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The Satisfaction and Perception of Contract Provisionally Registered Pharmacists in Kedah and Perlis towards their Internship Training

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Abstract

Background: Graduate pharmacists must undergo an internship training programme in order to practice in Malaysia. The current programme was modified in 2013 to include the private sector and again in 2017 to include those hired on a contractual basis. This internship programme is also known as the Provisionally Registered Pharmacist (PRP) training programme.
Objective: To measure the job satisfactions of interns under the current internship programme and evaluate their perceptions.
Method: A voluntary cross-sectional survey was conducted using a self-administered questionnaire amongst interns practicing in both the government and private sectors in the states of Kedah and Perlis, Malaysia.
Results: The response rate was 77.0%. Most respondents (91.3%) felt that the one-year internship duration is appropriate. In terms of logbooks, 37.6% of respondents found that the logbooks were too complicated, and 43.2% felt that the logbook targets were set too high. The mean scores on job satisfaction, based on a five-point Likert scale, were above average (3.51 ± 0.51). Some of the factors which influenced job satisfaction were the perception of fairness in the workplace, perceived self-competence at the end of the training duration, satisfaction towards the salary received, as well as the placement of interns in their workplace of choice.
Conclusion: There is moderate level of job satisfaction among the respondents. Generally, the internship programme meets the PRPs' expectations in terms of its duration, training facility and logbook appropriateness.
Keywords: perception, job satisfaction, pharmacist, internship, training

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Introduction

Pharmacist registration in Malaysia requires that pharmacy graduates enroll in the Pharmacist Internship Programme introduced in 2004(1). The initial internship programme includes a one-year internship training period in approved public hospitals and a three-year compulsory service in government health facilities. However in the year 2011, this intership programme is shortened to one year internship and one year compulsory service(2). This programme is widely known as the Provisionally Registered Pharmacist (PRP) Training Programme while graduates undertaking the internship programme are recognized as Provisionally Registered Pharmacist (PRP)(3). Through this programme, they are exposed to various pharmacy services within government health facilities, and thus gain hands-on experience(4). The PRPs will then be posted to various public health facilities for another year before receiving their full-fledge registration.

The Pharmacy Board of Malaysia (PBM) decided to include the non-public sector such as private hospitals and retail pharmacies as well as the pharmacy industry into their list of approved training sites in

2013(3). The decision was made to curb the over-congestion of public training hospitals. Under this liberalisation move, the private sector have additional requirements to be fulfilled before it can be acknowledged as a PRP training centre(3). For example, a retail pharmacist needs to be registered with the PBM and have at least four years of practicing experience. They are also required to undergo the PRP-Preceptor Training Module run by the Pharmacy Enforcement Branch.

Another measure was implemented in 2017 to address the worsening backlogged situation where successful PRPs failed to secure job postings after completing their training. The pharmacy graduates were then offered posts on a contractual basis in both their PRP and compulsory service period(5). Permanent positions will only be appointed based on merit and available vacancies. These changes have managed to ease the overcrowding of pharmacy graduates.

Amidst all the rapid development in pharmacist registration, it is also pertinent to ensure that the quality and the requirements of the internship programme meets the expectations of all parties, since this affects the future quality of pharmacy services in Malaysia. The changes in the registration policy proved equally challenging for both the teaching institutions and the pharmacy graduates. Pharmacy teaching institutions were tasked to adopt new teaching modules to ensure that graduates are prepared for both the government and private pharmacy sectors(6). Pharmacy graduates on the other hand, have to brace themselves for the choice they have to make before they were given a chance to train in either the government or private pharmacy sector. Hence, there is a need to study the perceptions of pharmacy graduates towards these changes in the PRP training programme.

One of the important key factors to the quality of the PRP training programme would be based on quality assurance studies. Studies showed that multiple factors affect job satisfaction. Factors such as pay, the work itself, the working environment and recognition are often the major determinants identified in these studies(7,8). A study in the United States found that job satisfaction were affected by age, income and practicing site(9) while another study in Australia added two other factors, namely workload and ability to utilize pharmacy skills(10). A more recent study in Malaysia also discovered the same results(11). Young *et al*(12) found that pharmacy students specifically identified that their preceptors should be role models and should show interest in teaching. These assurance studies are valuable as they provide insights for PRP training facilitators to improve and fine-tune the programme.

To date, there are three early researches on the job satisfaction of PRP towards their training programme in Malaysia. In the northern region of Malaysia, Phua *et al*(13) identified perceived fairness at work, preceptor competency, ethnicity and place of work to affect PRP job satisfaction significantly. Abida *et al*(14) expanded on this research to include PRPs in the whole of Malaysia but had limited their respondents to PRP practicing in public hospitals only. They further narrowed down the factors affecting job satisfaction to perceived fairness at work and preceptor competency. A recent study has echoed these findings where work recognition, training quality and support as well as great career planning played major roles in affecting job satisfaction(15).

As there is no research on PRP job satisfaction of the PRPs post changes to the registration policy, this pilot study aims to assess the current job satisfaction of contract PRPs to evaluate the effect of legislation change to the internship programme from 2014 till now. This study also aims to identify the factors affecting job satisfaction and in turn, evaluate the effect of registration policy changes.

Methods

Instrument

This study was cross-sectional using a validated questionnaire which consists of four sections (Appendix A). The questionnaire itself was adopted from Phua *et al.* and was granted approval of use by the original authors. As this research aimed to investigate and compare results with the previous study, the questionnaire was slightly modified in the first section (demographics) to capture the range of salary the PRPs were receiving at their workplace.

The first section of the questionnaire is a demographic tool to collect socio-demographic information of the correspondents, such as age, gender and marital status. It also captures data on the PRPs' practicing and previous learning institution, as well as the date of PRP training commencement. Questions such as whether the specific institution was their workplace of choice were in a 'Yes/No' format. Although the questionnaire inquired about the provincial state of the PRP workplace and their learning institutions, the PRPs were not required to name the particular institutions.

The second section measures job satisfaction, using the Brayfield & Rothe(16) job satisfaction scale. The third section investigates the PRP's perception of their training. The responses in these two sections were marked on a five-point Likert Scale. Similar to Phua *et al*(13), the third section of the questionnaire was further divided into three subsections; preceptor competence from Sonthissombat(17), self-competence after training adopted from Mak *et al*(18), and also perceived fairness in the workplace. A question on whether the teaching institutions have properly readied the PRPs for future job posting was also included in the questionnaire.

Shortly after the liberalisation of the PRP training programme, the PBM published different logbooks for PRPs working in different training settings. Due to the difference in the type of logbooks, this study opted to omit the investigation on the perception of the different subsections of the logbook and will only look at the general perception of the logbooks in its entirety.

Population and data collection

The targeted population of this study was all contract PRPs undergoing the training programme in both public and private sectors.

With help from the PBM, a list of potential candidates practicing in public health institutions was obtained. The list of potential candidates training in the private sector was obtained by the researchers personally contacting preceptors listed on the Pharmacy Service Division (PSD) website. Due to the vast number of preceptors registered with the PSD and limited number of researchers available, this study has limited itself to only include contract PRPs currently practicing in Kedah and Perlis. Sampling calculation was not employed as the study aimed to include all contract PRPs in both states.

The exclusion criterion for this study was PRPs who had trained for less than three months. The three-month cut-off was specifically chosen as it was only a quarter of the planned one-year training duration; the PRPs' responses at this stage may be inaccurate during this period due to short duration of training.

Data collection was conducted from June 2018 to September 2018. To achieve respondents' anonymity, each questionnaire was assigned a unique serial number before they were sent out. The questionnaires were distributed to the potential candidates via their designated liaison officer. Participation in this study was on a voluntary basis, hence those who did not submit their response within the data collection period were deemed opting out of this study. The completed questionnaires were collected and sent back to the investigators via registered post in sealed envelopes.

Data Analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 23.0. Questionnaires with missing data on place of training and date of training commencement were excluded, as were those with more than ten percent missing responses in the second, third and fourth sections. The item mean was used as a substitute in those with less than ten percent missing data.

Demographical data were analysed using descriptive statistics and expressed in frequencies and percentages. The Likert scale results were analysed using means and standard deviation. Univariate analyses (independent t-test, ANOVA, Pearson correlation) were employed to determine the factors which were significant in the job satisfaction construct. Multi-way ANCOVA were used to confirm the results. Statistical significance was set at 0.05.

Ethical approval was obtained from the Malaysian Research Ethics Committee, Ministry of Health Malaysia (NMRR-17-2163-37147).

Results

A total of 165 questionnaires were sent to 10 training hospitals, 9 health clinics and 8 retail pharmacies (Appendix B). Out of these, 127 questionnaires were returned, giving a response rate of 77%. However, only 126 questionnaires were analysed; one was excluded due to incomplete information. The demographics of respondents are shown in Table 1.

Table 2 shows the overall training experience. Only 11 (8.7%) respondents felt that the training period was either "too long" or "too short". More than one third of respondents (37.6%) felt that the training log books were too complicated for them, while nearly half (43.2%) thought that the logbook targets were too high. A majority of the respondents (78%) felt that they were sent to training sites that were adequately equipped for internship training.

The overall job satisfaction of the respondents was a mean of 3.51±0.51. The mean score of the perception towards self-competence after a year of training was 3.81±0.46, while the perception towards preceptor's competence was 3.90±0.55. Perceived fairness in the workplace had a mean score of 3.30±0.70 while the overall median score for university lesson adequacy is 4.00±1.00(Table 3).

Table 1: Demographics of PRPs from Kedah and Perlis (n=126)

Variable	n (%)	Median (IQR)
Age		25 (1)
Gender		
Male	27 (21.4)	
Female	99 (78.6)	
Ethnicity*		
Malay	93 (73.8)	
Chinese	25 (19.8)	
Indian	7 (5.6)	
Siamese	1 (0.8)	
Marital status		
Single	116 (92.1)	
Married	10 (7.9)	
Graduated from		
Public university	77 (61.1)	
Private/ Overseas university	49 (38.9)	
Workplace of choice		
Yes	115 (91.3)	
No	11 (8.7)	
Training facility type		
Government hospital	120 (95.2)	
Government clinics	4 (3.2)	
Retail pharmacy	2 (1.6)	

* One respondent (Siamese) was excluded from statistical analysis of job satisfaction based on ethnicity as no statistical analysis can be done for 1 subject. The respondent was included into the statistical analysis of job satisfaction based on other variables.

Table 2: Perception of the overall training experience

Item	n (%)
The total training period of 1 year (n=126)	
Too short	7 (5.6)
Just nice	115 (91.3)
Too long	4 (3.1)
Perception towards logbooks (n=125)	
Too simple	0 (0)
Just nice	78 (62.4)
Too complicated	47 (37.6)
The target sets by logbook (n=125)	
Too low	0 (0)
Just nice	71 (56.8)
Too high	54 (43.2)
The facilities available at the place of training (n=123)	
Not adequate	27 (22)
Adequate	96 (78)

Table 3: Overall job satisfaction perceptions of contract PRP towards their training

Domain	Mean (SD)
Job satisfaction	3.51 (0.51)
Perceived fairness in the workplace	3.30 (0.70)
Perception on self-competence after 1 year of training	3.81 (0.46)
Perception towards preceptors' competence	3.90 (0.55)
University lesson adequacy	4 (1) ¥
Salary satisfaction	3.94 (0.64)

¥ median score (IQR)

Table 4: Univariate analysis of factors affecting job satisfaction

Variable	n	Mean (SD)	Correlation (r)	F statistic (df)	P-value
Gender					0.684§
Male	27	3.55 (0.50)			
Female	99	3.50 (0.51)			
Ethnicity					0.510¶
Malay	93	3.49 (0.51)			
Chinese	25	3.54 (0.54)			
Indian	7	3.71 (0.38)			
Marital status					0.391§
Single	116	3.52 (0.51)			
Married	10	3.38 (0.48)			
Graduated from					0.092§
Public university	77	3.45 (0.48)			
Private/Oversea university	49	3.60 (0.54)			
Workplace of choice					0.005§
Yes	115	3.55 (0.51)			
No	11	3.11 (0.24)			
Training facility type				3.45 (2, 123)	0.035¶
Government hospital	120	3.49 (0.48)			0.083Ω
Government clinics	4	4.05 (0.75)			0.452Ω
Retail pharmacy	2	4.00 (1.13)			1.000Ω
University lesson adequacy				2.81 (4, 121)	0.029¶
Strongly Agree	12	3.87 (0.62)			0.438Φ
Agree	57	3.55 (0.49)			0.163Φ
Neutral	38	3.47 (0.51)			0.165Φ
Disagree	13	3.28 (0.44)			0.034Φ
Strongly Disagree	6	3.27 (0.21)			0.771Φ
Age	126		0.011		0.906Ψ
Perceived fairness in the workplace	126		0.350		<0.001Ψ
Perceived self-competence after 1-year training	126		0.396		<0.001Ψ
Perceived preceptors' competence	126		0.401		<0.001Ψ
Salary satisfaction	126		0.408		<0.001Ψ

§ independent T test
¶ One-way Anova
Ω Post-hoc test using Bonferroni correction, alpha= 0.05 or 1-[1-(0.05/3)^3]
Φ Post hoc test using Bonferroni correction, alpha= 0.049 or 1-[1-(0.05/5)^5]
Ψ Spearman's Rank Order

Table 5: Multivariate analysis of factors affecting job satisfaction

Variable	F-stat	P-value Δ
Workplace of choice	11.178	0.001
Training facility type	0.358	0.7
Perceived fairness in the workplace	6.426	0.013
Perception on self-competence after 1 year of training	7.753	0.006
Perception towards preceptors' competence	0.258	0.612
University lesson adequacy	0.211	0.647
Salary satisfaction	5.838	0.017

Δ Model = Two-way ANCOVA (R^2 = 0.404)

After subjecting the job satisfaction scores to univariate analysis, the factors that significantly affect job satisfactions were place of choice, training facilities, university lesson adequacy, salary satisfaction, perceived fairness in the workplace, perceived self-competency after training completion and perception towards preceptor's competence (Table 4). Interestingly, the perception of university lesson adequacy had a significant effect on job satisfaction, F=(4,121) 2.81, p=*0.029* . Respondents who felt that university lessons were inadequate had lower job satisfaction scores when compared with other respondents using the Bonferroni post-hoc test (p=*0.034*).

However, multivariable analysis on these factors showed that factors which significantly determined PRP job satisfaction levels were a combination of place of choice, perceived self-competence after training completion, perceived fairness at the workplace and salary satisfaction (Table 5).

Discussion

The PRPs in the current training system were moderately satisfied, with a mean job satisfaction score of 3.51±0.51. This is comparable to the job satisfaction levels before the aforementioned changes were made to the PRP training system where Phua *et al.* (13) and Adiba *et al.* (14) both found similar mean job satisfaction scores of 3.27±0.54 and 3.32±0.54 respectively.

Similar to previous studies, factors that significantly affect job satisfaction in this study were perceived fairness in the workplace as well as perceived self-competency after one year of PRP training (13,14). In addition, this study found that workplaces of choice and salary satisfaction also contributed to job satisfaction levels during PRP training which correlates with Chang *et al.* (15).

There is a positive correlation between perceived fairness at the workplace and job satisfaction, which was consistent with various other studies conducted (13–15,19). It is worth noting that fairness measurements in this study leaned towards distributive justice. Distributive justice is usually defined as the perception of equality in distributing workload and recognition (19). Respondents in this study felt that fairness at the workplace were moderately just (mean= 3.30±0.7), as compared to perceived fairness before the policy change (mean= 2.90±0.7 and 3.04±0.74 in Phua *et al.* (13) and Abida *et al.* (14) respectively). This slightly improved level in the perception of fairness may stem from increased numbers of PRP intake and proper training logbook after the change in policy and thus, reduced the incidence of receiving unwanted duties or receiving no work recognition. Ultimately, it would seem that the policy change resulted in increased PRP job satisfaction (r= 0.350, p<0.001).

High job satisfaction oftentimes indicate high self-competence in undertaking a work task (20,21). In this study, self-competence was defined as the PRPs' self-assessment of their ability to complete tasks such as medication dispensing, providing patient care and medicine information, as well as working as part of a multidisciplinary team. Perceived self-competence of respondents in this study was rated at 3.81±0.46, which was similar to previous studies (mean 3.65±0.53 and 3.70±0.57 in Phua *et al.* (13) and Abida *et al.* (14) respectively). It showed a positive correlation with job satisfaction (r= 0.396, p<0.001). This coincided with the majority of respondents (91.3%) who opined that the one-year training duration was appropriate. Hence, we could postulate that the year of training period was sufficient to prepare a PRP to confidently take up the responsibilities of a full-fledge pharmacist.

In many studies, it was shown that perceived self-competence and fairness at work were linked to perceived preceptor (manager) competence (12–14,19,22). The respondents felt that their preceptors were competent in guiding their trainees (mean 3.90±0.55) This study hypothesised that preceptors' capabilities

in handling interns such as through their work experience, teaching abilities, being a role model and providing opportunities to discuss and exchange opinions would be the determining factors in the respondents' job satisfaction. However, this was not observed. A possible reason behind this finding may be partly due to the merit selection system recently implemented to select full-time pharmacists (23). Current PRPs compete amongst themselves for permanent job positions; hence this policy had inadvertently served as a driving force for them to improve their learning and talents, independent of their preceptors' competence. Our study did not investigate this line of inquiry as the current questionnaire lacks in depth items to further explore in that direction.

The training site placement of choice was an unexpected factor found to affect job satisfaction. Both Phua *et al.* (13) and Abida *et al.* (14) did not note that the placement of graduates to their preferred training sites would significantly affect the job satisfaction. In this questionnaire, the preferred training site required a nominal response of "Yes" or "No" only. On further analysis, the mean job satisfaction measured was 3.55±0.51 and 3.11±0.24 for the "Yes" and "No" groups respectively. When all factors determining job satisfaction were cross-checked with each other, the placement of choice was found to be the highest determinant of job satisfaction (f = 11.178, p =0.001)

We reasoned that this phenomenon may have originated from the streamlined graduates' recruitment process, along with the changes in the pharmacist recruitment policy in 2016. Graduates were allowed to pick their prefered training sites from the list of expanded training facilities (23). This step appeared to "declutter" and reduced the training burden on the major training sites. However, graduate applications were dependent on available vacancies at the training sites. There may have been some graduates who were not able to secure their preferred site and the potential disapointment which follows may in turn affect their job satisfaction. Since our respondent number is small (n=126) future studies are required to explore this coincidental discovery.

Our study also showed that salary was another major determinant of job satisfaction (f =5.838, p=0.017). The mean salary satisfaction of our respondents was scored at 3.94±0.64. In addition, we showed that when the respondents were satisfied with their salary, their job satisfaction was scored at improved levels (r =0.408, p <0.001). This finding was consistent with Phua *et al.* (13), where the discussion about the cost of living in various cities where the training sites were situated might have played a role in salary satisfaction. Our findings complemented their results in that the demand for increased pay was more likely when there was increased workload. Spearman correlation test between perceived workload towards salary satisfaction shows an *r-value* of 0.898 (p <0.001). Although salary satisfaction was listed as one of the factors affecting job satisfaction, the study did not pursue further into this area. As the relationship between job and salary satisfaction is complex and complicated (24), a more focused study may be required to investigate the factors linking income satisfaction, remuneration and job satisfaction.

A majority of study respondents were practicing in the public sector (government hospitals and health clinics). The disparity between the number of PRPs working in the government (149) and non-government sectors (16) selected for this study were due to the identification process of potential candidates. The list of government PRPs were provided by the PBM with consent. However, PRPs working in the private sector were identified after the investigators personally contacted their preceptors. Some preceptors opted not to allow their PRPs to participate in this study due to unknown reasons. Hence, potential candidates from non-government institutions were far less recruited into the study, leading to the poor response rate (3) in the non-government PRPs. Thus, the comparison of job satisfaction levels of PRPs working in public and non-public setting was not permissible due to insufficient data.

Due to the voluntary nature of this study, any respondents from either public sector or private sector who did not send in their response during the data collection period was treated as not agree to participate in the study. No further actions were taken to increase the response rate. As a consequence, the completed questionnaire returned was a limiting factor as the power of the study may be compromised. It is also possible that the cross-sectional questionnaire method may have produced some level of bias. Intrinsic factors of the respondents such as stress levels, coping capabilities, co-worker relationships to name a few, may have an effect on job satisfaction and these factors were not considered in this study. This study also assumed that all PRPs received the same amount of training in their respective training sites. Therefore, any attempt to apply findings of this study to the general PRP population needs to be considered with caution.

Conclusion

The level of job satisfaction among PRPs working in Kedah and Perlis after the policy change in their training system was moderate (mean= 3.51±0.51 out of possible 5.00). This result is comparable to previously measured satisfaction levels. Factors found to influence job satisfaction were the workplace of choice, perceived fairness at the workplace, salary satisfaction and perceived self-competence upon training completion. Some possible suggestions to improve the level of job satisfaction among the PRPs would be to monitor their work progress from time to time, coupled with guidance on improving their shortcomings and reinforcing their strengths. Further focused studies may be required to explore the full range of possible reasons, intrinsic or extrinsic factors affecting job satisfaction.

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Conflict of Interest Statement

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Factors Affecting Glycaemic Control among Patients with Type 2 Diabetes Mellitus at Public Healthcare Facilities in the State of Kedah

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Abstract

Introduction: Diabetes mellitus cases continue to rise in Malaysia. With prevalence of 17.5% in 2015, the complexity of treating diabetes with its complication has huge economic impact to the government as Malaysia's healthcare is heavily subsidized.

Objective: The objective of this study was to determine the status of glycaemic control and identify factors associated with good glycaemic control among diabetic patients treated at public healthcare facilities in the state of Kedah.

Methods: This is a retrospective cohort study involving 390 diabetic patients randomly selected from nine hospitals and fourteen health clinics in Kedah. Consented patients were interviewed for their socio-demographic information. Patients' records in healthcare facilities were reviewed for data on laboratory results, complications and co-morbidities. Primary outcome is achievement of HbA1c target.

Results: Univariate analysis showed that glycaemic control was significantly associated with age, use of insulin, type of facility, counselled by pharmacist in the past 1 year, counselled by dietician in the past one year, patients with hypertension, practicing self-monitoring of blood glucose and duration of diabetes. However, multivariable analysis by using multiple logistic regression showed that only 3 factors, which were higher age (OR 0.93, 95% CI: 0.90, 0.97), not receiving insulin (OR 0.16, 95% CI: 0.07, 0.34) and having peripheral vascular disease (OR 0.13, 95% CI 0.03, 0.54) showed significantly better glycaemic control among type 2 diabetes mellitus patients.

Conclusion: Majority of diabetes mellitus patients did not achieve good glycaemic control. These results highlighted the need for appropriate management in diabetes mellitus patients. Besides, more attention should be given to patients prescribed with insulin.

Keywords: Type 2 Diabetes Mellitus, glycaemic control, factors, Kedah state

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Introduction

Diabetes Mellitus (DM) has been a major public health concern globally (1). DM related macrovascular and microvascular complications have significantly increased the burden on health care system. Besides high management cost, these DM related macro- and microvascular complications could also lead to preventable and premature mortality among the patients (2).

In Malaysia, the prevalence of DM has increased two-fold since 1996, with the current prevalence of 17.5% in 2015 (3,4). The total cost of management of diabetes was estimated to be around RM2.04 billion per year for year 2011 (both public and private sector), while nearly 70% was incurred by the government (5). This cost included patient follow-up cost, and cost to treat diabetes related complications such as nephropathy, myocardial infarction, stroke, heart failure, foot amputation, retinopathy and cataract extraction.

Maintaining good glycaemic control has been the shown to prevent the DM related macro- and microvascular complications (6). Strict glycaemic control, which is mainly achieved through adherence to treatment and good self-care behaviours, undeniably plays a pivotal role in DM management (7).

Several measures have been taken including the intervention from physicians (endocrinologist), dietitians, diabetes nurse educators, and pharmacists, for optimization of diabetes care. Lifestyle management, medical nutrition therapy, physical activity pharmacologic management and the use of technologies are some of the components of comprehensive measure which have been taken to manage patient with DM in Malaysia (8). However, many have still failed to achieve good glycaemic control. The reasons and factors that lead to poor glycaemic control are complex and multi factorial (9,10).

According to the National Health and Morbidity Survey (NHMS) 2015, the overall prevalence of DM (known and undiagnosed) among adults of 18 year and above was highest in Kedah State, recorded at 25.4%, compared to other states in Malaysia (3). As to the authors' knowledge, studies on glycaemic control among DM patient in the current region are limited. The aim of this study was to assess the status of glycaemic control and factors affecting glycaemic control in type 2 diabetic patients on follow-up Kedah state public health facilities.

Methods

This cross-sectional study was carried out in the year 2015 in public healthcare facilities in the state of Kedah, Malaysia. The study sites all nine public hospitals and 14 out of 52 public health clinics that were randomly selected. Sample size calculated was 130 samples each from 3 different groups which are hospital with specialist, hospital without specialist and health clinics.

Patients who were diagnosed with Type 2 Diabetes Mellitus (T2DM) for more than 1 year and not receiving any changes in drug regime for past 3 months were included. Patients who defaulted treatment in the past 1 year or referred to other healthcare facilities were excluded from this study. Besides, Gestational Diabetes Mellitus patients or diabetes patients cause by secondary causes such as acromegaly, steroid induced hyperglycaemia, pheochromocytoma (neuroendocrine tumour) or Cushing's Syndrome were also excluded.

This study was approved by the Medical Research and Ethics committee of the Ministry of Health Malaysia. Data such as age, sex, ethnic, BMI, laboratory data, co-morbidities and type of drug used were collected from the patients' medical records. In this study, all consented patients were interviewed using investigator-administered data collection form. The data collection form was developed by the investigators and was divided into two parts, consisting of patients' background, and patients' lifestyle activities, such as smoking status and physical activities. Patients were also asked whether they practiced self-monitoring of blood glucose.

All laboratory outcomes such as HbA1c, cholesterol level and serum creatinine level were based on patient's last medical record within the past three months. Data collected were analysed using the SPSS version 20.0. Logistic regression was used to compare among various factors (demographic factor, laboratory values, co-morbidities and complications) with HbA1c as the outcome.

