PHYSICAL EXAMINATION AND CHEMICAL ANALYSIS OF ERIMIN-5 TABLETS FOR FORENSIC DRUG PROFILING

RADWAN BIN MAIL

UNIVERSITI SAINS MALAYSIA

2021

PHYSICAL EXAMINATION AND CHEMICAL ANALYSIS OF ERIMIN-5 TABLETS FOR FORENSIC DRUG PROFILING

by

RADWAN BIN MAIL

Thesis submitted in fulfilment of the requirements

for the degree

Master of Science

November 2021

ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest appreciations to the All Mighty Allah, for his blessings to me and the journey to conduct this research. A special gratitude I give to my wife, my children, parents and family members for their support and considerations during my hard times. I would like to express my greatest gratitude to my supervisor, Associate Professor Dr. Ahmad Fahmi Lim Abdullah for the interesting and challenging research project, for providing critical advice and the knowledge he supplied over the duration of this project. Special thanks go to Dr. Chang Kah Haw for being endless helpful in providing his valuable advice, suggestions, guidance, and encouragement at all stages of my research. A very big thank you to Tuan Hj. Mohamed Zaini Bin Abdul Rahman, Director-General of the Department of Chemistry Malaysia who permitted me to pursue my postgraduate study. Special thanks to Teoh Way Koon for initiating the idea and for his strong support at the time the research was conducted. The entire staffs in Department of Chemistry Kelantan branch are also not to be forgotten in their part of this thesis. It would not have been possible without them. I would also like to specially acknowledge the Science Officers at the School of Health Sciences, Universiti Sains Malaysia for assisting me to conduct my research. Last but not the least, I would like to thank to all my friends and everyone who had directly and indirectly helped me throughout my study.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS, SYMBOLS AND ACRONYMS

%	Percentage
±	Plus–minus
°C	Degree Celsius
°C/min	Degree Celsius per minute
μL	Microliter
μm	Micrometer
λ	Lambda
A	Absorbance
ATR	Attenuated total reflectance
ATS	Amphetamine-type simulant
C	Carbon
ca.	*circa* - approximately
CDC	Centres for Disease Control and Prevention
Cl	Chlorine
cm	Centimeter
D&C	Drugs and cosmetics
DAD	Diode-array detector
DEA	Drug Enforcement Administration
et al.	*et alia* – and others
F	Fluorine
FD&C	Foods, drugs, and cosmetics
FID	Flame Ionisation Detector
FTIR	Fourier Transform Infra-red
HPLC	High Performance Liquid Chromatography
HCA	Hierarchy Cluster Analysis
g	Gram
GABA	Gamma-aminobutyric acid
GC	Gas chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
GHB	Gamma hydroxybutyrate
H	Hydrogen

HCA	Hierarchical cluster analysis
i.d.	Internal diameter
i.e.	*id est* – that is
INCB	International Narcotics Control Board
IR	Infrared
L	Liter
LD_{50}	Lethal Dose 50
m/z	Mass-to-charge
MAM	6-monoacetylmorphine
min	Minute
mg	Milligram
mg/mL	Milligram per milliliter
mL	Milliliter
mL/min	Milliliter per minute
mol	Mole
mm	Millimeter
M	Molar
MAM	6-Monoacetylmorphine
MDMA	3,4-Methylenedioxymethamphetamine
MSD	Mass spectrometry detector
NIDA	National Institute on Drug Abuse
NPS	New psychoactive substances
O	Oxygen
NIST	National Institute of Standard and Technology
p	*p*-value
PCA	Principal component
PCA	Principal component analysis
PDA	Photodiode array
PLS-DA	Partial least-squares-discriminant analysis
QC	Quality control
r	Correlation coefficient
R^2	Regression coefficient
RSD	Relative standard deviation

SD	Standard deviation
S$	Singapore dollar
SVM	Support vector machines
TLC	Thin layer chromatography
UNDCP	United Nations Drug Control Programme
UNODC	United Nations Office of Drugs and Crimes
UV	Ultraviolet
v	Volume
XRF	X-ray fluorescence

PEMERIKSAAN FIZIKAL DAN ANALISIS KIMIA BAGI PIL ERIMIN-5 UNTUK PEMPROFILAN DADAH FORENSIK

ABSTRAK

Rampasan dadah haram Erimin-5 telah dilaporkan di Malaysia dan ianya mencerminkan betapa seriusnya isu dadah ini. Dadah tersebut berkemungkinan mengandungi nimetazepam atau pengganti lain yang dikelaskan bawah benzodiazepin. Benzodiazepin menyebabkan tindakbalas kepada sistem saraf pusat manusia yang memberi kesan hipnotik dan sedatif kepada pengguna dan telah digunakan secara meluas bagi mengatasi masalah kemurungan. Disebabkan potensi penyalahgunaan, pelbagai benzodiazepin yang disenaraikan dalam Jadual IV Konvensyen Antarabangsa Bahan Psikotropik 1971 telah diharamkan di banyak negara termasuk Malaysia. Dalam rutin analisis forensik, kromatografi gas-spektrometri jisim (GC-MS) dan kromatografi cecair prestasi tinggi (HPLC) masing-masing telah digunakan untuk penentuan kualitatif dan kuantitatif benzodiazepin. Namun begitu, usaha untuk penjejakan sumber dan pembezaan sampel kepada sampel bagi dadah haram sedemikian tidak diutamakan sehingga kini dengan hanya maklumat yang terhad yang boleh diperoleh untuk perisikan forensik. Justeru, pemprofilan forensik bagi tablet Erimin-5 melalui pendekatan fizikal dan pendekatan kimia membolehkan penyiasatan seterusnya dengan tujuan bagi mewujudkan pembezaan atau pengumpulan sampel-sampel tersebut. Dalam kajian ini, 101 tablet Erimin-5 yang dikumpulan daripada kerja kes telah diperiksa secara visual dan dinilai dari segi bentuk, warna, diameter, ketebalan dan beratnya. Selepas pemeriksaan fizikal, campuran bahan dan pewarna dalam kandungan sampel Erimin-

