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Antifungal Treatment of Mucormycosis Associated with COVID-19

Chia Siang Kow^{1,2*}, Syed Imran Ahmed³, Syed Shahzad Hasan^{4,5}

Mucormycosis is an angioinvasive fungal infection due to fungi of the order Mucorales. The prognosis from mucormycosis can be poor despite early diagnosis and aggressive therapy. The systematic review and meta-analysis by Muthu and colleagues [1] investigated the rate of mortality in patients with pulmonary mucormycosis. While there had been a significant decrease in the mortality rate over time, the recent (2010-2020) rate of mortality is still substantial, in which about one in two patients (49.8%; 95% confidence interval 43.2% to 56.3%) with pulmonary mucormycosis died from the disease. Yet, patients originated from the lower-middle-income countries had a higher mortality rate, in which about three in four patients (71.5%; 95% confidence interval 58.7% to 84.3%) with pulmonary mucormycosis died from the disease. Indeed, there has been a recent surge in the occurrence of mucormycosis in lower-middle-income countries, especially in India. As raised by Szarpak [2], the increased incidence with a fairly severe course of mycormycosis was reported in patients with a history of coronavirus disease 2019 (COVID-19) and received systemic corticosteroid therapy.

The presence of multiple risk factors in patients with COVID-19, along with the additional immunosuppression caused by systemic corticosteroids, predispose the occurrence of mucormycosis, which could negate the mortality benefits offered by systemic corticosteroids in this patient population [3]. Common risk factors include the presence of diabetes mellitus, particularly with ketoacidosis. Noteworthy, the management of patients with mucormycosis, which is considered rare before the COVID-19 pandemic, had not been optimal as described in a case report [4]. Optimal antifungal

therapy is of utmost importance considering the substantial rate of mortality.

Intravenous amphotericin B is the drug of choice for initial therapy of mucormycosis; a lipid formulation of amphotericin B (liposomal amphotericin B or amphotericin B lipid) is preferred to reduce the risk of nephrotoxicity. In a meta-analysis of five randomized trials, the incidence of nephrotoxicity was significantly lower with liposomal amphotericin B compared with amphotericin B deoxycholate (15% versus 33%; relative risk = 0.48; 95% confidence interval 0.36 to 0.64) [6]. The usual starting dose for amphotericin B is 5 mg/kg daily, which can be increased up to 10 mg/kg daily to control the infection.

While amphotericin B is generally considered the first-line agent for the treatment of mucormycosis. Posaconazole or isavuconazole is used as step-down therapy for patients who have responded to amphotericin B. Therefore, once patients respond and are deemed suitable for discharge, they could be initiated with either one of the aforementioned antifungal agents. Posaconazole and isavuconazole are broad-spectrum azoles that are active in vitro against the pathogens of mucormycosis. A systematic review [7] of 96 case reports of patients with mucormycosis reported a response rate of 72.9% with posaconazole. On the other hand, isavuconazole has been evaluated in a multicenter open-label single-arm study that included a total of 37 patients with mucormycosis [8]. When the researchers compared patients, who received isavuconazole with their contemporary counterparts who received amphotericin B (the majority received a lipid formulation), it was observed that the weighted all-cause mortality was similar

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in those who received isavuconazole (33%) and in those who received amphotericin B followed by posaconazole (41%). Posaconazole (delayed-release tablets) can be dosed at 300 mg every 12 hours on the first day, then 300 mg once daily, with no dosage adjustment necessary for patients with a decline in renal function. Whereas isavuconazole can be loaded at a dose of 200 mg every 8 hours for 2 days, followed by a maintenance dose of 200 mg orally once daily starting 12 to 24 hours after the last loading dose.

Antifungal therapy should be continued until clinical resolution of the signs and symptoms, as well as resolution of radiographic signs of mucormycosis. Perhaps in the context where there is a widespread outbreak of mucormycosis, the use of systemic corticosteroids should be more judicious in patients at high risk, such as those with diabetes, keeping in mind that systemic corticosteroids could aggravate hyperglycemia. The use of intravenous pulse methylprednisolone therapy for as short as three days to limit its side effects can be considered [9]. Besides, baricitinib, a Janus kinase inhibitor, which has proven mortality benefits, can be considered as an alternative to systemic corticosteroids in patients with COVID-19 [10].

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Clinical Pharmacist in a COVID-19 Hospital- A Malaysian Experience

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has hugely affected healthcare services, particularly pharmacy services in a COVID-19 hospital. Before the COVID-19 outbreak, clinical pharmacists routinely reviewed patients' medications upon ward admission, actively participated in ward rounds and partook in transitional care activities focusing on medication reconciliation and patient education in the wards. However, in order to limit contact with COVID patients, hospital pharmacy department reacted promptly by establishing remote clinical pharmacy services in order to sustain the quality of inpatient pharmaceutical care. This commentary describes the challenges faced by clinical pharmacists in a Malaysian hospital as we continue to provide clinical pharmacy services amidst the new norm.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first identified in December 2019 in Wuhan, China [1]. The virus is thought to have been transmitted by respiratory droplets and contact routes. Droplets transmission can occur when an infected person with symptoms (e.g. coughing or sneezing) is in close contact (less than 1 m) with another person [2]. Infected droplets may also contaminate surfaces and objects and a person may get infected by touching contaminated surfaces or objects and then touching their eyes, nose or mouth [3]. Mild symptoms of COVID-19 includes fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing or gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea). Critically, it can progress to acute respiratory distress syndrome (ARDS) and may result in shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury [4].

According to the World Health Organization (WHO), as of 18 April 2021, the total number of confirmed COVID-19 cases stood approximately 141 million cases with 3 million reported deaths worldwide [5]. In Malaysia, the total number of cases are 375,054 with 1378 reported deaths [6]. In order to reduce the spread of COVID-19, Malaysian government implemented staggered movement control order starting from 18 March 2020 till early 2021 [7]. In addition to that, the Malaysian Ministry

of Health and the National Security Council have been actively urging the public to stay at home, practice social distancing, frequent hand hygiene and to wear mask at all times [8].

In combating COVID-19, the Ministry of Health has designated several hospitals and facilities to be COVID-19 referral and screening centres for centralized and standardized inpatient treatment [9]. For the state of Selangor, Hospital Sungai Buloh (HSgB) is the designated hospital to handle COVID-19 cases [10]. HSgB is a 620-bedded hospital serving as the centre of excellence for infectious diseases, emergency and trauma, neurosurgery, maxilla-facial surgery, burn and plastic surgery and also orthopaedic and traumatology. HSgB essentially covers Gombak, Petaling and Kuala Selangor districts where these make up to 40% of the Selangor population or approximately 2.18 million populations [11]. As of 14 April 2021, Selangor has amassed a total of 121358 cases, the highest in Malaysia with 350 deaths [12]. To date, HSgB has treated a total of 44100 cases, with 267 mortalities [13].

HSgB's clinical pharmacy service consists of 19 full time ward pharmacists in the following wards: neonatal intensive care unit, cardiac care unit, intensive care unit, medical wards (male and female), infectious disease wards, orthopedic male ward, surgical male ward, obstetrics and gynecology wards, neurosurgical ward and paediatric wards. Routinely before the COVID-19 pandemic, clinical pharmacists would review the appropriateness of medications by clerking patients' case notes, actively participate in ward rounds with physicians, partake in

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transitional care activities focusing on medication reconciliation, dispense patients' discharge medications at bedside and also handled patients' medication counseling and education in the wards.

Challenges but now the new norm

As soon as HSgB was declared as a COVID hospital, we swiftly changed our usual ways of daily duties, to better support the pharmacy department and hospital as a whole. Our routine changed to adapt the "new norm" way of life, to avoid 3Cs (crowded places, confined spaces and close conversation) and to practice 3Ws (wash, wear and warn). Some of the challenges that we faced were staggered working hours to ensure social distancing is practiced, limited assessment of patients in the ward with no participation in clinical rounds with the physicians, inadequate evidence for COVID-19 treatment, medication administration and charting accuracy in the wards, lack of assessment in patients' own medication history and the medication availability during their admission, and the increasing involvement albeit lack of experience, in clinical trials with the physicians.

Staggered working hours and work from home (WFH) schedule

In order to promote social distancing and less crowding at our work places, we had to rapidly rearrange our work force, and at the same time ensure adequate support to the entire pharmacy and hospital services. We utilized a pairing system among clinical pharmacists whereby one of the pair will be present at work and the partner will be contactable via phone during WFH hours. Effective communication and proper passing over had ensured that patients continuously received the best possible pharmaceutical care needed.

Limited assessment in inpatient pharmaceutical care

In order to limit contact with COVID-19 patients and to prevent unnecessary use of Personal Protective Equipment (PPE), we have resorted to remote inpatient review by clerking patients at pharmacy workstations instead of traditionally in the wards. Medication reviews are done through a local area network via electronic Hospital Information System (eHIS). On the other hand, medication-related interventions identified by clinical pharmacists are communicated to the wards via telephone. In addition, tele-pharmaceutical strategies have also been implemented for patient care [14, 15]. Such strategies include remote communication through phone or video call to obtain patients' medication history and medication counseling. Furthermore, instructional videos for medical device counseling such as insulin pen and inhalers are first sent to patients' smart phones for self-viewing. Once patients have

viewed the instructional video, pharmacists will proceed to make a video call to the patient for further assessment and clarification.

Another challenge faced by clinical pharmacists was verification of medication administration in the wards. Prior to the COVID-19 pandemic, most of the wards in HSgB fully utilized the electronic medication administration charting system. With this system, clinical pharmacists would normally verify that medication administrations were done properly and accurately in the ward. However during the pandemic, the wards employed a hybrid medication administration system of both electronic as well as manual charting. The addition of manual charting has been implemented as there has been extra nursing staff employed from other health facilities to cater to the large volume of patients and unfortunately, these nurses are unfamiliar with the hospital's electronic system. The clinical pharmacists thus have an added role to ensure that manual charting of medication administration is done properly and accurately in the wards. Moreover, patients are warded in isolation rooms and staffs entering these rooms are restricted to preserve PPE supplies. Hence, for patients who are well and independent, medications for the day are dispensed to patient's bedside and then self-administered by patients. With this new change in practice, clinical pharmacists face difficulties by ensuring that medications are indeed delivered to patients and the manual charting are recorded accurately by the nurses.

Availability of patient's own medication

During the COVID-19 season, we see heterogeneity of patients being admitted to the wards. Some patients have their underlying co-morbidities followed up in private health facilities and some of their prescribed medications are not readily available under the public hospital medication formulary. These patients will therefore need their home medications delivered to them directly during their inpatient stay for self-administration. With this challenging logistic issue in hand, clinical pharmacists have to liaise with patients' family members to ensure that complete patients' home medications are brought to the hospital soonest possible.

Antiviral stewardship, use of novel experimental agents and involvement in clinical trials

Most of the drugs which are currently being prescribed such as Favipiravir, Remdesivir, Tocilizumab and interferon, are either prescribed for experimental, compassionate or off-labelled use. As an infectious disease (ID) hospital, clinical pharmacists were actively practicing antimicrobial stewardship to ensure effective and judicious use of antimicrobials. However, at the start of COVID-19 outbreak in Malaysia in February 2020, we had to quickly adjust our direction to antiviral stewardship due

to the increased usage of antivirals in COVID-19 treatment. Antiviral stewardship has thus far helped in the development of local treatment protocol on repurposed antivirals, which currently guides practitioners in the best recommended doses and treatment regimes. On the other hand, this stewardship also helps to monitor and manage drug shortages due to supply chain interruptions.

The use of novel experimental agents proved to be an unprecedented and arduous decision based on their lack of clinical evidence in treating COVID-19, which is to be expected. For the ease of all health practitioners in HSgB, the clinical pharmacists have been working hand-in-hand with pharmacy resources and information unit and the ID physicians in creating a local, quick and comprehensive COVID-19 treatment guide. In addition, medications used for COVID-19 is not readily available in our local setting hence challenging us to race against time in providing the most efficient treatment, especially to the critically ill patients. Up until this moment in facing this adversity, clinical pharmacists have been working together closely with inpatient and procurement pharmacists to ensure the availability and timely supply of COVID-19 drugs are sustained.

The pandemic also created opportunities for clinical pharmacists to be involved in esteemed and renowned clinical trials such as the Solidarity Trial initiated by WHO and STORM Study initiated by the Malaysian Ministry of Health.

DISCUSSION

Clinical pharmacist contributed to a great extent in current pandemic, from administrative tasks to pharmaceutical interventions by optimizing medication therapy in severe and critically ill COVID-19 patients. Overall, with the help of technology and collaboration from all other healthcare givers, clinical pharmacists were able to carry out our tasks the best we possibly could in these unprecedented times. We were able to carry out our basic core duties of patient clerking remotely and giving patient education and counseling virtually. However, in term of inpatient medication reconciliation, this effort was largely limited due to the instability of COVID-19 patients particularly in patients with category 4 and above. We also encountered some difficulties when contacting family member or caregivers for medication reconciliation. Clinical pharmacists' involvement in the antimicrobial stewardship could have been further enhanced to ensure judicious use of antibiotic with the increased use of antibiotic in COVID-19 patients. This effort would require extended collaboration with other healthcare givers who are pre-occupied with patient-care now.

This commentary describes the main activities and challenges faced by clinical pharmacists during the first wave of the COVID-19 pandemic. Considering the lessons learnt, future effort should look into efficacy and safety of virtual patient care, the impact of COVID-19 on patient pharmaceutical care as well as healthcare-related cost-saving in middle income country.

CONCLUSION

In summary, we as clinical pharmacists in a COVID-19 hospital faced an unprecedented and challenging situation since the pandemic began globally. We needed to act swiftly and proactively in response to the Covid-19 outbreak in order to sustain the quality of patient care and continue to adapt the new norm as a way of work and life. We learnt the importance of a contingency plan to cater for sudden changes in usual practice, such as a pandemic of a novel virus. We need to be versatile and ever ready to accept and adapt to new changes. Last but not least, teamwork is important to achieve a greater good for the best patient care during the COVID-19 pandemic.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Warfarin - Fenofibrate Interaction: Hospital Kuala Lumpur Experience

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ABSTRACT

Case reports in western populations reported that fenofibrate enhances the anticoagulatory effect of warfarin. We are reporting ten cases of warfarin-fenofibrate interaction among Malaysian patients' cases that were managed at the anticoagulation clinic of Hospital Kuala Lumpur. Patients taking warfarin and micronized fenofibrate 145mg daily concurrently between the year 2014 to 2018 were identified in May 2018. Ten active patients were included, and the relevant data were retrieved retrospectively. All patients received warfarin for stroke prevention in atrial fibrillation (AF), with a target international normalised ratio (INR) of 2 to 3. No dose adjustment was done upon initiation of fenofibrate. Warfarin doses were adjusted to achieve the targeted range but fenofibrate was not discontinued. Eight patients had INR levels above the target range when INR being reassessed between 20 to 62 days after initiation of fenofibrate. Their weekly warfarin doses were between 17.5mg-46.5mg. Baseline INR ranged between 1.6 -3.1. Percentage of dose reduction ranged between 5%-60%. Four of the patients were on other concurrent interacting medications such as statin and levothyroxine. Only one patient, whose case was with an INR 3.1 before initiation of fenofibrate, required admission for hematoma (INR 12). Two patients had INR within the target range, and INR were assessed at 14 and 21 days after fenofibrate initiation. Their weekly warfarin doses were between 24.5mg and 26.5mg while baseline INR was 2.8 and 1.9 respectively. Interaction between fenofibrate and warfarin may increase INR among Malaysian patients, thus close monitoring of INR is warranted. Empirical warfarin dose reduction may be considered upon initiation of this drug combination for patients with AF. The next INR reassessment date should be arranged not later than three weeks after initiation of fenofibrate.

INTRODUCTION

Warfarin has been the most commonly prescribed oral anticoagulant in the management of atrial fibrillation (AF), venous thromboembolism and valvular heart disease, despite the emergence of direct oral anticoagulants (DOACs). This has led to a high number of patients referred to anticoagulant clinics for warfarin therapy. The management of warfarin is challenging because the drug has a narrow therapeutic index and is accompanied by drug-drug, drug-food, and drug-disease interactions that may influence the anticoagulant effects. This may lead to a change in patients' international normalized ratio (INR) and poses a risk of bleeding or thrombosis.

In Malaysia, fenofibrate is prescribed for patients with mixed dyslipidaemia and hypertriglyceridemia as well as patients

with mild to moderate hypercholesterolemia who are statin intolerant [1]. According to the Malaysian Statistics on Medicines 2011 – 2014, there was an increasing trend of prescribing fenofibrates in the public sector [2]. The prevalence of dyslipidaemia in a patient with AF is 46.3% according to International AF Registry therefore co-administration of warfarin and fenofibrate by patients is becoming more common [3].

Fenofibrate had been reported to have major interaction with warfarin from case reports [4-6]. These case reports showed a significant increase in INR upon initiation of fenofibrate in patients whose warfarin therapy had been stabilized [4-6]. An increase in INR values will place the patients at higher risk of bleeding and/or hospitalization due to over-warfarinization. In order to address the issue, warfarin dose reduction or

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Table I: Demographic data, baseline INR and weekly warfarin dose prior to initiation of fenofibrate of patients

| No | Age (years) | Gender | Ethnicity | INR before initiation of Fenofibrate (Pre) | INR within range (Pre) | Weekly Warfarin dose before initiation of Fenofibrate (mg) |
|----|-------------|--------|-----------|--|------------------------|--|
| 1 | 68 | Female | Indian | 2.8 | Yes | 24.5 |
| 2 | 51 | Male | Punjabi | 2.9 | Yes | 46.5 |
| 3 | 67 | Male | Chinese | 1.6 | No | 27.0 |
| 4 | 59 | Male | Indian | 1.8 | No | 28.0 |
| 5 | 69 | Male | Malay | 1.9 | No | 26.5 |
| 6 | 55 | Female | Indian | 2.0 | Yes | 17.5 |
| 7 | 68 | Female | Malay | 1.8 | No | 39.5 |
| 8 | 46 | Male | Malay | 3.1 | No | 46.5 |
| 9 | 76 | Female | Chinese | 2.0 | Yes | 17.5 |
| 10 | 61 | Male | Chinese | 2.5 | Yes | 17.5 |

discontinuation of fenofibrate are the options that had been discussed [4]. Different values of total warfarin dose reduction upon initiation of fenofibrate had been concluded from these reports [4-6].

The mechanism of interaction between warfarin and fenofibrate is not clearly understood. One of the postulated mechanisms proposed is that the metabolism of either or both fenofibrate and (R)-enantiomer of warfarin, which are metabolized via CYP 3A4 enzymes will be delayed, hence leading to the reduction in the clearance of warfarin [7]. On the other hand, fenofibrate inhibits CYP 2C9, a cytochrome that metabolizes the (S)-enantiomer of warfarin, thereby reducing warfarin elimination [7]. Pea F and Furlanut M. (2001) suggested that the interaction is due to fenofibrate affecting the coagulation synthesis factor by altering receptor synthesis [8]. Lastly, it had been proposed that fenofibrate displaces warfarin from its protein-binding sites, hence enhancing the hypoprothrombinaemia effects [9].

Currently, limited published data is describing warfarin-fenofibrate interaction among the multiracial Malaysian population. Genetic variations in CYP2C9 lead to the variations in the response in warfarin metabolism [10]. Zhao et al showed that there are genetic variations of CYP2C9 in different Singapore ethnic groups, namely Malay, Chinese, and Indian, which are similar to the Malaysian population [11]. The details on the effect of warfarin-fenofibrate interaction in the Malaysian population are scarce. We report ten cases of warfarin-fenofibrate interaction among patients managed at Hospital Kuala Lumpur (HKL), Malaysia. This clinic is co-managed by medical officers and clinical/ trained pharmacists to optimise anticoagulation therapy.

METHOD

The HKL Anticoagulation Registry was screened to identify patients prescribed with warfarin and fenofibrate concurrently, between 2014 and 2018. The relevant clinical information retrieved from the medical notes includes: demographic data, INR before and after initiation of fenofibrate, weekly warfarin

dose before and after initiation of fenofibrate, concurrent medications and incidences of bleeding. Incidences of bleeding include hematoma, gastrointestinal bleeding (GIB) and intracranial haemorrhage (ICH). Only incidences of bleeding that were documented by the medical practitioners in the case notes were considered. Results were limited to active adults of at least 18 years old who started on both warfarin and fenofibrate concurrently between 2014 and 2018.

Patients with missing needed data for the study, pregnant and lactating mothers were excluded. The study received approval from the National Medical Research Registration (NMRR-19-2171-48579).

RESULT

Ten patients who fulfilled the inclusion criteria were identified during screening. All 10 patients received Micronized Fenofibrate 145mg (Lipantyl Penta® by Abbott) and a mixed brand of warfarin between 2014 and 2018. The 10 patients received warfarin for the indication of stroke prevention in AF, with a target INR of 2 to 3. Six of the patients were male. The demographic data, baseline INR, and weekly warfarin dose prior to initiation of fenofibrate of patients are presented in Table I. Patients ranged from 46- to 76-year-olds. The baseline INR ranged from 1.6 to 3.1 with the weekly doses of warfarin between 17.5 mg to 46.5 mg.

Details of the study data are presented in Table II. After initiation of fenofibrate, only two patients had their INR levels maintained within the target range while 8 patients had INR above the target range. No adjustment to the weekly warfarin dose was made upon initiation of fenofibrate in all 10 patients. Fenofibrate was not discontinued in all 10 patients.

For the 8 patients who had INR above the target range, their levels were reassessed between 20 to 62 days after initiation of fenofibrate. Weekly warfarin doses were between 17.5mg to 46.5mg with baseline INR between 1.6 and 3.1 upon initiation

Table II: Detail data of patients after initiation of Micronized Fenofibrate 145mg.

| Patient No | Weekly Warfarin dose*(mg) | Time to reassessment of INR↓ (days) | INR ↓ | INR within range (post) | Adjusted Weekly Warfarin dose ↓(post) (mg) | Percentage of weekly Warfarin dose reduction (%) | Remarks |
|------------|---------------------------|-------------------------------------|-------|-------------------------|--|--|---|
| 1 | 24.5 | 21 | 2.8 | Yes | 24.5 | No change | - |
| 2 | 46.5 | 30 | 5.1 | No | 31.5 | 32 | Gemfibrozil was substituted with fenofibrate Simvastatin was initiated on the same day. |
| 3 | 27.0 | 57 | 3.6 | No | 25.0 | 7 | Gemfibrozil was substituted with fenofibrate Simvastatin was substituted with atorvastatin. |
| 4 | 28.0 | 62 | 3.4 | No | 26.5 | 5 | - |
| 5 | 26.5 | 14 | 2.7 | Yes | 26.5 | No change | - |
| 6 | 17.5 | 30 | 7.3 | No | 7.0 | 60 | - |
| 7 | 39.5 | 28 | 5.9 | No | 34.0 | 14 | - |
| 8 | 46.5 | 26 | 12.0 | No | 31.5 | 32 | Gemfibrozil substituted with fenofibrate. Patient was warded due to hematoma & elevated INR (12.0) during the follow up in anticoagulation clinic. |
| 9 | 17.5 | 39 | 4.65 | No | 11.5 | 34 | |
| 10 | 17.5 | 20 | 5.7 | No | 10.5 | 40 | Levothyroxine dose was increased from 75 mcg once daily to 100 mcg once daily. |

of fenofibrate. Warfarin doses were adjusted by the prescribers to achieve the target range. The percentages of weekly warfarin dose dosage adjustment to achieve the targeted ranged between 5% to 60%.

Four of the 8 patients were on other concurrent interacting medications such as statin and levothyroxine. Patient 2, patient 3, and patient 8 had fenofibrate initiated to substitute gemfibrozil. Patient 2 had simvastatin initiated on the same day as fenofibrate. This patient required 30% of the weekly warfarin dosage adjustment to achieve the targeted range. Patient 3 had simvastatin changed to atorvastatin on the day of fenofibrate initiation. This patient required 7% changes in the weekly warfarin dosage after initiation of fenofibrate to achieve the targeted INR range.

Patient 8 had an INR of 12 on the 26th days after the initiation of fenofibrate and required ward admission for hematoma. Fenofibrate was not stopped but the weekly warfarin dose was reduced by 32% to achieve the targeted INR range. The levothyroxine dose for patient 10 was increased from 75mcg to 100mcg on the day of initiation of fenofibrate.

Two patients who had INR within their targeted range were reassessed at 14 and 21 days after initiation of fenofibrate. Their weekly warfarin doses were between 24.5mg and 26.5mg while the baseline INR were 2.8 and 1.9 respectively.

DISCUSSION

Eight patients were reported to have INR above the targeted range. This is similar to the previously published case reports [4-6], whereby warfarin – fenofibrate interaction led to an increase in INR for most of patients. The degree of changes varied with reported case reports and among the multi-ethnic patients in this case series. The overall weekly warfarin dose reduction from baseline was highest among the Indians (2 patients; 5% & 60%), followed by Chinese (3 patients, ranging between 7% to 40%) and the lowest in Malays (2 patients; 14% & 32%, respectively). It is unclear whether the genetic variations of CYP2C9 in different ethnicities contribute to the result.

Half of the patients required reduction of 30% or more of their weekly warfarin dose to achieve the target INR range. One patient (Patient 8) had reported hematoma after initiation of fenofibrate. The effect of fenofibrate in warfarin could potentially influence the INR of 12 and resulted in a hematoma. Previous studies had reported that the risk of major bleeding is high when INR is above 9 [12-13]. Our results were aligned with previous published case reports that required up to 41% warfarin dose reduction to maintain a therapeutic INR after initiation of fenofibrate [4].

Two of the patients had INR maintained within the target range 14 and 21 days after initiation of fenofibrate. The other eight patients' INR was above the target range of 20 to 62 days after

initiation of fenofibrate. The degree of INR elevation in these patients may be affected by the duration of INR reassessment after initiation of fenofibrate and concurrent interacting medications. Our results indicated that the potential for the onset of interaction between warfarin and fenofibrate occurs after 3 weeks.

Three patients had their lipid-lowering fibric acid derivatives switched from gemfibrozil to fenofibrate. Two of them (Patient 2 and Patient 8) required 32% weekly warfarin dose reduction to achieve the target INR range, patient 8 eventually required to be warded due to hematoma. Another patient (Patient 3) required only 7% weekly warfarin dose reduction, however the patient's simvastatin (Known to cause an increase in INR when used concomitantly with warfarin) had been switched to atorvastatin (No interaction with warfarin) on the same day as initiation of fenofibrate [14]. The lower magnitude of fenofibrate-warfarin interaction for patient 3 may be affected by the switching of statins. Further investigation is needed to review the contribution of these confounding factors towards the degree of interaction between warfarin and fenofibrate.

There are potential limitations to consider in our case series. The data were collected retrospectively without a control group. We were unable to assess the patient's adherence to the prescribed medication. Concurrent factors such as concurrent medications and a mixed brand of warfarin used by patients may have affected the outcome of the data.

CONCLUSION

Empiric warfarin dosage reduction and close monitoring of patient's INR can be considered after initiation of fenofibrate based on authors' experience. Individual patient characteristics such as concurrent medications and patient's adherence to prescribed medications should be considered when determining the extent of empiric warfarin dosage reduction. The next INR reassessment date should be arranged not later than three weeks after initiation of fenofibrate.

Our data showed that the overall weekly warfarin dose reduction after initiation of fenofibrate varied among the multi-ethnic patients. The effect of different ethnicities on the degree of interaction between warfarin and fenofibrate requires further investigation.

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CONFLICT OF INTEREST

There is no conflict of interest.

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Monotherapy with Lopinavir/Ritonavir or in Combination with Interferon Beta-1b in Patients with Non-severe COVID-19 Disease: A Clinical Case Series

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ABSTRACT

The outbreak of Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV-2), has infected and killed millions of people worldwide. It has substantially increased the burden on healthcare system. However, the optimal approach to treatment of COVID-19 is uncertain. “Off-label” use of lopinavir/ritonavir (LPV/r) and interferons, particularly interferon beta (IFN- β), were the most suggested at the early stage. Although the United States National Institutes of Health’s (NIH) COVID-19 guidelines do not recommend the use of both medications for the treatment of COVID-19 in hospitalized patients, their roles in patients with non-severe disease are still unclear. Macau, a famous city for tourism, had 46 COVID-19 confirmed cases as of 2020. In this retrospective review, we summarized clinical and laboratory features of 39 COVID-19 patients admitted in the Centro Hospitalar Conde de São Januário (CHCSJ), of whom all did not receive oxygen therapy or ventilatory support during hospitalization. Of note, 12 (30.8%) of them were asymptomatic. The most common symptoms were fever and cough upon admission. They were all treated with LPV/r \pm IFN- β -1b plus supportive care. The mean length of hospitalization was 26.6 (SD \pm 12.6) days with LPV/r monotherapy, whereas 27.8 (SD \pm 10.1) days with LPV/r/IFN- β -1b combination therapy (p=0.65). The percentage of 28-day negative results for polymerase chain reaction (PCR) test were 67.9% (19 of 28) with monotherapy and 63.6% (7 of 11) with combination therapy (p=0.80). No fatal case was reported and all patients discharged successfully. No beneficial clinical outcome was observed with the addition of IFN- β -1b to LPV/r-based therapy. Further studies are warranted to confirm these findings.

INTRODUCTION

At the end of 2019, a novel coronavirus was identified as the cause of atypical pneumonia in Wuhan, a city in the Hubei Province of China and quickly spread in a number of countries. In February 2020, the World Health Organization (WHO) named the disease COVID-19, which stands for coronavirus disease 2019 [1]. The virus that causes COVID-19 is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of Dec, 2020, it has infected more than 79 million patients with over 1.7 million deaths globally [2]. Moreover, healthcare professionals are now facing a big challenge, in

particular on the treatment and the burden on the health care system. However, the optimal approach to treatment of COVID-19 remains uncertain. Lopinavir/ritonavir (LPV/r) and interferon beta (IFN- β), in particular interferon beta-1b were the most proposed treatment options in off-label use at the early stage of pandemic due to modest activity in vitro against SARS-CoV and Middle East respiratory syndrome (MERS)-CoV. Although the United States National Institutes of Health’s (NIH) COVID-19 guidelines in Oct, 2020 [3] did not recommend the use of both medications for treating COVID-19 in hospitalized patients, their roles in patients with non-severe disease are still unclear. Macau, a Special

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Administrative Region of the People's Republic of China reported a total of 46 COVID-19 cases in 2020. Among them, over 80 % were non-severe meaning that they did not need oxygenation or mechanical ventilatory support during hospitalization. In this retrospective study, we collected data from 39 patients with COVID-19 admitted to the Centro Hospitalar Conde de São Januário (CHCSJ), which is the designated hospital for managing all COVID-19 patients in Macau SAR, China. All patients were treated with LPV/r monotherapy or in combination with IFN- β -1b plus supportive care. This study was to observe whether any clinical benefit exists by adding IFN- β -1b to LPV/r-based therapy compared with LPV/r monotherapy.

