

ASSESSING THE PRESCRIBING TRENDS AND  
PATTERNS OF ORAL BENZODIAZEPINES AT  
OUTPATIENT PHARMACY OF HOSPITAL TENGGU  
AMPUAN AFZAN (HTAA), KUANTAN, PAHANG.

BY

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## ABSTRACT

The vast use of benzodiazepines has been a prime cause for concern to healthcare professionals and policy makers around the world. Nevertheless, there is a paucity of literature concerning benzodiazepines prescribing practice in Malaysia. Thus, this study aimed to evaluate the prescribing trends and patterns of oral benzodiazepines at the outpatient pharmacy of Hospital Tengku Ampuan Afzan, Kuantan, Pahang and assess the association between patient demographic characteristics with the prescribing patterns. The study conducted retrospectively using data of prescriptions issued from January 2014 until December 2016. The data were assembled using a data collection form and transferred to STATA® software for cleaning, processing and analysis. The descriptive analysis was used to report the demographic characteristic of the patients, prescriber's speciality, number of patients and prescriptions, as well as the type of benzodiazepine, duration of action, onset of action, dosing schedule, duration of supply, concurrent medications and diagnosis. Throughout the study period, we observed a drop of 12.6% number of prescriptions from 2014 (n=1956) to 2016 (n=1709). Likewise, the number of patients receiving benzodiazepines was also decreased by approximately 13% from 2014 (n=676) to 2016 (n=584). The defined daily dose (DDD/1000 patients/year) also showed a decreasing trend in which 1.9% and 7.25% decrease was observed in 2015 and 2016 respectively. Alprazolam, short-acting benzodiazepines and anxiolytics (N05BA) were the most frequently prescribed with 39.67%, 40.32% and 82.32% respectively. Approximately, 69.64% (n=6,218) of benzodiazepines prescribed were for a 15-30 days duration, while 57.28% (n=5,115) of benzodiazepines were prescribed with fixed dosing schedule rather than as per needed (PRN) dosing. Majority (81.53%, n=7,280) prescriptions generated were from the psychiatric and mental health department, and about 90.5% (n=8,081) of prescriptions were written with a diagnosis related to psychiatric disorders. Additionally, about 51.41% (n=2,945) prescriptions were issued for male patients, 56.77% (n=3,252) are among Malays and patient within the age band of 45-54 years old (29.42%, n=1,685) was the highest recipient. In general, there is a significant relationship seen between patient's age group and gender with the prescribing patterns of benzodiazepines. All chi-square tested towards the patterns showed result lower than the decided significance levels ( $p=0.005$ ). In conclusion, overall benzodiazepines prescribing trends in Malaysia was low throughout the three retrospective years compared to the increasing psychiatric problems in the country. Taking into account the downward trend of the benzodiazepines utilisation from 2011 to 2014 as identified in the Malaysian Statistics Of Medicines 2015, this study found that our results share corresponding trends with the nationwide consumption. Consequently, the DDD of benzodiazepines was found to be in declining trends and relatively low compared to other countries. As a whole, it is believed that this study provides sufficient data that could be a jump start for future work. The trends and patterns described in the study allow for an estimation of the prevalence of the medical condition, providing the basis of risk assessment and pharmacovigilance and also set a standard for future reference of trends and patterns of benzodiazepines in Malaysia.