5 telah ditentukan masing-masing dengan menggunakan spectroskopi transformasi Fourier Infra Merah dengan Pantulan Penuh Pengecilan (ATR-FTIR) and kromatografi lapisan nipis (TLC). Teknik GC juga telah diaplikasi untuk mengesahkan kehadiran bahan berkaitan dengan benzodiazepine, dan peratusan nimetazepam telah dikuantitikan menggunakan HPLC. Melalui kajian ini, pemeriksaan fizikal menunjukkan ciri-ciri unik tablet Erimin-5 dan membolehkan pembezaan sampel kepada sampel pada tahap tertentu. ATR-FTIR bergandingan dengan analisis komponen utama telah mengumpulkan sampel Erimin-5 di dalam kluster yang serupa kepada yang telah diadukkan dengan mannitol atau laktosa. Analisis TLC membolehkan penentuan pewarna yang berkemungkinan yang telah ditambah ke dalam kandungan tablet tersebut. Dalam kajian ini, kebanyakannya telah ditambah dengan pewarna sunset yellow. Melalui analisis GC, tablet Erimin-5 telah dikesan mengandungi sama ada nimetazepam atau etizolam. Nimetazepam telah dijadualkan bawah Akta Dadah Berbahaya 1952. Nimetazepam telah dikuantitikan dan dilaporkan dengan julat peratusan antara 0.62-4.49%. Secara kesimpulan, pembezaan forensik sampel Erimin-5 telah berjaya dilaksanakan, sekurang-kurangnya membolehkan perbandingan sampel kepada sampel. Kajian ini boleh memanfaatkan agensi-agensi penguatkuasaan undang-undang melalui satu siri strategi pemeriksaan fizikal dan pemeriksaan kimia bagi penyiasatan dan perisikan berkaitan dengan dadah haram.

PHYSICAL EXAMINATION AND CHEMICAL ANALYSIS OF ERIMIN-5 TABLETS FOR FORENSIC DRUG PROFILING

ABSTRACT

Seizure of illicit Erimin-5 drugs had been reported in Malaysia, indicating the seriousness of this issue. These drugs might contain nimetazepam or other substitutes that are classified under benzodiazepines. Benzodiazepines possess hypnotic and sedative effects, making them to be widely used as depressants on human central nervous systems. Due to potential of abuse, many benzodiazepines listed in the Schedule IV of the International Convention on Psychotropic Substances 1971 are banned in many countries, including Malaysia. In routine forensic analysis, gas chromatography-mass spectrometry (GC-MS) and high-performance liquid chromatography (HPLC) techniques are utilised for qualitative and quantitative determination of benzodiazepines, respectively. However, efforts on source tracking and sample-to-sample comparison of such illicit drug have not been prioritised thus far with only limited information could be retrieved for forensic intelligence. Therefore, forensic drug profiling of Erimin-5 tablets through physical and chemical means warrants further investigation with the aim to establish discrimination or clustering of these samples. In this study, 101 Erimin-5 tablets collected from case work were visually observed and evaluated in term of their shape, colour, diameter, thickness, and weight. Subsequently, the adulterants and colourants in the composition of Erimin-5 pills were determined using attenuated total reflectance-Fourier Transformed Infrared (ATR-FTIR) spectroscopy and thin layer chromatography (TLC), respectively. GC technique was also applied to confirm the

presence of benzodiazepine related substances, and percentage of nimetazepam was quantified using HPLC. Through this study, physical examination demonstrated the unique characteristics of Erimin-5 tablets, allowing certain degree of sample-to-sample comparison. ATR-FTIR coupled with principal component analysis grouped the Erimin-5 samples into the clusters similar to those adulterated with mannitol or lactose. TLC analysis allowed the determination of possible colourants that had been added into the composition of these tablets, and in this study, mainly with sunset yellow dye. Through GC analysis, the Erimin-5 tablets were detected to have contained either nimetazepam or etizolam, where the former was scheduled under the Dangerous Drugs Act 1952. Nimetazepam was subsequently quantified using HPLC and reported with percentage range between 0.62 – 4.49%. To conclude, forensic discrimination of Erimin-5 samples was successfully carried out, at least allowing for sample-to-sample comparison. This study could benefit the law enforcement agencies through a series of physical and chemical examination strategies for illiciti drug related investigation and intelligence.

CHAPTER ONE

INTRODUCTION

1.1 Background of the study

Misuse of drug continues to be a challenging issue confronting the law enforcement authorities worldwide. According to the United Nation Office of Drugs and Crime (UNODC), the number of drug users had achieved nearly 269 million people used drugs worldwide, and this figure was reported to be 30% higher than in 2009 (UNODC, 2019; UNODC, 2020a). The impact of COVID-19 pandemic is yet to be fully known; however, the cross-border restriction had led to the shortage of illicit in the black market, causing price increment and purity reduction. UNODC also stated in its report where the poorest could have been more vulnerable to drug use, as well as the drug trafficking and cultivation for money along with rising unemployment and reduced opportunities (UNODC, 2020a).

Benzodiazepine is a class of psychoactive drugs where its chemical structure fuses a benzene ring and a diazepine ring. From the medicinal perspectives, this class of drugs acts as depressants and frequently prescribed to treat anxiety, insomnia, and/or seizures. Benzodiazepine possesses hypnotic and sedative effects, making it a depressant towards the central nervous system (Fukinaga et al., 1998; UNODC, 2019). They had been detected in drug overdose cases, and potentially lead to adverse health effects or even death especially when consumed in combination with opioids (UNODC, 2021).

