SYSTEMATIC REVIEW OF FACTORS ASSOCIATED WITH MEDICATION ADHERENCE AMONG PULMONARY TUBERCULOSIS PATIENTS

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ABSTRACT

The burden of tuberculosis is still high despite various strategies implemented to curb the disease. Millions of people diagnosed with tuberculosis every year and more than half of tuberculosis incidence are from India, Indonesia, China, Nigeria, Pakistan and South Africa. Medication adherence become a growing concern of public health. Treatment interruption and poor adherence resulted in treatment failure, prolonged the period of infectiousness and development of drug resistance tuberculosis. Therefore, it is very important to find factors that associated with medication adherence to help improve the tuberculosis control program in general. This article aims to find evidence of various factors that associated with tuberculosis medication adherence among adult patients diagnosed with pulmonary tuberculosis. The selection criteria for considering studies for this review include and not restricted to geographical area, recent article published not more than 5 years and patients diagnosed as pulmonary tuberculosis according to World Health Organization standard. The search engine includes PubMed, Medline and CINAHL with the mesh terms used; ["tuberculosis/TB" AND "adherence/compliance/medication adherence/concordance"]. Total of 9 articles included in the review. Various factors have been linked with medication adherence among pulmonary tuberculosis patients and were divided into patient's factors, health provider factors, structural or system factors and others. Patients factors that improve adherence to tuberculosis treatment are knowledge pertaining to tuberculosis and its treatment. While, poor motivation to complete the treatment, belief of cured after one or 2 months on treatment and experiencing drug side effects were among the factors that significantly associated with tuberculosis non-adherent. Tobacco smoking, alcohol and drug substances abuse also found to be a risk factor of tuberculosis treatment interruption. Health provider factors such as inadequate drug supply and prolonged waiting time. System or structural factors such as access to healthcare facilities and other related factors are poor social support and underlying human immunodeficiency virus infection. In conclusion, thorough analysis on the factors associated with adherence according to the epidemiological situation and locals' factors is important to escalate the chances of treatment success among all tuberculosis cases and ultimately ending tuberculosis.

Keywords: tuberculosis, medication adherence

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1.0 Introduction

Tuberculosis has received considerable attention globally due to burden of disease. Despite various strategies implemented to curb the disease, it kept growing especially in low- and middle-income countries. In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children (WHO, 2016). More than half (60%) of tuberculosis incidence came from these 6 countries namely India, Indonesia, China, Nigeria, Pakistan and South Africa (WHO, 2016). Multiple factors lead to the escalating numbers of new tuberculosis cases worldwide. This can be divided into environmental factors and host factors. Environmental factors such as living in poverty and overcrowding area are classically associated with high tuberculosis incidence (Millet, Moreno, Fina, Del Bano, Orcau, De Olalla and Cayla, 2013). Host factors includes malnutrition, human immunodeficiency virus (HIV) infection and co-morbidities such as Diabetes Mellitus also increased the risk of getting active tuberculosis due to impair immune system (WHO, 2017). For example, people who are infected with HIV are 20 to 30 times more likely to develop active tuberculosis disease (WHO, 2017).

Without treatment, the death rate from tuberculosis is high. Studies of the natural history of tuberculosis disease in the absence of treatment with anti-tuberculosis drugs (that were conducted before drug treatments became available) found that about 70% of people with sputum smear-positive pulmonary tuberculosis and 20% of people with culture-positive (but smear-negative) pulmonary tuberculosis died within 10 years (WHO, 2016). Despite effective treatment is available, one of the growing concern of public health is medication non-adherence. A newly diagnosed patient with pulmonary tuberculosis requires them to take daily EHRZ (Ethambutol, Isoniazid, Rifampicin and Pyrazinamide) treatment regime for 2 months and daily HR (Isoniazid and Rifampicin) for the subsequent 4 months (Ministry of Health (MOH) Malaysia, 2012). Poor or non-adherence to tuberculosis medication resulted in treatment failure and low cured rate, which lead to prolonged disease transmission or infectiousness and increases the emergence of drug resistance tuberculosis (WHO, 2003). There are also evidenced of adverse outcome and increasing costs of care resulting from non-adherence to tuberculosis medication. Ensuring patients' adherence to the treatment regime is very important to further enhance the strategy to end tuberculosis.

