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Medication Nonadherence: Implications for patient health outcomes in pharmacy practice

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ABSTRACT

The primary objective of this review is (1) to better understand the prevalence and impact of medication nonadherence, (2) to identify risk factors for medication nonadherence, (3) to understand the association between nonadherence and its implications on patient health outcomes in pharmacy practice, and (4) to study interventions designed to improve patient adherence to prescribed medications for medical conditions, considering its impact on both medication adherence and patient health outcomes. Narrative review design by critical analysis of the literature of published paper-based journal articles were manually sorted. Additional references were obtained from citations within the retrieved articles. This narrative review surveyed the findings of the identified articles with data extracted to presents various strategies and resources on medication nonadherence related to patients and healthcare providers. Out of 121 published articles, only 64 articles have been considered according to surveyed identified articles to determine both subjective and objective medication adherence measures. The research in this field needs advances, including improved design of feasible long-term interventions, objective adherence measures, and sufficient study power to detect improvements in patient health outcomes. Current methods of improving medication adherence for chronic health problems are mostly complex and ineffective so full benefits of treatment cannot be realized. To date, monitoring of patient medication adherence and use of interventions to improve adherence are rare in routine clinical practice.

Keyword: Medication nonadherence, Drug utilisation, Medicines management, Patient behaviour, Medication-related care

INTRODUCTION

The World Health Organisation (WHO) defines *adherence* as 'an extent to which a person's behaviour (in taking medication, following a diet, and / or executing lifestyle changes) corresponds with agreed recommendations from a health care provider' (Sabaté and Sabaté, 2003). While the term *adherence* is often used interchangeably with *compliance* which is the extent to which a patient's behaviour matches the prescriber's recommendations (Horne *et al*., 2005), the latter is less preferred as it reflects poorly on patients' autonomy in treatment decisions. WHO reported that patients in developed countries with chronic diseases who are prescribed self-administered medications adhere to their medication regimens only 50% of the time. Medication nonadherence therefore is recognized as a significant public health issue, has it can lead to considerable morbidity, mortality, and increased health care costs.

Adherence to medication has long been recognised as a crucial factor in achieving good therapeutic outcomes while medication nonadherence has been linked to treatment failure (Farmer, 1999; Hassan, *et al.,* 2019; Lam and Fresco, 2015). Sokol *et al.* in a study among patients with diabetes and hypercholesterolemia, showed that higher medication adherence was significantly associated with lower disease-related medical costs, despite medication cost increase. The rate of hospitalisation was significantly lower among patients who maintained their adherence compared to those with lower adherence (Sokol, *et al*., 2005).

Medication nonadherence is multifactorial, extending beyond the patients' behaviour alone. In order to improve medication adherence rate among patients, it is important to understand the underlying factors that may cause this behaviour so effective strategies can be considered to overcome these barriers.

ASSESSMENT OF ADHERENCE

Clinicians around the world adopt various approaches to assess medication adherence among patients. Many of these approaches are quantitative, while some are qualitative in nature. However, with the dearth of a "gold standard" among these assessments, combination approaches are often recommended (Lam and Fresco, 2015).

Assessment of medication adherence can be classified into two major categories (Brown and Bussell, 2011), subjective measurement of adherence, and Objective measurement of adherence.

Subjective measurement of adherence

Most researchers consider subjective measurements as the least reliable approach. It involves assessment by inquiring the patient or the caregiver about the pattern of medication usage. This method however is still widely used in clinical practice due to ease of administration, low cost and the ability to generate fast response (Lam and Fresco, 2015).

Patient-Kept Diaries

This method relies on self-reporting where patients record information about their medication taking patterns such as how often they comply to dosing, the number of tablets taken, time of medication administration and relevant information on meal intake. This method is however subject to patient memory and their ability to successfully return the diary to the clinician for review and discussion. Furthermore, patients have the tendency to complete the diary retrospectively which may not reflect their actual medication-taking behaviour and lead to overestimation of adherence (Lam and Fresco, 2015; Oldenmenger *et al*., 2007).

Patient interview

This method involves interviewing patients about their medication-taking behaviour, general knowledge on disease, therapy-related knowledge Including details of medications taken by the patients, and administration timing. This method is subject to inter-assessor variability and evaluation technique.