In the context of drug control and legislation, the Commission on Narcotic Drugs is mandated and established the scope under the three International Drug Control Conventions, namely the Single Convention on Narcotic Drugs of 1961, the Convention on Psychotropic Substances of 1971, as well as the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988. Due to drug abuse potential of benzodiazepine, majority of the substances under this group classified under Schedule IV of the International Convention on Psychotropic Substances 1971 and banned in many countries (Drug Enforcement Administration, 2020; UNODC, 2021). A total of 38 substances under the classification of benzodiazepines are under international control (UNODC, 2021). The examples of banned benzodiazepine included nimetazepam, diazepam, nitrazepam and flunitrazepam. They are substances with high therapeutic value but possess the risks of abuse and minor threat to the public health, causing them listed in Schedule IV (UNODC, 2016). In Malaysia, nimetazepam are scheduled under the Dangerous Drugs Act 1952.

According to World Drug Report (2021), majority of the sedatives and tranquilisers seized worldwide in 2019 were gamma hydroxybutyrate (GHB). However, the benzodiazepines were mostly seized in Malaysia globally, indicating the seriousness of the drug issue in the country (UNODC, 2021). Benzodiazepines, mainly contain nimetazepam as the common active composition, collectively sold as Erimin-5 in the black market (Peh and Mahendran, 1989; Abdullah et al., 2012; UNODC, 2019). Erimin-5 is commonly in the form of tablets. These illicit drugs are sold in relatively cheap price, and they are easily accessible as compared to other conventional illicit drugs such as heroin and cocaine. It also makes Erimin-5 one of the commonly abused

sedatives (INCB, 2012; UNODC, 2019; Hilmy, 2020; Zolkepli, 2020). Similar use and distribution patterns were also reported in neighbouring countries, including Singapore and Indonesia (Erviani, 2016; The Jakarta Post, 2017; Ng, 2020; Tan, 2020). The severity of these illicit drugs had been frequently reported in media.

Despite harsh punishment on drug distributers and traffickers, Malaysia continues to be an attractive place for drug trafficking. This is partly due to its strategic geographical location and border entrance accessibility for the sale and distribution of Erimin-5 tablets. The Bureau of International Narcotics and Law Enforcement Affairs (2014) had also reported an increase of its trafficking activities, threatening the societal well-being of the population. Therefore, determination of these tablets is deserved to direct their respective sources and to subsequently link according to the different distribution networks (Bureau of International Narcotics and Law Enforcement Affairs, 2014).

To confirm the identity and determine the purity of illicit drug, the law enforcement authorities frequently submit the seized tablets to the forensic chemistry laboratories for analysis. Gas chromatography-mass spectrometry (GC-MS) technique is routinely utilised for testing of these tablets due to its strong resolving power and robustness (Abdullah et al., 2012; Abdul Rahim, 2013). The routine analytical technique had provided significant contributions to defensible qualitative of benzodiazepines in both biological and narcotic samples through the utilisation of certified reference standard, as well as the generated mass spectrum in GC-MS (Abdullah et al., 2012; Abdul Rahim, 2013). Upon determination of the identity, the amount of the target

compound, specifically the nimetazepam, was quantified using high performance liquid chromatography technique (Abdul Rahim, 2013). However, efforts on source tracking of such illicit drug based on their similar profiles have not been prioritised thus far with only limited information could be retrieved for forensic intelligence. Moreover, many reported analytical techniques often require special sample preparation procedures, thus making such analysis laborious.

As part of analytical studies on Erimin-5 tablets, discrimination of Erimin-5 tablets using various techniques including both the physical and chemical means are worth to be explore with aim to establish potential clustering of the seized Erimin-5 samples. Forensic drug profiling is a procedure involving the systematic characterisation of seized sample by physical and chemical approaches to support the intelligence and operational works by the law enforcement authorities (UNDCP, 2001). The potential linkage among samples could be established, and samples from different seizures could also be classified into different groups of related samples. Subsequently, forensic drug profiling could also provide information on the possible linkages with the suppliers, distributors, and users, as well as the distribution networks or patterns of the illicit drugs (UNDCP, 2001). It is hoped that the classification of the illicit Erimin-5 tablets encountered in this study could assist forensic investigation and intelligence in linking the street level seizures, as well as in facilitating sample-to-sample, case-to-case, and seizure-to-seizure comparisons.

1.2 Problem statement

The seizure of illicit Erimin-5 drugs had been reported in Malaysia, suggesting the seriousness of this issue (Hilmy, 2020; Zolkepli, 2020; Nambiar, 2021; Yakkub, 2021). Based on the experience of the researcher, the number of Erimin-5 samples submitted to the forensic laboratories for analysis had also increased annually, indicating the degree of problem due to such illicit drug. In addition to that, drug manufacturing laboratories involving in producing benzodiazepines were dismantled in six from a total of 139 drug manufacturing facilities dismantled in Malaysia throughout the years. Table 1.1 reported the number of illicit clandestine laboratories detected in Malaysia from 2015–2019 where illicit methamphetamine had dominated the statistics (UNODC, 2020a). Although the number of benzodiazepine laboratories dismantled was relatively low as compared other illicit drugs; however, the actual number of active and inactive laboratories in the country remained unclear given that the laboratory operators and syndicates always attempt to prevent from being detected and conceal their illegal activities. In view of this, the continual supply and distribution of Erimin-5 tablets into the domestic market would ultimately cause severe economic loss, and more importantly the deterioration of the societal well-beings of the country.