Results

A total of 390 patients were recruited for this study, where 130 patients were equally selected from hospital with specialist, hospital without specialist and health care centre. The average age of the study population was 59 ± 10 years with 40.8% of male and 59.2% of female. Our population comprised of 79% Malay, 10.5% Indian, 8.7% Chinese and 1.8% of other races. Majority of the patients in our population were married (86.4%, n=337) and 7.7% are widow (n=30). Whilst 4.6% of the study population (n=18) are single and 1.3% divorced (n=5).

Most of our recruited patients received primary (39.7%, n=155) and secondary (44.1%, n=172) education. Only 9.2% (n=36) of our recruited patients did not receive any formal education. Thus, patients in this study are literate. The goals for diabetic patients to healthy lifestyle were to achieve moderate intensity physical activity for at least 150-minute per week. However, only 35.6% of recruited diabetic patients from Kedah did moderate physical activity whereas majority of the population (58.7%) did not have any physical activity. Other demographic data were shown in Table 1.

Table 1: Demographic data according to the types of facility (n=390)

Factor		n	Type of facility			P-value[a]
			Hospital with specialist, n (%)	Hospital without specialist, n (%)	Health clinics, n (%)	
Age						0.019
	<30	5	5 (3.8%)	0 (0%)	0 (0%)	
	31-40	12	7 (5.4%)	2 (1.5%)	3 (2.3%)	
	41-50	53	18(13.8%)	15 (11.5%)	20 (15.4%)	
	51-60	146	49(37.7%)	49 (37.7%)	48 (36.9%)	
	(61 and above)	174	51 (39.2%)	64 (49.2 %)	59 (45.4%)	
Gender						<0.001
	Male	159	72 (45.3%)	44 (27.7%)	43 (27.0%)	
	Female	231	58 (25.1%)	86 (37.2%)	87 (37.7%)	
Race						0.001
	Malay	308	89 (28.9%)	119 (38.6%)	100 (32.5%)	
	Chinese	34	16 (47.1%)	6 (17.6%)	12 (35.3%)	
	Indian	41	22 (53.7%)	3 (7.3%)	16 (39.0%)	
	Others	7	3 (42.9%)	2 (28.6%)	2 (28.6%)	
Marital status						0.006
	Single	18	11 (64.7%)	5 (29.4%)	2 (6.9%)	
	Married	337	114 (33.8%)	110 (32.6%)	113 (33.5%)	
	Widow	30	3 (10.0%)	15 (50.0%)	12 (40.0%)	
	Divorce	5	2 (40.0%)	0 (0 %)	3 (60.0%)	
Level of education						0.001
	No formal education	36	6 (16.7%)	14 (38.9%)	16 (44.4%)	
	Primary	155	37 (23.9%)	58 (37.4%)	60 (38.7%)	
	Secondary	172	74 (43.0%)	53 (30.8%)	45 (26.2%)	
	College & university	27	13 (48.1%)	5 (18.5 %)	9 (33.3%)	
Occupation						<0.001
	Government sector	32	19 (59.4%)	8 (25.0%)	5 (15.6%)	
	Private sector	107	32 (29.9%)	36 (33.6%)	39 (36.4%)	
	Retired	99	51 (51.5%)	23 (23.2%)	25 (25.3%)	
	Student	1	1 (100%)	0 (0%)	0 (0%)	
	Unemployed	151	27 (17.9%)	63 (41.7%)	61 (40.4%)	
Living status						0.499
	Alone	32	5 (25.0%)	9 (45.0%)	7 (30.0%)	
	With family	369	125 (33.9%)	121 (32.8%)	123 (33.3%)	
Household income						0.002
	RM 0-1000	230	65 (28.3%)	85 (37%)	80 (34.8%)	
	RM 1001-2000	73	25 (34.2%)	29 (39.7%)	19 (26.0%)	
	RM 2001-3000	46	18 (39.1%)	5 (10.9%)	23 (50.0%)	
	RM 3001 – 4000	15	7 (46.7%)	4 (26.7%)	4 (26.7%)	
	Above RM 4001	26	15 (57.7%)	7 (26.9%)	4 (15.4%)	
Physical activity						0.028
	Yes – moderate (150min)	139	46 (33.1%)	54 (38.8%)	39 (28.1%)	
	Yes – moderate (90min)	22	13 (59.1%)	4 (18.2%)	5 (22.7%)	
	No	229	71 (31%)	72 (31.4%)	86 (37.6%)	

[a] Chi Square / Fisher's Exact test

Table 2: Characteristics of clinical variable of Type 2 DM patients

Variable	Mean (SD) / Median (IQR)	n (%)
Glycosylated Haemoglobin (HbA1c)	9.09 (2.38) *	
< 7%		80 (22.9)
> 7%		270 (77.1)
Body mass index (BMI)	27.47 (5.30) *	
< 23 kg/m^2		74 (19.0)
> 23 kg/m^2		316 (81.0)
Fasting blood sugar (FBS)	8.88 (4.55) *	
< 4.4 mmol/L		11 (3.0)
4.4-6.1 mmol/L		57 (15.6)
> 6.1 mmol/L		298 (81.4)
Serum cholesterol	4.77 (1.92) *	
< 4.5 mmol/L		123 (34.4)
> 4.5 mmol/L		235(65.6)
Low-density lipoprotein cholesterol (LDL)	3.23(1.05) *	
≤ 2.6 mmol/L		81(28.8)
> 2.6 mmol/L		200(71.2)
Triglycerides (TG)	1.60(0.94) #	
≤ 1.7 mmol/L		164(56.4)
> 1.7 mmol/L		127(43.6)
High-density lipoprotein cholesterol (HDL)	1.17(0.40) #	
≥ 1.1 mmol/L		170(60.5)
< 1.1 mmol/L		111(39.5)
Serum creatinine (SrCr)	75.00 (38.60) #	
< 50		55(14.3)
50-100		239 (62.3)
> 100		90(23.4)

* mean (SD); # median (IQR)
Abbreviation: SD – standard deviation; IQR – inter-quartile range

In this study, only 350 patients out of 390 had HbA1c test done in the past 3 months. The mean HbA1c level was 9.09 % ± 2.38 %. Based on Malaysian Clinical Practice Guideline (CPG) for Type 2 DM management 2015, individualized HbA1c target was set at 6.0%-6.5% for tight control in patients with newly diagnosed DM, younger age, healthier (long life expectancy, no cardiovascular complications) and low risk of hypoglycaemia; 6.6%-7.0% for all others patients and HbA1c 7.1%-8.0% for less tight control in patients with co-morbidities (coronary disease, heart failure, renal failure, liver dysfunction), short life expectancy and prone to hypoglycaemia (11). Hence, patients with HbA1c value ≤ 7 were classifies as good glycaemic control. Other laboratory values were shown in Table 2.

Referring to Table 2, 34.4% (n=123) subjects achieved total cholesterol target of below 4.5 mmol/L. 38.8% (n=47) subjects achieved target cholesterol in hospital with specialist, 40.0% (n=46) subjects achieved target cholesterol in hospital without specialist while 23.8% (n=29) subjects achieved target cholesterol in health clinics. Health clinics recorded the lowest percentage of target cholesterol while hospital with specialist and without specialist recorded almost same percentage. The mean total cholesterol recorded in hospital with specialist was the lowest among all, while health clinics have the highest mean total cholesterol level. Post hoc with bonferroni shown differences between Hospital with specialist and health clinic is significant. P=0.045.

Our study recorded a number of macro and micro vascular complications. For macrovascular complication, 15.3% (n=59) subjects presented with ischemic heart disease, 5.2% (n=20) subjects reported existence of cardiovascular disease and 3.3% (n=13) subjects reported with peripheral vascular disease. 2.1% (n=8) subjects found to have diabetic foot ulcer, and 1.6% (n=6) subjects had amputated before. For microvascular complication, 30.1% (n=116) subjects reported numbness. 36.0% (n=111) subjects had

reported positive proteinuria. 6.0% (n=23) subjects reported non-proliferative retinopathy. No subjects reported Charcot Foot.

High percentage of co-morbidities recorded in our study. Among all, 85.7% (n=329) subjects were diagnosed with hypertension while 72% (n=278) subjects were diagnosed with dyslipidaemia. For counselling session, 46% (n=179) subjects had been counselled at least once by pharmacist, 27.1% (n=105) subjects had been counselled by at least once by dietitian and 18.9% (n=73) subjects had been counselled at least once by diabetic educator.

Body mass index (BMI) was used for the measurement of obesity in this study. The target used was 23 kg/m^2 for Asian population (12). Looking at current results, 17.5% (n=67) subjects achieved BMI < 23 kg/m^2 and 83.5% (n=316) subjects had BMI >23 kg/m^2. The overall mean BMI was 27.47 kg/m^2± 5.30.

In comparing the achievement of target HbA1c between the facilities, 9.6% (n=11) subjects achieved HbA1c ≤7 % in hospital with specialist, 33.9% (n=38) subjects achieved HbA1c ≤7% in hospital without specialist while 25.2% (n=31) subjects achieved HbA1c ≤7% in health clinics in Kedah state. P <0.001. The lowest percentage of HbA1c target achieved was hospital with specialist, while the highest percentage was hospital without specialist. There was a statistically significant difference in favour of the mean HbA1c in different health care facilities. Hospital with specialist recorded mean HbA1c 9.79 % ± 2.27 %. Hospital without specialist recorded mean HbA1c 8.31% ± 2.07. Health clinics recorded mean HbA1c 9.14 % ± 2.46 %. The Bonferroni post hoc tests showed a significant difference (p <0.001) between Hospital with specialist and Hospital without specialist.

Univariate analysis showed that glycaemic control was associated with age (p<0.001), use of insulin (p<0.001), type of facility (p=0.013 and 0.047), counselled by pharmacist in the past 1 year (p=0.001), counselled by dietician in the past one year (p=0.021), patients with hypertension (p=0.011), practicing SMBG (p<0.001), duration of diabetes (p=0.021) and MMAS score (p=0.039) (Table 3). All variables with p-value <0.25 during univariate analysis were then included into multiple logistic regression.

However, multivariable analysis by using multiple logistic regression showed that only 3 factors, which were age, use of insulin and peripheral vascular disease significantly associated with glycaemic control among type 2 diabetes mellitus patients. Results also showed that patients with insulin were having poorer glycaemic control.

Discussion

In this study, 22.9 % subjects (n=80) had achieved HbA1c level below 7.0%, which is classified as good glycaemic control for all other patients based on the above classification by Malaysian CPG. Low level of glycaemic control has been similarly shown in other studies in Malaysia (13). A study on the status of diabetes control in Malaysia showed that Malaysia has poor glycaemic control with only 22% of the patients achieving HbA1c target of < 7% (14), while another study reported only 19.1 % of patients achieving target HbA1c in a tertiary hospital in Kelantan, Malaysia (13).

The higher mean of HbA1c in hospital with specialist might be explained by considering that the patients at the hospital with specialist were generally having more long-standing diabetes, complications and comorbidities and thus less stringent target HbA1c will be applied in the management of those patients. Group with higher risk may experience more severe hypoglycaemia if subjected to too aggressive target HbA1c (15). In Malaysia, the presence of effective referral system between the health clinics, hospital without specialist and hospital with specialist may contribute to the effective referral of patient with poorer glycaemic control to the hospital with specialist for further management.

Higher percentage of DM patients who follow up in hospitals achieved target cholesterol compared to those who follow up in health clinics. This result was found to be similar with a cross-sectional study based on the adult diabetes control and management (ADCM) registry 2009 in Malaysia in which the hospital with specialist recorded a better cholesterol control compared to the health clinics (16). This might be due to the vast availability of anti-cholesterol medication in hospital with specialist compared to health clinic in Malaysia health system.

In terms of BMI, this study found similar result with a recent study of type 2 diabetic patient in Malaysia which recorded only 18.5% of the subjects achieved target BMI at 23 kg/m^2 while 81.5% of the subjects had BMI more than 23 kg/m^2 (17). As reported by study in UK, Southeast Asia is facing the greatest threat of obesity and the increase in the prevalence of type 2 diabetes is closely linked to the upsurge in

obesity. About 90% of type 2 diabetes is attributable to excess weight (18). Thus, there is a great need of fundamental social and political changes in preventing obesity among Malaysian.

For factors affecting glycaemic control, our findings are similar with previous studies that showed older patients tended to achieve better glycaemic control (19-21). Results also showed that patients with insulin have poorer glycaemic control, which is not surprising because diabetes is a progressive disease and patients with diabetes that is not sufficiently controlled with oral hypoglycaemic agents will need insulin to achieve better control. Also, our findings showed that patients with peripheral vascular disease were less likely to have sustained poor glycaemic control, which may be due to the stricter glycaemic targets that were set for those patients.

Contrary to previous study (22-24), duration of diabetes did not significantly associated with glycaemic control in our study. Duration of diabetes was proven not significant in our study when other factors were taken into consideration during multivariable analysis. Perhaps duration of diabetes correlate strongly with other variables such as age or the use of insulin.

The main limitation of the study was unable to measure medication adherence. Besides, Future study can be conducted with proper medication adherence tool.

Conclusion

Only 22.9% of DM patients achieved good glycaemic control. These results highlighted the need for appropriate management in type 2 diabetes patients. Older age and present of vascular disease are factors that showed significantly better glycaemic control among type 2 diabetes mellitus patients. However, patients with insulin were having significantly poorer glycaemic control. Therefore, more attention should be given to patients prescribed with insulin.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Pharmacists' Knowledge, Beliefs and Attitudes towards Mental Health Illness in Johor, Malaysia – Mental Health Literacy Survey (2018)

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Abstract

Introduction: Mental health literacy is defined as the knowledge and beliefs about mental disorders which aid their recognition, management and prevention.

Objectives: To determine the mental health literacy of pharmacists in Johor and identify the demographic factors that influence pharmacists' mental health literacy.

Methods: A cross-sectional study was conducted from March to June 2018 on pharmacists in Johor using an adapted questionnaire. Questionnaire with either one of the depression vignette or schizophrenia vignette was sent to the respondents randomly. There were three domains in the questionnaire, which included identification of mental illness, helpfulness of interventions and long-term outcome of mental illness.

Results: A total of 109 and 91 responses were received for the depression and schizophrenia vignettes respectively, representing an overall response rate of 83.0%. Depression was correctly identified by 56.0% (n=61) of respondents from the depression vignette whereas schizophrenia was correctly identified by 68.1% (n=62) of pharmacists from the schizophrenia vignette. Younger pharmacists (29 years old and below) were significantly more likely to be able to identify depression correctly (p=0.013), whereas older pharmacists were significantly more likely to identify schizophrenia correctly (p=0.049). For long term recovery, older (p=0.017) and more experienced pharmacists (with more than four years working experience) (p=0.007) significantly rated that person with schizophrenia may get worse if no professional help was sought. Overall, older and more experienced pharmacists were found to have higher degree of mental health literacy in most domains such as the ability to identify professional intervention, proper medication, harmful lifestyle and long-term recovery.

Conclusion: Pharmacists in Johor were less able to identify common mental illness. With the increasing prevalence of mental health illness in Malaysia, pharmacists, especially the young and less experience ones, should receive more training and education to improve their mental health literacy.

Keywords: mental health literacy, schizophrenia, depression, pharmacists, demographic factor

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Introduction

Based on the National Health and Morbidity Survey 2015, increasing trend of mental health problem was observed from 1996 (10.7) to 2015 (29.2) in Malaysia (1). However, discrimination among the society towards people with mental health illness are common due to the misunderstanding of the illness and feeling ashamed to seek for professional help. Hence, the concept of mental health literacy was introduced by Jorm *et al*. in 1997. He defined mental health literacy as the "knowledge and beliefs about mental disorders which aid their recognition, management and prevention" (2 p.182). Mental health literacy comprised of the ability to recognize specific illness, knowledge and belief about causes and risk factors, self-help intervention and professional help available, as well as the attitude during recognition and appropriate help-seeking (2). As the prevalence of mental health illness increases over the years, pharmacists' interactions with mentally ill patients also increase. The role of pharmacists in providing pharmaceutical services in the healthcare setting cannot be denied and hence their attitude towards mentally ill patients as well as belief on treatments and outcomes of mental health illness is important.

While a number of studies about mental health literacy among the public, healthcare students and other healthcare professionals were recorded over the years, only a few studies were assessing mental health literacy among the pharmacists. Literature about mental health literacy among the pharmacists or pharmacy students was even more limited in Asia. Available literature reported mixed results in terms of the mental health literacy of the pharmacists. In a study conducted among the Japanese pharmacy students, the attitudes of pharmacy students towards mental illness were generally favourable. However, the study's participants were restricted to only one pharmacy school, which cannot represent all pharmacy students in Japan (3). A mental health stigma study among the pharmacy students in six countries reported that pharmacy students in India thought mentally ill patients will never recover (4).

Cates *et al*. reported that Alabama pharmacists showed positive attitudes towards patients with mental health illness. About 30-50% of them felt comfortable to perform pharmaceutical services to mentally ill patients. Cates *et al*. also measured the association between demographic factors and mental health literacy of pharmacists. Three groups of pharmacists felt more comfortable and confident when providing pharmaceutical care to mentally ill patients, namely male pharmacists, pharmacists more than 50 years old and those who practiced for more than 30 years (5). The study of Yakubu *et al*. in Nigeria showed slightly positive attitudes of pharmacists towards mentally ill patient and, in their opinions, mentally ill patients are harmless and cannot be blamed for their disease (6). In Australia, a generally high degree of mental health literacy was found among the pharmacists. Despite of this, they perceived electroconvulsive therapy (ECT) and hospital admission as not helpful as they feel no improvements will be observed in schizophrenia patients. However, it was noted that younger pharmacists had significantly positive view towards ECT though the focus of current pharmacy programmes emphasize more on pharmacological management (7).

In contrast, the findings by Morral *et al*. in 2017 showed that British community pharmacists were more comfortable to provide pharmaceutical care to patient with cardiovascular disease than mental health illness. Many of them had stigma and misperceptions towards schizophrenia and bipolar disorder. The results also showed that British pharmacists had higher degree of literacy about depression than schizophrenia and bipolar disorder (8). Phokeo *et al*. also reported that Toronto pharmacists felt less comfortable to discuss about symptoms and medications with mentally ill patients compared to patients with cardiovascular disease (9). Both British and Canadian studies mentioned that inadequate training during undergraduate might be the reason behind (8,9).

To date, there was no study about mental health literacy among the pharmacist population in Johor, Malaysia. As the stigma on mental illness and mental health literacy among the pharmacists can affect their decisions in pharmaceutical care (8), this study was carried out to determine the degree of mental health literacy among the pharmacists in Johor, as well as to identify demographic factors that influence the mental health literacy of pharmacists.

Methods

This was a cross-sectional study that was carried out from March to June 2018 in Johor, Malaysia, using a questionnaire that was adapted from the National Survey of Mental Health Literacy and Stigma (Main Survey 15+) Version 8, 2011 (2). Permission from the author was obtained to use and modify the questionnaire. As the original questionnaire was conducted through phone calls, all questions were adapted and arranged in the form of multiple choices, short answer or tick-box grid to allow for self-administration by the respondents.

This questionnaire consisted two sections. Section 1 consisted six questions about the demographic information of participants, such as age, gender, current site of practice, working experience and experience with mental illness. In section 2, there were a total of 21 questions with either one of the two different vignettes, which were depression vignette and schizophrenia vignette (Figure 1). Questionnaire with either one of the vignettes was sent to the respondents randomly.

The questions in Section 2 were classified into three domains, which included identification of mental illness, helpfulness of interventions and long-term outcome of mental illness. Questions about the identification of mental illness were used to determine the knowledge of respondent on their ability to identify symptoms of specific mental health illness (depression or schizophrenia) and how the mentally ill could be best helped. In the second domain, helpfulness of various interventions or management in mental illness was documented in order to determine the knowledge, belief and attitude of respondents on the helpfulness of various self-help or professional help available. Questions in the domain of long-term outcomes evaluated

the attitude and belief of pharmacists on the probability of long-term recovery and functioning among mentally ill, as well as the acceptance and discrimination of mentally ill among the society.

Figure 1: Illustration of the depression vignette and early schizophrenia vignette in the questionnaire.

Depression Vignette
John is 30 years old. He has been feeling unusually sad and miserable for the last few weeks. Even though he is tired all the time, he has trouble sleeping nearly every night. John doesn't feel like eating and has lost weight. He can't keep his mind on his work and puts off making decisions. Even day-to-day tasks seem too much for him. This has come to the attention of his boss, who is concerned about John's lowered productivity.
Schizophrenia Vignette
John is 24 and lives at home with his parents. He has had a few temporary jobs since finishing school but is now unemployed. Over the last six months he has stopped seeing his friends and has begun locking himself in his bedroom and refusing to eat with the family or to have a bath. His parents also hear him walking about his bedroom at night while they are in bed. Even though they know he is alone, they have heard him shouting and arguing as if someone else is there. When they try to encourage him to do more things, he whispers that he won't leave home because he is being spied upon by the neighbour. They realize he is not taking drugs because he never sees anyone or goes anywhere.

The study was approved by the Ministry of Health (MOH) Medical Research and Ethics Committee. Using the Kish. L (1965) method (10), the calculated sample size for this study was 241. An approval letter from the Pharmaceutical Services Division, Johor State Health Department, MOH was obtained in order to collect details of pharmacists who were registered under Registration of Pharmacists Act 1951 and Registration of Pharmacist Regulation 2004 and currently working in Johor, Malaysia. The email addresses of public sector pharmacists were obtained from the Drug Information Services of government hospitals and district health offices. For pharmacists who worked in the private setting, their email addresses were obtained from the Official Portal of Pharmaceutical Services Programme, MOH (11). A total of 771 pharmacists' email addresses were identified, listed and assigned with a sequential number. Random numbers were generated using Microsoft Excel to select 241 email addresses. The questionnaire containing the depression and schizophrenia vignette were sent out alternately to ensure equal sample size between the two groups. A reminder email was sent two weeks after the initial e-mail to those who had not yet responded. If the recipient failed to respond to the survey after two times of reminder email, an email address was randomly selected again from the pool of email addresses that were not chosen previously.

Data was analysed using the Statistical Package for Social Science (SPSS) version 22.0. The data were analysed using Mann Whitney U test to identify demographic factors that influence mental health literacy of pharmacists in both the depression and schizophrenia vignettes. Findings with P-value less than 0.05 was considered as statistically significant. For demographic factors with continuous variables like age and years of experience, the respondents were grouped into two categories for the analysis, which were less than and greater than the median age, and less than and greater than median years of working experience.

Results

Demographics

A total of 200 responses were received, representing a response rate of 83.0%. Figure 2 showed the simplified flow of data collection. The median age of the respondents was 29 years old (interquartile range (IQR) 27-31 years) and the median year of working experience as pharmacist was 4 years (IQR 2-7 years). Most of the respondents were female (75.2% for depression vignette and 76.9% for schizophrenia vignette) and their main area of practice were government hospital (80.7% for depression vignette and 83.5% for schizophrenia vignette). For depression vignette, 31.2% of respondents described having family experience with mental illness and 17.4% described having personal experience with mental illness. For schizophrenia vignette, 29.7% reported had at least one family member who experience mental illness and 6.6% reported having personal experience with mental illness (Table 1).

Identification of Mental Illness

Depression was correctly identified by 56.0% (n=61) of pharmacists from the depression vignette whereas schizophrenia was correctly identified by 68.1% (n=62) of pharmacists from the schizophrenia vignette. The numbers of respondents who were able to identify the vignettes correctly were presented in Table 2. It was found that younger pharmacists were significantly more likely to be able to identify depression correctly (p=0.013), whereas older pharmacists were significantly more likely to identify schizophrenia correctly (p=0.049).

Figure 2: Flow of the study

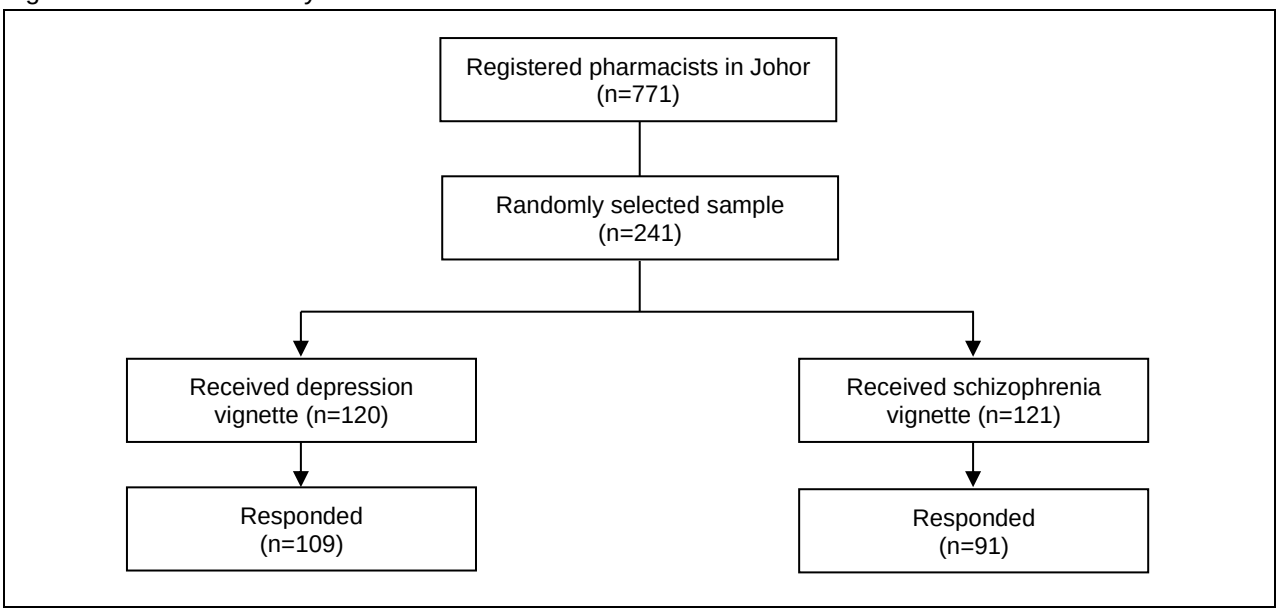

Table 1: Demographics of survey respondents (n=200)

Demographic factors	n (%)	
	Depression (n=109)	Schizophrenia (n=91)
Age		
≤29 years old	60 (55)	49 (53.8)
>29 years old	49 (45)	42 (46.2)
Gender		
Male	27 (24.8)	21 (23.1)
Female	82 (75.2)	70 (76.9)
Primary working site		
Government Hospital	88 (80.7)	76 (83.5)
Community Pharmacy	10 (9.2)	9 (9.9)
Private Hospital	2 (1.8)	2 (2.2)
Enforcement	2 (1.8)	2 (2.2)
Government Health Clinic	7 (6.3)	2 (2.2)
Working experience		
≤4 years	63 (57.8)	46 (50.5)
>4 years	46 (42.2)	45 (49.5)
Experience with mental illness		
Family experience	34 (31.2)	27 (29.7)
Personal experience	19 (17.4)	6 (6.6)
No experience	56 (51.4)	58 (63.7)

Table 2: Number of respondents that identified the vignettes correctly according to demographic factors (n=200)

Demographic factors	Depression (n=109)		Schizophrenia (n=91)	
	n (%) [a]	p-value	n (%) [a]	p-value
Age		0.013 *		0.049 *
≤29 years old	40 (66.7)		29 (59.2)	
>29 years old	21 (42.9)		33 (78.6)	
Gender		0.621		0.22
Male	14 (51.9)		12 (57.1)	
Female	47 (57.3)		50 (71.4)	
Primary working site		0.714		0.155
Government Hospital	50 (56.8)		49 (64.5)	
Community Pharmacy	4 (40.0)		7 (77.8)	
Private Hospital	1 (50.0)		2 (100)	
Enforcement	1 (50.0)		1 (50.0)	
Government Health Clinic	5 (71.4)		2 (100)	
Working experience		0.065		0.052
≤4 years	21 (33.3)		27 (58.7)	
>4 years	40 (87.0)		35 (77.8)	
Experience with mental illness				
Family experience	20 (58.8)	0.687	19 (70.4)	0.767
Personal experience	9 (47.4)	0.408	4 (66.7)	0.079
No experience	32 (57.1)		39 (67.2)	

[a] (%) referred to the percentage of respondents who identified the vignette correctly in each category.
* Statistically significant difference (p<0.05)

Helpfulness of Intervention

People who can help

In the depression vignette, only 72 pharmacists (66.1) agreed that people with depression require professional help but 75 pharmacists (82.4) in the schizophrenia vignette agreed that professional help is required for people suffering from schizophrenia. For the depression vignette, highest number of respondents rated counsellor (94.5%) as helpful followed by psychologist (89.0%) and psychiatrist (83.5%). Less than half of the pharmacists (46.8%) rated themselves as helpful for depressive patient (Table 3). It was found that significantly more pharmacists with age more than 29 years old and respondents who practiced in non-government hospital rated psychiatrist as helpful in depression (p=0.045 and p=0.008) while significantly more pharmacists with working experience less than 4 years rated priest as harmful (p=0.01).