Questionnaires

Questionnaires have been developed to overcome the limitations of self-reporting methods in the assessment of medication adherence. There are several validated instruments that are commonly used in practice

8-item Morisky Medication Adherence Scale (MMAS-8)

MMAS-8 is one of the most commonly used tools in clinical practice, developed by (Morisky, *et al*., 2008). It contains 8 questions, the total scores of which reflect the level of adherence. A score of 8 indicates high level of adherence and a score of less than 6 points towards low adherence to medications. It is particularly useful as a screening and monitoring tool in clinical practice to recognise patients at high risk for nonadherence issues.

Brief Medical Questionnaire (BMQ)

The BMQ, developed in 1999 by Svarstad *et al*, is unique compared to other adherence assessment tools in that it is able to elicit a patient's barriers to adherence. In particular, this questionnaire screens for 3 crucial issues which are potential nonadherence, belief barriers and recall barriers with respect to patients' medication taking behaviour (Svarstad, *et al*., 1999).

Self-Efficacy for Appropriate Medication Use Scale (SEAMS)

The SEAMS was developed to overcome the limitations of existing adherence tools among patients with low literacy level (Risser, *et al*., 2007). This instrument consists of 21 sets of questions with a three-point response about medication taking behaviour. The higher the score, higher the level of adherence to medications. However, administration of this questionnaire is time consuming given the number of items to be completed

Objective measurement of adherence

Objective measurements of adherence encompass pill counting, secondary database analysis, electronic monitoring and biochemical measures. Also known as direct measures, these methods are considered better compared to subjective measurements in assessing medication adherence as they reflect physical confirmation that patients have taken the medicine as prescribed.

Table I. Summary of medication adherence measurement.

	MEASUREMENT OF ADHERENCE	APPLICATION
Subjective Measurement	Patient-Kept Diaries	• Self-reported • Subject to reporting bias and overestimation of adherence • Inexpensive and easy to implement
	Patient Interview	• Subject to inter-assessor variability and evaluation • Subject to recall bias • Does not incur any cost
	8-item Morisky Medication Adherence Scale (MMAS-8)	• A validated questionnaire • Most widely used instrument in clinical practice • Requires license for use from the original author • Measures patient medication taking behaviour
	Brief Medical Questionnaire (BMQ)	• A validated questionnaire • Able to identify barriers for medication adherence • A reliable tool to be used in patients with low literacy level
	Self-Efficacy for Appropriate Medication Use Scale (SEAMS)	• Time consuming to implement due to number of items on the questionnaire
Objective Measurements	Pill-Counting	• Oldest and commonly used method as it is simple and easy to implement • Does not incur any cost • Used as a reference standard to validate other measures of adherence • Not a reliable measure for medications taken on ***when necessary (PRN)*** basis • Does not provide information on patients' medication-taking pattern • Eliminates "Hawthorne effect"
	Secondary Database Analysis	• Only applicable for those on long-term medications that require refilling • May overestimate actual adherence to medication • Unreliable if refill records are incomplete
	Electronic Monitoring	• Uses Electronic Medication Packaging (EMP) device to gather data • Relies on the assumption that patients actually consume the medications • Expensive • Requires hardware and software to implement
	Biochemical Measures	• Yields accurate results • Does not describe patients' medication-taking behaviour • May be subject to "white coat adherence" • Expensive

Pill counting 100%

The eponymous method involves asking patients to bring their medications at a scheduled appointment and counting the balance pills for a given course of the medication. The level of adherence is calculated based on the following formula:

(Number of Pills Dispensed – Number of Pills Leftover) in a given time period / Number of Pills Prescribed for the same time period = %

Patient is deemed adherent to the medication prescribed if the percentage is equivalent to or more than 80% with the assumption that the medication was truly taken by the patient (Brown and Bussell, 2011).

Whilst this zero-cost strategy can be easily applied to almost all pharmaceutical dosage forms, it may however underestimate adherence in patients who collect their medication earlier than they are supposed to. Furthermore, this method is unable to provide information on the actual medication-taking pattern of the patient (Osterberg and Blaschke, 2005).