The new taxonomy in defining medication adherence is the "process by which patients take their medications as prescribed" (Vrijens, Geest, Hughes, Przemyslaw, Demonceau, Ruppar,.... and Urquhart, 2012). The process starts with initiation followed by implementation and discontinuation phase. Initiation refers to the first dose of prescribed drugs the patient takes and continues with the implementation of the prescribed medication regimen, defined as the "extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken" (Vrijens, et al, 2012). Discontinuation mean the next dose of medication to be taken is omitted and no more doses are taken thereafter (Vrijens, et al, 2012). The period between initiation and the last dose, which immediately precedes discontinuation is describe as persistence. Therefore, non-adherence to medications can occur along the process for example in late or non-initiation of the prescribed treatment by the patients, sub-optimal implementation of the dosing regimen or early discontinuation of the treatment (Vrijens, et al, 2012).

Worldwide, there are many studies on factors associated with medication non-adherence specifically in tuberculosis disease and it highlighted the importance of adherence with treatment outcome. Adherence also essentials in preventing drug resistance tuberculosis which is more difficult to treat. This article aims to systematically reviewed evidence of various factors that associated with tuberculosis medication adherence among patients contracted with pulmonary tuberculosis (PTB).

2.0 Methods

This review is conducted in accordance to PRISMA (transparent reporting of systematic reviews and meta-analyses).

2.1. Types of studies

The criteria for considering studies for this review include cross-sectional studies, case-control studies, randomized control trials or qualitative studies. No geographic restrictions were applied. Articles published not more than 5 years were included for full review to ensure an updated information is gathered to meet the objective of this review.

2.2. Types of participants

Study must include adults/adolescents age 15 years and above receiving treatment for active pulmonary tuberculosis. Active pulmonary tuberculosis is defined as having sputum smear-positive sample, sputum culture-positive sample, or if negative for the latter two, typical pulmonary tuberculosis clinical findings together with radiographic assessment reports (WHO, 2008).

2.3. Types of outcome measures

Medication adherence or compliance outcome based on the new taxonomy defined by Vrijens et al (2012).

2.4. Searches methods for identification of studies

Searches was performed for all articles published in relevant databases which includes PubMed, Medline and CINAHL. The searched were done through following search terms: ["tuberculosis/TB" AND "adherence/compliance/medication adherence/concordance"].