For the schizophrenia vignette, highest number of respondents rated psychiatrist as helpful (97.8%), followed by psychologist (89.0%) and counsellor (82.4%). It is of concern that more pharmacists rated family and friends (75.8%) as helpful compared to pharmacist themselves (56.0%). Pharmacists aging more than 29 years old (p=0.023) and pharmacists with experience more than 4 years significantly (p=0.006) rated person with schizophrenia and dealing it themselves as harmful. It was found that significantly more male respondents rated psychologist (n= 0.019) and pharmacist (n=0.010) as helpful. Meanwhile, significantly more respondents who were currently practiced in non-government hospital rated counsellor (p=0.032), psychologist (p=0.006) and close family or friends (p=0.004) as helpful in schizophrenia vignette. Respondents without family experience significantly rated priest as harmful (p<0.001).

Medication

As for medication, 57.8% of respondents managed to identify antidepressant as helpful in depression vignette whereas 76.9% of respondents rated antipsychotic as helpful in schizophrenia vignette. In the depression vignette, larger number of respondents who age more than 29 years old significantly rated antidepressant (p=0.027) and tranquilizers (p=0.026) as helpful. Similarly, respondents who practiced for more than four years also rated antidepressant (p=0.006) and tranquilizers (p=0.014) as helpful for person with depression. On the other hand, significantly more respondents who practiced in non-government

hospital rated antidepressant (p=0.017) as helpful. In schizophrenia vignette, none of the medication intervention showed significant differences when compared across various demographic factors.

Table 3: Respondents' perceived helpfulness of various interventions for mental illness (n=200)

	Helpful n (%)	
	Depression (n=109)	Schizophrenia (n=91)
People who can help		
Psychiatrist	93 (85.3) *	89 (97.8)
Psychologist	97 (89)	81 (89) *
Family doctor	81 (74.3)	60 (65.9)
Pharmacist	51 (46.8)	51 (56) *
Counsellor	103 (94.5)	75 (82.4) *
Social Worker	63 (57.8)	45 (49.5)
Telephone Counselling	73 (67)	45 (49.5)
Close family or friends	89 (81.7)	69 (75.8) *
Priest	5 (4.6) *	2 (2.2) *
Let him deal himself	1 (0.9)	0 (0) *
Medications		
Antidepressant	63 (57.8) *	53 (58.2)
Antipsychotic	27 (24.8)	70 (76.9)
Tranquilizers	24 (22) *	40 (44)
Sleeping pill	47 (43.1)	29 (31.9)
Vitamin and minerals	20 (18.3)	7 (7.7)
Pain relieving	5 (4.6)	3 (3.3)
Antibiotic	2 (1.8)	0
Activities		
Psychotherapy	87 (79.8)	85 (93.4)
Cognitive behavior therapy	74 (67.8)	78 (85.7) *
Electroconvulsive therapy	20 (18.3)	34 (37.4) *
Admit to psychiatric ward	20 (18.3)	44 (48.4)
Attending courses on relaxation, stress management	105 (96.3) *	76 (83.5) *
Become more physically active	24 (86.2)	68 (74.7)
Reading self-help book	77 (70.6)	43 (47.3) *
On special diet	22 (21.1) *	16 (17.6)
Hypnosis	17 (15.6) *	24 (26.4) *
Having occasional alcoholic drink	7 (6.4) *	7 (7.7)

* Statistically significant differences observed for selected demographic factors (p<0.05)

Activities

In the depression vignette, respondents rated attending courses on relaxation and stress management (96.3%) was helpful, followed by physically active (86.2%) and psychotherapy (79.8%). For schizophrenia vignette, a larger number of respondents believed that psychotherapy (93.4%), cognitive behaviour therapy (CBT) (85.7%) and attending courses on relaxation and stress management (83.5%) were helpful. On the other hand, it was found that low number of respondents rated ECT and admission to ward as helpful in both vignettes.

In the depression vignette, significantly higher number of pharmacist aging above 29 years old and government hospital pharmacists rated occasionally alcoholic drink as harmful in person with depression (p=0.024 and p=0.034). However, hypnosis was rated significantly by government hospital pharmacists as neither helpful nor harmful (p= 0.044). Significantly more respondents without family or friends suffering from mental illness rated special diet as neither helpful nor harmful (p=0.044). On the other hand, significantly more respondents who themselves did not have any mental illness rated attending courses on relaxation, stress management, meditation or yoga to be helpful when compared to the respondents who declared to have mental illness (p=0.002).

In the schizophrenia vignette, it was found that significantly more young pharmacists (29 years old and below) rated attending courses on relaxation, stress management, meditation or yoga (p=0.048), reading self-help book (p=0.034), ECT (0.018) and CBT (p=0.034) as helpful. When comparing across the practice sites, significantly more government pharmacists rated hypnosis as neither helpful nor harmful in schizophrenia (p=0.032) but rated attending relaxation courses (p=0.046) as helpful. Pharmacists with no family members or friends suffering from mental illness significantly rated attending relaxation courses (p=0.027) and reading self-help book to be helpful (p=0.043).

When looking at the information seeking behaviour, most of the respondents rated health educator to be helpful in providing information to person with mentally ill in both the depression vignette (91.7%) and schizophrenia vignette (87.9%). On the other hand, sourcing information from website was rated to be helpful by least pharmacists and in fact it was rated as harmful by almost one third of the pharmacists in both the depression vignette (27.5%) and schizophrenia vignette (29.7%).

Long-term Outcomes of Mental Illness

Long-term recovery

A total of 61.5% of respondents in the depression vignette and 70.3% of respondents in the schizophrenia vignette believed that person with depression can fully recover but it would probably reoccur even if professional help was sought (Table 4). If a person with mental illness did not seek professional help, majority of respondents in both vignette (68.8% in depression vignette and 79.1% in schizophrenia vignette) believed that the condition could get worse.

For the depression vignette, none of the demographic factor showed significant differences in the belief of pharmacists on long term recovery. For the schizophrenia vignette, on the other hand, it was found that significantly more pharmacists aged more than 29 years old (p=0.017) and pharmacists who have practiced for more than 4 years (p=0.007) believed that person with schizophrenia would get worse if professional help was not sought.

Long term functioning

For the likelihood of long-term functioning when compared to other people in the community, the highest number of respondents believed that person with depression will be more likely to have poor friendships (45.9%) but less likely to be aggressive (47.7%) (Table 5). Similarly, the highest number of respondents believed that person with schizophrenia will be more likely to have poor friendships (45.1%) but a total of 47.3% of pharmacists believed these groups of patients will be less likely to be able to understand another people's feeling.

When looking at the effect of close contact experience, it was found that significantly more pharmacists who have family or friends with mental illness believed that people with depression will be less likely to be violent (p=0.049) or take illegal drugs (p=0.007) in long term when compared to other people in the community. However, significantly more pharmacists who have no family or friends with mental illness believed that people with depression will be less likely to understand other people's feeling (p=0.043). For schizophrenia, none of the demographic factors showed significant differences in terms of pharmacist belief on long term functioning.

Attitude towards mentally ill person

A total of 56.9% of respondents from depression vignette and 78.0% of respondents from schizophrenia believed that community would discriminate person with mental illness. When looking at the pharmacist's attitude towards mentally ill person, majority of the pharmacists agreed that person with depression (45.0%) and schizophrenia (65.9%) is unpredictable. However, 51.9% of the pharmacists disagreed that depression is a sign of weakness. It was also found that majority of pharmacists strongly disagreed with the idea of avoiding people with depression (45.9%) and schizophrenia (51.6%) to prevent themselves from the disease.

In terms of belief about discrimination in the community, majority of the pharmacists agreed that most people in the community will perceive depression (54.1%) and schizophrenia (59.3%) as a sign of weakness. A total of 56.0% of pharmacists also agreed that public would perceive schizophrenia patient as someone dangerous. Besides, majority of pharmacists agreed that most of the people in the community would not tell anyone if they have depression (57.8%) or schizophrenia (58.2%).

Looking at the aspect of contact with person who is mentally ill, it was found that most of the pharmacists were probably willing to have contact i.e. staying next door, socialize, making friends and working together with someone who has depression or schizophrenia. However, pharmacists were probably unwilling to have family member who suffer from schizophrenia (40.7%) compared to depression (35.8%).

Perceived risk factor of mental illness

Generally, majority of pharmacist believed that depression and schizophrenia were unlikely to be due to virus and allergy. Most of the pharmacists believed that depression was caused by stress (83.5%), recent death of close contact (74.3%) and problems from childhood (73.4%). On the other hand, problems from childhood (74.7%) and stress (73.6%) were perceived to be the risk factors for schizophrenia by most of the pharmacists. Of note, there was also quite a handful of pharmacists that believed that chemical imbalance in the brain was the cause of depression (53.2%) and schizophrenia (60.4%).

Table 4: Respondents' perceived probability of long-term recovery for mental illness

	n (%)	
	Depression (n=109)	Schizophrenia (n=91)
With professional help		
Full recovery with no further problems	18 (16.5)	13 (14.3)
Full recovery but problem would probably reoccur	67 (61.5)	64 (70.3)
Partial recover	9 (8.3)	1 (1.1)
Partial recover but problems would probably reoccur	15 (13.8)	13 (14.3)
No improvement	0	0
Get worse	0	0
No professional help		
Full recovery with no further problems	1 (0.9)	0
Full recovery but problem would probably reoccur	2(1.8)	1 (1.1)
Partial recover	2 (1.8)	1 (1.1)
Partial recover but problems would probably reoccur	18 (16.5)	9 (9.9)
No improvement	11 (10.1)	8 (8.8)
Get worse	75 (68.8)	72 (79.1) *

* Statistically significant differences observed for selected demographic factors (p<0.05)

Table 5: Respondents' perceived likelihood of long-term functioning of mentally ill person

	More likely		Just likely		Less likely	
	Depression	Schizophrenia	Depression	Schizophrenia	Depression	Schizophrenia
To be violent	29 (26.6)	33 (36.3)	28 (25.7)	21 (23.1)	52 (47.7) *	37 (40.7)
To drink too much	37 (33.9)	27 (29.7)	31 (28.4)	25 (27.5)	41 (37.6)	39 (42.9)
To take illegal drugs	33 (30.3)	30 (33)	30 (27.5)	22 (24.2)	46 (42.2) *	39 (42.9)
To have poor friendship	50 (45.9)	41 (45.1)	21 (19.3)	19 (20.9)	38 (34.9)	31 (34.1)
To attempt suicide	43 (39.4)	40 (44)	24 (22)	14 (15.4)	42 (38.5)	37 (40.7)
To be understanding of other people's feelings	32 (29.4)	27 (29.7)	32 (29.4)	21 (23.1)	45 (41.3) *	43 (47.3)
To have good marriage	27 (24.8)	24 (26.4)	34 (31.2)	32 (35.2)	48 (44)	35 (38.5)
To be caring parent	34 (31.2)	25 (27.5)	29 (26.6)	31 (34.1)	46 (42.2)	35 (38.5)
To be a productive worker	34 (31.2)	26 (28.6)	26 (23.9)	27 (29.7)	48 (44)	38 (41.8)
To be creative or artistic	24 (22)	24 (26.4)	38 (34.9)	38 (41.8)	47 (43.1)	29 (31.9)

* Statistically significant differences observed for selected demographic factors (p<0.05)

Discussion

In this study, it was found that near to half of the pharmacists were unable to identify depression while one third of them were unable to identify schizophrenia based on the scenario described in the questionnaire. The rate of recognition on these two mental illnesses was relatively lower compared to the result in a previous study (7). As pharmacy is easily accessible to the public, pharmacists potentially play an important role in screening and referring person with early relapse warning signs to the appropriate healthcare professional. Hence, the finding in this study was worrisome as it indicated that many pharmacists were unable to recognize these two common types of mental health illnesses. This may result in the incapability to provide necessary help or appropriate advice when they encounter such group of patients.

Looking at the self-help behaviour or help seeking behaviour, most of the results in this study was consistent with a previous study in Australia by O'Reilly *et al.* (7). In both studies, the pharmacists rated professional help as helpful in both vignettes except approximately half of the pharmacists in this current study did not rate themselves as helpful in both vignettes. This result was particular of concern as this probably indicated that pharmacists were generally not comfortable to provide pharmaceutical care to patients with mental health illness. This was evident from the result of another study (8) where the authors reported that pharmacists had a lower degree of willingness to provide pharmaceutical care to mentally ill patients than patients with cardiovascular disease due to the lack of knowledge in mental illness. The lack of knowledge in mental health illness was also probably the main reason that contributed to the lower recognition rate of mental illness in this study. In addition, lack of privacy setting in the pharmacy environment and pharmacists' perception on the challenging behaviour of mentally ill patients were the other reasons that were reported to be contributing to this situation (9,12-14).

In this study, it was found that significantly higher number of older pharmacists and more experienced pharmacists were able to identify the proper management of depression compared to the younger and less experienced one. The failure of the younger and less experience pharmacists to identify and provide proper management could further delay the appropriate healthcare services for this group of patients. Rubio-Valera *et al*. (2014) described that pharmacists could play an important role to screen the signs and symptoms of depression as they are more accessible by the community (15). Their ability to identify proper treatment in depressive patient, who was previously undetected, can assist the patient to receive appropriate health service as earlier as possible. Therefore, more specialized training or education should be provided for the younger and less experienced pharmacists in order to improve their mental health literacy and boost their confidence in managing psychiatry patients in the community.

Most of the pharmacists in this study did not rate admission to the psychiatric ward as helpful and generally most of them had negative view towards ECT in both vignettes. The results were consistent with the previous study on pharmacists (7) and public (16). This negative view on the standard treatment in psychiatry was particular of concern as this might affect the quality of counselling and advice given to these groups of patients. The possible reason could be due to insufficient exposure during undergraduate and insufficient training on mental health management as reported by a recent study done in Malaysia (17).

In terms of long-term recovery, it was found that pharmacists in Johor generally had reasonable and positive expectation on long term recovery. Pharmacist in this study generally also held negative view on long term recovery without professional help. Similar finding was also reported previously among the other healthcare professional and public (7,16). This finding perhaps showed that pharmacists generally agreed on the need of professional help and this positive view on professional help seeking behaviour would be particularly important when these patients seek help from the pharmacists in the community.

On the other hand, pharmacists in Johor generally were optimistic towards several negative presentations such as being violent, alcoholic and taking substance in both the depression and schizophrenia vignettes. This result was consistent with a previously reported finding where Australian pharmacists also reported that these negative items were less likely to occur in the long term (7).In the reality, however, patients diagnosed with mental illness could still be expected to experience these negative outcomes even after a long time. Hence, over optimistic towards the long-term functioning of mental health patients may probably indicate less familiarity with mental illnesses. This was evident from a previously reported study in Malaysia where most of the pharmacists agreed that they are lack of knowledge and training in mental health illness (17).

Nonetheless, majority of pharmacists rated negatively on the long-term social functioning of both vignettes, such as 'poor friendship', 'ability to care for others', 'good marriage', 'caring parents' and 'productive worker'. With proper treatment, patient with depression and schizophrenia may not necessarily have poor social functioning in the long term. Therefore, this result highlighted that majority of pharmacists in this study has certain degree of stigmatization towards mentally ill person in terms of their social functioning. This could adversely affect patient's help-seeking behaviour and compromise the chances of recovery as well as their functioning in the society in long term (18).

In this study, majority of the pharmacists felt that mentally ill patients, especially patients with schizophrenia, may be discriminated by the community. This was supported by a Malaysian study which reported schizophrenia to be the most common mental illness that was discriminated by public, followed by bipolar disorder and depression (18). Some neighbouring Asian countries also reported similar results (19-20). This was, however, in contrast with another Australian study where their pharmacists were generally having more positive belief and attitude towards mental illness (7). Cultural differences could probably the reason behind this. As reported by Ng *et al.* (21), Asian community tends to express stigma on mentally ill patients and their family due to their perception that mental illness is associated with violence, hereditary deficits and spiritual punishment. On top of that, dispensing separation in Australia could have probably increase the frequency of prescription medication filled by mentally ill patient in the community pharmacies. Therefore, this may increase the pharmacists' contact with mentally ill patient and give rise to the more positive view on the long-term outcome of mentally ill patients (22).

Majority of pharmacists in this study believed that person who suffers from mental illness does not tell anyone else about their condition. Besides, majority of our respondents also believed that mental illness is labelled as a sign of weakness and patients with schizophrenia is particularly dangerous. This was coherent with a previous study which reported that labelling, avoiding and employment discrimination were the most common types of discriminations towards mentally ill person in Malaysia (18). Due to the stigmatization, the sick ones may be worried to seek professional help or may default their treatment in order to conceal the condition (18,21).

There were some limitations that should be considered when interpreting the results of this study. Firstly, insufficient response from some sites of practice, such as community pharmacy, private hospital, industrial pharmacy and pharmacy enforcement, and inadequate response from male pharmacists had resulted in unequal distribution in these demographic factors. Hence, the differences in mental health literacy in these demographic factors need to be considered carefully. Secondly, there might be bias in the reporting of personal experience with mental illness as some individuals might not wish to disclose their own or family conditions. Besides that, the respondents were mainly below 32 years old. Comparing to the general retirement age in Malaysia which ranges from 55 to 60 years old, our respondents were relatively younger. Therefore, the result of this study might not generalize to the pharmacist population in Malaysia.

Conclusion

In general, a large number of pharmacists in Johor were still relatively less likely to be able to recognize common mental illness. Most of the pharmacists also did not perceive themselves as important in the management of mental health illness. However, older and more experienced pharmacists were found to have higher degree of mental health literacy in most domains of the study as this was indicated from ability to identify professional intervention, proper medicine, harmful lifestyle and long-term recovery. As the prevalence of mental illness increases over the years, pharmacists especially the young and less experience ones may require more intensive training and education on the handling and communication with mentally ill patients. Pharmacists should be aware that their attitudes and discrimination towards mental health illness may affect their services. As this is a preliminary study about mental health literacy focusing on pharmacists in Johor, a national level study could probably be done in future to better understand mental health literacy of pharmacists in Malaysia.

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Conflict of Interest Statement

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Patient's Perception on the Features of Interest and Barriers of Smartphone Medication Adherence Applications

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Abstract

Introduction: Well-designed smartphone applications (apps) can potentially help in enhancing adherence to medications, but its application was limited due to the lack of studies.

Objective: This study aimed to determine the factors that may lead to medication non-adherence, identify the important features of a smartphone medication adherence app that can improve medication adherence, and to understand the possible predictors and barriers in downloading such app.

Method: A cross-sectional survey was conducted at Outpatient Pharmacy of Hospital Enche' Besar Hajjah Khalsom, Kluang, Johor, where a structured self-administered questionnaire was distributed to the patients. The inclusion criteria were adults with confirmed diagnosis of any chronic illness, on repeated prescriptions of three or more medicines and owned a smartphone.

Result: A total of 154 responses was collected for final analysis. Forgetfulness or carelessness were reported as the most common factors causing non-adherence. About half of the respondents rated side effect management tool (52.2%), disease information (47.8%) and reminder system (41.3%) as the most important features in an app whereas offline internet access and the ability to create reports to be send to doctors were found to be the least important to them (15.2% and 19.6% respectively). Patients who lived in urban areas, had more than five medicines intakes daily and used smartphones for more than five times daily were significant predictors of interest to adopt an adherence app. The lack of knowledge about the usefulness of medication adherence app were the main reasons given by the participants for their disinterest in adopting an adherence app (43.8%).

Conclusion: Patients showed great interest to be more actively involved in the therapy. Thus, app developers should consider toinclude database of information about disease, medicine and self-management tools and wide range of reminder system to develop a functional and relevant medication adherence smartphone apps.

Keywords: compliance, adherence, smartphone, application

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Introduction

Adherence is defined as the extent of an individual, particularly a patient, to follow or stick to the healthcare professionals' recommendation, advices or instructions regarding his or her individualized therapeutic regimen (1). In 2016, The Ministry of Health Malaysia (MOH) reported that they disposed about RM 2 million worth of expired medicines returned by the patients (2). On top of that, a study conducted among hypertensive patients in 2007 at Hospital Tuanku Jaafar Seremban found that each patient had wasted around RM 42 of taxpayer's money due to unused medicine. A total loss of unused medicine amounting to RM 59,566.50 with monthly average of RM 9,927.75 was reported at the end of the study (3).

Adherence to medicines is commonly thought to be a patient's full responsibility. However, it is now known that medicine-taking behaviour is more complicated than it was thought to be and relies closely to the relationships between physicians, patients, and the healthcare system itself (4).

In a US-based report by Express Script, it was found that 69% of non-adherence was due to patients' behaviour (5). It can be divided into two major categories which were unintentional and intentional non-adherence. The latter is described as patient own decision to deviate from the therapeutic plans agreed

with the prescribers. According to the National Survey on the Use of Medicines (NSUM) by Malaysian Consumers 2015, almost half of the correspondents had admitted to consciously chosen not to take prescribed medicines (6). The fear of possible side effects and not feeling ill or any better upon taking the medicines were commonly seen among patients taking symptom-control medication regimens like antihypertensives and hyperlipidaemias. Shockingly, the lack of adherence could also be due to the patients' self-denial of current unwell conditions, i.e. patients refuse to take medicine as it reminds them of being ill or unhealthy (7).

Unintentional nonadherence is the passive type of nonadherence in which the patients are unable to take medications as indicated or instructed due to limited resource or capacity. According to the NSUM 2015, almost two-third of the surveyed subjects claimed that they had forgotten to take their daily medications (6). Physical impairments such as blindness or limited limb dexterity can also affect patients' efforts in adhering to the treatment (8). In the large-scale Aston Medication Adherence Study (AMAS) conducted in Birmingham, England, the researchers concluded that some demographic factors like ethnicity, religion practice and poor socioeconomic patients might also be associated with weak adherence to treatments (9). Prescribers are being considered as the gatekeeper for the healthcare sector but them being the front line of healthcare sector might indirectly lead to nonadherence among the patients. It was found that most general practitioners (GP) failed to identify adherence issue among the patients, probably due to time constraints (10). This could be due to overcrowding patients and limited resources in the healthcare (11).

In general, the common methods used to motivate patients to increase adherence are traditional reminder systems, education on medicine taking behaviour, counselling by healthcare professionals, simplifying the complex dose regimen, or a combination of these approaches (12). Smartphones could be a new platform for the healthcare system to reduce the barriers between the healthcare providers and patients. With the growing number of worldwide smartphone users, which was estimated to escalate up to 22.38 million in 2018 in Malaysia alone (13), it is a major indicator of heavy reliance on the gadget nowadays. Hence, it seems promising to introduce mobile downloadable medication adherence applications (apps) for smartphones.

As the market for medication adherence apps is relatively new, there is very little extensive research focusing on smartphone apps as a potential intervention to improve medication adherence. Only 1.5% out of 400 participants in a previous small-scale study realised the existence of such apps on their smartphones (14). As there are increasing reliance on smartphones among the Malaysians, a novel approach of improving medication adherence using mobile apps may be introduced. Therefore, this study aimed to determine the factors that may lead to medication non-adherence and to identify the important features of the app that can improve medication adherence from the patients' perspectives. In addition, we also aimed to understand the association between the patients' demographic factors and their interest in downloading a smartphone medication adherence app, and to identify any possible barriers hindering them from downloading any smartphone medication adherence applications**.**

Method

Questionnaire design and development

A draft questionnaire was devised based on validated questionnaire from previous studies (12,14,15,20). It was reviewed for content validity and the final questionnaire was approved after several amendments over four weeks.

In overview, the questionnaire constituted four sections which were personal details and smartphone usage information, medication regimen, features of interest in the medication adherence app and the perceived barriers in using the app. As this study was targeting respondents from the general public with different background of life, the questions were devised in the absence of technological terms or medical jargon. The questions were mostly designed in the form of multiple-choice questions (MCQs) and several questions were presented in Likert-scale statements. Most of the questions were closed questions which will help respondents to narrow down their choices and complete the questionnaire faster, in approximately five to ten minutes.