Secondary Database Analysis

Analysis of secondary databases such as pharmacy refill records allows quantification of medication adherence by using prescription refilling patterns. Whilst this method of assessment eliminates the "Hawthorne effect", which refers to the inclination of patients to change/ or improve their behaviour due to being assessed, it is only applicable for patients who are on long term medications as the data is derived based on the frequency of refilling. For those with acute illness and prescriptions without refills, this method is not suitable (Fairman and Motheral, 2000). Also, this method relies on the assumption that patients take the medication exactly as prescribed, which inadvertently leads to overestimation of adherence.

Electronic Monitoring

Adherence-monitoring devices such as the Electronic Medication Packaging (EMP) can be incorporated into the packaging of a prescription medication to gather data on adherence (Lam and Fresco, 2015). The conceptual structure of this technology is that whenever the patient opens the container to take medicine, a microprocessor embedded in the container cap will record the time and date of each opening (Diaz *et al*., 2001), which provides information about their adherence with the assumption that the medication is consumed by the patient.

However, this technology is not entirely fool-proof. Estimation of adherence from EMP devices may be spurious if patients discard the medication from the container without ingesting them or transfer the medication to another container. Furthermore, EMP devices are cost-intensive which includes hardware and software to retrieve data as well as operational costs.

Biochemical measures

Biochemical measurements involve determining the concentration of a drug or its metabolites in biological fluids, particularly blood and urine. In some instances, biological markers are given together with the drugs to ascertain the presence of a drug in the blood (Farmer, 1999; Lam and Fresco, 2015). These provide evidence that patients have indeed ingested their medications. Although this method flaunts accurate results, it does not always describe the patient's medication-taking behaviour. There are chances that patients who are aware that they must undergo testing may take their medication prior to clinic visit in order to appear as adherent to their medication. This is described as the "white-coat adherence". As most drugs have plasma half-life of 12 hours or less, it may only take 2 to 3 days of regular dosing prior to the blood tests to show a drug concentration within the therapeutic range, while any noncompliance that may have occurred previously goes undetected. Apart from that, these methods require qualified staff and techniques to operate which contribute to the operational cost. Illustrate the summary of medication adherence measurement tools and there applications (Table I).

GROUND OBSTACLES

Nonadherence is multifactorial and cannot be blamed solely on the patient. There are many other obstacles to adherence which must first be acknowledged and recognized. A WHO report by Sabaté E. (2003) linked barriers of adherence to five inter-related factors which includes: 1) socioeconomic status; 2) therapy; 3) patient factors; 4) condition or disease and 5) healthcare systems (Sabaté and Sabaté, 2003). Simpson *et al*. (2006) found that around a quarter of individuals have poor adherence to the treatment regimen prescribed which is a prominent obstacle to therapeutic outcomes and poses a great challenge to the healthcare providers (Simpson *et al*., 2006).

Socio economic status

Race and cultural beliefs

The race is not a predictor of medication adherence, irrespective of whether the affiliates of a specific race are living in their country of origin or away as foreigners. Cross-sectional national survey among Medicare beneficiaries ≥65 years of age, (n=14,829) were found Blacks and Hispanics were more likely than whites to report cost-related nonadherence (35.1%, 36.5%, and 26.7%, respectively, p< .001). There were no racial/ethnic differences in nonadherence caused by experiences or self-assessed needs (Gellad, Grenard, and McGlynn, 2009).

Age

Age has an inconsistent effect on adherence. WHO recommends to assess age independently for each disease, e.g., by patient characteristics and age-related developmental grouping (i.e. children, teenagers, adults and elderly patients) (Sabaté and Sabaté, 2003). Studies conducted in Malaysia by Paraidathathu *et al.*, (2013) and Chew *et al*., (2015) concluded that adherence to the medication improved with increasing age in diabetes (Ahmad, Ramli, Islahudin, and Paraidathathu, 2013).

The latter study reported a medication adherence rate of 64.2% in patients> 60 years old of age, compared to 49.4% in patients <50 years old (p=0.001) (Gellad *et al*., 2009). In contrast, the Sunderland study showed patients in younger age groups (30-40 years old) had high adherence (82%) compared to older patients (75%). These differences might be due to older patients having strong perceptions about disease treatment and medication adverse effects (Khan, *et al*., 2014).

