REVIEW ARTICLE

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Factors Affecting Adherence to Lipid-lowering Drugs: A Scoping Review

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ABSTRACT

Objectives: Dyslipidemia is an important risk factor for cardiovascular disease. In developed countries, only 50% of patients with chronic illness adhere to their long-term therapy. This article aimed to review the factors affecting adherence to lipid-lowering drugs (LLDs). ***Methods***: The searched articles were selected based on the available keywords in the title and abstract with the publication restricted between January 2010 and September 2020. Articles generated from the databases must fulfill both inclusion and exclusion criteria in the present systematic review. Our initial search retrieved 221 literature reviews. After excluding articles with irrelevant topics, a total of 23 articles were chosen for this current review. ***Results:*** The factors were classified based on three main factors: patient-related, medication-related, and healthcare workers-related factors. For patient-related factors, gender, age, number of family members, education level, post-hospitalization, comorbidities and cardiovascular disease risk, follow-up status, occupation, socio-economy, insurance, perception, ethnicity, and health plan were among the factors affecting adherence to LLDs. As for medication-related factors, timing, polypharmacy, duration of treatment, generic medication, intensity of medication, side effects, initiating dose, packaging, drug dosing, and type of drugs were revealed as contributing factors. In the light of healthcare workers, related factors shown were counseling, medication optimization, type of provider, and location of the hospital. ***Conclusions:*** Recommendations to improve adherence include educating patients on the disease itself and the importance of the treatment, modification of the dosing, timing and type of LLDs, and effective consultations by healthcare workers. Further studies need to be done in Malaysia as there is inadequate research on this topic.

Dyslipidemia is an important risk factor for cardiovascular disease (CVD). Reducing serum cholesterol (particularly the low-density lipoprotein cholesterol (LDL-C)) will reduce CVD risk.[1] The Malaysian National Health and Morbidity Survey 2019 illustrated that in every 10 people, four have raised serum cholesterol. However, in every four people in Malaysia, one did not know they had increased serum cholesterol.[2]

In the treatment of dyslipidemia, the main target is to lower LDL-C levels. Prescribing lipid-lowering medication is beneficial, especially for those with high CVD risks. Lipid-lowering drugs (LLDs), which have been proven to be effective for the prevention of CVD includes 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, fibrates, proprotein convertase subtilisin/kexin type 9 inhibitors, bile-acid sequestrants, nicotinic acid, and cholesterol absorption inhibitors.[3] The most widely prescribed therapy was HMG-CoA reductase inhibitors or statins, which act by competitively blocking HMG-CoA reductase, a rate-limiting enzyme in cholesterol biosynthesis, thus reducing intrahepatic cholesterol.[4] In Malaysia, this class of drug comprises 96% out of all LLDs used, and the trend of prescription was also increasing.[5] The use of simvastatin, atorvastatin, rosuvastatin, and other statins were 65%, 28%, 6%, and 1%, respectively.[5]

The World Health Organization defines adherence as the extent to which a person's behavior (such as taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed recommendations from a healthcare provider.[6] In developed countries, only 50% of patients who had chronic illness adhere to their long-term therapy. There are many types of non-adherence in the medical field. Firstly, primary non-adherence in

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which the healthcare providers issue a prescription but the medication is never filled or started. Secondly, non-persistence in which the patients stop taking the medication on their own after starting it, without consulting the physicians. Thirdly, is the non-conforming. This type consists of patients who do not take the medication as prescribed, such as skipping the dose, taking the medication at an incorrect time, or even taking more than prescribed. The effects of non-adherence include waste of medication, extension of the disease, decrease functional abilities, lower quality of life, and increased rate of hospital admission.[7]

There are many ways to assess the adherence to the medication of a patient. There are direct and indirect methods. For the direct method, we can monitor the medication intake through the metabolite levels in the blood or urine and direct observation by the nurses or physicians. Meanwhile, the indirect method also serves the same purpose, which is to assess the adherence to treatment of a patient. Pharmacy refills, questionnaires, and diaries are among the indirect methods to assess the patient's adherence to medication.[8]

Lastly, there are many studies done nationally and internationally on adherence to medication prescription. This shows the importance of adhering to medication among patients, especially patients on long-term treatment. This review aimed to systematically analyze and discuss the latest existing literature on factors affecting adherence to lipid-lowering medications from three perspectives: patient, medication, and healthcare workers. This review should be able to provide the latest and systematic information to all healthcare providers in improving care for their patients requiring lipid-lowering medication.

METHODS

The research question in this article was "what are the factors affecting adherence to LLDs?" We conducted a literature search of articles related to the research question using Scopus, PubMed, and Google Scholar databases. Several keywords were used and combined. The keywords used when searching for relevant articles were: 'adherence or compliance'; 'lipid or cholesterol'; and 'medication or drug or therapy or treatment'.

The articles search was selected based on the available keywords in the title and abstract with the publication restricted between January 2010 and September 2020. Articles generated from the databases must fulfill both inclusion and exclusion criteria in the present systematic review. The studies were included if they were: 1) related to factors affecting adherence to LLDs; 2) published; 3) in the English language; 4) available in full texts; and 5) quantitative studies.

Articles were excluded if the studies were: 1) not related to the objective of this systematic review; 2) review articles including systematic review and meta-analysis; 3) written in a language other than English; and 4) used a qualitative study design since this type of design will not give statistical results for comparison.

