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Citalopram is less effective for patients with neurological disorder and/or post-traumatic stress disorder

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ABSTRACT

Importance: Citalopram is a common antidepressant widely used and STAR*D study has indicated that most, more than 60%, of patients who receive it, do not benefit from their first antidepressant.
Objective: To identify whether citalopram is effective for patients with particular medical history.
Design: We used stratification to balance case/control study design.
Setting: We used the National Institute of Mental Health's STAR*D data, collected from 41 specialty and primary medical care settings spanning across a seven year time period.
Participants: The data included .mental and physical diagnoses of 4041 patients with major depression.
Intervention(s) (for clinical trials) or exposure(s) (for observational studies): Patients comorbidities were balanced using Stratified Covariate Balancing method. This algorithm uses Markov Blanket of both treatment and outcome to identify which comorbidities can be ignored. It uses stratification to remove confounding introduced by the covariates in the Markov Blanket of treatment and outcome.
Main outcome(s) and measure(s): A patient's remission was judged by weather there was a 50% reduction in the Hamilton Rating Scale for Depression.
Results: Patients exposed to neurological disorders were less likely to experience remission than controls without neurological disorder (odds = 0.74, chi-square=, alpha < 0.05). For exposure to PTSD, we stratified psychiatric illness in the Markov Blanket of PTSD and Neurological disorders in the Markov Blanket of Remission. The un-confounded odds of response for patients exposed to PTSD was 0.53 (Chi-square = 8.31, alpha < 0.05.)
Conclusions and relevance: Patients exposed to PTSD or neurological disorders were less likely to experience remission from depression. These data suggest that citalopram should not be a first line agent prescribed for patients with these disorders.

Background

More than 60% of depressed patients do not benefit from their first antidepressant [1–4], prompting some experts to argue that "the bar for antidepressants has been set far too low" [5]. To understand the magnitude of the problem, consider that of the 11% of Americans currently taking antidepressants [6,7], 25 million initially took an antidepressant that was not therapeutic. Months later, after repeated trials on antidepressants, more than 50% of the initial non-respondentseventually benefited from a different antidepressant [8]; indicating that these patients are not treatment resistant and more careful selection of an antidepressant could provide an earlier response. During the months of mistrial of antidepressants, patients continued to suffer from debilitating symptoms, many remained at risk of suicide and millions of dollars were spend on unnecessary medication [9]. Unfortunately, clinicians have limited guidance on which antidepressant might be the most effective for patients with different medical and psychiatric histories. Guidelines and previous studies have focused on the effectiveness of citalopram and not on characteristics of those who may or may not respond to this medication [10,11]. This paper provides clinicians with additional guidance on who would most likely respond to citalopram, a commonly prescribed antidepressant and one of the first selective serotonin re-uptake inhibitors.

The task of choosing an initial antidepressant is complex. Guidelines currently recommend basing the decision on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication, medication response in prior episodes, cost, and patient pref-

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erence [10]. While a great deal of information is available in numerous randomized clinical studies [11,12], these studies have excluded patients with major comorbidities, making it difficult to anticipate response to treatment for patients with comorbidities. A patient's race, gender, employment, education, and income have been shown to affect response to treatment [13]. Length of depression episode [14], cognition [22], and the presence of the following have also been shown to affect response to antidepressants: concurrent anxiety [15], substance use disorders [16,17], obesity [18], insomnia [19], cerebrovascular diseases [20,21], hormone imbalances [22–24], and post-traumatic stress disorder [25]. Many of these predictors do not have a consistent impact on response to treatment, making it more difficult for clinicians to decide among various treatment alternatives [26]. In addition, there are more than 24 types of antidepressants currently on the market [27], and many of them have several different brand names and can be prescribed in different dosages, further complicating the choice of the first antidepressant.

Attempts to improve the precision of antidepressant selection have had mixed results. Some studies have tried to use genetic markers to predict response with mixed success. One study found these markers work for patients with psychiatric disorders [28,29]. Another study found that genetic markers could accurately (78% correct) predict response in 2/3rd of cases but not all cases [30]. Others have tried to improve the precision of antidepressant selection by dividing depression into sub-types. One study identified 5 different symptom profiles predictive of response to antidepressants [31]. Unfortunately, these profiles did not map to patients' diagnoses (with the exception of melancholic depression), raising the possibility that these profiles were statistically significant but not clinically useful. In this paper, we examine if diagnoses from the Diagnostic and Statistical Manual of Mental Disorders can be used to predict response to antidepressants. Such an approach is advantageous because clinicians can readily implement the study findings into practice.