Gender

A study in Malaysia (Ahmad *et al*., 2013) and Hong Kong (Wong, *et al*., 2010) showed that Chinese females patients were more adherent to antihypertensive and anti-diabetic medications when compared to the Chinese male patients. Finding in the US reported however that were significantly more adherent than women in taking medication for chronic conditions (Manteuffel *et al*., 2014). It was postulated that women, as primary caregivers, spend less time and energy taking care of themselves then they do taking care of others (Geboers *et al*., 2015).

Social support

A study on heart and lung transplant patients (n=304) found adherence improved by 2.6 fold in patients who received family support compared to those who received no support at all (p<0.05). Gellad *et al.,* (2009) in a systematic review found that only four out of seventeen reviewed articles used a well-established tool to measure association between social support and patient adherence. He concluded that social support alone is not a strong, independent factor affecting adherence, as it also involves other factors such as patients, healthcare providers, systems and the disease itself (Gellad, *et al*., 2007).

Therapy

Complexity of treatment regimen

Treatment complexity highly contributes to patients nonadherence. Ingersoll and Cohen (2008) studied "regimen factors" on medication adherence for chronic diseases and found that poor adherence was associated with treatment complexity. However, another systematic review in HIV patients found the reduced tendency to report pill burden as a barrier to adherence (Shubber *et al*., 2016).

Adverse effects of the treatment

This refers to a form of intentional nonadherence in which patients stop taking their medication due to the adverse effects experienced, without consulting their healthcare providers. In Italy, a study on HIV patients found that no adherent patients reported 3.6-30% of adverse effects impacting their medication adherence (Ammassari *et al*., 2001).

Patient factors

Forgetfulness

Forgetfulness, categorised as unintentional nonadherence, is the main barrier to medication adherence. A national survey conducted in the US found that 20% of hypertensive patients have poor adherence to their medication and 46% of them reported forgetfulness as their main reason for nonadherence (Egan, Lackland, and Cutler, 2003). Similarly, a study conducted in Malaysia on hypertensive patients also found that the primary reason for the patient nonadherence was forgetfulness (Ramli, *et al*., 2012).

Lack of understanding and patient perception of the disease

Patient behaviours and beliefs about disease and medicines can influence adherence in meaningful and complicated ways (Martin, *et al*., 2005). A qualitative study done in Malaysia among diabetic Malay patients to assess their perspectives in managing the diseases revealed that the patients thought their disease can be cured and that should not restrict their diet when they are on insulin treatment (Ali and Jusoff, 2009). Therefore, robust

strategies need to be implemented to ensure provision of adequate patient education on the disease and its associated treatment.

Low health literacy

Health literacy can be defined as 'the degree to which people are able to access, understand, appraise, and communicate information to engage with the demands of different health contexts in order to promote and maintain health across the life-course' (Geboers *et al*., 2015). Patients with low literacy levels may experience problems in understanding directions given and may interpret medication instructions differently leading to poor adherence and poor therapeutic outcomes (Jimmy and Jose, 2011). William *et al.,* (1995) in a study comprising of more than 2500 patients found that almost 33% of the patients had minimal or no health literacy regarding their prescriptions, appointment schedules and on how to read an informed consent document (Williams *et al*., 1995). In contrast, a meta-analysis was done by Geboers *et al.* (2015) among elderly patients stated that this study provides the reason to feel ambiguous about the presence of robust evidence between health literacy and adherence among elderly patients (Geboers *et al*., 2015).

Condition or disease

Severity of the condition

Theoretically, patients who suffer from severe diseases or complications tend to have lower adherence to their medications due to the high pill burden. A study by Basco (2009) among bipolar disease patients found that 64% were no adherent to their medication prior to the admission (Basco and Smith, 2009), whereas Brown (2011) reported decrease in medication adherence after catastrophic events like stroke (Brown and Bussell, 2011). A meta-analysis done by DiMatteo *et al.* (2007) found that most patients with severe conditions (HIV, ESRD, cancer and heart disease) are less adherent to their medication, regardless of objective or subjective health assessment (DiMatteo, Haskard, and Williams, 2007). The reason could be the physical, psychological and other factors that significantly reduce patients' determination towards adherence.