Although illicit drug problem is a serious issue that needs attention from various parties especially the law enforcement authorities, limited information could be retrieved regardless their source of origin as well as the supply and distribution chain network. The availability of such information is important to serve as forensic intelligence information for agencies including Royal Malaysian Customs Department and Royal Malaysia Police to track down to the origin and network distribution. In routine forensic

analysis, the testing is limited to the scope in determining the identity of the illicit drug sample and the quantity of the active ingredient. Analytical characterisation through physical and chemical means was less likely to be conducted by the forensic laboratories, and therefore a need to explore further information is required for forensic comparison and intelligence. In this study, both the physical and chemical profiles of seized Erimin-5 tablets were established, and subsequently clustered and/or discriminated based on the analytical outcome.

1.3 Scope of the study

In routine analysis, drug samples in tablet form submitted to forensic laboratories are physically observed for their possible identities, and subsequently analysed by GC-MS and quantified by HPLC. In this study, both GC-MS and high-performance liquid chromatography (HPLC) were also carried out to confirm and quantify the illicit drugs. Apart from that, the physical characteristics of the submitted tablets as well as alternative analytical techniques, namely the attenuated total reflectance-Fourier transform infra-red spectroscopy (ATR-FTIR) and thin layer chromatography (TLC) were also performed to provide more information related to the illicit drugs. It was noted that samples tested in the current study was limited to those samples submitted to the Department of Chemistry Malaysia due to geographical constraints and only samples seized for a period of 18 months from September 2018 to April 2020.

1.4 Aim and Objectives

This study was aimed to characterise the illicit Erimin-5 tablet for forensic investigative intelligence. To achieve the aims, three objectives were set as follows:

i. To evaluate the physical characteristics of illicit Erimin-5 samples through physical examination.

ii. To evaluate the chemical characteristics of illicit Erimin-5 samples through instrumental analyses, including ATR-FTIR, TLC, GC and HPLC techniques.

iii. To compare the ATR-FTIR profiles of illicit Erimin-5 samples for discrimination and/or clustering.

1.5 Significance of the study

This study would benefit the law enforcement agencies for forensic intelligence. The current study utilised a series of physical and chemical examination strategies for analysis of the illicit Erimin-5 samples, and the information gathered from both the physical and chemical characterisation could provide clue in term of the similarities and differences among the illicit Erimin-5 samples. To certain extent, forensic drug profiling would allow the establishment on their possible source of production and distribution network. The output of this study could also advance the body of knowledge in drug related investigation in increasing the successful prosecution rate, and directly promote a safer society.

CHAPTER TWO

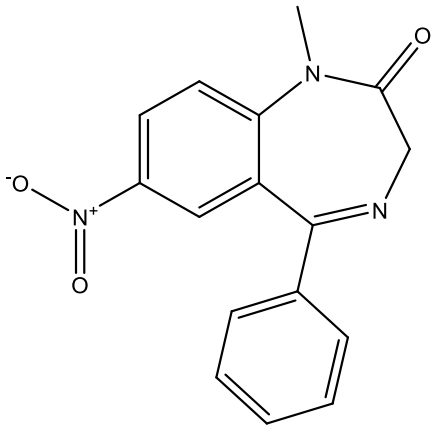
LITERATURE REVIEW

2.1 Introduction

This chapter provides a summary of literature review on benzodiazepines with particular focus on Erimin-5. An overview of the chemical structures and nomenclatures are included. The reasons of abuse, as well as the degree and trends of drug problems with selected cases in Malaysia are briefly discussed. The analytical techniques for drug analyses, specifically for benzodiazepines, and particularly Erimin-5 wherever related, were also discussed. A brief overview on statistical analysis of complex analytical data, such as those obtained from ATR-FTIR analysis is included before a summary is made at the end of the chapter.

2.2 Erimin-5 – A benzodiazepine

The history of Erimin-5 can be traced back to its licit production by its proprietary owner, Sumitomo Corporation of Japan, before it discontinued production in 2015 (UNODC, 2020a). It is used in medicinal disciplines as an intermediate acting hypnotic drug. Licit Erimin-5 contains 5 mg of the active ingredient named as nimetazepam, which is categorised under benzodiazepine based on its chemical structure. The IUPAC name of nimetazepam is 1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1, 4-benzodiazepin-2-one (UNODC, 1971), and its chemical structure is shown in Figure 2.1.



Nimetazepam (1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one)

Figure 2.1: The chemical structure and IUPAC name of active ingredient in Erimin-5.

Molecular formula for nimetazepam is $C_{16}H_{13}N_3O_3$ with a molecular weight of 295.3 g/mol. At room temperature, pure nimetazepam (98%) is a neat solid, with a stability of more than two years given that it is stored at -20°C. According to safety data sheet, the oral LD_{50} (on mouse) was reported to be 970 mg/kg while many toxicological effects have not been thoroughly studied (Cayman Chemical, 2021). Pharmacologically, nimetazepam carries sedative, anxiolytic, and anticonvulsant properties. It was also shown to have a moderately long duration of action. An elimination half-life of 14 to 30 hours was reported, and it can be converted to its metabolite, namely the nitrazepam (McMahon, 2010). As stated by McMahon (2010), nimetazepam is subjected to tolerance, dependence, and abuse like other benzodiazepines.

2.2.1 Erimin-5 and other chemically similar compounds

The class of benzodiazepines, since its first introduction of Librium (*i.e.* chlordiazepoxide, or its IUPAC name, 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide, Figure 2.2) in 1960, benzodiazepine drugs have become one of

the most widely prescribe drugs to treat insomnia, anxiety, suppression of convulsions and panic attacks. Note that chlordiazepoxide is an unusual structure with an oxygen atom on the nitrogen atom closer to the aromatic side ring (Kuhar, 2012).