A total of 221 literature reviews were obtained from the initial search; 67 from Scopus, 45 from Google Scholar, and 109 from PubMed. Out of these papers, 43 were selected after screening for the titles and abstracts to exclude any irrelevant topics. The articles were then further scrutinized for the final list for this current review.

The following information was extracted and keyed into a spreadsheet: title, journal, year of publication, author, country, study method, sample size and criteria, and key findings.

RESULTS

A total of 23 out of 43 shortlisted articles were selected for a more detailed review. Figure 1 shows the flow of article selection.

The characteristics of the 23 articles selected for final analysis were summarized in Table 1. The final list consists of five cross-sectional studies,[12,23,24,26,27] 10 cohort studies,[9,11,14,18–22,29,30] seven randomized controlled trials[10,13,15–17,28,31] and one mixed-method study.[25] Twenty-one were conducted globally while only two studies were conducted locally in Malaysia. Most of the studies were conducted in the USA (n = 5),[14,18,20,25,30] followed by the Netherlands (n = 4).[16,17,19,31] Malaysia,[27,28] New Zealand,[13,29] and Spain[11,15] had two studies each (n = 2). Lastly, India,[10] Iran,[26] Palestine,[12] Saudi Arabia,[24] Japan,[9] China,[22] Hong Kong,[21] and Israel[23] had one study each to be reviewed.

Six studies were done in 2013[10,18,22,23,26,31] and four in 2019.[9,15,24,28] Two studies were conducted each year in 2011,[21,30] 2012,[14,16] 2014,[13,17] 2016,[19,20] 2017,[25,27]and 2020,[12,29] and one in 2018.[11] Most of

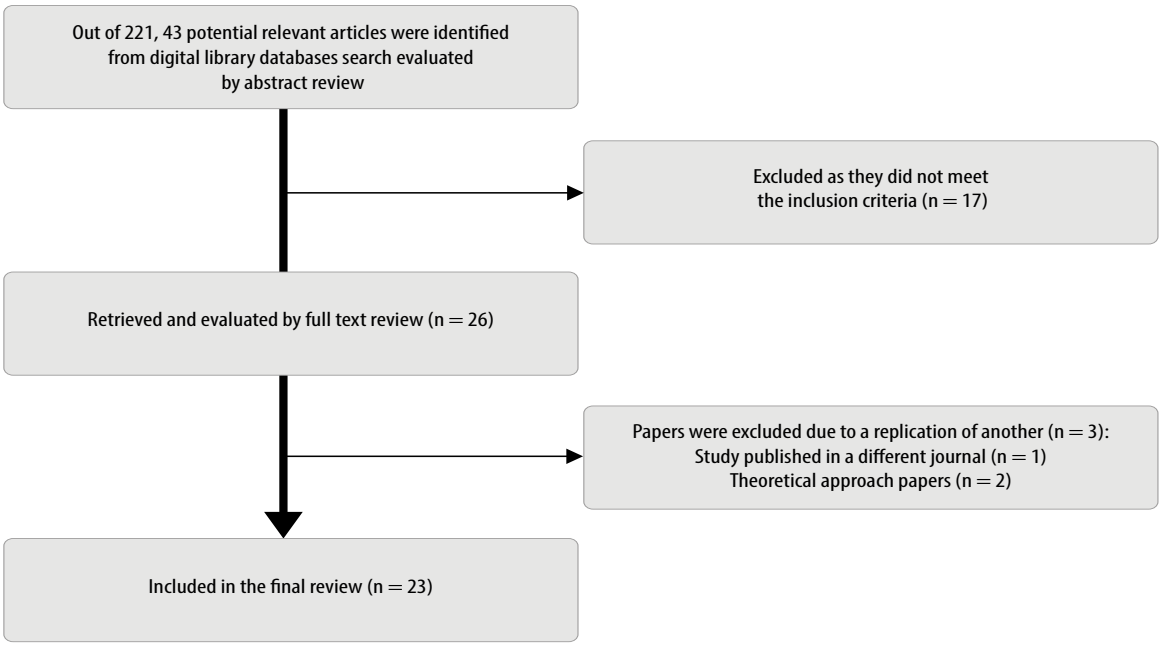

Figure 1: Flow diagram of literature search results.

Table 1: Final list of studies included in the systematic review.

