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PROFILE OF FINAL REPORT FRGS/RAGS/ERGS/PRGS

Important Notes

- Profile of Final Report is to be submitted to declare the project is completed.
- Full Report should be uploaded through IREP.
- All reports must be based on the actual findings of the reported project.

Guidelines for writing the Profile of Final Report

- Report should be written in 'Times New Roman 12' Font, with 1.5 line spacing
- Report should be 5 pages (excluding appendices/references)
- Report must be in English (Applicable for Research in Arabic as well)

Project ID/Title:

**FRGS/1/2018/SKK09/UIAM/02/6/
PATTERN ANALYZER ON CONCOMITANT USE OF OPIOID AND
BENZODIAZEPINE IN PATIENTS WITH CHRONIC NON-CANCER
PAIN: THE RISING OF OPIOID OVERDOSE DEATH**

**Project Sponsor:
Ministry of Higher Education**

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Research Summary and Findings

In the last fifteen years, opioid prescriptions have increased tremendously with a concurrent increase of opioid overdose deaths. [1] In the US, it was reported that approximately 100 deaths/day occurred due to opioid overdose.[2] The greatest risk contributed to the death was the concurrent use of opioids with benzodiazepines.[3] This concurrent use has received growing concerns as these medications may pose serious risks and limited therapeutic benefit.[4]Taken independently, opioids and benzodiazepines are known to increase the risk of fall-related injuries caused by over-sedation, particularly among the elderly, motor vehicle accidents and death due to respiratory depression.[5]

The practice of combining opioids and benzodiazepines has been recognized as both ubiquitous and substantial.[6] The extent to which the utilization of concurrent use of opioids and benzodiazepines and its clinical outcomes in Malaysia is unclear, but their co-prescribing presents a serious safety concern and is not well characterized. Given these uncertainties, this study was prompted to address the above-mentioned issues.

The results of the preliminary study of the project that was conducted among opioid users receiving concomitant medications at an outpatient tertiary hospital setting in Malaysia showed that 12.3% of patients received co-prescriptions of opioid + benzodiazepine, 19.3% received opioid + anticonvulsant, 6.3% received opioid + antidepressant and 10.9% received other co-prescriptions, including antipsychotics and hypnotics. The individual mean opioid dose was <100 mg/d of morphine equivalents in all types of co-prescriptions, and the dose ranged from 31 to 66 mg/d in the co-prescriptions of opioid + benzodiazepine. The overall individual opioid dose in this co-prescription was moderate. Other co-medications were also commonly used, and their opioid doses were within the recommended dose.[7]

Moving on to the investigation on adherence to opioid therapy, the current study was using the proportion of days covered (PDC) to measure the adherence. The PDC was derived by dividing the total number of days covered with any opioids by the number of days in the follow-up period. Generalized linear modeling was used to assess factors associated with PDC. A total of 10,569 patients with 36,650 prescription episodes were included in the study. Of these, 91.7% ($n = 9,696$) were opioid naïve patients and 8.3% ($n = 873$) were opioid existing patients. The median PDC was 35.5% (interquartile range (IQR) 10.3–78.7%) and 26.8% (IQR 8.8–69.5%) for opioid naïve

and opioid existing patients, respectively. A higher opioid daily dose (coefficient 0.010, confidence interval (CI) 0.009, 0.012 $p < 0.0001$) and increasing age (coefficient 0.002, CI 0.001, 0.003 $p < 0.0001$) were associated with higher levels of PDC, while lower PDC values were associated with male subjects (coefficient -0.0041 , CI -0.072 , -0.010 $p = 0.009$) and existing opioid patients (coefficient -0.134 , CI -0.191 , -0.077 $p < 0.0001$). The suboptimal adherence to opioid medications was commonly observed among patients with non-cancer pain, and the opioid existing patients were less adherent compared to opioid naïve patients. Increasing age and a higher daily opioid dose were factors associated with higher levels of adherence, while male and opioid existing patients were potential determinants for lower levels of adherence to opioid medications.[8]