## خلاصة البحث

يعد الاستخدام الواسع للبنزوديازيبينات سببا رئيسيا للقلق بين متخصصي الرعاية الصحية وصانعي السياسات في جميع أنحاء العالم، ومع هذا فإن هناك ندرة في المؤلفات العلمية المتعلقة بممارسات وصف البنزوديازيبينات في ماليزيا. ولذلك هدفت هذه الدراسة إلى تقييم اتجاهات وأنماط وصف البنزوديازيبينات الفموية في الصيدلية الخارجية لمستشفى تونغكو أمبوان أفران في مدينة كوانتان بولاية باهانغ، وتقييم العلاقة بين الخصائص الديموغرافية للمريض وأنماط وصف الأدوية. تم إجراء الدراسة بطريقة رجعية باستخدام بيانات الوصفات الطبية الصادرة من يناير 2014 حتى ديسمبر 2016. تم جمع البيانات باستخدام استبيان ومن ثم نقلها إلى برنامج STATA® للتصفية والمعالجة والتحليل. تم استخدام التحليل الوصفي للإبلاغ عن الخصائص الديموغرافية للمرضى، وتخصص كاتب الوصفة، وعدد المرضى والوصفات الطبية، بالإضافة إلى نوع البنزوديازيبين، ومدة عمل الدواء، وتوقيت بدء عمل الدواء، وجدول الجرعات، ومدة تموين الأدوية، والأدوية المتزامنة والتشخيص. طوال فترة الدراسة لاحظنا انخفاضا في عدد الوصفات الطبية بنسبة 12.6% من عام 2014 (ن=1956) إلى عام 2016 (ن=1709). وانخفض أيضا عدد المرضى الذين يتلقون البنزوديازيبينات بنسبة 13% تقريبا من عام 2014 (ن=676) إلى عام 2016 (ن=584). كما أظهرت الجرعة اليومية المحددة (1000/DDD) مريض/سنة) اتجاها تنازليا حيث لوحظ انخفاض بنسبة 1.9% في 2015 وبنسبة 7.25% في 2016 على التوالي. كان كل من الأبرازولام، والبنزوديازيبينات قصيرة المفعول، ومضادات القلق (N05BA) الأكثر شيوعا بنسبة 39.67% و 40.32% و 82.32% على التوالي. حوالي 69.64% (ن=6218) من البنزوديازيبينات الموصوفة كانت لمدة 15-30 يوما، في حين تم وصف 57.28% (ن=5115) من البنزوديازيبينات بجدول جرعات ثابت بدلاً من جدول الجرعات المطلوبة (PRN). تم إصدار معظم الوصفات الطبية (81.53%، ن=7280) من قسم الصحة النفسية والعقلية، وتم كتابة حوالي 90.5% (ن=8081) من الوصفات لتشخيصات متعلقة بالاضطرابات النفسية. تم أيضا إصدار حوالي 51.41% (ن=2945) من الوصفات للمرضى الذكور، حيث كان 56.77% (ن=3252) من عرق الملايو وكانت الفئة العمرية من 45 إلى 54 سنة (29.42%، ن=1،685) الأعلى استلاما للأدوية. كان هناك بشكل عام علاقة ملحوظة بين الفئة العمرية للمريض والجنس مع أنماط وصف البنزوديازيبينات. أظهر كل مربع كاي تم اختباره تجاه الأنماط نتيجة أقل من مستويات الأهمية المحددة (p=0.005). ختاماً، الاتجاهات العامة لوصف البنزوديازيبينات في ماليزيا كانت منخفضة طوال السنوات الثلاث الرجعية مقارنة بالمشاكل النفسية المتزايدة في البلاد. مع الأخذ بعين الاعتبار الاتجاه النزولي لاستخدام البنزوديازيبينات من 2011 إلى 2014 كما هو محدد في إحصائيات الأدوية الماليزية 2015، وجدت هذه الدراسة أن نتائجنا كانت مماثلة لاتجاهات الاستهلاك الوطني. ولذلك فقد وجد أن الجرعة اليومية المحددة للبنزوديازيبينات في اتجاه نزولي وكانت منخفضة نسبياً مقارنة بالدول الأخرى. قدمت هذه الدراسة بشكل عام بيانات كافية لتكوين بداية سريعة للأعمال المستقبلية، حيث تسمح الاتجاهات والأنماط الموضحة في الدراسة بتقدير مدى انتشار الحالات الطبية، وتوفير أسس لتقييم المخاطر واليقظة الدوائية، كما تضع معياراً للمراجع المستقبلية لاتجاهات وأنماط البنزوديازيبينات في ماليزيا.

## APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master in Pharmaceutical Sciences (Pharmacy Practice)

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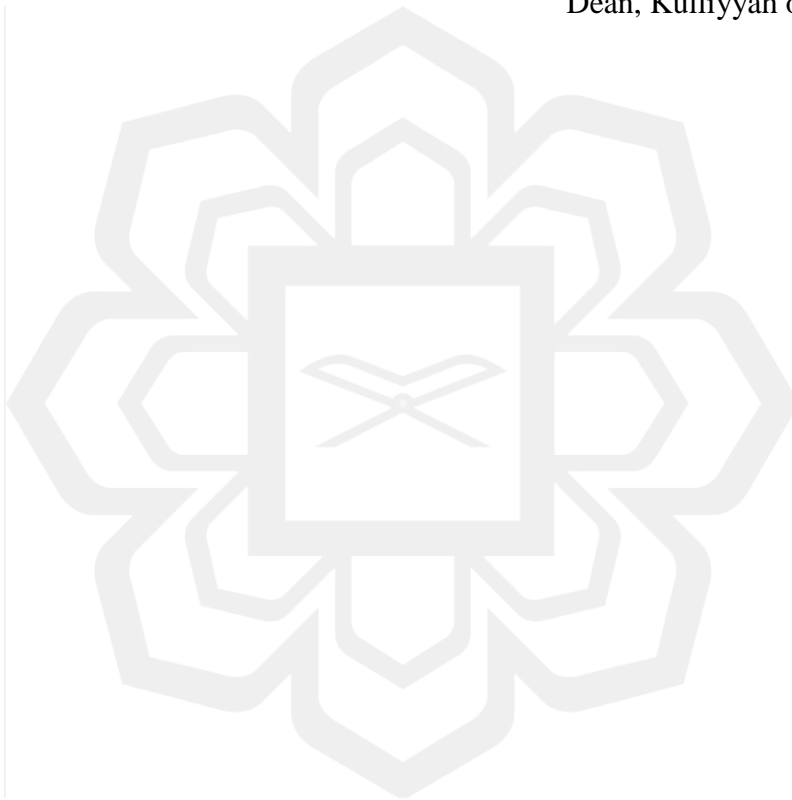
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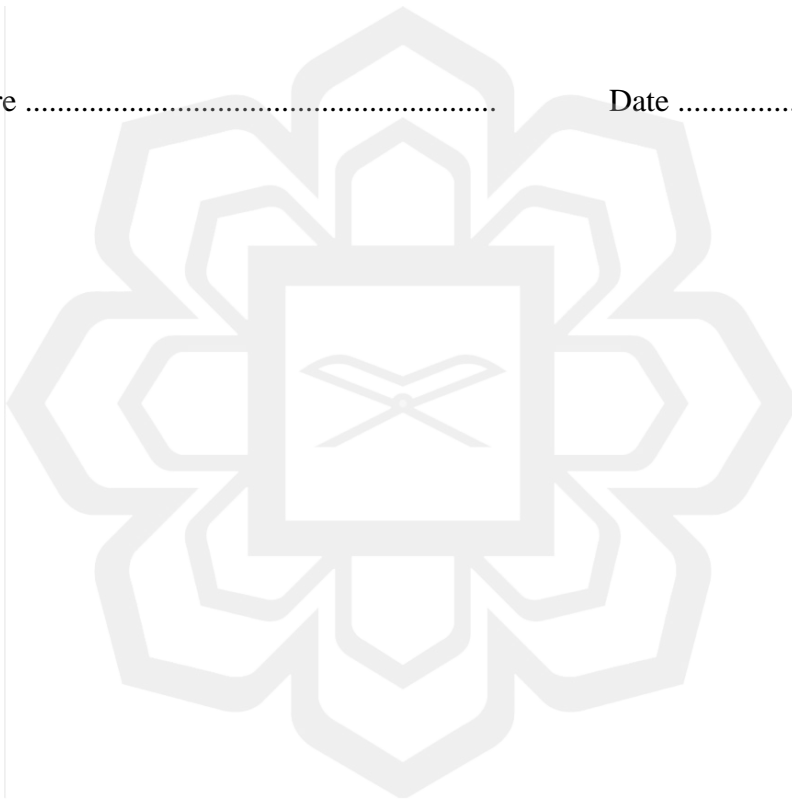


## DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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Signature ..... Date .....



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Firstly, it is my utmost pleasure to dedicate this work to my dear parents; Pakururazi B. Awang and Haslina Bt Daud, and to my siblings who granted me the gift of their unwavering belief in my ability to accomplish this goal: thank you for your support and patience.