Questionnaire distribution and participant recruitment

This cross-sectional study was conducted at the Outpatient Pharmacy of Hospital Enche' Besar Hajjah Khalsom, Kluang, Johor from August 2018 to September 2018. Using a sample size calculator, 195 participants were needed for the study with 95% confidence interval and marginal of error of 5%.

We performed convenience samplings with recruitment of respondents conducted at the outpatient pharmacy during prescription screening in order to identify suitable participants who fulfilled the inclusion criteria. The inclusion criteria of the study were adult from the age of 18 and above, diagnosed with any chronic disease (for example, cardiovascular diseases, diabetes mellitus, etc.), prescribed with at least three medicines and being an active smartphone user. Exclusion criteria were patients who were unable to understand Malay or English language and those who were already using such apps upon recruitment.

Consents to participate in the survey were obtained from the respondents. Upon agreement, respondents were given short briefing about the objective of the study and overview of different section of the questionnaire before completing the questionnaire.

Data analysis

Minitab Express Software was used to process and analyse the data. Microsoft Excel was mainly used to count the frequency of each demographic factors and factors of non-adherence. To identify any association between two observations, cross tabulations and Chi-square tests were conducted. P-values were calculated with statistical significance only if the P-value was less than or equal to 0.05 which implied that there was a 95% confidence in the analysis.

Ethical issue

The survey was approved by the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia. No findings, which could identify any individual participant, was published. Participation in this research was entirely voluntary.

Results

I total, 154 responses were included in the final analysis. According to Table 1, the cohort was dominated by males (n=94, 61%) and the mean age of the respondents was 52.86 (standard deviation (SD) 12.12) years. Malay participants consisted of 69.6% (n=107) of the whole respondents. In terms of education level, only 17.4% (n=26) of the respondents received tertiary education. Most of the respondents were pensioner which made up to 34.8% (n=54) of the participants and 67.4% of the respondents belonged to the urban locality. About 44% (n=67) of the respondents had monthly income of RM 1001-2000.

From Table 2, it was found that about two-third of the respondents used Android phones (71.7%), with more than half of them were considered as heavy smartphone users by using it more than five times daily (52.2%). Almost 80% of the respondents said that they used mobile data for smartphone internet connection while the rest only relied on WIFI connection (21.7%).

It was reported in Table 3 that almost 60% of the total respondents were taking more than three types of frequent medicines daily, while only 13% took more than eight medicines daily. Most of these respondents admitted already getting accustomed to the daily routine of medicines intake (80.4%). However, about 11% used written reminder to remind them to take the medicines on time.

From Figure 1, it was found that more than one third of the respondents (36.6%) admitted that they were careless or simply forgot with no specific reason which they did not take the medicines. This was followed by the fear of medicine side effects and the perception of being healthy (17.8% and 11.1% respectively) which hindered them to adhere to the therapy. It was found that most of the respondents did understand how their prescribed medicines help to control the disease and the health staffs did a satisfactory job in assisting patients to obtain the information throughout the therapy.

All participant had not used any medication adherence app previously. Despite the low number of app awareness, the interest in using an app was high in which more than half of the respondents (57.1%) showed their interest in downloading a medication adherence app in their smartphone.

Chi-square test was performed to identify any association between the demographic factors and respondents' interest in downloading the app. As shown in Table 5, there was significant associations between living area, smartphone usage and total medicine intake (p=0.0491, p=0.0431 and p=0.0448, respectively) and the respondents' interest in downloading the app. In other words, patients who lived in urban areas, have more than five medicines intake and those who used smartphone for more than five times

daily were significant predictors of interest to adopt an adherence app. The other demographic factors had not shown any significant association.

Figure 2 demonstrated that the respondents thought that side effect management tool was the most important feature in a medication adherence app (52.2%), followed by the access on disease information (47.8%) and reminder system (41.3%). Offline app access and the ability to create reports to be send to the doctors were found to be the least important feature for them (15.2% and 19.6% respectively).

Most of the respondents reported that they do not have enough information about the usefulness of medication adherence app, and this could prevent them from using such app in the smartphone (43.8%) (Figure 3). This was followed by the issue of technical difficulties when using the app (10.1%). The security of the app was not a considered as a big concern by the respondents (2.2%).

Table 1: The demographic background of the respondents (n=154)

Demographic factors		Frequency (n)	Percentage (%)
Gender			
	Male	94	61.0
	Female	60	39.0
Age			
	18 - 54 year	74	48.1
	55 - 64 year	50	32.5
	≥65 year	30	19.5
Ethnicity			
	Malay	107	69.6
	Chinese	20	13.0
	Indian	20	13.0
	Others	7	4.3
Education			
	Primary school	27	17.4
	Secondary school	97	63.0
	Pre-university / Diploma	13	8.7
	Degree	10	6.5
	Master	3	2.2
	No formal education	3	2.2
Occupation			
	Government	23	15.2
	Private	40	26.1
	Student	0	0.0
	Retired	54	34.8
	Self-employed	13	8.7
	Unemployed	23	15.2
Living area			
	City	104	67.4
	Rural	50	32.6
Income			
	Less than RM 1000	37	23.9
	RM 1001 - RM 2000	67	43.5
	RM 2001 - RM 3000	20	13.0
	RM 3001 - RM 4000	13	8.7
	RM 4001 - RM 5000	7	4.3
	More than RM 5000	10	6.5

Table 2: Smartphone usage among the respondents (n=154)

Smartphone Usage	Frequency (n)	Percentage (%)
Type of smartphone		
Android	110	71.7
Apple	7	4.3
Others	37	23.9
Usage per day		
1 - 3 times	54	34.8
3 - 5 times	20	13.0
More than 5 times	80	52.2
Internet connection		
Mobile data / WIFI	121	78.3
WIFI only	33	21.7

Table 3: Medication regimen information of the respondents

Medication Regimen Info	Frequency (n)	Percentage (%)
Total medicine intake		
3-5 types of medicine	90	58.7
5-8 types of medicines	44	28.3
More than 8 medicines	20	13.0
Approaches used to remember to take medicine		
Daily routine	124	80.4
Family / carer aids	10	6.5
Alarm	3	2.2
Written reminder	17	10.9

Table 4: Awareness and interest in downloading a smartphone medication adherence app (n=154)

Aware of the application existence, n (%)	Interest in downloading the apps, n (%)	
	Yes	No
Yes	13 (8.4)	10 (6.5)
No	87 (56.5)	44 (28.6)

Table 5: Association between demographic factors and interest in downloading smartphone medication adherence application

Demographic factors	Interest in downloading the apps, n (%)		P-value
	Yes	No	
Gender			0.0186
Male	60 (39.1)	33 (21.7)	
Female	40 (26.1)	20 (13)	
Age			0.0903
18 – 54 year	54 (34.8)	20 (13)	
55 - 64 year	27 (17.4)	23 (15.2)	
≥ 65 year	20 (13)	10 (6.5)	
Ethnicity			**0.0187**
Malay	64 (41.3)	44 (28.3)	
Chinese	17 (10.9)	3 (2.2)	
Indian	17 (10.9)	3 (2.2)	
Others	3 (2.2)	3 (2.2)	
Education			0.0756
Primary school	10 (6.5)	17 (10.9)	
Secondary school	64 (41.3)	33 (21.7)	
Pre-university / Diploma	3 (2.2)	0 (0)	
Degree	10 (6.5)	3 (2.2)	
Master	10 (6.5)	0 (0)	
No formal education	3 (2.2)	0 (0)	
Occupation			0.0912
Government	17 (10.9)	7 (4.3)	
Private	23 (15.2)	17 (10.9)	
Student	0 (0)	0 (0)	
Retired	37 (23.9)	17 (10.9)	
Self-employed	7 (4.3)	7 (4.3)	
Unemployed	17 (10.9)	7 (4.3)	
Living area			**0.0491**
City	74 (47.8)	30 (19.6)	
Rural	27 (17.4)	23 (15.2)	
Income			0.0814
Less than RM 1000	23 (15.2)	13 (8.7)	
RM 1001 - RM 2000	44 (28.3)	23 (15.2)	
RM 2001 - RM 3000	13 (8.7)	7 (4.3)	
RM 3001 - RM 4000	7 (4.3)	7 (4.3)	
RM 4001 - RM 5000	3 (2.2)	3 (2.2)	
More than RM 5000	10 (6.5)	0 (0)	
Frequency of smartphone usage			**0.0431**
1 - 3 times daily	37 (23.9)	17 (10.9)	
3 - 5 times daily	7 (4.3)	13 (8.7)	
More than 5 times daily	57 (37)	23 (15.2)	
Internet connection			0.1129
Mobile data or WIFI	74 (47.8)	47 (30.4)	
WIFI only	27 (17.4)	7 (4.3)	
Total medicine intake			**0.0448**
3 - 5 types of medicine	57 (37)	33 (21.7)	
5 - 8 types of medicines	27 (17.4)	17 (10.9)	
More than 8 medicines	17 (10.9)	3 (2.2)	

Figure 1: Factors that led to medicine non-adherence among the respondents

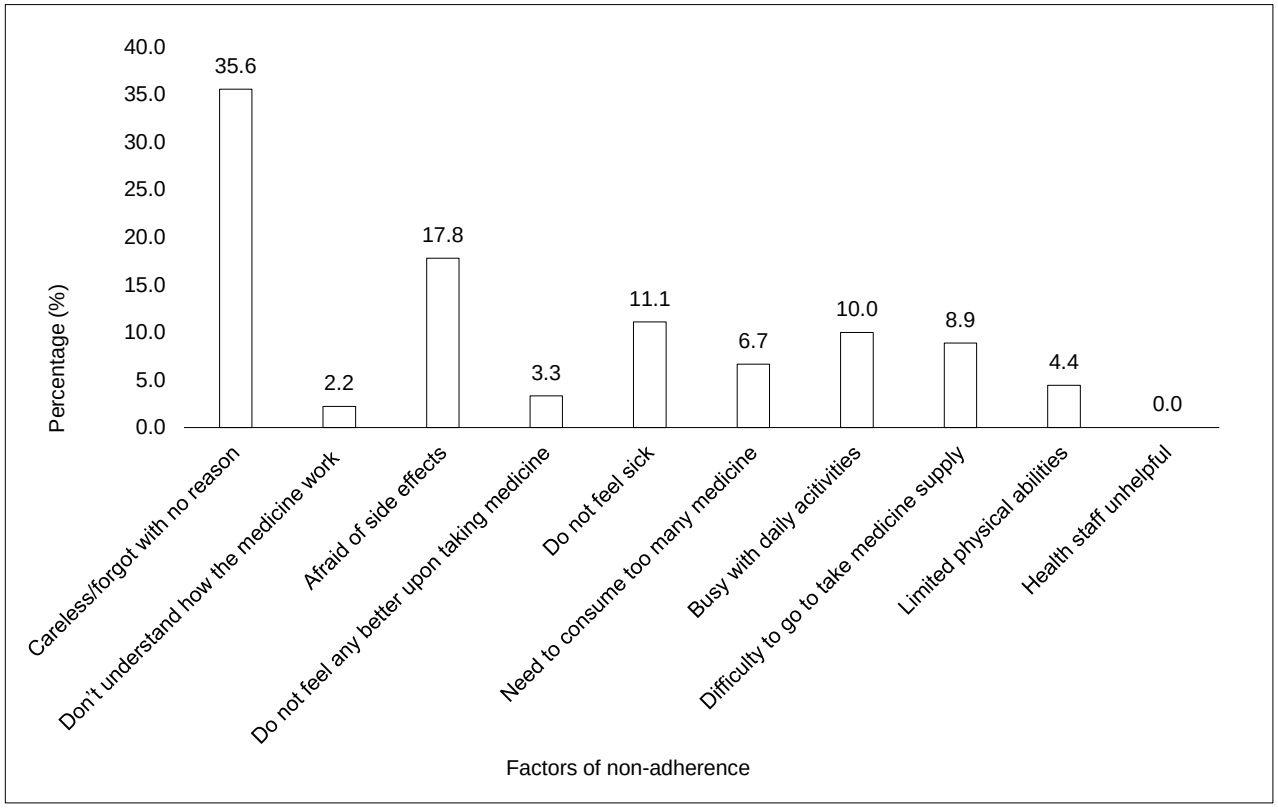


Figure 2: Level of perceived importance on different features in the app

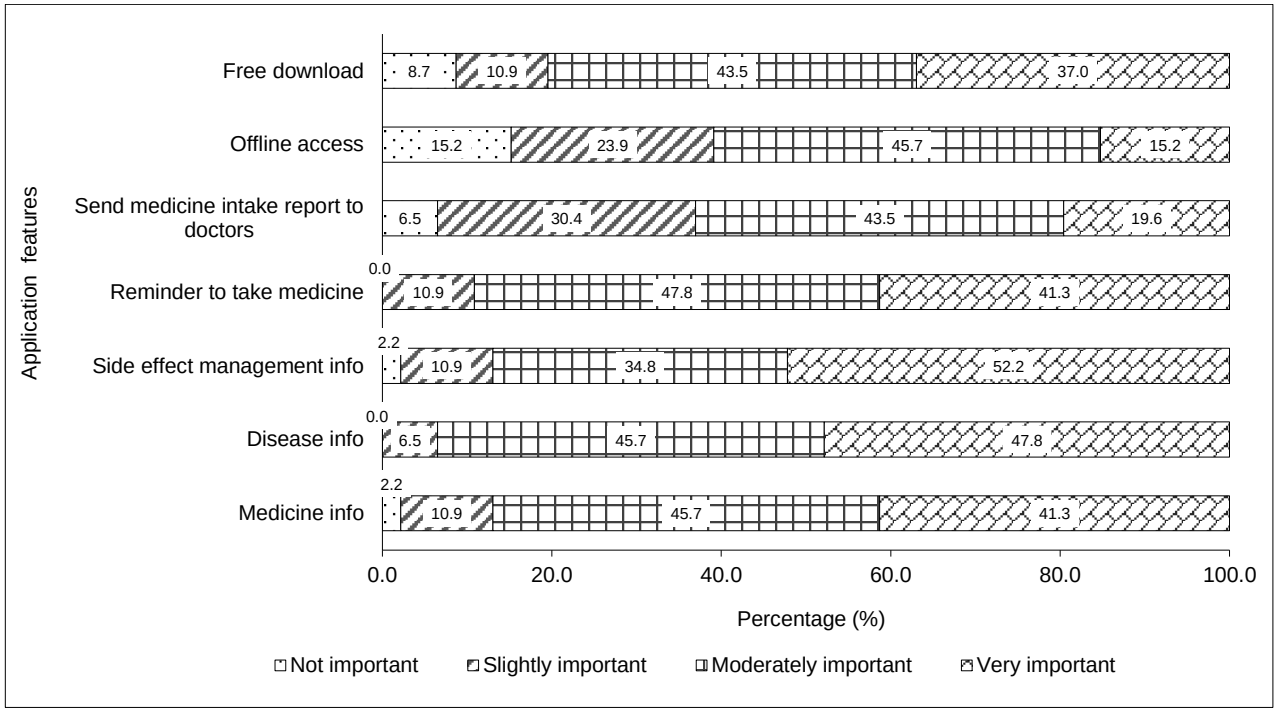
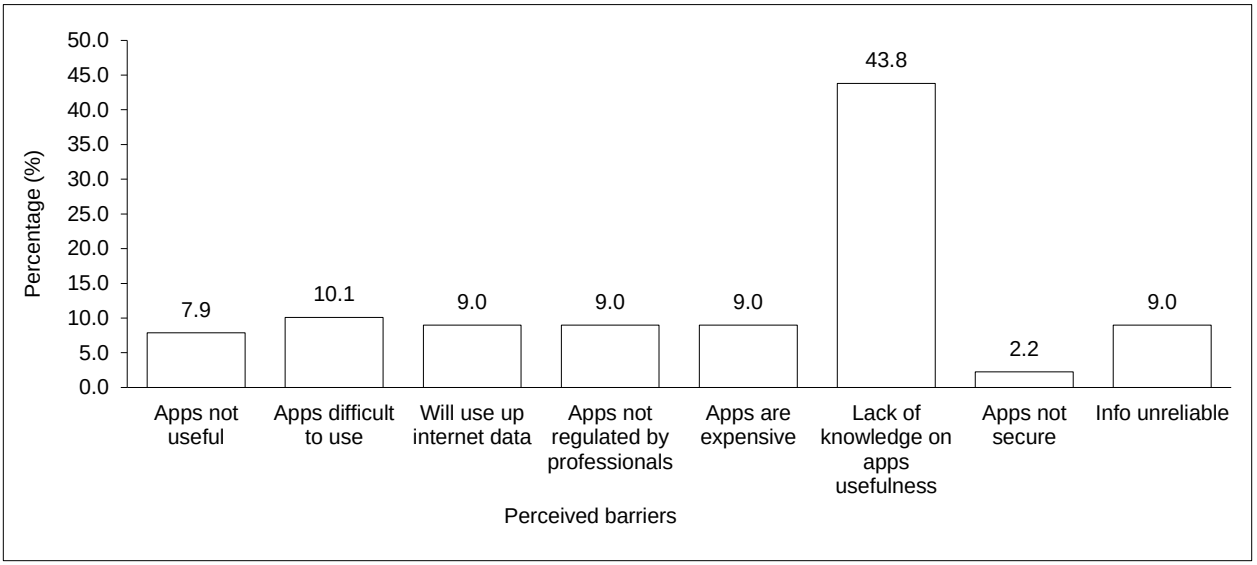


Figure 3: Perceived barriers among the respondents in using the app



Discussion

In this study, it was found that forgetfulness or carelessness were the most common factors causing non-adherence and this was consistent with the reviews by Jin (15). Hence, the reminder and side effect monitoring features were found to be among the most important features of interest among the respondents. It was also found that patients who lived in the cities who needed to take at least five medicines daily and heavy smartphone users are more likely to download the app to help to improve their compliance. However, the lack of exposure to the usefulness of the app were perceived as a barrier to use the app in real life by most of the respondents.

Smartphone intervention is the new, cutting-edge method in assisting adherence and to date, was proven to show promising results in some small-scale studies (17). However, this study found that only approximately 15% of the respondents knew about the existence of medication adherence apps. This might be due to most of the patients were satisfied or comfortable with the conventional adherence strategies which made them less interested in trying any new approach.

Nevertheless, this study also found good level of interest among the respondents especially in those from urban areas and considered as heavy phone users with many medicine intakes. One of the previous studies also showed that increasing number of prescribed medicines was associated with the higher intensity of using medication apps (18). This was probably because they need a more practical way to keep track with their therapy plan and smartphone seem to provide the best platform to improve medicine adherence in their hectic life (19). Hence, patients with these demographic backgrounds were good predictors for medication adherence application intervention.

The level of importance of application features in our questionnaire were adopted from a study conducted in Singapore (20). The findings from this study showed an urge to design a viable medication adherence application that includes information on disease, medicines and self-management of side effects. This can be classified as educational interventions (20). Therefore, a database of different diseases categorized in different classes of discipline like cardiovascular, neurological and oncology should be created to provide the end users with sufficient amount of information regarding each disease. Therefore, a database of medicine details like dosages, indication, common side effects and ways to manage should be included in the application to promote better understandings on how different medicines help patients to control their diseases as well as self-management of different side effects.

The findings from this study also indicated that the reminder feature was also considered to be a necessity in the app. Several previous studies also showed higher demand from users for this feature (20-23). This indicated the heavy reliance of people to reminder-based system in medication adherence apps which could relate closely to better adherence. A review was conducted to identify high quality adherence application and it was found that the application equipped with various effective reminder systems like

missed dose reminder or “snooze” feature, next medicine collection reminder and doctor appointment reminder were more clinically relevant for adherence intervention (24).

However, it was alarming to discover that most people do not want to send their medication intake history to healthcare professionals. The same result was also reflected in another smartphone app intervention study in Singapore (20). One possible explanation is that they want to prevent from being nagged by the doctors or pharmacists on the procrastination habits in taking their medicine. Others might feel demotivated upon seeing unsatisfactory adherence rate in the records which may lead to the loss of interest in taking their medicines. Some people could be over protective with their personal information which made them to decide not to share with anybody. Moreover, patients might have overlooked the usefulness of enabling health professionals’ monitoring, in terms of improving their adherence levels (25). Despite the low perceived importance of this feature, the ability to produce reports on monthly medicine intake is very important as this greatly provides healthcare staffs on the adherence level of patient that usually correlates to disease management. Therefore, app developers should include this feature if they want to create a more clinically relevant app.

The offline access feature is deemed to be least important which might indicate that most people nowadays have stable internet connection every day. Hence, this feature could be considered as redundant. This might be advantageous as app developer might not need to prepare offline database of all the information. Besides, it is possible to link the additional info to established health-based websites like WebMD. Hence, possible partnership with existing health websites might reduce the burden of app developer in fulfilling demands on information database of the app.

The perceived difficulty in using and the lack of knowledge about the usefulness of apps for medication adherence were the main reasons given by the participants for their disinterest in adopting an adherence app. This was consistent with theories of technology adoption. According to the technology acceptance model, perceived usefulness and ease of use greatly influence the acceptance and adoption of technology (26). These findings implied that app developers should consider user-centred approaches in designing adherence apps that are more age sensitive and user friendly.

It was surprising that most of our respondents did not find the security of the app important. This might be due to the underestimation on the need of data security as they were not fully aware about the possibility of privacy breach and misuse of health data from non-secured electronic data keeping and sharing (27). Some possible explanation was the thought that the revelation of their personal data to third party is insignificant as there were no perceived detriments to them, i.e. no harm to them if anyone knows about their health status (28). Nevertheless, the risk of unauthorized access to these information remains as potential violation towards one’s privacy. Therefore, it is advisable that app developer include a trustable security system in the app to make the app reliable and more trustable.

Data in this study were gathered from a convenience sample at a single institution, which could limit generalizability of the results. A small number of participants was obtained for the study, hence it could not represent the true population in the country. Furthermore, limited statistical test can be conducted using these limited data, thus reducing the impact of the study. As the target group of the study including elderly people, high rejection rate of questionnaire was observed from 50 years old and above respondents. This could be due to the lack of interest of the senior citizens towards technology mediated adherence aids which led them to leave some of the major sections in the questionnaire completely blank.

Conclusion

Smartphone intervention should be introduced as the new mainstay of adherence improvement among the patients due to its cheaper cost, portability and unlimited seamless access. Regardless of the limitation, this study provided an insight of what people desire in a medication adherence app. As the common non-adherence reason was forgetfulness, app providers should design an app that can overcome forgetfulness using a wide range of reminder system. Besides, to promote more active involvement in the disease management, database of information about disease, medicine and self-management tools should be included in the app. Massive efforts in promoting the potential benefits of medication adherence app is very much needed to provide better knowledge on the practicality of this new adherence tool.

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The Stability Study of Extemporaneous Preparations Prepared in The Outpatient Pharmacy of Tuanku Fauziah Hospital Stored in Patient's Setting

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Abstract

Introduction: There are concerns about the stability of extemporaneous preparations after being dispensed to and stored by patients.

Objectives: The objective of this study was to investigate the stability of extemporaneous preparations prepared using simple syrup and X-Temp® syrup in the outpatient pharmacy of Tuanku Fauziah Hospital (HTF) when they were stored in the refrigerator and at room temperature in patient's setting.

Methods: The study was carried out in August 2015. Extemporaneous Baclofen Suspension 10mg/ml, Clonazepam Suspension 0.1mg/ml, Propranolol Suspension 1mg/ml, Spironolactone Syrup 2.5mg/ml and Frusemide Syrup 5mg/1ml were included in this study. These medications were prepared using both simple syrup and X-Temp® syrup as vehicle according to the standard formulas in the Ministry of Health (MOH) Extemporaneous Formulation 2015. Each type of syrups were stored in both kitchen cupboard at room temperature and domestic fridge for 14 days and 30 days to mimic the storage at patients' home. At the end of the specified study periods, the syrups were assessed in terms of visual and odour, pH level and sterility. The syrups were considered stable if no changes were detected in all the criteria.

Results: All preparations showed no changes in colour, odour and pH except Baclofen Syrup prepared with simple syrup that turned darker when stored at room temperature for 14 days and 30 days, and when stored in the fridge for 30 days. All preparations passed the sterility test except Propranolol Suspension prepared using X-Temp® syrup and stored under the room temperature for 30 days in which seven Gram-negative bacilli colonies were detected.

Conclusion: Extemporaneous preparations using either simple syrup and X-Temp® syrup were stable up to 30 days, except for baclofen syrup which was only stable for 14 days, if stored in the refrigerator.

Keywords: stability, extemporaneous, preparation, outpatient

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Introduction

Extemporaneous preparation is defined as the preparation, mixing, assembling, packaging and labelling of a medicinal product based on a prescription order from a licensed practitioner for the individual patient (1). Despite the meaning, extemporaneous preparation is best described as the off-license use of a medicine, whereby a licensed medicine is reformulated into a preparation that is acceptable or appropriate for the patients (2-8). It is usually prepared due to lack of commercially available formulations for patients with specific needs (1).

Compounding of extemporaneous preparations consists of two main components which are the active ingredients and the excipients. Active ingredient is defined as any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals (9). Meanwhile, excipients are the vehicles and diluents for the active ingredient (10). The active ingredient or the oral medication (tablet or capsule) will be crushed and triturated using mortar and pestle, followed by the addition of the excipients and they are mixed until a homogenous solution or suspension is formed. There are many kinds of excipients that can be used as the vehicle or suspending agent during extemporaneous preparation. The examples include acacia, tragacanth, hydroxymethycellulose, sugar, carboxymethylcellulose, sorbitol and glycerin (11).

Normally, extemporaneous preparations are required by patients who are unable to swallow the oral solid medications such as neonates, paediatric patients and patients having throat problems. Therefore, most of the extemporaneous preparations involve the process of compounding of oral solid medications into oral liquid forms such as solutions or suspensions (2). In practice, however, commercially prepared solution or suspension will be preferred as the first choice for the patients. However, the choices are usually only limited to commonly used medications. Studies showed that most of drug manufacturers have little interest in supporting the research on developing oral liquid formulations for infants and children. This is probably due to the limited resources, small size of paediatric market and possible liabilities (3-5). In addition, the manufacturers may be reluctant to share the stability data of a drug in a liquid dosage form because the efficacy and safety of the drug in the paediatric population have not been evaluated (6).

