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Inhaler Refill Adherence among Patients with COPD/Asthma at a General Hospital in Northern Peninsular Malaysia

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ABSTRACT

Background: Most adherence studies are based on self-report measures. There are limited studies on medication refill adherence (MRA) conducted in Malaysia, especially on bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD). The study aimed to investigate the MRA for inhalers with fixed dosing indicated for BA or COPD, prescribed from paediatric and medical clinics in Hospital Tuanku Fauziah and the factors that may affect MRA of COPD/BA inhalers.

Methods: A cross-sectional study was conducted on repeat prescriptions (fixed-dose inhalers dispensed as the units of analysis) collected from 1st January 2015 to 31st December 2015 from the specialist clinic pharmacy. Descriptive analysis was conducted based on satisfactory MRA which was set as the dispensed refill of inhalers covering 80-120% of the prescribed treatment time. Logistic regression analysis was used to explore each variable (diagnosis, gender, ethnicity and age) in relation to MRA: overall satisfactory MRA (≥80% MRA) with undersupply (<80% MRA) as the reference group.

Results: Out of the repeat prescriptions analysed (N=199), the majorities were COPD (N=118; 64.3%), male (N=122; 61.4%), Malay (N=175; 88.0%), and aged 60-69 years old (N=56; 28.3%). 44.5% of repeat prescriptions (N=57) for COPD showed satisfactory MRA, compared to only 25.4% (N=18) in BA. Repeat prescriptions for fluticasone/salmeterol accuhalers showed the highest satisfactory MRA at 18.1% (N=36). Diagnosis, gender and ethnicity did not significantly influence the overall MRA while age marginally influenced the overall MRA.

Conclusion: More than half of the repeat prescriptions for BA and COPD inhalers showed undersupply and oversupply: patients may not be compliant nor using the inhaler correctly.

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Introduction

Bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) are highly prevalent obstructive pulmonary diseases that affect millions of sufferers worldwide in terms of morbidity and mortality. According to the Global Initiative for Asthma (GINA) 2017 (1), BA is "a heterogeneous disease, usually characterized by chronic airway inflammation". It has two key elements: "history of respiratory symptoms" and "variable expiratory airflow limitation". BA is often a 'neglected' non-communicable disease due to its relatively

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low mortality rate. However, the disease starts much younger and is persistent throughout a lifetime, hence having a high prevalence. From the self-report of medically certified conditions of National Health and Morbidity Survey (NHMS) Malaysia in 2011 (2), the prevalence rate of BA in Malaysia was 6.4% for adults alone. Asthmatic patients suffer for 3.7 to 4.6 days in each asthma exacerbation, this leads to the loss of productivity and quality of life for 2.4 days in each attack (3).

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 (4), COPD is a "common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation". The prevalence of moderate to severe COPD in adults of more than 30 years old was 6.3% in the Asia Pacific region and 4.55% in Malaysia in 2011 (2). Currently, COPD was ranked as the twelfth leading cause of disability but it is expected to rank fifth in 2020. COPD would be the third leading cause of death worldwide by 2030 (4). According to the World Health Organization (WHO), COPD is one of the 'big four' of non-communicable diseases (NCDs) currently (5).

In a report by WHO (6), adherence to treatment can be broadly defined as "the extent to which a person's behaviour corresponds with the agreed recommendations from a healthcare provider". Treatment success in any chronic illnesses, in this context, BA and COPD, is largely dependent on medication adherence. A variety of effective treatment options already exist for BA and COPD, but long-term adherence to medication is required for treatment success. Poor adherence (commonly defined as <80% adherence) is the main contributor to treatment failure, hence imposing a large economic burden as a result of increased emergency visits and unused, expired medications (7). There is significant variability in the definitions and measurements of patient adherence, hence assessing adherence by healthcare professionals remains a challenge. Adherence rates to BA and COPD treatments varied from 22% to 78% due to the various methods of measurement (7). Most adherence studies were based on self-report measures using medication adherence rating scales while there were limited studies on medication refill adherence (MRA) which is more objective by eliminating response bias of patients (7, 8). MRA is the proportion of drugs dispensed in relative to prescribed treatment duration, based on pharmacy database records or manual/electronic recording of collected repeat prescriptions (9).