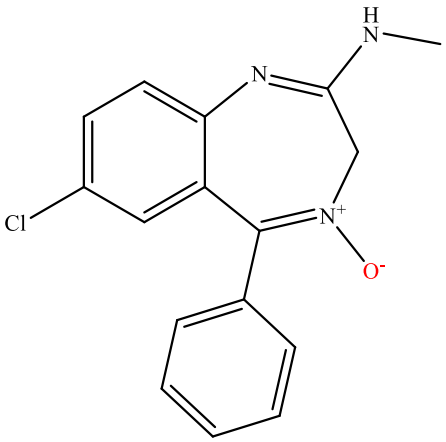
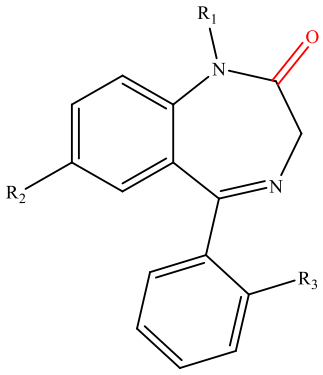


Figure 2.2: Chemical structure of chlordiazepoxide.

Pharmacologically, these drugs act by attaching the compounds to the receptor sites close to $GABA_A$ receptor in the membranes of neurons responsible for fear response. GABA is the acronym of gamma-aminobutyric acid, a substance produced by the body from substances in food. GABA can attach to the specific sites called GABA receptors. When benzodiazepines are in position, they intensify the attraction between GABA molecules and $GABA_A$ receptors, causing significant increase in the number of sites which can be occupied by GABA. As a result, the number of desensitized neurons is also increased. In such a way, benzodiazepines calm the fear response *via* boosting the calming effect of GABA on the nerve activity (Kuhar, 2012). It is therefore important to understand the chemical structure of benzodiazepines other than nimetazepam.

The general structure of benzodiazepines which are similar to nimetazepam have an oxygen attached to the seven-membered ring as indicated in Table 2.1. The different substituents in the position of R_1, R_2 and/or R_3 can differentiate among the nimetazepam related compounds (Mizuno, 2009). Note also that different R groups lead to different properties of the chemical compound, especially when the drug potency is a concern. For instance, with the slight difference in the substituents of R_2 and R_3 between diazepam (Cl, H) and flunitrazepam (NO_2, F), the latter is ten times more potent than the former (Schwartz and Weaver, 1998; Kuhar, 2012). Additionally, flunitrazepam is found to be commonly used as date-rape drug (Schwartz and Weaver, 1998). In Table 2.1, the product names of the respective compounds were also stated.

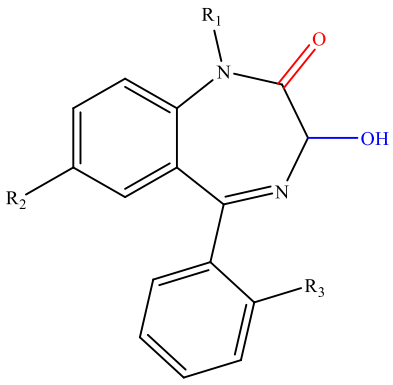
Table 2.1: Chemical structures of nimetazepam and related compounds.



Compounds	Example of product brand	R_1	R_2	R_3
Nimetazepam	Erimin	$-CH_3$	$-NO_2$	-H
Diazepam	Valium	$-CH_3$	-Cl	-H
Flunitrazepam	Rohypnol	$-CH_3$	$-NO_2$	-F
Clonazepam	Klonopin	H	$-NO_2$	-F
Nitrazepam	Mogadon	-H	-H	$-NO_2$
Flurazepam	Dalmane	$-CH_2CH_2N(C_2H_5)_2$	-Cl	-F
Halazepam	Pixapam	$-CH_2CF_3$	-Cl	-H
Quazepam	Doral	$-CH_2CF_3$	-Cl	-F
Note: These compounds have an oxygen attached to the seven-membered ring, as marked red.				

There is another group of benzodiazepines where the members are structurally very similar to the general structure as seen in nimetazepam and its related compounds but with an additional hydroxyl group (-OH) attached to the seven-membered ring (Kuhar, 2012). An example of such compound is lorazepam, which was also reported it misuse as a type of date rape drug (Meatherall, 1998). Table 2.2 lists a few examples of lorazepam and related compounds along with their respective product names.

Table 2.2: Chemical structures of lorazepam and related compounds.

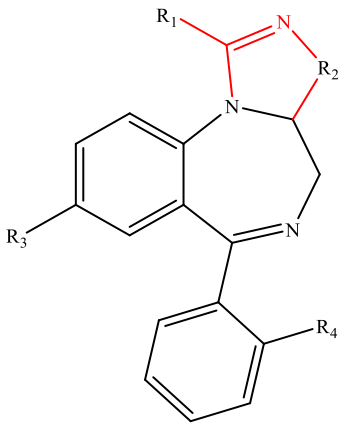


Compounds	Example of Product Brand	R_1	R_2	R_3
Lorazepam	Ativan, Temasta, Tavor	-H	-Cl	-Cl
Oxazepam	Serax, Alepam	-H	-Cl	-H
Temazepam	Restoril	$-CH_3$	-Cl	-H

Note: These compounds have an oxygen atom and a hydroxyl group attached to the seven-membered ring, as marked red and blue.

There are also tricyclic benzodiazepine derivatives with additional substituents that provides higher potency, for instance, triazolam, which is estimated to be 20 times more potent to diazepam (Kuhar, 2012). Together with alprazolam, triazolam was also used as a type of date rape drug (Meatherall, 1998; Walling, 2000). Table 2.3 shows the chemical structure of triazolam and its related compounds.

Table 2.3: Chemical structure of triazolam and related compounds.



Compounds	Example of Product Brand	R_1	R_2	R_3	R_4
Triazolam	Halcion	–CH3	–N–	–Cl	–Cl
Alprazolam	Xanax	–CH3	–N–	–Cl	–H
Estazolam	ProSom	–H	–N–	–Cl	–H
Midazolam ()–	Versed	–CH3	-CH–	–Cl	–F
Note: These compounds have a five-member ring attached to the seven-membered ring, as marked red.					