Comorbidities

Multiple comorbidities may contribute to nonadherence due to the pill burden in order to manage their diseases. A study by Rolnick *et al (2013)* showed lower adherence in patients with multiple conditions, drug regimen and frequency of dosing. Contrasting findings were reported by a Hong Kong study done in hypertensive patients (Rolnick, *et al*., 2013). Similarly, a study in Malaysia examining adherence in diabetics found that patients with comorbidities reported higher medication adherence compared to patients with no comorbidities (Gellad *et al*., 2009).

Health systems

Communication

Inadequate communication between providers and patients with chronic illnesses can further complicate patient comprehension of illness, its potential complications, and the importance of medication adherence (Brown and Bussell, 2011). Factors associated with poor communication from a prescriber perspective may include complex medication regimen prescriptions as well as inadequate explanation on the benefits and risks of the prescribed regimens (Osterberg and Blaschke, 2005), It may also include failure to obtain an accurate patient medical history and reduced time span to discuss any issues related to patient wellbeing. The Jimmy and Jose (2011) study on medication adherence found that 40-60% of patients incorrectly interpret what their doctors expect of them 10-80 minutes after consultation (Jimmy and Jose, 2011).

Health services

Disintegrated healthcare frameworks cause nonadherence. In an overburdened health care system where the patient population is large, lack of staff could lead to multitasking of the prescribers and thus, less time is available for them to engage with patients (Brown and Bussell, 2011).

Medications cost and health insurance plan reimbursement

Unreasonable drug costs may contribute to poor adherence. Egan *et al* (2003) reported that 24% of patients who were no adherent to anti-hypertensive agents said that the medications were too expensive (Egan *et al*., 2003). Another study highlighting the high cost of medication was conducted using pharmacy claim records of 6,236 patients taking statin medication, and reported significant reduction in adherence as the cost of medication rose ($p < 0.01$) (Pedan, Varasteh, and Schneeweiss, 2007). Inadequate or non-existent reimbursement by health insurance plans contributes to poor adherence due to potential partial coverage of medical costs, including medicines for eligible patients who may still need to pay a subsidy for health services and care. Additionally, patients who utilize public insurance were found to be four times more no adherent to

their medication and thus are at high risk of poor health outcomes (Dew *et al*., 2008).

ADHERENCE IMPROVEMENT STRATEGIES

Medication adherence is a key obstacle in achieving optimum treatment outcomes for patients as target outcomes cannot be obtained if adherence is low. Strategies need to be planned and implemented to enhance medication adherence by considering seven main factors, which are: 1) patient factors, 2) physician or healthcare providers, 3) medication regimens, 4) healthcare systems, 5) individualized care plans, 6) Multisystemic Therapy (MST), and 7) technology-mediated interventions (TMI). Diagram 1: shows the seven factors for adherence improvement strategies.

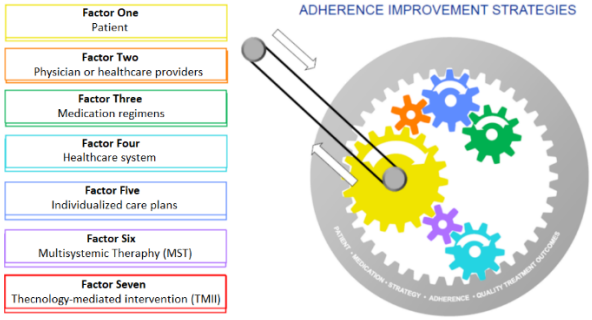

Diagram 1: Seven factors for adherence improvement strategies

Patient factors

The key stakeholder in determining medication adherence is the patient. Hence, they need to be provided with appropriate patient education in adherence improvement plans. A study by Balamurugan *et al.;* evaluated the effectiveness of a diabetes self-management education (DSME) program utilizing an intervention that provided patient education on nutrition and diabetes self-management. The study found that intervention patients registered a 0.45% reduction in HbA1c, and a reduced hospitalisation rate when compared to control (Balamurugan, *et al*., 2006). A systematic review showed that patient education by pharmacists improved adherence particularly when patients were educated about disease conditions, medications and its benefits, possible adverse drug reactions and lifestyle modifications. In this review, five out of eight studies showed significant improvement in patient adherence towards antidiabetic medications (Omran, *et al*., 2012). Patient education on medication side effects should be prioritized to alleviate patient concern as this may contribute to low adherence rates (Garner, 2010). Poor health literacy also impacts patient adherence. Studies show that encouraging universal precaution strategies and providing verbal counselling together with pictorial aids on medication labels can help to improve medication adherence (Katz, *et al*., 2006).