Authors, year of publication	Country	n	Study design	Outcomes
Umeda et al,[9] 2019	Japan	6921	Retrospective study	Good adherence: concomitant use of hypertension gout medication with OR (95% CI) of 1.27 (1.13–1.43) and 1.18 (1.01–1.39), respectively. Poor adherence: patients aged ≤ 54 years or ≥ 75 years with OR (95% CI) of 1.72 (1.52–1.94)
Thom et al,[10] 2013	India and Europe (England, Ireland, Netherlands)	2004	Randomized, open-label, blinded-end-point clinical trial	Good adherence: FDC group (77%) vs usual care group (23%) with (RR = 3.35, 95% CI: 2.74–4.09; $p < 0.001$)
Sicras-Mainar et al,[11] 2018	Spain	13 244	Retrospective cost consequences analysis	Poor adherence: generic vs branded name statins; 61.5% vs. 65.1% ($p < 0.001$)
Shakarneh et al,[12] 2020	Palestine	185	Cross-sectional study	Poor adherence: illiterate (OR = 2.52; 95% CI: 0.9–4.3), polypharmacy (OR = 3.18; 95% CI: 1.9–5.7), having a comorbidity (OR = 3.10; 95% CI: 2.2–4.6), and having concerns about side effects (OR = 2.89; 95% CI:1.1–4.6)
Selak et al,[13] 2014	New Zealand	513	Open label, RCT	Good adherence: FDC (72%) vs. usual care (46%) with relative risk = 1.56 (95% CI: 1.34–1.82; $p < 0.001$)
Raebel et al,[14] 2012	USA	16 173	Retrospective cohort study	Poor adherence: Hispanic ethnicity (OR: 1.47; 95% CI: 1.09–1.97), shorter health plan enrollment (OR = 1.20; 95% CI: 1.00–1.45), and three (OR = 1.38; 95% CI: 1.00–1.89) or four or more (OR = 1.59; 95% CI: 0.80–1.42) comorbidities
Oñatibia-Astibia et al,[15] 2019	Spain	746	RCT	Good adherence: community pharmacists' intervention with (OR = 2.34, 95% CI: 1.87–3.03; $p < 0.001$)
Nieuwkerk et al,[16] 2012	Netherlands	194	RCT	Good adherence: patients in the extended care group (nurse-led counselling; 95–100%) vs. routine care group (90–95%) with OR = 0.30 (95% CI: 0.03–0.63)
Vegter et al,[17] 2014	Netherlands	1000	RCT	Good adherence: MeMO program group RR = 0.49 (95% CI: 0.37–0.66)

Table 1: Final list of studies included in the systematic review.

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Authors, year of publication	Country	n	Study design	Outcomes
Virani et al,[18] 2013	USA	972 532	Cohort study	Poor adherence: high-intensity statin therapy (OR = 0.94; 95% Cl: 0.93–0.96), younger, female or black, have PAD only, and higher overall illness burden
de Vries et al,[19] 2016	Netherlands	7772	Cohort study	Poor adherence: low-dose group (median 83%; IQR = 46–96) vs. standard-dose group (median 86%; IQR = 52–97) (Wilcoxon-test; $p < 0.001$)
Vupputuri et al,[20] 2016	USA	1066	Retrospective cohort study	Good adherence: taking 10 or more medications at baseline and seeing a cardiologist during the follow-up period. Poor adherence: female, African American, or hospitalized during the follow-up period. However, no statistical analysis was done to determine its significant association
Wong et al,[21] 2011	Hong Kong	11 042	Cohort study	Good adherence: older age [‡ 50 years; AOR = 1.30–1.72, $p = 0.009$ to < 0.001], attend FMSC (AOR = 1.56, 95% CI: 1.25–1.95; $p < 0.001$), follow-up visits (AOR = 2.93, 95% CI: 2.56–3.36; $p < 0.001$), greater number of comorbidities (one comorbidity; AOR = 1.45, 95% CI: 1.24–1.70; $p < 0.001$; ‡2 comorbidities; AOR = 1.56, 95% CI: 1.31–1.87; $p < 0.001$)
Xie et al,[22] 2013	China	1890	Cohort study	Good adherence: men, administrative occupations, better (70% off cover rate) medical insurance, managed in province-level vs. county-level hospitals, treated by other than cardiologists, very high CVD risk, and using a statin. However, no statistical analysis was done to determine its significant association
Yoel et al,[23] 2013	Israel	200	Cross-sectional study	Good adherence: older (55 ± 12 vs. 50 ± 12; $p < 0.001$), female (64% vs. 49%; $p < 0.01$), socio- economically stronger, patient with diabetes (66% vs. 33%; $p < 0.0001$), and hypertension (71% vs. 50%; $p < 0.0001$) Poor adherence: agree more with negative statements of chronic disease and discontinued specific drugs because of side effects (47% vs. 31%; $p < 0.05$)
Alwhaibi et al,[24] 2019	Saudi Arabia	1532	Retrospective cross-sectional study	Good adherence: comorbidities (77.4%), without polypharmacy and men (p-value = 0.0001)
Bosworth et al,[25] 2017	USA	240	Mixed-method study (RCT)	Good adherence: 54% of the intervention group adhered to refill packaging. 7.6% have a greater refill rate than the intervention group (p-value = 0.24; 95% CI: -5–20)
Dehkordi,[26] 2013	Iran	82	Cross-sectional study	Good adherence: younger age ($p = 0.035$), men, high family members ($p = 0.033$), and high education level ($p = 0.000$). Poor adherence: a greater number of drugs ($p = 0.022$)
Devaraj et al,[27] 2017	Malaysia	452	Cross-sectional study	Poor adherence: men (OR = 1.31; 95% CI: 1.02–1.74), taking lipid-lowering drugs for a longer period of time [i.e., of more than five years (OR = 1.37; 95% CI: 1.09–1.72), and more than 10 years (OR = 1.48; 95% CI: 1.24–1.74)], taking their lipid-lowering drugs at night (OR = 1.71; 95% CI: 1.54–1.96) or non-specific timing (OR = 1.63; 95% CI: 1.46–1.83), those with less frequency of follow-ups in a year [one follow-up in a year (OR = 1.63; 95% CI: 1.51–1.92) and two follow-ups in a year (OR = 1.47; 95% CI: 1.22–1.87)], less number of follow-up clinics (OR = 1.61; 95% CI: 1.37–2.11), and lower knowledge scores
Heng et al,[28] 2019	Malaysia	147	Prospective, open-labeled, multicenter, randomized, and active comparator study	A significant difference of LDL-C percentage in three arms ($p < 0.001$). Good adherence: Simvastatin was taken just before bedtime
Hu et al,[29] 2020	New Zealand	946	Sub-cohort analysis	Good adherence: post hospitalization (OR = 2.49; 95% CI: 1.74–3.57) and having other comorbidities (OR = 1.50; 95% CI: 1.17–1.91). Poor adherence: younger age (OR = 0.67; 95% CI: 0.48–0.95)

Table 1: Final list of studies included in the systematic review.