A total of 627 articles were retrieved in this process and after the culling process, only 9 articles met the inclusion criteria. The rest were excluded for the reasons such as duplicate articles, non-relevant articles base on title, studies participant and outcome measure, articles published more than 5 years ago, and articles published in other than English language. 84 full-texts articles were reviewed and ultimately, 9 articles were included for full analysis. The consort flow of search is as Figure 2.1.
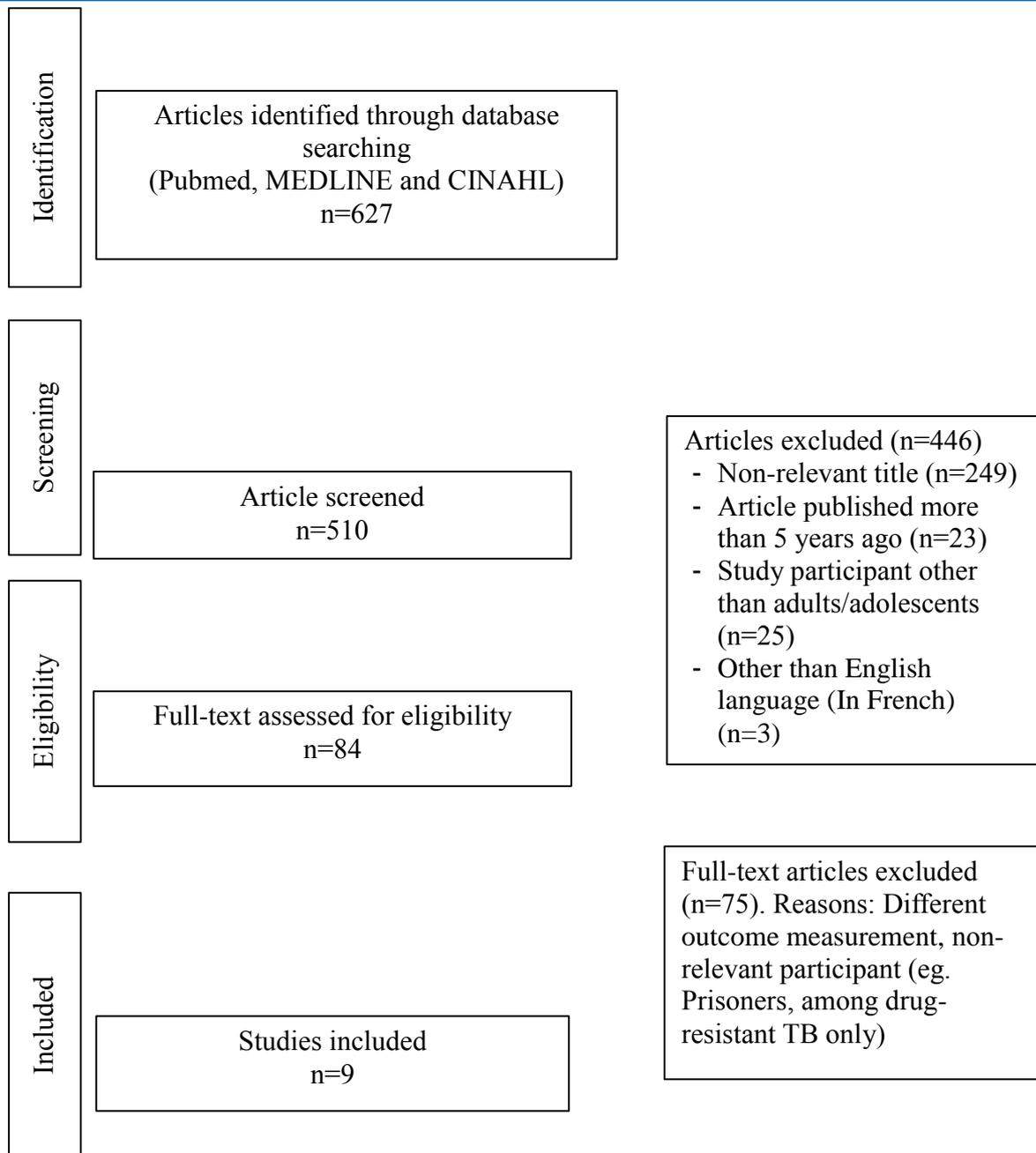
Identification

Articles identified through database searching
(Pubmed, MEDLINE and CINAHL)
n=627

Screening

Article screened
n=510

Articles excluded (n=446)
- Non-relevant title (n=249)
- Article published more than 5 years ago (n=23)
- Study participant other than adults/adolescents (n=25)
- Other than English language (In French) (n=3)

Eligibility

Full-text assessed for eligibility
n=84

Included

Studies included
n=9

Full-text articles excluded (n=75). Reasons: Different outcome measurement, non-relevant participant (eg. Prisoners, among drug-resistant TB only)

Figure 2.1: Consort flow chart of the review of literature on factors associated with tuberculosis treatment adherence

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3.0 Result

Total of 9 articles included in the review. The studies were done in African region (4), Nigeria (2), Indonesia (1), Ethiopia (1), Thailand (1) and multi-centred from African countries (1). The year of articles published ranges from 2013 to 2016. The main results derived from the article analysis are summarized in Table 3.1.