Due to this problem, compounding extemporaneous preparations is still a significant practice in the Ministry of Health Malaysia (MOH) healthcare facilities including the Tuanku Fauziah Hospital (HTF). Among the medications that are prepared extemporaneously in HTF are frusemide, spironolactone, propranolol and baclofen syrups. In HTF, extemporaneous preparations are prepared according to the MOH Extemporaneous Formulary 2015 (12). Prior to the preparation, the details of the preparation, such as dose, frequency, strength, total quantity and expiry date, will be determined by interpreting the prescription with reference to the standard strengths of syrup formulation available in the guideline (12).

In HTF, simple syrup and X-Temp® Syrup are the two commercially available vehicles that are normally used as excipients in compounding extemporaneous preparations. Simple syrup (66.7% w/w) contains sugar as the important component in extemporaneous preparation to act as diluent, binder and flavouring agent (13). Meanwhile, X-Temp® syrup is another vehicle that contains specialised suspending system formulated to assist in the extemporaneous preparations of oral liquid, non-soluble, aqueous dosage forms. It is an orange flavoured, sweetened (sugar-free) excipient containing suitable preservatives. X-temp® syrup also consists of purified water, sorbitol, glycerin, microcrystalline cellulose, carboxymethylcellulose sodium and sucralose as suspending agent (14).

Based on the current practice in HTF, expiry dates of extemporaneous preparations using simple syrup and X-Temp® syrup are 14 days and 30 days respectively. However, the stability of the extemporaneous preparation after being dispensed to the patients has not been fully studied especially when they are stored at home. Since there were lack of other similar studies conducted in Malaysia, the results of this study were hoped to provide more evidence for the pharmacists to make informed choices when choosing the vehicles of extemporaneous products to improve the stability the drug preparations. The objective of this study was to investigate the stability of extemporaneous preparations prepared using simple syrup and X-Temp® syrup in the outpatient pharmacy of HTF when they were stored in the refrigerator and at room temperature in patient's setting.

Methodology

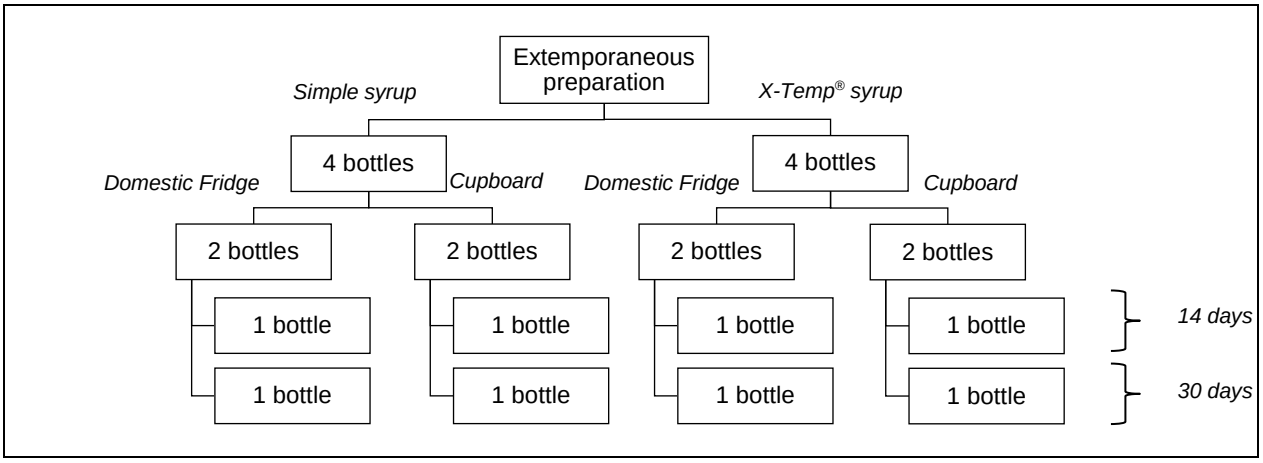
Extemporaneous Preparations

The extemporaneous preparations included in this study were extemporaneous preparation prepared in the outpatient pharmacy department of HTF using simple syrup or X-Temp® syrup with the prepared volume more than 10,000ml a year based on the record in 2014. Syrup medications that were available commercially in HTF and extemporaneous preparations using vehicles other than simple syrup or X-Temp® syrup were excluded. Considering the inclusion and exclusion criteria, the extemporaneous preparations included were Baclofen Suspension 10mg/ml, Clonazepam Suspension 0.1mg/ml, Propranolol Suspension 1mg/ml, Spironolactone Syrup 2.5mg/ml and Frusemide Syrup 5mg/1ml.

These preparations were prepared during the first week of August 2015 according to the standard formulas and methods in the MOH Extemporaneous Formulary 2015 (12). In total, ten types of preparations were prepared, as each of the five included preparations were prepared using both simple syrup and X-Temp® syrup as excipients. The active ingredients and excipients used for each type of preparations were of the same manufacturer as well as batch of expiry. The total volume prepared for each medication was 40 ml for each excipient. The preparations were then divided into four bottles of 10 ml each. Two of the bottles were stored in the domestic fridge while the other two were stored in the kitchen cupboard at room temperature. The domestic fridge and the kitchen cupboard were located at one of the researcher's home in Perlis. For each set of the preparations, one bottle was stored for 14 days while the other was stored for

a period of 30 days. The summary of the storage conditions for each type of extemporaneous preparation was shown in Figure 1.

Figure 1: Summary of the storage conditions for each type of extemporaneous preparation



Stability Tests

In this study, three main aspects were tested for the stability of the extemporaneously compounded medications, which included physical examination, pH and sterility. The tests were carried out on the samples at the beginning of the study (day 0) and at the end of the specified study period (day 14 or day 30). The syrups were considered stable if no changes were detected in all tests.

Physical examination was conducted to examine the visual appearance and odour of the products. The photos of each test samples were taken at the designated time using the same camera and used to record any significant visual changes. The odour of each test samples was recorded and verified by two investigators.

The pH test was conducted using pH indicator strips by MColorpHast™. The paper was dipped in the solution and the changes in colour were matched with the pH chart available along with pH test strip. The readings were taken and verified by two investigators.

For the sterility test, the extemporaneous samples were sent to the Pathology Unit of HTF to check for microbial contamination.

Results

The temperature in the domestic fridge was around 2°C to 8°C and kitchen cupboard was 27°C. All syrup preparations retained their initial colour from Day 0 to Day 30 except Baclofen Syrup prepared with simple syrup (Table 1). It was found that Baclofen Syrup prepared using simple syrup stored at room temperature for 14 days and 30 days turned to a darker colour. On the other hand, the same preparation stored in fridge showed no significant changes in visual appearance up to 14 days, but the colour turned darker after 30 days.

No changes in odour were detected after 30 days of the study for all samples. Similarly, the pH values of the test samples were constant throughout the period of study (Table 2). The results showed that the test samples were free from any microbial growth except for Propranolol Suspension 1mg/ml prepared using X-Temp® syrup as excipient and stored under the room temperature (in cupboard) for 30 days. There were seven colonies of Gram-negative bacilli detected in the sterility test (Table 3).

Table 1: Results of the visual appearance test

Medication	Storage temperature	Vehicle	Colour change	
			Day 14	Day 30
Baclofen Suspension 5mg/ml	27°C	Simple	Yes *	Yes *
		X-Temp®	No	No
	2-8°C	Simple	No	Yes *
		X-Temp®	No	No
Spironolactone Syrup 2.5mg/ml	27°C	Simple	No	No
		X-Temp®	No	No
	2-8°C	Simple	No	No
		X-Temp®	No	No
Frusemide Syrup 5mg/mml	27°C	Simple	No	No
		X-Temp®	No	No
	2-8°C	Simple	No	No
		X-Temp®	No	No
Propranolol Suspension 1mg/ml	27°C	Simple	No	No
		X-Temp®	No	No
	2-8°C	Simple	No	No
		X-Temp®	No	No
Clonazepam Suspension 0.1mg/ml	27°C	Simple	No	No
		X-Temp®	No	No
	2-8°C	Simple	No	No
		X-Temp®	No	No

* The colour of the preparation turned darker

Table 2: Results of the pH test

Medication	Storage temperature	Vehicle	pH		
			Day 0	Day 14	Day 30
Baclofen Suspension 5mg/ml	27°C	Simple	5	5	5
		X-Temp®	4	4	4
	2-8°C	Simple	5	5	5
		X-Temp®	4	4	4
Spironolactone Syrup 2.5mg/ml	27°C	Simple	5	5	5
		X-Temp®	4	4	4
	2-8°C	Simple	5	5	5
		X-Temp®	4	4	4
Frusemide Syrup 5mg/mml	27°C	Simple	4	4	4
		X-Temp®	4	4	4
	2-8°C	Simple	4	4	4
		X-Temp®	4	4	4
Propranolol Suspension 1mg/ml	27°C	Simple	4	4	4
		X-Temp®	4	4	4
	2-8°C	Simple	4	4	4
		X-Temp®	4	4	4
Clonazepam Suspension 0.1mg/ml	27°C	Simple	5	5	5
		X-Temp®	4	4	4
	2-8°C	Simple	5	5	5
		X-Temp®	4	4	4

Table 3: Results of the sterility test

Medication	Storage temperature	Vehicle	Microbial growth		
			Day 0	Day 14	Day 30
Baclofen Suspension 5mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
Spironolactone Syrup 2.5mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
Frusemide Syrup 5mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
Propranolol Suspension 1mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	7 colonies of Gram-negative Bacilli
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
Clonazepam Suspension 0.1mg/ml	27°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG
	2-8°C	Simple	NG	NG	NG
		X-Temp®	NG	NG	NG

Abbreviation: NG – no growth

Discussion

Stability refers to the chemical and physical integrity of the dosage unit and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination (15). The stability of pharmaceutical products could be influenced by their formulation, storage conditions and even containers. An extensive survey of the literature and investigation of 83 oral liquid formulations prepared extemporaneously by Glass and Haywood in 2006 found that the instability of the formulations is primarily due to interactions between drug substance and the excipients rather than degradation of the active pharmaceutical ingredient (16). It is thus important to consider not only the stability of the drug substance but the entire formulation. A study by Muśko and Sznitowska in 2012 found that propranolol hydrochloride suspensions prepared in three different compounding vehicles, i.e. Ora-Sweet, modified Ora-Sweet and simple syrup with glycerol and sorbitol, were stable with more than 95% of initial concentration remaining after being stored for 35 days in a dark place at 25°C and 4°C. However, suspensions prepared with modified Ora-Sweet should not be stored at 4°C due to crystallization of their buffer substances (17).

The colour of Baclofen syrup prepared using simple syrup turned darker after being stored for 14 days under room temperature. The same preparations that were stored in the fridge showed no colour changes up to 14 days, but not after 30 days. The suggested stability of Baclofen suspension 5mg/ml using simple syrup as vehicle is 35 days if refrigerated and protected from light (12). This implied that the changes in colour could be due to the storage temperature and light. Another possible reason was the chemical reactions that occurred between the active ingredient and the material of the storage bottles used in this study. The bottles in use were made from of plastic material and thus were susceptible to several reactions including migration of the drug through the plastic into the environment, transfer of environmental moisture, oxygen, and other elements into the pharmaceutical product, leaching of container ingredients into the drug and also the risk of adsorption or absorption of the active drug or excipients by the plastic surface (8). Therefore, it may be possible that either of the reactions happened and caused the colour of the baclofen syrup turned darker.

Extemporaneous Frusemide 5g/ml syrups prepared in this study were found to be stable in all storage conditions. A study by Shoosanglertwijit in 2011 found that extemporaneously compounded frusemide suspensions at the concentration of 2mg/ml made from two different suspending vehicles were

stable for at least 60 days when stored in glass bottles protected from light at three controlled temperatures. At least 93% of the initial frusemide concentration remained in both compounded frusemide suspensions for up to 60 days and there were no substantial changes in the appearance colour or odour of both formulations. The pH values of both formulations kept at certain temperatures demonstrated some changes. Both formulations maintained microbiological stability for 60 days (18). Thaweethamcharoen *et al*. in their research in 2014 found that frusemide syrup and spironolactone suspension prepared by the Pharmaceutical Production of Siriraj Hospital were stable for 360 and 60 days, respectively, when stored in light-resistant containers and 5 ± 3^{o}C condition (19).

There were no changes in the pH of all extemporaneous preparations in this study. The changes in pH were generally associated with drug degradation (2). The most common reactions causing drug degradation are hydrolysis, oxidation and reduction (20). The contributing factors to drug degradation were microbial contamination, exposure to sunlight and storage temperature. Therefore, preventing the extemporaneous preparations from microbial contamination is also important. Such contamination can alter the stability of preparations due to the presence of by-products of microbial metabolism. This may cause a change in the pH values of the preparation and reduce the chemical stability or solubility of the drug. On the other hand, the test samples were not exposed to direct sunlight. Due to photosensitivity properties of some ingredients in the test samples, it is crucial that they are stored in a cool, dark place. In addition, high temperature may also affect the stability of extemporaneous preparation as it can accelerate drug degradation process (20).

The Propranolol Suspension 1mg/ml prepared by using X-Temp® syrup failed the sterility test when it was kept under room temperature for 30 days. Nevertheless, this could be due to microbial contamination introduced by the investigator during the transfer of preparation from one container to another rather than the instability of the formulation. According to the International Pharmacopoeia by the World Health Organization (WHO) and other published literature, the sterility test was carried by direct inoculation of the culture medium method (21-27)**.** A small amount of quantity of the extemporaneous was transferred directly into the culture medium (blood agar). Then, the culture medium plus sample of extemporaneous was incubated for 24 hours. The incubated samples were observed. If no evidence of microbial growth is found, the product complied with the test for sterility and *vice versa* (15,22). If there was evidence of growth, culture and sensitivity test were done to identify the type of bacteria by performing gram stain procedure (21). According to Monica *et al.*, gram staining is a common technique used to differentiate two large groups of bacteria based on their different cell wall constituents (23). The Gram stain procedure distinguishes between Gram-positive and Gram-negative groups by colouring these cells red or violet (24).

The physical, chemical and microbiological stability testing of the drugs in the published literatures included pH and colour observation, standard microbiological testing, and measurements using High Performance Liquid chromatography (HPLC) or Ultra Performance Liquid chromatography (UPLC) (16-20,28). In this study, however, only three main aspects were tested for the stability of the extemporaneously compounded medications, which included physical examination, pH and sterility. Therefore, the main limitation of this study was the lack of analytical data to support the results. The presence of drug components in each extemporaneous preparation should be measured using HPLC to further quantify the exact amount of drugs in the test samples during the study period which was not done since there was no access to the necessary instrument. The second limitation was that actual microbial stability test was not performed according to the standards outlined in the British Pharmacopeia for non-sterile product (15). The study duration was also restricted to only 30 days. If the study was carried out for a longer period of time, we could continue observing the changes of each extemporaneous preparation in order to get better evidences on its stability. In addition, certain factors such as the temperature, humidity and brightness were not monitored and controlled throughout the study. Also, all the tests were only performed once for every sample in this study. The evidence would be stronger if the tests were repeated under the same conditions. The use of a pH meter would be a better choice since it can produce more accurate results. In this study, pH test strip papers were used in which the pH measurement was done only by visual comparison to a table of reference colours which may not be as accurate as a digital pH meter. Further studies should be carried out with improvements to these limitations.

Conclusion

All extemporaneous preparations prepared using X-Temp® syrup were stable up to 30 days if stored in the domestic fridge while syrup preparations prepared using simple syrup were stable up to 30 days if stored in the fridge except for baclofen syrup which was only stable for 14 days if being refrigerated. More studies should be carried out to ensure that the extemporaneous compounded for patients are stable and of high quality.

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Conflict of Interest Statement

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Barriers and Facilitators to Highly Active Antiretroviral Therapy (HAART) among Retroviral Disease (RVD)-Infected Patients in Tawau Hospital

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Abstract

Introduction: Adherence to highly active antiretroviral therapy (HAART) has become a formidable barrier for retroviral disease (RVD)-infected patients to maintain successful viral suppression and immune recovery. Therefore, both healthcare providers and patients face significant challenges concerning adherence to HAART.

Objectives: This study was conducted to understand the barriers and facilitators to treatment adherence among RVD-infected patients.

Method: This was an exploratory qualitative study. In-depth semi-structured interviews with RVD-infected patients were conducted. The questions covered topics related to the beliefs and knowledge concerning RVD and HAART, barriers to HAART adherence, and HAART adherence tools. The interviews were audio-recorded and transcribed, verified and translated into the English language. Thematic analysis was done parallelly with data collection.

Results: Data saturation was reached during the interview of 16th patient. The thematic analysis identified five themes which were Belief about HAART medications, Barriers to adhere with HAART treatment, Adherence tools, Supports, and Patients' attitude / perception. All interviewed patients believed that HAART was beneficial for their disease. The barriers to HAART adherence included HAART-related adverse effects, wrong belief, fear of stigma, and the complicated and strict treatment regimen. The facilitators to HAART adherence identified in this study included making use of adherence tools such as alarm, clock, mobile phone application, pillboxes and tag notes. In addition, the support from families, peers and healthcare providers, and patients' own attitude or perception were important facilitators to HAART adherence. Positive thinking, self-motivation and self-discipline were important attitudes to ensure continuous adherence to HAART treatment.

Conclusion: This study identified few common barriers and facilitators to HAART adherence which can be incorporated into HAART counselling to improve the adherence rates.

Keywords: highly active antiretroviral therapy, retroviral disease, barriers, facilitators, qualitative study

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Introduction

As of December 2014, the World Health Organization (WHO) estimated that 36.9 million people were living with human immunodeficiency virus (HIV) and 1.9 million people were newly enrolled on antiretroviral treatment. Highly active antiretroviral therapy, or HAART, is the standard treatment for people infected with HIV which consists of a combination of at least three drugs that suppress HIV replication, reduce morbidity and mortality rates among HIV-infected people, and improve their quality of life (1). In the East Asia and Pacific region, Malaysia is one of the countries with fastest-growing AIDS epidemics. From 1986 to 2017, 115,263 people were infected with HIV, while 42,864 people have died of acquired immunodeficiency

syndrome (AIDS). According to the Malaysia Country Progress Report on HIV/AIDS 2018, in 2017, 72,399 people in Malaysia were living with HIV and 3,347 new HIV cases were reported (2).

Although HAART has transformed HIV infection into a manageable chronic disease, many factors had contributed to HAART ineffectiveness including the inappropriate drug of choice, viral resistance and non-adherence to the therapy (3). Studies have shown that patient's adherence of higher than 95% to HAART therapy is the optimum requirement to succeed the treatment and less than that is associated with a virologic failure rate in more that 90% of the therapy (3). Therefore, the strict adherence to antiretroviral therapy is the key to sustained HIV suppression, reduced risk of drug resistance, improved overall health, quality of life and survival, as well as decreased risk of HIV transmission (4-6).

Poor adherence is the major cause of therapeutic failure among the retroviral disease (RVD)-infected patients and it remains the main issue to be solved. Adherence to HAART can be influenced by several factors, such as patient's social situation and clinical condition, prescribed regimen, and patient-provider relationship (7). Heavy pill burden, fear of stigma and discrimination, cost and access to transportation, lack of understanding of the benefit of taking the medication, economic problems in the household, and lack of nutritional support were the reported barriers to HAART adherence (8). Further more, common barriers faced by the developing settings were financial constraints and disruption in the access to medications (9).

The complexity of the HAART regime is also one of the significant challenges faced among the RVD-infected patients, whereby the adherence generally decreases with the increasing number of doses per day (10). Once-daily and twice-daily medication regimens were associated with significantly better compliance, which were 73% and 70% respectively, compared to medication regimens of three (52%) and four times daily (42%) (11).

Despite being given pre-HAART counseling, RVD-infected patients could be overwhelmed with the side effects of HAART and discontinue the regimen, resulting in treatment failure (12). For instance, side effects occured among the protease inhibitor-treated cohorts in up to 29% to 36% of subjects after 14 to 19 months of observation (13). As high as 33% of the patients were found to be unable to maintain complete adherence due to the side effects (14). Even with development of new antiretroviral agents, the frequency of side effects remains high (12) and therefore timely intervention by the healthcare providers are deemed very important.

In the Ministry of Health Malaysia (MOH) healthcare facilities, antiretroviral therapy is provided and the Retroviral Medication Therapy Adherence Clinics (RVD MTAC) are set up to provide counselling for patients receiving HAART. As it is crucial for the healthcare providers to recognise and overcome the key barriers faced by HIV-infected patients and promote measures to facilitate their adherence, this qualitative study was conducted to understand the barriers and facilitators to HAART treatment among the RVD-infected patients. The finding from this study could provide input to improve the counseling materials for RVD MTAC and help to structure the interventions that can be done by the healthcare providers to improve patients' adherence and treatment effectiveness.

Methods

This was a qualitative study conducted in Tawau Hospital, Sabah, starting from May 2016 to March 2017. It involved RVD-infected patients aged above 12 years who were receiving HAART and were able to communicate in Malay, English or Chinese language. Recruitment was done by convenience purposeful sampling and written consent forms were obtained from the respondents.

Face-to-face in-depth semi-structured interviews with RVD-infected patients were conducted privately in a clinic room on the same date of the patient's hospital appointment or follow upeither on one-to-one basis or alongside caregivers. The interview was conducted according to a interview guide that consists of a general set of open-ended questions that covered topics related to beliefs and knowledge concerning retroviral disease and HAART, barriers to HAART adherence, and HAART adherence tools (Appendix). Once the successive interviews become repetitive and redundant, and when no new information is forthcoming from newly sampled participants, the study achieved data saturation and the data collection was ceased.

The interviews were audio-recorded and transcribed, verified and translated into the English language. Thematic analysis was done parallelly with data collection. The collected data was then coded and categorized into themes by the investigators after reviewing and vetting the transcripts.

Results

A total of 16 participants were recruited to this study. The thematic analysis identified five themes which were Belief about HAART medications, Barriers to adhere with HAART treatment, Adherence tools, Supports, and Patients' attitude / perception.

Theme 1: Belief about HAART medication

HAART requires strict adherence to its complicated treatment schedule. In order for the patients to adhere to the regimen, they need to first believe that the treatment is helping them becoming better. All interviewed patients believed that HAART can help them with their disease.

> *''After taking these medications for more than ten years without any therapy alteration, I'm sure and believe that these medications can give a beneficial effect to us. It helps to improve our white blood cells and makes us healthier.'' (Patient B)*

> *"I believe that, since my body becomes healthy. I knew this medication is good. I felt like my body becomes healthy." (Patient G)*

> *"Yes. Previously I have known about RVD. I have google and read up and the solution is HAART treatment. So to me if you don't take HAART, it's like dying slowly. I can see the changes despite just started the medication." (Patient L)*

HAART treatment is notorious for its side effects that affect the adherence of RVD-infected patients. One of all interviewed patients, however, claimed that he still adhered to the treatment despite having side effects.

> *"I believe it even though I suffered from its side effects at the beginning of therapy. In my opinion, these medications are high quality and 99% trustworthy." (Patient D)*

There was one patient who did not believe in the treatment at first and sought alternatives to cope with the disease. Eventually, this patient managed to follow the regimen and believed that HAART is still better.

> *"Yes, I do believe. As you know, I stopped taking my medication for almost one and a half year to see what will happen to me. Eventually in the year of 2015, I get sick and started HAART since then. Been taking HAART for almost 3 months until now and I feel much better than before. If I take supplement alone, I don't think I can survive until today. Nevertheless, the combination of HAART and supplement is much better." (Patient A)*

Theme 2: Barriers to adhere with HAART treatment

The interviewees disclosed a few barriers that affected their adherence to HAART treatment, such as side effects, wrong belief, fear of stigma, and complicated and strict regimen.

Among the 16 patients, ten of them complained of side effects.

> *"I noted about the risk of having rashes induced by nevirapine as I experienced it at the first time of taking neverapine." (Patient A)*

> *"During the early time of therapy, I did experience some effects such as dizziness and nausea." (Patient B)*

> *"When I first started HAART, I experienced nausea and vomiting. It persisted for almost three days and resolved afterward." (Patient C)*

Nevertheless, the side effects might become tolerable as time passed.

> *"I was uncomfortable, very uncomfortable, for about 2 months or so. I found myself sweating, feeling uncomfortable for about two hours, after that I would get drowsy. We feel like vomiting, really like nauseous, but when we're used to it, after taking it for some time, it's like normal." (Patient E)*

> *"It was a lot. I refused to take the medications initially due to its side effect such as dizziness, nausea and vomiting. I stop taking the medications temporarily when the pain was too unbearable. Also, I experienced loss of appetite where my body weight by that time was only around 40kg." (Patient I)*

On the other hand, there could be wrong beliefs among the patients. For instance, one patient sought complementary medicines before following the HAART regimen. The Malaysian population may believe in alternative medicines more compared to prescribed medicines, and this could be a challenge for the healthcare professionals as this is a potential barrier to HAART adherence.

> *"Instead of taking HAART, I took lots of supplements throughout the year." (Patient A)*

> *"I mistakenly believed in my own theory and on the other hand, doubted the effectiveness of medical science." (Patient A)*

Also, the interviewees admitted being fear of stigma and thus were reluctant to share their conditions with the others including their family and friends.

> *"I do not want to share my problems with my family. I have to consider about their future and I am scared to let my children know about it." (Patient D)*

> *"I do not want other people to know what medicine I'm taking. I don't involve my family, because I think this is my personal matter." (Patient E)*

> *"Family knows nothing about this." (Patient H)*

> *"First barrier is people surrounding me, if I got back home, my family will ask me what the medication is. I have to lie saying that it is supplement." (Patient J)*

Complicated and strict regimen could also be a significant barrier to HAART adherence, as HAART medications must be taken at the same time every day without a miss. Patients recognized this as one of the barriers to their adherence.

> *"HAART is a therapy where we must follow the administration timing strictly. We need to take the medications on time without delay, not even five minutes delay." (Patient B)*

> *"At the beginning of therapy, I always took my medications late." (Patient D)*

> *"When I first started, I missed my medication. Sometimes when I got back from work at 5pm, I overslept until 9pm or 10pm. Hence I missed my 8pm dose. But now, no more." (Patient J)*

> *"I delay in taking my medications. This is because sometimes I go out for a drink." (Patient M)*

Patients use tool like alarm as reminder. Nevertheless, forgetfulness or technology failures could hinder them from keeping track of time.