As stated by UNODC (2020a), the street level Erimin-5 tablets may or may not contain nimetazepam and a range of other substances. Therefore, it is important to understand possible substances that can be used as the substitutes of nimetazepam. As mentioned earlier, nimetazepam belongs to a class of drugs largely known as benzodiazepines, which act as “downers” as described by John-Roger and McBay (2005) that brings one down by suppressing the central nervous system. They act opposite to the effects of “uppers” such as amphetamine-type stimulants. Benzodiazepines exemplified above have different degree of potency, but all are likely to be encountered in illicit tablets as abusers or traffickers could use the similar compounds available to produce the drugs in their local settings.

2.2.2 Erimin-5 as a drug of abuse

Erimin-5 was previously used as a prescription drug to treat insomnia and depression. Because of its properties of being hypnotic, anxiolytic, sedative, and musculoskeletal relaxant (Solace, 2019), Erimin-5 has ended up as a “soft” drug of

abuse for its desired effects to help set off addiction in different drug users, especially in Asia countries such as Hong Kong, Malaysia, and Singapore. To Ecstasy or methamphetamine users, Erimin-5 was reported to act as a sedative to help sleep after bingeing (Chong et al., 2004). Note that there are several distinctive stages that a methamphetamine user may experience, starting from the initial experience of rush, the high, the binge, tweaking, the crash, meth hangover and withdrawal experience (Foundation for a Drug-Free World, 2021). A binge is an uncontrolled urge to maintain the high taking more methamphetamine that might last three to fifteen days, and during bingeing, the abuser becomes both mentally and physically hyperactive (Foundation for a Drug-Free World, 2021). This explains why Erimin-5 is abused.

2.2.3 Reasons of Erimin-5 abuse with other chemically similar compounds

In general, Erimin-5 is believed to be used as a substitute for narcotic drugs such as heroin when the availability of the targeted drugs was low (Chong et al., 2004). This could be understood as its long sedative activity and availability at a low cost. An early study conducted by Navaratnam and Koong (1990) on 249 opiate addicts in Malaysia found that 75% of opioid abusers, mainly heroin users, have reported simultaneous use of benzodiazepines. The examples of benzodiazepines included flunitrazepam, alprazolam, triazolam, lorazepam, nimetazepam and nitrazepam. The main reason for the use of adjunctive drugs was to augment the effect of the opioid to achieve feeling of high from heroin. Other reasons of benzodiazepine abuse were to diminish the withdrawal symptoms or to treat sleep disturbance and the feeling of depressed (Navaratnam and Koong, 1990).

A study conducted by Gelkopf et al. (1999) on 263 patients receiving treatment of heroin addiction with methadone maintenance reported to have used benzodiazepines to self-medicate their emotional distress, although many of the patients responded to have also used them to 'get high'. In the study, flunitrazepam was the most abused benzodiazepines, followed by diazepam (ca. 54 %) and oxazepam (ca. 37%). However, it was also noted that no nimetazepam was reported by the study, indicating that different regions of the world could have different pattern and preference of drug use (Gelkopf et al., 1999).

A review by Jones et al. (2012) indicated that benzodiazepines are commonly co-abused with other drugs, most frequently opioids. By combining opioids drugs and benzodiazepines, drug abusers were reported to achieve a greater level of euphoria. The authors also opined that more clinical evidence is needed to test the hypotheses in controlled and laboratory settings. When dugs are used together such as by combining opioid and benzodiazepines, it could result in serious detrimental effects on both physical and mental health, increasing risk of overdose besides exacerbating both criminal and medical problems associated with the drug users (Jones et al., 2012).

It was believed that Erimin-5 was used as a soothing drug to reduce the effect during the bingeing stage of amphetamine-type stimulant (ATS) use (Foundation for a Drug-Free World, 2021, Chong et al., 2004). ATS, particularly 3,4-methylenedioxy methamphetamine (MDMA) or ecstasy and methamphetamine are "uppers" that increase wakefulness and focus because of the substance that causes the brain to flood neurotransmitters (dopamine and norepinephrine) in producing feelings of euphoria. On

the other hand, benzodiazepines act on the on the opposite way as to affect the feeling by taking amphetamines or as “downers” to give sedative, anti-anxiety, and muscle relaxant effects. Under proper patient management, benzodiazepines including lorazepam and midazolam have been used clinically as first-line medication for sedation to manage disturbed behaviour in patients with acute methamphetamine-related problems (Gowing and Holmwood, 2017).

A pilot study by Farnaghi et al. (2020) comparing clonazepam and lorazepam in the clinical treatment of 30 methamphetamine-poisoned children indicated that both drugs were equally effective at similar doses. However, it was also suggested that lorazepam was safer between the two drugs for oral maintenance treatment given that there was higher potency of clonazepam. Indirectly, it implied a potential risk of overdose if not properly administrated to children (Farnaghi et al., 2020). Though mixing ATS with benzodiazepines might give the abusers a sense of euphoria or to cancel out the effect of ATS but this could be fatal to the heart simply because ATS increases the heart rate while benzodiazepines as depressants act to slow down the heart rate. Potentially, this might result in dysrhythmias or heart failure in the drug abusers (Alston, 2020).

2.2.4 Effects of Erimin-5 abuse

The abuse of Erimin-5 could lead to adverse health complications. Peh and Maheridran (1989) have reported several cases of Erimin-5 abuse showing the clinical psychiatric complications and drug tolerance. Dependency was developed in a 20-years old man who had been taking four tablets of Erimin-5 for a period of two years, where

increased anxiety was developed (*i.e.* withdrawal symptoms) when the user attempted to decrease or stop taking the drugs. In another case, a 34-years old male Erimin-5 user of 2-3 tablets a day had suffered withdrawal psychosis. He was reported to have seen 10-20 Chinese man talking and running on the floor but disappeared when he shouted at them. It was a scenario known as "Lilliputian hallucination" (Peh and Maheridran, 1989). Note that Lilliputian hallucination refers to a type of hallucination in which people, animals or things appear smaller than they should be in real life. It was a term first introduced by the English psychiatrist, John Todd (1914-1987) (Shiel, 2018).

