
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<td>0.053</td>
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<td><strong>Overall Health Status</strong></td>
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<tr>
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<td>0.201</td>
<td>-0.061</td>
<td>-0.070</td>
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<tr>
<td>Phys Dx (Y/N)</td>
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<td>0.410</td>
<td>-0.246</td>
<td>0.175</td>
<td>-0.200</td>
<td>-0.295</td>
<td>0.283</td>
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<td>Dysthymia</td>
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<td>PD</td>
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<td>PTSD</td>
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<td>0.164</td>
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<td>0.073</td>
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<tr>
<td>Binge Eating</td>
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<td>-0.133</td>
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<td>-0.360</td>
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<tr>
<td>Worthless</td>
<td>0.711</td>
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<td>Restless</td>
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<td>0.661</td>
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<td>0.092</td>
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<td>Nothing cheered you up</td>
<td>0.642</td>
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<td>0.330</td>
<td>0.348</td>
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<td>-0.175</td>
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<td>Everything was an effort</td>
<td>0.670</td>
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<td>-0.011</td>
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<td><strong>Screening Survey</strong></td>
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<td></td>
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<tr>
<td>Appetite</td>
<td>0.408</td>
<td>0.626</td>
<td>0.272</td>
<td>-0.177</td>
<td>-0.270</td>
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<tr>
<td><strong>Txt and Substances</strong></td>
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<tr>
<td>Illicit Drug Use</td>
<td>-0.223</td>
<td>-0.380</td>
<td>0.480</td>
<td>0.068</td>
<td>-0.318</td>
<td>-0.302</td>
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<tr>
<td>Anti-Convulsant</td>
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<td>0.144</td>
<td>0.095</td>
<td>0.624</td>
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</table>

The variables with the largest loadings into each of the principal components are shown in bold.
### Table 7d

**Principal Component Loadings for Paroxetine**

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<tr>
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</tr>
<tr>
<td>Age</td>
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<td><strong>Lifetime MH Dx</strong></td>
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<tr>
<td>Bipolar Subthreshold</td>
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<td>MDD</td>
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<tr>
<td>Drug Dependence</td>
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<tr>
<td><strong>K10 Survey</strong></td>
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<tr>
<td>Hopeless</td>
<td>0.737</td>
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<td>Fidgety</td>
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<td>Tired</td>
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<tr>
<td>Everything was an effort</td>
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<td>-0.203</td>
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<td>-0.011</td>
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<tr>
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<tr>
<td>Anxiety</td>
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<td>0.049</td>
<td>0.331</td>
<td>0.565</td>
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<td><strong>Medications</strong></td>
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<td>Total # meds</td>
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<td>Anti-Psychotic</td>
<td>-0.119</td>
<td>0.903</td>
<td>-0.058</td>
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</table>

The variables with the largest loadings into each of the principal components are shown in bold.

### Table 7e

**Principal Component Loadings for Venlafaxine**

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<th>PC1</th>
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<td>0.763</td>
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<td>-0.380</td>
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<td>-0.118</td>
</tr>
<tr>
<td><strong>Lifetime MH Dx</strong></td>
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<tr>
<td>PTSD</td>
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<td>0.303</td>
<td>0.361</td>
<td>-0.181</td>
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<td>Adult Separation</td>
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<td>0.846</td>
<td>-0.370</td>
<td>0.026</td>
<td>0.119</td>
</tr>
<tr>
<td><strong>Txt and Substances</strong></td>
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<td></td>
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<tr>
<td>Illicit Drug Use</td>
<td>0.284</td>
<td>-0.366</td>
<td>0.237</td>
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<td>0.026</td>
<td>0.202</td>
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<tr>
<td>Hopeless</td>
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<td>0.086</td>
<td>0.268</td>
<td>-0.087</td>
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<tr>
<td>Worthless</td>
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<td>0.152</td>
<td>0.162</td>
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<td>-0.069</td>
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<tr>
<td>Depressed</td>
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<td>0.085</td>
<td>-0.088</td>
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<tr>
<td>Insomnia</td>
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<td>-0.147</td>
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</table>

The variables with the largest loadings into each of the principal components are shown in bold.
Table 7f

**Principal Component Loadings for Bupropion**

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<tr>
<td>Income to Needs</td>
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<tr>
<td>Dysthymia</td>
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<td>0.448</td>
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The variables with the largest loadings into each of the principal components are shown in bold.