Methods

Study sample

We used the STAR*D database, the largest available data set capturing response to antidepressants. These data include genetic markers and phenotypes of 4,041 patients with major depression. Demographic data (gender, age, race), data from 13 disorders (cardiovascular, vascular, hematopoietic, eyes, gastrointestinal, renal, genitourinary, musculoskeletal, neurological, psychiatric, respiratory, liver, and endocrine diagnostic disorders), and verified depression comorbidities (Alcohol, Cannabis, Panic, Post-traumatic Stress, and Generalized Anxiety disorders) were examined in this study. Data were collected from 41 clinical sites around the country, which included both specialty care settings and primary medical care settings, over a seven year time period. The response to citalopram was measured using the Hamilton Rating Scale for Depression (HRSD). Patient remission was recognized as a 50% decrease in HRSD score from the start of the trial.

Method of analysis

In order to accurately predict the response to citalopram for patients having a particular diagnosis, the influence of patient comorbidities should be accounted for. Until recently statistical approaches to control for comorbidities were not available. In 1983, Rosenbaum and Rubin proposed the use of propensity scoring to balance rates of occurrence of covariates/comorbidities [32]. Since then, the approach has been revised and used widely [33–46]. We used Stratified Covariate Balancing, where the propensity weights are derived analytically without statistical modeling and through stratification [47]. All patients had received citalopram and were assigned to cases and controls based on exposure to specific disorders. Thus, in evaluating the impact of exposure to post-traumatic stress disorder (PTSD) on remission, we considered all patients with PTSD as cases, all patients without PTSD as controls, and all other comorbidities as covariates that should be balanced through stratification.

One limitation of using stratification to control for effect of comorbidities is that as the number of covariates increases, only a few cases fall within each stratum. A number of methods are available to restrict the stratification to a smaller number of covariates. One approach that has been shown to be theoretically sound is to restrict the analysis to the Markov Blanket of outcome [48,49]. We fit a Bayesian probability network to the data to identify the covariates that are in the Markov Blanket of remission and them identified a temporal sequence between any two diagnoses using age at which the patients reported the diagnosis to accurately fit the network. The use of temporal sequence among a pair of variables to improve accuracy of network modeling has been reported elsewhere [50]. Diagnoses that occur later were prohibited from affecting earlier events. The BNLearn software package in R version (3.31) was used to fit the network model. Once the Markov Blanket for both (a) the exposure variable and (b) remission variables were identified, these covariates were stratified and the un-confounded impact of exposure on remission reported.

Results

Table 1 shows the demographics and comorbidities of patients in our sample. To show how patients exposed to specific disorders have different comorbidities and demographics, Table 1 reports the data for exposure to PTSD and neurological disorders. Patients exposed to PTSD differed from patients not exposed to PTSD in nineteen covariates. Patients exposed to neurological disorders also differed from patients not exposed to neurological disorders in twenty covariates. These data show significant variations in demographics and comorbidities. The impact of exposure to either PTSD or to neurological disorders on response to citalopram cannot be estimated without statistically controlling for the listed comorbidities.

We calculated the average age at which each diagnoses occurs to understand what variables are in the Markov Blanket of exposure and outcome. Age, race, and gender are events that occur at birth. The outcome variable occurs at end of the data collection effort and therefore no disorders can occur after it. Fig. 1 provides the age at which various diagnoses are given. For example, at alpha levels less than 0.05, cannabis abuse (Average Age = 411.30 months, Standard Deviation = 130.73 months) occurs prior to heart disease (Average = 589.76 months, standard deviation = 157.49 months). Based on these data, we organized the diagnoses into 8 categories as follows:

Time 1: Age, Gender, Race

Time 2: Panic Disorder, Cannabis Abuse

Time 3: Neurological Disorder, General Anxiety Disorder, Psychiatric Illness, Alcohol Abuse

Time 4: Gastrointestinal Disorder, Respiratory Disease, Hematopoietic Disorder, Eyes/Ears/Nose/Throat/Larynx Disorder

Time 5: Musculoskeletal/Integument Disorder, Genitourinary Disorder, Renal Disease

Time 6: Heart Disease, Endocrine Disorder, Liver Disease, Post-Traumatic Stress Disorder

Time 7: Vascular Disease

Time 8: Response to Citalopram

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