

# USING ASSOCIATION RULES TO STUDY PATTERNS OF MEDICINE USE IN THAI ADULT DEPRESSED PATIENTS

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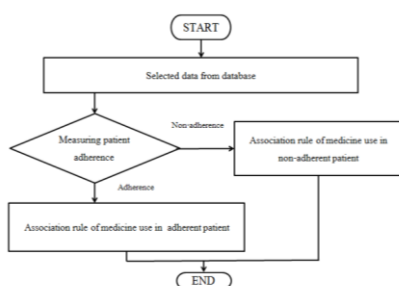
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## Graphical abstract



## Abstract

Depression is a mental disorder which is characterized by feeling of guilt, suicidal tendencies and disturbed bodily functions. In 2002, depression is ranked as the fourth of disease burden in worldwide and it will be changed to the second rank in 2030. Furthermore, more than 350 million people worldwide suffer from depression. Clinician staffs must take care of patients closely because these patients have medication adherence problem. To alleviate this problem, an adherence training program is introduced. Due to the limitation of budget and clinical stuffs, it is hard to educate all depressed patients. To deal with this problem, a method for finding rules of medicine use is proposed in three steps. The first step is finding the commonly used medicines with their adherences. In the second step, two groups of patients are classified, i.e., adherence and non-adherence groups for each commonly used medicines. For the last step, association rules are applied on each group of patients. From results, fluoxetine is a popular medicine for treatment depression. The numbers of medicines for a non-adherent group are more than those of an adherent group. Several patterns of drug interactions are found. These patterns should be reported to clinical staffs. In conclusion, results from the proposed method are applied for selecting a set of patients and drugs, which are filled in the adherence training program.

Keywords: Association rules, data mining, depressed, adherence, medicine

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## 1.0 INTRODUCTION

Depression is a mental disorder which characterized by feeling of guilt, suicidal tendencies and disturbed bodily functions. Furthermore, these persist for weeks [1]. Depression may be caused by decreased level of the neurotransmitters which are norepinephrine (NE), serotonin (5-HT), and dopamine (DA) in brain [2]. In present time, depressed patients have more than 350 million people worldwide. Depression is one of the major causes of the one million suicides committed every year [3]. In 2002, the depression ranked fourth in the burden of diseases worldwide. It is predicted that by 2030, it will rank second [4]. In Thailand, depression ranked third for burden of diseases in women and tenth in men as the cause loss of

disability adjusted life years (DALYs) [5]. One of the major problems for treatment of depression is medication adherence. Odds are three times greater than a depressed patient will become medication non-adherent than their non-depressed counterparts [6]. According to the Thai medical database, depressed patients classified as medication adherent patients, are only 23 percent [7]. This is an extremely important issue because if patients don't take their medicine as prescribed, their disease will most certainly escalate. Consequently, it becomes increasingly difficult for their physicians and clinical staffs to manage their illness effectively. To alleviate this problem, an adherence training program, which is critically important for non-adherent patients, needs to be

implemented. Due to budget constraints and limited clinical staffs, not all depressed patients can be educated at this time. This research proposes a method for finding rules of medicine use in depressed patients according to their medication adherence. To find patterns of medicine use, the association rule technique, a data mining technique is usually used. The patterns of drug items, used for treatment were collected and analyzed. The results can be used to implement an adherence training program for a set of patients and drugs. In the rest of this paper, medicines in depressed patients, association rules, finding patterns of medicine use by association rules, experimental settings and experimental results, as well as conclusion and future work are given in detail.

## 2.0 EXPERIMENTS

### 2.1 Background

#### 2.1.1 Medicines in Depressed Patients

In this section, some groups of medicine used for depressed patients, are described. The detail of main groups is described as follow.

Selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of 5-HT into the presynaptic neuron. They are generally chosen as first-line antidepressants because of their safety in overdose and improved tolerability compared to earlier agents. Examples of medicines for this group are fluoxetine, sertraline and escitalopram [2].

Tricyclic antidepressants (TCAs) such as amitriptyline, imipramine and nortriptyline are effective for all depressive subtypes, but their use has diminished because of the availability of equally effective therapies that are safer on overdose and better tolerated [2].

