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Research report

Prescription patterns following first-line new generation antidepressants for depression in Japan: A naturalistic cohort study based on a large claims database

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ABSTRACT

Background: Several studies have described real-world prescription patterns of first-line antidepressants for depression but little is known about their fate in terms of duration, intensity and changes.
Methods: An inception cohort of new onset non-psychotic depression initiating antidepressant treatment with a new generation antidpressive agent was identified in a large health insurance claims database in Japan between 2009 and 2010. The duration and intensity of first-line antidepressants, the timing and kind of second-line antidepressants and the total duration of antidepressant treatment were examined.
Results: We identified 1592 patients. The starting dose and the maximum dose attained with the first-line agent appeared to be largely in line with the guideline recommendations although the latter tended toward the minimum of the recommended range. The continuity of the first-line antidepressant was far below the guideline recommendations, with 28% never returning after the initial prescription and 55% dropping out within 3 months. Of all the first-line antidepressants, 14% were subsequently augmented by another psychotropic agent while 17% were switched to another antidepressant after a median of 3 or 2 months, respectively. The choice of the second-line agents varied extremely widely. The total duration of antidepressant therapy was as short as a median of 4 months, with 68% stopping treatment by 6 months.
Limitations: The diagnosis of non-psychotic unipolar depression in the claims database analyses remains approximate.
Conclusions: The current guidelines are grossly out of touch with the clinical realities. On the one hand, guidelines need to reflect the real-world practices; on the other hand clinicians should limit their treatment options and allow evidence-based comparative effectiveness research among them so that patients shall no longer be given less effective and more effective treatments without being able to distinguish among them.

1. Introduction

Current guidelines for treatment of major depression in adults unanimously list new generation antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenalin reuptake inhibitors (SNRIs) and other newer drugs, among first-line pharmacotherapeutic agents (Canadian Network for Mood and Anxiety Treatments in Canada (Lam et al., 2009), National Institute of Clinical Excellence in UK (NICE, 2009), American Psychiatric Association in USA (American Psychiatric Association, 2010), and Japanese Society of Mood Disorders in Japan (Japanese Society of Mood Disorders, 2012)).

They are less clear and more variable as to how long first-line agents should be tried before considering a treatment change, what second-line treatments should then be offered, and, once response is attained, how long antidepressant treatments should be continued. Guidelines list several second-line strategies in the face of non-response to the first-line agent, including dose increase of the initial agent, switch to a different antidepressant, and augmentation by another drug. But evidence suggesting superiority of any one of these strategies over the others or its appropriate timing is limited and weak (Furukawa et al., 2007; Ruhe et al., 2006a, 2006b). The length of continuation treatment to be recommended after remission is also variable: the APA guideline recommends "4–9 months" (American Psychiatric Association,

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2010) and the NICE guideline recommends "at least 6 months" (NICE, 2009), while the CANMAT guideline suggests benefit up to several years (Lam et al., 2009).

Clinical reality is much more diverse and dirty than clinical guidelines. The classes of antidepressants used as first-line agents among patients starting treatment for a new episode of depression appear to be new generation ones in many parts of the world. In USA a nationally representative survey of medical service utilization between 1996 and 2001 indicated that 75% of patients who initiated antidepressant treatment for depression started with selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenaline reuptake inhibitors (SNRIs) (Olfson et al., 2006), Medical and pharmacy claims database in more recent years also report similar figures (78% between 2001 and 2004 (Robinson et al., 2006), or 87% between 2001 and 2006 (Marcus et al., 2009)). In Europe a cohort study of consecutive patients commencing antidepressant treatment at over 400 primary and secondary care clinics indicated that across 12 countries, 63% started with SSRIs and 14% with SNRIs (Bauer et al., 2008). In Japan a survey of a health insurance claims database indicated that 84% of patients commencing treatment for their depression received new generation antidepressants (Onishi et al., submitted for publication).