METHOD

Study design and participants

Ethical approval (document no. 0067/DAH/N/2020) was obtained from the ethical committee of Centro Hospitalar Conde de São Januário, Macau Health Bureau, Macau SAR, China. Eligibility criteria for this study were patients with confirmed COVID-19 disease and hospitalized at CHCSJ, while fulfilled the below clinical classification of non-severe disease, and received LPV/r for a median of 21 days \pm IFN- β -1b for a median of 14 days plus supportive care (i.e. symptomatic drug treatment as well as general inpatient care including daily vital signs monitoring and regular biochemistry tests). We reviewed the details from medical records including demographics, past medical history, laboratory results, radiological findings, clinical management, length of hospitalization and time to completed negative result for polymerase chain reaction (PCR) test.

PCR assay for SARS-CoV-2

Samples were mainly taken from nasopharyngeal swabs (NPS) in all patients. The extraction of nucleic acid from samples was performed using EasyMag in accordance with the manufacturer's instructions (bioMerieux, France). Extracted nucleic acid samples were tested for SARS-CoV-2 with qRT-PCR using a commercial SARS-CoV-2 (previously known as 2019-nCoV) ORF1ab/N Gene Nucleic acid detection kit (BioGerm, China) and the LightCycler 480 real-time PCR system (Roche, Switzerland) in accordance with manufacturer's instructions.

Definitions for clinical classification

According to the United States National Institutes of Health's (NIH) COVID-19 guidelines [3], severe illness is defined as individuals who have SpO₂ <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300 mm Hg, respiratory frequency >30

breaths/min, or lung infiltrates >50%. Whereas critical illness refers to individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction. In this study, we defined non-severe COVID-19 disease patients as those who were asymptomatic or presymptomatic, mild illness with signs and symptoms compatible with upper respiratory tract infection (e.g. isolated low-grade fever, cough, rhinorrhea or myalgia), moderate illness that exhibited lower respiratory tract infection (e.g. pneumonia or bronchitis) but did not present with hypoxia (oxygen saturation \leq 94 percent on room air) or need for oxygenation or mechanical ventilatory support during hospitalization.

COVID treatments

All included patients with no contraindications received LPV/r (400 mg/100 mg) twice daily for a median of 21 days. Besides, they were given either azithromycin 500mg daily or levofloxacin 500-750mg daily as prophylactic agent for secondary bacterial infection. Patients with an early onset of illness (within 7 days) were given interferon beta-1b 250mcg (8 million IU) subcutaneously every other day for a median of 14 days when the drug was available in Macau. Symptomatic treatments (e.g. antipyretics, antihistamines and expectorants, etc.) were given when required. The standard biochemistry, imaging tests were systematically performed upon admission.

Criteria for discharge

Patients with completed negative result for PCR assay (i.e. two consecutive negative nasopharyngeal samples) were transferred to other units for medical observation then discharged in the absence of relapse.

Measured Outcomes

We interpreted the collected data including the length of hospitalization and the percentage of 28-day negative result for PCR test via nasopharyngeal swabs.

Data and statistical analyses

Patients' data are presented as absolute value, percentage, mean \pm SD or median ((interquartile range (IQR))). Continuous variables and categorical variables were compared using the Mann-Whitney U test and χ^2 test, respectively; P value of less than 0.05 was considered statistically significant. All tables were generated by JASP 0.14.1.

Table I Demographic and clinical characteristics of the patients at admission

| Characteristics | Lopinavir + ritonavir (n=28) | Lopinavir + ritonavir + interferon beta-1b (n=11) |
|---|---------------------------------|---|
| Age, median (IQR) — yr | 24.5 (18.5) | 44.0 (20.0) |
| <18y — no. (%) | 6 (21.4) | 0 (0.0) |
| 18 to 59 y — no. (%) | 21 (75.0) | 11 (100.0) |
| ≥60 y — no. (%) | 1 (3.6) | 0 (0.0) |
| Male — no. (%) | 16 (57.1) | 8 (72.7) |
| Comorbidity — no. (%) | | |
| Diabetes mellitus | 0 (0.0) | 2 (18.2) |
| Hypertension | 2 (7.1) | 4 (36.4) |
| Cardiovascular disease | 1 (3.6) | 0 (0.0) |
| Current smoker — no. (%) | 2 (7.1) | 2 (18.2) |
| Ex-smoker — no. (%) | 4 (14.3) | 3 (27.3) |
| Time between onset of symptoms and hospitalization, median (IQR) — days | 1.5 (8.0) | 1.0 (5.5) |
| Signs and symptoms — no. (%) | | |
| Fever, | | |
| Body temperature ≥37.5°C (%) | 10 (35.7) | 3 (27.3) |
| Body temperature, median (IQR) —°C | 37.0 (0.9) | 37.3 (1.2) |
| Cough | 8 (28.6) | 4 (36.4) |
| Sore throat | 3 (10.7) | 6 (54.5) |
| Myalgia | 3 (10.7) | 1 (9.1) |
| Diarrhea, ≥3 times/day | 3 (10.7) | 0 (0.0) |
| Headache | 3 (10.7) | 0 (0.0) |
| Rhinorrhea | 3 (10.7) | 1 (9.1) |
| Dizziness | 2 (7.1) | 1 (9.1) |
| Abdominal pain | 0 (0.0) | 1 (9.1) |
| Loss of smell | 1 (3.6) | 0 (0.0) |
| Respiratory rate ≥ 24/min (%) | 0 (0.0) | 0 (0.0) |
| Serum creatinine, median (IQR) — umol/L | 67.5 (22.3) | 77.0 (14.0) |
| White cell count, median (IQR) — x10 ⁹ /L | 5.4 (3.6) | 5.2 (3.8) |
| Lymphocyte count, median (IQR) — x10 ⁹ /L | 1.6 (0.9) | 1.3 (0.6) |
| Aspartate transaminase, median (IQR) — U/L | 20.0 (6.0) | 33.0 (11.5) |
| Alanine transaminase, median (IQR) — U/L | 15.0 (25.0) | 26.0 (38.0) |
| Lactate dehydrogenase, median (IQR) — U/L | 166.5 (53.3) | 176.0 (88.0) |
| C-reactive protein, median (IQR) — mg/dL | 0.1 (0.3) | 0.3 (0.5) |

Table II Treatment and outcome

| Outcomes | Lopinavir + ritonavir (n=28) | Lopinavir + ritonavir + interferon beta-1b (n=11) |
|---|---------------------------------|---|
| Death, no. (%) | 0 (0.0) | 0 (0.0) |
| Discharged, no. (%) | 28 (100.0) | 11 (100.0) |
| 28-day negative result for PCR assay, no. (%) | 19 (67.9) | 7 (63.6) |
| Time for completed negative PCR result, days | | |
| Mean ± SD | 25.7 ± 14.5 | 25.5 ± 5.4 |
| Min - Max | 6 - 63 | 18 - 33 |
| Length of stay in hospital, days | | |
| Mean ± SD | 26.6 ± 12.6 | 27.8 ± 10.1 |
| Min - Max | 6 - 61 | 12 - 47 |
| Possible adverse events, no. (%) | | |
| Dermatologic | 2 (7.1) | 4 (36.4) |
| Gastrointestinal | 19 (67.9) | 8 (72.7) |
| Endocrine and metabolic | 3 (10.7) | 2 (18.2) |
| Hepatic | 1 (3.6) | 0 (0.0) |
| Central nervous system | 4 (14.3) | 0 (0.0) |
| Neuromuscular and skeletal | 0 (0.0) | 1 (9.1) |

RESULT

A total of 46 patients were reviewed, seven patients did not fulfil the inclusion criteria. Therefore, 39 patients were lastly recruited which accounted for 85% of the confirmed COVID-19 cases in Macau in 2020. Of note, 12 (30.8%) of them were asymptomatic. 28 patients were treated with LPV/r monotherapy and 11 patients were treated with LPV/r/IFN- β -1b combination therapy. All patients received treatment on the day of admission, and successfully discharged in the end. The median age of patients was 24.5 years old (IQR 18.5) for the LPV/r monotherapy group; 44 years old (IQR 20.0) for the LPV/r/IFN- β -1b combination group. The most common symptoms were fever and cough (with the exception of sore throat in the combination group) in both groups at admission. The median time between onset of symptoms and hospitalization was 1.5 day (IQR 8.0) for the monotherapy group and 1.0 day (IQR 5.5) for the combination group (Table I). The mean length of hospitalization was 26.6 (SD \pm 12.6) days with LPV/r monotherapy whereas 27.8 (SD \pm 10.1) days with LPV/r/IFN- β -1b combination therapy ($p=0.65$). The percentage of 28-day negative results for PCR test were 67.9% (19 of 28) with monotherapy and 63.6% (7 of 11) with combination therapy ($p=0.80$). The most common adverse events possibly related to medications include diarrhea and skin rash. Those were minor and treated accordingly (Table II). There was a potential risk of interaction with the disease and other drugs.

DISCUSSION

In this retrospective review, no beneficial clinical effect was observed in hospitalized patients with COVID-19 with the addition of injectable IFN- β -1b (given within 7 days of symptom onset) to oral protease inhibitor (LPV/r)-based therapy. On the contrary, a multicenter, open-label, randomized, phase 2 trial conducted in Hong Kong, over 80% included patients with mild to moderate disease, compared 14 days of triple antiviral therapy ($n = 86$) (LPV/r [400 mg/100 mg q12h], ribavirin [400 mg q12h], IFN- β -1b [8 million IU x 3 doses q48h]) with LPV/r alone ($n = 41$). Results showed that triple therapy significantly shortened the duration of viral shedding and hospital stay in patients with mild-to-moderate COVID-19, the median time of combination therapy from the beginning of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [IQR 8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], $p=0.0010$) [4]. Another retrospective cohort study demonstrated that ribavirin therapy compared with supportive therapy in severe COVID-19, was not associated with improved negative conversion time for SARS-CoV-2 test and was not associated with an improved mortality rate⁵. Compared with our findings without ribavirin, the mean time to negative result was approximately 25 days between the two groups. Owing to small sample size and lack

of control group, the results of our study could not draw a conclusion on how effective is LPV/r in non-severe COVID-19 patients. It is worth noting that the patients' age in the combination group ranged from 18-59 years old. We postulated that these patients may have better immune response so that the results may be affected. In addition, most cases were imported from different parts of the world, the genotype or phenotype of different viral variants they carried might interfere with the findings.

At present, the COVID-19 pandemic has caused a huge burden to the economy and healthcare system around the world. Healthcare professionals work under stress every day. In Macau, CHCSJ, the designated hospital for treating COVID-19 offered adequate resources for in-hospital care and isolation wards throughout the outbreak even for asymptomatic patients. As a matter of fact, there are no clear criteria for hospital admission with COVID-19. The criteria may vary with the availability of hospital resources. Nonetheless, according to the US National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel3, most patients with mild illness can be managed in an ambulatory care setting or at home. Therefore, we believed that some of our non-severe cases may be treated in the outpatient setting in principle. Although several international guidelines against the use of LPV/r in hospitalized patient based on the results from multiple clinical trials [6-8], its role in the outpatient setting is being investigated. Therefore, our findings may provide an important reference for future investigation in such situation.

CONCLUSION

This series illustrated that no clinical benefit was observed with the addition of IFN- β -1b to LPV/r-based therapy plus general supportive care in hospitalized COVID-19 patient. In addition, it may also provide important information for the use of LPV/r in outpatient settings. In fact, more powerful evidences are warranted to confirm these findings.

CONFLICT OF INTEREST

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Impact of Medication Reconciliation by Clinical Pharmacist during Hospital Admission of Patients with Chronic Kidney Disease (CKD) Stage IV-V in Hospital Raub, Pahang

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ABSTRACT

Medication errors are more likely to occur during patient's transition of care. There was very little information about impact of medication reconciliation activities done for patients with chronic kidney disease (CKD) Stage IV-V during admission stage in Malaysian Primary Hospitals. The objective of this study is to evaluate the impact of clinical pharmacist's medication reconciliation activities during hospital admission of patients with CKD stage IV-V. This cross-sectional study was carried out in two multidisciplinary wards (male & female ward) in Hospital Raub, Pahang over 12 months with ethical approval. A clinical pharmacist was assigned to enroll potential study subjects in both wards. Patients over 18 years old who had previous history of CKD Stage IV-V were included in the study after obtaining informed consent. Medication reconciliation was carried out by the clinical pharmacist within 24 working hours during the admission of study subjects. All detected medication discrepancies were further classified as "intended" or "unintended" after discussion with the prescribing medical officer. The Severity Level of each unintended medication discrepancy was rated by a visiting medical specialist. Twelve patients with CKD stage V were recruited to the study. A total of 49 medication discrepancies were identified and most (89.8%) were found to be unintended. The most common unintended medication discrepancy identified was omission error. Most of the unintended medication discrepancies (59.1%) was rated as "No potential harm", while 40.9% were rated as "Potential for monitoring and/or Intervention to preclude harm". None of the unintended medication discrepancy was rated as "Potential harm". In conclusion, medication discrepancies were common during admission of patients with late-stage chronic kidney disease in a primary hospital. Medication reconciliation performed by clinical pharmacist during admission has a potential role in preventing potential harms that may arise from unintentional medication discrepancies.

INTRODUCTION

Chronic Kidney Disease (CKD) is indicated as gradual deterioration of renal function over time and CKD can cause major health complications [1]. It was reported that 10-13% of the population in China, Taiwan, and Japan have CKD [2]. Besides, Asian population has a higher prevalence of CKD as compared to American population [3].

According to a nationwide population-based cross-sectional study conducted by Saminathan et al. [4] from September 2017 to June 2018, the prevalence of respondents with stage I, stage II, stage III, stage IV and stage V CKD in Malaysia were

3.85%, 4.82%, 6.48%, 0.25% and 0.08% respectively in 2018 [4], as compared to 4.16%, 2.05%, 2.26%, 0.24% and 0.36% respectively from a similar study which included only respondents from West Malaysia in 2011 [5]. Saminathan et al. stated that out of all respondents with CKD, only 5% of them were aware of their diagnosis [4].

Patients with CKD are considered as a complex population. According to study conducted by Manley et al., patients with end stage renal failure undergoing haemodialysis were prescribed an average of 12 medications [6]. Medication errors are more likely to occur during patient's transition of care [7]. Besides, incidence of adverse drug reactions increases with

increasing number of medications used and worsening of renal function [8].

Medication reconciliation is defined as the process of comparing a patient's medication list ordered by prescriber to patient's previous medications during transition of care [9]. Based on data from Buckley et al., medication discrepancies during hospital admission are common and accounted for up to 67% of all hospitalised patients [10]. An unintentional medication discrepancy occurs when prescribers omitted, changed, or added a medication unintentionally [11]. Any unintentional medication discrepancy has the potential to become a medication error and cause patient harm [11].

A systematic review from Tam et al. showed that inaccurate or incomplete medication orders during patient's admission accounted for 27% of total hospital medication errors [12]. Obtaining accurate medication histories during patient's admission is crucial to improve medication safety as errors in medication history taking may lead to inappropriate drug therapy for hospitalised patients [12].

Based on a study conducted by Hassali et al., 90.1% of respondents consisting of 86 General Practitioners in the Penang State agreed that medication reconciliation can be a practical strategy in improving medication safety [13]. Medication Reconciliation was announced as 2005 National Patient Safety Goal #8 by the Joint Commission [9]. According to the safety goal, medication reconciliation should be implemented in all patient care settings [9].

There was only one similar study in Malaysia done by Islahudin et al. for medication reconciliation during admission of patients to healthcare facilities [14]. The study found out that medication reconciliation tool identified more medication discrepancies than standard medication history taking during patient admissions in a tertiary hospital [14].

The objective of this study was to evaluate the impact of clinical pharmacist's medication reconciliation activities during hospital admission of patients with CKD stage IV-V. To date there was very little information about impact of medication reconciliation activities done for specific populations (eg. Late-Stage CKD patients) during admission stage in Malaysian Primary Hospitals. The primary outcome of this study was the number of medication discrepancies detected during the admission of patients with CKD stage IV-V over the study period. As compared to the similar study conducted by Islahudin et al. [14], we also evaluated the "severity level of each unintended medication discrepancy if left undetected", which was the secondary outcome of this study.

METHOD

This was a cross-sectional study to determine the number of unintended medication discrepancies identified through medication reconciliation activities performed by a clinical pharmacist during admission of patient with CKD stage IV-V in multidisciplinary wards.

This study was carried out in two multidisciplinary wards (male & female ward) in Hospital Raub over a period of 12 months from 24th May 2018 to 23rd May 2019. Hospital Raub is a primary hospital with 89 beds and multidisciplinary wards comprise 56 beds. This study protocol was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia [Reference numbers: KKM.NIHSEC.P18-469(5) for initial ethical approval and KKM/NIHSEC/P18-469(9) for subsequent annual ethical renewal].

The mean of total admission of patients to these multidisciplinary wards in Hospital Raub from 2015-2017 were 3569 patients. As there was no study regarding prevalence of CKD patients admitted to ward, prevalence data from the study conducted by Hooi et al. [5] was used as it was the first study showing prevalence of CKD by stages in Malaysia, and newer prevalence data was yet to be reported in early 2018, when this study was initiated. According to Hooi et al., total percentage of noninstitutionalized adult patients with CKD stage IV-V in West Malaysia in 2011 was 0.60% [5].

The sample size of this study was calculated using the "Sample Size for Frequency" calculator from openepi.com [15]. After entering population size as 100,000 people, anticipated frequency (in percentage) is calculated as 0.60%, confidence limits as 5%, and design effect as 1. A sample size of 12 study subjects was required for 97% confidence level [15]. Convenient sampling method was used to recruit study subjects.

Patients over 18 years old who had previous history of CKD and with estimated Glomerular Filtration Rate (eGFR) of less than 30ml/min/1.73m² upon admission were included in our study. On the other hand, patients/caregivers who were unresponsive or unwilling to communicate with clinical pharmacist were excluded from this study. Besides, patients who were diagnosed as having Acute Kidney Injury (AKI) by ward Medical Officer (MO) during the time of admission were also excluded. Acute Kidney Injury is diagnosed when Serum Creatinine (SCr) level increases ≥ 26.5 $\mu\text{mol/l}$ from baseline value or patient's urine output is < 0.5 ml/kg/h for 6 hours [16].

The Modification of Diet in Renal Disease (MDRD) formula was used in estimating Glomerular Filtration Rate (GFR) for renal function assessment and drug dosage adjustment in this

Table I: Severity Level Ratings for Medication Discrepancies

| Severity Level of Medication Discrepancy [19] | Definition [20] * | Category of Medication Errors [20] involved in each Level* |
|---|---|---|
| Level 1 | No Potential harm | Category C: An error reached the patient but did not result in patient harm |
| Level 2 | Potential for monitoring and/or Intervention to preclude harm | Category D: An error reached the patient, monitoring and/or intervention is required to preclude harm. |
| Level 3 | Potential harm | Category E: An error reached the patient and may have caused temporary harm to the patient, intervention is required. Category F: An error reached the patient and may have caused temporary harm to the patient and may necessitate initial or prolonged hospitalization. |

*Adapted from the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) (www.nccmerp.org)

study. The eGFR Calculator mobile app (version 2.3) from the National Kidney Foundation (NKF) was used to calculate estimated GFR for each study subject [17].

This study focused on medication reconciliation activities conducted by a clinical pharmacist in detecting and resolving any unintended medication discrepancies within 24 hours post-admission of Late-Stage CKD patients. Patients that were admitted on weekends or public holidays were reviewed within 24 hours on the subsequent first working day. A clinical pharmacist (also as the investigator in this study) was assigned to cover both multidisciplinary ward on working days to screen each newly admitted patient to determine potential participant for this study. The clinical pharmacist informed each eligible patient that there would be no harm to participate in this study, as no invasive procedure or interventional product was to be introduced to him/her. Each participant was informed that he or she would not be reimbursed for participation in the study. Every eligible patient who agreed to take part in the study was required to complete the patient information leaflet/informed consent form.

After the patient or caregiver had completed the consent form, the clinical pharmacist determined the patient's actual stage of CKD by entering the patient's age, gender, and serum creatinine level in the "MDRD Study Equation" section of the eGFR Calculator mobile app [17]. Patients with an estimated GFR greater than 30ml/min/1.73m² were excluded from the study. After that, using a data collection form adapted from the Medication History Assessment Form (CP1) [18], the clinical pharmacist conducted an interview with the patient or caregiver to obtain the patient's demographic information, past medical history, history of drug allergy and past medication history. The list of medication history generated by the clinical pharmacist was used to compare to the list of medications prescribed during admission, and all medication discrepancies were documented.

The clinical pharmacist then contacted corresponding prescribing Medical Officer (MO) regarding the detected medication discrepancies and inquired whether each discrepancy was intended or unintended. Unintended medication discrepancy was determined when the MO indicated that the difference between the patients' previous medication list and the medication list prescribed at the time of patient admission was unintentional. Then, the clinical pharmacist requested ward MO to make corrections on ward medication chart if the medication discrepancies were found to be unintended or erroneous. The medication reconciliation process was considered complete once interventions were done for each unintended medication discrepancy.

In order to evaluate severity level of each unintended medication discrepancy if left undetected, a visiting medical specialist was invited to rate each medication discrepancy based on the 3 Severity levels (Table I). The severity levels ratings for medication discrepancies were adapted from the potential harm ratings from Gleason et al, 2010 [19]. The definition of each Severity Level and Categories of Medication Errors involved in each level were adapted from the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) *Index for Categorizing Medication Errors* [20].

The data collected was analysed descriptively with 'Statistical Package for the Social Sciences' (SPSS for Windows) version 21. For categorical variables, results were presented as frequency and its percentage whereas results for numerical variables were presented as Mean ± Standard Deviation (SD) or Median ± Interquartile Range (IQR). Only descriptive statistics were used in this study.

RESULT

Twelve patients with CKD stage IV-V were recruited to the study. Details of sociodemographic and baseline characteristics of the study population are summarized in Table II. All

recruited patients were evaluated as having CKD Stage V. Among all patients recruited, two patients (16.7%) had no medication discrepancies. This study identified a total of 49 medication discrepancies, and in which 44 (89.8%) discrepancies were found to be unintended. Details of different types of unintended medication discrepancies are shown in Table III.

Table II: Demographic Data of the Study Population (n = 12)

| Characteristics | Value |
|--|-------------|
| Gender, number (%) | |
| Male | 7 (58.3) |
| Female | 5 (41.7) |
| Median age (years) | 65.5 (10.8) |
| Stage of CKD, number (%) | |
| Stage IV | 0 (0.0) |
| Stage V | 12 (100.0) |
| Mean (SD) number of medications prescribed on admission | 7.2 (3.8) |
| Mean (SD) number of regular medications before admission | 9.0 (2.3) |
| §Source of medication history, number (%) | |
| Pharmacy Information System (PhIS) record | 11 (91.7) |
| Patient's current outpatient prescription | 6 (50.0) |
| Patient's own medication | 4 (33.3) |

§Cumulative percentage > 100% as some patients had >1 source of medication history.

Medications for Bone and Mineral Disease was found to be the most common medication class involved in unintended medication discrepancies during admission, followed by Vitamins/Iron supplements, Antihypertensives and Antidiabetic Agents (Table IV). Among all the unintentional

medication discrepancies, 59.1% were judged as Severity Level 1 (no potential harm if left undetected), while 40.9% were judged as Severity Level 2 (potential for monitoring and/or intervention to preclude harm if left undetected). No unintended medication discrepancy was classified as Severity Level 3 (potential harm to patient if left undetected).

Table III: Types of Unintended Medication Discrepancies Identified (n = 44)

| Type of Discrepancy | Number (%) ^Δ |
|---------------------|-------------------------|
| Omitted Drug | 34 (77.3) |
| Wrong Dose | 6 (13.6) |
| Wrong Frequency | 2 (4.5) |
| Wrong Drug | 2 (4.5) |

^Δ Percentages may not add up to 100% due to rounding.

Table IV: Medication Class Involved in Unintended Medication Discrepancies (n = 44)

| Medication Class | Number (%) ^Δ |
|---|-------------------------|
| Medications for Bone and Mineral Disease | 11 (25.0) |
| Other (Vitamin/ Iron) Supplements | 8 (18.2) |
| Antihypertensives | 7 (15.9) |
| Antidiabetic Agents | 6 (13.6) |
| Medications for Stress Ulcer Prophylaxis/ Gastritis | 4 (9.1) |
| Cholesterol-Lowering Agents | 3 (6.8) |
| Diuretics | 2 (4.5) |
| Antiplatelets | 2 (4.5) |
| Thyroid Replacement Medications | 1 (2.3) |

^Δ Percentages may not add up to 100% due to rounding.

DISCUSSION

None of the patient recruited in this study was classified under CKD Stage IV. This might be due to more patients with CKD Stage V were admitted during the study period. A study conducted by Go et al. found out that there was a graded association between lower levels of estimated GFR and the risks of hospitalization [21].

Most of the medication discrepancies were found to be unintended. The result in this study showed that the most common medication discrepancy identified during admission of patient was omission error, follow by wrong dose, and then by wrong frequency. This coincides with the similar study involving eligible patients admitted to the Orthopedic Service [22]. The most common interventions done in this study was addition of the omitted medications. This result is consistent

with the findings of other similar studies which also recruited patient from other disciplines [14,23–25].

Most of the unintended medication discrepancies (59.1%) was judged as Severity Level 1, which indicates that the discrepancies were unlikely to cause harm if left undetected. This result agrees with the findings from a similar study from Cornish et al., where eligible patients admitted to the general internal medicine clinical teaching units in a tertiary care teaching hospital were recruited [25]. The study found that 61.4% of the unintended medication discrepancies were considered as unlikely to cause harm [25].

Another finding from this study showed that 40.9% of the unintended medication discrepancies were deemed to have the potential to cause harm & monitoring and intervention may have been required to preclude harm (Severity Level 2). This

finding is in agreement with the systematic review conducted by Tam et al., where limited data suggested that 11-50% of medication history errors at admission to hospital were clinically important [12]. Besides that, this data also coincides with the findings from other studies, where more than 30% of the unintended medication discrepancies were deemed to have potential to cause moderate harm [23,25]. There is no medication discrepancy classified as Severity Level 3 in this study. On the contrary, the study from Cornish et al. revealed that 5.7% of the identified medication discrepancies were judged to have the potential to result in severe discomfort or clinical deterioration [25].

All recommendations proposed were accepted by the MO who did the admission with acceptance rate of 100%. Other studies involving medication reconciliation on admission also showed that most recommendations by pharmacy team regarding the unintended discrepancies were accepted [14,22,23].

In this study, more than 1 source of medication list were obtained from several patients as different sources of medication can be used to ensure the accuracy of patient's medication history [23]. This is important for those who are under follow up at different disciplines/facilities. The main source of medication list used in this study is the Pharmacy Information System (PhIS) [26].

Since 2016, PhIS had been implemented in most healthcare facilities in PAHANG State [26]. The PhIS system shows the complete current medication record for patients who are under follow up in Hospital Raub, including the regular medications from other Ministry of Health (MOH) facilities if patient opted the Integrated Drug Dispensing System (SPUB), a Value-Added Service (VAS) where patients can obtain the next drug supply of active prescriptions from any of the MOH health facilities listed in the MOH's SPUB Directory through a nationwide referral system [26,27].

PhIS system is accessible in emergency department and all wards in Hospital Raub. Patient's latest medication list from outpatient/ specialist clinics can be retrieved by clinical pharmacist from PhIS during ward round, thus improving the accuracy of the medication history taking as some patients might leave their regular medications at home while some might bring incomplete medication list to ward.

This study showed that PhIS system was underutilized among medical officers in Hospital Raub Emergency Department throughout the study period as most patients' complete medication lists were obtained from PhIS by the clinical pharmacist and yet the most common unintended discrepancy was omission of patient's regular medication. Further investigations are required to determine the root cause of PhIS

underutilization by medical officers during admission of patients in Hospital Raub.

Limitations

This study only involved small sample of patients from a primary hospital, so the result might not be generalized to other areas with bigger population. Besides, all recruited patients in this study were classified under CKD Stage V, thus the result might not be generalized to population with higher hospitalization rate of patients with CKD Stage IV. The potential harm of each unintended medication discrepancy was judged by only one visiting medical specialist, and there was possibility that other medical specialist might have different judgement on some of the medication discrepancies.

CONCLUSION

Medication discrepancies were common during admission of patients with late-stage chronic kidney disease in a primary hospital. Medication reconciliation performed by clinical pharmacist during admission has a potential role in preventing potential harms that may arise from unintentional medication discrepancies.