Tetracyclic antidepressants such as mianserin are potent alpha-2 adrenoceptor antagonists which cause an enhanced release of noradrenaline [1].

The triazolopyridines, e.g., trazodone and nefazodone, are antagonists at the 5-HT<sub>2</sub> receptor and inhibit the reuptake of 5-HT. They can also enhance 5-HT<sub>1A</sub> neurotransmission [2].

Depressed patients may use other medicines because they may have associated with anxiety and/or psychotics symptoms. These medicines are perphenazine, haloperidol, chlorpromazine, risperidone, amobarbital, flupentixol and melitracen. Due to various medicines can be applied on a patient, drug interactions may be occurred. For example, the treatment of patients by fluoxetine and amitriptyline, increases risk of toxicity from tricyclic antidepressants (increase causing an abnormal heart rhythm).

#### 2.1.2 Association Rules

Association rule learning, a data mining technique, is a popular and well researched method for finding

patterns of interesting associations and correlations between item sets in large databases. The result from association rules found the trend of data which is used to plan project or strategy. Medical research works develop mining techniques on association rule learning such as [10, 11]. Association rules have an associated confidence and support for a rule. Rule confidence is conditional probability of one interesting focus. The support for a rule is minimum percentage in database. There are criteria to filter interesting data or impact data [8]. This is a two-step process. The first step is item set generation. The rule create is not less than minimum rule confidence. Next step, association rules generated relational data between first rule and second rule. The rules have percentage of change not less than minimum support rule [8]. In this paper, a set of medicines for depressed patients is considered as a set of items. For example, a prescription for treatment a depressed patient, fluoxetine also tends to associate with perphenazine. This can be represented in association rule below:

Fluoxetine → Perphenazine [support=20%, confidence=80%]

A support of 20% indicates that 20% of all the transactions in all prescription suggest that both fluoxetine and perphenazine are found together. A confidence of 80% means that 80% of the total number of prescription which is composed of fluoxetine, is also found perphenazine. In this research, a set of rules generated on both adherent and non-adherent patients, provides useful knowledge for each group of patients. These can be used to set adherence training programs for depressed patients. A set of medicines which is caused problems or drug interaction, is included in the training program.

### 2.2 Experimental Settings

The inclusion criteria for selecting patients and medicines were as follow.

- I. Patients were outpatients of Somdet Chaopraya Institute of Psychiatry who visited more than one time.
- II. Patients were Thai depressed patients who were diagnosed depression using International Classification of Diseases, Tenth Edition Thai Modification (ICD-10TM) codes as F32 (Depressive episodes), F33 (Recurrent depressive disorder) and F34.1 (Dysthymia).
- III. Patients were received mainly medicines for treatment depressed patients which were groups of national list of essential medicines 2011 as 4.2.1 antipsychotic drugs, 4.2.2 antimanic drugs and 4.3 antidepressant drugs. Moreover, there were tablets and capsules and method of medicine use in prescriptions were not prn. (pro re nata, when necessary for)

IV. Number of medicines was not more than 10% of medication possession.

This study was retrospective cross sectional descriptive study used electronic medical record from a database of the Somdet Chaopraya Institute of Psychiatry, Thailand during the period between June 10, 2004 and August 14, 2012. This included 7,346 depressed outpatients. However, 2,834 depressed outpatients were selected according to the inclusion criteria. For medicines, the total numbers of medicines were 40 items. Data of medicines and patients are recorded in a database which is constructed by PostgreSQL, open source database management software and PHP language is used for calculating medication and patient adherences. Association rules of medicine use were analyzed by apriori technique.

### 2.3 Finding Patterns of Medicine Use by Association Rules

In order to apply association rule finding medicine using patterns, two lists of transactions of medicine use are generated. The first list is the transactions of adherent patients and the other one is for non-adherent patients. To classify a patient into adherent and non-adherent group, the method for calculating MPR from a database of medicine use, is proposed. The apriori method is presented to find patterns of medicine use in both adherent and non-adherent depressed patients.