Table 3.1: Summary of the review of literature on factors associated with tuberculosis treatment adherence

No	Author/Article	Year	Study design	Location/ Sample	Result/Findings
1	Naidoo, P., Peltzer, K., Louw, J., Matseke, G., Mchunu, G. & Tutshana, B. Predictors of tuberculosis (TB) and antiretroviral (ARV) medication non-adherence in public primary care patients in South Africa: a cross sectional study BMC Public Health,13(396), 10 pages	2013	Cross-sectional	14 public primary health care clinics in three provinces, namely, Northern Cape, Eastern Cape and Kwa-Zulu Natal in South Africa 3107 574 participants included in multivariate analysis	Multivariable analysis indicates that the following factors are more likely to predict TB treatment non-adherence: i. Medium levels of poverty [OR:1.73 (1.34–2.24), p<0.001], ii. High levels of poverty [OR:1.65 (1.14–2.39), iii. Having 1 chronic condition [OR: 1.86 (1.41–2.46), p <0.001], iv. Having 2 chronic conditions [OR: 2.44 (1.68–3.56), p <0.001], v. Having 3 or more chronic conditions [OR: 2.37 (1.45-3.88), p < 0.001], vi. Medium risk for alcohol misuse [OR: 1.65 (1.23–2.29), p<0.001], vii. High risk for alcohol misuse [OR: 3.06 (1.94–4.81), p < 0.001], tobacco use [OR: 1.35(1.04–1.75), p < 0.05],

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No	Author/Article	Year	Study design	Location/ Sample	Result/Findings
					iii. Having a partner who is HIV positive [OR: 1.43 (1.10–1.84), p< 0.01]. Multivariable analysis indicates that the following factors are more likely to predict adherence to TB treatment: i. perceiving health status as being 'poor' [OR: 0.44 (0.32–0.60), p < 0.001], ii. perceiving health status to be 'good' [OR: 0.50 (0.37–0.67), p< 0.001], iii. being HIV negative [OR: 0.44 (0.33–0.59), p < 0.001
2	Sariem, C.N., Gyang, S.S., Tayo, F., Auta, A., Omale, S. and Ndukwe, H.C. Factors Influencing Tuberculosis Medication Adherence in a Tertiary Health Institution in Nigeria West African Journal of Pharmacy, 24 (2), 66-75	2013	Cross-sectional	DOTS Clinic in Plateau State Specialist Hospital (PSSH), Jos North Local Government Area of Plateau State, Nigeria 272 TB patients	The level of non-adherence 14.7% from patient self-report through questionnaire, and 29.7% from patient's records None of the demographic variables (gender, education, occupation, marital status) was significantly associated with adherence (p>0.05) Percentages of respondents with correct knowledge of the cause of TB were 14% and 86% pre- and post-intervention respectively Interruption of

No	Author/Article	Year	Study design	Location/ Sample	Result/Findings
					medication taking was due to forgetfulness (44.7%) and side effects of the medications (37%).
					Adherence significantly associated with
					i. Knowledge level - patients with adequate knowledge of TB were 7 times more likely to adhere to TB medication taking (CI: 2-25, p=0.005) than those with inadequate knowledge level of TB.
					ii. Support from family/community improve adherence (p=0.003)
					iii. patient satisfaction with health worker's service -satisfactory with service from doctors (p=0.001) and nurses (p=0.046)
					iv. patient's visit to the clinic
					Adherence not significantly associated with belief TB is curable (p=0.763)

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No	Author/Article	Year	Study design	Location/ Sample	Result/Findings
3	Ibrahim, L.M., Hadejia, I.S., Nguku, P., Dankoli, R., Waziri, N.E., Akhimien, M.O.,… & Nsubuga, P. Factors associated with interruption of treatment among Pulmonary Tuberculosis patients in Plateau State, Nigeria. 2011 Pan African Medical Journal, 17(78), 6 pages	2014	Cross-sectional study	Plateau state north central Nigeria 378	378 records reviewed: i. 229 (61%): male; ii. mean age 37.6 ±13.5 years iii. 71 (19%): treatment interrupted Interruption of treatment was associated with: i. Lack of knowledge of duration of treatment (AOR:6.1; CI 95%: 2.8-13.2) ii. Living >5km from TB treatment site (AOR:11.3; CI 95%: 5.7-22.2) iii. Cigarette smoking (AOR:3.4; CI 95%: 1.5-8.0) Major reasons for the interruption were lack of transport fare (40%) and feeling well (25%) Unfriendly attitudes of health care workers as barriers to adherence to treatment.
4	Rondags, A., Himawan, A.B., Metsemakers, J.F.M. & Kristina, T.N. Factors influencing non-adherence to Tuberculosis treatment in Jepara, Central Java, Indonesia Southeast Asian Journal of Tropical Medicine & Public Health, 45(4), 859-868.	2014	Qualitative study using in-depth interview (triangulation design) Semi-structured questionnaire asked about	Jepara, Central Java, Indonesia 17 PTB patients	Three main themes for non-adherence to TB treatment: i. Lack of knowledge about TB ii. Lack of knowledge about TB treatment iii. The decision to change the health care location