In order to establish the evidence on the opioid use, we also evaluated risk of opioid dose escalation as it relates to sex differences among patients receiving opioids for long-term therapy. This retrospective cohort study was conducted in tertiary hospital settings in Malaysia using electronic prescription records. Opioid naïve patients, aged ≥ 18 years, who were undergoing long-term opioid therapy of ≥ 90 days, with at least one opioid prescription (buprenorphine, morphine, oxycodone, fentanyl, dihydrocodeine or tramadol) between 1st January 2011 and 31st December 2016, were included in the study. They were followed until (i) the end of the study period, (ii) death from any cause or (iii) discontinuation of therapy from their first opioid prescription without any intervals of ≥ 120 days between successive prescriptions. The risk of high opioid dose escalation to ≥ 100 mg/day and ≥ 200 mg/day relative to men and women was measured. [9]

A total of 4688 patients (58.8% women, 41.3% men) on long-term opioid therapy were identified. Among these patients, 248 (5.29%) were escalated to high opioid doses of ≥ 100 mg/day and 69 (1.47%) were escalated to ≥ 200 mg/day. The escalation to high-dose opioid therapy was more likely to occur in men than in women, even after adjustment for age (dose ≥ 100 mg/day [adjusted hazard ratio 2.32; 95% confidence interval (CI), 1.79 to 3.00; $p < 0.0001$] and ≥ 200 mg/day [adjusted hazard ratio 6.10; 95% CI, 3.39 to 10.98; $p < 0.0001$]). In conclusion, this study found that the risk of opioid dose escalation differed between men and women, as men were at higher risk than women for high opioid dose escalation.

Within this project, we conducted several other studies in order to strengthen the evidence-informed practice on the status of opioid use in Malaysia. These included the patterns of analgesic

prescribing in children. This study found that during a 7-year study period, a total of 5040 analgesic prescriptions of the nine NSAIDs, tramadol, and five other opioids were prescribed for 2460 pediatric patients (81.8% NSAIDs patients, 17.9% tramadol patients, and 0.3% opioid patients). Ibuprofen was the primary analgesic for children less than 12 years old whereas there was a wide range of analgesics prescribed for children age >12 years old including naproxen, diclofenac, and tramadol.[10]

Further exploration was also conducted on the trends and patterns of opioid consumption in Malaysia and other four Southeast Asian countries. The results showed that growing trends of strong opioids consumption in all five Southeast Asian countries demonstrated in this study may indicate improved access to opioid analgesics in these countries. Given the increasing trends, it is important to ensure that the utilization of opioids is according to the guideline to prevent the negative consequences of opioids particularly when used in chronic non-cancer pain.[11]

In conclusion, we need better evidence in order to evaluate the benefits and harms of clinical decisions regarding opioid prescribing. Effective implementation of the evidence requires recognition that there are no shortcuts to safer opioid prescribing (which includes assessment of benefits and risks, patient education, and risk mitigation) or to appropriate and safe reduction or discontinuation of opioid use. Future studies are warranted to further evaluate on the clinical outcomes associated with opioid use particularly on the opioid overdose death. This to ensure patient safety while giving optimal pain treatment to them.

Financial Report and Asset Report

Budget Approved (<i>Peruntukan diluluskan</i>)	: RM126500
Amount Spent (<i>Jumlah Perbelanjaan</i>)	: RM99430.25
Balance (<i>Baki</i>)	: <u>RM 27069.75</u>
Percentage of Amount Spent	: 78.60 %

Outputs

Human Capital Development

Details of students

2 PhD students

1. Student full name : Nor Elina Binti Alias (PhD in Pharmacy Practice)
IC/ Passport No. : **821226715008**
Student ID : **G1714280**
Citizenship : Malaysian
Year of Graduation : 2022-Expected to submit thesis in Nov 2022. Now is in the final stage of thesis writing.
Thesis Title : Patient-level tramadol utilisation in non-cancer pain: trends, patterns and clinical outcomes.

2. Student full name : Hasni Muniati Hassan (PhD in Pharmacy Practice)
IC/ Passport No. : **820501065632**
Student ID : **G2013418**
Citizenship : Malaysian
Year of Graduation : Study is still ongoing-expected to submit thesis in Oct 2023.
Thesis Title : Concurrent use of opioid and benzodiazepine in patients with chronic non-cancer pain: Prevalence, trends, and its related clinical outcomes.