> *"Sometimes, I have forgotten to take my medication. If you are referring to setting reminder alarm, yes, there is. But I have even forgotten to take my medication as I forgot to set my alarm." (Patient C)*

> *"When I was travelling by air, sometimes during the afternoon flight, I forgot to keep my medication in my pocket. That's what usually happened to me." (Patient J)*

> *"I forgot to bring medications to keep it inside the car." (Patient M)*

> *"I have missed for about half an hour. The alarm did not ring, I had forgotten before." (Patient O)*

Lack of understanding about HAART among the patients and healthcare-related personnel could have caused non-adherence.

> *"I did not know what medications I was taking." (Patient H)*

> *"The nurse served the medicines late. Only during that time (that I had difficulties with the compliance)." (Patient F)*

Theme 3: Adherence tools

Barriers to HAART were linked to the importance of administration time of medication. There were several facilitators that helped the patients in overcoming barriers. The most common facilitator was the use of adherence tools.

The most frequently used adherence tool among the interviewed patients was alarm. All interviewed patients used alarm to remind them on the timing of medication intake.

"I'll use my phone alarm to remind me about the time." (Patient A)

"Usually I use alarm, either clock or phone alarm." (Patient P)

"Clock… or phone alarm." (Patient C)

"I use alarm only to remind me so that I do not miss taking medications." (Patient M)

"I use my phone alarm and no problem." (Patient J)

One patient used mobile application as reminder.

"I use application 'medisafe', it'll remind me to take the medication and bring along the medication while travelling." (Patient J)

Some patients form a habit to take medication at the same time daily gradually with the aid of alarm.

"I did use my phone alarm previously. However, I don't need it anymore after been taking this medication for 7 years." (Patient I)

"I use my phone alarm to remind me to take medication. Gradually, I'll get used to it." (Patient L)

Other than alarm, pill box is one of the most useful tools for the interviewed patients.

"And I use pill box as well." (Patient L)

"I always bring my pill box along and I have 2 pill boxes. Big sized one is to be kept at home meanwhile the small sized one is for me to bring along to work." (Patient A)

Tag notes is another method used by patients in this study.

"I have used alarm clock, mobile phone and tag notes on mirror. Or I wrote it in notebooks." (Patient E)

Theme 4: Supports

Support is crucial for RVD-infected patients from the acceptance of disease diagnosis, to the initiation of treatment and life-long treatment.

Continuation of treatment was deemed easier with the love and support from the family.

"Sometimes I asked my family member at home to remind me. For example, if it was 10pm and I already felt asleep, they helped to wake me up." (Patient P)

"I have maid at home who helps to remind me to take medication. Sometimes my siblings and my parents help as well." (Patient L)

"My youngest child always ask "Mummy have you taken your medicines?" (Patient M)

Spousal support also played essential roles in reminding the patients to take their medications time.

"…my wife takes care of my medications. Most of the time my wife reminds me to take medications. For example, if I fall asleep while watching TV, she reminds me to take the medicines." (Patient G)

"My husband always reminds me." (Patient I)

Peer support among the RVD-infected patients could also enhance HAART adherence.

"We have a chatting group called "kasih" and this is the platform where we'll remind each other to take the medication on time." (Patient A)

In addition, the support from healthcare providers was important to help the patients to get through the initial treatment stage.

"During the early time of therapy, I did experience some effects such as dizziness and nausea. However, I tried to continue the medication after been motivated by the doctors and now I'm tolerating it." (Patient B)

One patient highlighted the importance of seeking treatment at the MOH facility.

"So for me it was the best that we seek treatment in a hospital under MOH, whom prescribed real medication. Plus we received counselling to support us if something's wrong. Plus we have review for us to follow everything." (Patient L)

Theme 5: Patients' Attitude / perception

Adherence to HAART therapy could be affected by the patients' perception towards the use of medication, possible side effects and the outcome of treatment.

Positive thinking provided the patients with healthy and peaceful mind to endure the life-long treatment.

"I think we have to be positive. If we keep denying the fact, we'll be going on not knowing and not adhering to the timing of administration. If we don't follow the instructions given, it will lead to much worse diseases. Others cannot feel how our bodies feel. So start within yourself to adhere. Hospital and counselling will assist but no one can help apart from yourself." (Patient L)

"For me, a HIV patient has to think positive and then he has to discipline himself. Although doctors say that there is no medicine to cure this disease but I believe that if I practice this HAART medicine, and if I follow the correct method and administration schedule, with God's grace, maybe this thing can disappear." (Patient E)

Self-motivation kept patients going through journey with HAART.

"My advice to other HIV patient was to never neglect taking the medications and always remember to bring the medications. If we miss taking medications once, it could eventually bring the unfavorable outcomes to ourselves." (Patient D)

"I have strong spirit to take these medications to make myself healthier." (Patient G)

"Because I have children. No matter what. I have to stay healthy and watch my children grow up." (Patient I)

Self-discipline is another important aspect to overcome the barriers in HAART adherence.

"To me, the most important thing is to discipline myself, disciplining myself to take the medicines on time." (Patient E)

"I never miss taking my medications. I bring my medications to the office, and even when I went to Kota Kinabalu as well." (Patient N)

Strong self-discipline enabled the patients to adjust themselves easily at any given situation.

"If I went out to visit my family, I'll make sure that I don't miss any dose. For example, if I went out before 9…. I will stop by elsewhere and make sure that I take the medication at 9. We can't delay the time, we can't be late." (Patient B)

Discussion

Highly active antiretroviral therapies (HAART) have demonstrated their efficacy in improving the immune function, reducing viral load and RVD-related morbidity and mortality. The complex therapy regime, however, requires patients' strict adherence and discipline. Despite rapid advancement of modern medicines and antiretroviral programs, the long-term success of these programs depends on patients' adherence to their antiretroviral therapy. Some of the barriers identified in this study are reportedly consistent with existing literature such as side effects, lack of understanding of treatment benefits (wrong belief), stigma, and forgetfulness (15). To date, the treatment-resistant variants of RVD had attracted great concern as they were rapidly developed due to the under-dosing and intermittent, irregular use of HAART medications (16).

All of the 16 RVD-infected patients that were interviewed regarding their belief towards HAART medications in this study believed that HAART give positive effects and improve their quality of life. The most common motivator to adherence is the belief in the efficacy of HAART (9). This is because patients' beliefs, knowledge, and expectations about the treatment strongly influence their medical decision making (17). When patients have positive perceptions toward HAART, they tend to have better adherence (18). It is important for patients to believe in the benefits of taking antiretroviral medications and thus the efforts to educate patients about the benefits and risks of HAART may help improving adherence (7). Without proper counseling and understanding, patients might default treatment easily when they feel better or when they encounter any side effects. Self-motivation and self-discipline are also the main determinant for adherence (19-21). All interviewed patients in this study had reported to be motivated and disciplined in adhering to treatment.

Adherence to HAART is essential to achieve successful and prolonged viral suppression and minimise the risk of resistance (13). Nevertheless, it is unavoidable to have some barriers that may avert patient from taking the medications. Out of 16 patients, 10 of them complained that side effects of HAART affected their compliance. Therefore, focusing on managing HAART-related symptoms and side effects can help to optimize HAART adherence (13).

In this study, one patient reported stopping HAART treatment and replacing with supplements, and the patient became unwell later and restarted HAART. Complementary and alternative medicine are any treatments used in conjunction or in place of standard medical treatment. The WHO estimated that around 4 billion people, which were equivalent to 80% of the world's population, were using herbal medicines in conjunction with conventional medicines. Some studies have reported large numbers of traditional health practices in the treatment of RVD. The concurrent use of traditional supplements and antiretroviral drugs may lead to drug interactions that could affect the effectiveness of HAART (22). The use of alternative medicines in HIV-positive patients should raise clinical and pharmacological concerns that need extra attention by all healthcare providers.

Therapeutic failure occurred in approximately half of HAART recipients and is often associated with RVD resistance due to inadequate adherence. While many RVD-infected patients were able to take their HAART medications as prescribed, over one-third (37%) of RVD-infected patients in the developed countries have difficulties in maintaining an adequate level of adherence (23). Forgetfulness may affect treatment success. Majority of the patients in this study reported that they forgot to take medications on time especially when they initially started HAART. In another study, patients also stated that being forgetful was the reason for non-adherence to HAART (24). Majority of the patients in this study were using active reminder devices such as phone reminder, clock alarm and application, and passive reminder devices like pill boxes and tag notes. Also, patients need to ensure that these reminders are functioning properly and it may be advisable for patient to keep multiple reminder devices.

HAART has to be taken same time every day to ensure consistent viral suppression. Facilitators reported in this study, such as the use of reminder devices or applications, supports from community, positive attitude and perceptions, were consistent with the approaches applied in other resource-limited settings to improve adherence (25). Cognitive-behavioral therapy, education, treatment supporters, directly observed therapy and active adherence reminder device have been used to increase HAART adherence (26).

RVD brings fears, prejudices and negative attitudes. RVD-infected patients may experience being insulted, rejected and excluded from social activities as a result of stigma. Stigma could be the worst enemy of RVD-infected patients, causing them to have difficulties engaging with people. Most RVD-infected patients avoid disclosure to their family or friends regarding their health status, but social support plays a vital role in treatment success. Greater social support predicts more consistent adherence (16). Previous studies demonstracted that good family support improved HAART adherence. For example, family member can help to remind medication intake time, support to overcome side effects and reinforce a stable routine life (27).

WHO characterized family as the primary social agent in the promotion of health and well-being (28). Studies showed that having an unsupportive social network often prevents patients from having successful adherence. Interpersonal relationships can affect patient's behaviors toward adherence. Lack of trust towards healthcare providers can also affect the treatment adherence. Openly disclosing RVD status to family and friends was reported as influential to adherence (9). Most patients in this study received support

from their family, friends and healthcare personnel, but some patients were afraid to tell their family about their RVD status. Family disclosure could be beneficial to patients as relatively high adherence rate could be attributed to high moral and psychological support given by family members (28).

Supportive friends and healthcare providers can also help in improving patients' adherence. One interviewed patient mentioned about the group chat among the RVD patients in Tawau Hospital served as a medium for sharing and mutual support. As healthcare providers are often the first person to break the news to patient and manage their life-long HAART treatment, healthcare providers should be supportive and provide proper counseling for patients to have positive belief on the treatment. Unsupportive and unconcern healthcare providers may discourage patient and causing them to be non-adhere to treatment (28-29).

The main limitation of this study is that complete demographic data of interviewed patients were not collected. Otherwise, description about the demography and socioeconomic status of interviewed patients could be presented. This was a qualitative study conducted to explore the barriers and facilitators to HAART treatment among the RVD-infected patients. Although qualitative studies are superior in identifying patient-important barriers and facilitators, combining qualitative and quantitative elements in future studies may result in more informative findings.

Conclusion

In conclusion, medication-related barriers comprised of HAART side effects and complexity of HAART regimen are among the major contributing factors to non-adherence among RVD-infected patients. Extra attention to patients with negative belief and fear of stigma is vital in order to help them achieving optimum adherence status towards HAART. Adherence tools, for instance mobile phone alarm and mobile application were among the widely used facilitators in improving the HAART adherence among RVD-infected patients. Likewise, support by the family and society is also crucial in overcoming non-adherence.

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Conflict of Interest Statement

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Appendix

Interview Guide

First Part
Focus: Beliefs and knowledge concerning retroviral disease and HAART
Do you belief that HAART benefits in retroviral disease?
Probes:
Do you agree that HAART being the only management in retroviral disease?
Do you have any idea on how HAART may bring benefits in retroviral disease?
Personally, how do you perceive the quality and safety of HAART?
Probes:
Do you think is there any harmful effects of HAART?

Second Part
Focus: Barriers on HAART adherence
Do you ever have any difficulty in adhering HAART?
What will be the barrier in adhering HAART you have encountered?
Probes:
Do you mind to elaborate (e.g. tight daily schedule, travelling, etc)

Third Part
Focus: HAART adherence tools
Generally, what is your opinion on the adherence tools for HAART?
Probes:
Are there any ways to overcome the barriers for adherence?
Are there any adherence tools (e.g. alarm)?

Conclusion
As a conclusion, do you have any additional comments about barrier on adherence?

Thank you very much for being able to participate in this study.

Assessment of Knowledge and Attitude of Pharmacy Staffs towards Handling of Hazardous Drugs in Tuanku Fauziah Hospital (HTF), Malaysia: A Questionnaire Validation

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Abstract

Introduction: Hazardous drugs are defined as agents that due to its inherent toxicity present danger to healthcare personnel. While the drugs were proven to have therapeutic benefits for its intended patients, they may cause adverse effects to healthy staffs who handle the hazardous drugs. Studies had shown that pharmacy staffs had low knowledge regarding proper handling of hazardous drugs.
Objective: This study aimed to develop a validated questionnaire to assess pharmacy staffs on their knowledge and attitude in hazardous drug handling.
Methods: The questionnaire was constructed based on published guidelines and studies. Content validation and face validation were carried out on three oncology pharmacists and three other pharmacists respectively. Data collection for construct validity and reliability test was carried out on a sample of 36 pharmacy staffs from selected health facilities in Perlis and Kedah. Construct validation was carried out using factor analysis, while internal consistency was tested through reliability analysis. For factor analysis, Principle Component Analysis was used as the extraction method.
Results: During the content validation, six questions were omitted while 23 questions were rephrased. After construct validation, six questions were removed due to zero variance, communality values of the correlation matrix below 0.5, and to improve the internal consistency. The final questionnaire comprised 61 questions in five domains: eight socio-demographic (Domain 1), 41 knowledge (Domain 2 to 4) and 12 attitude (Domain 5) questions. All questions and domains in the final questionnaire satisfied the requirement for anti-image correlation, Bartlett's Test of Sphericity and Kaiser-Meyer-Olkin Measure of Sampling Adequacy. The Cronbach's alpha values for Domains 2 to 5 were 0.618, 0.610, 0.839 and 0.609 respectively, which demonstrated the reliability of the domains.
Conclusion: A validated questionnaire to evaluate the knowledge and attitude in handling hazardous drug among the pharmacy staffs was developed.
Keywords: knowledge, attitude, hazardous, drugs, handling, pharmacy staffs

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Introduction

Hazardous drugs are drugs that are known or suspected to cause adverse health effects from their exposure in the workplace. Studies had shown that antineoplastic agents, antiviral agents, biological modifiers, hormones, and some other agents, despite providing therapeutic benefits to patients, may cause adverse effects to the health workers (1). Hazardous drugs could potentially manifest genotoxicity, carcinogenicity, teratogenicity, infertility, serious organ or other toxic manifestation at low doses as shown in animal or human experiments (2).

In 2006, American Society of Health-System Pharmacists (ASHP) published an update on the Guidelines on Handling Hazardous Drugs in order to provide better understanding of the risks associated with handling toxic agents and the advent of new technologies to minimize occupational exposure (2). There was also an alert by The Centers for Disease Control and Prevention through the National Institute for Occupational Safety and Health (NIOSH) to update the U.S. Department of Labor's Occupational Safety and Health Administration (OSHA) on establishing a comprehensive technical manual for employees who

were involved in the handling of hazardous drugs (3). Table 1 highlighted some important terminologies of hazardous drugs.

Table 1: Comparison of 2004 NIOSH and 1990 ASHP definitions of hazardous drugs

NIOSH	ASHP
Carcinogenicity	Carcinogenicity in animal models, in the patient population, or both as reported by International Agency for Research on Cancer
Teratogenicity or developmental toxicity	Teratogenicity in animal studies or in treated patients
Reproductive toxicity	Fertility impairment in animal studies or in treated patients
Organ toxicity at low doses	Evidence of serious organ or other toxicity at low doses in animal models or treated patients
Genotoxicity	Genotoxicity (i.e. mutagenicity and clastogenicity in short-term test systems)

Abbreviation: ASHP – American Society of Health-System Pharmacists; NIOSH – National Institute for Occupational Safety and Health
Source: ASHP Guidelines on Handling Hazardous Drugs (2, page 135)

Awareness on the effects resulting from long term occupational exposure to hazardous drugs among the pharmacy staffs should be emphasized as pharmacy staffs may be involved in the handling of hazardous drugs in their daily job. Improving the knowledge regarding safe handling of hazardous drug among the pharmacy staffs is crucial to minimise occupational exposure and the potential adverse effects. It is also important to provide a better working environment and proper guidelines for them. Based on previous study, pharmacists' knowledge on proper handling of hazardous drugs were unsatisfactory with an average score of only 25% (4). In the Malaysian public healthcare facilities setting, pharmacists and assistant pharmacists are usually the ones who store, prepare, distribute and dispose drugs (5). Therefore, it is necessary to ensure that their knowledge and attitude regarding hazardous drugs are satisfactory. As there was no study instrument to measure the knowledge and attitude for pharmacy staff towards the safe handling of hazardous drugs in Malaysia, this study aimed to develop a validated questionnaire to assess pharmacy staffs on their knowledge and attitude in hazardous drug handling.

Methods

This study involved both pharmacists and assistant pharmacists working in selected government hospitals and health clinics in the state of Perlis and Kedah from October 2017 to May 2018. The developed questionnaire underwent content validity, face validity, construct validity and reliability testing to ensure the consistency and homogeneity of the questions.

The questionnaire was constructed by the investigators based on literature review. The guidelines by ASHP (2) and NIOSH (3) were the main references used for the development of questionnaire. This is a self-administered questionnaire. The initial questionnaire comprised 73 questions and was divided into six domains: socio-demographics, hazardous drug handling, management of disposal and spillage, route of exposure, effects of exposure and attitude on handling hazardous drugs. Domains 2 to 5 were to evaluate the knowledge while domain 6 was to evaluate the attitude of the respondents (Table 2).

Table 2: Overview of the questionnaire before validation

Information		Domain	Number of questions
Socio-demographic	1	Socio-demographic	8
Knowledge	2	Hazardous drug handling	17
	3	Management of disposal and spillage	10
	4	Route of exposure	8
	5	Effects of exposure	17
Attitude	6	Attitude on handling hazardous drugs	13

For the purpose of questionnaire validation process, only questions from Domain 2 to Domain 6 will be analysed. Three stages of validity assessments including content validity, face validity and construct validity were carried out. Content validity was carried out by three experts who were oncology pharmacists. The comments from the experts were considered and the questionnaire was restructured following their constructive advices. In the next stage, face validity was carried out on three pharmacists from the Perlis Pharmaceutical Services Division and Kangar District Health Office to test the consistency of the meaning and comprehensibility of the questionnaire. In total, two rounds of content and face validity were conducted. Then, construct validation was carried out using factor analysis. The questionnaire was also tested for internal consistency or homogeneity through reliability analysis.

Data for construct validity and reliability analysis was collected by distributing the questionnaire to the pharmacists and assistant pharmacists from Sultanah Bahiyah Hospital, Sultan Abdul Halim Hospital, Kuala Nerang Hospital and Kangar Health Clinic. As this was a pilot study to test for the questionnaire's construct validity, the required sample size was ten percent of the projected study population (6). Based on the total number of pharmacy staffs in Tuanku Fauziah Hospital (HTF) in Perlis, which was 59, the targeted sample size was six respondents. The respondents were recruited using convenience sampling method. The respondents' involvement in this study was voluntary and their confidentiality as well as anonymity was ensured. Each participant was assigned and identified by a unique code known only to the investigators.

Data analysis was carried out using the Statistical Package for Social Science (SPSS) version 20.0. Continuous data were expressed as means and standard deviations (SD) while categorical data were expressed as frequencies and percentages. Factor analysis was done to determine the strength of the variables. For factor analysis, the data undergone several tests. Principle Component Analysis was used as the method of extraction. Anti-image correlation was a measure of the sampling adequacy for individual variables, in which the value should be more than 0.5 for each variable. Communality values were used to determine how the answers from each question correlated among each other in the anti-image correlation matrix. High value of communalities means that these questions explained most of the variables in the questionnaire. Only those questions with communalities above 0.5 with acceptable correlation will be considered to be analysed further in factor analysis. Bartlett's Test of Sphericity with significance level (p) less than 0.001 indicated the strength of the relationship among variables in the factor analysis while Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy value of 0.5 and above for overall variable showed the sample adequacy for the factor analysis. Internal consistency reliability of the questionnaire was assessed using Cronbach's Alpha value. Cronbach's alpha value of 0.6 and above showed the reliability of the domain.

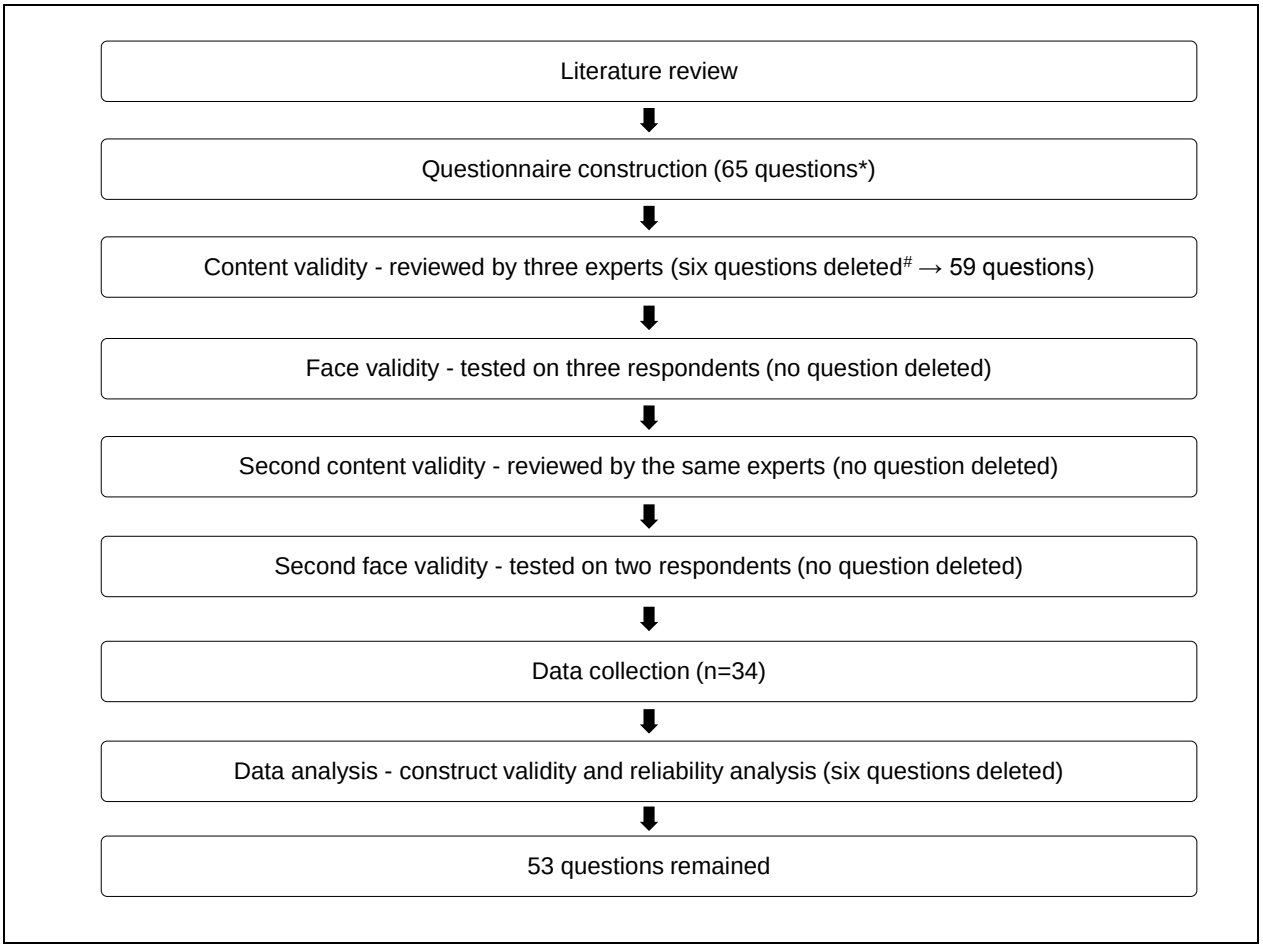
Results

During content validation, five questions were omitted in the Knowledge Domains (Domain 2 to 5) of the instrument in view of the questions being too general, repetitive of similar concept and not suitable to be presented to the respondents. Twenty-three questions were rephrased to make them more specific and easier to understand based on the experts' opinion. Meanwhile in the Attitude Domain, one question was omitted because the item was found to be controversial in the institutional practice. After the process of content validity, 47 knowledge questions and 12 attitude questions were retained.

During face validation, most of the items in the knowledge and attitude domains were fully understood by the respondents. The time spent to complete the questionnaire was approximately 20 to 30 minutes. No question was deleted during face validation.

After the content and face validation, the questionnaires were distributed to the targeted respondents. A total of 36 subjects were approached. Out of that, 34 subjects responded and thus the response rate was 94.4%. The process of data collection took around two weeks. The process of the questionnaire construction and validations was summarised in Figure 1.

Figure 1: Overview of the process of questionnaire construction and validations



* There were 65 questions in Domain 2 to 6 initially, excluding the eight questions in the socio-demographic domain.
# One question from Domain 2, one question from Domain 3, two questions from Domain 4, one question from Domain 5, and one question from Domain 6 were deleted.

Construct validation was carried out using factor analysis. Following factor analysis, all questions in Domain 2 (Hazardous drug handling) were retained resulting in a total of 16 questions (Table 3). There were 16 communalities values recorded to be more than 0.5 which satisfied the requirements for the questionnaire to be valid. Inspection of the anti-image correlation matrix also revealed that majority measures of sampling adequacy were well above the acceptable level of 0.5. Bartlett's test of sphericity showed significant values ($p<0.001$) while the Kaiser-Meyer-Olkin (KMO) test value was 0.418. The value of Cronbach's Alpha for Domain 2 was 0.618 (n=16, mean=26.85, SD=3.076) which had proven the reliability of the domain.