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			personal factors, knowledge about TB and its treatment, health care workers, stigma attached to TB, traditional treatments, organization of health care for TB and incentives.		
5	Kisambu, j., Nuwaha, f. & Sekandi, J.N. Adherence to treatment and supervision for tuberculosis in a DOTS program among pastoralists in Uganda Int J Tuberc Lung Dis 18(7):799–803	2014	Cross-sectional	Karamoja subregion, Kaabong District, Africa	91 (72%): adhere to treatment Poor adherence significantly associated with: i. Drug-related factors i.e a. Drug stock outs (OR 5.08, 95%CI 2.02–13.31), perceived b. drug side effects (OR 2.66, 95%CI 1.09–6.72) ii. DOT card not updated (OR 5.14, 95%CI 1.73–18.29). livelihood/economic

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No	Author/Article	Year	Study design	Location/ Sample	Result/Findings
					factors, patient-related factors and volunteer-related factors, did not have any significant effects on adherence
6	Tesfahuneygn, G., Medhin, G., Legesse, M. Adherence to Anti-tuberculosis treatment and treatment outcomes among tuberculosis patients in Alamata District, northeast Ethiopia BMC Research Notes, 8(503), 1-11	2015	Cross-sectional & Retrospective cohort study - to assess TB treatment outcomes for the last 5 & half years (between Jan 2007 - June 2012).	Addis Ababa, Ethiopia 200 TB patients Attending health facilities of Alamata District	2 outcome measures in this study: i. Treatment adherence as reported by patients ii. Treatment outcome from previous record either cured, treatment completed, defaulted, died or treatment failed. Non-adherence: 11.5% Poor adherence significantly associated with: i. <24 years of age (p=0.04) ii. No counselling on TB treatment (p=0.01) iii. HIV sero-positivity (p=0.02) iv. Alcohol consumption (p=0.03) v. Smoking (p=0.01) vi. Prolonged waiting time at the health facility to get medical services (p=0.01) Multivariate analysis→ i. <24 years (OR:5.1) ii. Prolonged waiting time (OR:3.6) Adherence not significantly associated

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No	Author/Article	Year	Study design	Location/ Sample	Result/Findings
					with: i. Gender (p=0.46) ii. Marital status (p>0.05) iii. Education (p=0.27) iv. Distance home to clinic (p=0.48) v. Type of TB (p=0.27) vi. Knowledge of TB (p=0.86) vii. Health education provided during treatment (p=0.16)
7	Peltzer, K. and Pengpid, S. Predictors of Non-adherence to Anti-Tuberculosis Medication in Tuberculosis Patients in Thailand J Hum Ecol, 52(1,2), 26-31	2015	Cross-sectional	Thailand 225 TB patients visiting TB outpatient's clinics from 28 hospitals	Non-adherence: 15.6% TB medication non-adherence significantly associated with: i. Male gender (χ^2=5.90, p=0.015) ii. Poor TB knowledge (χ^2=1.80, p=0.033) TB medication non-adherence not significantly associated with: i. Age (χ^2=1.70, p=0.428) iii. Education (χ^2=4.87, p=0.088) iv. Current Tobacco smoking (χ^2=0.29, p=0.59) v. Alcohol use in past week (χ^2=0.88, p=0.349) vi. Health care