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Authors, year of publication	Country	n	Study design	Outcomes
Kamat et al,[30] 2011	USA	42 460	Retrospective study	Good adherence: SPC group (0.56 ± 0.34) than in the MPC group (0.47 ± 0.33) ($p < 0.0001$), ezetimibe-based therapies, longer duration of therapy, hospitalization at baseline, higher ATP III risk categories were 60–63% more likely to be adherent to therapy than patients in the low-risk category
Kooy et al,[31] 2013	Netherlands	399	RCT	Good adherence: electronic reminder device group (not significant)

OR: odds ratio; FDC: fixed-dose combination; RCT: randomized control trial; MeMO: medication monitoring and optimization; RR: relative risk; PAD: peripheral artery disease; IQR: interquartile range; AOR: adjusted odd ratio; FMSC: family medicine specialist clinic; CVD: cardiovascular disease; LDL-C: low-density lipoprotein-cholesterol; SPC: single-pill combination; MPC: Multiple-pill combination.

the studies aimed to assess the control of LDL-C levels and factors affecting adherence to LLDs. The factors were classified based on patient factors, medication factors, and healthcare workers factors.

Out of 23 included articles, only 12 studies[10,11,13,15,16,18–20,24,25,28,31] focused on HMG-CoA reductase (pravastatin, lovastatin, simvastatin, atorvastatin, and rosuvastatin) to assess adherence, and the rest[12,14,17,21–23,26,27,29,30] include other LLDs such as fibrates (bezafibrates and gemfibrozil), niacin (nicotinic acid and acipimox), bile acid-binding resins (cholestyramine and colestipol hydrochloride), and cholesterol absorption inhibitor (ezetimibe).

Adherence rates were measured using various methods in the reviewed articles. Nine of the articles used proportion of days covered (PDC) to measure adherence,[9,14,18–20,24,29–31] and four articles used medication possession ratio (MPR).[11,21,22,25] Two articles used the Morisky Medication Adherence Scale-8 (MMAS-8),[27,28] while one article measured adherence by using Morisky Medication Adherence-4 (MMAS-4).[12] One article used the Morisky Green Levine Test to assess adherence.[15] An interventional study utilized the Dutch observational data in measuring adherence.[17] The other five articles used different definitions to measure adherence rate.[10,13,16,23,26]

Patient-related factors

SOCIODEMOGRAPHIC PROFILE OF PATIENTS

All the findings of patient-related factors are given in Table 2. According to the studies done by Xie et al,[22] and Alwhaibi et al,[24] there was a significantly higher percentage of patients having an adequate adherence to statin therapy among men. However, a study done by Yoel et al,[23] mentioned that females (49%) have higher adherence to a statin medication. There was a significant association between compliance to medication and age whereby the compliance to medication decreased with increased age.[26] In contrast, a study done in Israel found that the older the patient, the higher the adherence to medication.[23] Additionally, the higher the number of family members and higher education level will increase medication adherence.[26] Xie et al,[22] pointed out that those who were working in the administrative field and having better medical insurance coverage were found to have better adherence to LLDs. African-American[20] and Hispanic[14] patients were found to have lower adherence to LLDs. Shorter health-plan membership is one of the reasons for primary non-adherence to LLDs.[14] Besides the typical sociodemographic profile highlighted, the patients' perception of lipid medication can also determine their adherence.[23] For example, Yoel et a,l[23] found that patient's insight on traditional medicine should switch the designated drugs.

COMORBIDITIES AND CVD RISK

Umeda et al,[9] mentioned that patients on secondary prevention have been associated with better adherence than patients on primary prevention who have been associated with worse adherence. A study done in the USA and the UK stated that there was a significant improvement in adherence to the prescribed drug post-hospitalization.[29,30] Furthermore, as mentioned by Wong et al,[21] and Yoel et al,[23] the one that has more comorbidities tends to be more adherent to statins and the difference was statistically significant. Wong et al,[21] also stated that patients who had more follow-up visits in a year

Table 2: Findings on the patient-related factors affecting adherence to lipid-lowering drugs (LLDs).

