Epidemiology of pharmaceutically treated depression and treatment resistant depression in Taiwan

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ABSTRACT

Epidemiological data on treatment resistant depression (TRD) in Asia-Pacific countries are limited. We estimated the incidence of TRD in Taiwan using a cohort of 704,265 adults randomly sampled from Taiwan's National Health Insurance Research database for 2005. TRD was defined as a patient having pharmaceutically treated depression (PTD) not adequately responding to 2 antidepressant (AD) regimens, i.e., AD regimens that were followed by other AD regimens. Among 2751 PTD subjects, 576 (20.94%, 95% CI: 19.46, 22.49) developed TRD, a proportion similar to that in North American studies. TRD incidence was 0.82 (95% CI: 0.75, 0.89) cases/1000 population in 2005, increased with age, and was higher in females than in males. SSRI's were the most frequently used ADs. Augmentation with antipsychotics was common. The median time from PTD onset (first AD medication) to TRD onset was 416 days but psychiatrists practicing in Taiwan indicated they would switch within < =3 months if an AD medication was not effective. We therefore repeated the analysis with a 6 months cap on time from onset of PTD to TRD. In this supplemental, post-hoc, analysis, 68 PTD subjects, 2.47%, (95% CI: 1.94, 3.10) developed TRD; i.e., 0.10 (95% CI: 0.08, 0.12) incident cases/1000 population.

1. Introduction

Major depressive disorder (MDD) is a chronic disabling condition associated with high morbidity and mortality. The 12-month prevalence of MDD was estimated as 8% in the US, 3–6% in various European countries, and 2% in Japan (Bromet, 2011) and depression is associated with multiple adverse outcomes including marital disruption, unstable employment, and early mortality (Kessler and Bromet, 2013). The personal and societal costs of a treatment resistant depression (TRD) case are typically higher than those of a treatment-responsive depression case (Mrazek, 2014; Olchanski, 2013). Recent estimates for the proportion of pharmaceutically treated depression (PTD) that develops into TRD range from 35% in a study limited to PTD subjects with MDD (Nemeroff, 2007) to 6.6% in a study that included a wider range of depressive diagnoses among the PTD subjects (Kubitz, 2013). A recent systematic review of the global prevalence of common mental disorders (Baxter, 2014) found age-standardized MDD prevalences in East Asia (3.8% of females, 2.3% of males) and in Asia Pacific (3.2% of females, 1.9% of males) substantially below the worldwide prevalence (5.5% of females, 3.3% of males). The reasons for this variability are unclear, but Chien in a study of Taiwan's health care data from 1996 through 2003 (Chien, 2007) estimated the annual incidence of MDD as approximately 2/1000 person-years, concluded that MDD was underdiagnosed and undertreated in Taiwan, and suggested as possible explanations the greater availability of consistent social support, low rate of broken families, low comorbidity rates, and the possibility that depression may manifest differently in Chinese culture, e.g., as neurasthenia or somatization. To
our knowledge there have been few, if any, population-based studies of TRD in Asia-Pacific populations. Thus, there is a need for more information on the epidemiology of TRD for public health purposes, and to inform the effort to develop better treatments.

The concept of TRD involves depression that fails to improve adequately with treatment with antidepressant (AD) medications at doses and durations that would normally be effective, administered to a patient believed to be adherent (European Medicines Agency, 2013). However, definitions differ regarding what treatments should be considered in counting failed treatments: AD medications only (European Medicines Agency, 2013), a wider class of medications including antipsychotics (Corey-Lisle, 2002; Kubitz, 2013), or a still wider range including hospitalization or electroconvulsive therapy (ECT) (Gibson, 2010). There are also differences regarding the number of failures required to define a patient as having TRD (Berlin and Turecki, 2007; Fava, 2003; Harald and Gordon, 2012), and whether the failed AD medications must come from different classes (Berlin and Turecki, 2007; European Medicines Agency, 2013; Ruhe, 2012). Two failures of AD medications, not necessarily from different classes is a standard supported by the data (Ruhe, 2012; Rush, 2006). It is widely used (European Medicines Agency, 2013; Kubitz, 2013), recognized by regulators (European Medicines Agency, 2013) and is the standard adopted in the present study. Because TRD is defined in terms of AD medication failures, TRD can only develop in depression that is pharmacologically treated. Guidelines for clinical trials (European Medicines Agency, 2013) and clinical trial protocols typically define TRD as a subset of MDD, and protocols typically set strict standards for the diagnosis of MDD. However, in clinical care, diagnostic labels may not be applied with this level of precision, and observational studies from health care databases have based their definition of TRD on PTI that comprised not only MDD, but also other types of depression including dysthymic disorder (Kubitz, 2013) and adjustment reaction with depressed mood (Gibson, 2010).

Studies of TRD typically interpret failure of an AD medication as failure during a clinical episode of depression (Fava, 2003; Fekadu, 2009; Harald and Gordon, 2012; McIntyre, 2014; Mrazek, 2014; Nemeroff, 2007; Zhou, 2014), and trials of medications for TRD typically enroll patients who are currently depressed although treated with one or more AD medications, i.e. such trials are focused on treatment resistance within a single clinical episode, and are conducted for a limited period of time. Thus, though it’s not always explicit, the definition of TRD focuses on failure to relieve depression during a clinical episode.