Repeat prescriptions are prescribed by doctors based on clinical judgment on how frequent to review a patient on chronic diseases. Refilling medication without renewed consultation by prescribers is convenient to both prescribers and patients but repeat prescribing may lead to non-adherence as patients do not visit the doctors for a period of time (10). Pharmacists can reduce any drug-related problems and adherence issues associated with repeat prescriptions (11) by having information on the level of non-adherence of patients in the pharmacy settings they are working in.

Approximately only 50% of patients receiving long-term pharmacotherapy for chronic diseases were adherent to treatment (6). Adherence to inhalers fare worse than oral medications (12) and even injected medications13 among asthmatic patients, across all ages including children (14). Adherence to inhalers is worse than transdermal therapies among COPD patients (7). Patients may have a higher preference for oral tablets or weekly injections and may not perceive inhaled therapy as valuable (7).

Medication-taking behaviour is a complex and multifactorial issue (7). Clinicians should identify the adherence problems and discuss with patients the most effective solution, instead of putting the full blame on the patients. BA and COPD essentially require optimum therapeutic effects and clinical outcomes since both are considered two chronic diseases that depend on adherence to their respective medications (7). To date, there are limited studies using MRA in Malaysia. The level of adherence and the different influencing factors are essential to clinicians to develop future effective interventions in improving adherence. This pilot study aims to investigate the MRA of inhalers indicated for BA or COPD among outpatients based on repeat prescriptions collected.

Methods

This pilot study was conducted in Hospital Tuanku Fauziah, the one and only hospital in the state of Perlis which serves a population of 227,025 (15) and also the northern part of the neighbouring Kedah state. This study was a cross-sectional study conducted in the specialist clinic pharmacy unit by collecting repeat prescriptions for inhalers indicated for BA and/or COPD outpatients who received their treatment in medical and paediatric clinics from 1st January 2015 to 31st December 2015. Repeat prescriptions are defined as prescriptions with more than 30 days of treatment duration (16). All repeat prescriptions were valid from the date of issue to the doctor's next appointment date and the inhalers would be dispensed by exchange basis. Since only the Malay term "bila habis" (when finished) was written at the repeat prescriptions without the next collection date, patients would visit the specialist clinic pharmacy and collect their inhalers according to how frequently they use the drugs. The inclusion criteria were repeat prescription inhaler(s) with fixed dosing as grouped in the Anatomical Therapeutic Chemical (ATC) classification system (16): inhaled corticosteroid (R03BA), adrenergic and steroid in combination for inhalation (R03AK) and anticholinergic for inhalation (R03BB). The exclusion criteria were inhalers written in referral repeat prescriptions for patients to get the next refills in other healthcare facilities. If there was

an overlap of more than one prescriptions of the same patient, the latest prescriptions were taken into account. Data were analysed using SPSS version 20.0 (IBM Corp., Armonk, NY). MRA was expressed in percentage (%) and calculated in the formula below (9):

$$\text{Medication refill adherence (MRA)} = \frac{\text{(Number of prescribed treatment days)}}{\text{(Number of days between the fills)}} \times 100\%$$

If an inhaler was dispensed more than once within the validity period of the prescription, the mean MRA will be taken into account. Descriptive analysis was performed based on satisfactory MRA which was defined as dispensed refills covering 100±20% of the prescribed treatment time. This range of 80-120% is frequently used in adherence research (17). The number of prescribed treatment was defined as the number of days a patient would be dispensed a drug by the pharmacy. The number of days between fill was defined as the number of days a patient came to the pharmacy to get his/her next drug supply when his/her medication finished (9). The MRA value of less than 80% indicated undersupply while the value of more than 120% indicated as an oversupply of inhalers. For each prescription, the MRA for each inhaler was calculated as shown in the formula to evaluate either the patient had his/her COPD and/or BA drugs supply over time (9).