Table 7g

**Principal Component Loadings for Trazodone**

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<td>Income to Needs</td>
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</tr>
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<td>Bipolar Subthreshold</td>
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<td>Adult Separation Anxiety</td>
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<td>Alcohol Dependence</td>
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<tr>
<td>Alcohol Abuse</td>
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<td>0.134</td>
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<tr>
<td>Drug Dependence</td>
<td>0.580</td>
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<td>0.333</td>
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</tr>
<tr>
<td>Drug Abuse</td>
<td>0.832</td>
<td>0.463</td>
<td>0.134</td>
<td>0.048</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>K10 Survey</strong></td>
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<tr>
<td>Depressed</td>
<td>-0.346</td>
<td>0.486</td>
<td>0.491</td>
<td>0.283</td>
<td>-0.401</td>
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<td><strong>Screening Survey</strong></td>
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<tr>
<td>Appetite</td>
<td>-0.672</td>
<td>0.310</td>
<td>0.258</td>
<td>0.026</td>
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<tr>
<td><strong>Txt and Substances</strong></td>
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<tr>
<td>Illicit Drug Use</td>
<td>0.539</td>
<td>0.283</td>
<td>-0.384</td>
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<td><strong>Medications</strong></td>
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<tr>
<td>Total # Meds</td>
<td>0.610</td>
<td>-0.599</td>
<td>0.362</td>
<td>0.130</td>
<td>-0.059</td>
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<tr>
<td>Anti-Psychotic</td>
<td>0.488</td>
<td>-0.543</td>
<td>0.513</td>
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<tr>
<td>Benzodiazepines</td>
<td>0.429</td>
<td>-0.503</td>
<td>0.099</td>
<td>0.681</td>
<td>-0.014</td>
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<td>NBH</td>
<td>0.201</td>
<td>-0.165</td>
<td>0.764</td>
<td>-0.362</td>
<td>0.110</td>
</tr>
</tbody>
</table>

The variables with the largest loadings into each of the principal components are shown in bold.

**Multivariable logistic regression.** A multivariable logistic regression using the PCs as the independent variable and effectiveness of the drug at treating sadness as the dependent variable found coefficients to be significant for three out of the eight PCs for fluoxetine, three
out of the six PCs for sertraline, four out of the seven PCs for citalopram, four out of the four PCs for paroxetine, four out of the six PCs for venlafaxine, three out of five PCs for bupropion, and three out of the five PCs for trazodone (see Table 8).
### Multivariable Logistic Regression Results