CONFLICT OF INTEREST

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Pharmacy Value-Added Services: Experience in a Malaysian Public Hospital

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ABSTRACT

The Pharmacy value-added services (PVAS) has been implemented in Malaysian public hospitals to facilitate the collection of follow-up medications. In specific, PVAS include Integrated Drug Dispensing System, Medicine by Post, Drive-Through Pharmacy, and many more. While past studies examined the satisfaction towards PVAS and its impact on patients' waiting time, little explored the awareness and the experience of patients towards each type of PVAS. This study aims to explore the patient's awareness on PVAS, adoption of PVAS, their satisfaction towards PVAS, and willingness to adopt PVAS. This was a cross-sectional study conducted in January 2020. We invited the eligible patients or their family members to participate in the study. Respondents recruited at the Outpatient Pharmacy Department of Miri Hospital using convenient sampling. A questionnaire in the Malay language was developed and content validated to gather information on the demographic data, awareness on PVAS, adoption of PVAS, satisfaction towards PVAS, and willingness to adopt PVAS. A list of PVAS was included for the respondents to select the types they were aware of and used before. Results were presented as frequencies, percentages, mean and standard deviation. A total of 398 respondents participated in the study. Majority of the respondents (70.1%) were aware that PVAS offered in Miri Hospital. However, about a third of the respondents (31.4%) had experience using PVAS. The most commonly used PVAS was Appointment Card Dispensing System (49.6%) and that with the least usage was Local Partial Medication Supply Service (2.4%). The Drive-Through Pharmacy has the greatest satisfaction score, 4.40 (SD=0.70), whereas Call-and-Collect Service was the least satisfied, 3.88 (SD=0.91). Majority of the respondents (86.2%), specifically 95.8% of the experienced PVAS user and 90.1% of inexperienced group, were willing to adopt PVAS to collect their follow-up medications. The Drive-thru Pharmacy, which has the greatest awareness and satisfaction yet low usage, should be further promoted for greater adoption. Besides, such PVAS should be expanded to other healthcare facilities.

INTRODUCTION

Pharmacy value-added services (PVAS) is a nationwide, government-funded initiative introduced by the Pharmaceutical Services Division (PSD), Ministry of Health Malaysia (MOH) since 2003 [1]. In the Malaysian context, PVAS defined as a range of innovative and creative services provided by the pharmacy to optimise patient-oriented pharmaceutical care, through ensuring the continuity of medicines supply, reducing waiting time and travelling cost [1]. According to the National Survey on the Use of Medicines (NSUM) 2015, 30.3% of

Malaysians have chronic diseases that necessitate long term medication use [2]. In the government healthcare facilities, a policy under the Quality Use of Medicines (QUM) pharmacy practice guideline has been in place since 2011, where medications for prescriptions longer than one month will only be supplied monthly [3].

The successful implementation of the policy allowed monitoring of patient compliance, untoward effects of medications, reducing drug wastage and the risk of medication error caused by misuse of excessive medication supply by unintended individuals. However, these advantages come at the

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expense of increased patient load and waiting time at the outpatient pharmacy. Furthermore, transportation issues and the cost incurred from a repetitive visit to the outpatient pharmacy for monthly medication supply are factors that affect patient satisfaction [4]. In a study conducted in Taiwan showed that difficulty in finding a parking in the hospital was one of the reasons cited to failure to regular medicine refill [5]. Therefore, the introduction of PVAS aims to improve the healthcare accessibility and dispensing system by reducing waiting time, improving patient convenience and satisfaction, and ensuring continuity of medication supply.

In Malaysia, PVAS refers to a group of innovative services provided by over 500 government healthcare facilities [1]. Larger facilities may provide more types of PVAS whereas smaller facilities have at least one to two types of these services [1]. In this context, follow-up prescriptions are also known as refill prescriptions or partial supply prescriptions, and the terms used interchangeably. PVAS programmes include Integrated Drug Dispensing System (SPUB), Medicine by Post (UMP), Drive-Through Pharmacy, Appointment Card Dispensing System, Call-and-Collect Service, SMS-and-Collect Service, Fax-and-Collect Service, Email-and-Collect Service, Collect-Later Service, Local Partial Medication Supply Service (PPUSS) and Locker4U (1, 4). The following paragraph illustrates some of the most common types of PVAS.

SPUB enables medicines collection of patients' follow-up supply at any MOH health facility listed under the SPUB Directory throughout Malaysia. With the service, patients are able to select the facility, which is convenient and preferred for their medication collection [6]. UMP service engages the national courier service, Poslaju to deliver the medicine to the patients' preferred location with pre-determined postal charges [6]. Conversely, patients who prefer to self-collect their medicine, Drive-Through Pharmacy is the convenient alternative. The conventional waiting process at the pharmacy counters skipped and dispensing of the prepacked medication typically takes place at the dedicated Drive-Through counter or kiosk which does not require patients to exit their vehicles [1][6]. Both UMP and Drive-Through Pharmacy could help to ease the long waiting time and parking space constraints.

Other PVAS options include Call-and-Collect Service, SMS-and-Collect Service, Fax-and-Collect Service and Email-and-Collect Service, which require the patients' notification, for instance via making a phone call or sending a SMS, to inform pharmacy of the expected collection date, whereas the Collect-Later Service involves pre-notifying the pharmacy over the counter. In contrast, for Appointment Card Dispensing System, the pharmacy determines the collection date and prepares the refill medicine before the date. Meanwhile, Local Partial Medication Supply Service and Locker4U deliver the prepared medicine to a predetermined collection centre or place the

medicine in a locker, and allow the patients to collect at their convenience.

The Pharmaceutical Services Programme has actively organised campaigns to introduce and promote the adoption of PVAS. The key performance indicator for government facilities is 20% or more of the follow-up prescriptions dispensed via PVAS [7]. Despite the large monetary investment and human resources involvement, the adoption rate of PVAS was considerably low at its inception [1]. In 2013, PVAS employed in merely approximately 10% of 10 million follow-up prescriptions in the government healthcare facilities [1]. In the subsequent year, the number of prescriptions dispensed via PVAS has increased to 1.2 million, but it was still far from reaching the target (8). Besides the usual promotional activities, the government organised competitions and giving special awards to encourage active implementation among the facilities [9]. With continuous effort and promotion, PSD documented nearly 4 million follow-up prescriptions dispensed via PVAS in the country, amounting 22.29% of the total follow-up prescriptions in 2019 [7] [10]. However, there are opportunities for further improvement. Therefore, this study aims to explore the patient's awareness on PVAS, adoption of PVAS, their satisfaction towards PVAS, and willingness to adopt PVAS. Ultimately, this study aims to improve pharmacy service and patient care, which is in line with the objectives of PSD.

METHOD

Study Design and Participants

We conducted a single-centred, cross-sectional study in one of the major, government-subsidized hospital in Sarawak state of Malaysia. All patients or their family members, who aged 18 years and above, understood the Malay language, who collected their first or subsequent partial supply of chronic medications in Miri Hospital, were eligible for participation in the study. We excluded staff who assisted in collecting medication for daycare or home visit patients. Convenience sampling method applied to recruit respondents who met the eligibility criteria. This study is registered with National Medical Research Registry (NMRR-19-4193-49452) and was approved by Medical Research Ethics Committee, Ministry of Health, Malaysia.

We administered several close-ended questions to acquire information on respondents' demographics, their awareness on PVAS, adoption of PVAS, their satisfaction towards PVAS and willingness to adopt PVAS. The demographic data include age, gender, race, education level, monthly household income, and travelling duration from the house to the hospital. A list of PVAS included for the respondents to select the types they were aware of and used before. Respondents who used PVAS

before were required to rate their satisfaction level using a five-point Likert scale, which ranges from 1 (very dissatisfied) to 5 (very good). Besides, the open-ended questions allowed the respondents to express their opinion about PVAS and the reasons they are unwilling to adopt PVAS. In the current study, the monthly household income categorisation were: (i) low income group (B40) with monthly household income less than RM 4,850, (ii) mid income group (M40) with monthly household income between RM 4,850 and RM 10,959, and (iii) high income group (T20) with monthly household income of RM 10,960 or more (11). For the employment status, an employer refers to a person who hires employee to work, whereas the self-employed refers to a person who works for oneself. The questions were in the Malay language.

We invited the eligible respondents, obtained written informed consent and distributed the questionnaire over the pharmacy counter. The respondents returned the completed questionnaires during medication collection at the dispensing counter. It took approximately 10-15 minutes to complete the questionnaire.

The current study is part of a larger study which the minimum sample size was based on. Sample size calculation using the G*Power software version 3.1.9.4 showed that 395 respondents required to obtain a power of 80% at a type I error level of 0.05 [12]. The total number of respondents was raised to account for a 10% dropout and unusable data, hence the required sample size was 439 respondents.

Statistical Analysis

We conducted analysis using SPSS version 21. The demographic characteristics of respondents described as frequencies and percentages for categorical variables. Numerical variables, for example, age, was presented as mean and standard deviation (SD), or median and interquartile range (IQR) if non-normally distributed. The findings are descriptive in nature and no formal statistical hypothesis testing involved.

RESULT

Demographic Characteristics

A total of 440 questionnaires distributed, and 398 respondents completed and returned them, yielding a response rate of 90.45%. Table I summarises the demographic characteristics of the respondents. The age of respondents in this study ranged from 18 to 85 years old, with mean (SD) age of 42.48 (14.32) and they were predominantly female (57.3%). Most of the respondents were Chinese (30.4%), from the low-income group (B40).

Awareness on PVAS

Most respondents (70.1%) were aware of PVAS (Table II). Drive-Through Pharmacy and UMP were the most commonly known services among the 279 respondents who were aware of PVAS, with the percentage of 67.0% and 59.5% respectively (Table II). PPUSS was the least known (3.9%) among respondents who were aware of PVAS, followed by SPUB (12.5%).

Table I. Demographic Characteristics (n=398)

| Variables | Mean (SD) |
|---|---------------|
| Age (years) | 42.48 (14.32) |
| Travelling Duration to Hospital (minutes) | 35.57 (34.28) |

| Variables | Number, n (%) |
|--------------------------|---------------|
| Gender | |
| Male | 170 (42.7) |
| Female | 228 (57.3) |
| Ethnicity | |
| Malay | 78 (19.6) |
| Chinese | 121 (30.4) |
| Iban | 110 (27.6) |
| Kayan | 20 (5.0) |
| Melanau | 14 (3.5) |
| Others | 53 (13.32) |
| Not reported | 2 (0.5) |
| Education Level | |
| University | 69 (17.3) |
| College | 50 (12.6) |
| Vocational | 28 (7.0) |
| Secondary School | 194 (48.7) |
| Primary School | 31 (7.8) |
| No Formal Education | 22 (5.5) |
| Not reported | 4 (1.0) |
| Employment Status | |
| Employer | 13 (3.3) |
| Government Servant | 54 (13.6) |
| Private Employee | 102 (25.6) |
| Self-Employed | 54 (13.6) |
| Unemployed | 138 (34.7) |
| Retiree | 33 (8.3) |
| Not reported | 4 (1.0) |
| Household Income | |
| High Income (T40) | 5 (1.3) |
| Medium Income (M40) | 47 (11.8) |
| Low Income (B40) | 325 (81.7) |
| Not reported | 21 (5.3) |

* Percentages may not total 100 because of rounding

Table II. Awareness and Adoption of types of PVAS services (n=398)

| Types of PVAS | Awareness | | Adoption | |
|------------------------------------|------------|------------|-------------|---------------|
| | Aware | Unaware | Experienced | No Experience |
| SPUB | 35 (12.5) | 244 (87.5) | 7 (5.6) | 118 (94.4) |
| UMP | 166 (59.5) | 113 (40.5) | 31 (24.8) | 94 (75.2) |
| Call-and-Collect Service | 93 (33.3) | 186 (66.7) | 28 (22.4) | 97 (77.6) |
| Collect-Later Service | 59 (21.1) | 220 (78.9) | 24 (19.2) | 101 (80.8) |
| Drive-Through Pharmacy | 187 (67.0) | 92 (33.0) | 11 (8.8) | 114 (91.2) |
| Appointment Card Dispensing System | 106 (38.0) | 173 (62.0) | 62 (49.6) | 63 (50.4) |
| PPUSS | 11 (3.9) | 268 (96.1) | 3 (2.4) | 122 (97.6) |
| Medication Locker | 2 (0.7) | 277 (99.3) | | |
| Others | 1 (0.4) | 278 (99.6) | | |

Adoption of PVAS

More than half of the respondents (68.3%) had no experience of using PVAS for the collection of their follow-up medication supply (Table II). Among the 125 PVAS users, the most commonly adopted PVAS was Appointment Card Dispensing System (49.6%) (Table II). UMP was the second most used PVAS (24.8%) among the PVAS users, whereas PPUSS was least adopted (2.4%).

Satisfaction Towards PVAS

Table III shows the satisfaction score of respondents who have experience using PVAS. Overall, respondents were satisfied with their experience. The mean (SD) satisfaction scores for Drive-Through Pharmacy, Collect-Later Service, and PPUSS are 4.40 (0.70), 4.38 (0.50), 4.33 (1.16) respectively. Nevertheless, there were 11 Drive-Through Pharmacy users only in this study. Among the three respondents who was PPUSS users, two of them rated the service as 'very good' and one of them is satisfied with the service.

Willingness to Adopt PVAS

A large percentage of respondents (86.2%) were willing to adopt PVAS while only 7.5% said no to the service. In particular, 95.8% of the experienced PVAS user and 90.1% of inexperienced group, respectively were willing to adopt PVAS to collect their follow-up medications. However, 7.5% (n=30) of the respondents were unwilling to adopt PVAS.

DISCUSSION

This study provides the essential information on the implementation of PVAS in a public hospital in Sarawak. In this study, majority of the respondents (70.1%) were aware of PVAS. This result contrasts the findings of Tan et al., which reported that a large number of patients were not aware of the existence and benefits of PVAS via face-to-face interview [13]. The improved awareness could be as a result from the active promotion over years. Patients' awareness on PVAS and their

benefits is undeniably crucial in the adoption of this program. Lack of awareness is the important factor that impedes patients' intention to use PVAS [13].

Drive-Through Pharmacy and UMP were the two most commonly known PVAS in this study. Although Drive-Through Pharmacy is newly launched in Miri Hospital, the public has high awareness compared to other PVAS. This could be possibly due to the effective promotion, including the local newspapers and social media platforms. On the other hand, UMP gained popularity during the COVID-19 lockdown implemented in March 2020 nationwide as it does not require travelling and physically present at the pharmacy, hence reducing social contact. Moreover, MOH and the national courier service worked to provide free shipping of medicine to patients' home during the period to ensure the constant access to medical needs. Therefore, the awareness on the PVAS is higher. Medication Locker was the PVAS with least awareness among our respondents (0.4%). At the time of writing, the service is in the planning stage in our hospital. However, the service is available in some other government facilities [14] [15]. It is important to note that the service offered may differ from one facility to the other. Therefore, explanation is crucial to avoid misconception.

Among the PVAS users, we found Appointment Card Dispensing System as the most commonly used PVAS and that with the least usage is Local Partial Medication Supply Service. Despite the considerably high awareness among the

Table III. Satisfaction Towards PVAS

| Satisfaction Score | Mean (SD) |
|--|-------------|
| SPUB n=7 | 4.29 (0.95) |
| UMP n=31 | 4.12 (0.95) |
| Call-and-Collect Service n=28 | 3.88 (0.91) |
| Collect-Later Service, n=24 | 4.38 (0.50) |
| Drive-Through Pharmacy, n=11 | 4.40 (0.70) |
| Appointment Card Dispensing System, n=62 | 4.16 (0.85) |
| PPUSS, n=3 | 4.33 (1.16) |

respondents (70.1%), 31.4% of them adopted PVAS. Hence, there is a mismatch in the proportion of those who aware and those who adopt the service. This result reflects that awareness is not the sole factor that contributes to PVAS adoption.

In the open-ended question which explore refusal to adopt PVAS, one of the reasons cited was the poor understanding of the service. They refused to adopt PVAS as they did not fully understand how it works and were not given a proper introduction to this program. Some stated that they were familiar to the conventional over-the-counter collection method and would like to remain as such. Furthermore, another respondent quoted that he preferred self-collection. The reasons are similar to the belief that the sense of unfamiliarity and little control over patients' situation [1]. In another study, the researchers argued that the presence of pharmacist during the collection of medications may be essential and necessary to some patients, mainly when there is a concern of medication error or insufficient drug supply [13]. Patients may feel stressful and insecure especially when receiving different or unexpected medications via UMP and PPUSS when there is no pharmacist available for them to consult [13]. This could happen especially when there is a brand change. Therefore, this could hinder the adoption of the service.

In the current study, a small number of respondents thought that PVAS is not required as it was more convenient to self-collect their refilled medicine due to the short distance to hospital. Some cited that they were not ready to adopt the new service. One of the PVAS users revealed unpleasant experience from previous (UMP) use, in which he failed to receive his follow-up medications through PVAS. The finding is similar to one study which reported that the confidence and intention to use UMP may lower as the delay in delivery by the national courier service causes uncertainty and disappointment [13]. One of the respondents reported the absence of recipient during medicine delivery contributed to the refusal to adopt PVAS. It may be inconvenient to wait for the delivery as the delivery time is unknown. As discussed in a previous study, negative feelings or unpleasant experience with PVAS is one of the barriers that affect PVAS adoption and remains a significant challenge to overcome [13].

We also observed that Drive-Through Pharmacy has the greatest satisfaction score, 4.40 (SD=0.70), whereas Call-and-Collect Service is the least satisfied, 3.88 (SD=0.91). Although Call-and-Collect is one of the most popular PVAS among the respondents, the satisfaction score is the lowest. This could be due to the difficulty in telephone line engagement as frequently complained by many patients. Due to the limited phone line and high usage due to hectic daily works. Nonetheless, previous studies reported higher satisfaction score with PVAS in general when compared to conventional over the counter medication collection method [16] [17].

When commenting opinion on PVAS, most respondents gave positive notes on PVAS, acknowledging it as an excellent program. They acknowledged that PVAS smoothens their follow-up medication collection process as it is convenient, efficient, time-saving, and reduces their waiting time at the pharmacy counter. Some respondents commented that PVAS could reduce the risk of infectious disease transmission as they do not need to visit the hospital frequently. It could save the fuel cost for the respondents too.

Therefore, in this study, most respondents (86.2%) were willing to adopt PVAS. 95.8% of the experienced PVAS users and 90.1% of inexperienced respondents, respectively were willing to adopt PVAS to collect their follow-up medications. This could be translated into future adoption of PVAS if intention to adopt is successful instilled. Although constant promotion could be useful, Tan et al. postulated that the advantages of PVAS and how it works should be clearly conveyed to instill the intention to adopt these services [13]. Without a clear intention, PVAS adoption will be limited as intentions are the precursors of behaviour [13]. Hence, it is crucial for the promotional activities to enhance the understanding of the PVAS, besides increasing the awareness among patients. Therefore, the role of pharmacists is very much crucial in assisting patients in selecting the type of PVAS that suits their needs and provide help to overcome problems which arise during the PVAS adoption.

This study has some limitations. Firstly, this was a single-centre study, the local population characteristics and need may differ from another population. Hence generalisation of the results could be possible in a population which is similar to our study sample. In addition, the PVAS users in each subgroup was too small, therefore, not meaningful to perform inferences for their satisfaction scores. Further studies using stratified sampling method may be appropriate for direct comparison of satisfaction scores among types of PVAS.

CONCLUSION

This study suggested that most respondents were aware of PVAS with a total of 31.4% of the respondents were its users. Among the PVAS, Appointment Card Dispensing System service were the most used PVAS while Drive-Through Pharmacy and UMP were the most known PVAS. Respondents also indicated the highest satisfaction score for Drive-Through Pharmacy, and lowest for Call-and-Collect Service. Drive-thru Pharmacy has the greatest awareness and satisfaction yet low usage, hence there is a need to further promote the PVAS for greater adoption. Besides, such PVAS should also be expanded to other healthcare facilities.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Analgesic Dosing Behaviours in Patients with Chronic, Non-Cancer Pain: Does it Affect the Pain Control?

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ABSTRACT

Chronic pain has a significant impact on sufferers' quality of life. Furthermore, treatment inadequacies are often reported in the literatures. This study aims to investigate the prevalence of the different dosing behaviors in analgesics use in chronic, non-cancer pain and their correlation to pain control. This is a cross-sectional study and a convenience sampling method was applied. Brief Pain Inventory- Short Form and Pain Management Index was computed to assess pain control. Statistical analysis was performed with Pearson chi-square test and alpha value was set at 0.05. A total of 127 patients were analyzed. 70.9% of the patients reported inadequate pain control with their prescribed analgesic(s). 88.2% patients only took oral analgesics whenever they felt the pain while 11.8% patients took around-the-clock despite the absence of pain. Among them, 11.8-34.7% of patients did not follow their prescriber's instruction for oral and topical analgesic use respectively. However, no statistically significant result was found between the dosing behaviors and pain control ($p > 0.05$). It was also reported that 98% of patients were not aware of the maximum daily dose of their prescribed analgesic(s). The prevalence of 'as needed' dosing is higher than around-the-clock dosing in the management of chronic, non-cancer pain, with deviation from the prescribed instructions between 11.8-34.7%. However, those differences were not significantly associated with the pain control.

INTRODUCTION

Pain is often a symptom reported by patients suffering from various clinical conditions. 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' [1]. Pain should not be viewed as merely a symptom, as pain can persist for a long period of time even after an underlying injury or disease has resolved. When the pain persists for at least three months, it is categorized as chronic pain, and the cause can be cancerous or non-cancerous origins.

Among Asian adults, Malaysia has one of the lowest prevalence of chronic pain at 7.1%, in comparison to Northern Iraq (72%), Cambodia (48%) and Singapore (8.7%). However, the pain prevalence is notably higher among the geriatric population (42 to 90.8%) [2].

Pain should not be overlooked. This is because people with chronic pain were often reported to have a poor quality of life due to immobility, disability, disturbed sleep, isolation, anxiety, frustration, depression, poor appetite and nutrition, increased susceptibility to disease, dependence on medication, and long-term medical care [3-6]. Specifically, for chronic non-cancer pain (CNCP), it was found that as much as 80.8% of patients whose activities of daily living were affected by pain [7], further highlighting the inadequacy of pain management in this patient cohort.

Pain management starts with pain assessment since the choice of analgesic will be different based on the pain score. Pain assessment can be performed with Numerical Rating Scale (NRS), which uses an 11-point scale. Pain can range from none (score zero) to the worst pain ever possible (score ten). [8] After the determination of a pain score, the next step in pain management is analgesic selection. To guide analgesic selection, National Health Service (NHS) United Kingdom

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(UK) devised a treatment guideline for CNCP. In the guideline, it was recommended that every treatment should start with paracetamol, and this medication should be added to a subsequent regimen for its synergistic effect. If the pain persists, or not properly controlled, non-steroidal anti-inflammatory drugs (NSAIDs) or weak opioids can be prescribed. If the NSAIDs or weak opioids are still ineffective, a more powerful opioid like morphine or fentanyl should be given to the patient [9].

CNCP treatment is mostly based on the principles behind the World Health Organization (WHO) analgesic ladder [10], which was originally developed for cancer pain management. Because of this origin, the majority of institutional guidelines, reviews, and training manuals advocate the effectiveness of regular analgesic in both cancerous and non-cancerous chronic pain [9,11-14]. Unfortunately, in Malaysia, it was found that only 4.2 to 4.4% of the population take their analgesic regularly in chronic pain [15-16], which is lower than a chronic pain prevalence of 7.1% in the country. Therefore, this study was initiated to investigate the prevalence of the different dosing behaviors in analgesics use in CNCP outpatients and their correlation to pain control.

METHOD

Study design

This was a single-center, cross-sectional study conducted in the outpatient pharmacy department of Kuala Lipis Hospital in Malaysia. Convenience sampling was used to recruit study participants. Possible sampling bias was minimized by consistently recruiting patients during their clinic appointments, which are 8 a.m. to 1 p.m. from Mondays to Fridays, excluding public holidays.

Sample Size Estimation

With an estimated prevalence of chronic pain at 7.1% [2], a confidence level of 95%, and a confidence limit of 5%, a minimum sample size of 101 was calculated to provide $\geq 80\%$ power [17]. After considering a possible 15% dropout rate, the final calculated sample size was 117 subjects.

Study Subjects

All patients who presented to the outpatient pharmacy with a valid prescription were screened for eligibility. Patients who took at least one analgesic for a minimum of three months, as verified by the pharmacy dispensing record, were invited for study participation. We excluded patients who were less than eighteen years old, pregnant women, and those with a diagnosis of cancer-related pain.

Measurement of Outcomes

All study subjects were assisted by researchers to fill in a questionnaire. The questionnaire consisted of three sections. The first section consisted of baseline demographic characteristics of study subjects such as gender, age, race, occupational status, and pain diagnosis. The second section was about study subjects' pain management details such as the prescribed analgesic(s) (name and dosage form), dose, actual dose taken for each analgesic, and whether they used over-the-counter (OTC) analgesic and complementary medicines. If the prescribed instruction of the analgesics was 'as needed', we further investigated if the respondents can correctly identify the maximum allowable daily dose. Information for the second section was first extracted from medical records and pharmacy dispensing record, before verbally verified with the patients. The third part was the Brief Pain Inventory- Short Form (BPI-sf) to assess pain among study subjects. BPI-sf is a 9-item self-administered questionnaire and is chosen for this study due to its ability to assess the totality of pain experience (minimum, maximum, average and current pain score) [18]. The patient is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness. The Malay version of the BPI previously validated in local population [19] was used in this study. A pilot test of fourteen patients gave a Cronbach's alpha value of 0.677.

We used the pain management index (PMI) to assess the adequacy of pain control. The index is constructed upon the patient's worst pain level in the last twenty-four hours recategorized as zero (no pain), one (pain score one to three, mild pain), two (pain score four to seven, moderate pain), or three (pain score eight to ten, severe pain). To compute the index, the new pain level was then subtracted from the most potent level of their prescribed analgesic categorized as zero (no analgesic drug), one (non-opioid), two (a weak opioid), or three (a strong opioid). Ranging from -3 (a patient with severe pain receiving no analgesic) to +3 (a patient receiving morphine or an equivalent and reporting no pain), a score of zero and higher (positive value) indicated acceptable pain control with analgesic while a negative value suggested suboptimal pain control [20-21]. The index was computed with Microsoft Excel function and the accuracy of calculation was then manually cross-checked by the researchers.

Two dosing categories, regular or as needed, were used to investigate the prevalence of dosing deviation. The dosing behavior was classified as regular if the patient took analgesics at a fixed interval (once daily or several times a week) despite the absence of pain. On the other hand, if analgesics were used only in the presence of pain sensation, the dosing behavior was classified as 'as needed'.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics for Windows, Version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Descriptive statistic was used to summarize the demographic data in mean, standard deviation (SD), and proportion. Pain score was presented in median and interquartile range (IQR). Pearson chi-square and fisher's exact test were used to study the relationship between the dosing deviation and PMI. All the p-values were two-tailed and statistical significance was defined as $p < 0.05$.

Ethics Approval

The study was registered under Malaysia National Medical Research Registry (NMRR-16-1880-32144) and approved by the Medical Research and Ethics Committee Malaysia ((6)KKM/NIHSEC/P16-1549). All participants provided written informed consent before enrolment, and the study was conducted in accordance with the Declaration of Helsinki.

RESULT

Study Subjects

We approached a total of 130 patients. Three patients refused to participate in the survey due to time constraints. One hundred and twenty-seven (97.7%) outpatients with CNCP participated in the study and were included in the final data analysis. Of these patients, forty-eight (37.8%) were male, and seventy-nine (62.2%) were female. The mean (\pm SD) age was 55 (\pm 12.8) years. Majority of the patients were Malay (58.3%), followed by Indian (33.1%), Chinese (7.9%) and Siamese (0.8%). Most of them were in full-time employment (68.5%), while 30.7% were unemployed at the time of the interview. As shown in Table I, the most frequent pain diagnosis was osteoarthritis (31.5%), followed by cervical or lumbar degenerative disease (28.3%) and pelvic inflammatory disease (11.8%). Pain diagnoses such as fibromyalgia, bone fracture, spinal stenosis, and anterior cruciate ligament injury were collectively grouped under the category of 'others' due to the relatively low frequency in our study subjects.

For pain management, most of the patients had been prescribed a combination of oral and topical analgesic (74.8%). Of note, a tremendous 80.3% of the patients needed at least two analgesics for pain control, and only 19.7% of them were treated with just an analgesic. NSAIDs, especially celecoxib and weak opioid tramadol, were the most frequent oral analgesics prescribed by our doctors, with a total combined frequency of 73.2%. On the other hand, topical NSAIDs (diclofenac and ketoprofen) were also the most frequently prescribed topical analgesic in our study subjects.

Table I: Baseline characteristics of study patients (N=127) (a) demographic data and (b) Analgesic regimen

(a) Demographic characteristics

| Variable | Mean (\pm SD) |
|--------------------------------------|------------------|
| Age | 54 (\pm 12.8) |
| Variable | Number (%) |
| Gender | |
| Female | 79 (62.2%) |
| Male | 48 (37.8%) |
| Race | |
| Malay | 74 (58.3 %) |
| Indian | 42 (33.1%) |
| Chinese | 10 (7.9%) |
| Siamese | 1 (0.8%) |
| Occupational status | |
| Employed | 88 (69.3%) |
| Unemployed/Retired | 39 (30.7%) |
| Diagnosis of Chronic Pain | |
| Osteoarthritis | 40 (31.5%) |
| Cervical/Lumbar degenerative disease | 36 (28.3%) |
| Pelvic inflammatory disease | 15 (11.8%) |
| Lower back pain | 7 (5.5%) |
| Musculoskeletal injury | 3 (2.4%) |
| Rheumatoid arthritis | 3 (2.4%) |
| Cervical/Lumbar radiculopathy | 3 (2.4%) |
| Carpal tunnel syndrome | 3 (2.4%) |
| Supraspinatus inflammation | 3 (2.4%) |
| Others | 14 (11.2%) |

(b) Analgesic regimens

| Variable | Number (%) |
|---|-------------|
| Dosage form of analgesic | |
| Oral only | 32 (25.2%) |
| Topical only | 0 (0%) |
| Combination (Oral +Topical) | 95 (74.8%) |
| Number of analgesics | |
| 1 | 25 (19.7%) |
| 2 | 77 (60.6%) |
| 3 | 22 (17.3%) |
| More than 3 | 3 (2.4%) |
| Type of ORAL analgesic | |
| NSAIDs | 47 (37%) |
| Tramadol | 46 (36.2%) |
| Gabapentin | 1 (0.8%) |
| Paracetamol | 1 (0.8%) |
| Combination | 32 (25.2%) |
| Type of TOPICAL analgesic | |
| NSAIDs | 66 (52%) |
| Methyl salicylate ointment | 28 (22%) |
| Combination | 1 (0.8%) |
| Additional OTC analgesic from community pharmacy | |
| Yes | 16 (12.6%) |
| No | 111 (87.4%) |
| Complementary medicines | |
| Yes | 19 (15%) |
| No | 108 (85%) |

NSAIDs: Non-steroidal anti-inflammatory drugs; OTC: over the counter

In addition to medication supply from the hospital, 12.6% of patients bought OTC analgesics from a community pharmacy to supplement their prescription medicines, and nineteen (15%) patients practiced traditional and complementary medicines such as massage, acupuncture, meditation, and cupping as part of their pain management.

