PHARMACOEPIDEMIOLOGIC AND COST EVALUATION OF OFF-LABEL DRUG PRESCRIBING AMONG PAEDIATRIC PATIENTS AT HOSPITAL SUNGAI BULOH, SELANGOR, MALAYSIA

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PHARMACOEPIDEMIOLOGIC AND COST EVALUATION OF OFF-LABEL DRUG PRESCRIBING AMONG PAEDIATRIC PATIENTS AT HOSPITAL SUNGAI BULOH, SELANGOR, MALAYSIA

by

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DEDICATION

This thesis is dedicated to Lord Ganesha, the Lord of success and remover of evil and obstacles.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
BNF	British National Formulary
BNFc	British National Formulary for Children
CME	Continuous Medical Education
CPD	Continuing Professional Development
DCA	Drug Control Authority
DIS	Drug Information System
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FPP	Full Paying Patient
GP	General Practitioner
ICH	International Council for Harmonisation
MBS	Modified Budgeting System
MeSH	Medical Subject Headings
MIMS	Monthly Index of Medical Specialities
MoH	Ministry of Health
MREC	Medical Research and Ethics Committee
NDTI	National Disease and Therapeutic Index
NICU	Neonatal Intensive Care Unit
NPRA	National Pharmaceutical Regulatory Agency
PDR	Physician's Desk Reference
PICU	Paediatric Intensive Care Unit

PIL	Product Information Leaflet
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RM	Malaysian Ringgit
SD	Standard Deviation
SHI	Social Health Insurance
SmPC	Summary of Product Characteristics
SPSS	Statistical Package for Social Sciences
THIS	Total Hospital Information System
TPN	Total Parenteral Nutrition
UK	United Kingdom
UKMMC	Universiti Kebangsaan Malaysia Medical Centre
US	United States of America
USD	United States Dollar
USFDA	United States Food and Drug Administration
WHO	World Health Organization

PENILAIAN FARMAKOEPIDEMIOLOGI DAN KOS BAGI MEMPRESKRIPSIKAN UBAT DI LUAR INDIKASI DALAM KALANGAN PESAKIT PEDIATRIK DI HOSPITAL SUNGAI BULOH, SELANGOR, MALAYSIA

ABSTRAK

Penggunaan ubat di luar indikasi sering berlaku di kalangan pesakit pediatrik. Data bagi penggunaan dan kos ubat-ubat yang digunakan di luar indikasi serta alasan di sebalik keputusan kuantitatif dari kajian sebelumnya, masih belum dikaji lagi. Penyelidikan ini bertujuan untuk mengkaji, menilai dan menyifatkan penggunaan ubat di luar indikasi di kalangan pesakit pediatrik di Hospital Sungai Buloh. Empat kajian telah dijalankan dengan menggunakan kaedah bercampur untuk menepati objektif-objektif penyelidikan. Kaedah kualitatif digunakan untuk menyediakan maklumat dasar mengenai kesedaran, pengetahuan, sikap dan pendapat berkaitan penggunaan ubat di luar indikasi bagi pesakit pediatrik. Kaedah kuantitatif pula digunakan untuk mengenalpasti tahap, jenis dan kos ubat yang digunakan di luar indikasi serta mengenalpasti keperluan pembelajaran di kalangan doktor pediatrik dan pegawai farmasi berkaitan penggunaan ubat di luar indikasi. Kajian-kajian ini telah dijalankan di kalangan pegawai farmasi dan doktor di Jabatan Farmasi serta Jabatan Pediatrik, Hospital Sungai Buloh. Kebanyakan peserta kajian (93.4%) mengetahui terma pengunaan ubat di luar indikasi. Seramai 60% peserta kajian tidak sedar bahawa mereka mempreskrib dan mendispen ubat di luar indikasi. Terdapat perbezaan di antara pendapat peserta kajian berbanding keputusan kajian-kajian yang telah dilakukan sebelum ini. Peserta kajian lebih prihatin terhadap aspek keselamatan (63.7%) berbanding aspek efikasi (40.7%) ubat yang digunakan di luar indikasi. Penggunaan bukti saintifik disarankan sebagai langkah pengawalan yang penting.

Perbincangan bersama ibubapa pesakit serta pengambilan keizinan untuk menjalani rawatan, dianggap sebagai langkah yang penting semasa ubat digunakan di luar indikasi. Aktiviti 'merujuk' disarankan semasa membuat keputusan untuk menggunakan ubat di luar indikasi serta ciri-ciri panduan untuk praktis tersebut. Di antara 4101 pesanan ubat yang diberikan kepada 900 pesakit, 52.1% adalah pesanan untuk penggunaan ubat di luar indikasi. Kos ubat di luar indikasi adalah sebanyak RM61586.65 (54.1%) daripada jumlah kos ubat. Kebanyakan peserta kajian (95.6%) menunjukkan minat untuk mendapatkan tunjuk ajar mengenai penggunaan ubat di luar indikasi. Polisi atau garispanduan dinilai sebagai penting (73.6%) untuk ciri-ciri latihan dan panduan. Secara kesimpulannya, penggunaan ubat di luar indikasi adalah ketara di kalangan pesakit pediatrik di Hospital Sungai Buloh. Maklumat dasar berkenaan pengetahuan serta pandangan pegawai farmasi dan doktor adalah berbeza dengan penemuan kajian yang dijalankan sebelum ini. Penggunaan ubat di luar indikasi melibatkan separuh daripada jumlah kos ubat dan ini menekankan kepentingan kajian 'cost-effectiveness' dijalankan di masa hadapan. Usaha perlu diambil untuk memenuhi keperluan pembelajaran yang telah dinyatakan dari segi mengenalpasti ubat yang digunakan di luar indikasi, integrasi bukti saintifik, penekanan terhadap keselamatan pesakit, pengambilan keizinan, pakar rujukan serta aliran kerja untuk penggunaan ubat di luar indikasi.