Two questions from Domain 3 were deleted due to the variables of zero variance, and another one was omitted due to communalities value less than 0.5 and thus only six questions remained in the domain (Table 4). Inspection of the anti-image correlation matrix revealed that majority measures of sampling adequacy were well above the acceptable level of 0.5. The Bartlett's test of sphericity showed significance ($p<0.001$) and KMO test results was 0.545 which indicated that there was a good correlation among the variables. However, the Cronbach's Alpha was only 0.297 (n=6, mean=8.91, SD=1.311) which showed that the domain was unreliable.

One question in Domain 4 (Route of exposure) were deleted due to communality value less than 0.5, and only five questions remained in this domain (Table 5). Inspection of the anti-image correlation matrix revealed that majority measures of sampling adequacy were well above the acceptable level of 0.5. The results of Bartlett's test of sphericity was not significant ($p=0.078$) and KMO value was 0.495. The value of Cronbach's Alpha was 0.421 (n=5, mean=8.35, SD=1.790) showing that the domain was unreliable.

Table 3: Communality values of the correlation matrix for Domain 2 (Hazardous drug handling)

	Item	Initial	Extraction
1	A surgical mask provides protection from inhalation of hazardous aerosols	1.000	0.706
2	Wearing one pair of surgical gloves is enough to protect personnel from hazardous drug exposure	1.000	0.739
3	Polyethylene-coated gown is more appropriate than cloth gown during extemporaneous drug preparation of hazardous drug	1.000	0.682
4	Disposable gowns during hazardous drug preparation can be reused	1.000	0.886
5	Eye protection are recommended during hazardous drug preparation	1.000	0.707
6	Hazardous drugs should be stored in well-ventilated area	1.000	0.767
7	Some of the hazardous drug can be stored together with other drugs, example: hydroxyurea stored together with paracetamol	1.000	0.560
8	Containers of hazardous drug should clearly display warning labels stating the contents are 'Hazardous' in nature	1.000	0.810
9	In storage of hazardous drug, it should be kept below eye level	1.000	0.742
10	Any equipment can be used for counting and pouring of oral hazardous drugs	1.000	0.839
11	Hazardous drugs in the unbroken blister form can be held without gloves as protection is sufficient	1.000	0.855
12	Cutting hazardous drugs in tablet form can be done without wearing rubber gloves if it is needed in a smaller dose	1.000	0.907
13	It is not advisable to prepare hazardous extemporaneous preparation wearing only latex glove	1.000	0.841
14	All hazardous drugs have same handling measure *	1.000	0.446 *
15	Hand wash should be practice only before handling hazardous drugs	1.000	0.704
16	It is safe to use the same apparatus to prepare all extemporaneous preparation including hazardous	1.000	0.923

Note: Extraction method: Principle component analysis.
* Question was retained despite communality less than 0.5 and rephrased to "The same handling measures apply to all hazardous drug".

Table 4: Communality values of the correlation matrix for Domain 3 (Management of disposal and spillage)

	Item	Initial	Extraction 1	Extraction 2
1	The first step of spillage management is to wear PPE	1.000	0.718	0.723
2	Spillage kit should be made available at storage area of hazardous drug *	1.000	0.327 *	-
3	Pharmacist in charge of hazardous drugs is responsible for all spillage	1.000	0.549	0.576
4	It is not necessary to clean up spills immediately	1.000	0.825	0.841
5	Workers who handle hazardous drugs should receive proper training in spill management and the use of PPE	1.000	0.828	0.868
6	Spillage management for all dosage forms of hazardous drugs are the same	1.000	0.685	0.741
7	Hazardous drug-contaminated sharp or sharp items should be place in the designated sharp container	1.000	0.884	0.929

Note: Extraction method: Principle component analysis; Extraction 1: Communality values before deletion of question; Extraction 2: Communality values after deletion of question.
* Question was deleted due to communality value less than 0.5.

Table 5: Communality values of the correlation matrix for Domain 4 (Route of exposure)

	Item	Initial	Extraction 1	Extraction 2
1	Breathing in powder form of hazardous drug can cause organ damage in long term	1.000	0.771	0.770
2	Proper hand washing should be practiced before handling food to prevent ingestion of hazardous drug *	1.000	0.465 *	-
3	Hazardous drugs can only enter the body through open wound	1.000	0.503	0.655
4	Hazardous gas can enter the body through skin and mucous membranes	1.000	0.528	0.526
5	Effect to organ can only occur if hazardous drugs are inhaled or ingested	1.000	0.527	0.542
6	Hazardous drug can enter the body during removal of personnel protective equipment	1.000	0.620	0.616

Note: Extraction method: Principle component analysis; Extraction (1): Communality values before deletion of question; Extraction (2): Communality values after deletion of question.
* Question was deleted due to communality value less than 0.5.

No question was deleted from Domain 5 (Effects of exposure) and total of 16 questions remained in this domain. Anti-image correlation matrix showed that the communality values were more than 0.5 which reflected a strong correlation between the variables and therefore the data set was suitable for factoring (Table 6). Inspection of the anti-image correlation matrix revealed that all measures of sampling adequacy were well above the acceptable level of 0.5. Bartlett's test of Sphericity was significant ($p<0.001$) and KMO value was 0.530. The value of Cronbach's Alpha was 0.839 (n=16, mean=25.54, SD=7.085) and this confirmed that the domain was reliable.

For Domain 6 (Attitude of hazardous drug handling) under the Attitude Domain, the communality values were more than 0.5 which showed that there was a strong association between the items and the set of questions was accepted and suitable for factoring (Table 7). Inspection of the anti-image correlation matrix revealed that all measures of sampling adequacy were well above the acceptable level of 0.5. The Bartlett's test was significant ($p<0.001$) and KMO test value was 0.550. The value of Cronbach's Alpha was 0.609 (n=16, mean=25.54, SD=7.085) which demonstrated that the domain was reliable.

Table 6: Communality values of the correlation matrix for Domain 5 (Effects of exposure)

	Item	Initial	Extraction
1	Hypertension	1.00	0.798
2	Dryness of mouth	1.00	0.572
3	Erectile dysfunction	1.00	0.708
4	Temporary infertility	1.00	0.820
5	Permanent infertility	1.00	0.826
6	Constipation	1.00	0.767
7	Blood count change	1.00	0.856
8	Neuropathy	1.00	0.764
9	Nephropathy	1.00	0.666
10	Diabetes	1.00	0.801
11	Skin infection	1.00	0.729
12	Weight loss	1.00	0.777
13	Hearing impairment	1.00	0.711
14	Bone marrow damage	1.00	0.722
15	Lung/Heart damage	1.00	0.675
16	Loss of sight	1.00	0.739

Note: Extraction method: Principle component analysis.

Table 7: Communality values of the correlation matrix for Domain 6 (Attitude of hazardous drug handling)

	Item	Initial	Extraction
1	I am confident that I can handle hazardous drugs safely	1.00	0.786
2	The safe-handling measures make my job harder	1.00	0.753
3	I am not worried about the side effects of occupational exposure to hazardous drugs	1.00	0.526
4	Non-adherence to safe-handling measures is acceptable if I am too busy	1.00	0.912
5	Non-adherence to safe-handling measures among my colleagues is acceptable as long as I practice as recommended myself	1.00	0.866
6	My training on safe-handling of hazardous drug is sufficient	1.00	0.748
7	I agree that the standard procedure for safe handling of hazardous drug should be applied in the pharmacy department	1.00	0.825
8	I think it is my responsibility to clean up and report spillage of hazardous drugs	1.00	0.633
9	I agree that alternative duty should be offered to individual who are pregnant, breast feeding or attempting to conceive or father a child	1.00	0.686
10	I agree that all personnel who handle hazardous drugs should be routinely monitored in medical surveillance program	1.00	0.735
11	I think that the awareness in hazardous drug handling is the responsibility of both workers and institution	1.00	0.860
12	I would like to keep myself updated with the latest recommendations for safe-handling of hazardous drugs	1.00	0.628

Note: Extraction method: Principle component analysis

Table 8: Communality values of the correlation matrix for the revised Domain 3 (Disposal, spillage and route of exposure)

	Item	Initial	Extraction
1	The first step of spillage management is to wear PPE	1.000	0.615
2	Pharmacist in charge of hazardous drugs is responsible for all spillage	1.000	0.695
3	It is not necessary to clean up spills immediately *	1.000	0.804
4	Workers who handle hazardous drugs should receive proper training in spill management and the use of PPE	1.000	0.877
5	Spillage management for all dosage forms of hazardous drugs are the same	1.000	0.752
6	Hazardous drug-contaminated sharp or sharp items should be place in the designated sharp container	1.000	0.902
7	Breathing in powder form of hazardous drug can cause organ damage in long term	1.000	0.871
8	Hazardous drugs can only enter the body through open wound	1.000	0.704
9	Hazardous gas can enter the body through skin and mucous membranes *	1.000	0.640
10	Effect to organ can only occur if hazardous drugs are inhaled or ingested	1.000	0.587
11	Hazardous drug can enter the body during removal of personnel protective equipment	1.000	0.699

Note: Extraction method: Principle component analysis.

As the Cronbach's Alpha values of both Domain 3 and Domain 4 showed that the domains were unreliable, the questions from these two domains were combined into a single domain and renamed as Domain 3: Disposal, spillage and route of exposure. All eleven questions in the revised Domain 3 were retained as their communality values were more than 0.5 (Table 8). The communalities in the correlation matrix satisfied the requirements for validity. Inspection of the anti-image correlation matrix revealed that majority measures of sampling adequacy were well above the acceptable level of 0.5. Bartlett's test of sphericity was p=0.003 and KMO value was 0.476. The value of Cronbach's Alpha was 0.547 (n=11, mean=17.26, SD=2.609) which showed that the domain was near to the acceptable value. Then, two out of

eleven questions from the new Domain 3 were omitted to improve the internal consistency of the questions. The new value of Cronbach's Alpha was found to be 0.610 (n=9, mean=13.91, SD=2.479), which demonstrated reliability of the domain. The original Domain 5 and Domain 6 were then renamed as Domain 4 and Domain 5 accordingly.

Discussion

The initial questionnaire contained 73 questions regarding knowledge and attitude on the handling of hazardous drug. The number of questions was reduced to 63 questions following the content validation through experts' opinion. After the construct validation and reliability testing, 61 questions remained in the final version of questionnaire.

The construct validity of the questionnaire was examined through principal component analysis. Communality values less than 0.5 may indicate that the variables had considerable variance unexplained by the extracted factors which render the question not to be valid. In this study, however, we decided to retain a question with Communality value 0.446 in Domain 2 ("All hazardous drugs have same handling measure") because the question was deemed crucial to assess the knowledge of hazardous drug handling. In addition, all three experts had also recommended to retain and rephrase the question. This was also supported by further analysis that showed that retaining the question resulted in a higher value of Cronbach's alpha. Thus, the question was rephrased to "The same handling measures apply to all hazardous drug."

In terms of internal consistency, the threshold for Cronbach's Alpha value was set at 0.6 in this study. The domain with Cronbach's Alpha value above 0.6 was considered to be reliable. According to Nunnaly *et al*., the reliability testing of newly developed measures can be accepted when the alpha value is at least 0.60. Otherwise, 0.70 should be used as the threshold (7). The Cronbach's Alpha value for Domain 2, revised Domain 3 and Domain 6 were just slightly above 0.6 while only Domain 5 had a Cronbach's Alpha value above 0.7. Using 0.6 as a threshold, all domains in the questionnaire were considered to have acceptable internal consistency.

During the reliability analysis, the Cronbach's Alpha values of the initial Domain 3 and Domain 4 were less than 0.6. Studies reported that low Cronbach's Alpha values could be due to inadequate number of questions, poor inter-relatedness between the variables or heterogenous constructs (8). Also, the values from Bartlett's test was found to be significant for Domain 3 ($p<0.001$) but not Domain ($p=0.078$). Therefore, we decided to combine the questions from Domain 3 and Domain 4 and the new domain was renamed as Domain 3: Disposal, spillage and route of exposure. This revised domain initially comprised 11 questions that aimed to assess the knowledge about management of disposal and spillage of hazardous drug and the possible routes of exposure to hazardous drugs. Nevertheless, the reliability test showed that the revised domain was unreliable, resulting in the deletion of two questions to improve the internal consistency.

Domain 5 (Effects of exposure to the hazardous drugs) underwent some deliberations during the content validation process, as there was limited direct evidence that demonstrated that the hazardous effect of chemotherapy seen in the patients are the same as the effects of chronic long-term low dose exposure to all kinds of hazardous drugs among the healthcare workers. The domain was retained, however, in reference to the NIOSH guidelines which quoted that workplace exposure to hazardous drugs can cause either or both acute or chronic effects. Some examples were skin rashes, adverse reproductive outcomes which include infertility, spontaneous abortion and congenital malformations, and possibly leukaemia. The risk of exposure depends on the toxicity of the drugs as well as the amount of exposure of a worker to these hazardous drugs (9). The results of factor analysis and reliability testing for Domain 5 were satisfactory.

Our literature review failed to discover comparable studies that focus on the aspects of knowledge, attitude and practices (KAP) of pharmacy staffs towards the handling of a broad selection of hazardous drugs. Most published literature aimed to explore the KAP among healthcare workers on the handling of harmful drugs particularly anticancer agents. Most of these studies utilised validated questionnaires conducted either through cross-sectional design or pre-post interventional design with the aim to further improve the practice among the staffs in the institutional towards a safer operating procedures of handling antineoplastic agents. When these studies were used as our reference to derive the questions in the beginning stage of questionnaire development, it was found that most of the items contained in the final validated questionnaire were of similar dictions as those used in previous studies evaluating the KAP towards the handling of cytotoxic drugs among healthcare staffs. The main difference between our newly

validated questionnaire and the previous instruments was that our questionnaire aimed to measure the KAP of pharmacy staffs towards a broader range of hazardous drugs, not only limited to anticancer agents (10-14).

The main limitation of this study was the small sample size if compared to previous studies. Although the number of the recruited respondents in this study was well above the targeted sample size, it was recommended that pilot studies should include a larger sample size especially when there is no prior information available to the researchers (15). Moreover, a small sample size could also affect the values of Cronbach's alpha. According to Javali *et al*., the results from internal consistency reliability testing will be more consistent and comparable when the sample size is at least 50 (16).

Conclusion

A validated questionnaire to assess the safety-related knowledge and attitude in hazardous drug handling among the pharmacy staffs was developed. The final questionnaire with 61 questions was demonstrated to be valid and reliable. There were 16 questions in Domain 2 (Hazardous drug handling), nine questions in Domain 3 (Management of disposal and spillage and route of exposure) and 16 questions in Domain 4 (Effect of exposure) to evaluate the knowledge, and 12 questions in Domain 5 (Attitude on handling hazardous drugs) to assess the attitude towards hazardous drug handling. This survey instrument can serve as an important tool to evaluate knowledge and attitude in handling hazardous drugs among the pharmacy staffs.

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Conflict of Interest Statement

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Prescribing Pattern of Antibiotics in the General Pediatrics Ward of Tengku Ampuan Rahimah Hospital (HTAR): A Prospective Study

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Abstract

Introduction: The main issues with regards to antibiotics include choosing the correct antibiotic for the appropriate indication, dosage, and duration to achieve the optimum goal of therapy.
Objectives: To study the prescribing pattern of antibiotics in general paediatric wards of HTAR and to determine whether the prescribing of antibiotics was in accordance with the guidelines.
Method: A hospital-based cross-sectional prospective study was conducted to evaluate the prescribing pattern of antibiotics in paediatric inpatients. Data was extracted from the prescriptions issued during the month of August 2017 in the general paediatrics ward. All prescriptions of admitted patients who were prescribed with antibiotics were collected and followed up daily until patient was discharged. The data collected was analysed using Statistical Package for the Social Sciences (SPSS) software (Version 20).
Results: In total there were 545 antibiotics prescribed for 269 patients. It was found that the most prevalent disease among the patients was respiratory infections (56.5%). The most prescribed antibiotics among the general paediatric population were narrow spectrum antibiotics (71.1%) from the Penicillin class. Within the class of Penicillin, we found that Ampicillin was most frequently prescribed by the physicians. We found high adherence rate in the current medication management in the ward to the prescribing guidelines by (99.8%).
Conclusion: Our study highlighted that the antibiotics prescribed in the general paediatric wards of HTAR were mostly narrow spectrum antibiotics and the antibiotics were
prescribed according to the guidelines. Further studies with bigger study population over a longer study period are needed to obtain higher impact results.
Keywords: antibiotic, prescribing pattern, paediatric

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Introduction

Antibiotics are one of the commonly prescribed medications in both the community and hospital settings (1). Selection of appropriate antibiotics is the challenging part to the health care practitioners these days. Clinical practice guidelines play a vital role in providing guidance to the practitioner to select the best management for the patients while preventing the emergence of antimicrobial resistance. The main problems that they face in regards to antibiotics include choosing the correct drug for the appropriate indication, dosage, and duration to achieve the optimum goal of therapy (2).

Antibiotics are prescribed by the doctors for treatment or prevention of many types of bacterial infection (3). There are varieties of antibiotics, which are categorized either based on their chemical structures, mode of actions, or spectrum of activity. Antibiotics can be broadly categorized into six groups. The groups are penicillin, cephalosporin, aminoglycosides, tetracyclines, macrolides and fluoroquinolones.(4).

Antibiotics can be either broad spectrum or narrow spectrum based on the range of bacteria that have an antibiotic affect. The terms “narrow” or “broad” spectrum can be subjective, since some antibiotics can be broad but at the same time is narrower than the other broad antibiotics, and vice versa (5). The Penicillin group antibiotics such as penicillin and ampicillin are narrow spectrum antibiotics while some cephalosporin group antibiotics, tigecycline, piperacillin/tazobactam, polymyxins, carbapenem and amikacin are broad spectrum antibiotics (6,7).

The patterns of diagnosis and antibiotic choice did vary. A prospective observational study of drug utilization and antimicrobial prescription pattern among paediatrics cases in tertiary care hospital in India showed that the most frequently prescribed antibiotics were cephalosporins (43.6%) followed by penicillins. These antibiotics were commonly indicated for gastrointestinal tract infections (60.66%) followed by respiratory tract infection (27.2%). Most of the antibiotics were used as empirical treatment (8). Besides, a retrospective study of prescription pattern of antibiotics in paediatric inpatients at a tertiary care hospital in central India showed mean age of paediatric patients was 5.6 years old. The most common infections were acute gastroenteritis, followed respiratory tract infections, and meningitis. The results showed the most commonly prescribed antibiotics was cefexime and followed by amoxicillin-clavulanic acid combination from penicillin group (9). Another study on prescribing pattern of antibiotic in paediatric patients with pneumonia in India showed that the most commonly prescribed antibiotics for pneumonia was amoxicillin-clavulanic acid (43%) and ceftriaxone (36%). The mean age of the patients diagnosed with pneumonia was 26 months. Most patients (73%) were prescribed with single antibiotic then followed by 26% with two antibiotics (10).

However, there were inappropriate choice of antibiotic among paediatric patients shown by the following studies. A study done across six countries (Germany, Italy, South Korea, Norway, Spain, and the US in paediatric patients found that there was a vast difference in anti-microbial utilisation across these countries. Hence, they concluded that there was a need to optimise usage of anti-microbial in order to prevent resistance (11). A study conducted by Suparna Sharma *et al.* In 2016, proposed that Georgetown Public Hospital Corporation antibiotic’s use were inappropriate. Antibiotics were prescribed for diagnosis like asthma and viral infections, which were not bacterial infectious disease. Broad spectrums antibiotics were prescribed as a first line therapy even when used for infectious diseases still requires careful judgement (12). This shows there is a need for antibiotic usage review.

In Malaysia, there were similar findings of inappropriate choice of antibiotic among patients. A study by Hassali MA *et al.*(13) to assess the general practitioner’s attitude and knowledge on antibiotic prescribing for upper respiratory tract infections showed that many general practitioners prescribed antibiotics even when it was not required. Another study by V K *et al.* (14) conducted in six public hospitals in Malaysia found that there was a lack of adherence to guidelines in terms of antibiotic prescribing. Meanwhile, another study conducted in general paediatric wards across five different countries (Malaysia, United Kingdom, Germany, Hong Kong, and Australia) found that the most frequently prescribed medication was systemic anti-bacterial amounting to 25.2% (15). Another study by Boon Phiaw Kho *et al.* (16) in Sarawak, Malaysia reported that the antibiotic prescribing pattern for upper respiratory tract infections was found to differ between health care professionals and may be inappropriate. Lastly, a study by Teng *et al.* found high prescribing rate of antibiotics for febrile paediatric patients (17).

Since there is a lack of study focusing on the prescribing pattern of antibiotics in paediatric patients in Malaysia, this study will be targeting on general paediatric inpatient ward prescriptions containing antibiotics. The main objective of this study was to study the prescribing pattern of antibiotics in general paediatric wards and to determine whether the prescribing of antibiotics was in accordance to the guidelines.

Method

This was a cross sectional prospective study done to evaluate the prescribing pattern of antibiotics in the general paediatric ward of Tengku Ampuan Rahimah Hospital (HTAR), Klang. All prescriptions prescribed for patients who were admitted in paediatric wards 6A, 6B, and 7D of HTAR during the whole month of August 2017 were collected. The targeted sample size was 262 based on average admission of 817 per month calculated by using Raosoft formula.

Only complete prescriptions were included in the study. All incomplete prescription without age, gender, diagnosis, antibiotic prescribed, class of antibiotics, dose of antibiotic prescribed, frequency, duration of treatment and prescriber’s status was excluded from this study. In addition, prescription from the

Paediatric High Dependency Unit, Neonatal Intensive Care Unit and Special Care Nursery, and prescription for transfer-in patient from other hospitals were also excluded.

A validated data collection form was developed by the pharmacists from HTAR with reference to Chunnilall D *et al.* (2015) (18). Data was extracted from the included prescriptions using the data collection form. Baseline demographic, such as age, gender, diagnosis was collected as well as antibiotic prescribed, class of antibiotics, dose of antibiotic prescribed, frequency, duration of treatment, and prescriber's status. The data that was collected was analysed descriptively using Statistical Package for the Social Sciences (SPSS) software (Version 20).

This study was done in HTAR with the verbal approval from Paediatric Head of Department. No informed consent is required as data was merely collected from prescriptions without any intervention and no patient identifiers. Ethics approval was also obtained from Malaysian Research Ethics Committee (MREC).

Results

During the study period, a total of 544 prescriptions of antibiotics were prescribed for 269 patients in the paediatric wards in HTAR. Among the patients that were included in this study, the highest number of patients were in age group between 1 to 5 years old (54.6%) and lowest number were in age group above 5 to12 years of age (14.5%). The percentage of male and female patients was almost equal with 57.2% of male and 42.8% female, respectively. The most prevalent disease among the studied patients was respiratory tract infections (56.5%) followed by ear, nose and throat (ENT) infections (13.8%), and gastrointestinal infections (5.2%) being in third position. Other disease encountered during the study was as per Table 1.

Table 1: Demographic and diagnosis distribution (n= 269)

Demographic	n (%)
Age group	
<1 year	83 (30.9)
1-5 years	147 (54.6)
>5-12 years	39 (14.5)
Gender	
Female	115 (42.8)
Male	154 (57.2)
Sites of infection	
Blood	5 (1.9)
Brain	6 (2.2)
ENT	37 (13.8)
Gastrointestinal	14 (5.2)
Nephrology	6 (2.2)
Respiratory	152 (56.5)
Skin	3 (1.1)
UTI	12 (4.5)
Others	34 (12.6)

Abbreviation: ENT - ear, nose and throat; UTI – urinary tract infection

Our study found that penicillin was the most prescribed antibiotic, at 55.9%, followed by cephalosporin at 22.4%. The least prescribed antibiotics in paediatric ward in HTAR belonged to quinolones with 0.4%. As penicillin class of antibiotic was the frequently prescribed class, we further analysed and found that ampicillin was ranked the highest in the penicillin class, followed by penicillin antibiotic (48.4% and 22.0% respectively) (Table 2).

Based on the 544 prescriptions of antibiotics reviewed in the paediatric wards in HTAR, approximately 156 prescriptions were prescriptions for broad-spectrum antibiotics and 388 prescriptions for narrow spectrum antibiotics. It was noted that narrow spectrum antibiotics was the most frequently

prescribed to paediatric patients in the ward followed by broad spectrum antibiotics with the percentage of 71.3% and 28.7% respectively (Table 2).

Table 3 showed that 99.8% of the prescriptions with antibiotics were prescribed correctly to patient in the paediatric ward in terms of indication, dose and route of administration according to the National Antibiotic Guidelines (NAG) (19), Pediatric Protocols 3rd Edition (20), Lexicomp (4)and Frank Shann 17th Edition (2017) (21).

Table 2: Classes of antibiotics prescribed, types of penicillin antibiotics and broad spectrum versus narrow spectrum antibiotics (n=544)

Prescribing Pattern	n (%)
Classes of antibiotics prescribed	
Penicillin	304 (55.9)
Cephalosporin	122 (22.4)
Macrolide	86 (15.8)
Aminoglycoside	16 (2.9)
Carbapenem	6 (1.1)
Quinolones	2 (0.4)
Others	8 (1.5)
	Types of Penicillin antibiotics prescribed
Ampicillin	147 (48.4)
Penicillin	67 (22)
Amoxycillin	45 (14.8)
Cloxacillin	24 (7.9)
Amoxicillin/Clavulanic Acid	20 (6.6)
Piperacillin/Tazobactam	1 (0.3)
Broad Spectrum versus Narrow Spectrum	
Narrow	388 (71.3)
Broad	156 (28.7)

Table 3: Appropriateness of antibiotic prescribing (indication, dose and route of administration) according to the guidelines (n=544)

Prescription According to Guideline	n (%)
Yes	543 (99.8)
No	1 (0.2)

Discussion

Antibiotics are usually prescribed empirically upon diagnosis and subsequently are adjusted according to the culture and sensitivity results (22). In the paediatric departments, antibiotics were the most commonly prescribed medications and one of the main drugs prescribed (23). This study was carried to determine the prescribing patterns of antibiotics in the general paediatric wards of HTAR, Klang, Malaysia.

When analysed according to the age distribution, higher number of patients belonged to the age group of more than 1-5 years. This was common because at this age, the children's immune system is still developing (24). According to a study by Pradeepkumar *et al.* (2017), it was found that the median age of paediatric patients receiving antibiotic was 3 years old, and the age group that received antibiotics more frequently than other children was patient with age group below 1-year-old. This indicated that patient with age group of below 1-year-old was more susceptible to infectious diseases (25). Less percentage was observed in the children of age group more than 5-12 years (14.5%). However, our study population had an approximately equal gender distribution not statistically affecting our results (26).