Pain Assessment

On average, patients reported their worst pain score at eight out of ten, while the least pain score was one out of ten (Fig. 1). The median percentage of pain relief from the prescribed analgesic(s) was seventy percent. With regards to the location of pain, 33.9% of patients experienced pain at more than one body part, 31.5% at trunk regions, 29.9% at lower limb(s), and only 4.7% at upper limb(s).

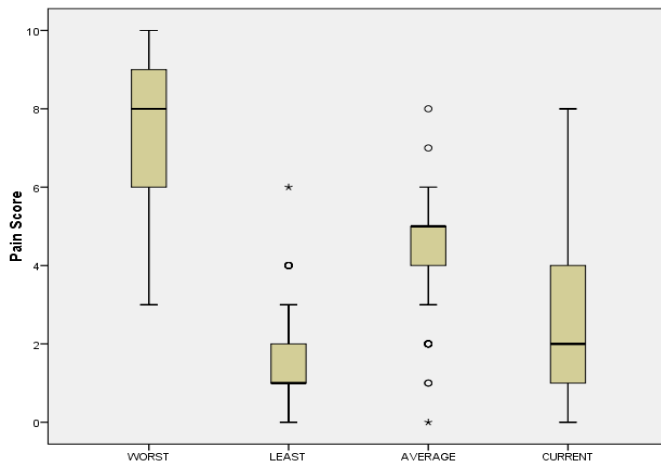


Fig. 1: Pain scores reported by 127 study patients as collected from Brief Pain Inventory-Short Form (BPI-sf)

Prevalence of Different Analgesic Dosing Behaviors

An analysis of the prescribing pattern for oral analgesics showed that 95.3% of prescribers annotated ‘as needed’ dosing. Meanwhile, 88.2% of patients took their oral analgesic(s) ‘as needed’. (Table II) The study showed cases of discrepancy between the prescribed dose and the actual dose taken, but the frequency was minimal. For oral analgesics, only fifteen

Table II: Analgesic dosing behaviors among patients (N=127)

| Type of Analgesics | Prescriber Instruction, N (%) | | Patient Dosing, N (%) | | Total N |
|--------------------|-------------------------------|---------|-----------------------|-----------|---------|
| | As Needed | Regular | As Needed | Regular | |
| Oral | 121 (95.3) | 6 (4.7) | 112 (88.2) | 15 (11.8) | 127 |
| Topical | 94 (98.9) | 1 (1.1) | 61 (64.2) | 34 (35.8) | 95 |

(11.8%) patients did not take their analgesic according to the prescribed instruction. Meanwhile, about one-third (34.7%) of patients applied topical analgesics regularly despite being instructed to apply only ‘as needed’ (Table II). We also discovered an alarming 98.4% of patients did not know the maximum allowable daily dose of the analgesic(s) prescribed to them when instructed to take as needed.

PMI and Pain Control

Our study demonstrated that as high as 70.9% of patients were under-treated for their chronic pain, represented by negative PMI as shown in Table III. No significant relationship was found between the dosing deviation with PMI; whether taking it via oral analgesics (p=0.534), topical analgesics (p=0.767), or the combination routes (p>0.95) (Table III).

Table III: Percentage of patients with negative and positive PMI scores based on deviation of oral and topical analgesic dosing

| Dosing Deviation | Pain Management Index (PMI) | | | p-value |
|------------------|-----------------------------|------------|------------|--------------------|
| | Positive | Negative | Total | |
| Oral only | | | | |
| Yes | 1 | 1 | 2 | 0.534 ^a |
| No | 9 | 21 | 30 | |
| Total | 10 | 22 | 32 | |
| Topical only | | | | |
| Yes | 10 | 23 | 33 | 0.767 ^b |
| No | 17 | 45 | 62 | |
| Total | 27 | 68 | 95 | |
| Overall | | | | |
| Yes | 4 | 11 | 15 | >0.95 ^a |
| No | 33 | 79 | 112 | |
| Total | 37 (29.1%) | 90 (70.9%) | 127 (100%) | |

^aFisher's exact test ^bPearson chi-square test

DISCUSSION

From this study, we observed a discrepancy in analgesic use between the prescribed dose and the actual dose taken by patients. There were 11.8% and 34.7% of patients who did not follow their prescriber's instruction when using oral and topical analgesics. Earlier results of a qualitative study in 2006 also proved the existence of self-dosing behavior in analgesic use [22].

Regardless, the self-dosing behavior especially in the consumption of oral analgesics was not apparent in our study. 88.2% of patients took oral analgesic(s) ‘as needed’, which aligned with 95.3% of the ‘as needed’ prescribed instruction. However, the matching preference of both prescribers and the patients in our study subjects was far from good news. Current recommendations advocated regular administration of analgesics in chronic pain management [9,11-14], but only 4.7% of the prescriptions were written for ‘regular dosing’,

highlighting a guideline non-adherence in chronic pain management among our healthcare professionals.

Pain control was not found to be significantly associated with dosing deviation ($p > 0.95$). Negative PMI, an indication of poor pain control with analgesics, was the major observation in our patients, regardless of whether they followed or deviated from the prescribed dose. Hence, additional analgesic should be added to the existing regimen for better pain control. In the study, none of the patients was prescribed a strong opioid, despite the fact that a few patients reported their worst pain score at 10, the highest pain score. In Kuala Lipis Hospital, strong opioids are reserved for cancer patients. Thus, the strongest analgesic available for CNCP patients in our setting is weak opioids. The prescribing practice will need to be reviewed following the results of the study, as the majority of CNCP patients in our study subjects were inadequately treated. Strong opioids should be used to manage severe pain, based on the WHO analgesic ladder [10] and local guidelines [23].

The most frequently prescribed oral analgesics in our setting were celecoxib and tramadol. Other oral analgesics that were prescribed to our patients were paracetamol and diclofenac. Gabapentin and pregabalin were also used as adjuvants in neuropathic pain. There were no prescribing records found for strong opioids in the management of CNCP. Celecoxib, a selective cyclooxygenase-2 inhibitor, was the most commonly prescribed analgesic within the family of NSAIDs due to its better gastrointestinal safety profile. It was also well-accepted among doctors in Malaysia due to the general belief that celecoxib is more efficacious than conventional NSAIDs in reducing pain and inflammation [24]. On the other hand, the only weak opioids in our hospital formulary are tramadol and dihydrocodeine. Since dihydrocodeine is classified as a dangerous drug and hence more stringent prescribing criteria, the cheap and easily accessible tramadol is a popular add-on option for CNCP patients whose pain is uncontrolled with NSAIDs and paracetamol.

It was shown in our study that 98% of CNCP patients did not know the maximum allowable daily dose of analgesic(s) which they were taking. They claimed to take their analgesic(s) as needed without knowing the maximum allowable quantity per day. This situation is alarming as it can increase the risk of medication misuse and accidental overdose. In fact, an Australian report on injury research and statistics revealed that paracetamol, a type of analgesic, was accountable for the 2nd highest pharmaceutical poisoning cases (11%, $n=718$) [25]. Not only that, but the deficiency in patient knowledge about paracetamol use was also highlighted in a few descriptive and cross-sectional studies [26-28]. Therefore, the knowledge gap among patients on the safe use of analgesics could be an opportunity for pharmacists to play a bigger role in preventing cases of pharmaceutical poisoning. However, a hospital survey

on the counseling practice of pharmacists showed disappointing results. The survey confirmed that less than half of the pharmacists provided counseling and precautionary warnings when dispensing paracetamol [29]. Therefore, pharmacists need to do more in educating patients about the safe use of not just paracetamol but of all analgesics in pain management.

Besides the conventional analgesics, traditional and complementary medicines are gaining popularity and have become one of the popular alternatives in chronic pain management. It was found that 69.4% of the Malaysian population used traditional and complementary medicines throughout their life, and 55.6% of them used them annually [30]. In our study, nineteen (15%) patients sourced traditional and complementary medicines such as massage, acupuncture, meditation, and cupping; and reported efficacy from these alternatives. The positive experience with traditional and complementary medicines is also demonstrated overseas. In fact, a patient survey in Singapore found that as much as 72% of patients reported better pain relief with complementary medicines [31]. Gathering from the current evidence, traditional and complementary medicines can become an effective alternative approach in chronic pain management, especially among those patients who found limited pain relief from their current analgesics. However, they should be guided by informed healthcare professionals during the selection process so as not to fall victims to unscrupulous dealers, which eventually may give rise to other health complications.

CONCLUSION

The prevalence of 'as needed' dosing is higher than around-the-clock dosing in the management of chronic, non-cancer pain, with deviation from the prescribed instructions between 11.8-34.7%. However, those differences were not significantly associated with the pain control. Our study highlighted that poor pain control in CNCP patients was due to fundamental error at the prescribing stage, starting from inappropriate analgesic choice and description of dosage frequency. Poor pain control was impacted less by patients deviating from prescribing instructions.

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CONFLICT OF INTEREST

None declared.

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Utilization Review of Anti-peptic Ulcer Drugs at an Outpatient Pharmacy Setting of a Private Hospital in Malaysia

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ABSTRACT

Anti-peptic ulcer drugs (APUDs) such as proton pump inhibitors (PPI), H2 receptor antagonists (H2A), antacids are widely prescribed. This study is aimed to describe the utilisation pattern of APUDs based on WHO Defined Daily Dose (DDD) and identify most commonly used APUD in the selected hospital. A retrospective study was carried out in outpatient of the selected hospital for year 2017. Sample size was calculated using Raosoft. DDD of APUDs and direct drug cost were calculated. Data were collected through electronic medical record by retrieving patients' registration number. Inclusion criteria were patients above 18 years old and APUDs prescribed for gastrointestinal related indications. A total of 160 prescriptions were randomly selected for data analysis. Based on the DDD calculated, Rabeprazole 20mg was most prescribed drug among PPI (n=33), while Maalox is most prescribed drug among the antacids (n=23). Based on the DDD calculated, Pantoprazole 20mg recorded highest rates per user per day about 1.26 DDD / user / day while antacids, Actal reported highest usage rate with 7.11 DDD / user / day. Besides, there are 5.4 days supplied per user for this drug. Dexlansoprazole 60mg is the most expensive drug among all the PPI listed in hospital formulary. It has 18.5 days supplied/user, which is the second shortest duration of treatment among all the other PPIs. In contrast, omeprazole 20mg is the lowest cost PPI but the duration supplied per user is longer resulting in higher total cost of therapy. In conclusion, PPIs were the most commonly prescribed.

INTRODUCTION

Peptic ulcer disease (PUD) has been common ailment, where annual incident report stated 0.03% to 0.17% were diagnosed by medical examiner and treated as outpatient and 0.03% to 0.17% during hospital stay. The incidence of PUD has decline on recent time in some countries, this is attributed to the decrease in *Helicobacter pylori* infection, particularly in Western populations [1]. Asian countries recorded lower peptic acid disorder prevalence rate compared to advance nation meanwhile Malaysian recorded prevalence 9.5% for duodenal ulcer and 9.4% gastric ulcer respectively [2].

Reports on prevalence and incidence of peptic ulcer secondary to geographical variation exists with differences in relative occurrences of duodenal and gastric ulcers. Ethnic variations on peptic ulcer incidence has been reported on the pattern of peptic ulcer in Malaysia from endoscopic data at University Medical unit at Kuala Lumpur that states Chinese of both gender have a higher susceptibility to peptic ulcer [3].

Anti-Peptic Ulcer Drugs (APUDs) such as H2-receptor antagonists (H2RA), proton pump inhibitors (PPI), and antacids are commonly used by medical partitioner, on other hand synthetic prostaglandins and cytoprotective agents has been promptly used by gastroenterologist in private clinics. Besides peptic ulcer disorder this agents are also used in

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treatment non-ulcer dyspepsia and heartburns. These group drugs are co-prescribed as prophylaxis agents during nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, anti-platelet and anticoagulation therapy [4]. Many physicians had raised concern regarding adverse events due to long-term acid suppression therapy. On other hand with PUD drug endoscopic study reveal 30% of patient suffered with peptic ulcer whom co-prescribed NSAIDs [5]. Therefore, there is a need to develop a policy on APUD and drug formulary.

Common acid suppressants used in gastrointestinal disorders are PPI and H2RA. The trend of drug consumption in Malaysia has transformed significantly from H2RA to PPI and currently, there are overconsumption of PPI [6]. A huge number of patients, as many as 90% in one study consume these drugs with no appropriate guideline-based indication [7]. Since PPIs are easily available, this makes them one of the most widely prescribed medications; thus irrational use and unnecessary exposure prone to happen. Long-term consumption of a proton pump inhibitor may lead to gastric carcinoids and increases the risk of hip fractures [8]. Moreover, PPIs are costly thereby increasing the economic burden on the patients. PPI over usage has become very critical, where this study need to be commenced in order to provide a better understanding in healthcare sector [9].

According to Kandasami, the total cost of PUD patient prescription surges as more than half of patients suffering from peptic ulcers are usually associated with comorbidities that necessitates treatment [10]. Although the prevalence of acid related disorders in Malaysia is in the region of 8-10%, , only 0.6% of the population have been prescribed with medications for acid related diseases by Malaysian Society of Gastroenterology and Hepatology. This shows that there is a treatment gap. Therefore, there is a need to standardise treatment algorithms for acid related disorders in Malaysia and the important role of anti-peptic ulcer drugs in the management of acid related disorders needs to be clearly defined.

The over-prescribing of APUD highlighted the importance of the need to examine the current utilization and appropriateness of the anti-peptic ulcer drugs. The outcome of this study will be beneficial to develop a policy on APUD usage and drug formulary at the selected hospital. Drug utilization review may help the prescribers to interpret, understand, and expand the prescribing, administration and usage of the medication. This may directly have a positive impact on patient health and financial status.

METHOD

Overview of Research Design

A retrospective observational study on drug utilization of anti-peptic ulcer drugs had been carried out in the outpatient department of a private hospital located at Seremban, Negeri Sembilan Malaysia. A retrospective study design that trace information backwards was used. The selected hospital uses KPJ Clinical Information System (KCIS) and Hospital Information Technology System (HITS) which is the Electronic Medical Record (EMR).

KCIS creates a boundless communication among the healthcare professionals which manages the clinical aspects of the hospital, while HITS is a system of the hospital management that integrates all patients' information since the patient been registered until billing from KPJ Annual Report. These systems are used to obtain data that are needed for this study. Inclusion and exclusion criteria were applied to select the appropriate drug utilisation data.

Patient selection criteria

Prescriptions from newly registered patients as well as regular follow-up patients were included in the study according to the inclusion and exclusion criteria. Prescriptions that fulfilled the following inclusion and exclusion criteria adopted from literature were included [11].

Inclusion criteria

- Prescription with patient more than age of 18 years old receiving anti-peptic ulcer drugs.
- Pharmacologically treated for peptic ulcer with or without comorbidities.

Exclusion criteria

- The prescription with incomplete patient data for data collection form.
- Non-KPJ prescriptions.

Sampling Method

The sampling technique that has been used in this study were block randomization as well as convenience sampling. Block randomization method was used to randomize subjects into groups that result in equal sample sizes. Then, in order to choose the sample, convenience sampling was used.

Sample study

The sample size required for this study was estimated based on a formula stated by Daniel [12]. For this study, the significance level was set at $\alpha = 0.05$ (two tailed) and 95% degree of confidence interval (CI) fixed in the calculation sample size by using the formula as stated above. The minimum sample size calculated was 138 patients with peptic ulcer from the outpatient department.

Variable Definition

The KPJ Clinical Information System (KCIS) was used to access the list of all patients that are previously prescribed with anti-peptic ulcer drugs in 2017 and record in a data collection form. Only prescriptions that met the inclusion and exclusion criteria were included in this study. So, these patients' prescriptions records were retrieved between January till December 2017 by using their medical record number (MRN) or identification card number (IC).

The following data were collected for each prescription: Demographic data which includes the age, sex and weight of patient, diagnosis and relevant prescription data. This includes the name of medication, pharmacological class, dose prescribed, dosage regimen which includes frequency and route of administration and number of drugs per prescription. The collected prescriptions were evaluated based on criteria of prescription and standard guideline on DDD.

The prescription was assessed based on the following criteria, number of drugs prescribed, number prescribed in generics, dose strength, dosage of drug and duration of therapy. Meanwhile, the guideline on DDD that was used as the main reference in this study are CPG of Non-variceal Upper Gastrointestinal Bleeding and National Drug Formulary.

Defined Daily Dose Formula

The Defined Daily Dose (DDD) for a drug is its assumed average maintenance dose per day for a drug used as a main indication in adults as WHO guideline (Eq. 1).

$$\text{Total DDDs} = \frac{\text{Dosage form strength} \times \text{Quantity of drug dispensed}}{\text{WHO assigned DDD for the drug}} \quad (\text{Eq. 1})$$

To provides a rough estimate of the proportion of the population treated daily with a specific drug, rates per residents per day is calculated using Eq.2.

$$\text{DDD per day per 1000 residents} = \frac{\text{DDDDs per year}}{30 \text{ days} \times 30,000 \text{ residents}} \times 1000 \quad (\text{Eq. 2})$$

To determine whether the DDD is close to the average daily maintenance dose for the drug's main indication (as determined by WHO), the rates per user per day is calculated (Eq.3)

$$\text{DDD per day per user} = \frac{\text{DDDDs per year}}{30 \text{ days} \times \text{Number of users}} \quad (\text{Eq. 3})$$

Use of DDDs Clinically

A clinical measure can also be calculated to help interpret the DDDs/user/day value which assumes dispensation to users over an entire year. This can be done in two steps:

Firstly, an intermediate rate of the number of days supplied per user is calculated by summing the number of days supplied recorded on each prescription claim and dividing by the number of users.

Secondly, the measure of how the drug is actually being used was calculated by dividing the rate of the DDDs per user by the rate of the number of days supplied per user which is also known as DDDs / day supplied.

Outcome Parameter

The DDD between the standardized DDD by WHO were compared with DDD based on the drugs prescribed by the prescribers and patient's characteristics. The DDD/1,000 inhabitants/day which expressed as DDD methodology and the drug classification system, Anatomical Therapeutic Chemical (ATC) were used in estimating the usage of APUD in the selected private hospital. Data of DDD of APUD in the selected hospital were then analysed and compared to the standard DDD of WHO classification of ATC/DDD.

Ethical Consent

The ethical approval for this study was obtained from the Research Ethic Committee of KPJ University College, Nilai, Malaysia (KPJUC/RMC/BPH/EC/2017/100). This approval has been obtained before conducting the study. All data obtained were used solely for research and be kept confidential.

RESULT

Patients' selection and description

The prescription data that have met all the inclusion criteria were critically analysed. From the total outpatient prescriptions in 2017, 200 prescriptions were found matched the criteria based on the studies requirement and 22 prescriptions were excluded due to the diagnosis as *Helicobacter pylori* positive. However, due to some incomplete data were found, only 160 prescriptions were finally chosen.

Demographic Characteristics of Patients

Table I shows the demographic characteristics of the populations in this study and depicts that the most common age group in which APUDs were prescribed in both male and female was 50-59 years 31.88% (n=51) whereas the least age group prescribed with APUDs are below 20 years, 3.13% (n=5). The prescriptions of these drugs were slightly more among male patients 55% (N = 88) compared to female patients 45% (n=72). The major ethnicity found to be prescribed the most were Malay 63.75% (n=102) followed by Chinese 18.75% (n=30) and Indian 17.50% (n=28).

Table I. Gender and ethnicity of population based on age category

| Category | Number of APUDs prescriptions, n (%) | |
|---------------------|--------------------------------------|----------------|
| | Male n=88 | Female n=72 |
| Age category | | |
| Below 20 | 2 (1.25) | 3 (1.9) |
| 20 to 29 | 2 (1.25) | 4 (2.5) |
| 30 to 39 | 12 (7.5) | 12 (7.5) |
| 40 to 49 | 27 (16.9) | 16 (10) |
| 50 to 59 | 30 (18.8) | 21 (13.1) |
| Above 60 | 15 (9.4) | 16 (10) |
| Ethnicity | | |
| Malay | 59 (36.9) | 43 (26.9) |
| Chinese | 16 (10) | 14 (8.8) |
| Indian | 13 (8.1) | 15 (9.4) |

Patterns of Anti-Peptic Ulcer Drugs Utilization

In this study, the number of drugs prescribed varied according to the severity of patient condition and requirement of therapy. Drugs prescribed per prescription among 160 patients ranged from 1 to 2 types of drug products.

Table II illustrates the utilization pattern of anti-peptic ulcer drugs according to their classification and it reveals that most common class of anti-peptic ulcer drug prescribed to adult population in that corresponding hospital setting was proton pump inhibitors which accounted for 82% (n=159) followed by Antacids about 18% (n=35) and no usage of H₂ antagonist.

Table II. Frequency of anti-peptic ulcer drug prescribed by medical officer and consultant.

| Drug Classification | Drugs | Consultant | Medical officer |
|------------------------------------|-----------------------|------------|-----------------|
| Proton pump inhibitor (82%, N=159) | Dexlansoprazole 60 mg | 28 | 0 |
| | Esomeprazole 40mg | 27 | 2 |
| | Omeprazole 20mg | 21 | 6 |
| | Pantoprazole 20mg | 18 | 11 |
| | Pantoprazole 40mg | 9 | 4 |
| | Rabeprazole 20mg | 31 | 2 |
| Antacid (18%, N=35) | Actal Tablet | 5 | 0 |
| | Maalox Suspension | 17 | 6 |
| | Zellox Suspension | 6 | 1 |

The drug utilization was further examined specifically based on each type of drug products. PPI was the one most commonly prescribed drug class, 17% (n=33) was contributed by rabeprazole 20mg whereas the least usage of drug under the PPI category is pantoprazole 40mg, about 6.7% (n=13). Besides, the main PPI prescribed by consultant is rabeprazole 20mg while the most frequent PPI prescribed by medical officers is pantoprazole 20mg. The distribution of anti-peptic ulcer drugs utilization varied based on the strength of medication. The highest maximum usage of antacids is Zellox suspension, about 11.9% (n=23) whereas the least prescribed is Actal tablet about 2.6% (n=5).

Figure I demonstrates 40% (n=64) of prescriptions administered combination of anti-peptic ulcer drugs whereas 60% (n=96) of them administered a single APUD. The highest number of samples administering single group of APUDs are from the age group of 50 to 59 years old.

Frequency of anti-peptic ulcer drugs prescriptions from various department are illustrated in Figure II. It shows that out of the 160 prescriptions of APUDs, most number of outpatient prescriptions were found in general surgery department 26.9% (n=43) followed by 23.1% (n=37) from general medicine department. On the other hand, APUDs were least prescribed in urology, otorhinolaryngology (ENT) and obstetrics and

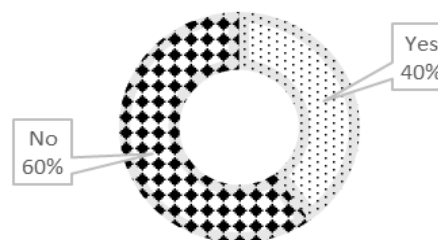


Figure I. Percentage of sample administering combination of anti-peptic ulcer drugs

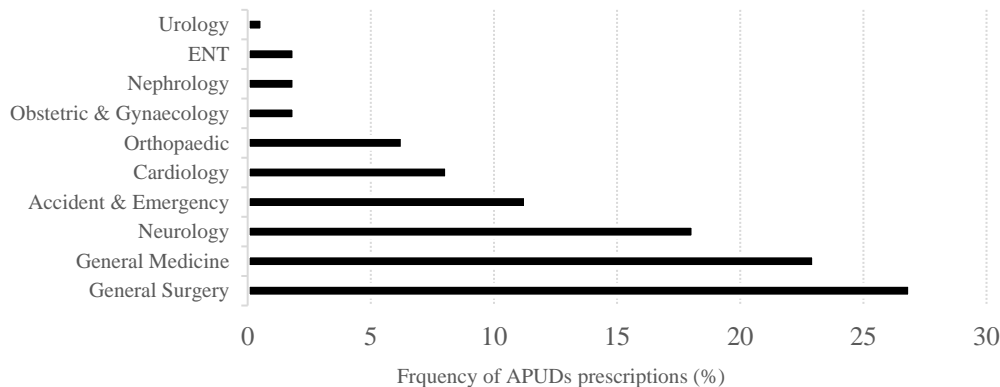


Figure II. Distribution of anti-peptic ulcer drug prescriptions of the study in outpatient department

gynaecology. There are two different categories of physicians commonly prescribe APUDs in the particular hospital which local and internationally educated physicians. Education background of a physician, indirectly related to the type of APUDs prescribed by the physician. Consultants from local and overseas education background for specialist training prefer different types APUDs for their patients. The most of APUDs prescribed by consultants from local universities are esomeprazole 40mg, 10.3% (n=20) whereas consultants from overseas universities prefer rabeprazole 20mg, 11.9% (n=23). In this hospital, all of the medical officers are from local universities and the highest number of APUDs prescribed by medical officers from local universities are pantoprazole 20mg, 5.7% (n=11).

Demographic variables and types of anti-peptic ulcer drugs prescribed

The frequency of anti-peptic ulcer drugs prescribed varies according to the age categories of patients. Table III shows the diverse number of APUDs prescribed to the different age categories of patients. The most commonly APUD prescribed for patients below 20 years is Pantoprazole 20mg, 1.5% (n=3) and two types of APUDs are among 20 to 29 years old patients, pantoprazole 20mg and Omeprazole 20mg, 1.03% (n=2). Next, Omeprazole 20mg is the maximum usage of drug among 30 to 39 years old, 3.09% (n=6) whereas among 40 to 49 years old patients is esomeprazole 40mg, 6.2% (n=12). The highest amount of APUD accounted among 50 to 59 years old patients is rabeprazole 20mg, 6.7% (n=13) however among the age group of more than 60 years are two different APUDs, omeprazole 20mg and dexlansoprazole 60mg about 3.6% (n=7). Furthermore, the highest APUD users belongs to age group of 50 to 59 years old.

Defined Daily Dose (DDD) of Anti-Peptic Ulcer Drugs (APUDs)

Table IV shows the results obtained from the calculation of DDDs / days supplied per user of APUDs at the selected hospital. Based on the DDD calculated, pantoprazole 20mg was the most prescribed drug among proton pump inhibitors (PPI) whereas Actal tablets has the highest usage among the antacids. There are differences in all the anti-peptic ulcer drugs usage although the difference among APUDs are significantly low. Although ranitidine from H2 antagonist is available in the drug formulary of the hospital, it is never been prescribed during the study period. Besides, there is a clear comparison among unit price of APUDs and it shows that dexlansoprazole 60mg is the highest cost PPI whereas Maalox 250ml is the highest cost antacid available.

DISCUSSION

Demographic Characteristics of Patients

In this retrospective study, a total of 160 prescriptions were reviewed as per the inclusion and exclusion criteria. In terms of gender of the patients receiving the prescriptions, there are higher population of male patients, around 55% and 45% are female patients. According to Department of Statistics Malaysia, there are 1.12 million of total populations in Negeri Sembilan and there are slightly more males (555,935) residents in the state capital city of Seremban. Cigarette smoking may lead to decrease in the circulating growth factor as well as rise of free radical production in gastric mucosa and it becomes the prominent factor of peptic ulcer disease [13]. Although smoking data was not available in this study, however the higher number of male patients is possibly related to increased smoking habit.

Among Malay, Chinese and Indian ethnics, there are greater number of Malay patients in this study and it is due to a vast difference in the distribution of ethnic groups in Negeri Sembilan: Malay (61.35%), Chinese (23.2%) and Indian (15.45%). Ethnicity predisposition differences does not alter the gastric acid secretion among peptic acid patients. The frequency of anti-peptic ulcer drugs usage increases with age as depicted in Table 1 whereby the highest number of APUDs prescribed in both male and female was in the 50-59 years age group. Study has confirmed that age group is not a risk factor of peptic ulcer disease, however, stress due to numerous health complications in this age group is described as the main source of peptic ulcers, which are termed as stress induced ulcers [13]. Evidence has suggested that *Helicobacter pylori* infection plays a major contributory role in peptic ulcer disease and preliminary studies have reported that the incidence of *Helicobacter pylori* infection increases with age [14].

Anti-Peptic Ulcer Drugs Utilization Patterns

According to Narayanan, management of peptic ulcer disease (PUD) has improved tremendously following the administration of proton pump inhibitors and therapy for *Helicobacter pylori* eradication [15]. This revealed from the decline in the incidence of *Helicobacter pylori*-associated PUD, and the lower percentage of *Helicobacter pylori* infection, particularly in complicated PUD. Table 2 shows the variety and proportion of anti-peptic ulcer drugs found in the study prescriptions. Most common class of anti-peptic ulcer drug

prescribed was PPIs followed by antacids with no usage of H2 antagonist. Of all these drugs, rabeprazole 20mg was prescribed the most whereas the least prescribed was pantoprazole 40mg. The maximum usage of antacids in the hospital is Zellox suspension 100mL whereas the least usage is Actal tablet. Ranitidine was the only H2 blocker that was found in the hospital but there is no any usage of ranitidine during the study period. A recent meta-analysis displayed the effectiveness of PPI therapy by a drop of re-bleeding rate and frequency of surgery in patients with upper gastrointestinal bleeding following successful endoscopic therapy, compared to H2RA therapy. [16] Additionally, PPIs were superior to H2RAs for prevention of LDA-associated GI erosion or ulcer as according to another meta-analysis [16].