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ABSTRACT

Off-label drug prescribing is common among paediatric patients. Prevalence and cost data on off-label drug prescribing among paediatric patients in Malaysia as well as the reasons behind the quantitative findings of previous studies remains unexplored. This research aimed to explore, evaluate and characterise the practice of off-label prescribing among paediatric patients in Hospital Sungai Buloh. Four studies were conducted using mixed-methodology approach to address the research objectives. The qualitative method provided a baseline and ground information on the awareness, knowledge, attitudes and views on off–label drug prescribing among paediatric patients. The quantitative method was used to determine the extent, nature and drug cost involved in off–label drug prescribing among paediatric patients and to assess learning needs among pharmacists and doctors towards off-label drug prescribing. The studies were conducted among the pharmacists and the doctors at the Pharmacy and the Paediatric Department of Hospital Sungai Buloh. Most of the study participants (93.4%) were familiar with the term off-label drug prescribing. About 60% of the study participants were prescribing or dispensing off-label drugs unknowingly. There was a mismatch between the views of study participants and the findings of previous studies. The study participants were more concerned regarding the safety (63.7%) than the efficacy (40.7%) of off-label drugs Evidence-based practice was quoted as most important gate-keeping method. Disclosure to parents and obtaining consent was viewed as an important action to be taken when using off-label drugs. The act of ‘referring’ was quoted when discussing the decision making to

prescribe or dispense off-label drugs and the features of preferred guidance options. Among the 4101 drug orders administered to 900 patients, 52.1% were off-label. Off-label use accounted for RM61586.65 (54.1%) of the total drug cost. Most of the study participants (95.6%) indicated their interest to receive educational material or training regarding off-label prescribing. The policy or guideline was ranked as the most preferred (73.6%) training or guidance options. In conclusion, off-label drug prescribing is noticeably prevalent among paediatric patients at Hospital Sungai Buloh. The baseline and ground information on the perceived knowledge and views among pharmacists and doctors highlighted a disparity with actual findings from previous studies. Off-label drugs accounted for half of the total drug cost and this highlights the need for further cost-effectiveness studies. Efforts should be directed in addressing the exhibited learning needs in terms of identifying off-label drugs, integration of evidence, ensuring safety, consent taking, referral person and workflow to prescribe or dispense off-label drugs.

CHAPTER ONE

GENERAL INTRODUCTION

1.1 Introduction

The Child Act 2001 in Malaysia, classifies a child is a person under the age of eighteen years (Percetakan Nasional Malaysia Berhad, 2005). The Malaysian classification of "children" or "paediatric" was adopted from the European Medicines Agency (EMEA) and the International Council for Harmonisation (ICH) classification which include neonates, infants, child and adolescents up to 18 years old.

Table 1. 1 Age classification of paediatric population (Ceci et al., 2002)

Age category	**Age range**
Preterm newborn	<37 weeks gestation
Term newborn	0 to 27 days
Infants and toddlers	28 days to 23 months
Child	2 to 11 years
Adolescents	12 to 18 years

Prescribing in children is associated with many challenges and one that has received considerable attention is off-label drug prescribing (World Health Organization, 2007, Keith, 2015). Off–label drug prescribing is generally defined as "drugs which are prescribed and used outside their licensed indications with respect to dosage, age, indication, or route" (Pandolfini and Bonati, 2005). Another term which is commonly used interchangeably with off–label drug prescribing is unlicensed drug use. Unlicensed drugs are those where the drug formulation is either modified, that are prepared as extemporaneous preparations, are imported or used before a license is granted, or chemicals used for therapeutic purposes (Pandolfini and Bonati, 2005).

The issue with off-label drug prescribing is that the balance between efficacy and adverse effects has usually not been established. Previous studies reported that off-label drug prescribing in paediatric patients was significantly associated with

incidence of adverse drug reactions (ADRs) (Horen et al., 2002, Neubert et al., 2004, Santos et al., 2008). Studies to evaluate efficacy of off-label drugs in paediatric patients reported findings that supports and opposes the effectiveness of some drugs in treating certain diseases (Falcon-Neyra et al., 2016, Maratea et al., 2016, Puttgen et al., 2016, Zeng et al., 2017). Despite the uncertainties in the outcome, drugs are continued to be used in an off-label manner among paediatric patients.

This research focused on off–label drug prescribing among paediatric patients at Hospital Sungai Buloh. Hospital Sungai Buloh is located approximately 25km from Kuala Lumpur in Mukim Batu, Gombak, in the central state of Selangor. The 620-bedded hospital provides service to the population in the district of Gombak, Petaling and Kuala Selangor which makes up to 40% of the total population in the Selangor state. Details on the prevalence of off-label drug prescribing among paediatric patients and factors leading to such practice is discussed in-depth in the subsequent chapters.