Physician or healthcare providers

Healthcare providers should practice patient-centred care by promoting active involvement of the patient in the decision-making process throughout their health journey. Good communication skills using universal precaution strategies to reinforce patient education are essential to confirm patient understanding. Cultural competency will gain patient trust as healthcare providers will be able to respect different beliefs and attitudes their patients have towards health and medication adherence.

Medication regimens

Polypharmacy can result in lower adherence to medications as patients struggle with complicated medication regimens (Benner *et al*., 2009). Deprescribing should be practiced to provide simple, effective and safe therapy to patients as simplification of medication regimens has been linked to an increase in medication adherence (Schroeder, *et al*., 2004). This is particularly helpful for patients suffering from multiple comorbidities and long-term chronic conditions (Richter, *et al*., 2003). Effective ways of simplifying medication regimens include reducing dose frequency in favour of longer dosing intervals, introducing polypills or combination-therapies, and preventing duplication of therapy when treating a medical condition (Claxton, *et al*., 2001; Malo *et al*., 1995; Monedero and Caminero, 2011; Thiele *et al*., 2012)

Health care systems

Interprofessional collaboration will encourage time-based efficiency and multidisciplinary input within healthcare systems in providing patient education and promoting medication adherence for patients (Hassan *et al*., 2019).

Patient-centred care

Patient-centred care takes into account patient factors such as lifestyle and medication

preferences, health attitudes and beliefs with an aim to tailor treatment recommendations and patient education to optimize patient adherence. Research has shown that patient-centred care plans result in higher patient compliance towards medications including repeat prescriptions (Gray *et al*., 2012). Medication adherence clinics create specialty-focused patient-centred care plans for patients with long-term chronic care conditions. An example of this would be the Medication Therapy Adherence Clinics (MTAC) in Malaysian government hospitals that offer patient education, patient reminders, educational aids and booklets to patients suffering from diabetes, respiratory conditions, or those who may have been prescribed with antiretroviral (ARV) therapy or warfarin.

Multisystemic Therapy (MST)

Multisystemic therapy refers to intensive family- or community-based programs designed to result in positive changes across society, developed originally with the goal to manage social behavioural problems among at-risk youth. This interventional model has also been explored further to support adolescents suffering from chronic diseases such as HIV, diabetes or asthma. A study to determine the effect of MST in treatment of adolescent diabetes in comparison to telephone support services found a significantly greater reduction of HbA1c in the MST-intervention group when compared to the telephone-support group (1.01% vs 0.74%). The MST intervention involved family education focused on diabetes, medication and lifestyle management as well as developing parent communication skills to provide supportive care to their diabetic children. Schools were involved with personnel trained to provide glucose testing for diabetic students and weekly reports to parents while community-based interventions involved setting up support groups. Parents reported an improvement in their children's diabetes management adherence according to the Diabetes Management Scale at 7 months [5.72 (95% CI: 1.61, 9.83)] and 12 months [5.10 (95% CI: 1.21, 8.99)] (Ellis *et al*., 2012). This model can also be used in adult patients who require intensive health support. An example is the methadone maintenance therapy which aims to treat and rehabilitate drug addiction with a combination of pharmacology, psychology and sociology therapy with the support of family, peers, community support groups and health care providers (Rusdi, *et al*., 2008).

Technology-mediated interventions (TMI)

Technology-mediated intervention (TMI) incorporates elements of digital health to provide patient education and aid patients in self-management of their medical conditions. Digital technology such as telehealth platforms, smart devices, health applications and software, chat messaging or text reminder services have been used increasingly especially in the pandemic era. Mistry *et al* found that 19 out of 38 studies showed significant adherence outcomes when TMIs were used to improve patient adherence (Mistry *et al*., 2015).