Author, year	Study design, number of participants	Summary of the findings on factors affecting adherence to LLDs
Umeda et al,[9] 2019	Retrospective study, n = 6921	Poor adherence: patients aged ≤ 54 years or ≥ 75 years with OR (95% CI) of 1.72 (1.52–1.94)
Shakarneh et al,[12] 2020	Cross-sectional study, n = 185	Poor adherence: illiterate (OR = 2.52; 95% CI: 0.9–4.3), having a comorbidity (OR = 3.10; 95% CI: 2.2–4.6), and having concerns about side effects (OR = 2.89; 95% CI: 1.1–4.6)
Raebel et al,[14] 2012	Retrospective cohort study, n = 16 173	Poor adherence: Hispanic ethnicity (OR = 1.47; 95% CI: 1.09–1.97), shorter health plan enrollment (OR = 1.20; 95% CI: 1.00–1.45), and three (OR = 1.38; 95% CI: 1.00–1.89) or ≥ 4 (OR = 1.59; 95% CI: 0.80–1.42) comorbidities
Virani et al,[18] 2013	Cohort study, n = 972 532	Poor adherence: younger, female or black, have PAD only, and higher overall illness burden
Virani et al,[18] 2013	Retrospective cohort study, n = 1066	Poor adherence: Female, African American, or hospitalized during the follow-up period. However, no statistical analysis was done to determine its significant association
Wong et al,[21] 2011	Cohort study, n = 11 042	Good adherence: older age [‡ 50 years; AOR = 1.30–1.72; p = 0.009 to < 0.001], follow-up visits (AOR = 2.93, 95% CI: 2.56–3.36; p < 0.001), and greater number of comorbidities (one comorbidity; AOR = 1.45, 95% CI: 1.24–1.70; p < 0.001; ‡2 comorbidities; AOR = 1.56, 95% CI: 1.31–1.87; p < 0.001)
Xie at al,[22] 2013	Cohort study, n = 1890	Good adherence: men, administrative occupations, better (70% off cover rate) medical insurance, very high CVD risk. However, no statistical analysis was done to determine its significant association
Yoel et al,[23] 2013	Cross-sectional study, n = 200	Good adherence: older (55 ± 12 vs. 50 ± 12, p < 0.001), female (64% vs. 49%, p < 0.01), socio- economically stronger, patient with diabetes (66% vs. 33%, p < 0.0001), and hypertension (71% vs. 50%, p < 0.0001). Poor adherence: agree more with negative statements of chronic disease
Alwhaibi et al,[24] 2019	Retrospective cross-sectional study, n = 1532	Good adherence: comorbidities (77.4%) and men (p = 0.0001)
Dehkordi,[26] 2013	Cross-sectional study, n = 82	Good adherence: younger age (p = 0.035), men, high family members (p = 0.033), and high education level (p = 0.000)
Devaraj et al,[27] 2017	Cross-sectional study, n = 452	Poor adherence: men (OR = 1.31; 95% CI: 1.02–1.74), those with less frequency of follow-ups in a year [one follow-up in a year (OR = 1.63; 95% CI: 1.51–1.92) and two follow-ups in a year (OR = 1.47; 95% CI: 1.22–1.87)], a smaller number of follow-up clinics (OR = 1.61; 95% CI: 1.37–2.11), and lower knowledge scores
Hu et al,[29] 2020	Sub-cohort analysis, n = 946	Good adherence: post hospitalization (OR = 2.49; 95% CI: 1.74–3.57) and having other comorbidities (OR = 1.50; 95% CI: 1.17–1.91). Poor adherence: younger age (OR = 0.67; 95% CI: 0.48–0.95)
Kamat et al,[30] 2011	Retrospective study, n = 42 460	Good adherence: hospitalization at baseline and higher ATP III risk categories were 60–63% more likely to be adherent to therapy than patients in the low risk category

OR: odds ratio; PAD: peripheral artery disease; AOR: adjusted odd ratio; ATP III: adult treatment panel III.

proved to be more adherent to statin or other drugs prescribed to them. Those having a very high CVD risk were also found to be more adherent to their lipid medications.[22] Meanwhile, non-adherence to LLDs was associated with the patient's concern about the side effects of the drugs.[12,23]

Medication-related factors

TYPE, NUMBER, AND TIMING OF MEDICATIONS

All findings related to medication-related factors are given in Table 3. A study conducted in the USA reported that patients who were on at least 10 types of medications had high adherence to LLDs.[20] Furthermore, another study in Japan revealed that patients who were on gout and hypertension treatment showed better adherence to LLDs.[9] In contrast, other studies showed that polypharmacy was one of the factors of non-adherence to LLDs.[12,24,26]

Regarding the packaging of LLDs, an intervention study was done by Bosworth et al,[25] using blister packaging among veterans to improve adherence. This study revealed a greater refill rate, but the differences were not significant. Nevertheless, users reported the benefits of this type

Table 3: Findings on the medication-related factors affecting adherence to lipid-lowering drugs (LLDs).