1.2 Off-label drug prescribing among paediatric patients in Malaysia: A brief overview

Malaysia is a developing country with a population of approximately 30 million with 7.2 million of them aged 15 years old and below (Health Informatic Centre, 2016). Just like children around the world, children in Malaysia are also prescribed with off-label drugs. Doctors in many countries are allowed to prescribe drugs in an off-label manner, provided they adhere to certain pre-requisites (Ventola, 2009, Molyneux and Bogaert, 2010, Yamashiro et al., 2012). Likewise, in Malaysia, the existing acts and regulations does not prohibit doctors from prescribing drugs in an off–label manner. However, doctors in Malaysia are urged to obtain a written consent before prescribing an off-label drug (Director General of Health, 2016a). The reason for obtaining written

consent is to ensure that the risk of using off-label drugs is communicated with the patient (or parents and guardians) as well as to ensure proper documentation of such practice and serves as evidence should any undesirable outcome take place which can lead to malpractice lawsuits (Director General of Health, 2016a).

Previously published data on the extent of off-label drug prescribing among paediatric patients in Malaysia are limited. Three studies describing the extent of off-label drug prescribing in Malaysian paediatric patients were published previously (Lee et al., 2013, Mohamad et al., 2015, Tan and Shah, 2016). One study highlighted that off–label drug prescribing occurs in 34.1% of the prescriptions for paediatric patients in the intensive care settings (Lee et al., 2013). The prevalence of off-label drug prescribing in the outpatient and ward settings were reported to be 35.6% and 60.8% respectively (Mohamad et al., 2015, Tan and Shah, 2016). Details on the findings of these studies as well as initiatives taken regarding off-label drug prescribing among paediatric patients are discussed further in detail in the next chapter.

1.3 Study objectives

The objective of this research was to explore, evaluate and characterise the incidence of off-label drug prescribing among paediatric patients in Hospital Sungai Buloh.

The specific objectives were:

i. to provide an overview of the awareness, knowledge and views of off–label drug prescribing among paediatric patients.
ii. to explore the knowledge, view and attitude of paediatric doctors and pharmacists towards off–label drug prescribing among paediatric patients.
iii. to determine the extent, nature and drug cost involved in off–label drug prescribing among paediatric patients.

iv. to assess the learning needs among paediatric doctors and pharmacists towards off-label drug prescribing in paediatric patients.

1.4 Justification of the study

Studies on prevalence of off-label drug prescribing among paediatric patients were well-represented globally. However, the differences in the regulatory requirements, prescribing habits and drug utilization pattern as well as culture and patient characteristics in Malaysia, calls for further investigation and identification of the extent and nature of off-label drug prescribing among Malaysian paediatric patients. Moreover, there were limited studies conducted in Malaysia and the findings are insufficient to identify the magnitude of off-label drug prescribing among paediatric patients in Malaysia.

The Ministry of Health (MoH) definition for off-label drug prescribing lacks clarity and inclusion of the many categories of off-label drug prescribing in Malaysia (Director General of Health, 2016a). A clearer definition for off-label drug prescribing in paediatric patients in Malaysia, which includes the many categories of such practice is required to be used for practice, research and future regulatory purposes.

Given the lack of initiatives taken in Malaysia to improve drug use in paediatric population, the reasons why doctors and pharmacists choose to prescribe and dispense off-label drugs to paediatric patients, and how much knowledge they have regarding this practice as well as what would be a good guidance to them is also poorly understood. Since decades ago till now, knowledge and healthcare professionals' personal characteristics have been reported as a factor influencing prescribing and dispensing habits (Hemminki, 1975, Bradley, 1992, Caamaño-Isorna et al., 2005, Ljungberg et al., 2007). Ultimately, it is known that interventions to change prescribing

or dispensing behavior are more likely to be effective if they are perceived as relevant by the recipients (Cutts and Tett, 2003). Therefore, further understanding and investigation into knowledge and personal characteristics of paediatric doctors and pharmacists is warranted to in order to recognise the reasons behind off-label use of drugs in paediatric patients as well as to identify possible knowledge gap.

Findings on the cost incurred by off-label drug use is scarce and were reported from countries which have different healthcare financing systems compared to Malaysia. Additionally, in the era of financial constraint especially in healthcare financing, the practice of optimal allocation of limited resources sometimes fail to provide importance to drugs without substantial evidence on effectiveness and safety (Drummond et al., 2008, Largent and Pearson, 2012). Therefore, there is need to identify the cost of off-label drugs used in paediatric patients in order to guide allocation, coverage and reimbursement decisions of off-label drugs in paediatric patients.

1.5 Overview of the thesis

Chapter 2 consists of the literature review which was initiated with the brief discussion on the factors leading to off-label drug prescribing among paediatric patients and the initiatives taken around the world to improve drug use in children. Additionally, the worldwide scenario of the prevalence of off-label drug prescribing in paediatric patients as well as the extent and nature of off-label drug prescribing in paediatric patients was collated and discussed in this chapter. A brief discussion on the off-label drug expenditure as well as the reimbursement and coverage for off-label drugs were also included in this chapter. Lastly, the concerns on off-label drug prescribing among paediatric patients was outlined and briefly discussed.

