

## Executive Summary

There is only one Korean study so far on antidepressant adherence, which is the most important factor on the success of depression drug therapy, though depression is a major disease with a significant burden on patients. The objectives of this study is to seek for more effective treatment of depression in Korea by identifying factors affecting adherence and to help clinical practice guideline development by providing cost effectiveness analysis among different treatment paths. Since the antidepressants have various spectrums of efficacy and side effects profiles and there is no study showing an absolute superiority among them, there exists a difficulty selecting a first line therapy. One of the major long term goal of the Clinical Research Center for Depression (CRCDD) is to develop a Korean clinical practice guideline on depression and this study on cost effectiveness analysis on treatment paths will be helpful for the guideline development.

In this study, extensive literature reviews and outcomes research using the Health Insurance Review Agency (HIRA) claims database from January 1, 2006 to December 31, 2008 (3 years) on patients characteristics, antidepressants prescribing patterns, medication adherence patterns and related factors were performed and a cost effectiveness analysis model was developed based on these results.

### **[Literature review]**

In this study, efficacy of each antidepressant class - tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), and new antidepressants (NAD) - was confirmed through a review on systemic literature review articles. From the final 24 studies selected,

efficacy, recurrence, discontinuation, and suicide were compared among antidepressant classes. In terms of efficacy and recurrence, most of three pairwise between-class comparisons did not reveal significant differences. In terms of discontinuation comparison between TCA and SSRI, discontinuation from side effects was significantly higher in TCA while discontinuation from inefficacy did not show any significant difference. As a result, overall drop out did not reveal any significant difference between TCA and SSRI. In the comparison between SSRIs and NADs, most of studies did not show a significant difference in terms of discontinuation though few studies did. There was a small number of studies comparing NADs and TCAs in terms of discontinuation and most of them did not show any significant difference. Finally, antidepressant classes were compared in terms of suicide, only comparisons between TCAs vs SSRIs, and SSRIs vs NADs were available and did not show any significant difference. A quality assessment on the final 24 studies show 9 'moderate's and 15 'high's.

### **[Status of antidepressants use in Korea]**

The subjects included in the current status analysis of antidepressants use were the patients in age of 18 to 85 who has a diagnosis of depression and prescribed with antidepressants between January 2006 and December 2008. Those patient used a community health center (public) service, a medical aid service, a non-electronic claim, or a Disease Related Group (DRG) claim were excluded from the analysis to minimize bias in drug utilization.

The percentage of claims by female patients was 65.80% while the total expenditure by them was 56.51%, hence, female patients with depression tend to have a lower average expenditure than the male patients. The use of new antidepressant drugs (NADs) in monotherapy only has been annually increased from about 537,000

claims in 2006, about 788,000 claims in 2007, and about 1,064,000 claims in 2008 whereas the corresponding claims (SNRI+others) in 2004 was only about 265,000, reported in Kim et al. (2008) which had slightly different exclusion criteria. Among different classes of antidepressants, TCAs monotherapy took 40.21% followed by SSRIs monotherapy 25.96%, NADs monotherapy 14.19% SSRI+NAD combination therapy 5.79%, TCA+SSRI combination therapy 5.37% TCA+NAD combination therapy 3.21%, and so on.

For the analysis of antidepressant adherence, the subjects in 18 to 85 years old were selected based on the first antidepressant prescription (index date) between January 2007 and June 2008 with at least one inpatient diagnosis of depression or two outpatient diagnoses of depression in one year prior to the index date. The Medication Possession Ratio (MPR) used in antidepressant adherence analysis was defined as the ratio of total antidepressants administration days during the 180 days after the index date. In addition, to reflect other profiles of adherence, persistency was defined as the continuously prescribed period for antidepressants from the index date.

In antidepressant adherence analysis data set, female patients took about 66.34% (211,279), the average MPR was 52%, and the average persistency was 118.08 days. The adherent group defined by MPR (more than 75% of MPR) was 34.12% of total research subjects and the adherent group defined by persistency (more than 90 days) was 64.30%. When restricted to prescriptions from a psychiatry specialty only, the antidepressant adherence was higher in terms of both MPR and persistency. Among the monotherapies prescribed from psychiatry specialty physicians, NADs monotherapy recorded highest percentage (59%) of patients who has MPR greater than 75% (adherent group) followed by 54% in SSRIs and 45% in TCAs. Among the combination therapies, SSRI+NADs showed 61%, followed by TCA+SSRI+NADs 57%, TCA+NADs 53%, and TCA+SSRIs 49%.

For 90 day or more persistency by monotherapy prescriptions from psychiatry specialty physicians, SSRI 18.26% followed by TCAs 10.03%, and NADs 8.63%. For that of combination therapy prescriptions from psychiatry specialty physicians, the use of SSRI+NADs showed 9.65%, followed by TCA+SSRIs 8.40%.

In a multivariate analysis of factors affecting the antidepressant adherence, the low antidepressant adherence in terms of MPR was associated with female gender, organic disorder, anxiety disorder, somatoform neurotic disorder, eating disorder, personality disorder, chronic obstructive pulmonary disease (COPD), peptic ulcers, minor liver diseases, and severe liver diseases. In case of persistency, female gender, TCA+SSRI combination therapy, TCA+NAD combination therapy, SSRI+NAD combination therapy, hospitalization before the index date, eating disorder, nonorganic sleep disorder, congestive heart failure, peripheral vessel diseases, COPD, peptic ulcers, minor liver diseases and severe liver diseases were found to be significantly associated with the low antidepressant adherence.