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No	Author/Article	Year	Study design	Location/ Sample	Result/Findings
					services satisfaction (χ^2=1.85, p=0.397)
8	Theron, G., Peter, J., Zijenah, L., Chanda, D., Mangu, C., Clowes, P.,…. & Dheda, K. Psychological distress and its relationship with non-adherence to TB treatment: a multicentre study BioMed Central Infectious Diseases, 15(253)	2015	Pragmatic, randomised (1:1), parallel arm, multi-centric trial	Primary care TB clinic in Cape Town (South Africa), Durban (South Africa), Harare (Zimbabwe), Lusaka (Zambia), and Mbeya (Tanzania) 1502 TB patients	26% (69/261) of patients with confirmed TB who were placed on treatment and followed-up at two or six months were non-adherent. In multivariate analysis, Non-adherence significantly associated with: i. Increased psychological distress [1.082(1.033,1.137); p=0.0012] ii. Heavy alcohol usage [14.83(2.083, 122.9); p=0.0002], iii. Decreased health literacy score [0.798(0.696, 0.906); p=0.0008]
9	Fagundez, G., Perez-Freixo, H., Eyene, J., Momo, J.C., Biyé, L., Esono, T., Ayecab, M.O.M, Benito, A., Aparicio, P., Herrador, Z. Treatment Adherence of Tuberculosis Patients Attending Two Reference Units in Equatorial Guinea. PLoS ONE 11(9): e0161995. doi:10.1371/journal.pone.0161995	2016	Cross-sectional	Equatorial Guinea. 98 TB patients attending 2 TB reference centres in Bata and Malabo Age ≥18 years	78.57% of respondents were adherent according to the Morisky-Green-Levine test. The worst scored question was was forgetting to take the TB drugs. TB medication non-adherence significantly associated with: i. Re-infection - 46.15% of the re-infected cases were found to be non-adherent compared

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					to 17.65% of those patients with no re-infection (p=0.020). ii. Shortage of drug causing interruption of treatment (p=0.035) iii. Poor knowledge on diet (p=0.010). iv. No motivation to complete treatment (p=0.008) v. Poor family support (p=0.020) TB medication non-adherence not significantly associated with: i. Gender (p=0.399) ii. Age (p=0.545) iii. Marital status (p=0.807) iv. Educational level (p=0.312) v. Received information about TB (p=0.100).

4.0 Discussion

Medication non-adherence is a major barrier to the optimal care of tuberculosis patients. Completion of treatment or medication adherent is the necessary condition for the patient's treatment success and the prevention of multi-drug resistant tuberculosis which definitely more difficult to be cured. Various factors have been linked with medication adherence among pulmonary tuberculosis patients. From the review, the factors can be divided into patient's factors, health provider factors, structural or system factors and others.

Lower socioeconomic status of the patient such as lower education, economically restraint and unemployed is linked with poor adherence to tuberculosis treatment (Naidoo, et al, 2013). However, other studies found no significant association between adherence level with sociodemographic or economic status of the patients (Sariem, et al, 2013; Peltzer & Pengpid, 2015; Tesfahunegyn, et al, 2015; Fagundez, et al, 2016). These findings are contradicts to the

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facts pertaining to social determinants of health which indicates that demographic and socioeconomic status play a roles in determining the health outcomes of a person.

The patient's factors also include knowledge pertaining to tuberculosis and its treatment, such as side effects of treatment and duration of the treatment need to be completed. Patients with inadequate knowledge of the duration of the treatment associated with non-adherent to the medication (Ibrahim et al, 2014). This is also contributing by the feelings of cure or better after being taking the treatment just one or two months' duration where the symptoms usually has subsided. At this stage patient, may have no physical cues to the illness and may forget and stop to complete the medication prescribed. Therefore, it is very important to educate patients on the importance of completing their treatment although they do not feel the need for it. Many studies also supported that the more the patients were educated about tuberculosis disease, the more likely they would adhere to anti-tuberculosis medications (Sariem, et al, 2013; Rondags, et al, 2014; Tesfahuneygn, et al, 2015; Peltzer & Pengpid, 2015; Theron, et al, 2015). 1 articles showed that there are no significant association between patients who received information and not received information on tuberculosis treatment adherence, but the study does not include the type of information that was given to patient whether it is health education or not (Fagundez, et al, 2016).