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# CHAPTER ONE

## INTRODUCTION

### 1.1 BACKGROUND OF THE STUDY

The story of how benzodiazepines infiltrated the global medical systems began when Hoffman La Roche introduced and marketed the first original invention of its class - Chlordiazepoxide (Librium) in 1960. It was welcomed with exuberance and anticipation, that finally, the clinician might obtain a magic potion to address mental disorders. “Downers”, “Nerve Pills” and ‘Sleepers’ are among many nicknames or street names bestowed upon this class of drugs, to describe benzodiazepines. Because it possesses rather broad-ranging properties such as sedative, hypnotics, anxiolytics, amnestic and muscle relaxants; it is often medically used to ameliorate sleep deprivation and disorder, mitigate stress, alleviate seizures and relieve many other conditions (Ashton, 1994a; Khawaja et al., 2005)

Noted as breakthrough drugs, they were believed to surpass its predecessor's effectiveness. Before benzodiazepines, Barbiturates once had possessed extensive popularity as sleeping pill and tranquilliser. However, barbiturates side effects such as peripheral and respiratory depression, and excessive drowsiness that manifest as hangover sleepiness till the next day had led to fatal consequences and public disarray (Wick, 2013). The problem with barbiturates is, they are hard to control. Meaning, their dosage was variant, but at the same time, they own a much bounded therapeutic index. Also, barbiturates can cause a dependency that eventually turns into habit-forming, its prolonged use can lead to a tolerance that demand increase of dose, and

bear a high chance of drug-drug interactions with other medications and overdosing (Bryan, 2009).

Thus, as soon as benzodiazepines were offered for sale, it became the “most commercially profitable drug” at that time (Shorter, 2005). Also notably known by the term “benzos” or “BZDs”, they were thought to be a flamboyant solution by many prescribers because they are therapeutically efficacious on insomnia, anxiety, panic attacks, depression, and other conditions while at the same time established high safety profile than any drugs used for the same reason (Shorter, 2005). Malcolm Lader, an Emeritus Professor of clinical psychopharmacology at the Institute of Psychiatry, King’s College, London, had mentioned that in contrast to barbiturates, people saw good results when taking benzodiazepines as they were pleasant to take. Besides, the manufacturers were assuring the crowds and medical world through vigorous advertisements that, “there was no risk of dependence with the low doses they were prescribing” (Bryan, 2009). Hence, the benzodiazepines chronicles continue to unroll.

Ultimately, the joy of prescribing it in abundance has taken its toll. Albeit benzodiazepines have a legitimate indication and efficacious to many conditions, it also had its risk and harm that should not be overseen. The early 1980s is the beginning of a love-hate relationship between benzodiazepines, the public, medical practitioners and legislator. There is also a substantial concern in many parts of the world - with varying levels of inclination and trepidation – of whether to use them or not to use. The primary basis of the worry seems to be about the risk of normal and excessive usage of benzodiazepines, the tolerance level, dependence potential and the abuse liability of benzodiazepines. The Committee on the Review of Medicines in the United Kingdom, for example, has issued a warning regarding the regular long-term

use of benzodiazepines and express their concern on the high number of patients with repeat prescriptions for an unusually long period of time (Committee on the Review of Medicines, 1980)

Impetuously, benzodiazepines users begin to manifest tolerance to the intoxicating effects of the drugs. Tolerance narrows the safety margin between a therapeutic and a lethal dose and they may need higher and higher doses to get to the same effect. After the tolerance period, users have a high possibility to reach the dependent stage and materialise withdrawal symptoms when discontinued without proper monitoring and dose tapering (Ashton, 1994b). Intended to forbear the event, doctors under normal conditions will prescribe benzodiazepines for a short duration of time, recommended not to be more than four weeks (McElroy & Armstrong, 2014).

Despite years of practical and clinical research, the relevant duration of use and to what extent should we apply benzodiazepines remains a source of discourse. Some prescriber argues that short-term use of this medication is generally beneficial and support their use, and only the long-term usage of benzodiazepines is up to question (Rivas-Vazquez, 2003). The other half of prescriber believe that their risk-benefit ratio as unfavourable. However, Norman S. Miller (2008) noted that regardless of justification we can lay upon its usage, benzodiazepines will still produce tolerance, high risk of dependence and addiction in either short and long-term treatment.