Telephone-based services have been provided successfully to patients with studies showing this method to be convenient, cheap, feasible and applicable for a variety of monitoring and lifestyle modification support services. A study using monthly structured telephone interviews to monitor depression symptoms in patients, and provide medication self-management and adherence advice found increased medication adherence in intervention groups using the modified Morisky score (2.7 vs 2.53, p=0.0042) (Gensichen *et al*., 2009). Text reminders have also been helpful in addressing nonadherence. In Maduka *et al.*, a strategy integrating adherence counselling together with text reminders for HIV patients taking ARV therapy showed a significant difference in medication adherence outcomes between two groups (p=0.022) where intervention group achieved 76.9% of targeted adherence while only 55.8% of the control group achieved this target. Clinically significant outcomes saw a rise in CD4 cell count for the intervention group when compared to control group (p=0.007), proving that adherence counselling with text reminders can help HIV patients to successfully adhere to ARV therapy leading to better clinical outcomes (Maduka and Tobin-West, 2013). Engaging younger patients to develop better medication adherence behaviours can also be explored through the use of video games which were found to be effective in Kato *et al* where adolescent and younger adult cancer patients were given condition-specific and medication-specific knowledge as well as encouraged to adopt self-care behaviours through gamification strategies. The intervention group showed a higher concentration of anticancer metabolites (p=0.002) and positive outcomes in cancer-related knowledge and self-efficacy when compared to control (Kato, *et al*., 2008).

PHARMACOECONOMICS

The purpose of studying pharmacoeconomics is to identify, estimate and compare the cost of medications as well as to consider the risks and benefits of any therapy, service or programme (MTM) (Mauskopf, 2001). Nonadherence not only affects treatment benefits, but also affects financial burden on patients, payers and society (Richter *et al*., 2003). A systematic review by Chiatti *et al.* found that out of 21 selected studies, 23.8% of the studies (5/21) measured economic burden due to nonadherence. Most adherence-related pharmacoeconomics studies (4/5) demonstrated that nonadherence was related to cost loss. At the same time, the studies concluded that adherence interventions were cost-effective (Chiatti *et al*., 2012). An observational study was done by Truong *et al*. to evaluate potential cost saving based on cost avoidance by handling four years of Medication Therapy Management (MTM) for pharmacoeconomical clarification of the intervention programme. Medication-related problems (MRPs) were identified by pharmacists, and categorised into indication, effectiveness, safety or adherence. The result showed that the main MRPs detected were subtherapeutic dose (38%), nonadherence (19%) and untreated indication (16%). Correspondingly, detected nonadherence savings cost about $ 25,434–118,535 (Truong *et al*., 2015). Another study showed that an intensive asthma treatment programme which includes the same attending physician, continuous patient and family members' education and adequate dose physician referral can reduce the cost of the treatment in cost differences evaluated before and after the intervention. The study found that the cost per patient per year for inpatient care before the treatment was $22,999 ± $20.64, but surprisingly reduced to $1107± 1618 after the intervention (p<0.0017) (Levenson, Grammer, Yarnold, and Patterson, 1997). A cohort study was done to evaluate long-term cost and outcome of treating hypertension, comparing the effect of physician-pharmacist intervention and physician management alone. This finding supported the physician-pharmacist programme demonstrated cost-effectiveness especially for high-risk patients (Kulchaitanaroaj *et al*., 2017). Clinical pharmacists also play a major role in decreasing the cost of care, hospitalization and medications (Dunn *et al*., 2015). Clinical pharmacists also help to improve medication adherence and reduce medication cost by simplifying patient medication regimens. Prescribers should collaborate with pharmacists always to therapy regimen effectiveness, cost and propensity for adverse drug events to optimise patient adherence. Simplification of medications is very useful for a disease that is very dependent on the patient adherence such as HIV and tuberculosis treatment. Simplification of HIV treatment has shown benefits toward life-expectancy, quality-adjusted life expectancy and cost of treatment. The cost for lifetime was estimated to be less for the simplification strategy group than the standard of care group. The difference was estimated at $26,500-$72,400 per person (Schackman *et al*., 2007).