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Appendix 1

List of publications

Indexed Journal

- 1.** *Che Suraya Zin*, Nor H. Taufek Mazlila M Ahmad (2019) *Differential patterns of adherence to opioid therapy in opioid naïve and opioid existing patients with different age groups*. *Frontiers in Pharmacology* 10: 1286 (ISI indexed impact factor 3.845)
- 2.** *Che Suraya Zin*. *Ten years of strong opioid analgesics consumption in Malaysia and other Southeast Asian countries* *Journal of Pharmacy and Bioallied Health Sciences* 2020;12:S846-51
- 3.** *Che Suraya Zin* *Prescribing of non-steroidal anti-inflammatory drugs, tramadol and opioids in children: patterns of its utilization*. *Journal of Pharmacy and Bioallied Health Sciences* 2020;12:841-845
- 4.** *Che Suraya Zin*, Nor Asma Abdullah, Noorul Atiqah Ramli, Noorsyahiruh Khadir, Nor Shahfiza Zain, Nor Fatin Rosley and Siti Halimah Bux. *A bibliometric analysis on the productivity of opioid research in Malaysia* *Journal of Pharmacy and Bioallied Health Sciences* 2020;12:S667-70
- 5.** *Che Suraya Zin*, Nor Hidayah Taufek and Siti Halimah Bux (2020) *Drug Utilization and Drug Pricing in the Private Primary Healthcare System in Malaysia: An Employer Price Control Mechanism*. *Frontiers in Public Health* 8:551328. doi: 10.3389/fpubh.2020.551328
- 6.** *Che Suraya Zin*, Nor Elina Alias, Nor Hidayah Taufek, and Mazlila Meor Ahmad (2019). *Sex Differences in High Opioid Dose Escalation among Malaysian Patients with Long Term Opioid Therapy*. *Journal of Pain Research*,12 1251-1257 (ISI indexed impact factor 2.6)
- 7.** *Che Suraya Zin*, Norzaini Ros Nozid, Siti Nuraisyah Hashim, Nur Aimi Mazlan, Norhayati Daud, Amalia Athirah Razak and Siti Halimah Bux (2020). *Research on non-steroidal anti-inflammatory drugs in Malaysia: A bibliometric analysis*. *Journal of Pharmacy and Bioallied Health Sciences* 2020;12:707-710
- 8.** Asween Sani and *Che Suraya Zin**. *Comparison of the clinical outcomes between short-term and long-term opioid users with non-cancer pain at pain clinics*. *Journal of Pharmacy and Bioallied Health Sciences* 2020;12:S728-32

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Appendix 2

Additional Outputs

Detail list of other outputs e.g.: non-indexed journal, conference proceeding/ book/ book chapters/ policy paper etc.

List of Indexed journals

1. Mastura Ahmad, ***Che Suraya Zin**** and Ab Fatah Ab Rahman. *Intra-peritoneal Antibiotic Utilization among Continuous Ambulatory Peritoneal Dialysis (CAPD) Patients with Peritonitis at a Tertiary Hospital Setting in Malaysia*. Journal of Pharmacy and Bioallied Health Sciences 2020;12:S737-42
2. Mohammed A. Kubas, Fatiha Hana Shabaruddin, Wardati Mazlan-Kepli, Nirmala Jagan, Sahimi Mohamed, Nor Ilyani Mohamed Nazar, ***Che Suraya Zin****. *Assessing adherence and persistence to the non-vitamin k antagonist oral anticoagulants (NOACs) among patients with atrial fibrillation in tertiary-care referral centres in Malaysia*. Journal of Pharmacy and Bioallied Health Sciences 202;12:S781-6

List of Conferences

1. ***Che Suraya Zin***, and Taufek, Nor Hidayah and Meor Ahmad, Mazlila (2019) *Patterns of adherence to prescribed opioids: the differential between opioid naïve and opioid existing patients of different age groups*. In: 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), 24th-28th August 2019, Pennsylvania Convention Center, Philadelphia
2. ***Che Suraya Zin***, and Taufek, Nor Hidayah and Alias, Nor Elina and Meor Ahmad, Mazlila (2019) *High opioid dose escalation to 100 and 200 mg per day in patients with long term opioid therapy: Sex difference*. In: 8th Congress of the Association of South-East Asian Pain Societies (ASEAPS) 2019, 11th-14th April 2019, Kuching, Sarawak Malaysia
3. ***Che Suraya Zin***. *Prescribing of non-steroidal anti-inflammatory drugs, tramadol and opioids in children: patterns of its utilization*. International Conference on Pharmaceutical Research and Pharmacy Practice (ICPRP) 2019, 19-20th October Kuala Lumpur Malaysia
4. Asween Rowena Abdullah Sani and ***Che Suraya Zin***. *Comparison of the clinical outcomes between short-term and long-term opioid users with non-cancer pain at pain clinics*. International Conference on Pharmaceutical Research and Pharmacy Practice (ICPRP) 2019, 19-20th October Kuala Lumpur Malaysia
5. Hussam Mizher, ***Che Suraya Zin***, Abul Bashar MH, Abdul Hadi M, Tan HL, Munira MI. *Plasma concentrations of pro-inflammatory cytokine IL-6 and anti-inflammatory cytokine IL-10 in short and long term opioid users with non-cancer pain*. International Conference on Pharmaceutical Research and Pharmacy Practice (ICPRP) 2019, 19-20th October Kuala Lumpur Malaysia
6. Nor Elina A, ***Che Suraya Zin***, Nor Ilyani MN, Norny Syafinaz AR, Nor Hidayah. *Prescription-level of tramadol utilisation at a tertiary hospital setting in Malaysia: changing trends over a 7-year follow-up period*. International Conference on