In **chapter 3**, the general methodology of the study is presented. The methodology employed in the four parts of the study was explained, beginning with the explanation and justification of the methodology used to conduct the systematic review of awareness, knowledge and views of off-label drug prescribing among paediatric patients; followed by the methodology for the qualitative interview among hospital-based paediatric doctors and pharmacists. Then the methodology used to quantitatively analyse the prevalence, nature and extent of off-label drug prescribing among paediatric patients as well as the drug cost analysis was also discussed. Lastly, the methodology used for the learning needs assessment survey conducted among the hospital-based paediatric doctors and pharmacists was deliberated.

Chapter 4 presented the findings from the systematic review of awareness, knowledge and views of off-label drug prescribing among paediatric patients. Then in **chapter 5**, the findings of the qualitative interview among hospital-based paediatric doctors and pharmacists was presented. **Chapter 6** contains the description of the findings from the study on prevalence, nature and extent of off-label drug prescribing in paediatric patients as well as the drug cost analysis. In **chapter 7**, the findings of the learning needs assessment survey are presented. Finally, **chapter 8** draws the thesis to an overall conclusion, followed by recommendations for future research.

1.6 Significance of the study

This study serves as an addition to the vast body of existing knowledge portrayed in the literature regarding the worldwide scenario of off-label drug prescribing among paediatric patients. The findings of this research provide information on off-label drug prescribing among paediatric patients from a niche population in Malaysia, creating

basis for further investigation of off-label drug prescribing among paediatric patients around the country to obtain a nationwide analysis of the situation.

The systematic review serves as the baseline data of what is already known regarding awareness, knowledge and views of off-label drug prescribing in paediatric patients among healthcare professionals, parents and children. Moving forward, the qualitative study, will provide ground information to help in providing deeper understanding on the knowledge, view and attitude of paediatric doctors and pharmacists on off–label drug prescribing among paediatric patients in Hospital Sungai Buloh. The paediatric doctors ultimately decide what drug to offer to their patients and the pharmacists dispenses the drug according to the doctors' prescription. Sometimes, the decision on the doctors' choice of drug for their patients is altered based on recommendations from the pharmacists. Therefore, it is important that the perspectives of the paediatric doctors and pharmacists on off-label drug prescribing are understood. This is especially important in the treatment of paediatric patients, whose maturing bodies may be more sensitive to the drug's effects. The results from this study will provide an understanding of factors that influence a paediatric doctor's decision to prescribe and a pharmacist's decision to dispense an off-label drug to paediatric patients, thus may lead to strategies for promoting more informed off-label drug prescribing among paediatric patients.

From a practice standpoint, the off-label drug cost analysis performed in this study is relevant and timely for the healthcare sector, which is currently in the midst of significant changes in the way of financing the provision of healthcare in the country. Currently the healthcare financing in Malaysia uses the two-tiered system whereby the funding sources for the public medical services are mainly derived from tax revenue whereas the private sector medical services are at large financed through out-of-pocket

expenses. Through healthcare reform strategies, the future proposed healthcare financing system will mainly involve insurance scheme and data on cost of off-label drugs will be an important element in planning the reimbursement decision framework.

The learning needs assessment will identify the level of knowledge and the need for training or guidance to be provided on off-label drug prescribing in paediatric patients among paediatric doctors and pharmacists. Rather than assuming that all doctors and pharmacists needs guidance on off-label drug prescribing among paediatric patients, the management can make informed decisions on what are the knowledge gaps (if any) and decide the best ways to address the knowledge gap on off-label drug prescribing in paediatric patients that exists among paediatric doctors and pharmacists.

1.7 Operational definition

Several fundamental concepts and terms that were used in this thesis are classified as the operational definitions (Table 1.2).

Table 1. 2 Operational definitions used in the thesis

Terms	Operational definitions
Pharmacoepidemiology	The pharmacoepidemiology component was the study of the extent and nature of off-label drug prescribing among paediatric patients in Hospital Sungai Buloh.
Paediatric	Paediatric refers to any individual below or at the age of 18 years old. The term 'children' is also used interchangeably with 'paediatric'.
Off-label drug prescribing	The use of a drug outside Drug Control Authority (DCA) indication (Director General of Health, 2016a) with regards to age, indication, dose and route of administration, the use of a drug without dosing information in children, use without safety/efficacy/tolerability data in children and contraindicated and unapproved in children.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

This literature review chapter is aimed to identify similar work done on the practice of off-label drug prescribing among paediatric patients and objectively report the updated knowledge as well as the gaps identified in the literature that requires further investigations within the area. This chapter has five related subtopics. First, the factors leading to off-label drug prescribing in paediatric patients we gathered and discussed. Secondly, the initiatives taken by regulatory, legislative, governmental and professional bodies to improve drug use in children, particularly in Malaysia, were discussed. This was followed by the discussion on the worldwide overview of the prevalence of off-label drug prescribing in paediatric patients. This overview was compiled and discussed according to the various paediatric treatment settings. Next, the cost of off-label drugs was briefly discussed in relation to the off-label drugs expenditure and reimbursement as well as coverage for off-label drugs. Lastly, the concerns related to off-label drug prescribing in paediatric patients were listed and discussed. The chapter was finalised with a chapter summary.

2.2 Factors leading to off-label drug prescribing in paediatric patients

The factors associated with off-label drug prescribing in paediatric patients are multifaceted and the discussion on this prescribing trend begins with the presumption that it can be viewed as standalone segments but the problem is, it is difficult to do so. For example, a parent's decision to accept or refuse a treatment for their children is based on many factors which is greatly influenced by input from healthcare professionals (Lantos, 1987, Partridge et al., 2005). Likewise, in clinical trials, as with

medical treatment, obtaining consent is an important aspect in determining participation of children. These factors tend to be realistically interconnected hence addressing these factors requires a holistic approach.