A univariate (simple logistic regression) analysis was used to explore each variable (age, gender, ethnicity, diagnosis) independently in relation to MRA. In this analysis, satisfactory MRA and oversupply were grouped together as 'overall satisfactory MRA' being compared with 'undersupply'. In the literature, many studies do not indicate an upper level of MRA (18), as oversupply is difficult to interpret than satisfactory MRA and undersupply. Therefore, only overall satisfactory MRA (≥80% MRA) and undersupply (<80% MRA) were reported. To reduce misclassification bias, the data were keyed in by one of the co-authors and the first author checked for any erroneous coding of categorical variables and erroneous outlier values for continuous variables. This study was registered with the National Medical Research Registry (NMRR-15-2011-28524) and was approved by the Medical Research Ethics Committee (MREC) Malaysia.

Results

Out of the repeat prescription inhalers analysed (N=199), the majorities were COPD (N=128; 64.3%), male (N=133; 66.8%), Malay (N=168; 84.4%) and aged 60-69 years old (N=64; 32.2%), as shown in Table 1. The median age (interquartile range) was 64 (47, 81).

Table 1. Demographic characteristics of repeat prescription inhalers (N=199).

Variables	N (%)
Diagnosis	
BA	(35.7) 71
COPD	(64.3) 128
Gender	
Male	(66.8) 133
Female	(33.2) 66
Ethnicity	
Malay	(84.4) 168
Non-Malay	(15.6) 31
Age range (years)	
0-19	(4.5) 9
20-49	(11.6) 23
50-59	(18.1) 36
60-69	(32.2) 64
70-79	(26.1) 52
> 80	(7.5) 15

BA: bronchial asthma, COPD: chronic obstructive pulmonary diseas

Comparing the two diagnoses, which are COPD and BA, Table 2 shows that COPD (28.6%) had higher satisfactory MRA of inhalers compared to BA patients (9.0%). Five types of inhaler were included in this study (Table 3), namely metered dose inhaler (MDI) ipratropium/salbutamol, fluticasone/salmeterol accuhalers, MDI inhaled corticosteroids (ICS), tiotropium capsule for inhalation and budesonide/formoterol turbohaler. It shows that fluticasone/salmeterol accuhalers were the most commonly prescribed inhalers to patients (43.2%) and also has the highest percentage of satisfactory MRA (18.1%) and undersupply category (22.6%) among these five types of inhaler.

Table 2. MRA according to diagnosis, N (%): bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD).

Diagnosis	MRA for repeat prescriptions N (%)		
	Undersupply	Satisfactory MRA	Oversupply
COPD	59 (46.1)	57 (44.5)	12 (9.4)
BA	38 (53.5)	18 (25.4)	15 (21.1)

Table 3. MRA according to types of inhaler (N=199), presented as N (%).

Types of inhalers	MRA for repeat prescriptions N (%)			Total N (%)
	Undersupply	Satisfactory MRA	Oversupply	
MDI ipratropium/ salbutamol	26 (13.1)	18 (9.0)	6 (3.0)	50 (25.1)
Fluticasone/salmeterol accuhaler	45 (22.6)	36 (18.1)	5 (2.5)	86 (43.2)
MDI ICS	4 (2.0)	6 (3.0)	16 (8.0)	26 (13.1)
Tiotropium capsule for inhalation	3 (1.5)	8 (4.0)	0 (0.0)	11 (5.5)
Budesonide/formoterol turbohaler	19 (9.5)	7 (3.5)	0 (0.0)	26 (13.1)
Total	97 (48.7)	75 (37.7)	27 (13.6)	199 (100)

Simple logistic regression was conducted independently on diagnosis, gender, ethnicity and age (Table 4). Only age showed marginal significance in affecting MRA: on further analysis on age range, only 20-49 years old patients show a significantly lower adherence compared to 0-19 years old patients. Based on the Hosmer-Lemeshow goodness of fit test, $\chi 2$ (df=7, N=199)=18.6, p=0.009. Significance ($p<0.05$) indicated that the multiple logistic regression model was not able to distinguish between undersupply and 'overall satisfactory MRA', hence multiple logistic regression was unable to be performed.