Author, year	Study design, number of participants	Summary of the findings on factors affecting adherence to LLDs
Umeda et al,[9] 2019	Retrospective study, n = 6921	Good adherence: concomitant use of hypertension gout medication with OR (95% CI) of 1.27 (1.13–1.43) and 1.18 (1.01–1.39), respectively
Thom et al,[10] 2013	Randomized, open-label, blinded-end-point clinical trial, n = 2004	Good adherence: FDC group (77%) vs. usual care group (23%) with (RR = 3.35, 95% CI: 2.74–4.09; $p < 0.001$)
Sicras-Mainar et al,[11] 2018	Retrospective cost-consequences analysis, n = 13 244	Poor adherence: generic vs. branded-name statins; 61.5% vs. 65.1% ($p < 0.001$)
Shakarneh et al,[12] 2020	Cross-sectional study, n = 185	Poor adherence: polypharmacy (OR = 3.18; 95% CI: 1.9–5.7)
Selak et al,[13] 2014	Open label, RCT, n = 513	Good adherence: FDC (72%) vs. usual care (46%) with relative risk of 1.56 (95% CI: 1.34–1.82), $p < 0.001$)
Virani et al,[18] 2013	Cohort study, n = 972 532	Poor adherence: high-intensity statin therapy (OR = 0.94; 95% Cl: 0.93–0.96)
de Vries et al,[19] 2016	Cohort study, n = 7772	Poor adherence: low-dose group (median = 83%; IQR = 46–96) vs. standard-dose group (median = 86%; IQR = 52–97) (Wilcoxon-test; $p < 0.001$)
Vupputuri et al,[20] 2016	Retrospective cohort study, n = 1066	Good adherence: taking ≥ 10 medications at baseline However, no statistical analysis was done to determine its significant association
Xie at al,[22] 2013	Cohort study, n = 1890	Good adherence: using a statin. However, no statistical analysis was done to determine its significant association
Yoel et al,[23] 2013	Cross-sectional study, n = 200	Good adherence: discontinued specific drugs because of side effects (47% vs. 31%, $p < 0.05$)
Alwhaibi et al,[24] 2019	Retrospective cross-sectional study, n = 1532	Good adherence: without polypharmacy ($p = 0.0001$)
Bosworth et al,[25] 2017	Mixed-method study (RCT) n = 240	Good adherence: 54% of intervention group adhere to refill packaging. 7.6% have greater refill rate of the intervention group ($p = 0.24$; 95% CI: -5–20%)
Dehkordi,[26] 2013	Cross-sectional study, n = 82	Poor adherence: a greater number of drugs ($p = 0.022$)
Devaraj et al,[27] 2017	Cross-sectional study, n = 452	Poor adherence: taking LLDs for a longer period of time [i.e. of > five years (OR = 1.37; 95% CI: 1.09–1.72) and > 10 years (OR = 1.48; 95% CI: 1.24–1.74], taking their LLDs at night (OR = 1.71; 95% CI: 1.54–1.96) or non-specific timing (OR = 1.63; 95% CI: 1.46–1.83)
Heng et al,[28] 2019	Prospective, open-labelled, multicenter, randomized and active comparator study, n = 147	Significant difference of LDL-C percentage in three arms ($p < 0.001$) Good adherence: simvastatin was taken just before bedtime
Kamat et al,[30] 2011	Retrospective study, n = 42 460	Good adherence: SPC group (0.56 ± 0.34) than in the MPC group (0.47 ± 0.33) ($p < 0.0001$), ezetimibe-based therapies, longer duration of therapy
Kooy et al,[31] 2013	RCT, n = 399	Good adherence: electronic reminder device group (not significant)

OR: odds ratio ; FDC: fixed dose combination; IQR: nterquartile range; LDL-C: low-density lipoprotein-cholesterol; SPC: single-pill combination; MPC: Multiple-pill combination.

of packaging and would recommend it to others during the interview. Additionally, drug dosing was also found to affect adherence rate. Studies done by Selak et al,[13] Thom et al,[10] and Kamat et al[30] investigated the association between fixed-dose combination, also known as single-pill combination, to adherence rate. Fixed-dose combination or single-pill combination is the combination of two or more drugs into a single pill. Interestingly, all studies showed significant improvement in the adherence rate. The type of LLDs may improve adherence, where patients prescribed statin were found to be more adherent compared to other LLDs.[22] However, another study by Kamat et al,[30] revealed that using ezetimibe-based therapy significantly increases adherence rate.

A randomized control trial study that took the respondents from primary healthcare clinics in Malaysia discovered that patients who took the drug before bedtime had better adherence to LLDs although this finding was not significant.[28] However, in a cross-sectional study, patients who consumed drugs at night or random timing were likely to have poor adherence to LLDs.[27]

DURATION AND SIDE EFFECTS

Significant positive outcome was observed in a study[30] among patients who took the medication over a long period of time but another study demonstrated the negative outcome.[27] Non-adherence of LLDs was higher among patients who use generic statins,[11] initiate with low-dose statins,[19] and develop side effects of medication effect such as myalgia and insomnia.[23] Also, unsurprisingly, many patients withdrew the drug due to unwanted effects.[23]

Healthcare worker-related factors

Several studies were conducted to investigate the association between healthcare workers and patients' adherence [Table 4]. Three intervention-based studies were reviewed including studies by Nieuwkerk et al,[16] Oñatibia-Astibia et al,[15] and Vegter et al.[17] The first study used nurse-led counseling as an intervention for adherence, which reported significant improvement in the intervention group.[16] The second study also reported a significant increase in adherence in the intervention group, after tailored interventions by community pharmacists.[15] The study identified each individual cause of non-adherence before tailoring the intervention accordingly. The third interventional study recruited a pharmaceutical care program, medication monitoring and optimization, in community pharmacies. The study reported significant improvement in the rate of adherence in the intervention group.[17]

In a study by Raebel et al,[14] on primary non-adherence, patients with providers in non-primary care have a significantly lower likelihood of having primary non-adherence compared with primary care. In contrast, a study investigating secondary non-adherence by Wong et al,[21] found significantly more adherence in attending Family Medicine Specialist Clinic (FMSC). Moreover, seeing a cardiologist was reported to increase the adherence rate.[20] Contrarily, Xie et al,[22] found that patients treated by specialists other than cardiologists had significantly more proportion of patients with good adherence. This study also reported that patients treated at a province level had more adherence compared to county-level hospitals.[22]