These arguments are understandable because benzodiazepines were for many years, are the “most commonly prescribed group of drugs” for hypnotics and anxiolytics - notably in The United Kingdom (UK), European countries and the United States of America (USA) (Colman, Wadsworth, Croudace, & Jones, 2006; Donoghue & Lader, 2010; Mehdi, 2012; Ohayon, Caulet, Priest, & Guilleminault, 1998). This situation was also well described in studies by Moore, Pariente, & Bégau

(2015) and Reay (2008), which estimates that 1.5 million people were addicted to benzodiazepines in the UK in 2007; while about 46.9 million benzodiazepines prescriptions were dispensed to the Americans in 2008. However, the clinical reasons for prescribing them are unable to be determined from their prescription data. After clinician society discovered benzodiazepines and addictiveness were in one packaged, it left uncertain how addictive they can be when measured comparatively with other similar psychotropic drugs (Shorter, 2005). This notion brings to the relatively grey area of whether benzodiazepines are indeed good, or bad, or are they both. The scarcity of lucidity in clinical practice when describing dependence, addiction, misuse, abuse and tolerance leads to installation and continuation of the toxicity and inappropriate effects of the benzodiazepines.

In a study to investigate the association of benzodiazepines with risk factors and adverse outcomes, Kroll, Nieva, Barsky, & Linder (2016) discovered that adverse drug events and a high-rise mortality rate were affiliated frequently with benzodiazepines use. They acknowledged that risk factors for benzodiazepines-mediated side effects include lung disease, substance abuse, and vulnerability to fracture. Although mortality has not been affirmatively reported, significant relations between prescribing of benzodiazepines especially in primary care and increased risk of mortality is described in specific patient groups especially in elderly, women and single living individual (Weich et al., 2014).

A review of more recent literature on benzodiazepines strongly suggests that abuse, addiction, tolerance and dependence occur readily and habitually in general populations. These lead to higher needs in healthcare, increase morbidity and longer and frequent hospital admission that ultimately sums to higher cost (Kroll et al., 2016a). These issues have a vital need for investigation on their usage patterns in

order to motivate possible reduction of use. Insight in usage patterns and exposure of use, in particular, long-term use, generates necessary information which can contribute to knowledge about the development of prolonged use, dependence, and interventional options. The above proposal answers well to Miller & Gold (1990) when the author concludes that rational and scientific evaluation is ambiguous and equivocal because of strong emotional reactions, economic and medical considerations on both healthcare practitioners' and patient's side. Notwithstanding, benzodiazepines continues relatively unchanged as a drug of choice for treatment of a variety of disorders by thousands of physicians throughout the world.

The disputes encircling the use of benzodiazepines are still open for debate. Benzodiazepines prescribing trends and patterns may vary in each country. However, their long-term usage is often seen and sometimes treated as the norm, despite constant warnings and scrutinise from the medical regulatory bodies and healthcare providers. Although benzodiazepines have many health-benefit roles and the aftereffect of benzodiazepines are usually well received in the general public, its toxicity and adverse effect is still the source for morbidity and casualty for certain patients.

## **1.2 PROBLEM STATEMENT**

Despite being recommended for intermittent, brief and acute symptomatic relief, benzodiazepines are the most commonly prescribed psychoactive drug in many parts of the world. This practice of common prescribing is either because of insufficient knowledge of prescribing or because of inadequate data about the adverse effects and clinical outcomes associated with benzodiazepines usage. The evidence supporting its