In our study, a total of 269 patients with 544 antibiotics prescriptions were recorded in the duration of one month. Penicillin was widely prescribed for our paediatric patients followed by cephalosporins. Our results were comparable to Suparna Sharma *et al.* (12) who also found that penicillin group antibiotics were

frequently prescribed at a frequency as high as 51.4%. Amoxicillin was the drug of choice (33.9%) and the various diagnoses found were asthma (20 %), respiratory infections (19.5 %), and gastrointestinal infections (12.1 %). It was not surprising that the quinolones are prescribed in caution due to the fear of adverse effects such as arthralgias (27).

In our study, only 28.7% of the prescriptions contained broad spectrum antibiotics while the remaining were narrow spectrum antibiotics. The commonly prescribed antibiotic was narrow spectrum antibiotic, and as per the recommendations in the guidelines. This study, however, did not verify the culture and sensitivity results. In contrast, another study found that only 27% of providers prescribed narrow-spectrum therapy in the emergency department, but more narrow spectrum antibiotics were prescribed during discharge (56%) (28). This could be due to different guidelines being practiced. Antibiotics use is influenced by the preference of hospital doctors, experience using the antibiotics, availability of medication, and also publicity by the pharmaceutical industries (28).

Appropriate usage and doses of antibiotics for the treatment in paediatric ward were analysed by referring to the guidelines such as the National Antibiotic Guidelines (NAG) (19), Lexicomp (4), Frank Shann (21) or Pediatric Protocols (20). From the collected data, ampicillin from penicillin class was the major antibiotic prescribed in the wards for respiratory infection treatment. According to the NAG (19), ampicillin is one of the preferred antibiotics for respiratory infection. Therefore, it showed that the prescribed antibiotics were given correctly according to guidelines in the ward.

The limitation of this study was that the data collection duration was only one month. This may impose limitation for seasonal variation. Besides, this was a single-centred study conducted in the general paediatric patients only and all cases from the Paediatric High Dependency Unit, Neonatal Intensive Care Unit, and Special Care Nursery were excluded. Hence, generalization of the observed results from this study to other paediatric population was not possible. Future study should include other paediatric population and duration of the study should be extended quarterly for a year in order to allow generalization and to prevent bias.

Conclusion

Our study highlighted that antibiotics prescribed in the general paediatric wards of HTAR were mostly narrow spectrum antibiotics and the antibiotics prescribing was done according to the guidelines. Further studies are needed with extensive collaboration with physicians and microbiologists to obtain higher impact results in terms of culture and sensitivity, diagnosis, and bigger study population over a longer study period. Continuing education about rational drug use and development of easy to use treatment guidelines for common diseases in the paediatric wards are highly recommended to ensure the sustainability of good practices.

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Conflict of Interest Statement

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The Occurrence of Acute Kidney Injury (AKI) in Intensive Care Unit (ICU) Patients Treated with Piperacillin/Tazobactam and Meropenem – an Observational Study

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Abstract

Introduction: Piperacillin/Tazobactam was seen to be associated with increased acute kidney injury (AKI) and exhibited delayed improvement in serum creatinine level during antibiotic therapy. Among the intensive care unit (ICU) patients, however, the evidences were conflicting with non-critically ill patients.
Objective: To compare AKI development or delayed renal recovery during therapy or after completion of therapy in adult critically ill patients who received Piperacillin/Tazobactam or Meropenem.
Method: This was a retrospective observational study. All eligible adult patients treated with Piperacillin/Tazobactam or Meropenem in ICU at Hospital Sultanah Aminah Johor Bahru from January 2015 – June 2018 were included in the study. The patients were followed up until the completion or discontinuation of antibiotic, transferred out from ICU or died. Paired sample t-test was performed to compare the renal recovery in both groups from the initiation of antibiotic to the last day of follow up.
Results: A total of 232 patients were included in the study, with 120 patients in the Piperacillin/Tazobactam group and 112 patients in the Meropenem group. Comparable occurrence of AKI was observed in the Piperacillin/Tazobactam and Meropenem group on the initiation of antibiotic treatment (55.8%, n=67 vs 65.2%, n=73; p=0.146) and last day of follow up (56.7%, n=68 vs 54.5%, n=61; p=0.7). Significant improvement of creatinine clearance (CrCl) in Meropenem group from the first to last day of antibiotic treatment was observed (mean CrCl 55.16 ml/min (SD 51.14) to 83.01 ml/min (SD 108.48), $p<0.05$), but not in Piperacillin/Tazobactam group (mean CrCl 66.79 ml/min (SD 63.82) to 72.66 ml/min (SD 66.24), p=0.149), indicating a delayed renal recovery in patients receiving Piperacillin/Tazobactam.
Conclusion: The occurrence of AKI in the Piperacillin/Tazobactam group was comparable with the Meropenem group but renal recovery in the Piperacillin/Tazobactam group was delayed compared with Meropenem group at the last day of follow up.
Keywords: Acute kidney injury, renal recovery, critically ill, piperacillin/tazobactam, meropenem

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Introduction

Piperacillin-Tazobactam is a penicillin and β -lactamase inhibitor combination drug that is widely prescribed in the hospital or critical care setting as first line empirical therapy for nosocomial infections. It is used in the treatment of moderate to severe nosocomial infections including hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP), ventilator-associated pneumonia (VAP), community-acquired pneumonia (CAP) with risk factors for *Pseudomonas aeruginosa*, catheter related blood stream infection, complicated skin and soft tissue infections including diabetic foot and necrotizing fasciitis, complicated urinary tract infections, complicated intra-abdominal infection, neutropenic fever, and severe sepsis as well as septic shock (1).

Meropenem is a broad-spectrum antibiotic of the carbapenem family, indicated as the empirical therapy prior to the identification of causative organisms or for diseases caused by single or multiple susceptible bacteria with a broad range of serious infections such as complicated intra-abdominal infection, complicated skin and skin structure infection, nosocomial pneumonia, septicaemia, febrile neutropenia and

for the treatment of severe CAP. Meropenem has a broad spectrum of in vitro activity against Gram-positive and Gram-negative pathogens, including extended-spectrum β-lactamase (ESBL) producing bacteria (2).

Previous studies showed that the combination of Tazobactam and Piperacillin was identified as a cause of delayed renal recovery in critically ill patients. This nephrotoxicity was not observed with the other β -lactam antibiotics (3). In a study conducted by Choudhury *et al.* (4), the combination was only known to increase the level of serum creatinine due to a reduction in tubular creatinine secretion, caused by inhibition of the organic anion transporter. However, in other studies done by Navalkele *et al.* (5) and Hammond *et al.* (6), the combination of Vancomycin and Piperacillin/Tazobactam showed increased risk of acute kidney injury (AKI). A recent series of articles suggested that the combination of Vancomycin and Piperacillin/Tazobactam was synergistically nephrotoxic (7-11). When compared to Meropenem, patients treated with Piperacillin/Tazobactam exhibited delayed improvement in their creatinine during antibiotic therapy (3).

Studies have shown that the use of extended infusion of Piperacillin/Tazobactam did not seem to reduce the risk of AKI compared to standard infusions (12). The two most commonly proposed mechanisms for Piperacillin/Tazobactam-induced AKI were acute interstitial nephritis (AIN) or toxic effects on the renal tubule (13-19). Renal insufficiency from drug-induced AIN usually occurs between three to five days and several weeks from the beginning of the therapy and typically resolves upon discontinuation of the therapy. However, some patients may progress to develop chronic renal failure (20). In a recent study, Piperacillin/Tazobactam had been implicated in causing AIN in at least three case reports (14-16). Furthermore, Piperacillin had been shown to competitively inhibit the organic anion transport system, in a fashion similar to probenecid where it causes the increase in serum creatinine level (21-22)

Many studies were proposing the possibilities of Piperacillin/Tazobactam inducing AKI. There were three intensive care unit (ICU) studies reporting a high rate of AKI with Vancomycin + Piperacillin/Tazobactam (21.2-40.5%) (7, 23-24). Another two of the ICU studies showed a significantly higher rate in the combo group of Piperacillin/Tazobactam and Vancomycin compared with Vancomycin alone (25-26). However, no significant difference was found in the incidence of AKI development or other outcomes between the groups (6) and no studies were showing that Piperacillin/Tazobactam alone increases the risk of AKI.

The high incidence of AKI was reported in combination therapy with Vancomycin and Piperacillin/Tazobactam and to date there was limited study of incidence of AKI in patients treated with Piperacillin/Tazobactam alone. Therefore, this study was designed to compare the occurrence of AKI development or delayed renal recovery during therapy or after completion of therapy in adult critically ill patients who received Piperacillin/Tazobactam or Meropenem.

Method

This study was designed as a retrospective observational study. Patients that were eligible for this study were from the ICU of Hospital Sultanah Aminah, Johor Bahru who fulfilled the inclusion criteria during the study period from 1 January 2015 – 30 June 2018. In this study, the inclusion criteria were all adult patients over the age of 18 years in ICU who were treated with intravenous Piperacillin/Tazobactam or Meropenem, patients who stayed in the ICU for at least 24 hours, diagnosed with severe sepsis or septic shock with or without AKI, and patients who received a minimum of 72 hours of Piperacillin/Tazobactam or Meropenem therapy. Meanwhile, patients who had AKI on chronic kidney disease (CKD) and end-stage renal failure (ESRF), sepsis with meningitis and those who received the studied antibiotics other than via the intravenous route of administration were excluded. The Piperacillin/Tazobactam and Meropenem were supplied by the inpatient pharmacy of the hospital.

The sample size was calculated using Power and Sample Size Calculation software version 3.0.43. (Vanderbilt University, Nashville, TN, USA). Allowing for a 10% dropout, a final sample size of 170 per group will be used.

Patients who were prescribed with Piperacillin/Tazobactam or Meropenem were identified by screening the Pharmacotherapy Review Forms (CP2 form). The CP2 is a form used by pharmacists in the Ministry of Health Malaysia (MOH) to document the findings and interventions related to pharmaceutical care issues of warded patients. Patients prescribed with Piperacillin/Tazobactam or Meropenem were registered in a patient's master list. Using the master list, the inclusion and exclusion criteria were reviewed and qualified patients were assigned a running number based on the antimicrobial use in their treatment

either Piperacillin/Tazobactam or Meropenem. Then, further data was obtained from the CP2 form, patients' case notes and laboratory investigation data from the hospital's IT system (Omega system) using a data Collection Form – PTZ01 Study Form. The patients were followed up until the completion or discontinuation of Piperacillin/Tazobactam or Meropenem antibiotic therapy, patient was transferred out from ICU or patient's death.

Comparisons were made between the two groups using Students t-test (for normally distributed continuous data) and Mann Whitney U test (for non-normally distributed continuous data). Pearson Chi-Square test was used to test categorical variables. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) version 24. A two-sided P value of 0.05 and less was considered to be statistically significant.

Results

Clinical Characteristics of the Cohort

A total of 522 patients that were eligible for the study were screened. Of these patients, 290 were excluded. Thus, only 232 patients were included in the study, with 120 patients in the Piperacillin/Tazobactam group and 112 patients in the Meropenem group (Figure 1).

Table 1 summarised the demographic and clinical characteristics of Piperacillin/Tazobactam and Meropenem groups. The Piperacillin/Tazobactam group had a statistically significant shorter mean duration of antibiotic treatment and ICU stay (5 (standard deviation (SD) 2.5) days, and 9.52 (SD 5.9) days, respectively) than the Meropenem group (7 (SD 3.7) days, and 14.62 (SD 9.2) days, respectively). Meanwhile, a significantly higher proportion of patients in the Piperacillin/Tazobactam group was given the antibiotic empirically as opposed to the Meropenem group (85.8% versus (vs) 61.6%; $p<0.05$). Less number of patients in Piperacillin/Tazobactam group showed growth of microorganism in the culture and sensitivity test when compared to the Meropenem group (15% vs 43.8%, $p<0.05$). Three cases (2.5%) of ESBL organisms were identified in the Piperacillin/Tazobactam group compared to 42 cases (37.5%) in Meropenem group. These organisms were categorised as resistant organisms in Table 1.

Occurrence of AKI

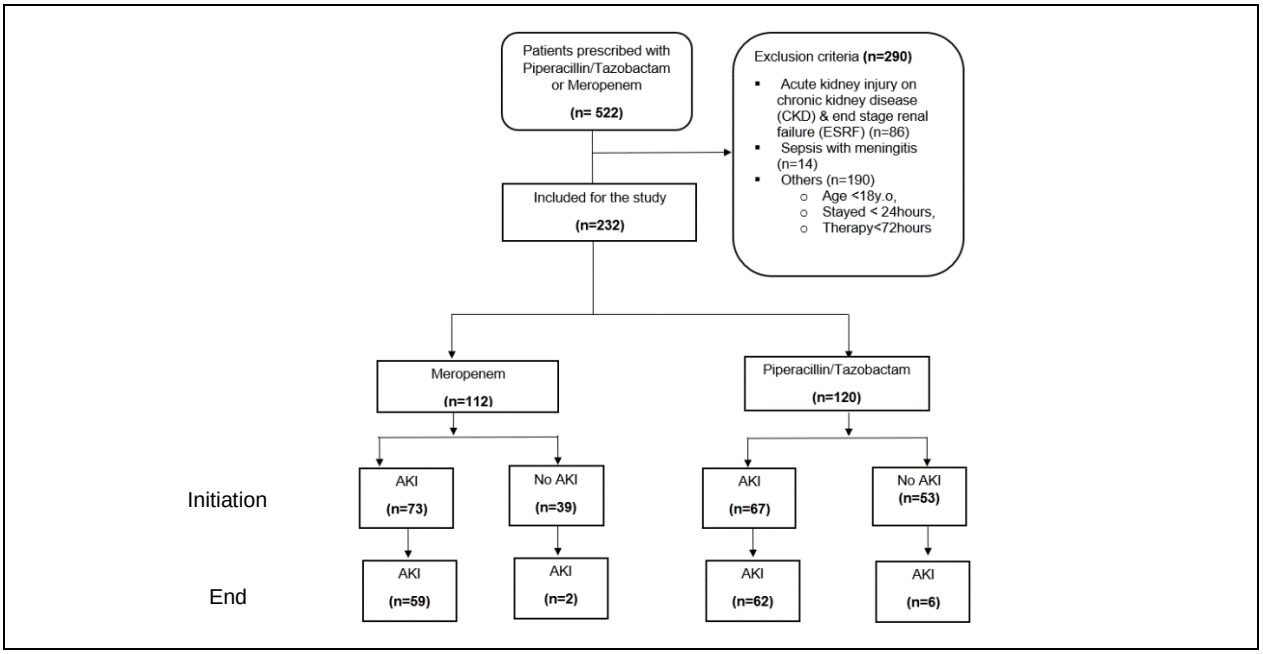
The difference between the number of patients presented with AKI during the initiation of antibiotics in patients receiving Piperacillin/Tazobactam and Meropenem was not statistically significant ($p=0.146$) as reported in Table 2. Similarly, during the last day of follow up, no statistically significant difference was found between the two groups ($p=0.7$).

Renal recovery

This study showed that the occurrence of severely impaired renal function was slightly increased in the Piperacillin/Tazobactam group (Table 3) during the last day of follow up (n=41, 34.%) compared to during initiation of antibiotic (n=36,30%). This was the opposite for the Meropenem group in which during initiation, 43.8% (n=49) of the patients had severely impaired renal function but it decreased to 36.6% (n=41) on the last day of follow up. Meanwhile, an increase in the number of patients with a normal renal function from initiation to the final day of follow up can be seen in both the groups. In Piperacillin/Tazobactam group, the percentage of patients with normal renal function increased from 38.3% (n=46) to 41.7% (n=50) meanwhile in the Meropenem group, it increased from 33.9% (n=38) to 42.9% (n=48).

To investigate further on renal recovery, the CrCl of all patients in both groups during initiation was compared to the CrCl on the last day of follow-up using paired sample t-test (Table 4). In the Piperacillin/Tazobactam group, no renal function improvement was observed (mean CrCl 66.79 ml/min (SD 63.82) to 72.66 ml/min (SD 66.24), $p=0.149$),. In contrary, the Meropenem group showed a significant improvement in CrCl from initiation to the last day of follow up (mean CrCl 55.16 ml/min (SD 51.14) to 83.01 ml/min (SD 108.48), $p<0.05$).

Figure 1: Schematic presentation of the patient selection process for the Piperacillin/Tazobactam and Meropenem groups



Abbreviation: AKI – acute kidney injury; ESRF – end-stage renal failure

Table 1: Demographic and clinical characteristics of the piperacillin/tazobactam and meropenem groups (n=232)

	Pip/Tazo	Meropenem	P-value*
Number of patients, n	120	112	
Age, years, mean (SD)	53.27 (14.8)	50.07 (16.1)	0.12 ǂ
Weight, kg, mean (SD)	68.69 (17.2)	69.74 (16.3)	0.63 ǂ
BMI, kg/m^2, mean (SD)	26.51 (6.34)	26.37 (5.8)	0.87 ǂ
Number of comorbidities, mean (SD)	1.45 (1.3)	1.25 (1.2)	0.23 ǂ
Duration of treatment, mean (SD)	5 (2.5)	7 (3.7)	<0.05 ǂ
Duration of ICU stayed, mean (SD)	9.52 (5.9)	14.62 (9.2)	<0.05 ǂ
Discipline, n (%)			
Medical	77 (64.2%)	61 (54.5%)	
Surgical	34 (28.3%)	47 (42%)	0.06 ł
Others	9 (7.5%)	4 (3.6%)	
Site of Infection, n (%)			
Abdomen	23 (19.2%)	16 (14.3%)	
Urinary Tract	7 (5.8%)	3 (2.7%)	
Respiratory	47 (39.2%)	29 (25.9%)	0.02 ł
Blood	29 (24.2%)	51 (45.5%)	
Skin & Soft Tissue	5 (4.2%)	8 (7.1%)	
Unknown	8 (6.7%)	4 (3.6%)	
Indication of therapy, n (%)			
Empirical	103 (85.8%)	69 (61.6%)	<0.05 ł
Targeted	17 (14.2%)	43 (38.4%)	
Type of Microorganism, n (%)			
No organism	102 (85%)	63 (56.3%)	
Sensitive organism	15 (12.5%)	7 (6.3%)	<0.05 ł
Resistant organism	3 (2.5%)	42 (37.5%)	
Patient outcome, n (%)			
Alive	106 (88.3%)	91 (81.3%)	0.13 ł
Death	14 (11.7%)	21 (18.8%)	

Abbreviation: Pip/Tazo – piperacillin/tazobactam; SD – standard deviation
Note: ǂ - Independent t-test; ł – Pearson Chi Square test

Table 2: Occurrence of AKI among the study population during the initiation of antibiotic treatment and last day of follow up (n=232)

	Initial			Last Day		
	Pip/Tazo	Meropenem	P-value	Pip/Tazo	Meropenem	P-value ǂ
AKI	67(55.8%)	73(65.2%)	0.146	68(56.7%)	61(54.5%)	0.7
Normal renal function	53(44.2%)	39(34.8%)		52(43.3%)	51(45.5%)	

Abbreviation: AKI – acute kidney injury; Pip/Tazo – piperacillin/tazobactam
Note: ǂ – Pearson Chi Square test

Table 3: Renal function of the study population during the initiation of antibiotic treatment and last day of follow up (n=232)

	Pip/Tazo		Meropenem	
	Initial	Last Day	Initial	Last Day
Normal renal function (CrCl: >60 ml/min)	46(38.3%)	50(41.7%)	38(33.9%)	48(42.9%)
Moderately-severely impaired (CrCl: ≤60 ml/min)	38(31.7%)	29(24.2%)	25(22.3%)	23(20.5%)
Severely impaired (CrCl ≤30 ml/min)	36(30%)	41(34.2%)	49(43.8%)	41(36.6%)

Abbreviation: Pip/Tazo – piperacillin/tazobactam; CrCl – creatinine clearance (ml/min)
Note: CrCl was assessed using the Cockcroft and Gault method (28)

Table 4: Recovery of renal function in Piperacillin/Tazobactam and Meropenem groups (n=232)

	Initiation, mean CrCl (SD)	Last day, mean CrCl (SD)	Mean difference in CrCl (SD)	95% confidence interval	P-value *
Pip/Tazo	66.79 (63.82)	72.66 (66.24)	-5.87 (44.21)	-13.86, 2.12	0.149
Meropenem	55.16 (51.14)	83.01(108.48)	-27.85 (81.00)	-43.01, -12.69	p<0.05

Abbreviation: Pip/Tazo – piperacillin/tazobactam; CrCl – creatinine clearance; SD – standard deviation
Note: * - dependent t-test

Discussion

Piperacillin/Tazobactam was widely prescribed in the hospital or ICU setting as first line empirical therapy for nosocomial infections. The recent findings showed that the usage of Piperacillin/Tazobactam in combination with Vancomycin may predispose patients to the increased risk of AKI. This study was caried out to compare AKI development or delayed renal recovery during the therapy or after the completion of therapy in adult critically ill patients who receive Piperacillin/Tazobactam or Meropenem alone. Meropenem is a carbapenem antibiotic that is also commonly used as empirical therapy for nosocomial infections for the patients that had been exposed to another broad-spectrum antibiotic or as targeted therapy. Therefore, Meropenem was chosen as the comparator in this study.

When comparing the two groups, Meropenem was given for a longer duration and the patients in the Meropenem group were associated with a longer ICU stay. This might be because a larger proportion of patients in the Meropenem group (38.4%) was indicated as targeted therapy as compared to Piperacillin/Tazobactam (14.2%).

Our study compared the occurrence of AKI in patients treated with Piperacillin/Tazobactam and Meropenem in the ICU. The occurrence of AKI was found to be comparable between the two groups, but the study by Kadomura *et al.* (28) in non-ICU patients found that the incidence of AKI in patients treated with Piperacillin/Tazobactam (8.6%) alone was significantly higher than that in patients treated with Cefepime (0.9%). Cefepime is an antibiotic from the fourth generation of cephalosporins group. As compared to Meropenem, Cefepime does not provide coverage against anaerobic infection thus it was not

favoured as the first line empirical antibiotic in ICU. As for targeted treatment, Cefepime was also not favoured in view of the resistance pattern caused by ESBL organism. Therefore, the low usage of Cefepime has become the limitation to be used as comparator for this study. Alternatively, Meropenem had been used as comparator by other studies (6).

The incidence of AKI in patients treated with Vancomycin in combination either with Piperacillin or Cefepime was alarming. Hammond *et al.* (7) found that there were no significant differences in the incidence of AKI development between Vancomycin with Piperacillin/Tazobactam and Vancomycin with Cefepime combination groups in critically ill patients. A meta-analysis by Hammond *et al.* (6) found that concomitant use of Vancomycin and Piperacillin/Tazobactam appeared to be associated with a greater incidence of AKI compared to Vancomycin without Piperacillin/Tazobactam. However, this relationship did not exist in studies with at least 50% of patients receiving care in an ICU setting. In both mentioned studies, Vancomycin was given concomitantly with the studied drugs. While Vancomycin has long been associated with AKI, assessment of the impact of Vancomycin trough on incidence of AKI by Navalkele *et al.* (5) found that a discordance in the impact of Vancomycin troughs on toxicity in patients receiving Vancomycin with Piperacillin/Tazobactam compared to those receiving Vancomycin with Cefepime combination. Therefore, incidence of AKI in patients receiving Vancomycin with Piperacillin/Tazobactam was not associated with Vancomycin trough levels.

Meanwhile, in a study by Gomes *et al*. (30), it was found that the incidence of AKI was significantly higher in the Piperacillin/Tazobactam and Vancomycin group (34.8%) compared with the Cefepime-Vancomycin group (12.5%). However, these different findings in non-ICU setting may not be generalizable, as the risk of AKI in critically ill patients may also be increased by various factors such as dynamic volume status, presence of sepsis and its associated inflammation, endothelial dysfunction, adaptive cellular responses to injury, coagulation disturbances, and use of nephrotoxic medications like vasoactive agents, antibiotics, and contrast media (7). The critically ill population also has an increased baseline risk of AKI (31).

Our study also found that renal recovery in the Piperacillin/Tazobactam group was delayed when compared to the Meropenem group. This observation supports the finding by Jensen *et al.* (3), where Piperacillin/Tazobactam was identified as a cause of delayed renal recovery in critically ill patients. In the study, renal recovery was 1.0 ml/min/1.73 m^2/24 h during exposure to Piperacillin/Tazobactam as compared to Meropenem recovering at higher rate of 2.9 ml/min/1.73 m^2/24 h. The mechanism of delayed renal recovery may be the competitive inhibition of renal tubular secretion (3). Meanwhile, Piperacillin had also been shown to competitively inhibit the organic anion transport system, in a fashion similar to Probenecid (21-22). Therefore, this “pseudo-nephrotoxicity” that delays in creatinine reduction may not reflect a true reduction in renal function or actual renal damage.

This study had several limitations. In this study, we used CrCl as the measurement of renal function. Although the changes in CrCl reflect the changes in renal function, CrCl is not the most accurate measure of renal function. It was still used in this study, however, since it has been validated and is closely related to the outcome of these studies. The design of this study utilised retrospective data, thus the accurate documentation had to be assumed. Other than that, the diagnosis of AKI was made based on the recorded creatinine level and diagnosis. The confounding factors that might increase the risk of AKI such as underlying conditions, concomitant use of other nephrotoxic agents or antibiotics were not analyzed. Furthermore, the severity of the patients was not measured in this study and patients were only classified as AKI or non-AKI. Other than that, the shorter ICU stay in the Piperacillin/Tazobactam group comparing to the Meropenem group might contribute to the current finding as there were less time for renal recovery in Piperacillin/Tazobactam due to shorter follow-up period.

Conclusion

The occurrence of AKI in critical care patients receiving Piperacillin/Tazobactam was comparable to those receiving Meropenem, but the renal recovery in the Piperacillin/Tazobactam group was delayed. This study suggested that Piperacillin/Tazobactam does not increase the incidence of AKI in ICU patients but it could delay their renal improvement. These findings may not be generalizable to the whole critically ill population, and thus bigger studies at the national level are recommended.

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Conflict of Interest Statement
No external funding was received and the authors declared no conflict of interest.

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