Figure I demonstrates higher population are administering single group of APUD, primarily PPIs whereas only 40% of them are prescribed combination of APUDs. Irrational use of PPIs alone should be avoided because few studies proved that the usage of PPIs alone can cause detrimental to the consumers. In two randomized controlled trials (RCTs), it is evident on the presence of dyspepsia in 20% to 44% of healthy volunteers after discontinuation of four to eight weeks of PPI therapy. Furthermore, as according to a systemic review, long-term practice of PPIs for more than two years is linked with an increased risk of vitamin B12 deficiency due to the alteration of intragastric pH levels. Observational data based systemic reviews and meta-analyses shown a connection between chronic PPI usage with the risk of fractures in both male and

Table III. Distribution of anti-peptic ulcer drugs prescriptions according to patients' age

| Anti-peptic ulcer drugs | Patient's Age Group (n) | | | | | |
|-------------------------|-------------------------|-------|-------|-------|-------|-----|
| | <20 | 20-29 | 30-39 | 40-49 | 50-59 | 60> |
| Actal Tablet | 1 | | 1 | 1 | 2 | |
| Dexlansoprazole 60 mg | | 1 | 2 | | 10 | 7 |
| Esomeprazole 40mg | | | 5 | 12 | 8 | 4 |
| Maalox Suspension | | | 1 | 1 | 4 | 1 |
| Omeprazole 20mg | | 2 | 6 | 4 | 8 | 7 |
| Pantoprazole 20mg | 3 | 2 | 5 | 8 | 8 | 3 |
| Pantoprazole 40mg | 1 | 1 | 2 | 1 | 4 | 4 |
| Rabeprazole 20mg | | 1 | 4 | 9 | 13 | 6 |
| Zellox Suspension 100ml | 2 | 1 | 4 | 5 | 8 | 3 |

Table IV. DDD/day supplied and unit price of each anti-peptic ulcer drugs

| Type of APUDs | WHO DDD | Rates per residents per year | Rates per user per day | Intermediate rate | Clinical measure | Unit price (RM) |
|----------------------|-----------|------------------------------|------------------------|-------------------|------------------|-----------------|
| Pantoprazole 20mg | 2 DDD | 0.12 | 1.26 | 17.76 | 0.07 | 4.60 |
| Pantoprazole 40mg | 1 DDD | 0.04 | 0.82 | 22.38 | 0.04 | 6.00 |
| Dexlansoprazole 60mg | 0.5 DDD | 0.03 | 0.32 | 18.50 | 0.02 | 8.50 |
| Esomeprazole 40mg | 0.75 DDD | 0.08 | 0.86 | 30.10 | 0.03 | 2.80 |
| Omeprazole 20mg | 1 DDD | 0.09 | 0.95 | 28.37 | 0.03 | 1.00 |
| Rabeprazole 20mg | 1 DDD | 0.11 | 1.01 | 30.33 | 0.03 | 5.10 |
| Actal tablets | 11.11 DDD | 0.12 | 7.11 | 5.40 | 1.32 | 1.30 |
| Zellox 100ml | 0.38 DDD | 0.03 | 0.37 | 11.05 | 0.03 | 30.00 |
| Maalox 250ml | 0.13 DDD | 0.04 | 0.15 | 8.86 | 0.02 | 37.50 |
| Pantoprazole 20mg | 2 DDD | 0.12 | 1.26 | 17.76 | 0.07 | 4.60 |

female patients. Whereas, this connection has not seen with the use of H₂ receptor antagonists [17]. Alternatively, a H₂ antagonist or over-the-counter antacids should be tried before prescribing the most potent PPIs because according to table 3, highest number of population administering single group of APUDs are from the age group of 50 to 59 years old and according to a nationwide case-control study from New Zealand, estimated there were about 20 cases of acute interstitial nephritis per year among every 100 000 current PPI users with more than 60 years old [18]. Thus, as an early preventive measure, it is better to prescribe H₂ antagonist for patients with the age group of more than 50 years old.

Figure II shows that out of the 160 prescriptions of APUDs, most prescriptions were from general surgery department followed by general medicine department. On the other hand, APUDs were least prescribed in nephrology and otorhinolaryngology (ENT). This observation was justified in accordance to a study done at North India where the surgeon may prescribe acid reducers such as H₂ Antagonists and PPIs to ease any discomforts after surgery. Likewise, it has been proven that a standardised prescribing of APUDs after surgery lead to significant reduction in postoperative complications such as postoperative pain, nausea and vomiting [19]. Similarly, high utilization of these APUDs was also seen in general medicine department because the use of PPI according to FDA is indicated as in cases of evident GI diseases comprise of treatment of symptomatic gastroesophageal reflux disease (GERD), maintenance treatment of erosive esophagitis, eradication of *Helicobacter pylori* infection, healing and maintenance of gastric ulcers, prevention and treatment of NSAID-induced gastric ulcers and treatment of hypersecretory condition as Zollinger-Ellison syndrome [20].

This study also indicated that rabeprazole 20mg is the most prescribed PPI in the hospital and followed by esomeprazole 40mg because rabeprazole and esomeprazole increase cure rates compared to pantoprazole, omeprazole and lansoprazole, the first generation PPIs. This advantage of new-generation PPIs has been reported earlier in reviews and retrospective studies and these new PPIs has been reported to affect eradication rates due to the higher acid inhibition power. Meanwhile, the clinical advantage may be restricted from a cost-effective perspective due to higher prices of rabeprazole and esomeprazole when compared with omeprazole [21]. In contrast, pantoprazole 40mg has the minimum usage amongst all the PPI. The results of a comparative study on esomeprazole 40mg versus pantoprazole 40mg illustrates a therapeutic advantage of esomeprazole 40 mg over pantoprazole 40 mg by providing healing of erosive esophagitis (EE). This result predicted as the healing of EE is inversely related to gastric acidity, and esomeprazole has been shown to deliver a greater suppression of gastric acidity than standard doses of all other PPIs [22].

McNicholl, states that five studies compared the eradication rates of rabeprazole versus esomeprazole [21]. The comparison was not heterogeneous and found no statistically significant differences. Rabeprazole has the eradication rates about 76.7% while esomeprazole shows 78.7%. According to a meta-analysis, CYP2C19 phenotype is not affected by the eradication rates of esomeprazole and rabeprazole, while first-generation PPIs demonstrates a clearer tendency towards lower eradication rates in patients. Meanwhile, majority APUDs prescribed by medical officers from local universities are Pantoprazole 20mg because it was approved by FDA in 2000 for the treatment of erosive esophagitis associated with GERD and PUD plus it is one of the few PPIs existing in multiple dosage forms. According to Mathews, pantoprazole has an excellent safety profile, is as effective as other PPIs, and has a low incidence of drug interactions when evaluated over 100 clinical trials. Pantoprazole has also been presented as a safe and effective among special patient populations, such as the elderly and those with renal or moderate liver disease [23].

Defined Daily Dose (DDD) and unit price of APUDs

In order to avoid recurrences of both symptoms and mucosal lesions, PPI is one of the mandatory maintenance therapy. Table IV clearly demonstrates DDD / day supplied for all the APUDs used and the result justified that APUDs over usage did not occur in this hospital. This demonstrates that several patients discontinue PPI therapy after redeeming their first prescription, whereas only a minority administer PPI continuously. Based on the DDD calculated, Pantoprazole 20mg reported highest rates per user per day among proton pump inhibitors (PPI) about 1.26 DDD / user / day. The maximum usage of this drug can be due to the compulsory triple regimen inclusive of pantoprazole for *Helicobacter pylori* eradication. Furthermore, administration of the slow-release pantoprazole results in the significantly faster onset of action taking place compared to the administration in a form without retarding such release [24]. In addition, Actal reported highest rates per user per day among the antacids, which is about 7.11 DDD / user / day. This can be seen clearly due to the lowest cost among all the antacids available in this hospital. Besides, there are 5.4 days supplied per user for this drug which shows much less duration than the other two different antacids. Thus, it is known as cost effective drug which indirectly reduce burden for the patients.

According to Table IV, dexlansoprazole 60mg is the most expensive drug among all the PPI listed in hospital formulary and it has 18.5 days supplied / user, which is the second shortest duration of treatment among all the other PPIs. This is because, dexlansoprazole is a modified-release drug because the active ingredients are manufactured in the form of two types of granules, which are released from capsule twice, at dissimilar pH values. One part of the drug dose, is released in the proximal

duodenum at more acidic pH, significantly at pH level of 5.5 while the second part of drug dose are released in the distal small intestine at the lesser acidic pH, significantly at the pH of 6.75. This twofold release mechanism enable the drug to attain two peak serum concentrations of the drug. Therefore, this modified release drug ensures the longer drug retention period in the circulation as well as the most dominant inhibitory effect on the proton pump inhibitors. Besides, numerous clinical trials states that dexlansoprazole has a good safety profile and hardly produces adverse reactions which usually do not require drug discontinuation because safety profile of dexlansoprazole at doses of 30, 60 and 90 mg plus oral administration has been assessed in clinical trials covering a period of 1 year [25]. In contrast, omeprazole 20mg is the lowest cost PPI but the duration supplied per user is longer resulting in higher total cost of therapy. Thus, dexlansoprazole could potentially the most cost-effective PPI although the single capsule is most expensive among all the other PPIs.

CONCLUSION

In conclusion, the obtained result of utilization of all anti-peptic ulcer drugs in the selected hospital is lower as compared to WHO DDD. However, this might not show an underutilization of anti-peptic ulcer drugs but may be due to a lower number of samples collected, which cannot be used to reflect the overall utilization. Next, most common class of anti-peptic ulcer drug prescribed in this studies were Proton Pump Inhibitors which accounted for 97% followed by Antacids about 32.5% and no usage of H₂ Antagonist. Based on the DDD calculated, Pantoprazole 20mg was the most prescribed drug among PPI, about 1.26 DDD / user / day. Actal is the most commonly used drug among the antacids, which is about 7.11 DDD / user / day. The distribution of anti-peptic ulcer drug prescriptions in outpatient department was highest used in general surgery 26.9% and general medicine 23.1% department. Dexlansoprazole 60mg is the most expensive drug among all the PPI listed in hospital formulary. It has 18.5 days supplied/user, which is the second shortest duration of treatment among all the other PPIs. In contrast, omeprazole 20mg is the lowest cost PPI but the duration supplied per user is longer resulting in higher total cost of therapy. Based on the WHO DDD, it was found that Pantoprazole 20mg and Actel tablet had highest DDD with 0.12 per 1000 residents per day.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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The Effect of Pharmacist's Interventions on Anaemia Management among Continuous Ambulatory Peritoneal Dialysis Patients in Terengganu Tertiary Hospital

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ABSTRACT

Pharmacist's interventions in anaemia management have been shown to improve clinical and economic outcomes. To determine the outcome of hemoglobin (Hb) level after the implementation of ESA monitoring card and counselling, a prospective, single-blinded randomised controlled study involved patients attending the CAPD clinic in Terengganu tertiary hospital, Malaysia was carried out. Intervention group received ESA injection counselling based on a validated checklist and ESA monitoring card, while the standard care group only received standard care. Result showed a total of 118 eligible patients with 68 of them in the standard care group and 50 patients in the intervention group with an average age of 50.8 (± 14.57) and 49.4 (± 13.69) years, respectively. Mean Hb showed significant improvement in both standard care and interventional groups with $p < 0.001$. Intervention group had a higher percentage increment in mean Hb 6.7% compared to standard care group 5.9%. However, mean difference Hb between standard care and interventional group after at least 1 month of interventions was not significant with 0.59 (± 1.78) and 0.692 (± 1.68) respectively ($p = 0.764$). In conclusion, pharmacist's interventions, including counselling and ESA monitoring card may help in improving Hb level in CAPD patients.

INTRODUCTION

Anaemia is a common complication among chronic kidney disease (CKD) patients and, its prevalence rises with decreasing estimated glomerular filtration [1]. Anaemia in CKD presents as normochromic, normocytic and associated with symptoms such as fatigue, shortness of breath, insomnia, and headache [2]. Inadequate erythropoietin production is the most common cause of anaemia [1–3]. It contributes to reduced quality of life and is associated with cardiovascular disease, hospitalisation, cognitive impairment, and mortality [4].

Erythropoietin stimulating agent (ESA) and iron supplementation are the standard treatment for anaemia among end stage renal failure (ESRF) patients in Malaysia. Each patient is treated according to the haemoglobin (Hb) target with the lowest effective ESA dose while avoiding large fluctuations

in Hb levels or prolonged periods out of target Hb [5]. Studies have shown the beneficial effects of anaemia treatment, such as improved quality of life protection against cardiovascular disease, morbidity, mortality, and hospitalisation rates reduction [6]. However, anaemia management in ESRF patients is complex, and there are barriers to effective anaemia treatment, including patient non-adherence to the treatment regimen, lack of familiarity with clinical practice guidelines for anaemia treatment, and complexity of patients with CKD [7]. In addition, managing renal anaemia with ESA and iron replacement poses clinical challenges, including maintaining stable Hb levels within narrow target ranges, balancing iron and ESA dosages, and optimising the erythropoietin response with the lowest possible effective ESA dose [8]. Therefore, a multidisciplinary approach is necessary to overcome the challenges and barriers in anaemia treatment. Pharmacist clinical activities in anaemia management, including providing

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drug information to the physician, compiling guidelines for proper use of ESA and iron, dosing and monitoring ESA therapy, patient education had effectively improved Hb level, and compliance with ESA use criteria [8–10].

The effectiveness of a treatment depends on patient adherence and proper ESA injection technique. Inadequate knowledge on ESA injection can influence patient medication adherence. However, we have limited data on patient medication knowledge and ESA injection technique. Besides, one of the key performance indicators (KPI) in our nephrology department is that at least 70% of continuous ambulatory peritoneal dialysis (CAPD) patients achieved the target Hb level (10g/dl), but we did not meet the KPI to date. Despite renal pharmacists have been part of renal team and participate in the treatment of CKD, there is no relevant study on the effectiveness of renal pharmacy service in Malaysia. Therefore, we would like to investigate the effectiveness of interventions by pharmacists in optimising anaemia management in CAPD patients. The main objective of this study was to investigate the effect of pharmacist interventions on Hb outcome in CAPD patients receiving subcutaneous (SC) ESA.

METHOD

Study Design and Setting

This is a prospective, single-blinded randomised controlled study. The study was conducted for 6 months in the CAPD clinic of Terengganu tertiary hospital, Malaysia. The recruitment and data collection was performed from March to August 2017. The setting for pharmacist educational intervention consisted of a private counselling room in the CAPD clinic. The study was approved by Medical Research and Ethics Committee, Ministry of Health Malaysia (MOH) Malaysia (KKM.NIHSEC.P17-1202). Informed consent was obtained from all individual participants included in the study.

Participants and randomisation

Based on the study done by Wei Yang et al., the sample size required for detecting difference of mean Hb is 0.5g/dl with power of study =80%, and type 1 error at 0.05 was 48 subjects for both intervention group and standard care subjects [11]. A total of 55 subjects for each arm were included in this study by considering a dropout rate of 10%. Participants randomised into the interventional group and standard care with a 1:2 ratio using simple randomisation technique. For the allocation of the participants, a list of all CAPD patients was created in the software of SPSS Version 22 by one pharmacist and then a randomisation sequence was created using this computer-generated list of numbers into both interventional and control groups. Three pharmacists involved in patient enrollment.

Patient did not know which group they are in as this is a single-blinded study.

Research tool

- ESA monitoring card initiative from the MOH Malaysia to properly monitor Hb level in dialysis patients with ESA therapy. Physician updated the latest Hb level and ESA dose on the ESA card for each appointment. ESA card consists of ESA dose titration and monitoring parameter guidelines developed based on KDIGO clinical practice guideline for anaemia in CKD 2012 to assist the physician in adjusting ESA dose and monitoring. Adjustment of ESA dose was based on patient current Hb level, rate of change in Hb concentration, current ESA dose and clinical circumstances [12]. ESA monitoring card is attached as Appendix 1.
- Counselling checklist for ESA injection initiative from MOH Malaysia is intended as a reference document for pharmacist or nursing staff to counsel patients prescribed with ESA. Counselling checklist is attached as Appendix 2.
- Data collection form was used to collect information regarding the patient's social demographic data, medical history, current ESA dose, current medications, laboratory parameters, and medication adherence. We included CAPD patients above 18 years old who attended CAPD clinic, received SC erythropoietin beta injection and been taught on ESA injection technique by CAPD nurse. Excluded patients including who received blood transfusion two weeks before recruitment and within the study period; pregnant patient and cancer patient.

Standard care

The standard care of patients consisted of physician-patient meetings in the CAPD clinic. Patients who are newly prescribed ESA injection referred to CAPD nurse for ESA injection technique related education. Patients collected their monthly ESA injection from the hemodialysis unit and self-injected ESA at home. Patients in the standard care group did not receive intervention from pharmacists.

Intervention

Patients in the intervention group received standard care of physician-patient meetings and pharmacist interventions. Intervention group patients were required to attend hospital at the baseline, three months, and six months during the intervention. Patients' follow-up visits were arranged according to patient-physician appointment to reduce dropout. At the baseline visit, demographic data; current medication; current

ESA dose; laboratory parameters such as Hb level, iron status, serum ferritin, TSAT, and TIBC level were collected. On each follow-up visit, patients were assessed on ESA injection knowledge based on ESA counselling checklist, including its function, dose of injection, side effects, storage, and ESA transport from hospital to home, injection technique and adherence. Patients were required to answer all questions in ESA checklist correctly; any wrong answer given was considered inadequate knowledge. Pharmacists provided counselling and education for patients with inadequate knowledge or wrong injection techniques to improve their knowledge or injection technique. Monitoring of laboratory parameter and ESA dose were performed, and any intervention was spoken to the nephrology physician.

Outcome measures

Primary outcome of the study was Hb level. The target Hb in our setting is 10-12g/dl. Monitoring of Hb level, iron status, serum ferritin, TSAT, TIBC level was performed every 3 months as recommended by Kidney Disease Improving Global Outcome (KDIGO) anaemia guideline for CKD 2012.

Secondary outcome of the study was the adherence to ESA injection post-intervention. Adherence to ESA injection was assessed based on the ESA sticker. The patient was required to detach the sticker from the ESA injection syringe before use and paste it on the CAPD booklet as evidence of use. Pharmacists calculated the number of ESA injections dispensed for the patient last month and the total number of stickers found on the CAPD booklet. The total doses missed was inferred from the sticker count observed from the CAPD booklet. A patient is defined as adhering to ESA injection if the adherence score (Eq.1) is $\geq 90\%$ [13].

$$\text{Adherence score} = \frac{\text{Total doses dispensed} - \text{Total dose missed}}{\text{Total dose dispensed}} \quad (\text{Eq.1})$$

Data analyses

All data were analysed using IBM® Statistical Package for Social Sciences version 22.0 (IBM corp. 2013). Baseline characteristics of both groups were compared using Independent t-test for continuous variables, Person chi-square, and Fisher-exact for categorical variable. Comparison of mean difference in Hb was performed using Independent t-test and Paired t-test. All statistical tests with p-values of <0.05 denote statistical significance.

RESULT

Demographic and Clinical Characteristics

Of the 146 eligible patients, 50 patients were randomised to the intervention group, and 70 patients were randomised into the standard care group. 2 patients dropped out of the study due to deceased. A total of 118 patients completed the study. Figure I. shows the trial flow diagram prepared according to CONSORT guidelines. The average ages were 50.8 (± 14.57) and 49.4 (± 13.69) years in the standard care and interventional groups. Gender was found to be approximately equal, and subjects were predominantly Malay in both groups. Details of patient characteristics are shown in Table I. There was no significant difference in the baseline demographic and clinical characteristics of participants.

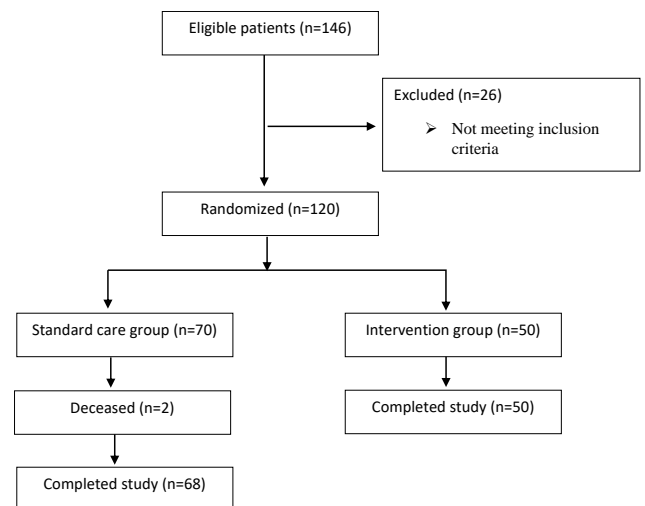


Figure I. Trial flow diagram in accordance with CONSORT guidelines

Table I: Demographic data and clinical characteristics (N=118)

| Characteristics | Standard Care Group (n = 68) | Interventional Group (n=50) | P-Value* |
|--------------------------------------|------------------------------|-----------------------------|----------|
| Age, mean (SD), year | 50.8 (14.5) | 49.4 (13.6) | 0.593 |
| Gender, n (%) | | | |
| Male | 34 (28.8) | 23 (19.6) | 0.404a |
| Female | 34 (28.8) | 27 (22.8) | |
| Ethnicity, n (%) | | | |
| Malay | 68 (57.6) | 49 (41.6) | 0.347b |
| Chinese | 0 | 1 (0.8) | |
| Body weight, mean (SD), kg | 60.9 (13.8) | 60.7 (12.5) | 0.957 |
| Transferrin saturation, mean (SD), % | 30.7 (13.4) | 29.3 (10.3) | 0.541 |

*Independent t-test, ^a Pearson chi-square, ^b Fisher-exact tests were used

Hb level in pre-and post-intervention for standard care and interventional groups

Mean Hb showed significant improvement in both standard care and interventional groups with $p < 0.001$ (Table II). The intervention group had a higher increment in mean Hb (6.7%) than the standard care group (5.9%). However, the mean difference Hb between standard care and interventional group after at least one month of interventions was found to be not significant with 0.59 (± 1.78) and 0.692 (± 1.68) respectively ($p = 0.764$) using Independent T-test (Table III).

Adherence to ESA administration post-intervention for standard care and interventional groups

The intervention group had higher adherence to ESA administration (76%) than the standard care group (66.1%) post-intervention. No significant difference was found between the standard care and intervention group ($p = 0.309$) using Chi-square test (Table IV).

Table II. Mean Hb of pre and post-intervention for standard care and interventional group

| Characteristic | Pre intervention mean Hb (SD), g/dL | Post interventions mean Hb (SD), g/dL | CI | P-Value* |
|------------------------------|-------------------------------------|---------------------------------------|--------------|----------|
| Standard Care Group (n = 68) | 9.84 (± 1.89) | 10.44 (± 1.91) | -1.02, -0.16 | <0.001 |
| Interventional Group (n=50) | 9.74 (± 1.68) | 10.43 (± 1.90) | -1.17, -0.21 | <0.001 |

*Paired t-test was used

Table III. Mean difference Hb for standard care and interventional group

| Characteristic | Mean difference Hb (SD), g/dL | CI | P-Value* |
|------------------------------|-------------------------------|-------------|----------|
| Standard Care Group (n = 68) | 0.594 (± 1.78) | -0.74, 0.54 | 0.764 |
| Interventional Group (n=50) | 0.69 (± 1.68) | -0.73, 0.54 | |

*Independent t-test was used

Table IV. Adherence to ESA administration between both groups

| Characteristic | Yes (n, %) | No (n, %) | P-Value* |
|------------------------------|------------|-----------|----------|
| Standard Care Group (n = 68) | 45 (66.1) | 23 (33.9) | 0.309 |
| Interventional Group (n=50) | 38 (76) | 12 (24) | |

*Chi-square test

DISCUSSION

Severe anaemia (Hb < 9.0g/dl) is associated with increased risks of cardiac complications, such as left ventricular hypertrophy and cardiovascular disease, and low quality of life [14]. Correction of anaemia has been associated with improved health-related quality of life, including physical functioning and fatigue [15]. With the increasing health care cost over the past several years, pharmacists have a critical role in providing the most cost-effective and beneficial pharmaceutical care in anaemia treatment. Available studies reported the benefits and impact of pharmacy services in anaemia management. A study conducted showed that active participation of pharmacists in anaemia management significantly improved mean Hb level [8,16]. Other studies reported that pharmacist education program led to significant Hb improvement. [17,18].

Our study demonstrated that intervention group showed significant improvement in mean Hb, but the mean difference Hb was statistically non-significance against the standard care group. Likewise, previous studies also did not show significant differences in haemoglobin outcome between standard care and pharmacist intervention group [10,18]. The lack of significance was explained by achievement of haemoglobin target was very high in standard group compared with other studies [10]. Study by Mateti et al. reported that the insignificant result was due to both control and intervention group had achieved the optimal Hb level of 10g/dl, and increasing the target Hb above the target range had no benefit [18]. In our study, the insignificant result could be due to lack of blinding in pharmacist activities such as counselling and ESA card, which may increase overall patient care by healthcare providers. Besides, similar physicians who attended patient's follow-up visits in both control and interventional groups may lead to bias. Deficiency of vitamin B12, folic acid, and iron are associated with anaemia [12]. Adherence to oral iron and different dietary intake could be factors affecting haemoglobin level. However, our study lacks data on patient adherence to oral iron and dietary pattern, so a definite conclusion cannot be draw.

ESA injection adherence compliance was a common problem in peritoneal dialysis patients. Peritoneal dialysis patients are generally taught to self-administered SC ESA at home. Two studies showed that adherence rates with self-administered ESA ranged between 45% and 65% (non - adherence defined as less than 90% use of prescribed dose) [13,19]. This low percentage revealed the difficulty of PD patients to adherence with this treatment. In our study, we assessed patient adherence to ESA administration post-intervention. The result showed that the intervention group had a higher percentage of adherence to ESA administration than the standard group; however, there was no significant difference between the groups. Medication teaching emphasising patient adherence is an area in which pharmacists can positively affect patient care.

Educational interventions by pharmacists had significantly improved hemodialysis patients medication knowledge and medication adherence [20,21]. One study reported that pharmacist educational programme consisting of medical and therapeutic information, information on injection device, training of pen, self-injection of the first dose in front of pharmacists resulted in a higher level of adherence and leading to optimal Hb level within 2 months [17]. These strengthen the importance of patient education and medication teaching by pharmacists to improve adherence, achieve patient self-care, and attain therapeutic goals. However, this study has limitations. First, a short duration of the study was a limitation to draw a conclusion about the service's long-term effectiveness or to assess the clinical impact of the service. Besides, this was a single institutional study, and the result may not be generalisable to other practice settings. Future studies with similar design can be conducted at multiple centres to produce more reliable and generalisable results.

CONCLUSION

Pharmacist's interventions, including ESA injection counselling and ESA monitoring card may help in improving Hb level of CAPD patients.

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CONFLICT OF INTEREST

Authors declared no conflict of interest.