Adherence: Data of medicine uses from database were calculated adherence by Medication Possession Ratio (MPR). The MPR method was appropriate measuring adherence for long-term treatment medications. The MPR can be calculated with this equation (MPR = Number of days supplied within refill interval/Number of days in refill interval). The concept of MPR in our proposed method can be represented in the equation 1.

$$MPR_{ij} = \frac{NM_{ij}}{ND_{ij}} = \begin{cases} 1 & \text{when the ratio is } \geq 0.8 \\ 0 & \text{when the ratio is } < 0.8 \end{cases} \quad (1)$$

Here, the MPR of the  $i^{th}$  medicine for the  $j^{th}$  patient is defined as the number of days supplied the  $i^{th}$  medicine for the  $j^{th}$  patient ( $NM_{ij}$ ) / the number of treatment day for the  $i^{th}$  medicine for the  $j^{th}$  patient ( $ND_{ij}$ ). In this paper, a medicine is a sets of drug with same generic names for all strengths. For example, two strengths are available for Fluoxetine, i.e., 20 mg. and 40 mg. These two strengths are grouped as the same medicine. If the value of the ratio in the equation 1 is greater than or equal to 0.8, the MPR is set to 1. On the opposite, when the value of the ratio is less than 0.8, the MPR is set to 0. With the  $MPR_{ij}$ , two types of adherence are proposed in the papers, i.e., medication adherence by patient and medication adherence by medicine. The detail of each type of adherence is described.

Measuring Medication Adherence by Patient (MA-P): This is the ratio of medication possession by equation 1 from all medicines for a patient to the number of medicines which were taken by the patient. The MA-P can be represented in the equation 2.

$$MA - P_j = \frac{\sum_i MPR_{ij}}{TM_j} \quad (2)$$

Here,  $MA-P_j$  is the medication adherence of the  $j^{th}$  patient and  $TM_j$  is the total number of medicines that were taken by the  $j^{th}$  patient. If the value of  $MA-P_j$  is greater than or equal to 0.8, the  $j^{th}$  patient is accepted as a medication-adherent patient.

$$MA - M_i = \frac{\sum_j MPR_{ij}}{TP_i} \quad (3)$$

Here,  $MA-M_i$  is the medication adherence of the  $i^{th}$  medicine and  $TP_i$  is the total number of patients who took the  $i^{th}$  medicine. If the value of  $MA-M_i$  is greater than or equal to 0.8, the  $i^{th}$  medicine is accepted as the drug is a medication-adherent medicine. The patterns of medicine use of these two groups (adherent and non-adherent patients) are analyzed by an association rules technique.

Association Rules: The lists of medicine uses for each visit of patients for both groups, i.e., adherent and non-adherent patients, are used. The apriori algorithm, which is the standard algorithm for association rule is applied in the work. Due to the varieties of medicines use for depressed patients, the value of support is set to 10%.

## 3.0 RESULTS AND DISCUSSION

### 3.1 Commonly Used Medicines in Depressed Patients

In the first step, the percentages of medication adherence by medicine were calculated from data in the database using equation 1 and 3. The top ten most commonly used medicines are sorted by their supports in descending order. The result is shown in Table 1.

From the result, some observations can be made. Medicines use in some depressed patients, were not only antidepressants but also antipsychotics, e.g., amitriptyline and perphenazine. The top ranked common medicines used in depressed patients were fluoxetine (49.75%), amitriptyline (23.82%), perphenazine (15.81%) and mianserin (14.57%). The percentages of adherence for these medicines were 48.23%, 52.30%, 41.52% and 54.00%, respectively. The result suggests that the group of medicines which is the most commonly used group is Selective Serotonin Reuptake Inhibitors (SSRIs), e.g., fluoxetine, sertraline and escitalopram. The most commonly used medicine is fluoxetine which obtained low percentage of medication adherence. In contrast,

sertraline is more advantage than fluoxetine and escitalopram in term of medication adherence. Therefore, sertraline may be considered for treatment of choice on depressed patients who had adherence problem. Moreover, a set of training program for applying these medicines should be set

for depressed patients. Average of medication items use were 1.50 items for adherent group and 2.08 items for non-adherent patients. This suggests that non-adherent patients have taken medicines more than those of adherent patients.