Household surveys (Bromet, 2011; Kessler, 2003; Pratt, 2014) and data from groups of care providers (Gaynes, 2007; Yates, 2004) provide substantial information on the epidemiology of depression. Retrospective tabulations from health care databases use different criteria for depression and report rates that typically differ from the household surveys, but have also been rich sources of information on the epidemiology, treatment, and costs of depression (Andrade, 2003; Chien, 2007; Fava, 2006; Onishi, 2013) and of TRD (Corey-Lisle, 2002; Crown, 2002; Greenberg, 2004; Ivanova, 2010; Kubitz, 2013; Olchanski, 2013). Such studies have typically used changes of AD medication regimens (augmentation, dose titration, switching, or addition of a new medication) as evidence of a regimen’s failure (Gibson, 2012; Greenberg, 2004; Harald and Gordon, 2012).

Because people who have had an episode of depression are at increased risk, psychiatrists may treat depressed patients prophylactically between episodes of clinical depression (Bondolfi, 2010; Kumar, 2003; Segal, 2010; Spanier, 1996). American Psychiatric Association (APA) practice guidelines for MDD recommend that patients who have been treated successfully with AD medications in the acute phase should continue treatment with the same medication and dosage for 4–9 months, and may require some form of maintenance therapy indefinitely (American Psychiatric Association, 2010). Though one retrospective database study used a period free of AD medication dispersions and outpatient depression diagnoses (Kubitz, 2013) as evidence that an episode has ended, most retrospective database studies cited above either followed the subjects to the end of the available data or for a fixed time period of up to 2 years. Except for a single retrospective database study that limited observation to a short fixed time period after the first AD medication was given, i.e., to a period when the subject was likely to be clinically depressed (Byford, 2011), none of the retrospective database studies cited above distinguished between the use of AD treatment for ongoing clinical depression versus prophylactic treatment after the clinical episode had ended (Corey-Lisle, 2002; Crown, 2002; Gibson, 2010; Russell, 2004). To the extent that this led to over-counting medication failures, these studies may have overestimated the proportion of episodes that became TRD.

2. Methods

The data for this study came from a random sample of approximately 1 million participants in Taiwan’s National Health Insurance program (NHIRD) for 2005, a large population-based claims database provided by the Taiwan National Health Research Institute. The claims are from the National Health Insurance program, implemented in March 1995 and providing mandatory universal health insurance for approximately 99% of the more than 23 million people residing in Taiwan. The NHIRD offers a comprehensive set of patient and clinical information on demographics, ICD-9 diagnostic codes, procedures, dispensed prescription drugs, and expenditures. All personally identifiable information is encrypted to protect patient privacy. The NHIRD has provided the data for many recently published peer-reviewed studies (Tsai, 2016; Wu, 2016; Yang, 2017; Yin, 2016). In the present study, AD medication dispensings with missing values for days’ supply were assigned 30 as the days’ supply. Analyses were done in SAS version 9.4 and Episheet (Rothman, Accessed April 20, 2016). Comparisons of incidence by sex or by age group were assessed for statistical significance based on a chi-square statistic applied to the number of subjects in each group.

Patients were eligible for inclusion in the PTD cohort if they were aged ≥18 in 2005, enrolled in the database continuously since January 1, 2004 (ignoring breaks of < 30 days), and, in the last 4 months of 2004, had not received an exclusion diagnosis, a diagnosis of depression, or a dispensing of an AD medication. These last conditions were imposed to assure the depression episodes were of new onset rather than ongoing, i.e., were incident rather than prevalent. The exclusion diagnoses and their respective ICD-9 codes were mania or bipolar disorder (296), schizophrenia (295), and dementia (290, 294). MDD with psychotic behavior was not an exclusion diagnosis. Subjects were included in the cohort at the onset of their first episode of PTD, i.e., when they were dispensed an AD medication within 30 days either before or after a diagnosis of depression. A diagnosis of depression was defined by an ICD-9 code of: 296.2 (MDD single episode), 296.3 (MDD recurrent episode), 300.4 (dysthymic disorder, depressive) or 311 (depressive disorder NOS). The subject’s index date for PTD was the date of that dispensing, and was required to fall in 2005. An episode ended when the subject had 120 days with no diagnosis of depression and no dispensing of an AD medication. Follow-up ended with the first of: Meeting an exclusion criterion, the end of the last episode that began in 2005, the end of the study period (December 31, 2013). No subject was allowed to enter the cohort more than once.

A regimen failed if, at least 15 days after it began, a regimen of a different AD medication was begun. The change could be a substitution or addition and need not be from a different class. The failure date of the earlier regimen was the date when the later regimen began, but the end date of the earlier regimen was not affected, i.e., the two regimens could overlap. An episode of PT and became an episode of TRD on the date (the TRD index date) when the second AD medication regimen failed but the episode also remained an episode of PT with its original index date. AD medication regimens were required to have ≥42 days’
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