ADHERENCE COUNSELING

Pharmacists are responsible for not an easy task for adherence counselling, since they need to tailor the counselling to the patient's behaviour and real-life barriers. Adherence counselling has been ancillary in many adherence interventions because behaviour and cognitive are the fundamental determinant of adherence (Coetzee, *et al*., 2016). There are skills and models that can be considered in adherence counselling to make sure that the counselling is effective and meaningful. The purpose of the adherence counselling is to increase patients' knowledge about their disease and treatment, enhance their motivation and build patient's self-efficacy. Information-motivation-behavioural (IMB) model is a method of informing a positive behaviour that the patient needs to have, motivating the patient to have the behaviour, and coaching the patient to execute the behaviour in their life. The outcome of the IMB is patients that have confidence in their life at any occasion or situation (Lin and Scott, 2012). Rubak *et al* conducted a systematic review to evaluate the effectiveness of motivational interviewing in different areas of disease and to identify factors shaping outcomes. 72 randomised controlled trial RCTs were included in the analysis, which 39% (28/72) of the studies were for the treatment of alcohol addiction. Besides that, motivational interview also was implemented in the counselling of diabetes and asthma (3/72), smoking cessation (12/72), weight loss or physical activity (10/72) and psychiatric or addiction problem (19/72). Out of these studies, 73% (53/72) showed a significant effect towards the treatment. The median counselling duration was 60 minutes, with 81% (26/32) of the 60 minutes counselling session showing significant effect. Besides that, the total of encounter counselling was examined to find the

optimum effect of the counselling. It was proved that 87% (13/15) of the studies with more than five encounters demonstrated better effect. In addition, the median of follow up duration was 12 months, which supported 81% (26/32) of the 12-months follow up period that showed better effect (Rubak, *et al*., 2005). Continuing training should be done to train pharmacists and other health care providers about these motivational interview skills in order to produce a good counsellor. Discharge counselling is one of clinical pharmacist job scope that has been implemented to overcome incidence of discharge adverse events by enhancing medication adherence. It is found that about 23% of discharge patients experience post discharge adverse events, mainly due to newly prescribed medications. An observational study was done to evaluate the effect of discharge counselling towards medication adherence, the study showed that the adherence rate significantly increased from 51% to 66.7% ($p<0.01$) from the observational period and after intervention. Percentage of unfilled medications also reduced significantly from 50.2% to 32.5% ($p<10\text{-}7$). This finding highlights that counselling before discharge is very important (Leguelinel-Blache *et al*., 2015).

LIMITATIONS

This is not a comprehensive review on all the existent medication adherence measures. Rather it is focused on the different types available and the most commonly used in different settings. The types of setting and population in the studies that are used as examples vary in different measures which can make comparisons cumbersome. If researchers and healthcare professionals are looking for measures for a specific or rare condition, they should refer to studies that have a clearer validation. This review is limited to researchers and health professionals conducting studies in English language

IMPLICATION AND DIRECTION FOR FUTURE RESEARCH

There are ongoing public health reforms worldwide to minimize unnecessary healthcare expenditure and maximise public health outcomes. Improving medication adherence is a significant outcome in clinical practice and research. The lack of a universal guideline on medication adherence measures provides room for research on which measure, or which combination of measures, is the most appropriate for different target populations and health problems. Meanwhile, research on improving the currently available measures and/or on the development of new ways to measure and uncover reasons behind medication nonadherence should also be further explored.

CONCLUSION

Adherence to medication has been recognized as a crucial factor to achieve therapeutic outcomes. Poor to nonadherence is viewed as a prominent obstacle to patient therapeutic outcomes, poses a great challenge to healthcare providers, is found to reduce the quality of life and results in additional healthcare costs. Nonadherence cannot be blamed solely on a patient. It is multifactorial and thus, in order to increase adherence, various obstacles to adherence must therefore be acknowledged and recognized. Despite the fact that patient education is the ultimate way to increase adherence, utilization of adherence aids, strong motivation and moral support are also shown to improve medication adherence. Health care providers should be able to recognize possible intervention that is practical for implementation to improve medication adherence within their capabilities. It should be a multidisciplinary approach that is accomplished with collaborative support of all key stakeholders involved in medication use.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this review article are inserted within the manuscript and openly available in a public repository that issues datasets with DOIs as cited from the references below.

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