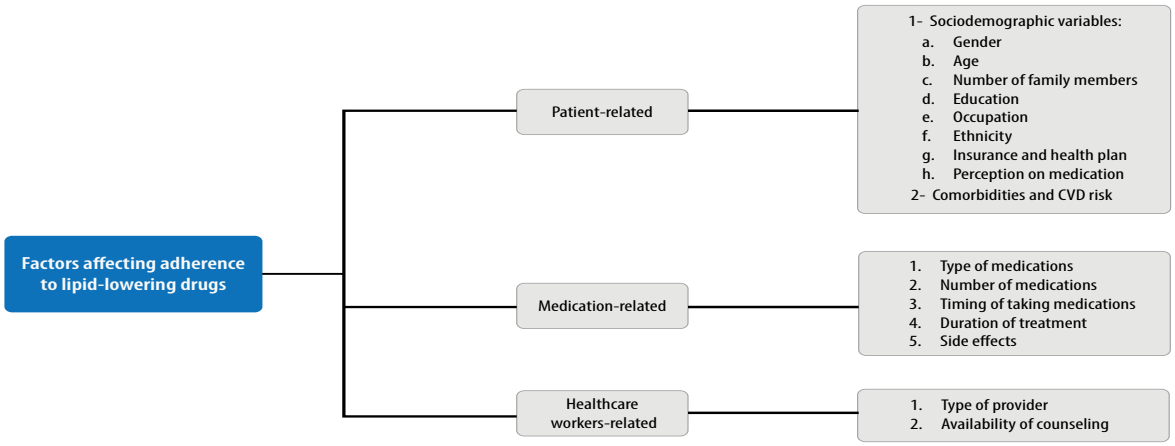
DISCUSSION

According to the results of our scoping review, a variety of factors, such as those relating to patient, the medication, and the healthcare workers can influence adherence to lipid-lowering medications [Figure 2]. To increase the adherence rate, each of these aspects needs to be taken into consideration.

Table 4: Findings on the healthcare workers-related factors affecting adherence to lipid-lowering drugs.

Author, year	Study design, number of participants	Summary of the findings on factors affecting adherence to lipid-lowering drugs
Oñatibia-Astibia et al,[15] 2019	RCT, n = 746	Good adherence: community pharmacists' intervention with OR = 2.34, 95% CI: 1.87–3.03; $p < 0.001$
Nieuwkerk et al,[16] 2012	RCT, n = 194	Good adherence: patients in the extended care group (nurse-led counseling; 95-100%) vs. routine care group (90–95%) with OR = 0.30; 95% CI: 0.03–0.63)
Vegter et al,[17] 2014	RCT, n = 1000	Good adherence: MeMO program group RR = 0.49; 95% CI: 0.37–0.66
Vupputuri et al,[20] 2016	RCT, n = 1066	Good adherence: seeing a cardiologist during the follow-up period However, no statistical analysis was done to determine its significant association
Wong et al,[21] 2011	Cohort study, n = 11 042	Good adherence: attend FMSC (AOR = 1.56, 95% CI: 1.25–1.95; $p < 0.001$)
Xie at al,[22] 2013	Cohort study, n = 1890	Good adherence: managed in province-level vs. county-level hospitals and treated by other than cardiologists. However, no statistical analysis was done to determine its significant association

RCT: randomized control trial; OR: odds ratio; MeMO: medication monitoring and optimization; RR: relative risk ; FMSC: family medicine specialist clinic; AOR:adjusted odds ratio.



CVD: cardiovascular disease.

Figure 2: Summary of the factors affecting adherence to lipid-lowering drugs.

Patient-related factor

In this review, there were two articles stated that men were more adherent to LLDs while one article stated otherwise.[22–24] Gender-based disparities in adherence to drugs were not yet definitive, but it was confirmed that women who consume multiple drugs and fail to comply with the guidelines of healthcare providers were factors that affect women's decision not to adhere with the prescription given. Furthermore, the results of the reviewed studies indicate that women were consistently less likely to stick to their medication regimes than men. This finding is consistent with several other reviews on the similar topic.[32,33] Another review found that female sex contributes to the negative impact on adherence to statins.[34] This disparity can be explained by the fact that women experience more drug-related side effects than men;[35] however, the side effects of these drugs are generally shown to affect both genders. In some societies, women might have a lower level of educational background, and that could explain the discrepancy in gender-related adherence to drugs.[22]

Moreover, this review also found that a higher number of family members also improve someone's adherence to LLDs.[26] This could be because the patient has a support system that can act as a reminder to take the drug on time and adhere to the prescription. In addition, those with a higher level of educational background were more adhered to their lipid medication.[26] This could be because patients who had a high educational level also tend to have good awareness about being adherent to the medication and the negative effects of skipping the medication. This finding is consistent with a systematic review, which found that a higher level of education is associated with statin adherence.[32] Interestingly, that review found a link between educational level and gender in which men with higher educational levels were found to be more adherent, but the opposite effect was observed in women.[32]

Those who had at least one experience of hospitalization, CVD accident, or other comorbidities have a better realization regarding adherence and subsequently improved their adherence to the drugs regimes.[9,11,29] In agreement with this, a prior review on this topic found that high number of comorbidities and previous cardiovascular events have a positive influence on adherence to statins.[34] Apart from that, we found that African-American and Hispanic ethnicity corresponded to low adherence to LLDs. This was supported by the finding in a systematic review in which non-white patients were 53% more likely to be non-adherent to statin therapy.[33] The possible explanations may arise from their conviction, knowledge, cultural norm, preference, and doctor-patient relationship.[14,20,36] Patient's concern about the side effects of medication should be taken into account to ensure adherence to LLDs.[12,23,37] Knowledge and attitudes play an important role in a patient's perception of the drug. For example, the Bedouin, the minority population, who still try to catch up with Western knowledge, attitudes, and lifestyle opt for traditional medicine compared to modern healthcare facilities.[23]

Medication-related factor

Two studies demonstrated that polypharmacy has a potential positive factor in drug adherence.