Beyond this first-line choice, however, the clinical pictures remain mixed, obscure and remote from the pictures that the clinical guidelines draw. First, continuity of therapy appears to be far shorter than is recommended. The medical service utilization survey in USA, cited above, revealed that slightly less than half (42%) of the patients discontinued antidepressant therapy during the first 30 days, and nearly three quarters (72.4%) did so during the first 90 days (Olfson et al., 2006). Other surveys reveal similar pictures: Only 15% (Sewitch et al., 2007) to 31% (Sheehan et al., 2008) of patients starting treatment for a new episode of depression continued treatment for more than 6 months.

Second, information regarding choices of second-line antidepressant strategy in the real world remains scanty. A questionnaire survey of clinicians indicated that they would consider dose increase (55%), switching (32%) and augmenting with another agent (13%) for no to partial responders to the first-line treatment (Fredman et al., 2000). However, the clinicians' actual behaviors may or may not be the same as what they say they do. For example, among patients who initiated antidepressant therapy and who continued treatment for more than 3 months, switching antidepressants took place only in 9% (Marcus et al., 2009). To the best of the present authors' knowledge no other study looked at how switching and other second-line strategies are employed in the clinical practices.

It is therefore very important and informative to examine what happens to the first-line SSRIs, SNRIs and other new generation antidepressants for patients initiating pharmacotherapy for depression in the real world. The current study aims to examine, based on a large health insurance claims database in Japan,

(i) adequacy and length of first-line antidepressant treatment with new generation antidepressants
(ii) choice and timing of second-line antidepressant treatment

among patients starting treatment for their new episode of unipolar, non-psychotic depression.

2. Methods

2.1. Database

Japan Medical Data Center (JMDC) Co. Ltd. (Tokyo, Japan) prepares and maintains a database of health insurance claims submitted by medical institutions to health insurance societies of corporates representing 600,000 beneficiaries (employees and their dependents). Japan has a universal health insurance coverage mainly through the "Social Insurance System" and the "National Health Insurance System": the former covers employees of corporates and their dependents (approximately 30 million people, or one quarter of the Japanese population), while the latter covers the remaining population. The claims database maintained by the JMDC therefore represents approximately 2% of those covered by the Social Insurance System and 0.5% of the total population in Japan.

2.2. Study cohort

We conducted a retrospective cohort study, defining the inception cohort as follows from the JMDC database. In brief, we focused on new onset non-psychotic unipolar depression starting treatment with a single new generation antidepressant, with or without anxiolytics/hypnotics, in 2009 or 2010.

2.2.1. Inclusion criteria

1) The patients were registered with health insurance societies contributing claims to the JMDC database between January 1st, 2008 and December 31st, 2011
2) Aged 18 or older
3) At least one diagnosis corresponding with unipolar depression between January 1st, 2009 and December 31st, 2010 [This date is designated as the index diagnosis day or month.]
4) Prescription of any one of the following SSRIs, SNRIs or NaSSA as the only antidepressant initiated in the index diagnosis month SSRIs: fluvoxamine (first marketed in Japan in 1999), paroxetine (2000), sertraline (2005) SNRIs: duloxetine (2010), milnacipran (2000) Noradrenergic and specific serotonergic antidepressant (NaSSA): mirtazapine (2009) These drugs represent all the new generation antidepressants marketed during the study periods in Japan.

2.2.2. Exclusion criteria

1) Any diagnosis corresponding with bipolar disorder, organic mental disorder, schizophrenia or delusional disorder in the index diagnosis month or its following month, or before the index diagnosis month
2) Any prescription of antidepressants, antipsychotics or mood stabilizers before the index diagnosis month
3) Any co-prescription of antipsychotics (including sulpiride) or mood stabilizers with the above-defined first line SSRI, SNRI or NaSSA: co-prescription of benzodiazepines or other anxiolytic/hypnotic agents was allowed.

Exclusion criteria #1 and #2 aimed at excluding possible bipolar, psychotic or organic mental disorders. We set the exclusion criteria #3 to focus on the fate of new generation antidepressant when used as monotherapy, while ensuring adequate generalizability as prescription of benzodiazepines is still very prevalent in Japan (Onishi et al., submitted for publication).

2.2.3. Data extraction and analyses

Our primary outcomes of interest were the duration and amount of the first-line antidepressant prescription, the timing and kind of the second-line antidepressant prescription if any, and the total duration of antidepressant treatment.