2.2.1 Clinical trial factor

The hurdles associated with conducting clinical trials in children is intertwined in every stage of a clinical trial but mainly in choosing the right methodology (Conroy et al., 2000b) and outcome to measure (Smyth and Weindling, 1999), logistical planning and financial aspects of the trial (Choonara, 2000, Gennery, 2000), recruitment and retention of participants, and identifying and managing trial sites and staffs (Cohen, 1999). Due to these challenges, many drugs lack scientific evidence derived from clinical trials, to support its use, efficacy and safety in children. This causes drugs to be used in an off-bale manner. Alternative study designs can be considered to overcome the challenges of paediatric clinical trials (Sable et al., 2017).

2.2.2 Drug factor

Another factor that arises significantly as a result of the difficulties in conducting clinical trials and research in children is the drug factor. Many established and commonly used drug references fail to provide adequate dosing information for drug use in children due to insufficient data from clinical trials conducted in children (Wilson, 1999, Tan et al., 2003, Benjamin et al., 2006, Permala et al., 2010). Clinical trials or research conducted specifically for paediatric drug formulation development endure the same sets of challenges including methodological and ethical requirements for paediatric trials, high developmental costs, and a small and fragmented market (Ivanovska et al., 2014). The lack of paediatric dosing information and paediatric

formulations often leaves healthcare professionals no alternative but to use adult medicines in an off-label or unlicensed manner for their paediatric patients.

2.2.3 Healthcare professional factor

Studies conducted in the past have established that complacency or the need to fulfil what healthcare professionals perceived as being patients' or parents' expectations, lead to overprescribing and misprescription (Lopez-Vazquez et al., 2012, Sirota et al., 2017). Some of these perceptions held by doctors on patients' and parents' expectation is sometimes wrongly assessed and interpreted (Stivers et al., 2003). A mere act of questioning a doctor's treatment can send out a signal that parents are expecting prescriptions from their doctors (Mangione-Smith et al., 2006) and most of the time, these expectations are obliged. Moreover, healthcare professionals were reported to have varying degree of knowledge and low level of awareness on off-label drug prescribing in paediatric patients (Mukattash et al., 2011a, Mukattash et al., 2011b), resulting in high possibilities of fulfilling the patients' or parents' expectations on treatment, with off-label drugs. Healthcare professionals were also reported to not seek informed consent from parents when prescribing off-label drugs (McLay et al., 2006) causing deficiency in knowledge among parents or caregivers regarding off-label drug prescribing in paediatric patients. Lastly, it is discreditable to come upon the fact that off-label drug prescribing in paediatric patients also occurs as a result of unethical promotion and encouragement by pharmaceutical companies (Kesselheim et al., 2011).

2.2.4 Parents or caregivers factor

Factors associated with parents or caregivers are more behavioural in nature and has an indirect impact on the off-label drug prescribing in paediatric patients. However, parents or caregivers factor has a great direct impact on healthcare professional and clinical trial factor, making it a significant point of discussion. Firstly, due to lack of knowledge on off-label drug prescribing in paediatric patients, many parents 'accepted' the use of off-label drug for their children (Lenk et al., 2009, Bang et al., 2014, Shah, 2017). Upon gaining knowledge on off-label drug prescribing, many parents tend to ask for a change of treatment (Bang et al., 2014) or refuse the use off-label drugs (Lenk et al., 2009). Secondly, desperation for treatment was demonstrated in parents of children with illness. Demanding for, and accepting futile treatments (Forbat et al., 2015) as well as making emotional decisions in the disease management of their children have rendered parents to be in a desperate position and ultimately adds pressure on healthcare professionals to provide treatment for their patients. Additionally, parents or caregivers usually perform multiple tasks in the process of care of their children with illness and this can go on for a long period of time if the child suffers from chronic illnesses. Over time, parents or caregivers are at risk of burnout associated with the complexity and diversity of responsibilities of care (Sullivan-Bolyai et al., 2003). This, coupled with the desperation for treatment and the genuine hope to positively and promptly manage the illness faced by their children, creates the basis for the expectations that parents or caregivers place on their healthcare providers.

2.3 Initiatives concerning off-label drug prescribing in children

Several initiatives were introduced and implemented globally to gain better knowledge about effects of drugs in children and to guide health care professionals to use quality drugs that are efficacious and causes no harm to children. This includes the drug licensing which was aimed to ensure drug quality, safety and efficacy. Unfortunately, a large proportion of drugs for children lack licensing or marketing authorisations (Riedel et al., 2016). This suggest that a lot of drugs used for children still lacks evidence derived from pharmacokinetic, dose finding, or formulation studies properly conducted in the paediatric population (Coté et al., 1996, Rocchi and Tomasi, 2011) hence causing it to be used in an off-label manner.

2.3.1 Global initiatives

The United States of America (US) and the European Union (EU) (Choonara, 2007) legislative and regulatory frameworks were at the forefront to increase the number of paediatric studies required to improve paediatric labelling. To follow suit, other countries, for example Canada (Turner et al., 2014), Australia (Hoppu et al., 2012), Japan (Uchiyama, 2002), China (Zheng et al., 2017) and Korea (Yang et al., 2008) have somewhat attempted to take other forms of initiatives in order to provide safe and efficacious drugs to children. However, no significant difference in the resulting situation was found.