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Appendix 1
ESA monitoring card

Erythropoietin Stimulating Agent (ESA) Monitoring Card

Name : Age :
MRN / IC No. : Gender : Male / Female
Date of started ESA :
Date of started CAPD : Counselling : Yes No

| No. of Visit | Date | Hb Level (g/dL) | Dose (unit) | Remark(s)** |
|--------------|------|-----------------|-------------|-------------|
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | | | | |
| 9 | | | | |
| 10 | | | | |

**ADR detected, change in brand etc
Target Hemoglobin Range: 10-11.5 g/dl (subjected to change according to the latest

Appendix 2
COUNSELLING CHECKLIST FOR ERYTHROPOIETIN STIMULATING AGENTS

This checklist is intended as reference document for use by pharmacist and/or nursing staff to counsel EVERY PATIENT who are prescribed with Erythropoietin Stimulating Agents (ESAs). The completed counselling form should be kept in the respective patient file and/or pharmacy counselling folder for future reference.

| NAME: | UNIT: | | | | | | | | | | | | |
|--|---|---|----------|--------|----------|--------|---------|---------|-------|--------|--|--|--|
| | YES | NO | REMARKS | | | | | | | | | | |
| 1. What is EPO & why it is important to you? Erythropoietin is a hormone produced by healthy kidney. It is importance to produce red blood cells. When kidney fail, the production of erythropoietin is reduced. Hence you need to inject erythropoietin to maintain your haemoglobin level between 10-11.5g/dl <i>*Target Hb may be changed according to latest evidence.</i> | | | | | | | | | | | | | |
| 2. What EPO has doctor prescribed for you? The erythropoietin that the doctor has prescribed for you is Dose / frequency/ timing ESAunitstime(s) a week/month. Inject preferably at the same time on the day at the schedule day | | | | | | | | | | | | | |
| 3. Possible/ common side effects of ESA Experiencing side effects from medications is not unusual. Side effects from ESA is generally not serious. The commons one are: - irritation at site of injection - headache - Joint / muscle pain - High blood pressure <i>NOTE: BP cut off point for ESA administration is individualised for each patient. Generally ESA withheld if BP >160/100 mm Hg. Patient has to be informed on their BP cut off point to either withhold or continue ESA at home.</i> | | | | | | | | | | | | | |
| 4. What can you do if you experience side effect that you cannot tolerate? Seek advice from the outpatient department pharmacy or dialysis unit | | | | | | | | | | | | | |
| 5. Storage & transport ESA from hospital to home - Transport of ESA is only allowed in cool box with ice packs - Preferably to return home immediately after you get ESA from pharmacy to facilitate fast storage. - ESA is very sensitive to light and temperature Protect ESA from light Store ESA in refrigerator, do not freeze. Keep in 2-8 degree celcius. Avoid fridge door, and vegetable compartment. Ensure there is proper air circulation around your ESA. | | | | | | | | | | | | | |
| 6. Preparing your ESA before injection Do not take out your ESA from fridge UNLESS it is time for use. If you have accidentally left your ESA outside the fridge, it must be used ASAP before the ESA is damaged. <table border="1" style="width: 100%; margin-left: 20px;"> <thead> <tr> <th>Product</th> <th>Maximum period before damage once out from the fridge</th> </tr> </thead> <tbody> <tr> <td>Recormon</td> <td>3 Days</td> </tr> <tr> <td>Binocrit</td> <td>3 Days</td> </tr> <tr> <td>Mircera</td> <td>1 month</td> </tr> <tr> <td>Eprex</td> <td>7 Days</td> </tr> </tbody> </table> | Product | Maximum period before damage once out from the fridge | Recormon | 3 Days | Binocrit | 3 Days | Mircera | 1 month | Eprex | 7 Days | | | |
| Product | Maximum period before damage once out from the fridge | | | | | | | | | | | | |
| Recormon | 3 Days | | | | | | | | | | | | |
| Binocrit | 3 Days | | | | | | | | | | | | |
| Mircera | 1 month | | | | | | | | | | | | |
| Eprex | 7 Days | | | | | | | | | | | | |
| 7. How to use injection Please refer to section B and C | | | | | | | | | | | | | |

Section B and C : Injection Technique for Recormon and Mircera

| B | INJECTION TECHNIQUE FOR SUBCUTANEOUS RECORMON | Done (✓) |
|-----|--|----------|
| 1. | Remove one syringe and check that the solution is clear, colourless and free from visible particles. | |
| 2. | Allow Recormon to reach room temperature. | |
| 3. | Wash your hand. | |
| 4. | Remove the cap from the syringe. | |
| 5. | Remove one needle from the pack, fix it on the syringe and remove the protective cap from the needle. | |
| 6. | Expel air from the syringe and needle by holding the syringe vertically and gently pressing the plunger upwards. | |
| 7. | Clean the skin at the site of injection using an alcohol wipe. | |
| 8. | Form a skin fold by pinching the skin between thumb and forefinger. | |
| 9. | Insert the needle into the skin fold with a quick, firm action. | |
| 10. | Inject Recormon solution. | |
| 11. | Withdraw the needle quickly and apply pressure over the injection site with a dry, sterile pad. | |
| 12. | Dispose the empty syringe in special wastes container. | |

| C | INJECTION TECHNIQUE FOR SUBCUTANEOUS MIRCIERA | Done (✓) |
|-----|--|----------|
| 1. | Remove one syringe and check that the solution is clear, colourless and free from visible particles. | |
| 2. | Allow Mircera to reach room temperature. | |
| 3. | Wash your hand. | |
| 4. | Remove the cap from the syringe. | |
| 5. | Remove one needle from the pack, fix it on the syringe and remove the protective cap from the needle. | |
| 6. | Expel air from the syringe and needle by holding the syringe vertically and gently pressing the plunger upwards. | |
| 7. | Clean the skin at the site of injection using an alcohol wipe. | |
| 8. | Form a skin fold by pinching the skin between thumb and forefinger. | |
| 9. | Insert the needle into the skin fold with a quick, firm action. | |
| 10. | Inject Mircera solution. | |
| 11. | Withdraw the needle quickly and apply pressure over the injection site with a dry, sterile pad. | |
| 12. | Dispose the empty syringe in special wastes container. | |

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Abstract 001

Development and Evaluation of a Microsphere Loaded Cream Containing Solanum Lycopersicum for Tyrosinase Inhibition

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Introduction: Hyperpigmentation is a common skin disorder caused by excessive melanin synthesis. Hydroquinone, the current gold standard used for the treatment of hyperpigmentation disorders has been reported to cause several adverse effects. Medicated topical formulations are commonly associated with irritation and allergic reactions. Alternatively, botanically-derived agents have gained increased attention in the pursuit of novel effective depigmenting agents with milder side effects. Solanum lycopersicum or tomato has been linked with numerous health benefits and its tyrosinase inhibitory activity has also been reported. However, the current botanical formulations have been associated with ineffectiveness of skin penetration, shorter duration of action, less final quality, and lower depigmenting effects. Controlled drug delivery achieved via microsphere system may help to overcome the obstacles with enhanced stability and efficacy. Hence, a cream formulation incorporating tomato-loaded microspheres, currently unavailable in the market, would be the first and possibly a potential alternative for hyperpigmentation control. **Objective:** The objectives are to formulate tomato microsphere loaded cream and to determine its tyrosinase inhibition activity. **Method:** Double emulsion technique was used for the formulation of microspheres. The microspheres were evaluated for percentage yield, entrapment efficiency, loading capacity, surface morphology and drug-polymer interaction. The drug-loaded microspheres were then incorporated into the water removable cream followed by determination of tyrosinase inhibitory activity. GraphPad Prism was used for the construction of results and determination of IC₅₀. **Result and Discussion:** The 85.27% yield of tomato seed oil-loaded microspheres was prepared with an entrapment efficiency of 65.85% and a loading capacity of 21.95%. The formulated cream had desirable organoleptic characteristics. The mean pH of cream was 5.55 ± 0.09 with comparable spreadability with commercial products. The tyrosinase inhibitory activity of the formulated

cream was statistically significant compared with tomato seed oil (8.32 ± 0.23 mg/mL) and blank cream (10.87 ± 0.31 mg/mL) alone with the lowest IC₅₀ value (26.85 ± 0.24 µg/mL) but comparable to the positive control, kojic acid (1.65 ± 0.50 µg/mL). **Conclusion:** Solanum lycopersicum microsphere loaded cream was successfully formulated with a desirable *in vitro* tyrosinase inhibitory activity, suggesting its potential as an alternative for the treatment of hyperpigmentation disorders.

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Abstract 002

Expectation and Perception of Contract Pharmacists Regarding their Pharmacy Career

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Introduction: Ministry of Health (MOH) Malaysia introduced the contract system for pharmacists to reduce pharmacy graduates waiting period for the training program in government health facilities. Studies have been conducted to assess perception towards the training program in government facilities [1,2] and the overall job satisfaction among pharmacists [3], but little is known about the perception of contract pharmacists following the new policy. **Objective:** To explore contract pharmacists' expectation and perception of their pharmacy career in terms of future career plans and general perception of employability. **Method:** A cross-sectional study was conducted using a validated, self-administered online questionnaire involving contract pharmacists working in government health facilities within Kuala Lumpur and Putrajaya. Data were collected in November and December 2020 and sent through facilities' email. The questionnaire contains 24 main questions that assess career expectation and experience in job search using 5-point Likert-type questions and an open-ended question for

suggestions to improve aspects of their training. **Result and Discussion:** The response rate was 68.8% (n=97). Of the respondents, 92.8% expressed a desire to work with MOH, but only 24.7% were confident that they could obtain a permanent position within MOH, and only 27.8% believed that they could secure any job offer. Among the respondents, 35.1% (n=34) have started looking for alternative employment, but only eight of them managed to secure a job offer. The respondents perceived community pharmacy as the sector that offers the most job opportunities (88.5%). Long-term job security, work environment and opportunities for career development were rated the three most essential factors in choosing their career. Preference to work with the government may be attributed to long-term job security being the most crucial factor in career choice. **Conclusion:** The contract system poses various challenges for the new generation of pharmacists. There was an excess of demand for jobs in the government sector, with many uncertainties in employment opportunities. Early career advice and broader exposure to pharmacy career pathways are essential to broaden their career perspectives and equip them with the necessary skills to adapt and develop new roles to keep up with changing times.

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Abstract 003

An Evaluation on the Practices about the Use of Paracetamol among Parents in Treating their Children in Penang, Malaysia

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Introduction: Paracetamol is a common antipyretic used to treat fever in people of all ages, including children. The widespread availability of paracetamol over the counter has

led to its usage by parents, often without proper consultation with healthcare practitioners, putting children at risk of paracetamol poisoning. **Objective:** This study aims to evaluate the practices of paracetamol use among Malaysian parents in treating their children. **Method:** This was a cross-sectional quantitative structured interview using a questionnaire. Data was collected from a total of 93 parents from Penang, Malaysia, in August 2019. **Result and Discussion:** Most parents were between age 26 to 40 years (67.7%) and had at least two children (74.2%). About 54.2% of parents had children between 4 - 9 years old. The majority of parents (87.1%) had used paracetamol to treat their children, with 77.9% of them using it for fever. Approximately half (53.1%) of the parents used paracetamol when their children's body temperatures were between 37.5°C – 38°C. Syrup (66.1%) and chewable tablets (20.2%) were the most popular forms of paracetamol used to treat children. The parents mostly use paracetamol every 6-hourly (45.7%) and 4-hourly (38.3%). Among the 1 – 3 years old children who used paracetamol syrup, 37.5% of them exceeded the recommended total daily dose. Conversely, 64.7% of the children aged 10 – 12 years who consumed paracetamol syrup were found to have below the recommended total daily dose. **Conclusion:** In conclusion, the practices of paracetamol usage among the parents need to be improved to ensure better treatment outcomes for the children.

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Abstract 004

Antimicrobial Stewardship Integrated Approach: An Outcome Evaluation in Perak (AMSIA Study)

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Introduction: The antimicrobial stewardship (AMS) program has been implemented in most public healthcare facilities in Malaysia to promote judicious antimicrobial usage and minimize antimicrobial resistance. The AMS integrated approach (AMSIA) was implemented by ward pharmacists and the AMS team concurrently at five specialist hospitals in Perak to enhance several AMS initiatives. The initiatives include creating an antibiotic quick reference guide, intravenous-to-oral conversion algorithm, engagements, and continuous medical education (CME) sessions with stakeholders. **Objective:** To evaluate the impact of the AMSIA in terms of clinical outcomes among patients, and the antimicrobial cost savings based on the AMS recommendations provided. **Method:** This is a retrospective evaluation of the AMS database at the study hospitals comparing data between two phases before and after implementing the AMSIA. Data from the AMS review forms were extracted and analyzed. **Result and Discussion:** A total of 544 cases were referred for AMS recommendations during both phases. Of those recommendations, 474 (87.1%) were accepted by the primary team. Most patients (76.7%) were discharged well. Recommendations provided by ward pharmacists were more likely to be accepted than those offered by the AMS team ($p=0.022$). There was no association between 30-day infection-related mortality ($p>0.95$) with acceptance of those recommendations. However, accepting the recommendations contributed to a shorter duration of antimicrobial therapy ($p=0.001$), a shorter length of hospitalization ($p<0.001$), and a total antimicrobial cost saving of RM427.28, while rejection resulted in a cost increment of RM2122.32 over the study period ($p<0.001$). There were no differences in terms of the rate of acceptance of the recommendations as well as the clinical outcomes and

cost savings between the study phases. **Conclusion:** AMS recommendations resulted in cost savings, shorter hospitalizations, and duration of antimicrobial therapy without compromising patients' survival. Ward pharmacists played equally important roles as the AMS team in the AMS program.

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Abstract 005

Impact of an Antibiotic Stewardship Program on the Use of Carbapenem in a Malaysian Tertiary Hospital

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Introduction: Antimicrobial Stewardship (AMS) program has been advocated to promote the rational use of antibiotic prescribing. However, the outcome of AMS in promoting the judicious use of carbapenem and minimising resistance is not widely studied in Malaysia. **Objective:** To investigate the types of interventions made by the AMS team, its acceptance, and the impact on carbapenem consumption and carbapenem-resistant Enterobacteriaceae (CRE) pattern. **Method:** This was a retrospective study conducted in adult medical wards of Kuala Lumpur General Hospital (HKL), where data were extracted from AMS form of patients reviewed by the HKL AMS team from January to December 2016. **Result and Discussion:** The mean (SD) age of 169 patients included in this study was 59.2 (10.6) years, where almost half were male. Ertapenem was the most prescribed carbapenem (44.4%), followed by meropenem (34.3%) and imipenem/cilastatin (21.3%). Despite only 32% being empirically initiated, there were 68 cases (40.2%) classified as unjustified by the Antimicrobial Stewardship (AMS) team. Out of these, 39 cases (57%) were recommended to be discontinued, 25 cases (37%) to be de-escalated and 4 cases (6%) for changing/escalation. Acceptance rate was reported

to be around 73.5% (50 out of 68 cases). Post one year of AMS implementation, carbapenem consumption shown by defined daily dose/1000 inpatient bed-days reduced significantly (33.7%; $p < 0.0001$). Similarly, a notable decrease in CRE cases (33.3%; $p < 0.0001$) was seen post one year of AMS initiation. **Conclusion:** In conclusion, AMS-guided interventions were shown to be a useful strategy to reduce non-judicious use of carbapenem in a tertiary hospital. It was also able to demonstrate a reduction in carbapenem consumption as well as CRE rates in the medical wards. Therefore, future long-term studies are required to assess long-term effectiveness of AMS.

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Abstract 006

Factors Affecting Adoption of Electronic Medical Record System at Private Hospitals in Klang Valley

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Introduction: Electronic Medical Record (EMR) is one of the revolutionary digital technologies that has been able to produce a system for seamless documentation workflow of patients and this revolution has brought parallel developments that have not only structured the healthcare system but also provided better means of communication. The continuous determination of EMR also depends on the adoption and support from the core user of this system. The aim of the study is to explore the main factors that encourage the adoption of EMR systems among the medical specialists in private hospitals by using The Unified Theory of Acceptance and Use of Technology (UTAUT) model. **Method:** A cross-sectional survey was used to collect data from 95 respondents by using a quota sampling. The study used partial least square (PLS) method; a statistical analysis technique based on the structural equation modelling (SEM) to analyse the collected data. **Result:** There was a positive

and moderate relationship between performance expectancy with behavioural intention ($\beta = 0.581$, $T = 6.024$). The factor of social influences ($\beta = 0.106$, $T = 1.267$) was not significant while effort expectancy ($\beta = 0.174$, $T = 1.633$) represented a low significance and weak relationship. The relationship between facilitating condition and use behaviour was moderate but of significant impact ($\beta = 0.392$, $T = 4.128$). Behavioural intention influenced indicated ($\beta = 0.507$, $T = 5.223$) a moderate effect of intention toward the adoption of EMR. **Conclusion:** The findings suggest that healthcare providers adopt EMR systems and improve the system via customization based on the needs or make it more user friendly. The healthcare provider should consider technical sufficiency and training to facilitate the use of the EMR system.

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Abstract 007

Patterns of Prescription Medicines' Sales through E-Marketplace in Malaysia and Associating Factors

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Introduction: Self-diagnose and obtaining various health products via the internet were extremely dangerous practices as it may increase the risks of patient injury or even death. **Objective:** This study aims to explore the patterns of prescription medicines' sales through e-marketplace (specifically: Shopee) in Malaysia as well as the associated factors. **Method:** Cross-sectional study secondary data of 983 Advertisement Screening Reports (reported from 1st January 2020 – 30th June 2020) in Johor State were collected. Descriptive statistics using frequency, percentages and/ bar charts using Microsoft Excel 2013 were used to report the patterns of prescription medicines' sales through e-marketplace (specifically: Shopee) in Malaysia based on types of prescription medicines that being advertised,

registration status of prescription medicine that being advertised as well as frequently violated Malaysia's law related to prescription medicine by sellers in Shopee. Factors associated were explored by logistic regressions using IBM SPSS Version 22 via Simple (Enter Method) and Multiple (Backward Elimination (LR) Method). **Result and Discussion:** 796 out of 852 (93.4%) prescription medicines' samples were not registered with the Drug Control Authority, Malaysia's Health Ministry. Hormones (62.6%, while sex hormones which were anabolic steroids showed the highest frequency; 58.3%) were the highest prescription medicines sold through the e-marketplace (specifically: Shopee) in Malaysia, while antibiotics, clomiphene (fertility drug), sibutramine (slimming pill) and prostaglandins and its synthetic derivatives (abortion pill) denote 4.8%, 2.2%, 1.8%, 0.4% respectively. The unregistered prescription medicines were found to be the highest to violate Section 13(a) of Poison Act 1952 which include 766 samples. Multiple logistic regression tests indicate that violation of Section 13 (a) of Poison Act 1952 (95%CI; 0.002, 0.058%; $p=0.000$), Regulation 7(1)(a) of Control of Drug and Cosmetic Regulations 1984 (95%CI; 194.694, 2726.963%; $p=0.000$) and Section 4B of Malaysia Advertisement and Sales Act 1956 (95%CI; 0.014, 0.260%; $p=0.000$) were the possible associated factors registration status prescription medicines' sales through e-marketplace. **Conclusion:** The findings in this study may give a brief idea for improving the current practice in order to curb the freely illegal prescription medicines' sales through e-marketplace (specifically: Shopee) without the supervision of professionals.

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Abstract 008

Medication Administration via Enteral Feeding Tubes: A Survey of Nurses' Knowledge and Practice

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Introduction: Enteral feeding is a type of nutritional support for critically ill patients who are unable to tolerate oral feeding. It is vital to ensure that nurses practise proper administration technique via enteral feeding tubes (EFT) to ensure that medication can be delivered safely and effectively. **Objective:** This study aimed to assess knowledge and practice of nurses on medication administration through EFT. Association between baseline characteristics and knowledge was also being explored. **Method:** This was a cross-sectional, self-administered, content-validated, pre-tested questionnaire survey involving all nurses who worked in ward setting at Hospital Queen Elizabeth II from August to December 2020. **Result and Discussion:** A total of 409 questionnaires were sent out with 252 responses received. Majority of respondents were female ($n=240$, 95.6%) with median working experience of 88 months (interquartile range of 44 months). Most nurses knew that the immediate released dosage forms ($n=237$, 94.4%) should be crushed and administered through EFT, but not the sublingual nitroglycerin (GTN) tablets ($n=232$, 92.8%) and nystatin suspension ($n=212$, 85.1%). About half of the nurses responded incorrectly on the EFT administration of sustained-release medications ($n=152$, 60.6%), soft gelatin capsules ($n=111$, 44.4%) and hard gelatin capsules ($n=102$, 40.6%). In terms of practice, majority of the nurses would routinely flush the EFT before ($n=226$, 90.4%) and after ($n=245$, 98.8%) the administration of medications. Only a small proportion of nurses ($n=93$, 37.5%) demonstrated good practice where they administer all medications separately all the time. It was also worth noting that nurses from the intensive care setting had more correct responses on some of the knowledge-based questions when compared to those from general ward setting ($p<0.05$). **Conclusion:** Knowledge gap and inconsistent practice may lead to suboptimal delivery of medication and potentially compromise patient outcomes. Hence, continuous educational programs should be carried out to ensure safe and effective drug administration through EFT.

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Abstract 009

Factors Associated with Oral Anti-Diabetic Drugs Preventable Returned Medications Among Type II Diabetes Mellitus Patients

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Introduction: In Malaysia, Type II Diabetes Mellitus (T2DM) is estimated to have a 31.3% prevalence rate among the adults by year 2025. Oral anti-diabetic drugs (OADs) are used to lower blood glucose level in T2DM treatment. In our setting, OADs was recorded to have the highest returned medication proportion (51.0%) as compared to other drugs. Substantial proportion of returned OADs has raised our concern in patients' medication taking behavior or drug related problems at home and their glycemic control. **Objective:** This study aimed to investigate the factors associated with preventable OADs returned to pharmacy and to identify reasons for the return. **Method:** This was a cross-sectional study conducted at public health clinics in Klang district over a 4-week period. Patients with active prescriptions containing OADs were recruited using systematic sampling method whereby they have given their consent prior to the study and subsequently answered a validated questionnaire. From the unused OADs with potential return, patients are grouped into case (with return) and control (without return). The reasons for OADs return divided into non-preventable (e.g., change to other treatments) and preventable (e.g., non-compliance). Patients with non-preventable reasons for return were excluded due to no interventions by pharmacists. Computed data were analyzed using descriptive statistics and multiple logistic regressions. **Result:** Out of 168 patients interviewed, 43.4% (n=73) patients had preventable return, 13.7% (n=23) patients had non-preventable return and 42.9% (n=72) patients of the control group had no return. The main reasons for returning were non-compliance (76.7%) and difficulty in following instructions (21.9%). OADs return was significantly associated with the patient's educational level (OR 0.038; p-value 5.472 with 95% confidence interval [1.097-27.296]) where 63.7% of them from lower education background. Factors such as age, gender, T2DM diagnosis years, polypharmacy, OADs pill burden and traditional medicine taking showed no significant association with OADs return. **Conclusion:** Patient education level is a significant factor in preventable OADs return. By instilling

better knowledge on the importance of patients' medication taking, patients will be self-empowered to manage their medication and disease better. Future study is recommended to assess the possible interventions such as providing simplified education materials and utilizing patient teach-back method to improve patient's medication knowledge and eventually, improving compliance and preventing unnecessary medication return.

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Abstract 011

Perception and Attitude of Malaysian Community Pharmacists Towards the Implementation of Telepharmacy

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Introduction: Telepharmacy refers to the delivery of pharmaceutical care through telecommunications to patients in locations where they may not have direct contact with a pharmacist [1]. The role of community pharmacist has expanded during the COVID-19 pandemic to provide pharmaceutical care services remotely through telepharmacy [2]. This study aimed to assess Malaysian community pharmacists' perception and attitude towards implementing telepharmacy. **Method:** This cross-sectional study was carried out using an online questionnaire. 217 community pharmacists in Klang Valley were recruited through the convenience sampling method. 5-point Likert scales were used to evaluate the respondent's perceived benefits, perceived barriers, and attitude towards the implementation of telepharmacy. **Result:** 37.8% of the respondents showed positive perception while 53.9% are moderately positive towards the benefits of telepharmacy. Age (p=0.019) and familiarity with the term 'telepharmacy' (p=0.014) was shown to influence the perceived benefits on implementation of telepharmacy. On the other hand, only 8.3% of the community pharmacists perceived low barriers in telepharmacy implementation. Community pharmacists who have a Master's qualification have lower perceived barriers of implementing telepharmacy, as compared to those with a Bachelor's qualification (p=0.032). This may imply that

higher education level may lead to a broader view and understanding of the barriers faced in implementing telepharmacy. Overall, the respondents showed a positive attitude towards the implementation of telepharmacy. Younger community pharmacists were more likely to have a positive attitude towards the implementation of telepharmacy ($p < 0.001$), which is consistent with the study done by Biruk and Abetu, where 56% of healthcare provider within the age group of 20-29 showed positive attitude towards telemedicine [3]. Community pharmacists who were familiar with the term 'telepharmacy' and have more years of working experience were more likely to have a positive attitude towards the implementation of telepharmacy ($p < 0.001$). **Conclusion:** In conclusion, most Malaysian community pharmacists practicing in the urban area have shown positive perception towards the benefits of telepharmacy, and overall positive attitude towards its implementation. Nevertheless, the perceived barriers towards its implementation are high. A separate telemedicine education or training may be useful to promote the development of telemedicine to all the pharmacists [4].

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Abstract 012

Knowledge, Attitude and Practice of Malaysian Private Hospital Pharmacists on Medication Review Service

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Background: Medication review is emerging as one of the vital components of medication management to prevent medicine-related problems [1]. Studies have demonstrated a high prevalence of potentially inappropriate medication use in private aged care facilities [2]. Hence, there is a strong need for medication review in the private healthcare system in Malaysia to ensure pharmaceutical safety and effectiveness. This study aimed to determine the knowledge, attitude, and practice of private hospital pharmacists on

medication review service in Malaysia. **Method:** This cross-sectional study was carried out from October to November 2020 using an online questionnaire. Private hospital pharmacists in Malaysia were invited to participate in a validated 36-items questionnaire. Descriptive statistics, Spearman's Rank Order Correlation test, Mann-Whitney U test and Kruskal-Wallis H test were performed to analyze the data. **Result:** Survey questionnaires were completed by 104 out of 226 private hospital pharmacists, giving a response rate of 46.0%. From the total number of responses obtained, 80 pharmacists (76.9%) presented with a high level of knowledge on medication review, while 92 pharmacists (88.5%) had a positive attitude. Approximately two-third ($n = 68$, 65.4%) are providing medication review in the pharmacy, whereas 45 of them (43.3%) did not obtain patient's medication history at the time of admission or as early as possible. Besides, only 69 of the participants (66.3%) reconciled patient's medication with the prescribed medicines, and less than half of the respondents ($n = 47$, 45.2%) performed medication chart review throughout the patient's admission. Factors associated significantly with practice of medication review include age ($p = 0.010$) and years of experience as a private hospital pharmacist ($p = 0.016$). The knowledge on medication review had a statistically significant moderate positive correlation with attitude regarding medication review ($p < 0.001$). Three major perceived challenges of implementing medication review were lack of time (82.7%), insufficient training (79.8%) and lack of manpower (60.6%). **Conclusion:** Private hospital pharmacists in Malaysia have a high level of knowledge, a positive attitude, and a fair practice regarding medication review service. However, several challenges such as lack of time, insufficient training and lack of manpower might obstruct the practice of medication review in private hospitals.

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Abstract 013

Prevalence of Nosocomial Infections in Pediatrics High Dependency Unit and Neonatal Intensive Care Unit Patients, their Bacteriological Profile and Antimicrobial Susceptibility Pattern in Tengku Ampuan Rahimah Hospital: A Retrospective Observational Study

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Introduction: Nosocomial infections (NIs) represent serious public health concern worldwide, and it is difficult to control especially in developing countries, due to financial constraints. The identification of pathogenic bacteria patterns and resistance trends in a facility is useful as a guide for the physician in choosing proper empirical antibiotic therapy for patients, and this is even more important in pediatric populations. **Objective:** To identify common pathogens causing NIs in Neonatal Intensive Care Unit (NICU) and Pediatrics High Dependency Unit (PHDU) HTAR, and the susceptibility and resistance patterns of these pathogens. **Method:** Single center study was carried out from January 2018 until June 2020 which includes all neonates aged 72 hours of life and pediatrics that showed positive cultures who have stayed in the facility for more than 48 hours. The data was collected from the Patients' Notification of Health Care Acquired Infection form and analyzed using SPSS version 22. **Result:** Number of NIs in NICU were 33 (2018), 36 (2019) and 9 cases (2020) while NIs in PHDU were 3 (2018), 5 (2019) and 0 (2020). Eye infection was the most common type of NIs in the NICU for the year 2018 (39.4%), 2019 (44.4%) and 2020 (55.6%). In PHDU, the most common type of NIs were respiratory tract infections, 66.7% (2018) and blood-related infections, 80.0% (2019). 'Coagulase-negative staphylococci (CONs), *P. Aeruginosa* and ESBL *Klebsiella* were found to be the most common organisms isolated in NICU, with 24.2%, 27.8% and 27.8% cases in the year 2018, 2019 and 2020, respectively. *P. Aeruginosa* was the most common isolates in 2018 (66.7%) and *Staph. Aureus* (60%) in 2019 for patients in PHDU. In NICU, CONs was susceptible to chloramphenicol and resistant toward

erythromycin; *P. Aeruginosa* was susceptible to gentamicin and ceftazidime but resistant toward imipenem. ESBL *Klebsiella* was susceptible to gentamicin but resistant to ampicillin. The resistance and susceptibility patterns were unable to be established for PHDU cases. **Conclusion:** Common organisms causing NIs in NICU HTAR are CONs, *P. Aeruginosa* and ESBL *Klebsiella*. This information will allow a more targeted choice of empirical antibiotics to eliminate these potential bacteria causing NI in the NICU.

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Abstract 014

Formulation and Evaluation of Solid Lipid Nanoparticles Containing *Kappaphycus alvarezii* Extract in A Cosmetic Gel

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Introduction: Marine algal extracts have been used in the formulation of cosmetics for years. In this study, the chloroform, methanol, and water extracts of marine algal were analyzed for their antibacterial and antifungal actions. The extract with maximum antimicrobial activity was selected for the preparation of Solid Lipid Nanoparticles (SLNs). The prepared nanoparticles were suspended in a cosmetic gel. **Objective:** To formulate and evaluate the cosmetic gel containing SLNs of *Kappaphycus alvarezii* (KA) chloroform extract to localize the extract topically for a longer duration to exert its antimicrobial properties. **Method:** Disc-diffusion agar plate method was used to evaluate the antimicrobial activity towards *Escherichia coli* (Gram-negative), *Staphylococcus aureus* (Gram-positive) and *Candida albicans* (Fungi). The SLNs were prepared using film hydration technique with ultrasonication. The dried SLNs were evaluated for its physical characteristics, Zeta potential, and the duration taken to release the

encapsulated extract for the antimicrobial activity. Carbopol and HPMC were chosen as the gelling agent after compatibility studies with nanoparticle dispersions [1]. The formulated gel was analyzed for its pH, visual appearance, and in-vitro drug release. **Result and Discussion:** By comparing the zone of inhibition, chloroform extract of KA (120 µg) showed maximum antimicrobial activity than methanol and aqueous extracts. The SLNs prepared using chloroform extract showed a smaller cloudy and blurry zone of inhibition instead of a clear zone of inhibition. This result was due to the low diffusion of encapsulated drugs through the outer lipid layer of SLNs. SLNs showed a Zeta potential ranging between -11.0 to -37.4 mV. The formulated gel containing SLNs of chloroform extract of KA had an average pH value of 5.37, which was suitable to be used on human skin [2]. The maximum drug release was 60.28% over 5 hours. **Conclusion:** In this study, algal extracts were successfully encapsulated within the SLNs, and when applied topically, the SLNs can reside on the surface of the skin for localized action for a prolonged duration. The Zeta potential obtained for the SLNs was approximately within the limit of -30 mV that yields a formulation with reasonably good physical stability [3].

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Abstract 015

Pharmacist-assisted Transition of Care versus Standard of Care towards Effect on Healthcare Resource Utilization among Patients from Medical Wards

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Introduction: Suboptimal patient care transition upon discharge may potentially increase subsequent healthcare system utilization. Preserving the resources from the predictable overwhelmed healthcare system use under COVID-19 landscape is important. The pharmacist-assisted transition of care is a transformational service approach to support patient care continuum after discharge before the

next healthcare facility visit. **Objective:** This study aimed to compare the effect of pharmacist-assisted transition of care versus standard of care towards healthcare resource utilization among patients from medical wards. **Method:** A cluster randomized controlled study was conducted among medical ward patients in a Malaysian secondary care public hospital from July 2019 to December 2019. Consented patients were stratified into two clusters and randomized to an intervention or control group. The sample size was estimated by using the two-proportions method. The intervention group received pharmacist-assisted discharge medication reconciliation, bedside discharge medication delivery with counselling and a timely post-discharge phone call. The control group followed the standard discharge process with medication collection at the ambulatory pharmacy without a post-discharge phone call. Study endpoints included pharmacy first refill persistency, resolution rate on unintended discharge medication discrepancies with associated medication cost-savings and 30-days all-cause rehospitalization. The study endpoints were compared using the Chi-square test, Mann-Whitney U test or Kaplan Maier curve, where appropriate. **Result and Discussion:** A total of 168 patients with 84 patients in each arm was recruited. The intervention resulted in a higher pharmacy first refill persistency (70.2% versus 50.0%, $p < 0.05$), indicating a lower subsequent unscheduled pharmacy refill rate. Under the intervention, a consistent rate of resolution from unintended medication discrepancies (100.0%, IQR 0 versus 100.0%, IQR 67; $p < 0.05$) was demonstrated that corresponded to medication cost-savings of RM6.80 per prescription over control group. Unplanned rehospitalization was not significantly different between the groups but towards a trend of 10% reduction after the intervention. **Conclusion:** Pharmacist-assisted transition of care demonstrated a promising effect towards reducing the healthcare resource use compared to standard care. Future studies to explore its implementation across institutions is warranted to facilitate service expansion, particularly in the post-pandemic era.