A transient (*i.e.* lasting for only a short time) drug psychosis was also reported on a 27-years old man consuming 10 Erimin-5 tablets and the consumption had led to aggressive behaviour (Peh and Maheridran, 1989). These cases indicated the danger of uncontrolled abuse of Erimin-5 while the users thought that it could be used to reduce the effect of withdrawal symptoms of taking illicit drugs such as MDMA and methamphetamine (Solace, 2019).

It is important to point out that the potential of overdose which could cause death. The fatal rate could be higher if it were associated with multiple drugs usage, especially in combination with alcohols. This can be simply explained by the drug metabolism and alcohol using the same cytochrome P450 system. It could lead to have overloaded the metabolic capacity of the liver, thus resulting in toxicity due to the presence of excessive free drugs in blood stream (John-Roger & McBay, 2005). Subsequently, the intoxication can cause respiratory suppression and potential death in the drug abusers.

2.3 Legal status of Erimin-5

Erimin-5 is a trade name and therefore, when discussing on the legal status, the active ingredient in Erimin-5 is the main concern. The licit Erimin-5 contains nimetazepam, in which, according to The Convention on Psychotropic Substances 1971, the compound is listed as controlled substance in Schedule IV of the list of substances under this convention (UNODC, 1971). Note that the Convention is a United Nations treaty aimed to control psychoactive drugs (*i.e.* mind-altering substance) by imposing import and export restrictions, as well as other rules with the ultimate propose to limit the drug use to scientific and medical purposes.

In this Convention, there are four schedules of controlled substances, named from Schedule I containing the most restrictive substances to Schedule IV containing the least restrictive substances. In brief, Schedule IV substances include hypnotics, tranquilizers (benzodiazepines) and analgesics, where nimetazepam is one of the benzodiazepine compounds (UNODC 1971). Table 2.4 provides a bigger picture on the international control of benzodiazepines under the United Nations Convention on Psychotropic Substances of 1971.

Table 2.4: The international control of benzodiazepines under the United Nations Convention on Psychotropic Substances of 1971.

Year of Scheduling Decision	Schedule	Substance Name	
1984	IV	Alprazolam	Haloxazolam
		Bromazepam	Ketazolam
		Camazepam	Loprazolam
		Chlordiazepoxide	Lorazepam
		Clobazam	Lormetazepam
		Clonazepam	Medazepam
		Clorazepate	Nimetazepam
		Clotiazepam	Nitrazepam
		Cloxazolam	Nordazepam
		Delorazepam	Oxazepam
		Diazepam	Oxazolam
		Estazolam	Pinazepam
		Ethyl loflazepate	Prazepam
		Fludiazepam	Temazepam
		Flurazepam	Tetrazepam
		Halazepam	Triazolam
1990	IV	Midazolam	
1995	III	Flunitrazepam	
	IV	Brotizolam	
2016	IV	Phenazepam	

(Source: UNODC Early Warning Advisory (EWA) on NPS. "April 2017 – UNODC: Several countries place benzodiazepine derivatives under national control." April 2017)

In the United States, nimetazepam is scheduled in Schedule IV controlled substances by Drug Enforcement Administration, Department of Justice as in Part 1308 of Title 21 (DOJ). While nimetazepam is a Class C controlled substances in Schedule II under the Misuse of Drug Act 1974 in the United Kingdom, it is also scheduled in

Misuse of Drugs Regulation 2001 as Schedule 4 Part 1 controlled drugs (UK Statutory Instruments, 2001). In Singapore, nimetazepam is strictly regulated by Misuse Drugs Act (Chapter 185) (Singapore Statue Online, 2021) as Class C controlled drugs in Schedule I of the Act. Note that the Act lists the controlled drugs in Schedule I with the substances being classified as Class A, Class B and Class C drugs (Singapore Statue Online, 2021). As Singapore is known for her strict drugs law, the penalties for the possession or consumption of nimetazepam can be up to ten years of jail or S$20,000 fine or both. For illegal traffic of nimetazepam, the offender could be served up to ten years of imprisonment and five strokes of cane. Anyone convicted to illegal import or export of nimetazepam could get up to 20 years of imprisonment and 15 strokes of the cane (Central Narcotics Bureau, 2021).

In Malaysia, the Dangerous Drugs Act (1952) has put nimetazepam as controlled drug in Part III is the First Schedule of the Act that consists of part I drugs of the highest potential of abuse and addiction, and part IV drugs of the lowest potential of abuse and addiction. As in Singapore, Malaysia has very strict drugs law that impose severe punishment to offenders of illegal possession, trafficking, import and export of controlled drugs (Dangerous Drugs Act, 1952). In brief, most countries have listed nimetazepam as a drug of control in the class of low to moderate potential of abuse and addiction.

2.4 Trends of benzodiazepines abuse

From the perspective of clinical settings of benzodiazepines, the increasing rise on the use of benzodiazepines, especially with polydrug abuse, has become a big concern to the authorities. In the United States, the National Institute on Drug Abuse (NIDA) database showed the continual rise of the country's drug overdose deaths involving opioids and benzodiazepines from the cases involving victims of all ages in 1999 to 2019 as demonstrated in Figure 2.3 (NIDA, 2020).