2.3.2 Malaysian initiatives

In Malaysia, the DCA is tasked with ensuring the quality, safety and efficacy of drugs through the registration, including quality control, inspection and licensing and post-registration activities. Part of the registration requirement is to provide specific

indication(s) for a drug to be approved by DCA. This indication is referred to as the DCA indication. In the year 2012, a directive from the Director-General of Health marked the initial endorsement on the definition of off-label drug prescribing by MoH (Appendix 1). The directive also urged for written consent to be taken for off-label use of drug. However, awareness regarding the existence of the consent form was questionable and the use of the form was uncommon (Director General of Health, 2016a).

In the year 2015, a list of drugs commonly used off-label among Malaysian patients was prepared by the Pharmaceutical Services Division. The drugs included in the list were approved by the Director-General of Health to be used in an off-label manner and were exempted from the written consent process. Unfortunately, 95% of the drugs listed were commonly used off-label among adult patients. Paediatricians were still required to obtain written consent for all drugs prescribed in an off-label manner. Institution level initiatives were taken to guide the paediatricians to identify common off-label uses of drugs in paediatric patients and to prompt them to obtain written consent when such drugs were prescribed (personal communication). Effort needs to first be devoted to build a standardised nationwide framework to further address the needs for better medicine for children in Malaysia.

Overall, despite numerous global legislative and regulatory initiatives, children are still found to be underprivileged with regards to participation in clinical trials, labelling of drugs prescribed to children, availability of appropriate drug formulations for children as well as the evidence-based use of drugs which led to off-label drug prescribing in children (Corny et al., 2015).This suggest that legislative, regulatory, governmental and professional initiatives alone may not be sufficient to improve drug use in children. Behavioural and knowledge aspects related to prescribing in children,

particularly off-label drug prescribing, also need to be evaluated and consolidated as part of the concerted efforts to narrow the gaps in prescribing for children.

2.4 Overview of the prevalence studies on off-label drug prescribing in paediatric patients

In total, 108 studies performed between 1996 and 2016 on off-label drug prescribing in paediatric patients were reviewed. Most of the studies (74/108) were conducted from the year 2006 to 2016. The number of patients ranged from 34 to 312 million and the number of prescriptions ranged from 88 to 484 million. Most of the studies (68/108) were prospective studies. These studies reported that the proportion of paediatric patients who received at least one off-label drug was between 4 to 100%. The overall rates of off-label drug prescribing in paediatric patients reported was 1.2 to 99.7%.

2.4.1 Off-label drug prescribing in neonatal intensive care units

There were 24 studies performed between 1999 and 2016 which involved neonatal wards particularly the neonatal intensive care unit (NICU) (Conroy et al., 1999, Avenel et al., 2000, Barr et al., 2002, O'Donnell et al., 2002, Cortizas et al., 2003, Dell'Aera et al., 2007, Kumar et al., 2008, Prandstetter et al., 2009, Dessì et al., 2010, Neubert et al., 2010, Lass et al., 2011b, Nguyen et al., 2011, Carvalho et al., 2012, Oguz et al., 2012, Jain et al., 2014, Kieran et al., 2014, Laforgia et al., 2014, Mesquita et al., 2014, Thomas, 2014, Riou et al., 2015, Silva et al., 2015, de Souza et al., 2016, Cuzzolin and Agostino, 2016, Schweigertova et al., 2016) (Table 2.1). The number of patients ranged from 34 to 2304 with the number of prescriptions ranging from 88 to 8891. Rates of off-label drug prescribing among paediatric patients in the NICU ranged from 27.7% to 95.6%.

Table 2. 1 Summary of studies reporting off-label drug prescribing in NICUs

Author, Year	Country	Study duration (Study design)	Age group	Primary reference source	n (no. of prescriptions)	% OL	% of patients receiving at least 1 OL drug	Common category of OL	Common OL drug or drug group
Conroy S et al, 1999	United Kingdom	13-week period (P)	n/r	Data Sheet Compendium 1998–99	70 (455)	54.7	90.0 (UL/OL)	Dose	Benzyl-penicillin
*Avenel S et al, 2002	France	1-month period (n/r)	0-128 days	n/r	47 (257)	62.0 (pre-mature infants) 64.0 (new-borns)	n/r	Age	n/r
Barr J et al, 2002	Israel	4-month period (P)	n/r	PDR 2000	105 (525)	63.0	n/r	Dose	Theophylline
O'Donnell CPF et al, 2002	Australia	10-week period (P)	n/r	Australian Prescription Products Guide 2002	97 (1442)	47.0	80.0 (UL/OL)	Indication	Morphine
*Cortizas BF et al, 2003	Spain	n/r	n/r	*Dirección General de Farmacia y Productos Sanitarios.*	346 (n/r)	n/r	17.6	Age	n/r
Dell'Aera M et al, 2007	Italy	2-month period (P)	n/r	SmPC	34 (176)	44.3	n/r	Dose	Systemic antibiotics