**[Relationship between antidepressant adherence and recurrence of depression]**

In this study, the relationship between antidepressant adherence for the initial 3 months after the index date and the recurrence rate of depression was examined. Those recurrences in 6 months from the index date were excluded. The recurrence rate of the adherent group was about 10% lower than non-adherent group whether in monotherapy or in combination therapy. However, there was a difference among the antidepressant classes: a lower recurrence rate was found in SSRI and NAD groups whereas TCA group showed a higher rate. Although there was a limitation in time period observed, it seems the non-adherence group by MPR has about 28 days earlier recurrence and non-adherence group by persistency has about 27

days earlier recurrence. The factors found to be significantly associated with recurrence of depression were over 30 years of age (especially 60-69 years old), female gender, comorbidity such as myocardial infarction, cerebrovascular diseases, diabetes melitus, cancer and hypertension. When these factors along with adherence and persistency were considered together, the adherent group revealed 35.4% lower risk of having recurrence compared to the non-adherence group and the persistent group ( $\geq 90$  days) showed 38.9% lower risk of recurrence with respect to the non-persistent group.

#### **[CRCD cohort analysis]**

One critical limitation of a claims data based analysis is severity of depression cannot be easily reflected in the analysis though it is an important factor in drug adherence. To solve this problem, a linked data between Clinical Research Center for Depression (CRCD) cohort with depression severity information and HIRA claims data was used to examine the results of claims data based analysis by depression severity. However, there were only 834 patients with antidepressant treatment in the linked data and limited our examinable ability. In this data, the adherence was higher in the order of NADs > SSRIs > TCAs. There was no significant relationship found between depression severity and antidepressant adherence though all classes of antidepressants revealed quite higher adherence compared to the adherence estimated by claims data. This result may be attributable to the facts that clinical research environment is different from real world and these patients were recruited from mostly general hospitals. Another more reasonable explanation is exclusion of patients with minor depression (HAM-D score less than 7) in one of the CRCD cohort selection criteria.

**[Status of non-pharmaceutical psychotherapies]**

A combined use of non-pharmaceutical psychotherapies and antidepressant therapies has been reported to improve antidepressant adherence in several studies (CRCD, 2010). Although there is limitation in interpreting the results of claims data analysis as a causal relationship, it seems that the use of psycho-therapies (excluding a routine therapy) above certain frequency ( $\geq 4$  times in male,  $\geq 3$  times in female) along with antidepressant therapies is associated with increased adherence. Since the number of suicide attempts is lower in adherent group, it is expected that the use of psychotherapies is associated with a lower suicide attempts. According to the HIRA claims data, it seems that claims of antidepressant prescriptions are increasing while the use of psychotherapies is reduced about 25% in 2008. Therefore, it is necessary to introduce some efforts to encourage psychotherapies in treatment of depression.

**[Cost effectiveness analysis]**

According to the results of cost effectiveness analysis on treatment paths, SSRI group was found to be the most cost effective treatment as a first line therapy. Specifically, when comparing monotherapies, the effect measured as the probability of avoiding recurrence was high in the order of NADs, SSRIs, and TCAs. However, TCAs was a dominated strategy since it had a high cost than SSRIs. Also NADs was less cost effective than SSRIs since the incremental cost effectiveness ratio (ICER) comparing to SSRIs was more than 73 million KRW which is clearly above the threshold level in Korea. This result was consistently observed in various sensitivity analyses as well. In switching therapy comparisons, a similar results were obtained - starting with NADs had better effect but ICER was

worse than monotherapy results, i.e. more than 140 million KRW. For the combined model considering both monotherapy and switching paths, SSRIs were the most cost-effective treatment as a first line therapy given Korean CE threshold level around 20 million KRW. The use of TCAs as a first line therapy was an inferior strategy compared to others. However, a caution is needed to interpret this results since CEA considers the employed strategies are all exchangeable, i.e. the CEA results do not hold for a situation such that antidepressants are not exchangeable, for example, depression accompanied by any of severe anxiety, insomnia, somatization, etc.

### **[Conclusions]**

Twenty nine percent of patients were adherent (more than 75% MPR in 90 days from the index date) among the patients who were prescribed with antidepressants for an acute depression and 34% of patients among the ones already diagnosed as depression before were adherent (more than 75% MPR in 180 days from the index date). These results were comparable to the ones reported in the international literature. As antidepressant adherence increases, recurrence risk, defined as hospitalization in psychiatry department, emergency visit for depression, suicide attempt, and restart of antidepressant therapy after 6 months from discontinuation, decreases. In addition, adherence was higher in the patients who received psychotherapies along with antidepressants. This result suggests various attempts to promote psychotherapies along with antidepressants is necessary. From a cost effectiveness analysis on treatment paths, it seems SSRIs are most cost effective first line antidepressant class unless patients have severe anxiety, insomnia, or accompanied with physical symptoms where NADs are more appropriate.