PATTERNS OF OPIOID USE IN PATIENTS WITH CANCER AND NON-CANCER PAIN AND ITS RELEVANT CLINICAL OUTCOMES IN NON-CANCER PAIN

BY

ASWEEN ROWENA BINTI ABDULLAH SANI

A thesis submitted in fulfilment of the requirement for the degree of Doctor of Philosophy in Pharmacy Practice

Kulliyyah of Pharmacy
International Islamic University Malaysia

MAY 2020

ABSTRACT

Opioids are the gold standard for the treatment of moderate to severe acute pain and cancer pain. However, opioids are increasingly prescribed to treat non-cancer pain for long-term which has become a public health concern due to increasing evidences of opioid-related harms such as abuse, misuse, and opioid overdose-related deaths associated with long-term opioid therapy. Little is known about the patterns of opioid prescribing among non-cancer pain patients and the characteristics of those on long-term opioid therapy in Malaysia. Information is also lacking on the risks of opioid abuse/misuse among non-cancer pain patients receiving opioid treatment for their pain. This study therefore investigated individual patient level opioid prescribing patterns and the differential patterns of opioid persistence between cancer pain and non-cancer pain patients at Malaysian outpatient tertiary hospital settings over 3 follow-up years (part 1). This study also investigated the clinical outcomes and risks of opioid abuse/misuse in non-cancer patients attending pain clinics (part 2). For part 2, non-cancer patients were stratified into short-term and long-term opioid user groups. The clinical outcomes were assessed using the Brief Pain Inventory – Short Form (BPI-SF), the Medication Quantification Scale – III (MQS-III), the Short Form-36v2 (SF-36v2) Health Survey and assessed for opioid adverse effects. The risk of opioid abuse/misuse were assessed using the Screener and Opioid Assessment for Patients with Pain - Revised (SOAPP-R). Factors influencing long-term opioid use and high risk of abuse/misuse were also analysed using multivariable logistic regression. Opioids included in this study were dihydrocodeine, oxycodone, morphine, fentanyl, and buprenorphine. In the first part of the study, a total of 922 patients with a mean age of 60 (±15.4) years who received opioids were identified. A comparative analysis indicated that compared to cancer pain patients (n = 665), non-cancer pain (n = 257) patients were prescribed relatively lower doses of opioids of <100 mg/day and for longer periods of at least 60 days of opioid days' supply on average in a follow-up year. The differential persistence patterns of opioid use over time revealed a pattern of tapering off opioid treatment among persistent opioid users in the non-cancer pain group in contrast to the cancer pain group. In the second part, a total of 61 non-cancer pain patients were recruited where no significant differences in the clinical outcomes were found between the short-term (n=30/61) and long-term opioid users (n=31/61). Notably, 62.3% of these non-cancer pain patients were found to be at high risk of opioid abuse/misuse. Predictors of high risk of abuse/misuse included younger age (OR 0.90, 95% CI 0.86, 0.98) and higher pain interference (OR 2.17, 95% CI 1.14 – 4.13). These findings suggest that opioid prescribing practices for non-cancer pain at outpatient tertiary hospital settings in Malaysia is in accordance with opioid prescribing guidelines which recommend against high dose opioid therapy and encouraging tapering off opioid treatment. Nonetheless, the high proportion of non-cancer pain patients attending pain clinics at high risk of opioid abuse/misuse is worrisome which calls for further investigation into the risks of opioid abuse/misuse among non-cancer pain patients attending pain clinics.