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Abstract 016

Awareness, Expectation and Satisfaction towards Ward Pharmacy Services among Patients in Medical Wards: A Multi-Centre Study in Perak

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Introduction: Patients' awareness and satisfaction towards ward pharmacy services may influence perceptions towards effectiveness and safety of drugs. This subsequently affects their medication adherence and clinical outcome [1]. **Objective:** To evaluate awareness, expectation, and satisfaction of ward pharmacy services among patients in medical wards and determine their association with demographic characteristics. **Method:** This was a cross-sectional study using a self-administered questionnaire. The study was conducted in the medical wards of fourteen Perak state public hospitals from September-October 2020. Inpatients aged ≥ 18 years old eligible for ward pharmacy services were included. The questionnaire consist of four domains: demographic characteristics, awareness, expectation and satisfaction towards ward pharmacy services. The awareness, expectation and satisfaction were evaluated using a 5-point Likert scale. A pilot study was conducted to establish the reliability of the questionnaire (Cronbach alpha > 0.7). **Result and Discussion:** 467 patients agreed to participate (response rate=83.8%), but only 441 were included. The mean age of the patients was 54.9 years. Majority was male (56.2%), Malay (77.3%), with secondary education (62.9%), rural residents (57.1%) and reported good medication adherence (61.6%). The mean awareness score was 49.6 out of 60 [2]. Patients were less aware of drug-drug interaction (3.85 ± 1.15) and proper medication storage (3.98 ± 1.06). Elderly patients ($\beta = -2.82$, $P < 0.001$) obtained lower awareness scores. Patients with tertiary education ($\beta = 3.87$, $P = 0.001$), rural residents ($\beta = 3.65$, $P < 0.001$) and with good

medication adherence ($\beta = 2.55$, $P = 0.002$) had higher awareness scores. The mean expectation score was 44.0 out of 50. The patient had a higher expectation of encountering a polite ward pharmacist (4.51 ± 0.56). Patients with tertiary education ($\beta = 1.86$, $P = 0.024$), rural residents ($\beta = 1.79$, $P = 0.001$) and with good medication adherence ($\beta = 1.48$, $P = 0.006$) demonstrated higher expectation. The mean satisfaction score was 43.6 out of 50. The patients had high satisfaction in the language used (4.45 ± 0.57) and level of knowledge demonstrated (4.41 ± 0.62) by the ward pharmacists. Patients with tertiary education ($\beta = 2.16$, $P = 0.009$), rural residents ($\beta = 1.82$, $P = 0.001$) and with good adherence ($\beta = 1.44$, $P = 0.009$) towards medication demonstrated higher satisfaction, while elderly patients ($\beta = -1.17$, $P = 0.031$) had lower satisfaction towards ward pharmacy services. **Conclusion:** Patients demonstrated good awareness, expectation, and satisfaction towards ward pharmacy services in Perak state public hospitals.

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Abstract 018

Exploring Barriers to Retention in Methadone Maintenance Therapy among Opioid Dependent Clients in Klang Health Clinics: A Qualitative Study

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Introduction: Methadone maintenance therapy (MMT) was initiated in Malaysia back in 2005 as part of the national Harm Reduction strategy. Despite proven benefits of methadone in improving client's quality of life, issues such as non adherence and poor therapy retention rates remained as perturbing "mysteries" at Klang health care settings. **Objective:** This study was designed in unearthing client's perception of MMT and in identifying a confluence of multi-dimensional barriers faced by MMT clients leading to therapy defaults and proposed mitigation strategies. **Methods:** Heuristic qualitative mode using a transcendental phenomenological approach was selected. Data collection

through audio taped, face to face in depth interviews (IDIs) in adherence to the COREQ-32 item checklist was carried out between November 2019 to January 2020 at three primary health care clinics (Pandamaran, Bandar Botanik, Bukit Kuda) with existing MMT services. Informational saturation of salient themes was achieved through 24 participants (10 clients & 14 health care professionals) during the six stages of thematic analysis. **Results & Discussion:** 3 major themes and 25 subthemes significantly emerged as study findings. Initial theme on T1 : Perception towards methadone maintenance therapy (MMT) displayed constructive benefits in the context of client's health status, enhanced social functioning within a benevolent health care institution. Second theme vis-à-vis T2 : Drivers to therapy non-adherence were most commonly quoted from the client's domain in adherence to the theory of planned behaviour (TPB). Intrapersonal devoid of client's insights on the significance of methadone, worsened by the nature of addiction (lepas rindu and sulam menyulam) lead to one's diminished self efficacy. Gaps due to volatile employment status, aggravated by dysfunctional dynamics in their social support systems and exposure to unshielded public opprobrium were equally reiterated. Additionally, patients subjected to poorly regimented methadone doses with risks of co-infection morbidities faced superior strains in therapy continuation. Porous provider-client engagements with limitations to MMT service flexibility, internal staff stigmatisation and interference from private methadone sectors (new emergent subtheme) were justified. Robust target-oriented T3: Mitigation Strategies to Improve Methadone Therapy Outcomes were suggested in compliance with the social ecological model of nested intervention planning. **Conclusion:** Implementation of client centred correctional mechanisms are imperative in addressing the shift in drugs addiction paradigm from traditional heroin agents to a myriad of stimulant types and new psychoactive substances, whilst sustaining the noble role of methadone in the community.

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Abstract 019

Exploring Local Challenges and Solution for Progress in Medication Supply through Ubat Melalui Pos Services during Nationwide Movement Control Order

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Introduction: Ubat Melalui Pos (UMP) is one of the value-added services (VAS) majorly used during nationwide MCO to reduce patient's physical engagement at the local health care facilities. **Objective:** This study is aimed at identifying local challenges and solutions for progress in medication supply through UMP services during nationwide MCO in population dense Klang city. **Methods:** Retrospective cross-sectional study covering the health clinics in Klang district was conducted from 18th March 2020 to 12th May 2020. Participants were conveniently sampled based on their online requests for UMP services through customised Google sheet filling. A total of 403 participants were recruited. Inclusive criteria for UMP were stable patients having at least one tablet medication on their valid prescriptions. Patients on insulin, inhalers and less postage friendly medications were excluded from the study. **Results & Discussion:** Demographically from the active pool of 403 UMP requests received, (n=265, 65.8%) of them were from female patients. Common challenges were mainly technical strains with (n=41, 10.17%) due to incomplete prescription attachment, (n=38, 9.43%) with expired prescription and (n=33, 8.19%) UMP requests for less postage friendly medication. Geographically, most UMP requests were from urbanised clinics in comparison to suburban counterparts. Ground breaking analysis discovered that most applications of client's UMP were performed by their inner social circle, in comparison to (n=33, 8.19%) UMP requests successfully delivered by the patients themselves. Robust approaches are required in improving primary care UMP services within our Klang vicinity. Acts in strengthening client's awareness with regards to UMP, in addition to inculcating positive familial support in medication seeking behaviours of vulnerable geriatrics are necessary. Concerted health care teleconsultation for stabilised UMP clients, followed by vigorous health promotion campaigns through dignified

social representatives (DUTA Kenali Ubat Anda) are encouraged. Additionally, introduction to subsidised UMP, innovative Pharmacy Value Added Services (VAS) and training of trainers (TOT) are pivotal health promotion efforts in sustaining medication accessibility and availability at times of unprecedented crisis. **Conclusion:** UMP services are indeed beneficial in the context of prompt, efficient and cost effective mechanisms of medication supply. A handful of local challenges centred towards client's knowledge, attitude and practice to UMP requests are modifiable through timely public health education towards the community.

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Abstract 021

Pre and Post Medical Deployment Experiences of Military Healthcare Professionals

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Introduction: Military field hospitals provide crucial medical service for injured soldiers on the battlefield. Although war no longer becomes the primary displacement of the human population, natural and man-made disasters take place. Inherited from the battlefield, military field hospitals currently continue to serve the disaster's victims and refugees. The healthcare professionals served in military field hospitals face numerous challenges during field operation especially for the first timers. By sharing their previous experiences perhaps, it will help military and other organizations for conducting medical deployment. **Objective:** This study is conducted to determine the pre and post medical deployment experiences of military healthcare professionals. **Method:** Semi-structured interviews were conducted with healthcare professionals who served in various field hospital deployments. Purposive and snowball sampling were employed to ensure a diverse group of

informants. The interviews are audio-recorded, transcribed verbatim, and data analyzed using thematic analysis. Data collection, coding, and interpretation were carried out until the saturation point was reached. **Result and Discussion:** Twenty-one respondents from different demographic characteristics were recruited. Seven major themes were identified. Four themes emerged for pre deployment experiences such as operation preparation, personal preparation (mental and family readiness), preventive medicine (vaccination and medical check-up), and logistic preparation. Meanwhile, three themes emerged for post medical deployment experiences such as operation withdrawal, preventive medicine (mental and physical check-up), and logistic withdrawal. During the medical deployment, challenges include harsh environment, extreme weather, different cultural and tasteless food which require their sacrifices, mental strength and physical endurance in order to accomplish the mission. **Conclusion:** Based on healthcare professionals' experience, four things needed to be done before a mission, namely preventive medicine, operation, personal and logistic preparations. Meanwhile, three things needed to be done after a mission, namely preventive medicine, operation and logistic withdrawal. By understanding the experience before and after a mission, organisations may prepare more efficiently and improve the medical service in the future deployment.

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Abstract 022

Factors Associated with Non-adherence to Medication among Type II Diabetes Mellitus Patients in A Tertiary Hospital in Kelantan, Malaysia

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Introduction: It is estimated that around the globe, 40% to 50% of type II diabetes mellitus (T2DM) patients are not adherent to their medications. This is alarming as non-

adherence can lead to worsening of health outcomes as well as unnecessary cost burden to the healthcare system. **Objectives:** The aim of the study is to determine the prevalence of non-adherence to medication and its associated factors among T2DM patients treated in Raja Perempuan Zainab II Hospital (HRPZ II), Kelantan. **Method:** A cross-sectional survey was carried out among T2DM patients using convenience sampling at the outpatient pharmacy from November 2018 to March 2019. A minimum sample size of 189 subjects was estimated using a single mean formula. Medication Compliance Questionnaire (MCQ), a self-administered validated instrument consisting of seven items, was given to eligible patients to assess the level of medication adherence. Those with a score of less than 27 out of 28 were considered non-adherent. All data were gathered and analyzed using IBM SPSS Statistics for Windows version 25.0. **Results and Discussion:** A total of 200 patients were recruited and they were mostly between the age of 40 to 60 years old. The mean (SD) score for MCQ was 26.0 (1.6) with more than half non-adherent (55.0%, n=110). It was noted that the common reason for non-adherence was forgetfulness with mean (SD) score of 3.35 (0.69). In the multiple logistic regression model, non-adherence was found to be associated with marital status [AOR 4.50; 95% CI: 1.95-10.41, $p < 0.001$], financial income [AOR 0.37; 95% CI: 0.19-0.73, $p=0.004$] and types of diabetes medications [AOR 0.23; 95% CI: 0.12-0.44, $p < 0.001$] which were consistent with previous findings. **Conclusion:** The prevalence of non-adherence to medication among T2DM patients was high in HRPZ II. It was observed that patients who were married, had a low salary and were prescribed with insulin were more likely to become non-adherent. Future intervention targeting these subgroups should be designed within the facility to improve adherence.

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Abstract 025

Diabetes-Related Quality of Life and its Determinants: A Single Centre Analysis

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Introduction: Type 2 diabetes mellitus (T2DM) is a devastating chronic disease which if uncontrolled, often leads to other serious health conditions. The debilitating consequences such as retinopathy and nephropathy can significantly impact their quality of life (QoL). **Objective:** The study was conducted to measure diabetes-related QoL and identify its determinants among T2DM patients attending Raja Perempuan Zainab II Hospital (HRPZ II), Kelantan. **Method:** In this cross-sectional study, a total of 200 adult T2DM patients were recruited through convenience sampling at the outpatient pharmacy from November 2018 to March 2019. Then, the revised version of Diabetes Quality of Life (DQOL) instrument containing 13 items in Malay language was self-administered by eligible respondents. A higher average score indicated a poorer QoL with the possible range of score was between 13 to 65. Statistical Package for the Social Sciences (SPSS) software version 25.0 for Windows was used to perform multiple linear regression. **Result and Discussion:** The majority of T2DM patients were between the age of 40 to 60 years old. The mean (SD) score for the overall revised DQOL was 25.5 (8.9) while each domain of "satisfaction", "impact" and "worry" had mean (SD) scores of 12.0 (5.0), 7.7 (3.4) and 5.9 (2.7), respectively. Stepwise regression model which accounted for 40% of the variability in QoL, showed that a higher DQOL score was found to be associated with older age [β : -4.93 (95% CI: -7.18, -2.67), $p < 0.001$], female gender [β : 4.69 (95% CI: 2.62, 6.77), $p < 0.001$], married status [β : -8.34 (95% CI: -10.78, -5.89), $p < 0.001$] and shorter disease duration [β : -4.85 (95% CI: -7.03, -2.67), $p < 0.001$]. All four variables were commonly reported to influence QoL in previous literature. Interestingly, the current study observed a contradiction to the previous finding whereby older patients in the current study had better QoL. **Conclusion:** The T2DM patients in HRPZ II showed satisfactory diabetes-related QoL. It seemed that the disease did affect their QoL but not to a great extent. More attention should be paid to male, single patients of working age and diagnosed with T2DM for over 10 years who are more likely to have poorer QoL score.

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Abstract 028

Carers' Perspectives on Home Medication Review conducted by Medical Outreach Team of a Hospital in Malaysia

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Introduction: Home Medication Review (HMR) is a continuation of patient care from health facilities to their home to assess patients' pharmacotherapy by a multidisciplinary team. Bedridden patients are the leading group receiving this service. To improve the provision of HMR, we need to understand carers' viewpoints of the current service. **Objective:** To explore the carers' perspectives of HMR conducted by the medical outreach team (MOT) of a Malaysian hospital. **Method:** A qualitative study was conducted among carers involved in the HMR programme for more than six months. Four themes identified: understanding of the services, perceived benefits, difficulties faced and suggestions for improvement. Carers are chosen as respondents as patients have impaired cognitive function or cannot communicate/cooperate in the interview. Subjects were recruited by purposive sampling from August 2019 to December 2019. In-depth interviews were conducted at patients' homes, until data saturation. The audio recordings were transcribed verbatim and afterwards subjected to thematic analysis. **Results and Discussion:** Nine carers were interviewed. All respondents had limited understanding of HMR although they claimed to be adequately counselled prior to admission into the programme. Carers' good understanding of the programme may improve patients' preparedness and lead them to be actively engaged in decision making during the home care visits. The convenience of not having to go to the hospital was perceived as the primary benefit. Healthcare providers were welcomed

during each visit. Recognising the presence of a pharmacist in the MOT was not a problem. There was a concern about requiring them to refill medications from the hospital. Some participants suggested increasing the frequency of visits and hoped for more financial aids. **Conclusion:** In this study, carers' comprehension of HMR was generally poor although they were satisfied with our HMR programme. Furthermore, several aspects of our HMR need to be strengthened to improve patients' wellbeing. Despite HMR being temporarily replaced by telemedicine during the current pandemic, HMR remains relevant in the post-COVID-19 era.

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Abstract 029

Investigation of the Moisturizing Effect of Cocoa Butter on Skin Cream

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Introduction: Cocoa butter (CB) is a natural product that has been incorporated as a moisturizer in various topical creams over the years. However, CB is not the main ingredient despite numerous studies claimed about its moisturizing capacity. [1] [2]. The chemical compositions of CB could contribute to its potentiality as an occlusive agent that helps to maintain skin hydration [3]. **Objective:** The main objective of this research was to investigate the effect of CB as the primary ingredient of skin moisturizing cream. **Method:** The oil-in-water emulsions were prepared by adding an aqueous phase to the oil phase in several pre-determined proportions before subjecting to high-speed homogenization. A total of 15 prototype formulations were prepared. The oil phase consisted of CB, beeswax and PEG 200, whereas the aqueous phase included Poloxamer 188 and distilled water. Other ingredients (Poloxamer 407, Cinnamon Oil, Almond Oil and Vanillin) were added to enhance the product attributes. The developed cream formulations were characterized by pH, spreadability, in-vitro occlusivity, sun protection factor (SPF), antioxidant activity using hydrogen peroxide method and antimicrobial activity by disc diffusion method. **Result and Discussion:** The physicochemical parameters of formulations S1-S14, i.e. pH, occlusion factor and spreadability were found to be in the range of 5-5.5,

54.10-24.20, 0.850-2.917 cm respectively. The formulation, S14 showed the lowest occlusion factor ($F=24.20$), high spreadability (1.533 cm) and improved sun protection factor (SPF) of 25.4 and was found to be more effective compared with the other prototype formulations. There was also a general trend of increase in antioxidant activity when the concentration of the sample increased. Besides, the S14 formulation showed greater inhibition against the *S. aureus* than *E. coli*. The formulation, S14 was stable at the accelerated conditions ($40 \pm 5^\circ\text{C}$, $75 \pm 5\%$) regarding color, liquefaction, pH and phase separation for three months. **Conclusion:** To conclude, CB has the potential to be used as the main ingredient of skin moisturizing cream due to its optimum pH, spreadability, occlusivity, SPF, antioxidant activity and antimicrobial activity. However, clinical studies were required to evaluate its further benefits in maintaining skin hydration *in vivo*.

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Abstract 030

Development of *In vitro* Dissolution Method for Nateglinide Formulations

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Introduction: Nateglinide (NTG) is a derivative of D-phenylalanine, an agent that stimulates insulin secretion in pancreatic β cells. NTG is under BCS Class II drug, which is characterized by low solubility and high permeability. Thus, the dissolution of NTG is a rate-determining step for bioavailability. For this reason, to correlate the *in vivo* performance of NTG, the development of *in vitro* dissolution method is important. **Objective:** The objective was to develop an *in vitro* dissolution method for NTG formulations to correlate the *in vitro-in vivo* performance of NTG. **Method:** Two formulations (tablets and capsules) were prepared and evaluated for their physical properties. The dissolution mediums were developed based on the solubility of NTG in different six dissolution mediums. The dissolution

study for NTG tablets and capsules was investigated by using USP Apparatus 2 (paddle) and USP Apparatus 1 (basket), respectively. Each aliquot at predetermined intervals was filtered through 0.45 μm syringe filter and measured using UV spectrophotometer. For each formulation sample, drug concentrations were determined from the standard calibration curve. **Result and Discussion:** The solubility of pure NTG in six different dissolution mediums were as follows: water (0.0748 mg/mL), 0.5% w/v SLS in water (1.1695 mg/mL), 1% w/v SLS in water (1.0697 mg/mL), buffer pH 7.4 (1.8840 mg/mL), 0.5% w/v SLS in buffer pH 7.4 (2.5150 mg/mL), and 1% w/v SLS in buffer pH 7.4 (2.8259 mg/mL). The prepared NTG tablets showed the highest percentage of drug dissolved in 1% w/v SLS in buffer pH 7.4 (104.97%) whereas NTG capsules showed the highest percentage of drug dissolved in 0.5% w/v SLS in buffer pH 7.4 (105.46%). **Conclusion:** Hence, 1% w/v SLS in buffer pH 7.4 and 0.5% w/v SLS in buffer pH 7.4 are suitable dissolution media for NTG tablets and capsules respectively. The *in vitro* drug release kinetic properties of NTG formulations can be used to provide the desired *in vitro-in vivo* correlation information.

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Abstract 031

Drug Utilization Review in Emergency Department of Hospital Tuanku Ampuan Najihah: A Major-Specialist Hospital

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Introduction: Drug utilization review (DUR) is required to initiate discussions on rational drug use. Furthermore, suggestions and measures to improve prescribing habits can be performed. Unfortunately, DUR in the emergency departments (ED) in Malaysia is rarely performed. **Objective:** This study aimed to identify the pattern of drug utilization among patients discharged from the ED in a tertiary hospital in Malaysia. **Method:** A one year retrospective drug utilization study was conducted in the ED

of Hospital Tuanku Ampuan Najihah. A total of 833 patients discharged prescriptions were reviewed to extract data on the pattern of drug use excluding incomplete prescriptions and patients discharged from wards. The rationality of prescriptions was evaluated using WHO core indicators of drug utilization. **Result:** The three most prescribed categories of drugs were respiratory (39%), analgesia (20%) and gastrointestinal (16%). The rationality of prescriptions was average of 2.6% drugs per encounter, 15.7% antibiotics per encounter, essential drugs list or formulary was 100% of drugs prescribed, and percentage of drugs prescribed by generic names was 66.8%. All drugs were found to be used rationally. The use of generic names was lower than the recommended optimal level of 100%. **Conclusion:** The rational use of drugs in the ED, HTAN as a major specialist hospital was successful based on standard WHO prescribing indicators. However, there was a lack of generic names used during prescribing.

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Abstract 032

Community Pharmacists' Perceptions on Medication Review Service Model Implementation in Retail Setting in Malaysia

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Introduction: Pharmacists' roles have been evolving to include more patient-centered care services such as medication review that help patients to get the most benefits out of the medication [1-3]. In Malaysia, although medication review services have been established in the government health care settings, it is yet to be widely implemented in community pharmacy setting. Since the two settings have different patient population and orientation, it is important to develop the service model that specifically design for community pharmacy. Hence, input from community pharmacists and their stakeholders is important to propose a feasible medication review service module in Malaysia. **Objective:** To explore the community pharmacists and their stakeholders' perceptions on the barriers, facilitators and

strategies for the implementation of a medication review service model in Malaysia. **Method:** A focus group discussion with semi-structured interviews were conducted among purposively sampled community pharmacists. Respondents were continued to be recruited until saturation was achieved in which no new coding or themes aroused from two consecutive interviews. The interview was video and audio-recorded and transcribed verbatim. Data was analysed using thematic analysis with ATLAS.ti version 8 software and themes were classified according to the framework for implementation research on pharmacy services [4]. **Result and discussion:** A total of 14 pharmacists participated in this study. Among them, 9 pharmacists were from independent pharmacies and the remaining from chain pharmacies. Participants reported 13 barriers, 14 facilitators and 9 recommended strategies for medication review service model in Malaysia. The main barriers reported were absence of a structured service model and health care system that will support the service, lack of monetary value and remuneration and pharmacist's poor knowledge, communication skills and lack of confidence to implement the service. The current factors that were found to facilitate future implementation of the service were the availability of other advanced services and medication review that are currently being offered in some community pharmacies, presence of well-trained pharmacists with passion to conduct the service. Recommended strategies included the need for a standardized model, fee and documentation system to guide pharmacists as well as the need for accreditation and training for community pharmacists. The service model suggested included engaging customers to the service through good communication and education, appointment-based service, targeting customers who benefit most and collaborating with doctors. **Conclusion:** The findings will help to guide the development of a medication review service model that is suitable for implementation in the community pharmacy settings in Malaysia.

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Abstract 033

Evaluation of Warfarin Related Knowledge and International Normalized Ratio (INR) Control Among Atrial Fibrillation Patients in Rural Area

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Introduction: INR control is important for warfarin patients to maintain the ideal anticoagulation effect of warfarin. Warfarin related knowledge affects INR control among patients where patients with higher warfarin related knowledge will have better control. **Objective:** This study aimed to assess warfarin related knowledge and INR control among atrial fibrillation patients, and to identify the association between warfarin related knowledge and INR control. **Method:** A cross-sectional survey was carried out among atrial fibrillation patients on warfarin therapy at the Medical Outpatient Department (MOPD) in Hospital Tuanku Ampuan Najihah (HTAN). A convenient sampling was used to recruit the subjects. A validated questionnaire which consists of mainly 3 parts covering the demographic data, INR level and Oral Anticoagulation Knowledge (OAK) test. **Result:** A total of 133 subjects were recruited and the mean knowledge score of the subjects was 51.39 ± 18.11 which indicates moderate level of warfarin related knowledge. Most of the subjects (95.5%) know the indication of warfarin. There was a statistically significant difference for warfarin related knowledge between patient with different education level as determined by one-way ANOVA ($p < 0.001$). The mean time in therapeutic range (TTR) of our respondents is 71.7% which indicates moderate INR control. Kruskal Wallis test showed a significant difference in TTR ($p < 0.001$) and percentage of days in range ($p = 0.004$) with different warfarin related knowledge levels. There was a significant relationship between total knowledge score with TTR ($r = 0.268$; $p = 0.002$) and anticoagulation knowledge and percentage of day in range ($r = 0.233$; $p = 0.007$). **Conclusion:** Atrial fibrillation patients on warfarin therapy in HTAN were observed to have moderate warfarin related knowledge and moderate INR control. Warfarin related knowledge is significantly related to INR control.

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Abstract 034

Quality and Quantity of Patient's Own Medicine's Brought to Hospital Tuanku Ampuan Najihah during Admission: A Cross-Sectional Study

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Introduction: Patients' Own Medicines (POMs) is a relatively recent programme in Malaysia, with its management guidelines first published in 2016. Studies relating to the quantity and quality of POMs are limited in Malaysia. **Objective:** This study aimed to evaluate the quality and quantity of POMs brought by patients admitted to Hospital Tuanku Ampuan Najihah (HTAN). **Method:** A cross-sectional study was carried out among patients admitted in the medical ward, in HTAN. Convenient sampling was applied and 170 respondents were recruited from the medical ward. Data was collected by interviewing patients using a structured data collection form by investigators. The parameters studied were the quality, quantity and socioeconomic characteristics that might influence the quality of POMs. Data were analysed using Chi-Square tests to identify potential associated factors and Spearman's analysis to assess the correlation between the number of POMs and their usability. **Result:** Total number of patients who brought POMs were 170, and the calculated total number of POMs were 752. POMs brought by patients to HTAN were generally in good condition in which 93.7% ($n=679$) of POMs were usable while 6.3% ($n=46$) of POMs were unusable. Out of 752 POMs, 87% were in good condition, 98% were not expired and 72% of them were labelled with batch number, expiry date and presented in original packaging. No significant associated factors was found between POM's usability and patient's socioeconomic characteristics. There was a correlation between the number of medicines and the usability of POMs (R -value= -0.151, p -value= 0.049). **Conclusion:** Most of the POMs brought by patients are usable in the ward. Pill burden could be the

reason for poor management of medicines at home. Future study shall include the cost and savings incurred of POMs.

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Abstract 035

Public Knowledge and Practices Regarding Antibiotic Use: A Nationwide Cross-Sectional Survey in Malaysia

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Introduction: Antibiotic resistance is a global threat to human health worldwide, and a major contributing factor is the inappropriate use of antibiotics. There is a need for a nationwide study on the Malaysian general public to identify knowledge gaps regarding antibiotic use, its resistance, and practices related to antibiotic use. **Objective:** This nationwide study aimed to assess the knowledge of antibiotic use and resistance, and to identify any inappropriate practices related to antibiotic use among the Malaysian general public. **Method:** A cross-sectional survey was conducted, where Malaysians aged 18 years old and above from all states in Malaysia were recruited via quota sampling, followed by convenient sampling. A validated self-administered questionnaire was used to collect data. **Result:** A total of 1971 respondents were recruited. Half of them had engaged in at least one inappropriate practice related to antibiotic use (56.6%), with the most common being not completing an antibiotic course (48.8%). The mean total knowledge score was 8.57 ± 4.24 (range 0-20). The majority of the respondents were unsure or incorrectly answered that antibiotics work on viral infections (79.1%) and colds and coughs (77.0%), and 42.8% were unsure or incorrectly answered that antibiotics could be stopped when symptoms improved. Most respondents were unsure or wrongly answered that antibiotic resistance occurs when the body becomes resistant to antibiotics (90.2%), and antibiotic resistance is not an issue in Malaysia (62.9%). Respondents who had engaged in at

least one inappropriate practice related to antibiotic use were observed to have lower mean total knowledge scores (8.11 ± 4.00 versus 9.26 ± 4.40 , $p < 0.001$). Respondents who reported had ever not completed their antibiotic courses had significantly lower mean knowledge scores (8.09 ± 3.93 versus 9.10 ± 4.42 , $p < 0.001$). **Conclusion:** Important knowledge gaps on antibiotic use and resistance, and a high rate of non-completion of antibiotic courses were observed among the general public. Improving the knowledge of antibiotic use and resistance among the general public may be a key strategy to correct misconceptions and promote the prudent use of antibiotics.

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Abstract 036

A Study on Knowledge, Attitude and Practice on Medication Error Reporting Among Healthcare Practitioners in a Primary Care Setting.

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Introduction: Medication error (ME) is a worldwide issue affecting the healthcare system. In Malaysia, a total of 17357 medication error reports were submitted to the National Medication Error Reporting System (MERS) in 2016. However, the majority of the medication error reports come from pharmacists. **Objective:** To assess the knowledge, attitude and practice (KAP) on medication error reporting among healthcare practitioners working in primary care settings under the District Health Office of Kota Bharu. **Method:** A cross-sectional survey was conducted between Nov 2020 and Jan 2021 using a web-based self-administered questionnaire with 6 closed-ended questions for each section: knowledge, attitude and practice. Participants included healthcare practitioners (physicians, pharmacists and nurses) working in the 20 primary care health clinics within Kota Bharu District. KAP toward

medication error reporting was assessed using three options (yes, no or maybe). **Result and discussion:** A total of 221 respondents participated in the survey. Almost half (46%, n=101) of the healthcare professionals were not knowledgeable and 44% of them (n= 97) had negative attitudes towards medication error reporting. The pharmacists had the highest proportion, 65% (n=26) of them were knowledgeable and 73% (n=29) had a favorable attitude. Almost half of them (57%, n=126) have previous experience in reporting ME. Among the listed variables, respondents' attitude and practice of medication error reporting are significantly associated to gender with $p=0.002$ and $p=0.043$, respectively. This data was found quite similar to the previous study. There was a weak correlation between knowledge-attitude ($p<0.001$, $r=0.330$) and attitude-practice ($p<0.001$, $r=0.391$). A moderate correlation was found between attitude-practice ($p<0.001$, $r=0.561$). Meanwhile, knowledge and practice show moderate correlation and significance ($p<0.001$, $r= 0.561$). **Conclusion:** Our study revealed that knowledge, attitude and practice among the respondent are above borderline, i.e. merely above 50%. Therefore, more efforts are needed to improve the knowledge and attitude of the healthcare workers. Educational talk, disseminating ME material or displaying a clear flow chart on the reporting process are some of the examples that could be carried out.