Pharmaceutical Research and Pharmacy Practice (ICPRP) 2019, 19-20th October Kuala Lumpur Malaysia

7. **Che Suraya Zin**, Nor Asma Diyana Abdullah, Noorul Atiqah Ramli, Noorsyahiruh Khadir, Nor Shahfiza Zain, Nor Fatin Rosley, Siti Halimah Bux. *A bibliometric analysis on opioid research productivity in Malaysia*. International Conference on Pharmaceutical Research and Pharmacy Practice (ICPRP) 2019, 19-20th October Kuala Lumpur Malaysia
8. **Che Suraya Zin**, Norzaini Ros Nozid, Siti Nuraisyah Hashim, Nur Aimi Mazlan, Norhayati Daud, Amalia Athirah Razak. *Research on non-steroidal anti inflammatory drugs in malaysia: a bibliometric analysis*. International Conference on Pharmaceutical Research and Pharmacy Practice (ICPRP) 2019, 19-20th October Kuala Lumpur Malaysia
9. **Che Suraya Zin** *Ten years of strong opioid analgesics consumption in Malaysia and other Southeast Asian countries*. International Conference on Pharmaceutical Research and Pharmacy Practice (ICPRP) 2019, 19-20th October Kuala Lumpur Malaysia

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Appendix 3

References:

1. Kandel D, Hu M, Griesler P, Wall M. Increases from 2002 to 2015 in prescription opioid overdose deaths in combination with other substances. *Drug Alcohol Depend.* 2017;178.
2. Geissert P, Hallvik S, Otterloo J Van, Kane NO, Alley L, Carson J, et al. High-risk prescribing and opioid overdose : prospects for prescription drug monitoring program – based proactive alerts. 2018;159: 150–156.
3. Morley KI, Ferris JA, Winstock AR, Lynskey MT. Polysubstance use and misuse or abuse of prescription opioid analgesics : a multi-level analysis of international data. *Pain.* 2017;158: 1138–1144.
4. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *JAMA.* 2016;315: 1624–1645. doi:10.1001/jama.2016.1464
5. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002–2014. *Am J Prev Med.* 2016;51: 1–10. doi:10.1016/j.amepre.2016.02.014
6. Dowell D, Haegerich T, Chou R. No Shortcuts to Safer Opioid Prescribing. *N Engl J Med.* 2019;380: 2285–2287.
7. Zin CS, Ismail F. Co-prescription of opioids with benzodiazepine and other co-mediations among opioid users : differential in opioid doses. *J Pain Rsearch.* 2017; 249–257.
8. Zin CS, Taufek NH, Ahmad MM. Differential patterns of adherence to opioid therapy in opioid naïve and opioid existing patients with different age groups. *Front Pharmacol.* 2019;10: 1–9. doi:10.3389/fphar.2019.01286
9. Zin CS, Alias NE, Taufek NH, Ahmad MM. Sex differences in high opioid dose escalation among Malaysian patients with long term opioid therapy. *J Pain Res.* 2019;12: 1251–1257. doi:10.2147/JPR.S199243
10. Zin CS. Prescribing of Nonsteroidal Anti-inflammatory Drugs, Tramadol, and Opioids in Children: Patterns of Its Utilization. *J harmacy Bioaalied Sci.* 2020.
11. Zin CS. Ten Years of Strong Opioid Analgesics Consumption in Malaysia and Other Southeast Asian Countries. *J Pharm Bioallied Sci.* 2020.