خلاصة البحث

الأفيونات هي المعيار الذهبي لعلاج الآلام السرطانية والمتوسطة والحادة .ومع ذلك، قد أصبح العلاج طويل الأمد عن طريقها للآلام غير السرطانية مصدر قلق للصحة العامة .تتركز الدراسات المتعلقة بنمط وصفها ومخرجات الدراسات السريرية في الدول المتقدمة .بينما في ماليزيا فلا يعرف الا القليل حول انماط وصف هذه الأدوية لمرضى الألم غير السرطاني للأمد الطويل ومخاطر سوء استخدامها .تحقق الجزء الأول لهذا البحث من أنماط وصفها على المستوى الفردي لمرضى الألم السرطاني وغير السرطاني ويأخذونها في العيادات الخارجية بتتبع زمني لثلاث سنوات .وتم أيضا فحص الأنماط التفاضلية لاستخدامها المستمر باستخدام مقياس الثبات والمتضمن ثلاثة أبعاد لاستهلاك الأدوية .ركز الجزء الثاني من الدراسة على مرضى الألم غير السرطاني والذين تم احالتهم لاحقا الى عيادات الألم .تم تقييم النتائج السريرية لكل من المستخدمين على المدى القصير والطويل مع قائمة جرد الألم المختصرة–النموذج المختصر، المقياس الدوائي الكمي، النموذج القصير لدراسة الصحة وتقييم الآثار الضارة لها .كما تم تقييم أيضا خطر تعاطي وسوء استخدامها لدى هؤلاء المرضى عن طريق الفرز المنقح .تم تحليل العوامل التي تؤثر على استخدام الأفيونات وخطورة سوء استخدامها عن طريق الانحدار اللوجستي متعدد المتغيرات .أظهرت النتائج بالمقارنة مع مرضى الألم السرطاني أنه تم وصف لمرضى الألم الغير سرطاني جرعات أقل نسبيا <100مغ/ يوم ولمدة 60 يوم على الأقل في المتوسط من أيام اعطاء الأفيونات خلال سنة متابعة .كشف تباين الانماط المستمرة لاستخدامها مع مرور الوقت عن نمط من العلاج بها بالشكل ،المتناقص بين مجموعة مرضى الألم غير السرطاني على العكس مع مجموعة مرضى الألم السرطاني .في الجزء الثاني تم توظيف 61 مريض من مرضى الألم غير السرطاني ولم يتم ملاحظة اي فرق كبير في النتائج السريرية بين وبين المستخدمين على المدى الطويل (n=30/61) مستخدمي الأفيونات على المدى القصير والبالغ عددهم (n=31/60). .وجد أن 62.3 %من مرضى الألم غير السرطاني معرضين للخطر بسبب سوء استخدامها (OR 0.90, 95% CI 0.86, 0.98) تنبؤات الخطر الكبير لسوء الاستخدامها شملت السن الأصغر تقترح هذه النتائج أن ممارسات وصف (OR 2.17, 95% CI 1.14 – 4.13)والتداخل العالي للألم الأفيونات لمرضى الألم غير السرطاني في المستشفيات الخارجية في ماليزيا تتوافق مع ارشادات وصفها و التي تنصح بعدم تناول جرعة عالية منها و توقف العلاج تدريجيا .ومع ذلك، ان النسبة العالية لمرضى الألم غير السرطاني والذين يرتادون عيادات الألم أمر مقلق حيث انهم معرضون لخطر سوء استخدام الأفيونات .وهذا .يحث البحوث المستقبلية للمزيد من التحقيق وتوصيف سوء استعمالها لدى مرضى الألم غير السرطاني

APPROVAL PAGE

The thesis of Asween Rowena Abdullah Sani has been approved by the following:

_____
Che Suraya Mohd Zin
Supervisor

_____
Zaswiza Mohd Noor
Co-supervisor

_____
Abdul Hadi Mohamed
Co-supervisor

_____
Lisa Nissen
Co-supervisor

_____
Aznan Md Aris
Internal examiner

_____
Mohd Baidi bin Bahari
External examiner

_____
Noorizan Abd Aziz
External examiner

_____
Jesni Shamsul Shaari
Chairman

DECLARATION

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

Asween Rowena Abdullah Sani

Signature …… Date ……..

INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA

DECLARATION OF COPYRIGHT AND AFFIRMATION OF FAIR USE OF UNPUBLISHED RESEARCH

PATTERNS OF OPIOID USE IN PATIENTS WITH CANCER AND NON-CANCER PAIN AND ITS RELEVANT CLINICAL OUTCOMES IN NON-CANCER PAIN

I declare that the copyright holder of this thesis is jointly owned by the student and IIUM.

By signing this form, I acknowledged that I have read and understand the IIUM Intellectual Property Right and Commercialization Policy.

Affirmed by Asween Rowena Abdullah Sani

…… ...…...…..……...

Signature Date

This thesis is dedicated to my beloved parents, Abdullah Sani and Adeda Rahimah, for their endless love, unconditional support, and encouragement.

ACKNOWLEDGEMENTS

First and foremost, all praises are due to Allah, the Most Beneficent and the Most Merciful, for His mercy and blessings which enabled me to complete this thesis.

I would like to express my heartfelt gratitude to my enthusiastic supervisor, Assoc. Prof. Dr. Che Suraya Mohd Zin, for her guidance, patience, motivation and invaluable knowledge imparted throughout the course of this research project and in accomplishing this thesis. I would also like to express my appreciation to my co-supervisors, Assoc. Prof. Dr. Abdul Hadi Mohamed, Assoc. Prof. Dr. Zaswiza Mohd Noor, and Prof. Lisa Nissen for their insightful suggestions, support, and encouragement during the course of this project.

I would also like to express my deepest appreciation to all staff who were involved in this project at pharmacies and pain clinics at Hospital Tengku Ampuan Afzan (HTAA), Hospital Kuala Lumpur (HKL), and Hospital Selayang for their kind support and assistance in facilitating the process of data collection and patient recruitment for this project. Many thanks to all patients who participated in this study as well.