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Abstract 037

Prevalence of polymorphisms in gastrointestinal (GI) disorder-related gene, Tryptophan hydroxylase 1 (TPH1) among Healthy Malays

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Introduction: Polymorphisms in the genes associated with genetic disorders have shown variable prevalence among different populations in the world. Today, the genetic polymorphisms database is considered a key to success in guiding treatment decision-making for genetic diseases. Tryptophan hydroxylase 1 gene (TPH1) which encodes the enzyme that catalyzes the rate-limiting step in the serotonin or 5-hydroxytryptamine biosynthesis pathway, is one of the leading candidate genes associated with gastrointestinal (GI) disorders. **Objective:** With these perspectives, this research aimed to study the genotype distributions and allele frequencies of two single nucleotide polymorphisms (SNPs) of TPH1 among healthy Malays in Malaysia. **Method:** Nested allele-specific multiplex polymerase chain reaction (PCR) was performed on 404 archived Malays' DNAs to determine the distributions and frequencies of TPH1 SNPs; rs4537731 (A-6526G) and rs211105 (T1803375G). Genotyping results were confirmed through direct Sanger sequencing. **Result and Discussion:** The genotype frequencies of A/A (A-6526G) and T/T (T1803375G) were 51.49% and 59.16%, respectively. The heterozygous frequency for A/G (A-6526G) was 36.39% and for T/G (T1803375G) was 33.66%. The homozygous variant was only found in A-6526G with a frequency of 12.13%. Concurrently, the wild type allele frequencies appeared to be higher than the mutant type in both SNPs with 69.7% to 30.3% for rs4537731 and 76.0% to 24.0% for rs211105. The findings from this study described low frequencies of TPH1 variants rs4537731 and rs211105 among healthy Malays, to which the symptoms of irritable bowel syndrome and severe GI including bloating, diarrhea and watery stool can be attributed. However, more studies should be performed to solidify the findings. For example, studies on Malaysian patients with GI disorders are recommended to determine the association of TPH1 polymorphisms to the condition, locally. **Conclusion:** The genetic polymorphism data obtained from this study is important to enhance our current knowledge on the genetic profiles among healthy Malays. Such data can be used to explore more on the association of GI disorders and the genetic variations of Malaysians in the future.

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Abstract 038

The Impact of Lithocholic Acid as A Surfactant on the Characteristics and Cytocompatibility of Azithromycin Loaded Self-Emulsifying Drug Delivery System

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Introduction: The self-emulsifying drug delivery system (SEDDS) has emerged as an effective pharmaceutical strategy for addressing the issue of poorly soluble drug bioavailability, specifically candidates belonging to BCS classes II and IV including azithromycin (AZM, log p = 4). Aside from oil, the main component in SEDDS is the surfactant, which is presented in high concentrations leading to complex physiological interactions raising the possibility of toxicity. Surfactants derived from bile acid have transpired as an excellent choice of bio-compatible pharmaceutical excipient. Unconjugated lithocholic acid (LA) has recently been reported to improve formulations' drug release and stability. **Objective:** To investigate LA as a safe and effective surfactant in liquid SEDDS (L-SEDDS) and compare it with LA-free L-SEDDS and solid SEDDS (S-SEDDS) states of AZM. This is in terms of reduced particle size (PS), dispersity (Đ), self-emulsification efficiency (T%), zeta potential charge in distilled water (DW), 0.1 mM HCl, and simulated intestinal fluids (SIF), as well as cellular viability. **Method:** L-SEDDS was formulated with Capryol 90[®] oil (22.22%), Tween 20[®] as surfactant and Transcutol HP[®] (2:1 ratio) as co surfactant. S-SEDDS was produced by adsorbing the L-SEDDS(s) to Aerosil 200[®] as a solid carrier (at 2:1 ratio of L-SEDDS to Aerosil 200[®]). In L-SEDDS, LA was incorporated at high (B-L-SEDDS3), medium (B-L-SEDDS2), and low (B-L-SEDDS1) concentrations of 7.75, 3.6, and 1.03 mg/ml respectively. Later, AZM was loaded. MTT assay was performed on human Colon carcinoma cell lines. **Result and Discussion:** Significant reduction in PS and Đ values was observed upon the addition of LA (p<0.05) in both blank and loaded B-L-SEDDS and compared to LA-free AZM-loaded liquid and solid SEDDSs, respectively. Besides, the size reduction was LA concentration-dependent and could be advantageous for drug absorption and lymphatic uptake, while the Đ reduction represents SEDDS improved

homogeneity. After the addition of LA, T% increased up to ~ 100%, while ZP charges were negative in DW and SIF, with charge shift to positive in HCl diluent. Almost all SEDDSs formulations exhibited good cytocompatibility (> ~85%). **Conclusion:** LA is a potential surfactant for desired features of SEDDS (PS, Đ and T%) with a good safety profile.

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Abstract 039

COVID-19: Embracing the New Normal; Are We Ready for This? A Cross-Sectional Study

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Introduction: The rapid spread of Coronavirus brought fear and chaos to Malaysians. Amidst pandemic, educating, engaging, and mobilising the public to become active participants may help achieve public health emergency preparedness, reducing the overall population's vulnerability. However, false media information may mislead Malaysians, making it necessary to access Malaysians' baseline knowledge and preventive practices against COVID-19. **Objective:** The study aimed to evaluate the knowledge, attitude, perception and practices towards the prevention of COVID-19 among the general public in Malaysia. **Method:** A cross-sectional study was conducted online among the general public in Malaysia from June 2020 to August 2020. Participants were conveniently recruited through multiple social media platforms to encourage nationwide participation. A patient-administered questionnaire was used to assess their knowledge, attitude and practice towards the prevention of COVID-19. Descriptive analysis, percentage, mean, and standard deviation were used to report demographic characteristics, knowledge, attitude, and practice scores. For inferential analysis, t-test, ANOVA, Pearson's correlation, Spearman's correlation, Chi-square test and binary logistic regression was used to analyse the

differentiation, association and correlations of the study variables. The confidence interval selected for this study was 95%. **Result:** A total of 420 respondents participated in this survey. The majority of the participants (n=412, 98%) were aware of COVID-19. Most participants learnt about the pandemic through social media. About half of the participants had inadequate knowledge (45.5%) and a negative attitude (43.3%). Participants residing in urban areas showed good preventive practices than those residing in rural areas ($P < 0.05$). There was a significant association between participant's attitudes and preventive practices towards COVID-19, where the majority of the participants (57.4%) who showed negative attitudes were more likely to follow poor preventive practices. Malaysians each hold a perception that differs from individuals according to their mindsets, perspective and acceptance towards COVID-19. **Conclusion:** Despite having good knowledge, participants with a negative attitude towards COVID-19 were less likely to follow the preventive practices of COVID-19. The Public's mindset and willingness may play an important role in influencing their practices, giving them another perspective, which may change their perceptions. As a result, strategies should be made to change the mindset of these vulnerable groups through proper counselling and education.

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Abstract 041

A Study on Academic Stress Level among Undergraduate Pharmacy Students

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Introduction: Pharmacy course has always been regarded as a highly stressful program among university undergraduates. This worsens tremendously during the Covid-19 pandemic when there is a sudden shift to e-learning. **Objective:** To examine the severity of academic stress among pharmacy students and the factors affecting it. **Method:** A cross-sectional study using a convenient sampling technique was conducted among undergraduate pharmacy students in a tertiary university in Malaysia. A self-administered validated

questionnaire was distributed to the students through emails. The questionnaire includes sociodemographic information and questions to examine the academic-related factors which render student stress during the Covid-19 pandemic. All the data were analysed using SPSS version 26.0. **Result and Discussion:** Overall, 102 pharmacy students participated in this study. The majority of the students face a moderate level of academic stress (63.8%), followed by severe stress (23.5%) and mild stress (12.7%). Academic factors, such as struggling with difficult subjects through e-learning, feeling stressed when deadline submission is approaching, and dealing with high academic workloads might be the reasons for stress.

Furthermore, this study discovered that the year of study, especially for students in year one and smoking, were two significant independent factors causing academic stress among students (P -value < 0.05). **Conclusion:** This study highlights the worsening academic stress which could affect the psychological well-being of the students. The mental health status of the students should not be neglected. Therefore, school management needs to develop effective counselling modules and intervention strategies to help students alleviate academic stress.

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Abstract 043

Qualitative Analysis on Interprofessional Collaboration in the Management of Paediatric Bronchial Asthma: Challenges and Suggestions for Improvement

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Introduction: Multi-disciplinary healthcare providers need to move beyond task-based responsibility towards a more

collaborative approach. Chronic childhood diseases such as bronchial asthma demanded effective multidisciplinary team meetings to improve patient care. **Objective:** We aimed to examine the interprofessional collaboration between physician and pharmacist in the management of paediatric bronchial asthma, to explore the views and experiences of both pharmacists and physicians on the important aspects of paediatric respiratory medication therapy adherence therapy (PRMTAC) and patient-centredness, and to identify barriers to shared decision-making in the management of paediatric bronchial asthma. **Method:** The study involved a face-to-face interview involving the paediatric medical team and pharmacists involved with PRMTAC. The semi-structured interview included four pharmacists and three paediatric residence from Hospital Tuanku Fauziah, Perlis, Malaysia. A full audio recording was used for detailed data retrieval and verbatim transcription. The session was deemed completed once all the probed questions have reached the thematic conclusion. **Result and Discussion:** There were three main themes emerged: (i) The relevance and necessity of PRMTAC service to complement paediatric outpatient bronchial asthma management, (ii) the lack of communication between pharmacist-physician in outpatient bronchial asthma management, and (iii) recommendation for the combined clinic in the management of outpatient paediatric bronchial asthma. PRMTAC services were rated as highly relevant in the management of outpatient bronchial asthma among all study respondents, irrespective of profession. The detailed assessment of medication compliance and technical demonstration provided by PRMTAC services were deemed fundamental in holistic patient care. The current clinical scenario demonstrates that the pharmacist and paediatric medical team work independently and in parallel rather than collaboratively—such workflow challenges in tandem decision-making regarding patient-focused medication. The lack of interaction also impedes sharing of ideas and new knowledge that could benefit both parties in relation to the management of outpatient bronchial asthma. A combined clinic was synonymously suggested to remedy this. **Conclusion:** Therefore, proper planning regarding allocation of support system and mobilisation of human resources needs to be instituted to realise the implementation of a nationwide combined clinic in the management of paediatric bronchial asthma.

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Abstract 044

Views, Barriers and Facilitators of Pharmacists Regarding Trastuzumab Biosimilar in the Treatment of HER2+ Breast Cancer

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Introduction: Despite the introduction of trastuzumab biosimilar in 2019 and scientific proof that biosimilar has no clinically meaningful difference from its originator, the uptake of trastuzumab biosimilar in one teaching hospital in Malaysia was still low in 2021.^{1,2} Therefore, we aimed to explore the views, barriers and facilitators of pharmacists regarding trastuzumab biosimilar in the treatment of HER2+ breast cancer.^{3,4} **Method:** This qualitative study was conducted from March to September 2020 at the University Malaya Medical Centre. Pharmacists involved in the procurement, dispensing, and reconstitution of trastuzumab was recruited. In-depth interviews were conducted in either English or Malay, using a semi-structured topic guide. Interviews were audio-recorded, transcribed verbatim and analysed using a thematic approach. **Result and Discussion:** Eight out of 14 pharmacists agreed to participate. They were 31-59 years of age with 6-34 years of work experience. Three themes emerged from our data analysis: 1) Affordability of trastuzumab biosimilar. The introduction of trastuzumab biosimilar reduced the price of the originator. This allowed patients and healthcare professionals to choose which trastuzumab they preferred. Some pharmacists did not like the idea of having both options available in the pharmacy as this complicated trastuzumab's inventory. 2) Efficacy and safety of trastuzumab biosimilar and its originator. Most pharmacists believed that trastuzumab biosimilar and its originator had no clinically meaningful difference. However, they were not confident in assuring doctors and patients on the efficacy and safety of trastuzumab biosimilar due to lack of training. 3) Who should decide if trastuzumab biosimilar or the originator should be used. Pharmacists believed that the decision lies with the doctor or the patient as they were not directly involved in the management of breast cancer. **Conclusion:** The price war between trastuzumab biosimilar and its originator has provided the option for doctors and

patients to choose between the two. Pharmacists believed that trastuzumab biosimilar has no clinically meaningful difference from its originator. However, they were not confident in recommending trastuzumab biosimilar due to lack of training. Ultimately, they believed that the decision should be made by either the doctors or the patients.

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Abstract 045

Evaluation of Patient's Knowledge and Perception Regarding Generic and Innovator Drugs and its Associated Factors Among Patients in Public Health Clinics in Rembau District

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Introduction: Healthcare costs are on the rise. Generic drugs are a cheaper alternative to innovator drugs. Thus, it is vital for the public to have adequate and precise knowledge regarding innovator and generic drugs. **Objective:** The objectives of this study were to describe the level of knowledge and perception regarding generic and innovator drugs among patients in health clinics in Rembau district and to determine the relationship between patient's sociodemographic factors (age, gender, educational level, and income) and their level of knowledge and level of perception about generic and innovator drugs. **Method:** This cross-sectional study involved 368 outpatients who collected their medications at health clinics under Health Division of Rembau District from September 2020 to November 2020. **Result and Discussion:** The term generic and innovator drugs were only recognized by 49.4% (n=182) of the respondents. Despite this, only 21.74% (n= 80) of the respondents have good knowledge about generic drugs. Most

of the surveyed patients obtained information about generic drugs mainly from health care provider (44.3%) and electronic media (33.4%). Age [χ^2 (1, n=368) = 4.995, p = .025], educational level [χ^2 (1, n=368) = 9.180, p = .002] and income level [χ^2 (1, n=368) = 17.505, p = .0001] are factors associated with level of knowledge. As for perception towards generic drugs, 56.8% (n=209) of the respondents have a positive perception. About 43.2% believed that generic drugs are equal in quality. Almost half of the respondents, 53.8%, agreed that generic drugs are cheaper; nonetheless, only 18.5% believe that it can help in reducing medication cost. Factors found to be associated with level of perception are age [χ^2 (1, n=368) = 5.484, p = .019] and income level [χ^2 (1, n=368) = 7.842, p = .005]. **Conclusion:** Based on this study, the knowledge on generic drugs are still lacking among patients in Rembau district. Nevertheless, most of the patients have positive perceptions of generic drugs. Therefore, educational and promotional activities on generic drugs should be emphasized to improve patient's knowledge on generic drugs and maintain the positive perception among the patients.

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Abstract 046

Military Pharmacists' Roles in Medical Logistics & Supply Chain During COVID-19 Pandemic

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Introduction: Coronavirus disease 2019 (COVID-19) outbreak has immensely impacted healthcare management globally. Malaysia, in particular the Malaysian Armed Forces (MAF), has experienced shortage of vital medical supplies as most of the pharmaceutical items, active pharmaceutical ingredients, raw material for medical devices and medical devices were heavily imported from other countries. In the MAF, military pharmacists play crucial roles in managing

medical logistics and supply chain. The pandemic has implicated the ability of military pharmacists to provide stable and steadfast medical logistics support for the troops to combat the COVID-19 outbreak and to execute routine operational activities. **Objective:** To study the impacts of COVID-19 pandemic on military pharmacists' roles during COVID-19 pandemic. **Result & Discussion:** (1) Deployment need to Tawau Field Hospital which consists of 100 beds (15 Oct 20 until 6th Jan 2021) as military pharmacist and also medical logistics officer to support Ministry of Health, Tawau Hospital and treating non-COVID-19 patients particularly medicine, general surgery, obstetrics and gynaecology, orthopaedic and paediatric services. Responsibility of military pharmacists was not limited to continuity of pharmacy services but also ensuring availability of medical assets and many other medical equipment throughout the operation. (2) Agility needs to support PPEs distribution for Operasi Penawar nationwide. Operasi Penawar is an operation by the MAF together with the Royal Malaysian Police during Movement Control Order (MCO). It was started on 18th March until 3rd May 2020 for MCO 1.0. Military pharmacists' good networking skills had ensured sufficient and timely deliveries of PPEs nationwide including to East Malaysia within 5 hours after receiving the initial instruction until the end of operation. (3) Increased need to coordinate the distribution of PPEs, medicines and vaccines to ensure stock readiness at all MAF health facilities nationwide. There are 60% increment of logistics communication frequencies using the Royal Malaysia Air Forces (RMAF) A400M and C-130 aircrafts to support East Malaysia. (4) Military pharmacists managed to increase 60% of PPE stocks sustainability rate in the MAF from 36.9% to 96.4% in one month. Despite having difficulties to secure stocks during pandemic, Military pharmacists were able to maintain PPE stocks sustainability rate above 90% from April 2020 onwards. This was achieved by rigorous effort of doing supplier mapping, identifying source of materials and shifting to other alternatives. Maintaining smart partnership also contributed to the success of ensuring 100% PPE stocks sustainability. **Conclusion:** COVID-19 pandemic has really impacted the conventional roles and tasks of military pharmacists in the MAF. Despite ordinary roles and tasks, military pharmacists must be agile and able to execute extra tasks without failed by practicing good networking skills with other stakeholders and good management skills to provide stable and steadfast medical logistics support for the troops to combat the COVID-19 outbreak as well as to execute routine operational activities.

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Abstract 047

Metabolomics of Metformin in Urine Samples of Healthy Volunteers

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Introduction: Metformin is a first-line anti-diabetic agent that has been widely used for treatment of type 2 diabetes mellitus (T2DM). The drug is responsible for increasing the glucose uptake in the liver and skeletal muscles, and suppressing gluconeogenesis in the liver and interstitial glucose absorption. Non-targeted metabolomics is a comprehensive investigation to identify the pharmacological effects and adverse effects of a medicine (1). **Objective:** The objective of this study is to identify the metabolic pathways of metformin in urine samples of healthy subjects. **Method:** The study is registered with ClinicalTrials.gov, approved by ethics committee and performed in accordance to Malaysian Good Clinical Practice (2). Subjects who underwent at least 10 hours fasting were given single doses of metformin 1000mg tablet. Urine samples for six subjects at pre-dose and every 4 hours post dose until 12 hours after oral administration were analyzed using Liquid Chromatography Mass Spectrometry Quadrupole Time-of-flight (LCMS-QTOF) with reverse phase column. Modified METLIN method (3) was used in the instrumental setting for global metabolomic analysis in positive and negative modes. Pooled quality control samples and internal standards were spiked into the samples to control the analysis and batch-to-batch consistency. The chromatograms were further processed using MetaboAnalyst software (4). Multivariate analysis and parametric statistical analysis were performed to identify compounds. The compounds were paired with the Kyoto

Encyclopedia of Genes and Genomes (KEGG) to predict the biological perturbation involved after metformin absorption. **Result and discussion:** From the untargeted metabolomic analysis, metformin was found in all the post-dose urine samples but not available in any pre-dose sample. Metformin was absorbed and excreted through urine in healthy subjects. Figure 1 demonstrates the metabolic pathways for pre-dose versus 4-hour post-dose. In the 4-hour and 8-hour post-dose urine samples, urea cycle or amino group metabolism and glycine, serine, alanine and threonine metabolism are having

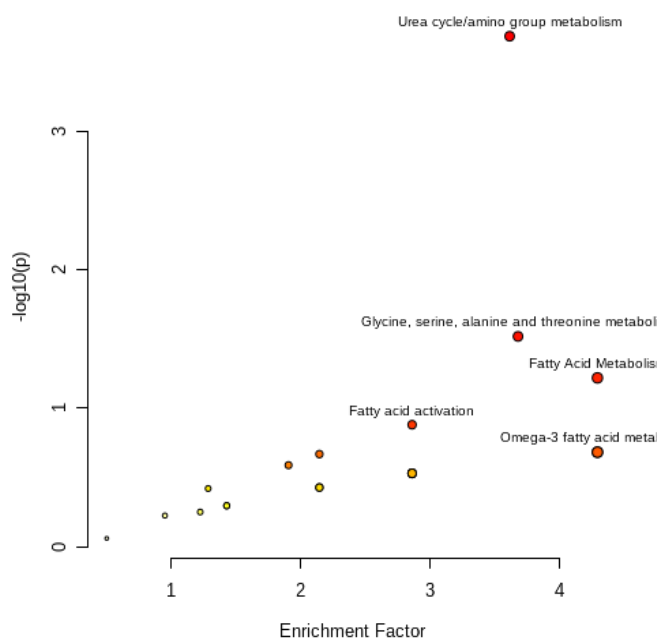


Figure 1. Metabolic Pathways using Mummichog Enrichment Analysis for pre-dose versus 4 hours post-dose urine samples.

significant biological perturbation in the control environment. Similar metabolic pathways were observed by study on T2DM subjects (5). **Conclusion:** Untargeted metabolomic analysis in urine samples using LCMS-QTOF is able to identify biological perturbation of metformin. This emerging approach sheds light on the pharmacological effects of the drug during phase one clinical trials.

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Abstract 049

Transforming Pharmacy Education via a Gamified Flipped Classroom Approach

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Introduction: Pharmacy education in the 21st century has fast-transformed from the traditional classroom to flipped classroom lessons where instructional videos are viewed prior and scheduled lessons have instead become avenues for working through problems. In collaborative learning, engagement is key. **Methods:** Using an open-source application, QuizWhizzer, two academic pharmacists together with an undergraduate developed an online, interactive teaching and learning mode for pharmacotherapeutics – a subject often considered ‘dry’ by students. Two or more players could engage in a competitive game, where their goal is to answer as accurately as possible the questions on cancer-associated thrombosis (CAT). Questions were designed in sets of 10 seconds, with varying degrees of difficulty: from easy, medium to difficult. The two academic pharmacists reviewed and rated the reliability of questions. Pilot testing of undergraduates’ perception was done. A 4-item questionnaire, with a 5-point Likert scoring, was distributed to 30 students who attempted QuizWhizzer. These students had completed the course “Neoplastic disorders”. Areas assessed were: engagement, evaluation of intellectual skills, problem-solving skills and motivation. A bivariate correlation was performed to evaluate the correlation between game scores and student perception. **Results and discussion:** The game is web-based and compatible on all gadgets and operating systems. It used two concepts of engagement: quiz and utilising a board game. Score keeping via a leaderboard meant that students effectively compete and positively challenge one another. With every accurate answer, the student gets a turn to roll a virtual dice, which will determine how far “up the ladder” he or she will proceed. Upon completion of each level, the player is to advance to a more complex level of difficulty throughout the game. The player who reaches the top first, is awarded as the winner. It took the 30 students an average of approximately 30 minutes per pair to complete the game. The accompanying questionnaire was filled in within an average

of 2 minutes. From the student's feedback, the average score obtained was 20 out of 30 marks (70%, ± 2.4). Students (100%) perceived the game as exciting and fun (engagement). Students (100%) rated the game as positive in helping them solve problems. While a majority (86.7%) felt that the game was challenging, promoted healthy competition among themselves to remain motivated, 4 students were not satisfied with the feedback available in the game as it did not assist with enhancing their intellectual skills. Game scores and perception levels were found to be moderately positively correlated, $r = 0.34$, $p = 0.032$. The game can be rolled out to undergraduate students enrolled into a course on neoplastic disorders in order to assess the effectiveness of the novel teaching and learning or assessment method. **Conclusion:** Preliminary evaluation of students' perceptions regarding QuizWhizzer, showed positive ratings in the aspects of engagement, assessing intellectual skills, problem-solving ability, academic performance and motivation. Future directions to include perceptions of educators to assess student knowledge and memory retention of the lessons delivered via the flipped classroom approach are plausible.

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Abstract 050

Evaluation of Degradation Kinetics of Flibanserin Bulk Drug under Oxidative Stresses

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Introduction: Flibanserin was approved by the United State Food and Drug Administration (USFDA) as the first drug for the treatment of hypoactive sexual desire disorder (HSDD). It is also prescribed as a treatment for mental disorders such as Schizophrenia, depression, anxiety as well as Parkinson's disease. Drug stability studies play an essential role in pharmaceutical products to ensure its quality, safety and efficacy. Determination of degradation kinetics is extremely

crucial as it can be used to determine the half-life and shelf life of the drugs under specific storage conditions. **Objective:** The objectives of this study are to evaluate the degradation kinetics and to determine the half-life and shelf life of flibanserin bulk drug under oxidative stresses. **Method:** The study was conducted using oxidative stress on flibanserin. The oxidising agents used were hydrogen peroxide (H_2O_2) and radical initiator, azobisisobutyronitrile (AIBN) at room temperature and at $50^\circ C$, respectively. The analysis was performed using High Performance Liquid Chromatography (HPLC) equipped with a Phenomenex C-18 column. The mobile phase used was acetonitrile: ammonium acetate buffer (60:40 ratio). The flow rate was set at 0.5 ml/min. The injection volume was $10 \mu L$. The detection wavelength used was 250 nm. The time for each analysis was 20 minutes. **Result and Discussion:** Degradation of 62.45 % had been observed after 8 hours treatment under H_2O_2 oxidation. A by-product was detected in the HPLC analysis. The degradation kinetics of flibanserin under H_2O_2 oxidation followed the first order kinetics. The half-life determined was 5.527 hours while the shelf life ($t_{90\%}$ and $t_{95\%}$) was 0.837 hours and 0.409 hours, respectively. Free radical degradation of flibanserin was observed to be 82.97 % following the first order kinetics. Four unknown by-products were detected. The half-life obtained was 2 days while the shelf life ($t_{90\%}$ and $t_{95\%}$) obtained was 7.848 hours and 3.840 hours, respectively at $50^\circ C$. **Conclusion:** Flibanserin was sensitive to H_2O_2 oxidation and radical degradation. Both oxidation degradation follows first order reaction.

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Abstract 051

Evaluation of a Local Protocol of Vancomycin-Therapy in Haemodialysis Patients Based on Targeted Trough Level and Extrapolated Area Under the Curve in a General Hospital

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Introduction: Recent published data from the 2020 IDSA guidelines on vancomycin dosing has no longer advocated the use of trough concentrations as surrogate markers for clinical efficacy. Protocols developed before the revised targets may not reflect the true efficacy marker for vancomycin, which is AUC 400-600. Vancomycin exposure in haemodialysis patients is influenced by both patient pharmacokinetic parameters and variables of the haemodialysis units which reduces the likelihood of target attainment. **Objective:** To evaluate the clinical efficacy of local vancomycin dosing protocol in achieving target trough concentration and area under the curve (AUC) among haemodialysis patients in Hospital Tengku Ampuan Rahimah (HTAR). **Method:** Retrospective record review of eligible research participants according to previously validated data collection form. The AUC of each individual was extrapolated via the use of a PK modelling software, PrecisePK. Chi-square test of independence was used to determine the association between trough concentrations to extrapolated AUC/MIC (minimum inhibitory concentration). A p-value of 0.05 was considered statistically significant. **Result and Discussion:** Eighty HD patients were included after the screening, involving cases between December 2019 and January 2021. 62.5% of haemodialysis study patients show AUC/MIC >800 (mean \pm SD=2320.2 \pm 1418.2). The trough concentrations across all four groups of AUC/MIC (<400; 400-600; 600-800; >800) remain similar in distribution. Chi square analysis between trough concentrations and extrapolated AUC/MIC showed a lack of association ($X^2(6) = 11.370, p=0.51$). AUC/MIC was heavily influenced by MIC of the infecting microorganism, ($X^2(12) = 164.93, p=0.00$). Majority of MRSA cases were found in the AUC/MIC > 800 with MIC values of 0.38 μ g/ml.

Conclusion: Exclusive trough guided dosing may not translate well in achieving the clinical efficacy of vancomycin in haemodialysis patients. Other contributing factors such as MIC should be factored, as small MIC values account for greater reciprocal AUC/MIC values. AUC/MIC > 800 in haemodialysis patients risks the loss of residual kidney function. Preserving residual kidney function of HD patients serves as an important prognostic factor for reduced mortality in this patient population.

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Abstract 052

Knowledge, Attitude & Practice of Alcohol Use among University Students: A Cross-sectional Study

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Introduction: Alcohol consumption is frequently reported among university students in many countries. It is a social issue that should not be overlooked as they are the pillars of the country's future. **Objective:** To study the knowledge, attitude, and practice of alcohol use among university students and to associate demographic variables with alcohol use among university students in Kuala Lumpur. **Method:** A cross-sectional study was conducted and participants aged 18 to 30 years old were recruited using the convenience sampling method at UCSI University, Kuala Lumpur. The questionnaire was validated by a panel of experts and a pilot test was done among 37 university students to ensure the reliability. Data were collected between August and September 2020 and analyzed by SPSS version 20. **Result and Discussion:** A total of 374 participants completed the survey. The findings showed that 54% of participants had good knowledge of alcohol use while 46% of them had poor knowledge of alcohol use. About 54.3% of participants had a positive attitude towards alcohol use, while 45.7% of them had negative attitude towards alcohol use. A total of 69% of participants started their first drink < 21 years old. Friends influenced alcohol use the most, followed by parents, siblings, or relatives, and curiosity. Approximately 72% of participants rarely consume alcohol. Also, 58.3% of the participants received a low level of harm from alcohol use

while 22.7% of them received a high level of harm from alcohol use. The level of harm experienced was significantly associated with gender, religion, course studied, and perceived parents' socioeconomic status with p-values showed <0.05. **Conclusion:** Majority of the university students had good knowledge of basic alcohol information but they had inadequate knowledge of standard drinking, binge drinking, and heavy episodic drinking terms. More than half of them had positive attitudes toward alcohol use and the majority of university students tend to experience a low level of harm from alcohol use. Even though most of the university students in the study rarely consume alcohol, interventions to reduce alcohol consumption among university students should not be disregarded.

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