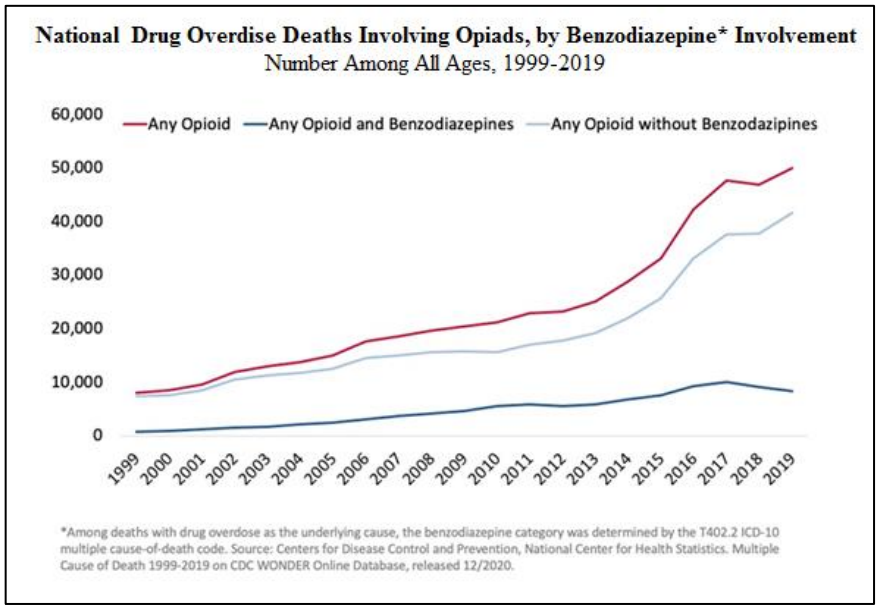


Figure 2.3: US drug overdose deaths involving opioids and benzodiazepines (Source: NIDA, 2020)

A study on benzodiazepine prescriptions and overdose mortality conducted by Bachhuber et al. (2016) showed that the number of adults in the United States who filled a benzodiazepine prescription had increased by approximately 67% from 8.1 million to 13.5 million people between 1996 and 2013. The findings indicated that although the trends of fatal overdoses involving benzodiazepines, in general, have plateaued;

nonetheless, the authors concluded that there was no evidence of decreases was found. The authors also highlighted that the trends in prescriptions and overdose mortality were found to be varied between demographic groups (Bachhuber et al, 2016).

Several authors cautioned that alcohol or polydrug use could increase the risk of fatal overdose. It was therefore suggested that interventions are needed to reduce the use of benzodiazepines or to improve the safety of the drugs (Bachhuber et al, 2016; Sun et al., 2017). Due the associated risk of using benzodiazepines with other medications, especially the opiates, the Centres for Disease Control and Prevention (CDC) had established and issued new guidelines for the prescribing of opioids in 2016. Among the highlights, it was recommended that clinicians, whenever possible, shall avoid prescribing benzodiazepines concurrently with opioids (Dowell et al., 2016).

From the perspective of non-medical use of benzodiazepines, it has been a long-established problem across the globe associated with many death and intoxication cases due to overdose, especially with opioid and polydrug use (UNODC, 2017). UNODC, *via* its global SMART update series, have expressed the concerns on the use of "legal" benzodiazepines and "designer" benzodiazepines that pose a huge treat to the public health (UNODC, 2020a). The types of benzodiazepines abused could be varied among the varying geographical areas. As reported by Warner et al. (2016), in the United States alone between 2010 and 2014, alprazolam and diazepam were the most frequently found concomitant benzodiazepines. In a more recent report, Hedegaard et al. (2017) have reported the regional differences in the specific drugs most frequently involved in drug overdose deaths in the United States. Among the findings, diazepam which ranked

among the top ten in 2011–2016 ranked 12th in 2017, while clonazepam was ranked 11th in 2017. It was also highlighted by the authors where information on regional differences in the drugs most frequently involved in drug overdose deaths could help in planning of prevention and policy making (Hedegaard et al., 2017).

It is important to point out that over time, some pharmaceutical benzodiazepine products might have stopped production. At the same time, some new classes of benzodiazepines might also be established and misused. One of such examples was nimetazepam marketed under the brand name "Erimin" had stopped from production several years ago but, perhaps because of familiarity of the users to the name, unlicensed preparations of nimetazepam are still available in some regions especially in Asian countries (UNODC, 2017).

2.5 Erimin-5 situation in Malaysia

Due to its prevalence, the name Erimin-5 tablets, commonly known as "Happy", "Five", "Give me Five" or "Happy Five" are still misused and detected in Malaysia drug market. Appearing as orange to pink round tablets, they are frequently found in the form of illicit products. The degree of problem related to Erimin-5 trafficking and misuse in Malaysia can be delineated by several large seizure cases reported. In early 2017, Royal Malaysian Police together with Royal Malaysian Customs at Port Klang seized a container shipped from Taiwan containing 2.5 million tablets containing nimetazepam. Police intelligence source indicated that these nimetazepam tablets were intended for the domestic market as well as for the market of Indonesia, Singapore, and Thailand (Mohamed Radhi, 2017). Figure 2.4 shows the photo during Royal Malaysian Police

press conference by the Director of Federal Police Narcotics Department, Datuk Seri Mohd Mokhtar Mohd Shariff exhibiting the Erimin-5 tablets found hidden inside 15 sofas of a container.

Figure 2.4: Photo taken during Royal Malaysian Police press conference showing Erimin-5 tablets concealed in sofas of a container at Port Klang (Source: The New Straits Times, 10 March 2017).

Another large seizure in a Erimin-5 "factory" was reported in September 2018 by the joint operation of Penang and Perak state police where 2.13 million Erimin-5 tablets, 742.6 kg of Erimin-5 powder, 27.3 kg syabu, 5,080 ecstasy pills and 53.7 kg of liquid chemicals were discovered in a factory (Figure 2.5). Two men and a lady who were believed to be the experts in processing and producing Erimin-5 tablets were caught. In fact, the drug seizure was one of the biggest cases in the country since 1996 (Hassan, 2018).