Table 2.1 - Continued

Author, Year	Country	Study duration (Study design)	Age group	Primary reference source	n (no. of prescriptions)	% OL	% of patients receiving at least 1 OL drug	Common category of OL	Common OL drug or drug group
Kumar P et al, 2008	United States	3-year period (R)	n/r	USFDA approval for use in neonates	2304 (n/r)	n/r	20.0	n/r	Fentanyl
*Prandstetter C et al, 2009	Austria	3-month period (R)	n/r	n/r	84 (748)	34.0	77.0	n/r	n/r
Dessı A et al, 2010	Italy	1-month period (P)	n/r	Product data sheets	38 (88)	47.7	n/r	Age	Gentamicin
Neubert A et al, 2010	Germany	11-month period (P)	n/r	SmPC	183 (1978)	34.0	70.0 (OL/UL)	Age[1]	Analgesics and cardiovascular drugs
Lass J et al, 2011	Estonia	12-month period[d] (P)	postnatal age <29 days	SmPC	490 (1981)	65.0	98.0 (UL/OL)	n/r	Antibacterials,
Nguyen KA et al, 2011	France	4-month period (P)	>32 weeks GA	SmPC in Vidal 2009	55 (265)	29.4	71.0	Age	Ferrous fumarate
Carvalho CG et al, 2012	Brazil	6-week period (P)	n/r	USFDA list of approved drugs	129 (318)	27.7	78.7 (UL/OL)	Age	Dose: ampicillin, Age: glycerin, Indication: meto-clopramide

Table 2.1 - Continued

Author, Year	Country	Study duration (Study design)	Age group	Primary reference source	n (no. of prescriptions)	% OL	% of patients receiving at least 1 OL drug	Common category of OL	Common OL drug or drug group
Oguz SS et al, 2012	Turkey	1-month period (P)	n/r	Package insert in Rx MediaPharma 2010 version 10.0.0 interactive program	464 (1315)	62.3[2] (OL/ UL)	n/r	Lack of information	n/r
Kieran E et al, 2013	Ireland	2-month period (P)	born before 35 completed weeks of gestation	SmPC contained in the packaging insert provided with the medication.	110 (900)	32.0	n/r	n/r	Benzyl-penicillin and gentamicin
Jain S et al, 2014	India	3-month period (P)	n/r	USFDA list of approved drugs	156 (568)	50.3	n/r	Age	Anti-infective and antiepileptic drugs
Laforgia N et al, 2014	Italy	1-month period (P)	n/r	Specific marketing authorization	126 (483)	46.5	n/r	n/r	Frusemide
Mesquita M et al, 2014	Paraguay	3-month period (P)	0 - 28 days	USFDA list of approved drugs	105 (92)	n/r	39.0 (OL/UL)	n/r	Antibiotics
Thomas A et al, 2014	South Africa	3-month period (P)	≤ 28 days	Package insert	112 (759)	51.0	91.0 (OL/UL)	Dose	Amino-phylline

Table 2.1 - Continued

Author, Year	Country	Study duration (Study design)	Age group	Primary reference source	n (no. of prescriptions)	% OL	% of patients receiving at least 1 OL drug	Common category of OL	Common OL drug or drug group
Riou S et al, 2015	France	1-year period (P)	n/r	SmPC in a French independent formulary named Theriaque 2013	910 (8891)	59.5	94.8 (OL/UL)	Age	Calcium folinate
Silva J et al, 2015	Portugal	6-month period (R)	0-27 days of postnatal age	SmPC	218 (1011)	52.7	69.7 (OL/UL)	Dose and/or frequency	Age: Paracetamol, Amikacin, Fluconazole Indication: Midazolam Route: Calcium Polystyrene Sulphonate Dose and/or frequency: Gentamicin, Ampicillin, Paracetamol
Cuzzolin L et al, 2016	Italy	1-day period (P)	n/r	Package insert, SmPC	220 (720)	59.0	n/r	Age	Fluconazole, fentanyl, ranitidine

Table 2.1 - Continued

Author, Year	Country	Study duration (Study design)	Age group	Primary reference source	n (no. of prescriptions)	% OL	% of patients receiving at least 1 OL drug	Common category of OL	Common OL drug or drug group
de Souza et al, 2016	Brazil	6-month period (R)	≤ 28 days	Information leaflets	192 (3290)	95.6	99.5	Age	Heparin, fentanyl, multivitamin
Schweigertova J et al, 2016	Slovakia	6-month period (n/r)	<1month	Slovak SmPC in SIDC homepage	202 (962)	43.0	87.1	Age[1]	Ketoconazole

GA = gestational age, n/r = not reported, OL = off-label, P = Prospective, PDR = Physicians' Desk Reference, R = Retrospective, SIDC = State Institute for Drug Control, SmPC = Summary of Product Characteristics, UL = Unlicensed, USFDA = United States Food and Drug Administration, *Data tabulated from study abstract as full-text was available in other language besides English, [1]This study only analysed age category for off-label drug use, [2]Study reported OL/UL rate based on two references sources, data reported is based on national database

A total of twelve studies reported a comparison of off-label drug prescribing rates in preterm and full-term babies. Six studies reported that off-label drug prescribing rates were higher in full-term babies compared to preterm babies (Avenel et al., 2000, Dell'Aera et al., 2007, Dessì et al., 2010, Carvalho et al., 2012, Laforgia et al., 2014, Schweigertova et al., 2016). The remainder of the studies reported otherwise (Neubert et al., 2010, Lass et al., 2011b, Kieran et al., 2014, Riou et al., 2015, Silva et al., 2015, de Souza et al., 2016). A study by O'Donnell et al. reported that off-label drug prescribing rate was higher in infants who weighed ≤1000g (O'Donnell et al., 2002). The two most common categories of off-label drug prescribing among paediatric patients in the NICU were age and dose.