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Confidence Interval</th>
<th>OR</th>
<th>Confidence Interval</th>
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<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td>Lower</td>
<td>Upper</td>
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<tr>
<td><strong>Fluoxetine</strong></td>
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</tr>
<tr>
<td>Intercept</td>
<td>0.138</td>
<td>-0.392</td>
<td>0.668</td>
<td>1.148</td>
</tr>
<tr>
<td>PC1</td>
<td>1.330*</td>
<td>0.804</td>
<td>1.855</td>
<td>3.780*</td>
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<tr>
<td>PC2</td>
<td>-0.276</td>
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<tr>
<td>PC3</td>
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<td>0.136*</td>
</tr>
<tr>
<td>PC4</td>
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<td>-2.386</td>
<td>-0.409</td>
<td>0.247*</td>
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<tr>
<td>PC5</td>
<td>0.378</td>
<td>-0.170</td>
<td>0.926</td>
<td>1.460</td>
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<tr>
<td>PC6</td>
<td>0.023</td>
<td>-0.286</td>
<td>0.331</td>
<td>1.023</td>
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<tr>
<td>PC7</td>
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<td>-0.651</td>
<td>0.262</td>
<td>0.823</td>
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<td>PC8</td>
<td>-0.302</td>
<td>-0.844</td>
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<tr>
<td><strong>Sertraline</strong></td>
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<tr>
<td>Intercept</td>
<td>0.658*</td>
<td>0.218</td>
<td>1.097</td>
<td>1.930*</td>
</tr>
<tr>
<td>PC1</td>
<td>0.983*</td>
<td>0.575</td>
<td>1.391</td>
<td>2.673*</td>
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<tr>
<td>PC2</td>
<td>-0.071</td>
<td>-0.399</td>
<td>0.258</td>
<td>0.932</td>
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<tr>
<td>PC3</td>
<td>0.433</td>
<td>-0.0001503</td>
<td>0.866</td>
<td>1.542</td>
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<tr>
<td>PC4</td>
<td>0.432</td>
<td>-0.204</td>
<td>1.069</td>
<td>1.541</td>
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<tr>
<td>PC5</td>
<td>-0.226</td>
<td>-0.596</td>
<td>0.144</td>
<td>0.798</td>
</tr>
<tr>
<td>PC6</td>
<td>1.083*</td>
<td>0.642</td>
<td>1.523</td>
<td>2.952*</td>
</tr>
<tr>
<td><strong>Citalopram</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-1.105</td>
<td>-2.317</td>
<td>0.107</td>
<td>0.331</td>
</tr>
<tr>
<td>PC1</td>
<td>1.920*</td>
<td>0.904</td>
<td>2.937</td>
<td>6.822*</td>
</tr>
<tr>
<td>PC2</td>
<td>-0.287</td>
<td>-0.993</td>
<td>0.418</td>
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<tr>
<td>PC3</td>
<td>0.170</td>
<td>-0.683</td>
<td>1.023</td>
<td>1.185</td>
</tr>
<tr>
<td>PC4</td>
<td>-0.799*</td>
<td>-1.295</td>
<td>-0.304</td>
<td>0.450*</td>
</tr>
<tr>
<td>PC5</td>
<td>0.889*</td>
<td>0.036</td>
<td>1.741</td>
<td>2.432*</td>
</tr>
<tr>
<td>PC6</td>
<td>1.415*</td>
<td>0.191</td>
<td>2.639</td>
<td>4.117*</td>
</tr>
<tr>
<td>PC7</td>
<td>1.362</td>
<td>-0.329</td>
<td>3.053</td>
<td>3.904</td>
</tr>
<tr>
<td><strong>Paroxetine</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.465</td>
<td>-1.013</td>
<td>0.083</td>
<td>0.628</td>
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<tr>
<td>PC1</td>
<td>3.164*</td>
<td>1.819</td>
<td>4.508</td>
<td>23.662*</td>
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<tr>
<td>PC2</td>
<td>-0.777*</td>
<td>-1.536</td>
<td>-0.017</td>
<td>0.460*</td>
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<tr>
<td>PC3</td>
<td>1.127*</td>
<td>0.632</td>
<td>1.623</td>
<td>3.088*</td>
</tr>
<tr>
<td>PC4</td>
<td>-1.270*</td>
<td>-1.871</td>
<td>-0.668</td>
<td>0.281*</td>
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<tr>
<td><strong>Venlafaxine</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.945*</td>
<td>-1.224</td>
<td>-0.665</td>
<td>0.389</td>
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<tr>
<td>PC1</td>
<td>-1.182</td>
<td>-2.800</td>
<td>0.436</td>
<td>0.307</td>
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<tr>
<td>PC2</td>
<td>1.978*</td>
<td>0.407</td>
<td>3.549</td>
<td>7.230*</td>
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<tr>
<td>PC3</td>
<td>-4.291*</td>
<td>-6.857</td>
<td>-1.725</td>
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<td>PC4</td>
<td>2.981</td>
<td>-0.370</td>
<td>6.332</td>
<td>19.704</td>
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<tr>
<td>PC5</td>
<td>-0.952*</td>
<td>-1.152</td>
<td>-0.752</td>
<td>0.386*</td>
</tr>
<tr>
<td>PC6</td>
<td>-0.023</td>
<td>-0.240</td>
<td>0.194</td>
<td>0.978</td>
</tr>
<tr>
<td><strong>Bupropion</strong></td>
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<tr>
<td>Intercept</td>
<td>-0.264</td>
<td>-1.334</td>
<td>0.806</td>
<td>0.768</td>
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<tr>
<td>PC1</td>
<td>3.492*</td>
<td>2.453</td>
<td>4.532</td>
<td>32.866*</td>
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<tr>
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<td>-2.697</td>
<td>-1.197</td>
<td>0.143*</td>
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<td>PC3</td>
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<td>-2.603</td>
<td>-1.497</td>
<td>0.129*</td>
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<tr>
<td>PC5</td>
<td>0.823</td>
<td>-0.670</td>
<td>2.316</td>
<td>2.277</td>
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<tr>
<td><strong>Trazodone</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>4.096*</td>
<td>0.837</td>
<td>7.354</td>
<td>60.077*</td>
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<tr>
<td>PC1</td>
<td>-7.201*</td>
<td>-7.554</td>
<td>-6.848</td>
<td>0.001*</td>
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<tr>
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<td>2.504</td>
<td>4.952</td>
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<tr>
<td>PC3</td>
<td>2.142*</td>
<td>0.729</td>
<td>3.555</td>
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<td>-2.603</td>
<td>5.329</td>
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<tr>
<td>PC5</td>
<td>2.752</td>
<td>-1.622</td>
<td>7.125</td>
<td>15.667</td>
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</table>