Special acknowledgement to Dr. Michael Ling King Hwa, for his guidance and advice in the earlier days of my PhD journey in UPM, and for his reassurance to pursue this doctoral degree. I have learned the values of selflessness, high ethics, and passion for science during my brief period of working under him in UPM.

Thanks also to my dear friends in UPM for the short getaways and luncheons which uplifted me in my moments of crisis and kept me going on my path to success. Their friendship has made my PhD journey a wonderful experience. Special thanks to my husband and strong supporter, Hamzeh Al-Khatib, for his prayer, encouragement, and support in completing this thesis.

Last but not least, my greatest gratitude is towards my parents who have been a constant source of strength throughout my journey, and also to my brother, Asrul Hadi, and my sister, Asreen Ayumi, for giving me the encouragement I needed during my PhD journey. Words cannot express my appreciation for their unconditional support and especially tolerance during my lengthy periods of absence from important family events. This journey would not have been possible without their complete understanding, patience, and unfailing belief in me.

Once again, I would like to convey my greatest appreciation for everyone that encouraged, supported, and assisted along the completion of this thesis. May this research benefit the future of pain management in this country.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

95% CI	95% Confidence Interval
ADRBs	Aberrant drug-related behaviours
BPI-SF	Brief Pain Inventory – Short Form
CCI	Charlson Co-morbidity Index
CDC	US Centers for Disease Control and Prevention
CNCP	Chronic Non-Cancer Pain
DDD	Defined Daily Dose
DIRE	Diagnosis, Intractability, Risk, and Efficacy Score
GOF	Goodness-Of-Fit
HKL	Hospital Kuala Lumpur
HRQoL	Health-Related Quality of Life
HTAA	Hospital Tengku Ampuan Afzan
IASP	International Association for the Study of Pain
ID	Identification
IQR	Inter-Quartile Range
LR	Logistic Regression
LTOT	Long-Term Opioid Therapy
MCS	Mental Component Summary
MME	Morphine Milligram Equivalents
MQS-III	Medication Quantification Scale - III
NRIC	National Registration Identity Card
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OMEQ	Oral Morphine Equivalent
OR	Odds Ratio
ORT	Opioid Risk Tool
PCS	Physical Component Summary
PRN	Pro Re Nata / "As Needed"
QoL	Quality of Life
RCT	Randomized Controlled Trials
S-DDD	Defined Daily Doses for statistical purposes
SD	Standard Deviation
SF-36v2	Short Form - 36 version 2 Health Survey
SOAPP-R	Screener and Opioid Assessment for Patients with Pain – Revised
TCA	Tricyclic Anti-Depressants
WHO	World Health Organization

CONFERENCE PRESENTATIONS

Asween Rowena Abdullah Sani, Che Suraya Zin, Zaswiza Mohd Noor, Abdul Hadi Mohamed, Lisa Nissen. Differential patterns of persistent opioid use in patients with cancer and non-cancer pain. ***Value in Health***, 2016;19 (Issue 7): A814. **Oral presentation**, The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 7th Asia-Pacific Conference, 4th-6th September 2016 at Suntec Convention Centre, Singapore.

Asween Rowena Abdullah Sani, Che Suraya Zin, Abdul Hadi Mohamed, Munira Izat, Tan Hung Ling, Ng Kim Swan. Persistence patterns of opioid use over 3 follow-up years: The difference between non-cancer and cancer pain. **Poster presentation,** The 6th Biennial Scientific Meeting 2018 of the Malaysian Association for the Study of Pain, 17th – 18th March 2018 at National Cancer Institute, Putrajaya, Malaysia.

LIST OF PUBLICATIONS

Sani, Asween R., Zin, Che Suraya, Mohamed, Abdul H., Izat, M., Tan, Hung L., Ng, Kim S., & Nissen, L. (2019). Exploration of change in persistence patterns of opioid use among patients with non-cancer and cancer pain over a three-year follow-up period. ***Journal of Pharmacy Practice and Research***, 50(1). pp. 28-35. doi:10.1002/jppr.1573

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Studies showing increasing trends of opioids prescribed for non-cancer pain especially chronic non-cancer pain (CNCP) are extensive in literature despite the scarcity of evidence supporting the effectiveness of opioid use with regards to improved analgesia and functionality in these patients (Bosetti et al., 2019; Chou et al., 2015; Curtis et al., 2019; Hollingworth et al., 2015; Mojtabai, 2018). At the same time, increasing evidence of opioid-related harms such as endocrine deficiencies, cardiovascular events, abuse, addiction, overdose, and overdose-related deaths began to emerge in non-cancer patients particularly those on long-term opioid therapy (Baldini et al., 2012; Chou et al., 2015). Nonetheless, there is a legitimate need for opioids in especially CNCP patients and literature suggests long-term opioid therapy may benefit a subgroup of carefully selected and monitored CNCP patients (Noble et al., 2010; Saïdi et al., 2018). Consequently, opioid prescribing guidelines have been developed and improvised over the years which adopt an individualized approach to ensure appropriate opioid prescribing and proper selection of patients where the benefits of opioid therapy outweigh risks (Ballantyne, 2015a; Jason W. Busse et al., 2017; Chou, Fanciullo, Fine, Adler, et al., 2009; Dowell et al., 2016).