long-term usage is not strongly justified; it is either because of the insufficient of a systematic database documenting such efficacy or because of an extensive literature establishing the risk of prolonged usages, such as dependence. Since there is no evidence-based clinical guideline on the management of benzodiazepines in Malaysia, most practitioners are using their judgment and based on patients' preference and history in making a decision. The data on prescription of medications, especially on benzodiazepines at the population level are rare, with a few exceptions. Current information on benzodiazepines consumption in Malaysia was obtained from a national-level medicine utilisation report published in 2014 that reports the total medicine used in the country from 2011 to 2014. Nevertheless, after 2014, there is no new publication, and conversely, we saw the need for an analysis of how prescribing trends and patterns have changed over recent years. Quantifying benzodiazepines usage in populations helps to reaffirm the current prescribing practices and pinpoint the existence of problematic consumption that could be prophetic for primary adverse outcomes. While several developed countries have established a nationwide register of patient's data to enable them to conduct a study not only on benzodiazepines but also other medications related to current pharmacoepidemiology issues, scant information is available about the nature of benzodiazepines prescribing in Malaysia compared to other countries. Due to this limitation, the data on the trends and patterns of benzodiazepines prescriptions and its use in Malaysia are still limited. Therefore, this topic has become our primary interest.

### **1.3 RESEARCH OBJECTIVES**

1. To evaluate the prescribing trends of oral benzodiazepines.

2. To evaluate the prescribing patterns of oral benzodiazepines.
3. To assess the association between patient demographic characteristics with benzodiazepines prescribing patterns

#### **1.4 RESEARCH QUESTIONS**

1. What are the prescribing trends of oral benzodiazepines?
2. What are the prescribing patterns of oral benzodiazepines?
3. What are the association between patient demographic characteristics with benzodiazepines prescribing patterns?

#### **1.5 SIGNIFICANCE OF THE STUDY**

This research will be a pertinent endeavour in identifying the prescribing trends and exploring the patterns of benzodiazepines in Malaysia's healthcare facility. The analysis of trends in the study provides the premise for risk assessment in regards to benzodiazepines' usage and a basis for pharmacovigilance investigation. By evaluating the benzodiazepines patterns at the prescription level and further assessing patient demographic characteristics, this study also supports the implementation and monitoring of the National Medicines Policy (DUNas) that aims to promote the rational use of medicines in Malaysia. The defined daily dose (DDD) of oral benzodiazepines enables the study to compare the prescribing trends and patterns in Malaysia with previous studies. It will also benefit the healthcare practitioners as the study will be set as a benchmark of how we should manage the art of benzodiazepines' prescribing to the patient. Besides, the study is vital in providing a

rough estimation of disease prevalence, determining the number of benzodiazepines' patients and prescriptions and also assessing the prescriber's speciality. Along with improving the therapeutic care, this study is expected to provide a foundation and encouragement of the building of assessment tools, recommendation guidelines and intervention strategies. Fundamentally, it will further reduce the number of fatalities resulted from the abuse liability, inappropriate or unnecessary use of benzodiazepines.

## **1.6 DEFINITIONS OF TERMS**

### **Defined daily doses per 1000 patients per day (DDD/1000 patients/day)**

It is defined as “the assumed average maintenance dose per day for a drug used for its main indication in adults”. In general idea, the DDDs per-1,000 patients per-day provides a rough estimation of the proportion of the population treated daily with a drug. For example, the figure 10 DDD/1000 patients/day indicates that 10 in 1,000 or 1% of the population was prescribed or administered a particular drug or group of drugs every day in a particular year, on the average.

### **Defined daily doses per 1000 patients per year (DDD/1000 patients/year)**

The definition is almost the same as DDD/1000 patients/day. This is an assumption of an average maintenance dose per year for a drug used for its main indication in adults. It summarised an estimation of yearly usage of a population treated with a drug.

## **Psychiatric Disorders**

Diagnosis of a patient that is written in the prescription consequently categorised into two categories. One of them is psychiatric disorders. This categorisation is to ensure concise interpretation and was coded by referring to International Classification of Diseases 10th Edition (ICD-10) (World Health Organization, 2013). The study includes the following as part of psychiatric disorders; F10-F19: Mental and behavioural disorders due to psychoactive substance use; F60-F69: Disorders of adult personality and behaviour; F70-F79: Mental Retardation; G00-G99: Diseases of the nervous system (Table 3.2).

## **Non-Psychiatric Disorders**

The written diagnosis on the prescription that does not fall under psychiatric disorders as per the International Classification of Diseases 10th Edition (ICD-10) (World Health Organization, 2013).

## **Psychiatry**

The numerous medical specialities in the data were divided into two types; psychiatry and non-psychiatry. 'Psychiatry' belongs to a prescriber who works under the Psychiatry and Mental Health Department.