For example, patients with dyslipidemia who have concomitant gout and suffered severe pain have a better understanding of the importance of the drugs.[9,20] However, many studies proved the contradictory statement.[12,26,38–40] These inconsistent findings are not surprising as a systematic review also found similar results and eventually suggested no association between polypharmacy and adherence.[32] Being prescribed with many drug regimens, especially among patients with dyslipidemia and type II diabetes mellitus, has a likelihood to poor adherence to the drug due to the capability of drug-drug interaction and side effects of it.[38] To make the situation even worse, patients taking multiple drugs due to many comorbidities have a higher risk of mortality due to the disease or the treatment itself.[41] To overcome this factor of non-adherence, many studies investigated the combination of medications into a single pill to reduce the patient's overall pill burden. Although many physicians avoid giving combined pills due to the lack of freedom to titrate each medications' dosage, in the case of LLDs, the drugs were not that frequently titrated. So, this would be a beneficial modification to improve adherence to multiple LLDs.[30]

A growing barrier to adherence to the drug was the adverse effect of the medication.[23,42,43] This is consistent with the findings from previous reviews.[32,34] The well-known side/adverse effects of statin include muscle related (ranging from mild muscle ache to severe rhabdomyolysis), hepatic, and renal dysfunction. One study found that one in 10 people complain of 'very unpleasant' or persistent unwanted effects, especially from statins, however, this study did not assess the nature of the side effects.[40] In another study conducted in the USA, frequent muscle side effects due to statins were reported that lead to poor adherence and discontinuation.[44] However, the usage of statins may also increase adherence. This may be due to its greater potency as compared to other drugs, in lowering the lipid level.[22]

As a primary reason for non-adherence, difficulty remembering the dose consumed is an important factor to consider. As such, by utilizing blister packaging, patients can self-monitor their own medication consumption which will improve adherence. This type of packaging also allows healthcare workers to monitor patients' adherence during their follow-ups.[25]

Healthcare worker-related factor

Several studies using interventions by healthcare workers were done and many proved its effectiveness. This includes counseling by nurses,[16] pharmacists,[15] as well as monitoring and optimization of medications regime among others.[17] Patients receiving risk factor counseling increased their sense of control about their disease, hence improving adherence. In addition, studies also reported that personal contact by improving relationships between patients and healthcare workers may increase adherence.[16] Also, personalized intervention for each patient according to their problems for non-adherence was found to be an effective way to improve adherence, and this intervention should be done by the community pharmacists.[15] This finding proved that healthcare workers play a vital role in improving patient's adherence. A previous review found that lack of communication between the physician and the patient during the consultation has a negative impact on adherence to statins.[34] Healthcare workers should be able to counsel their patients holistically regarding dyslipidemia and lipid-lowering medications. The communication skills that can improve the relationship between healthcare workers and patients must always be emphasized. The availability of updated local guidelines on this topic is one of the best modes of training for healthcare workers.

As for the drug providers and monitoring, patients attending FMSC may have more comorbidities as compared to general outpatient clinics. In the Health Belief Model, sicker patients were found to be more adherent to their medications. This may be the explanation for adherence improvement in FMSC attendees.[21] Contradicting results were found for seeing a cardiologist. Seeing a cardiologist may improve a patient's adherence, which may be explained by more active monitoring and counseling from a cardiologist as opposed to other physicians. However, this may also be associated with the motivation of the patient themselves, where motivated patients tend to seek treatment from a cardiologist.[20] Furthermore, a study in Dubai found that patients receiving treatment from tertiary care have better lipid control compared to those receiving treatment from primary care.[45] Another study found an increase in adherence for patients treated by other than cardiologists, but it could be due to patients' different characteristics, as this factor was not statistically significant after adjusting

for other factors.[22] This was further supported by a study involving six Arabian countries that found most patients with established atherosclerotic cardiovascular disease, including those treated in the tertiary center, did not achieve the non-high-density lipoprotein cholesterol target.[46]

As for the location of the hospitals, the province has undergone urbanization, resulting in a better healthcare system as compared to the county level, and higher health literacy among urbanized patients.[22] This may explain why patients at the province-level hospital were more adherent to their LLDs.

CONCLUSION

Dyslipidemia is a silent killer, and many people are unaware of the importance to control this disease. Many factors were found to affect adherence to LLDs including patient, medication, and healthcare workers-related factors. As such, by understanding all these factors, efforts need to be made to improve patient adherence. Recommendations to improve adherence include educating patients on the disease itself and the importance of the treatment, modification of the dosing, timing, type of LLDs, and effective consultations by healthcare workers. Further studies need to be done in Malaysia as there is inadequate research on this topic.

Disclosure

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