OR = Odds Ratio; * = result is statistically significant (p<0.05)
Prediction of individual response to second-generation antidepressants. The coefficients in Table 8 were used to create predictions of the efficacy in treating sadness for each of the seven drugs in two example patients (see Figure 3). Patient A is a young female with moderate depression and very few socioeconomic risk factors, and patient B is a middle-aged female with moderate to severe depression and many socioeconomic risk factors.

In patient A, the model predicts that sertraline has the greatest odds of being effective, although these odds are still less than one. In patient B, the model predicts that venlafaxine has the greatest odds of being effective, with an odds ratio of 2.3.

Model accuracy and validity. In the training cohort, accuracy ranged from 77.4% to 99.7%, with a mean of 84% (see Table 9). In the testing cohort, internal validity ranged from 58.2% to 66.6%, with a mean of 62% (see Table 9).
Table 9

**Accuracy and Internal Validity of Predicted Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Training Cohort</th>
<th>Testing Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>80.1%</td>
<td>58.2%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>77.4%</td>
<td>60.8%</td>
</tr>
<tr>
<td>Citalopram</td>
<td>83.7%</td>
<td>62.2%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>84.4%</td>
<td>63.0%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>73.8%</td>
<td>58.8%</td>
</tr>
<tr>
<td>Bupropion</td>
<td>85.5%</td>
<td>65.2%</td>
</tr>
<tr>
<td>Trazodone</td>
<td>99.7%</td>
<td>66.6%</td>
</tr>
</tbody>
</table>

Accuracy is defined using the training cohort. Internal validity is defined using the testing cohort.

**Discussion**

The purpose of this study was twofold: 1) to explore how symptom clusters impact the efficacy of second-generation antidepressants in treating sadness, and 2) to create a model that uses demographic and clinical characteristics of depression to predict the efficacy of different second-generation antidepressants in treating sadness.

**Symptom Cluster Associations**

Sadness is often the primary symptom that characterizes depression, and there are also many secondary symptoms associated with depression, such as anxiety, fatigue, appetite changes, and sleep changes. Few studies have been conducted to see whether the presence or severity of these secondary symptoms impact a drug’s efficacy at treating sadness. This study found that when controlling for demographics, current mental health treatment and medications, past medical history, and medication compliance, fluoxetine would be less effective if the sadness is accompanied by high levels of anxiety, sertraline would be less effective if the sadness is accompanied by high levels of fatigue, and paroxetine and venlafaxine would be less effective when the sadness is accompanied by other symptoms of a low mood. Physicians can use these broad generalizations to help choose antidepressants when treating sadness.
Individual Predictions of Drug Effectiveness