Table 4. Simple logistic regression analysis relating different factors to MRA on 'undersupply' and 'overall satisfactory adherence' (N=199).

Variable	Crude OR	(CI 95%)	P-value
Diagnosis			
BA	1.00	(.ref)	-
COPD	1.39	(2.49 ,0.78)	0.268
Gender			
Female	1.00	(.ref)	-
Male	1.46	(2.64 ,0.81)	0.211
Ethnicity			
Malay	1.00	(.ref)	-
Non-Malay	1.66	(3.84 ,0.72)	0.236
Age(years)	1.02	(1.04 ,1.00)	**0.034
Age range (years)			
0-19	1.00	(.ref)	-
20-49	0.17	(0.92 ,0.03)	**0.040
50-59	0.51	(2.23 ,0.12)	0.370
60-69	1.33	(5.46 ,0.33)	0.689
70-79	1.39	(5.81 ,0.33)	0.652
> 80	0.70	(3.68 ,0.13)	0.674

**p<0.05

BA: bronchial asthma, COPD: chronic obstructive pulmonary disease

Discussion

In our setting, all prescriptions were written manually by prescribers as our hospital was not equipped with hospital information system (HIS). A study assessing MRA comparing pharmacy record database and manually collected prescriptions produced similar results during a one-year period (19) which our study shared the same period.

In this pilot study, the unit of analysis was not based on individual patients but was based on repeat prescription inhalers. It is because the same individual can have different MRA patterns for different drugs. A patient might use more than one COPD and/or BA inhalers and may have different MRA for different inhalers, hence it is more informative to study individual inhalers (20). Almost half of the repeat prescription inhalers (48.7%) for COPD and BA were undersupplied. There are several possible reasons for undersupply. The trans theoretical model of health behaviour change (21, 22) proves that patients' perception on the severity of a disease contributes as a factor in the decision making of whether to adhere to their medication(s) or otherwise. The decision is made by balancing the actual and feared side effects, the threats posed by the disease against the perceived benefits of treatment: this concept is known as "decisional balancing". Undersupply of medications happened when patients did not come to refill their drugs immediately after the drugs finished. Patients might not experience fast relief using a preventer inhaler, hence relying only on reliever inhaler. Symptoms of BA/COPD are usually intermittent or periodical, patients might only use it on 'when needed' basis which the medications in the study were meant to be used regularly. If patients did have this misconception, patients might have poorer adherence as they did not experience relief using these controller inhalers. There might be also a fear among patients of perceived side effects for the use of fixed-dose inhalers which the majority contains steroid (3) that might lead to undersupply. Other patient factors that may cause undersupply could be no transportation, money, time to come to the hospital to collect their drugs on time.

In public hospitals, Malaysian citizens pay a nominal fee of MYR 5 (approx. to USD 1.21 as of 22nd September 2018) for each specialist consultation visit which the cost includes the supply and refill of medication from the pharmacy (23). The cost of medication was not of concern to the patients as this cost was included in the consultation fee, regardless of how many medications were dispensed. The difficulty of refilling medications was expected to be minimal as the Pharmaceutical Services Division, Ministry of Health Malaysia offers value-added services (VAS) of dispensing medicines through various Pharmacy Appointment System (PhAS) initiatives such as Park and Take Pharmacy, Short Messaging Service (SMS) and Take and Call and Collect services implemented by our setting in which patients could collect their medications without the need of waiting and parking problems by making prior appointments on an agreed time of collection. This is in contrary with the traditional counter service (TCS) in which patients have to be present to the pharmacy counter, are given a queue ticket and have to wait for their turn to get their medications dispensed via a queuing system

13.5% of repeat prescription inhalers for both COPD and BA were oversupplied. The oversupply of inhalers might be due to wrong inhaler technique or unnecessary priming. There might be some patients who misled to believe that the inhalers were to be used as "when needed" which led to overuse. There was a possibility of stockpiling, especially if patients have numerous 'spare, empty' inhalers obtained from other healthcare facilities but the inhaler exchange basis policy implemented would help to keep this to a minimum.