However, most of these researches on opioid use patterns and risks were conducted in developed countries such as the US, Canada, and Nordic countries, and opioid prescribing guidelines were developed based on evidences from these studies. Little is

known on opioid prescribing patterns in Malaysia as there is limited research in the patterns of opioid use particularly among the non-cancer pain population in this country. The available aggregate data on national opioid consumption in this country is inadequate to provide information on actual patterns of opioid use in clinical practice and at the patient-level. Moreover, a majority of the research on opioid use in this country is focused on illicit drug abusers under methadone maintenance therapy. There is also a lack of information on the characteristics of non-cancer patients prescribed opioids for long-term and on the patient characteristics vulnerable to opioid-related harms such as misuse, abuse, and addiction in this region.

In this light, this thesis was conducted to add to the body of knowledge of appropriate opioid prescribing specifically for the better management of non-cancer pain involving opioids. This thesis investigated patterns of opioid use including the differential patterns of persistent opioid therapy at the patient level in cancer and non-cancer pain population at outpatient tertiary hospital settings. This thesis further focused on patients with non-cancer pain at pain clinic settings by evaluating the clinical outcomes of short-term and long-term opioid use and also identified risk factors associated with low risk and high risk of opioid abuse or misuse in these patients.

1.2 PAIN

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP Terminology Working Group, 2017). Pain is inherently subjective, a multidimensional experience as a result of various influences ranging from genetic predispositions to environmental, social, psychological, and sensory factors (Melzack & Katz, 2013). The sensation of pain is not simply an end product of activation of pain receptors as a result of injury, inflammation, or other tissue pathology but it is a complex process involving generation of neural signals influenced by past experience, culture, environmental and personal factors (Melzack & Katz, 2013). Essentially, pain serves as a warning signal for survival but can also be a disease in itself.

1.2.1 Pathophysiology of Pain

Pain can be classified based on its underlying pathophysiology as nociceptive and/or neuropathic pain. Nociceptive pain is pain generated from the activation of nociceptors at the periphery due to injury or tissue damage (Basbaum et al., 2009; Gangadharan & Kuner, 2013; R. D. Treede, 2018). Nociceptors are free nerve endings of primary afferent sensory neurons found in the peripheral nervous system which convert noxious stimuli such as tissue damage into electrical impulses (Ellison, 2017). These electrical impulses are then transmitted to the central nervous system which the brain interprets to produce pain sensations (Ellison, 2017). Nociceptive pain is further subdivided into somatic or visceral pain (Basbaum et al., 2009). Somatic pain is pain arising from tissues such as skin, muscle, joints, and bones. It is described as aching, stabbing, gnawing, or throbbing and can either

be intermittent or constant (Anwar, 2016). Visceral pain is pain arising from visceral organs which are not sensitive to pain (Anwar, 2016; Ellison, 2017). It is also known as "referred pain" because pain is usually perceived as occurring in a region of the body which is either remote or adjacent from the actual source of pain1. Visceral pain is often described as dull, aching, and diffuse (Anwar, 2016; Visser & Davies, 2009).

Neuropathic pain is pain arising from lesion or disease affecting the sensory nervous system (Ellison, 2017). Neuropathic pain is commonly caused by metabolic disorders (e.g. painful diabetic neuropathy), infection (e.g. HIV), nerve compression, inflammation, trauma, and tumors (Colloca et al., 2017). It is usually described as sharp and burning (Colloca et al., 2017). Neuropathic pain is generally classified as peripheral (damage to peripheral nerve, plexus, dorsal root ganglion, or root) or central (damage to the brain or spinal cord) (Colloca et al., 2017; Ellison, 2017).

1.2.2 Acute pain versus Chronic pain

Pain can also be classified based on its time course and duration as either acute or chronic pain. Acute pain has been defined as "pain of recent onset and probable limited duration; it usually has an identifiable temporal and causal relationship to injury or disease" (Ready et al., 1992). It is self-limiting and typically lasts less than 3 months (Anwar, 2016; Ellison, 2017). It is usually nociceptive and resolves upon healing of the underlying tissue injury (Anwar, 2016). Acute pain is commonly due to surgery, traumatic injury, tissue damage, medical procedures, and acute disease states (McCormick & Law, 2016). Acute pain is vital for survival as it provides warning signals of potential injury and the magnitude of an injury. This biological significance is evident in individuals with "congenital insensitivity to pain",