While the symptom clusters can be used as a generic approach to prescribing second-generation antidepressants, a patient’s specific demographic and clinical information can be plugged into the model for a more individualized approach. Inputting a patient’s data into the model will show the odds of each drug being effective at treating sadness. These odds ratios can then be compared to each other to determine which specific drug has the greatest chance of being effective in a particular patient. The models created have a mean accuracy of 84% and a mean internal validity of 62%. Notably, these results are similar to a study that used machine learning and available clinical information, such as demographic characteristics and clinical symptoms, to predict treatment response to citalopram. In that study, Chekroud et al. (2016) created a model with a 64.6% accuracy at predicting the efficacy of citalopram, and this same model was then externally validated using escitalopram data from a separate study, achieving an external validity of 59.6%.

Public Health Implications

Depression poses a high disease burden on society in terms of personal impacts, economic impacts, and social impacts (Thomas & Morris, 2003). Antidepressants are the mainstay of treatment for depression, and the use of second-generation antidepressants such as SSRIs, SNRIs, bupropion, and trazodone are on the rise. Currently, choosing between second-generation antidepressants is mostly trial-and-error, so finding a more efficient and effective use of these antidepressants can have significant public health benefits.

Morbidity and mortality. Depression can lead to substantial morbidity and mortality. The indirect costs from decreased productivity and increased morbidity account for 70-80% of the total cost of depression (Hawthorne, Cheok, Goldney, & Fisher, 2003). Less than one-half of
people obtain full remission from depression after their first adequate trial of antidepressants. Ineffective treatment is associated with continued symptoms, higher rates of relapse and recurrence, increased hospitalizations, increased suicide risk, and impaired productivity (Sonawalla & Fava, 2001), all of which increase morbidity of the disease. In addition, approximately one-third of all patients with treatment-resistant depression attempt suicide at least once, increasing the mortality associated with depression (Hantouche et al., 2010). A more effective way of choosing antidepressants has the potential to decrease the time it takes for a patient to achieve remission. This would decrease overall prevalence of depression, as well as the morbidity and mortality associated with the disease.

**Cost-effectiveness.**

**Cost.** Demographic characteristics and clinical symptoms are readily accessible information, so the cost of obtaining and utilizing this information is minimal. This is in sharp contrast to pharmacogenomics (i.e., the use of genetic data to guide treatment decisions), which has been increasingly used as a way to individualize and optimize the choice of a second-generation antidepressant (Rosenblat et al., 2018). Pharmacogenomics requires obtaining a DNA sample from a patient and then having this sample processed in a lab. This costs roughly $2,000 (Maciel, Cullors, Lukowiak, & Garces, 2018). Although patients with insurance often do not pay the full $2,000, the remaining cost of this lab work is simply passed onto society.

**Efficacy.** Currently, fewer than 50% of people respond to their first treatment of antidepressants. Individualized treatment has the potential to increase this percentage. A meta-analysis of four RCTs and two open-label controlled cohort studies found preliminary evidence that pharmacogenomics can improve response and remission rates to antidepressants (Rosenblat et al., 2018). The company with the largest remission rate was CNSDose with a 72% remission
rate. However, most of the studies in this meta-analysis were not blinded, and some of the observed effect could be due to placebo effect from patients knowing they are getting treatment tailored specifically to them. Our model, which has a mean accuracy of 84% and an internal validity of 62% also has the potential of improving the response to antidepressants.

**Accessibility.** GeneSight is a commonly used pharmacogenetic company. While there is no copay for GeneSight in patients with traditional Medicare or Medicaid, a patient with private insurance can expect a copay of around $330 (GeneSight, 2019). Those without insurance can expect to pay more. This cost can be a significant barrier to access to individualized treatment. In contrast, using a model that combines demographic and clinical characteristics would not have cost as a barrier to access. In addition, pharmacogenomics requires special equipment and laboratories, both of which might not be available in rural areas. In contrast, demographic and clinical characteristics are readily accessible to all providers.

**Strengths and Limitations**

A strength of this study is that the data comes from a sample that is representative of the entire United States population. Many RCTs have strict inclusion and exclusion criteria, making it difficult to generalize the results to the general population. However, while our model should theoretically be applicable to the general United States population, external validity using a separate dataset was not tested to verify this claim. In addition, the CPES data was collected from 2001 to 2003, so many of the newer drugs, such as escitalopram and duloxetine, were not included in this study.