In identifying factors that affect MRA, gender and diagnosis did not significantly affect the overall MRA of COPD/BA inhalers prescribed in our setting and were supported by a similar MRA study in Jämtland County, Sweden (9). In contrary, a review (11) shows that COPD patients have a lower adherence than asthmatic patients whereby an average of 60% of COPD patients do not adhere to the prescribed inhaler therapy.

In our study, an increase in one-year of age has a 1.02 higher odd of adherence. However, several studies (24-26) indicate that increasing age generally causes a decrease in adherence. When comparing age range, only one age range shows significance against the reference group of 0-19 years old: 20-49 years old patients (young adults) has 0.17 times the odds of MRA than 0-19 years old (children and adolescents). Adherence to inhaled asthma therapy tends to be worse in young adults than in children (7,27), which was similar to our study. This may be due to lack of parental care, support and reminder. However, a study (28) showed similar rates of adherence on ICS among paediatric and younger adults, suggesting parents may not be a facilitator of adherence. In contrast, a study (29) shows that young adults to be more adherent to inhaler therapy than adolescents and children, while there are other studies that show no difference (30). The causes of suboptimal adherence due to the lack of knowledge and misconception on treatment and/or diseases are similar for the groups of children and adolescents, and young adults. However, the misconception may be more prevalent in younger patients (children and adolescents) who are symptom-free (28). Children and adolescents succumb to intentional non-adherence rather than non-intentional non-adherence: denial of disease illness, embarrassment among peers and rebellion are the predominant factors of non-adherence among children and adolescents despite parental support (29, 31).

For ethnicity, our result shows no significant difference. This was concordant with a systematic review that

concludes that ethnicity may not be a true predictive factor of poor adherence, due to the inconsistent results in the various research literature (32). Two studies using the 8-item Morisky Medication Adherence Scale (MMAS-8) in public health clinics in the state of Selangor, Malaysia (33,34) produces exactly opposite results: in a study on 3 clinics (Seri Kembangan, Dengkil, Salak) (33): the order of adherence to T2DM medications was Indian, Malay, Chinese (adj. OR= 1.05, 1.00 and 0.98, respectively while in another study of 7 clinics in Hulu Langat district (34): the order of adherence to antihypertensive was the exact opposite, which was Chinese, Malay, Indian (adj. OR=2.68, 1.68 and 1.00, respectively).

Nevertheless, the pilot study has some limitations. Individual patients were not being observed clinically as this study was only based on information in the prescriptions. Information on the severity of disease, clinical conditions, concomitant illnesses and co-morbidities were not taken into account. BA and COPD may share some symptomatic characteristics but in many ways two separate diseases. Ideally, these two conditions should be analysed separately but conventionally in MRA studies involving inhalers (7, 9, 18, 20), both were analyzed together. No reason was found but the most probable reason was due to the possibility of asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS) in some patients. BA and COPD are increasingly recognised as heterogeneous diseases with a large inter-individual variability in terms of clinical manifestations, disease progression and treatment responsiveness, making a clear-cut diagnosis challenging at times (1,4).

In conclusion, 37.7% (N=75) repeat prescriptions had satisfactory (80-120%) MRA towards BA and/or COPD inhalers, which means more than half of the repeat prescriptions for BA and COPD inhalers showed undersupply and oversupply: patients might not be compliant nor using the inhaler correctly. All factors: diagnosis, gender and ethnicity did not significantly affect the overall MRA except forage in which marginally affects the overall MRA. However, this pilot study could serve as a preliminary study to assess other factors such as patients' clinical severity and smoking history. Qualitative studies can be conducted to explore behaviours that may affect MRA. Healthcare professionals should work collaboratively to improve patients' compliance and inhaler technique.

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