Apart of that, patient perception towards stopping tuberculosis where they believe they can stop treatment any time if they feel better also a risk factors for non-adherence to the medication (Ibrahim, et al 2014). Poor or no motivation to complete treatment was found to be significantly associated with medication non-adherence among pulmonary tuberculosis patients (Fagundez, et al, 2016). However, a study has shown no significant association between adherence to tuberculosis medication with belief of disease is curable (Sariem, et al, 2013). Other than that, tobacco smoking, alcohol and drug substances abuse also found to be a risk factor of TB treatment interruption and unsuccessful treatment (Naidoo, et al, 2015; Tesfahuneygn, et al, 2015; Theron, et al, 2015; Peltzer & Pengpid, 2015). Patients who experiencing drug side effects also significantly associated with medication non-adherence (Sariem, et al, 2013; Kisambu, et al 2014). Moreover, patient who suffered more than 2 chronic diseases such as having tuberculosis with underlying HIV and/or Diabetes Mellitus at the same time significantly associated with poorer adherence compared to patient who do not have co-morbidity (Naidoo, et al, 2013; Tesfahuneygn, et al, 2015). Dual or triple diseases requires that they take two or more sets of drugs, which could prove to be quite burdensome to the patient. The use of a multiple combination of drugs may also lead to unmanageable side-effects which is unpleasant and causing physical discomfort and ultimately leading to treatment default.

Provider factors include inadequate drug supply and not implementing directly observed therapy (DOT) strategy as recommended by WHO are associated with tuberculosis medication non-adherence and treatment failure (Kisambu, et al, 2014). Poor adherence also significantly associated with prolonged waiting time at the health facility to get medical services (Tesfahuneygn, et al, 2015). Patient satisfaction towards care given by the healthcare workers at clinic resulted in good adherence among the patients to take their medication correctly (Sariem, et al, 2013).

Although non-adherence has often been perceived as the fault of patients, and not of healthcare providers, there is evidence that healthcare system factors also have an important impact on adherence. Structural or system factors includes the access to the health care

facilities (Ibrahim, et al, 2014; Tesfahuneygn, et al, 2015). Poor access is one of the barriers for adherence to medication. It is not only due to the distance to the nearest health facilities but also the associate cost that patient need to pay in order to get the treatment for tuberculosis, for example the cost for the drug regimens and cost for the transportation. The sudden decision to change the health care location to provide tuberculosis treatment may also reduce the extent to which patients follow the treatment plan by the healthcare providers (Rondags, et al, 2014). Lower patient satisfaction towards healthcare services also found to be significantly associated with tuberculosis treatment adherence (Peltzer & Pengpid, 2015). Other related factors are lack of social or family support and having partner who is positive HIV status are found to be associated with non-adherence behaviour (Naidoo, et al, 2013; Fagundez, et al, 2016). However, being HIV negative and getting support from family or community are protective factors for adherence to medication (Naidoo, et al, 2013; Sariem, et al, 2013).

This review gives evidence that medication adherence is affected by various factors. The development of interventions to enhance patient adherence to medication, and maintain long term persistence, requires at least an understanding of the determinants of patient non-adherence to prescribed therapies. This is especially important when the determinants are modifiable risk factors, which, once identified, can then be targeted for beneficial changes.

5.0 Conclusion and recommendation

The successful treatment outcome and cure of tuberculosis is dependent on adherence to treatment. The reviews found that multiple factors associated with medication adherence among patients with pulmonary tuberculosis and the individual factors can be concluded as the main factors for adherence. Nevertheless, every organisation experienced difference issues pertaining to adherence to tuberculosis treatment. Therefore, thorough analysis on the factors associated with adherence according to the epidemiological situation and locals' factors is important to escalate the chances of treatment success among all tuberculosis cases and ultimately ending tuberculosis.

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Declaration

No conflict of interest is declared

Authors contribution

Author 1: information gathering, preparation and editing of manuscript

Author 2: final review of the manuscript

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