Effectiveness in this study was self-reported, and patients were asked to rate the perceived effectiveness of the drug in treating sadness on a Likert scale. The responses were subsequently dichotomized into two groups: effective and ineffective. Because most other
studies use decreases in HAM-D and other surveys as their outcome measure, it is difficult to compare our results to those of other studies.

Future studies should be conducted to include the newer drugs, use a validated survey as an outcome measure, and directly compare the efficacy of using demographic and clinical characteristics to pharmacogenetics and current standard of care.

**Conclusion**

Depression is the sixth most costly health condition in the United States, and treatment-resistant depression contributes significantly to this cost. As such, choosing effective starting antidepressants has the potential to decrease the overall cost of depression to society by 10%. While current guidelines for choosing antidepressants is mostly trial-and-error, there have been some attempts at individualizing this treatment using pharmacogenomics to help guide antidepressant choice. However, this process is expensive and not readily accessible to all. This study attempted to find symptom clusters that can help guide antidepressant choice, in addition to creating a model that could predict efficacy of second-generation antidepressants using demographic and clinical characteristics, information that is readily accessible and inexpensive. One model was created for each of the seven second-generation antidepressants studied. Together, these models had a mean accuracy of 84% and an internal validity of 62%. Given that fewer than 50% of individuals respond to their first adequate trial of antidepressants and those who fail their first antidepressant contribute significantly to the overall disease burden of depression, our models have the potential to decrease the overall morbidity, mortality, and economic costs depression poses on society.
References


doi:10.1016/j.psychres


doi:10.1111/j.1440-1819.2007.01679.x


doi:10.1016/j.jad.2006.02.010


Chart 1: Is an Activity Research Involving Human Subjects Covered by 45 CFR part 46?

February 16, 2016

Activity is research. Does the research involve human subjects?

Is the activity a systematic investigation designed to develop or contribute to generalizable knowledge? [45 CFR 46.102(d)]

Activity is research involving human subjects. Is it covered by the regulations?

Does the research involve obtaining information about living individuals? [45 CFR 46.102(f)]

The research is not research involving human subjects, and 45 CFR part 46 does not apply.

The research involving human subjects is covered by the regulations.

Is it conducted or supported by HHS? [45 CFR 46.101(a)(1)]

Is the information individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information)? [45 CFR 46.102(f)(2)]

The research involving human subjects is NOT covered by the regulations.

Does the institution hold an FWA under which it applies 45 CFR 46 to all of its human subjects research regardless of the source of support?

Unless exempt under 45 CFR 46.101(b), 45 CFR part 46, subpart A applies to the research, and as appropriate subparts B, C, and D also apply.

Go to Chart 2

Other Federal, State and local laws and/or regulations may apply to the activity. [45 CFR 46.101(f)]
Appendix B: List of Competencies Met in Integrative Learning Experience

CEPH Foundational Competencies

<table>
<thead>
<tr>
<th>Evidence-based Approaches to Public Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Apply epidemiological methods to the breadth of settings and situations in public health practice</td>
</tr>
<tr>
<td>2. Select quantitative and qualitative data collection methods appropriate for a given public health context</td>
</tr>
<tr>
<td>3. Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software, as appropriate</td>
</tr>
<tr>
<td>4. Interpret results of data analysis for public health research, policy or practice</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Planning &amp; Management to Promote Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Assess population needs, assets and capacities that affect communities’ health</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>19. Communicate audience-appropriate public health content, both in writing and through oral presentation</td>
</tr>
</tbody>
</table>

WSU MPH Population Health Concentration Competencies

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Use evidence based problem solving in the context of a particular population health challenge.</td>
</tr>
<tr>
<td>2. Demonstrate application of an advanced quantitative or qualitative research methodology.</td>
</tr>
<tr>
<td>3. Demonstrate the ability to contextualize and integrate knowledge of specific population health issues.</td>
</tr>
</tbody>
</table>