**Table 1** The top ten commonly used medicines sorted by their supports

No.	Generic name	Percentage of support (%)	Percentage of adherence (%)
1	Fluoxetine	49.75	48.23
2	Amitriptyline	23.82	52.30
3	Perphenazine	15.81	41.52
4	Mianserin	14.57	54.00
5	Trazodone	8.93	54.55
6	Haloperidol	8.47	42.50
7	Nortriptyline	8.05	55.26
8	Imipramine	7.20	52.94
9	Sertraline	6.53	62.16
10	Escitalopram	4.66	53.03

**Table 2** The results of association rules by medicine adherence's group

Rule No.	DI sig. rating	Associated medicine
1	2	Amitriptyline → Fluoxetine (21.9, 29.9)
2	2	Fluoxetine → Amitriptyline (46.9, 62.1)
3	1	Trazodone → Fluoxetine (15.3, 19.0)
4	2	Nortriptyline → Fluoxetine (12.5, 14.8)
5	2	Imipramine → Fluoxetine (<10.0, 11.4)
6	1	Trazodone, Fluoxetine → Amitriptyline (<10.0, 13.9)
7	1	Trazodone, Fluoxetine → Perphenazine (11.8, 16.1)
8	1	Trazodone, Fluoxetine → Mianserin (10.0, 21.0)
9	2	Imipramine, Fluoxetine → Perphenazine (<10.0, 10.4)
10	2	Imipramine, Fluoxetine → Mianserin (<10.0, 10.0)
11	2	Nortriptyline, Fluoxetine → Perphenazine (<10.0, 11.5)
12	2	Nortriptyline, Fluoxetine → Mianserin (<10.0, 12.6)
13	1	Chlorpromazine, Fluoxetine → Perphenazine (<10.0, 13.2)

### 3.2 Finding Patterns of Medicine Use in Depressed Patients.

In the second step, four medicines from Table 1, i.e., fluoxetine, amitriptyline, perphenazine and mianserin have supports greater than 10%. Therefore, patterns of medicine usage of these four medicines were divided into two groups based on calculation from equation 1 and 2, i.e., adherent patients' group and non-adherent patients' group. Transactions of medicine use for each group were analyzed by apriori algorithm in the last step. Associated medicines caused of drug interaction rating (DI sig. rate) 1 and 2 with these four medicines are shown in Table 2. The percentage of supports for adherent patients' group and non-adherent patients' group, are presented in parenthesis, respectively.

From the result in Table 2, these patterns have the support of non-adherent group more than adherent group. Moreover, the popular associated medicine was fluoxetine. Serious drug interactions (significance rating 1, risk of death) are found, e.g., fluoxetine associated with trazodone as well as fluoxetine and chlorpromazine associated with perphenazine. The

most popular pattern of associated medicines which is the cause of drug interaction significance rating 1 is Trazodone → Fluoxetine. These have support values of 15.3% and 19.0% in adherent and non-adherent patients, respectively. This means depressed patients who are good adherence uses trazodone associated with fluoxetine. This rule occurs 15.3% from patients who use fluoxetine. These patterns appears 19.0% from patients who use fluoxetine in non-adherent patients. Although fluoxetine and chlorpromazine associated with perphenazine does not frequently use, it should be aware because the serious drug interact may occur. If patients take these medicines together, clinical staffs should monitor closely.

### 4.0 CONCLUSION

Due to the limitation of budget and clinical stuffs, it was hard to educate all depressed patients to apply their medicine effectively. A set of methods for constructing an adherence training program was introduced in this paper. In the first step, a method for

finding medication adherence by medicines was used. From this step, a set of medicines commonly used in depressed patients with their percentage of their medication adherences were investigated and selected. In the next step, patients were classified into two groups using medication adherence by patients, i.e., adherent group and non-adherent group for each commonly used medicine. In the last step, a method for finding rules of medicine use in non-adherent patients was applied. From the results, Thai adult depressed patient is low adherence. Fluoxetine is the most popular associated medicine. Numbers of medicines from non-adherent group were more than those of adherent group. Several drug interactions among medicines for treatment depressed patients were found. Some patterns of medicine use can cause severe drug interactions and these should be concerned. The training program about common medicines which are obtained low percentage of medication adherence by medicines should be set with high priority, especially in non-adherent patients. This training program will improve patient adherence, effective of treatment, patient's safety and reduce cost of treatment.

In this paper, a support is the main parameter to select a set of medicines and association rules. For future work, other parameters, e.g., confidence and lift, should be applied.

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