The drug group and drug reported to be most commonly used in an off-label manner among paediatric patients in the NICU were systemic antibiotics and fentanyl. Even though the drugs used among paediatric patients in the NICU were mostly off-label, some studies demonstrated that such use were justified with evidence on the safety and efficacy of drugs in the neonates. The study by Jain et al. reported that one third of drugs which lacks United States Food and Drug Administration (USFDA) approval had level I-II evidence of safety and efficacy for use in neonates (Jain et al., 2014) whereas Kumar et al. identified that more than 90% of all prescriptions for off-label use of parenteral medications were for drugs with level I evidence of efficacy and safety (Kumar et al., 2008).

2.4.2 Off-label drug prescribing in paediatric intensive care units

Nine studies performed between 1996 and 2016 were conducted among paediatric patients in the paediatric intensive care unit (PICU) (Turner et al., 1996, Carvalho et al., 2003, Gavrilov et al., 2003, Bavdekar et al., 2009, Yang et al., 2011, Ferreira et al.,

2012, Czaja et al., 2015, Jobanputra et al., 2015, García-López et al., 2016) (Table 2.2). The majority of the studies (8/9) were conducted prospectively with one study (Gavrilov et al., 2003) which was conducted at two different hospitals with data from one hospital collected retrospectively and the other prospectively. The number of patients ranged from 42 to 66896. The off-label drug prescribing rates resulting from these studies ranged from 23% to 70.6% with the proportion of paediatric patients in the PICU receiving at least one off-label drug ranged from 62.7% to 100%. The most common categories of off-label drug prescribing among paediatric patients in the PICU were dose, age, and indication. The drugs commonly used in an off-label manner among paediatric patients in the PICU were morphine, midazolam, chloral hydrate, frusemide, triclofas, salbutamol, ipratropium bromide, dopamine, fentanyl, adrenaline, noradrenaline, and oseltamivir.

Subgroup analysis was performed in the study by García-López et al. and Ferreira et al. showed that off-label drug prescribing rates decreased with higher age groups (Ferreira et al., 2012, García-López et al., 2016). This trend was not depicted in the study by Jopanputra et al. and Bavdekar et al, whereby the off-label drug prescribing rates were higher in children aged 1-12 months and 5-12 years old compared to age 1-5 years old (Bavdekar et al., 2009, Jobanputra et al., 2015).

Table 2. 2 Summary of studies reporting off-label drug prescribing in PICUs

Author, Year	Country	Study duration (Study design)	Age group	Primary reference source	n (no. of prescriptions)	% OL	% of patients receiving at least 1 OL drug	Common category of OL	Common OL drug or drug group
Turner S et al, 1996	United Kingdom	4-month period (P)	1 day - 15 years	ABPI data sheet compendium 1995-96	166 (862)	23.0	70.0	n/r	Morphine, midazolam, chloral hydrate[1]
Carvalho PRA et al, 2003	Brazil	6-week period (P)	1 month – 18 years old	USP DI 2001	51 (747)	49.5	100.0	n/r	Frusemide
Gavrilov V et al, 2003	Israel	7-month period (R&P)[1]	0-18 years	PDR 2000 and the Israel Drug Compendium 1995	158 (874)	41.9 (OL/ UL)	n/r	Age	Epinephrine, midazolam, triclofas, salbutamol, ipratropium bromide
Bavdekar SB et al, 2009	India	6-month period (P)	28 day-12 years old	BNF version 2005	300 (2237)	70.6	96.0	Dose	Dopamine
Yang CP et al, 2011	United States	2-month period (P)	n/r	USFDA approval status as stated in Thomson Micromedex online database	n/r (49707)	66.9	n/r	Age[2]	Salbutamol
Ferreira LDA et al, 2012	Brazil	9-month period (P)	n/r	ANVISA package insert list	73 (1054)	23.4	86.0	Dose	Fentanyl
Czaja AS et al, 2015	United States	1-year period (n/r)	0-18 years	USFDA list of approved drugs	66896 (n/r)	n/r	85.0	Indication	Cardiovascular drugs
Jobanputra N et al, 2015	India	12-month period (P)	1 month-12 years	Product insert provided by the manufacturer	482 (1789)	41.3	62.7	Indication	Adrenaline, Noradrenaline, Oseltamivir

Table 2.2 - Continued

Author, Year	Country	Study duration (Study design)	Age group	Primary reference source	n (no. of prescriptions)	% OL	% of patients receiving at least 1 OL drug	Common category of OL	Common OL drug or drug group
García-López I et al, 2016	Spain	6-week period (P)	0-18 years	SmPC	42 (696)	52.9	100.0	Indication	Fentanyl

ABPI = The Association of the British Pharmaceutical Industry, ANVISA = National Health Surveillance Agency, BNF = British National Formulary, n/r = not reported, OL = off-label, P = Prospective, PDR = Physicians' Desk Reference, R = Retrospective, SmPC = Summary of Product Characteristics, UL = Unlicensed, USFDA = United States Food and Drug Administration, USP DI = United States Pharmacopeia Drug Information for the Health Care Professional, [1] This study was conducted at two different hospitals with data from one hospital collected retrospectively and the other prospectively, [2] This study only analysed age category for off-label drug use